ANSES Opinion
Request No 2018-SA-0180

The Director General

Maisons-Alfort, 30 March 2021

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on the "assessment of the risk of hepatotoxicity associated with the coumarin content of certain plants that can be consumed in food supplements or in other foodstuffs"

ANSES undertakes independent and pluralistic scientific expert assessments.
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It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.
It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).
Its opinions are published on its website. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 30 March 2021 shall prevail.

On 27 July 2018, ANSES issued an internal request to conduct the following expert appraisal: assessment of the risk of hepatotoxicity associated with the coumarin content of certain plants that can be consumed in food supplements or in other foodstuffs.

1. BACKGROUND AND PURPOSE OF THE REQUEST

The use of plants in food supplements is governed by Decree No. 2006-352 of 20 March 2006 and the Ministerial Order of 24 June 2014, hereinafter referred to as the Plants Order.

Coumarin is a natural aromatic compound found in certain plants such as cinnamon, tonka bean and sweet clover. The coumarin content in these plants varies widely, from trace levels to more than 0.3% (m/m). Annex I of the Plants Order states that coumarin is a "substance to be monitored" for the species *Cinnamomum cassia* and *Cinnamomum verum*. However, other plants authorised for use in food supplements also contain coumarin, and yet no coumarin limit has been specified for these products in the Plants Order.

In 2004, EFSA established a tolerable daily intake (TDI) of 0.1 mg/kg bw/day for coumarin (EFSA 2004). This dose was confirmed on the basis of new data by the BfR[1] (BfR 2007) and during EFSA's re-assessment (EFSA 2008). EFSA also indicated that the consumption of food supplements containing high doses of cinnamon constituted a risk situation for people with type II diabetes.

In 2006, the BfR stated that high consumption of cinnamon may lead to excessive exposure to coumarin and therefore advised against the consumption of Chinese cinnamon, given its relatively high coumarin content (BfR 2006). In addition, a small sub-population of individuals – between 0.4% and 6.5% of the Caucasian population – is sensitive to coumarin, with adverse effects observed at low doses, and is therefore regarded as an at-risk population (Tisserand and Young 2014).

The cinnamon or coumarin content in some food supplements, along with the recommended daily intakes for these products and exposure to other food products containing cinnamon, could lead to the TDI set by EFSA being greatly exceeded.

This led ANSES to issue an internal request for an assessment of the risk of hepatotoxicity associated with the coumarin content of plants that can be consumed in food supplements or in other foodstuffs. Its expert appraisal took into account all foodstuffs likely to contain plants or plant extracts containing coumarin – especially cinnamon – that can be consumed in France. Substances other than coumarin found in these plants were not taken into account in the assessment.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French standard NF X 50-110 "Quality in Expert Appraisals – General Requirements of Competence for Expert Appraisals (May 2003)".

The issues being appraised fall within the scope of the Expert Committee (CES) on "Human Nutrition". ANSES entrusted the expert appraisal to the Working Group (WG) on "Plants". This WG contributes to the missions of the CES on "Human Nutrition", to which it reports, by providing it with specific scientific support in the area of pharmacognosy. The work and conclusions of the WG on "Plants" were based on the reports of two experts from this WG.

ANSES's nutrivigilance scheme was asked to analyse reports of adverse effects suspected of being caused by the consumption of food supplements containing coumarin, as well as reports provided by the ANSM as part of the pharmacovigilance scheme, reports provided by ANSES's Health Monitoring & Alerts Department (DAVS) and information provided by health agencies in the European Union, Canada and the United States.

The Food Observatory Unit (UOA) was asked (under the scientific and technical support request AST 2019-ASTDER-29) to provide data on the presence of certain ingredients that may contain coumarin in processed products available on the French market (Annex 3).

[1] The BfR (in German: *Bundesinstitut für Risikobewertung*) is the German Federal Institute for Risk Assessment.

The Methodology and Studies Unit (UME) was asked (2019-ASTDER-32) to assess the exposure to coumarin of the population living in France, using data from the third Individual and National Study on Food Consumption (INCA3) (Annex 4).

The methodological and scientific aspects of the work were presented to the CES on 5 February 2020. They were adopted by the CES on "Human Nutrition" at its meeting of 19 November 2020.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals. The analysis of the declared interests revealed one that could lead to a potential risk of conflict of interest for two experts. These experts did not therefore take part in the expert appraisal and review.

The experts' declarations of interests are made public via the ANSES website (www.anses.fr).

3. ANALYSIS AND CONCLUSIONS OF THE WG ON "PLANTS" AND THE CES ON "HUMAN NUTRITION"

The analysis and conclusions presented below summarise the expert appraisal undertaken by the WG on "Plants" and the CES on "Human Nutrition".

3.1. Coumarin

3.1.1.Chemical characterisation of coumarin

Coumarin is a natural volatile aromatic substance known in the international nomenclature as 2H-1-benzopyran-2-one (CAS number 91-64-5). It is a 2-hydroxy-Z-cinnamic acid lactone, formed in the plant kingdom by the shikimic acid pathway. It is soluble in ethanol, chloroform and diethyl ether, and poorly soluble in water (Lake 1999).

In this opinion, the term "coumarin" in the singular will refer to coumarin or 2H-1-benzopyran-2-one (Figure 1). It is therefore important to make the distinction between coumarin and coumarin derivatives (the latter are often referred to as "coumarins" in the literature), which are widely distributed in the plant kingdom and can take different forms: hydroxylated, methylated, prenylated or involved in glycosidic bonds. While coumarin derivatives are very common in species belonging to the Fabaceae, Asteraceae, Apiaceae or Rutaceae families, coumarin is rarer and only seems to be concentrated to a significant degree in certain species such as tonka bean or cinnamon bark.

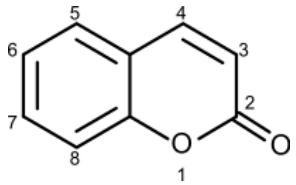

Figure 1: molecular structure of coumarin [2H-1-benzopyran-2-one (CAS number 91-64-5)]

A distinction therefore needs to be made between the various coumarin derivatives, whether or not of natural origin, which have different chemical structures (described in Annex 2) and different pharmacological properties and toxicological profiles. Coumarin derivatives cannot therefore be equated with each other. Similarly, the toxicity of coumarin is specific to this compound and cannot be extrapolated to coumarin derivatives, including simple hydroxylated coumarins.

3.1.2. Pharmacokinetic data on coumarin

- ***Absorption, bioavailability and distribution***

According to Lake (1999), pharmacokinetic studies in humans show that coumarin is completely absorbed from the gastrointestinal tract after oral administration and extensively metabolised during the first pass through the liver, with only 2-6% reaching the systemic circulation in its original form. Coumarin has a rapid absorption rate.

Furthermore, a study carried out in humans showed that the metabolism of coumarin into 7-hydroxycoumarin (in free and conjugated form) can vary according to the forms ingested. Indeed, 8 hours after oral intake of isolated coumarin in a capsule or cinnamon tea, the

measured urinary concentration of 7-hydroxycoumarin (in free and conjugated form) was equivalent (Abraham *et al.* 2011), whereas the other formulations tested (bark powder capsule or pastry containing cinnamon bark) showed lower bioavailability of coumarin.

- ***Metabolism and excretion***

In humans, coumarin is extensively metabolised in the liver by the CYP2A6 isoform of cytochrome P450 into 7-hydroxycoumarin, which then leads to rapid elimination in urine in the form of glucuronide-conjugated derivatives, corresponding to 80-90% of the absorbed coumarin (Egan *et al.* 1990, Abraham *et al.* 2010, Born *et al.* 2000, Wittgen *et al.* 2012).

Although 7-hydroxycoumarin is the main metabolic pathway of coumarin identified in humans, because of human genetic polymorphism in coumarin metabolism (Fernandez-Salguero *et al.* 1995), a significant proportion of the human population produces a potentially toxic epoxide intermediate (Lake 1999). For example, comparative studies in Southern Europe and Asia have shown that a large number of individuals have CYP2A6 polymorphisms that induce the use of metabolic pathways other than 7-hydroxycoumarin (Iscan *et al.* 1994, Oscarson *et al.* 1999).

An *in vitro* study showed a strong relationship ($r^2 = 0.97$ and $p < 0.001$) between the intrinsic clearance of 7-hydroxycoumarin and different CYP2A6 variants (Hosono *et al.* 2017). The same authors also showed that 14 out of the 34 CYP2A6 variants studied were characterised by a marked reduction in enzyme activity, opening the way to potential molecular markers for susceptible populations (Hosono *et al.* 2017).

7-Hydroxycoumarin was not detected in urine collected within 8 hours of coumarin administration (2 mg orally) from an individual who was homozygous for the CYP2A6∗ 2 variant allele. Around 50% of the ingested coumarin dose was eliminated as 2-hydroxyphenylacetic acid, which is the end product of coumarin 3-hydroxylation. In similar tests, members of the homozygous individual's immediate family, who were heterozygous for the CYP2A6∗ 2 allele, excreted a small amount of 2-hydroxyphenylacetic acid and mainly 7-hydroxycoumarin (Hadidi *et al.* 1997).

A clinical study was conducted in Jordan in healthy men and women (n = 103) who were administered 2 mg coumarin orally. Participants' 0 to 8h urine was collected and analysed by GC-MS to determine the concentration of 7-hydroxycoumarin and 2-hydroxyphenylacetic acid, the latter being a metabolite of the 3-hydroxylation pathway. The results showed high inter-individual variability in the excretion of 7-hydroxycoumarin and 2-hydroxyphenylacetic acid, with the ratio between the two metabolites suggesting the existence of a genetic polymorphism in the study population (Hadidi *et al.* 1998).

Another clinical study was conducted in healthy Chinese male and female volunteers (n = 120) to demonstrate the distribution characteristics of CYP2A6 activity in this population. This activity was measured using the ratio of urinary 7-hydroxycoumarin excreted after 8 hours to the amount of coumarin (40 mg) taken orally. The measured coefficient of variation of CYP2A6 activity was 27%. The proportion of the population with degraded CYP2A6 activity was 13%. The results show the existence of pronounced inter-individual variations and phenotypic polymorphism of CYP2A6 activity in the Chinese population (Xu *et al.* 2002).

In addition, an *in vitro* study has shown that cinnamaldehyde acts as an inhibitor of CYP2A6 activity in human liver microsomes. The high concentration of cinnamaldehyde in cinnamon essential oils (65-80% in Ceylon cinnamon essential oil, 90% in Chinese cinnamon essential oil) could also increase the risk of coumarin-related hepatotoxicity (Chan *et al.* 2016).

In dogs and large mammals in general, the pathways for coumarin metabolism are broadly the same as in humans, whereas in rodents, other metabolic pathways for coumarin have been identified (Figure 2).

In rats, the main pathway of coumarin metabolism involves the formation of coumarin-3,4-epoxide in a reaction primarily catalysed by CYP2A1 (Figure 2).

This coumarin 3,4-epoxidation pathway is also the main pathway in mice; however, the susceptibility of this species to coumarin toxicity is much lower than for rats (Born *et al.* 2003). This has led some authors to conclude that it is the transformation of 2-hydroxyphenylacetaldehyde into 2-hydroxyphenylacetic acid that represents the main factor of variability and susceptibility between species, since in rats the main metabolite found is 2-hydroxyphenylethanol and not the corresponding acid as observed in mice (Born *et al.* 2003, Vassallo *et al.* 2004).

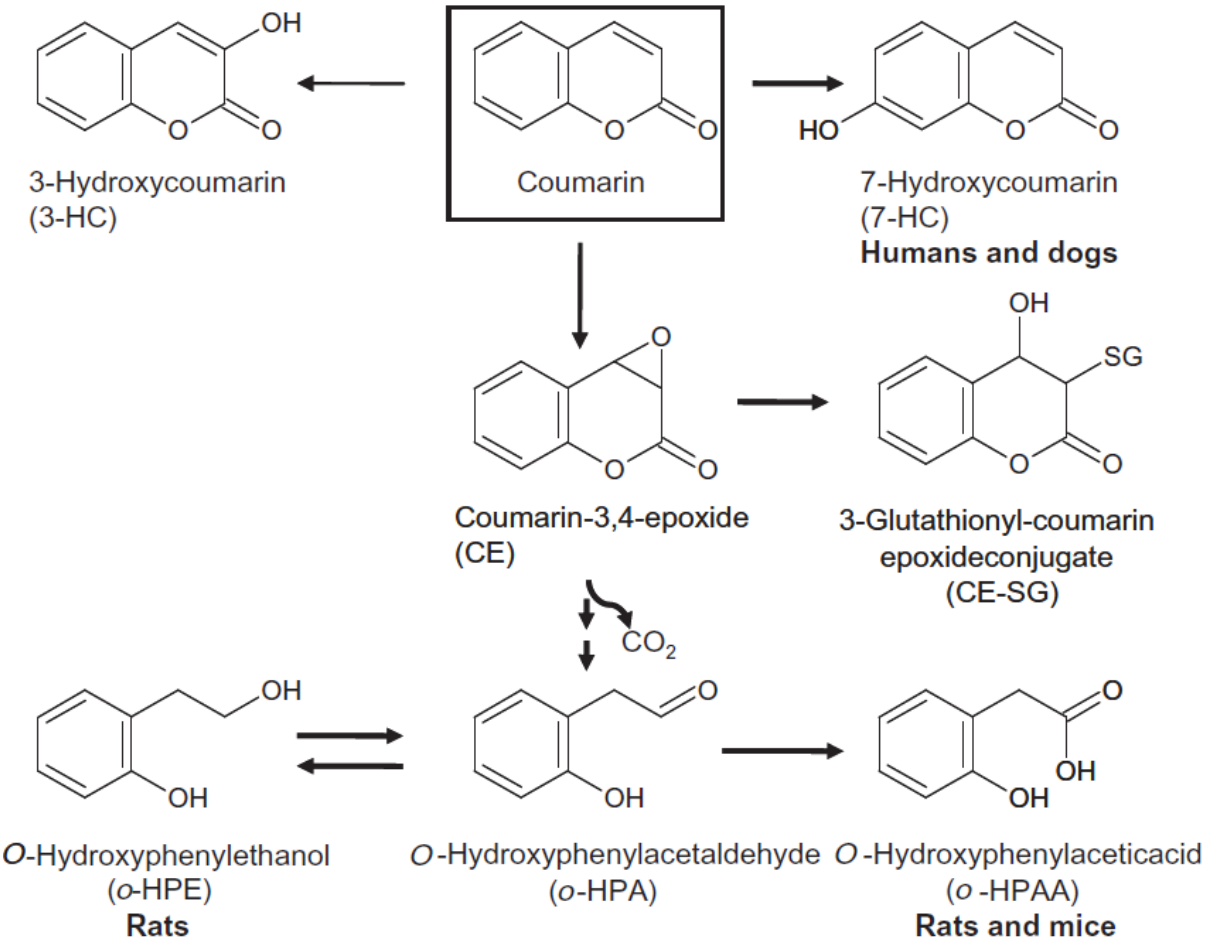

Figure 2 Major metabolic pathways of coumarin transformation after oral administration, based on EFSA (2004).

3.1.3.Pharmacological and physiological properties of coumarin

Coumarin and simple non-prenylated coumarins seem to have venotonic properties, mainly due to their ability to reduce capillary permeability (Hoult and Paya 1996, Hu and Piller 2017). Furthermore, coumarin is said to stimulate the reticuloendothelial system and the proteolytic capacity of macrophages (Bruneton 2016).

Plants containing coumarins (hydroxylated or not), such as sweet clover or horse chestnut (bark), are authorised for use as venotonics in phytotherapy (EMA 2012, 2017). However, coumarin, primarily through the use of cinnamon, is most often associated with claims about "maintaining blood sugar levels". This effect has been observed in studies conducted mainly in diabetic patients (Kim, Hyun, and Choung 2006, Altschuler *et al.* 2007, Pham, Kourlas, and Pham 2007). This use also comes from traditional Asian medicine and is mentioned in particular for cinnamon-based food supplements.

The anticoagulant properties attributed to coumarins are specific to dimeric derivatives, in particular dicoumarol produced during the fermentation of sweet clover in the event of fungal contamination. Simple coumarins, whether hydroxylated or not, do not have these anticoagulant properties (Bruneton 2016).

3.1.4.Toxicological data on coumarin and plants containing coumarin

- **Acute toxicity**

An oral LD_{50}[2] value of 202 mg/kg bw in guinea pigs has been determined for coumarin (Jenner *et al.* 1964). After oral administration to rats by gavage, the LD_{50} of coumarin ranged from 290 to 680 mg/kg bw (Hazleton *et al.* 1956, Cohen 1979).

After oral administration to mice by gavage, the LD_{50} of coumarin ranged from 196 mg to 780 mg/kg bw, depending on the strain used (Endell and Seidel 1978).

- ***Subchronic and chronic toxicity***

Toxicity studies in rats have shown that consumption of a diet containing 0.5% coumarin over a period of 2 years results in liver fibrosis and delayed growth. A diet containing 1% coumarin caused delayed growth, testicular atrophy, liver damage and death in all rats within 8 weeks (Hagan *et al.* 1967).

Chronic consumption (104 weeks) of feed containing 0.3 to 0.5% coumarin resulted in an increased incidence of parenchymal liver cell tumours in Sprague-Dawley rats and CD-1 mice (Carlton, Aubrun, and Simon 1996).

- ***Reproductive and developmental toxicity***

Studies have examined the teratogenic effects of coumarin alone or in combination with rutin. Intravenous administration to New Zealand White rabbits of coumarin alone or a combination of coumarin/rutin at 10 and 100 times the therapeutic dose did not show any increase in malformation rates compared with control animals, or any increase in resorptions or foetal mortality (Grote and Weinmann 1973, EMA 2017).

[2] LD_{50}: Median lethal dose, i.e. the dose of substance that kills 50% of a group of animals.

Coumarin, 4-hydroxycoumarin and 7-hydroxycoumarin were studied in the Frog Embryo Teratogenic Assay on Xenopus (FETAX), a screening method to identify potential developmental toxicity. The assay was performed at two concentrations (0.08 and 0.18 mg/L), with and without metabolic activation. It showed that metabolic activation increased the developmental toxicity of coumarin and the toxic potential of 4-hydroxycoumarin, while the toxic potential of 7-hydroxycoumarin remained unchanged. The authors suggested that highly toxic epoxide intermediates may be produced from oxidative P450 metabolism and that epoxide hydrolase may play a role in detoxification of these reactive intermediates (Fort *et al.* 1998, EMA 2017).

- ***Genotoxicity***

EFSA concluded that there was no DNA adduct formation in the kidney and liver of rats, showing that coumarin does not bind covalently to DNA and suggesting a non-genotoxic mode of action for the observed tumour inductions (EFSA 2004).

The NTP (1993) and IARC (2000) assessed numerous studies conducted on the mutagenicity and genotoxicity of coumarin. In the Ames test, coumarin induced gene mutations in *Salmonella typhimurium* strain TA100, exclusively with metabolic activation (hamster S9) and at high doses (1000 µg/box) (Haworth *et al.* (1983) as cited in IARC (2000)). A positive result was also observed in *Salmonella typhimurium* strain TA7002, which responded specifically to T:A to A:T reversions. However, coumarin failed to induce gene mutations in other strains targeting the same type of mutation. At the same time, negative results were noted for *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA7001, TA7003, TA7004, TA7005 and TA7006 (IARC 2000).

In the *in vitro* micronucleus assay, coumarin was weakly positive in human hepatocytes (Hep-G2 cell line) but negative in rat hepatocytes. Coumarin was also weakly genotoxic in the *in vitro* chromosomal aberration test in hamster ovary cells (CHO cells) with metabolic activation, but did not induce gene mutations in these same cells.

In vivo, coumarin did not induce micronuclei in the peripheral blood cells of male and female B6C3F mice exposed orally for 13 weeks (NTP 1993) or in the bone marrow of male and female ICR mice (IARC 2000). Lastly, coumarin was not mutagenic in the sex-linked recessive lethal mutation assay in *Drosophila melanogaster*.

Although there are some discrepancies in the *in vitro* results, taken together these studies suggest that coumarin is probably not a genotoxic agent *in vivo*. On this basis, EMA provisionally concluded that coumarin was not genotoxic (EMA 2017).

- ***Carcinogenicity***

A review of the available literature on the toxicity of coumarin by the SCF (1999) concluded that coumarin administered orally was a carcinogen in rats and potentially in mice. In rats, adenomas and carcinomas of the liver and bile ducts and adenomas of the kidney have been observed (San and Raabe 1994). In mice, adenomas and carcinomas of the lung and adenomas of the liver have been observed (San and Wagner 1994).

According to the IARC (IARC 2000), coumarin cannot be classified as carcinogenic to humans (Group 3) because of limited evidence in animals, differences in metabolism between humans and rodents (Figure 2), and the lack of epidemiological studies. Moreover, the carcinogenicity of coumarin may only be expressed (after it has been metabolised) in animal species in which tissue toxicity is observed (EMA 2017).

- ***Hepatotoxicity***

As previously described, coumarin is extensively metabolised in the liver by the CYP2A6 isoform of cytochrome P450 into 7-hydroxycoumarin, which then leads to rapid elimination in urine in the form of glucuronide-conjugated derivatives, corresponding to 80-90% of the absorbed coumarin (Wittgen *et al.* 2012). The toxicity mechanism associated with CYP2A6 deficiency has not been demonstrated in humans with a sufficiently high level of evidence. The lack of a clear dose-dependent relationship in the severity of the response in the subgroup with CYP2A6 polymorphism suggests that an immune mechanism may also be involved in coumarin-induced hepatotoxicity in humans (Tisserand and Young 2014, Abraham *et al.* 2010, Rietjens *et al.* 2008). In rodents, non-hydroxylated coumarin derivatives such as dihydrocoumarin, 3,4-dimethyl-coumarin or 6-methyl-coumarin did not cause liver toxicity (Lake *et al.* 1994). The liver toxicity characterised for coumarin therefore appears to be specific to this compound and cannot be extended to others in this class.

Animal data

In rats, in which coumarin causes marked liver toxicity, the main route of coumarin detoxification is through the formation of coumarin-3,4-epoxide, a reaction mainly catalysed by CYP2A1 (see Figure 2).
Data on liver toxicity of coumarin were reported in rats and other mammalian species at high doses (>100 mg/kg bw) as early as 1950. In rats, the development of liver tumours has been observed (Abraham *et al.* 2010).

The coumarin 3,4-epoxidation pathway is also the main pathway in mice. However, gavage tests with a single dose of coumarin (200 mg/kg bw) show the susceptibility of this species to coumarin hepatotoxicity to be much lower than in rats, with comparable levels of epoxide (Born *et al.* 2003). These data indicate that *in vivo* liver toxicity is not associated with the rate of epoxide and aldehyde formation observed in *in vitro* studies. The balance between bioactivation (epoxide formation and rearrangement to hydroxyphenylaldehyde) and detoxification (conjugation of epoxide with glutathione and oxidation of hydroxyphenylaldehyde to o-hydroxyphenylacetic acid) determines a species' *in vivo* susceptibility to the liver toxicity of coumarin (Edwards *et al.* 2000, Api 2001, EFSA 2004, Vassallo *et al.* 2004).

Hepatotoxicity was also observed in Beagle dogs and was classified as the most sensitive toxic effect[3] (Hagan *et al.* 1967). In this study, hepatotoxic effects (histological damage) were evident in animals given a coumarin dose of 25 mg/kg bw per day, but not significant in animals given a coumarin dose of 10 mg/kg bw per day (necropsies between day 297 and day 350), which was considered to be the NOAEL in dogs. The latter value was converted, applying an uncertainty factor of 100, to derive a TDI of 0.1 mg/kg bw/day in humans (EFSA 2004).

Clinical data in humans

In humans, an analysis of cases of hepatotoxicity associated with the use of coumarin in three European countries (France, Ireland, Germany) showed that liver damage could not be ruled out from a coumarin dose of 25 mg/day (Bergmann 1999).

[3] In general, a guidance value can be derived from a reference dose (NOAEL and/or Benchmark dose) from the pivotal study, based on the most relevant effect observed in the most sensitive species and applying safety factors.

A placebo-controlled clinical study in 140 patients with chronic lymphoedema of the arm after surgical treatment of breast cancer showed that oral administration of 200 mg coumarin twice daily for 6 months increased the incidence of hepatotoxic effects. In these cases, serum transaminase levels returned to normal after cessation of coumarin administration (Loprinzi *et al.* 1999).

A clinical study in patients with chronic venous insufficiency showed that after oral administration of 90 mg coumarin and 540 mg troxerutin per day for 16 weeks, 8% of treated patients had elevated transaminase levels, greater than 2.5 times the upper limit of normal (Vanscheidt *et al.* 2002, Burian *et al.* 2003, Schmeck-Lindenau *et al.* 2003).

A summary of these and other clinical studies is given in table 1.

Table 1: Summary of results of clinical studies on the hepatotoxicity of coumarin

Number of patients	Indication	Daily dose	Duration	Hepatotoxic effect	Frequency of occurrence	Reference
2173	Melanomas, renal carcinomas, chronic infections	100 mg	1 month	Twofold or greater increase in serum bilirubin, transaminase and alkaline phosphatase levels	0.4%	(Cox, O'kennedy, and Thornes 1989)
		50 mg	2 years			
140 women	Lymphoedema following breast cancer surgery	2 x 200 mg	6 months	2.5-fold or greater increase in bilirubin levels	6%	(Loprinzi *et al.* 1999)
48	Metastatic prostate carcinoma	3000 mg	12 months	3-6 fold increase in serum AST levels	6%	(Mohler *et al.* 1992)
114	Chronic venous insufficiency	3 x 30 mg (+ 180 mg troxerutin)	16 weeks	Twofold or greater increase in serum bilirubin, transaminase, alkaline phosphatase and gamma-GT levels	4.9%	(Vanscheidt *et al.* 2002); (Schmeck-Lindenau *et al.* 2003); (Burian *et al.* 2003)

In humans, clinical data on the use of coumarin show variations in the frequency of this hepatotoxic response depending on the method used (clinical observation or determination of liver enzymes in blood).

In these cases, coumarin toxicity is manifested by an increase in circulating concentrations of liver enzymes (which is reversible after cessation of treatment) and, at higher doses, by more serious liver damage (increase in bilirubin levels, hepatic cytolysis, hepatitis and liver failure), although it has not been possible to clearly define dose thresholds because of inter-individual variability (Abraham *et al.* 2010).

Other cases of adverse effects associated with the consumption of products on the market have been reported in the literature and by the vigilance schemes run by national and international health agencies. They are described in the section on "Adverse effects associated with the consumption of coumarin".

- ***Health-based guidance values for coumarin***

The results of the toxicity study in Beagle dogs exposed to coumarin for two years were used to establish a NOAEL for coumarin of 10 mg/kg bw per day on the basis of liver damage (histological damage) observed at 25 mg/kg bw per day. After applying an uncertainty factor of 100, a TDI of 0.1 mg/kg bw was established for humans (EFSA 2004). The assessment of new data did not result in this value being changed (EFSA 2008).

EFSA also examined the health risk of exceeding the TDI of coumarin for a period of one to two weeks. The studies show that clinical symptoms associated with coumarin hepatotoxicity appear after one to two weeks of daily exposure and are reversible after cessation of exposure to coumarin. EFSA therefore concluded that exceeding three times the TDI of coumarin for a period of one to two weeks was not a health concern.

More recently, a "benchmark dose" (BMD) approach was developed (Fotland *et al.* 2012). The Benchmark dose 05 (BMD05), defined as the dose corresponding to a level of response (increase in liver weight) in excess of 5% compared with the background, was calculated in two species. From this point, the lower bounds of its 95% confidence interval (BMDL05) were determined to be around 30 mg/kg bw/day (over 5 days per week) in mice (male and female) and 10 mg/kg bw/day (over 5 days per week) in female rats, or 7 mg/kg bw/day (over 7 days per week). The latter value was converted, applying an uncertainty factor of 100, thus corresponding to a tolerable daily intake in humans of 0.07 mg/kg bw/day (Fotland *et al.* 2012).

Based on the analysis of cases of liver damage in humans and applying a safety factor of 5, the BfR set a coumarin dose of 5 mg/person/day that would exclude any possible risk of hepatotoxicity (BfR 2006). EFSA's TDI value is reinforced here by the available results on humans and was therefore selected for assessing the health risks (acute and chronic) for the different exposure scenarios.

The available toxicological data confirm the liver toxicity of coumarin at high doses (> 25 mg/day in humans). These data also indicate that coumarin is neither carcinogenic nor genotoxic. The TDI of 0.1 mg/kg bw/day set by EFSA ensures the safe use of foodstuffs containing coumarin. The health risk from exceeding this dose is not considered to be of concern for a period of one to two weeks, including for at-risk populations (EFSA 2008). This reference value was selected by ANSES for this health risk assessment.

3.2. The different uses of coumarin

3.2.1.Regulatory status of coumarin

In the United States, since 1954, food containing any added coumarin as such or as a constituent of tonka beans or tonka extract is deemed to be adulterated (USFDA 2018). The *Codex Alimentarius* recommended in 1985 and then confirmed in 2006 that coumarin should not be added to food or beverages. However, coumarin may be present only in the form of natural flavouring materials (e.g. tonka bean extract) with a limit of 2 mg/kg[(4)] in foodstuffs or beverages and 10 mg/kg in special caramels used as additives in alcoholic beverages (FAO/WHO 1985).

In Europe, coumarin is listed in Annex III of Regulation (EC) No 1334/2008[5], which is the list of substances that shall not be added as such to food or that are naturally present in flavourings and food ingredients with flavouring properties, and for which maximum levels of coumarin have been set. These levels are shown in table 2.

Table 2: Maximum regulatory levels of naturally occurring coumarin in the ingredients of the following products (Annex III to Regulation (EC) No 1334/2008)

Products that may contain flavourings or food ingredients with naturally occurring coumarin	**Maximum coumarin level** (mg coumarin/kg of product)
Traditional and/or seasonal bakery ware containing a reference to cinnamon in the labelling	50
Breakfast cereals including muesli	20
Fine bakery ware, with the exception of traditional and/or seasonal bakery ware containing a reference to cinnamon in the labelling	15
Desserts	5

However, there is no proposed limit for coumarin in food supplements. EFSA has set a TDI for coumarin of 0.1 mg/kg bw (EFSA 2004, 2008). Furthermore, coumarin is listed as a naturally occurring substance of possible concern for human health in EFSA's *Compendium of Botanicals*. The extracts studied in this framework concern dried plant parts (0.4-1.7% coumarin), essential oils (0.5-4% coumarin) and seed extracts (3.6-25%).

In France, coumarin is listed in the Plants Order (2014) as a "substance to be monitored" for *Cinnamomum cassia* (L.) J.Presl, (syn. *Cinnamomum aromaticum* Nees) and *Cinnamomum verum* J.Presl (syn. *Cinnamomum zeylanicum* Blume), without any restriction on the dose or level or any warning for at-risk populations. However, other plants known to contain significant amounts of coumarin, possibly after drying, including *Melilotus altissimus* Thuill., *Melilotus officinalis* L. and *Galium odoratum* (L.) Scop., are also on the list of the Plants Order and the list of 1011 plants of the DGCCRF (2019b). It should be noted that for these plants, the "substances to be monitored" are specified as "coumarins". The health recommendations for this new list are expected to be updated shortly. In addition, the DGCCRF (2019a) has also published on its website the list of essential oils regarded as traditional that are authorised in food supplements, some of which may contain coumarin. This list should also be updated with plant-specific health recommendations.

[4] The acceptable dose was to be lower but the analytical methods available at the time did not allow for a lower limit of detection.
[5] Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC.

In Italy[6] and Belgium[7], the lists of plants authorised in food supplements are the same as those authorised in France, but without any warning about the levels of coumarin(s).

In Canada, cinnamon (*Cinnamomum aromaticum* and *Cinnamomum verum*) is classified as a natural health product, with risk statements for diabetics and pregnant or breastfeeding women, and a statement regarding the risk of a known adverse reaction of hypersensitivity or allergy, only for *C. aromaticum*.

It should be noted that no health claims are permitted for coumarin, cinnamon or other plants containing coumarin according to Commission Regulation (EU) No 432/2012 of 16 May 2012[8].

In summary, the fortification of normal foods with coumarin (as a substance) is not permitted. However, plants containing it, notably cinnamon, can be used as flavouring substances in certain food products and under certain conditions of use, such as a maximum coumarin level. For food supplements, however, no limits are proposed.

3.2.2.Coumarin in food

- ***Plants containing coumarin***

The tonka bean, obtained from the fruit of the Brazilian teak or cumaru, *Dipteryx odorata* (Aubl.) Willd. (Fabaceae), usually contains 1-4% coumarin, which gives it a pleasant aroma of vanilla or fresh hay (Ehlers *et al.* 1995).

Coumarin was synthesised in 1868 and subsequently became widely used as a flavouring agent until its hepatotoxicity was discovered and it was prohibited in food products (USFDA 2018). Most of the coumarin used commercially for the cosmetic and chemical industries is nowadays synthesised from salicylaldehyde, but naturally occurring coumarin isolated from tonka beans is also available on the market (Abraham *et al.* 2010).

Coumarin is also found in many food plants and in some spices. Depending on the species, coumarin may be found mainly in the free state or the glucoside state at the time of harvest. It is therefore important that the coumarin content is expressed as the amount of the aglycone form.

Thus, in the bark of Chinese cinnamon (*Cinnamomum cassia* (L.) J.Presl, syn. *Cinnamomum aromaticum* Nees) and Ceylon cinnamon (*Cinnamomum verum* J.Presl, syn. *Cinnamomum zeylanicum* Blume), coumarin is mainly found as free coumarin, whereas in the aerial parts of sweet woodruff (*Galium odoratum* (L.) Scop., syn. *Asperula odorata* L.) and yellow sweet clover (*Melilotus officinalis* (L.) Pall) and in the leaf of bastard balm (*Melittis melissophyllum* L.), its precursor is mostly found in glucoside form (Bruneton 2016, Ieri, Pinelli, and Romani 2012). Although the coumarin content in these plants or plant parts is variable, coumarin is the substance in them identified as a concern by EFSA in its *Compendium of Botanicals* list.

[6] List of plants updated in September 2018: Regulation on the use of plant substances and preparations in food supplements in Italy.
[7] Belgian Royal Decree of 29 August 1997 on the manufacture and trade of foods composed of or containing plants or plant preparations (consolidated version, February 2017).
[8] Commission Regulation (EU) No 432/2012 of 16 May 2012 establishing a list of permitted health claims made on foods, other than those referring to the reduction of disease risk and to children's development and health.

According to some sources, essential oils of lavender (*Lavandula angustifolia*) or lavandin (*Lavandula* × *intermedia* Emeric ex Loisel) contain coumarin (Rychlik 2008). However, the presence of coumarin in these products is not mentioned in other publications, notably in Tisserand and Young (2014).

Mahaleb is an aromatic spice obtained from the stone of the Saint Lucie cherry (*Cerasus mahaleb* (L.) Mill.), which is used in the Middle East and surrounding areas. Its coumarin content has been estimated at 870 mg/kg (Ieri, Pinelli, and Romani 2012), equivalent to the coumarin content of some cinnamon. The dried leaf of *Melittis melissophyllum* has a coumarin content that can exceed that of Chinese cinnamon.

A vodka flavoured with bison grass (*Hierochloe odorata* (L.) Beauv., syn. *Anthoxanthum nitens* (Weber) Y. Schouten & Veldkamp) contains around 4 mg of coumarin per kg of product (Sproll *et al.* 2008).

Considering the coumarin levels of the different plants listed in table 3, and their uses in food, cinnamon is regarded as the main dietary source of coumarin.

Table 3: Coumarin levels of various plants, extracts and spices adapted from Rychlik (2008)

Plants, extracts and spices	**Plant parts or extracts**	**Coumarin level**	
		mg/kg	%
Dill (*Anethum graveolens* L.)	essential oil (fruit)	0.21	$0.21 \cdot 10^{-4}$
Sweet woodruff (*Galium odoratum*)	aerial parts	203	0.02
Camomile (*Matricaria recutita* L.)	essential oil (flower)	3.23	$0.323 \cdot 10^{-3}$
Chinese cinnamon (*Cinnamomum cassia*)	sticks (bark)	1250 – 1490	0.125 – 0.15
Chinese cinnamon (*Cinnamomum cassia*)	essential oil (bark)	4370	0.44
Ceylon cinnamon (*Cinnamomum verum*)	sticks (bark)	2.40	$0.24 \cdot 10^{-3}$
Ceylon cinnamon (*Cinnamomum verum*)	sticks (bark)	0.86	$0.86 \cdot 10^{-4}$
Ceylon cinnamon (*Cinnamomum verum*)	essential oil (bark)	40	$0.4 \cdot 10^{-2}$
Lemon (*Citrus limon* (L.) Osbeck)	essential oil (fruit)	3.86	$0.386 \cdot 10^{-3}$
Coriander (*Coriandrum sativum* L.)	essential oil (fruit)	0.30	$0.30 \cdot 10^{-4}$
Curry (powdered spice mix)	-	0.46	$0.46 \cdot 10^{-4}$
Fenugreek (*Trigonella foenum-graecum* L.)	seeds	0.34	$0.34 \cdot 10^{-4}$
Lavender (*Lavandula angustifolia* Mill.)	essential oil (flower)	124	0.012
Peppermint (*Mentha x piperita* L.)	essential oil (leaf)	0.30	$0.3 \cdot 10^{-4}$
Cinnamon tea	-	0.74 – 0.94	0.74 – $0.94 \cdot 10^{-4}$
Green tea (*Camellia sinensis* (L.) Kunze),	leaf	0.21	$0.21 \cdot 10^{-4}$
Blue-white clover (*Trigonella caerulea* (L.) Ser.)	seed	37	$0.37 \cdot 10^{-2}$

- ***Special case of cinnamon (bark from the stem of cinnamon trees)***

The cinnamon species *Cinnamomum cassia* (Nees & T.Nees) J.Presl (Chinese cinnamon) and *Cinnamomum verum* J.Presl (Ceylon cinnamon) are on the list of the Plants Order, with coumarin and estragole for *C. cassia* and coumarin, methyl eugenol, estragole and eucalyptol for *C. verum* as "substances to be monitored".

In many products, the commercial term cinnamon can refer to either Ceylon cinnamon or other species of cinnamon. When the origin is not mentioned, the cinnamon used by the food industry is most often Chinese cinnamon, *C. cassia*, or Indonesian cinnamon, *C. burmannii* (Nees & Nees) Blume (Bruneton 2016). It should be noted that Chinese cinnamon has a very high coumarin content, whereas Ceylon cinnamon contains only trace amounts (Acia 2016). As Chinese cinnamon is generally much cheaper than other cinnamons, it is the most widely sold.

In addition, food supplements rarely specify the type of cinnamon used in their ingredients or indicate the respective quantities of each species when both species are mentioned, even though the coumarin content can vary greatly depending on the species. Moreover, while botanical differentiation is easy for whole forms, whether scraped or not, it is far less easy for powdered forms (Teuscher, Anton, and Lobstein 2002). However, microscopic observation under UV illumination at 365 nm allows *C. cassia* (intense yellowish-green fluorescence) to be distinguished from *C. verum* (blue-green fluorescence) (Wichtl and Anton 2003). Other species of cinnamon can also be found in foodstuffs, such as *C. burmannii* (Indonesian cinnamon) (Wang *et al.* 2013), which appears on the Italian list[6], or cinnamons used locally to replace Ceylon cinnamon.

In France, the DGCCRF (2018) published a survey on spice inspections targeting mainly importers, traders and wholesalers (181 establishments and 179 samples). A quarter of the inspections found quality defects. The inspection services noted declared qualities that did not correspond to reality (presence of substitute ingredients, non-compliance with physico-chemical criteria, a higher category declared than the one observed, etc.) and the presence of other non-declared spices or ingredients. In particular, one cinnamon sample was declared as originating from Sri Lanka (low coumarin content) when in fact it was Chinese cinnamon (cheaper and lower quality) containing a high quantity of coumarin.

In Germany, a study of 47 cinnamon samples (sticks and powder) showed relatively high and homogeneous average coumarin levels (from 0.35 to 0.4%). However, while the coumarin content in the powder ranged from 0.2 to 0.8%, the content in the cinnamon sticks was more variable: from "not detected" to 1% (Woehrlin *et al.* 2010).

In the Czech Republic, a study of 60 samples of cinnamon powder representing twelve brands showed coumarin levels ranging from 0.3 to 0.7% (Blahova and Svobodova 2012).

In the United States, a study showed that the bark of four species of the *Cinnamomum* genus was sold in the US market under the name "cinnamon", and that 90% of US imports were *C. burmannii* (Indonesian cinnamon), which had a coumarin content in bark of more than 0.2% (Wang *et al.* 2013).

In Canada, studies have been conducted by the Canadian Food Inspection Agency on the coumarin content of food products containing cinnamon in their ingredient list (Acia 2015, 2016). Coumarin was found in 95% of the samples analysed, with levels ranging from 10^{-5}% to 0.25%. Spice mixes and dried tea samples contained the highest concentrations of coumarin.

Other studies have shown coumarin levels of 0.9% in cinnamon powder (Sproll *et al.* 2008) and up to 1.2% in cinnamon sticks (He *et al.* 2005). A summary of coumarin levels in cinnamon samples from different countries is provided in .

table 4.

Table 4: Average coumarin levels in cinnamon samples (bark, powder, sticks)

Cinnamon samples	**Parts of plants**	**Coumarin level**		**Market/Reference**
		mg/kg	%	
Cinnamon (not specified)	Not specified	2000 – 6190	0.2 – 0.62	US market (Wang *et al.* 2013)
Ceylon cinnamon (*C. verum*)	Bark	17	0.0017	
Ceylon cinnamon (*C. verum*)	Bark	7 – 25	0.0007 – 0.0025	
Chinese cinnamon (*C. cassia*)	Bark	310	0.03	
Chinese cinnamon (*C. cassia*)	Not specified	85 – 262	0.0085 – 0.0262	
Indonesian cinnamon (*C. burmannii*)	Bark	2140	0.2	
Indonesian cinnamon (*C. burmannii*)	Not specified	2370 – 9300	0.24 – 0.93	
Saigon cinnamon (*C. loureirii*)	Bark	6970	0.7	
Saigon cinnamon (*C. loureirii*)	Not specified	1060	0.11	
Cinnamon (not specified)	Sticks	50	0.005	Norwegian market (Fotland *et al.* 2012)
Cinnamon (not specified)	Powder	2350	0.24	
Cinnamon (not specified)	Powder (organic)	3330	0.33	
Cinnamon	Bark (organic)	4070	0.41	
Chinese cinnamon (*C. cassia*)		2650 – 7017	0.27 – 0.7	Czech market (Blahova and Svobodova 2012)
Chinese cinnamon (*C. cassia*)	Powder	1740 – 7670	0.17 – 0.77	German market (Woehrlin *et al.* 2010)
Chinese cinnamon (*C. cassia*)	Sticks	< LD – 9900	0.00 – 0.99	
Cinnamon (*C. cassia, C. wilsonii, C. mairei, C. loureirii*)	Bark, powder or sticks	40 – 12180	0.004 – 1.2	Chinese and Hong Kong market (He *et al.* 2005)
Japanese cinnamon (*C. japonicum*)		10 – 1260	0.001 – 0.13	
Indonesian cinnamon (*C. burmannii*)		Not detected		
Ceylon cinnamon (*C. verum*)	Sticks	Not detected		Australian market (Archer 1988)
Chinese cinnamon (*C. cassia*)	Bark	1400 – 7000	0.14 – 0.7	
Indonesian cinnamon (*C. burmannii*)	Bark	400	0.04	

These data show the great variability of coumarin levels in cinnamon on the spice market. Chinese cinnamon (*C. cassia*) and Indonesian cinnamon (*C. burmannii*) are the cheapest cinnamons, with the highest estimated coumarin levels. In this context, there is a high likelihood of consuming this type of cinnamon – and therefore a high dose of coumarin – when consuming foods or food supplements containing cinnamon (extract or powder). The botanical identity of the cinnamons used and their coumarin content are therefore essential for estimating coumarin exposure and ensuring safe use of these products.

3.2.3.Coumarin in food supplements

- ***Uses of coumarin***

Companies marketing cinnamon-based food supplements often use statements about the "maintenance of normal blood sugar levels". This comes from "traditional Asian medicine" and is used as an indication for many cinnamon-based food supplements. It should however be noted that coumarin, cinnamon and other plants containing coumarin are not included in the list of substances and foods for which health claims are permitted according to Commission Regulation (EU) No 432/2012. In addition, the DGCCRF (2020) conducted a survey of websites specialising in this sector and found a very high rate of non-compliance (76%). The survey showed that one of the most frequently identified non-compliances was the use of therapeutic claims, which are strictly prohibited in food.

The companies' recommended doses for food supplements were expressed in terms of quantity of cinnamon, without specifying the botanical identity or the coumarin content. In addition, these products may contain both cinnamon extract and cinnamon powder. Given the wide variability in coumarin content in these ingredients, it is difficult to estimate a theoretical intake of coumarin from the consumption of cinnamon-based food supplements alone.

Analyses have been carried out on cinnamon-based food supplements in Norway. For two of the 15 products tested (capsules or tablets), consumption according to the company's recommendations amounted to 6 mg of coumarin per day for an adult, which for a weight of 60 kg corresponds to EFSA's TDI (Fotland *et al.* 2012).

The plants known to contain coumarin and currently authorised in food supplements in France, without any restriction on the dose or level or any warning for at-risk populations, are shown in table 5.

Table 5: List of plants that may contain coumarin authorised in food supplements in France (source DGCCRF (2019b))

Scientific name [Botanical family]	**Vernacular name**	**Parts used or extracts**	**Substances to be monitored according to the DGCCRF[9]**
Capparis spinosa L. [Capparaceae]	Caper bush	*Not specified*	*Not specified*
Cerasus mahaleb (L.) Mill. [Rosaceae]	Saint Lucie cherry	*Not specified*	*Not specified*
Cinnamomum cassia (Nees & T.Nees) J.Presl [Lauraceae]	Chinese cinnamon	Bark, leaf, twig, essential oil	**Coumarin**, estragole
Cinnamomum verum J.Presl [Lauraceae]	Cinnamon, Ceylon cinnamon	Bark, leaf, essential oil	Methyl eugenol, estragole, **coumarin**, eucalyptol
Galium odoratum (L.) Scop. [Rubiaceae]	Sweet woodruff, Sweet-scented bedstraw	Aerial parts	*Not specified*
Hierochloe odorata (L.) Beauv. [Poaceae]	Bison grass	*Not specified*	*Not specified*
Jumellea fragrans (Thouars) Schltr.	Faham	*Not specified*	*Not specified*

[9] In France, coumarin is listed in the Plants Order (2014) as a "substance to be monitored" for *Cinnamomum cassia* (L.) J.Presl, (syn. *Cinnamomum aromaticum* Nees) and *Cinnamomum verum* J.Presl (syn. *Cinnamomum zeylanicum* Blume), but it is also found in other plants listed in the Order and on the list of the DGCCRF (2019b).

Scientific name [Botanical family]	Vernacular name	Parts used or extracts	Substances to be monitored according to the DGCCRF[9]
[Orchidaceae]			
Justicia pectoralis Jacq. [Acanthaceae]	Carpenter bush, freshcut	*Not specified*	*Not specified*
Lavandula angustifolia Mill. [Lamiaceae]	Lavender, True lavender	Aerial parts, essential oil	Thujones, eucalyptol, camphor
Lavandula × *intermedia* Emeric ex Loisel. [Lamiaceae]	Lavandin	Aerial parts, essential oil	*Not specified*
Melilotus altissimus Thuill. [Fabaceae]	Tall yellow sweet clover, Tall melilot	Aerial parts	Coumarins
Melilotus officinalis (L.) Pall. [Fabaceae]	Yellow sweet clover	Aerial parts	Coumarins
Melittis melissophyllum L. [Lamiaceae]	Bastard balm	*Not specified*	*Not specified*
Trigonella foenum-graecum L. [Fabaceae]	Fenugreek	Seed	*Not specified*
Trigonella caerulea (L.) Ser. [Fabaceae]	Blue-white clover	Leaf	*Not specified*

Food supplements containing coumarin available on the French market are most often formulated with cinnamon or standardised cinnamon bark extracts. Examples of products available on the internet are shown in table 6.

Table 6: Examples of food supplements containing cinnamon

Composition and content	Information indicated by the company on the label	Precautions for use indicated by the company on the label
- Cinnamon (*C. verum*): 250 mg/capsule - Astragalus extract: 16 % polysaccharides (*Astragalus membranaceus*): 50 mg/capsule	4 capsules per day, to be taken in the morning with breakfast. *"A 3-month course of treatment helps restore your blood sugar balance."*	Not recommended for women with a personal or family history of breast cancer (astragalus).
- Cinnamon powder (*C. burmannii*): 200 mg/capsule - Cinnamon bark extract (*Cinnamomum spp.*): 300 mg/capsule	not specified	not specified
- Ceylon cinnamon dried bark extract: 300 mg/capsule - Zinc: 10 mg/capsule - Chromium: 25 µg/capsule	1 capsule per day. *"A food supplement specially formulated to maintain normal blood sugar levels."*	Avoid combining several food supplements containing zinc. Not recommended for pregnant or breastfeeding women or for children under 18 years of age.
- Cinnamon powder [Ceylon cinnamon dried bark extract (5:1)]: 2500 mg/capsule - Chromium: 40 µg	1 capsule per day. *"Blood sugar regulation and cell protection".*	not specified
- Cinnamon bark extract 2000 mg (30:1) standardised to 67 mg (*C. cassia*): 2000 mg/tablet - Chromium: 6 µg/tablet	2 to 4 capsules a day	If you are undergoing treatment, have a medical condition or have any doubts, consult your doctor before taking food supplements. Pregnant or breastfeeding women should consult a doctor before taking supplements. Stop taking the supplements and consult your doctor if any side effects occur.

The daily doses of cinnamon recommended by the companies in these products are between 1000 mg and 8000 mg. With the exception of products containing Ceylon cinnamon (*C. verum*), and assuming an average coumarin content of 3000 mg/kg cinnamon for *C. burmannii* and *C. cassia*, the recommended daily doses may correspond to intakes from 3 to 24 mg coumarin per day (without considering other sources of exposure). With these doses, the TDI of 0.1 mg/kg bw per day (i.e. 6 mg/day for a 60 kg adult) may therefore be largely exceeded and a risk to human health cannot be ruled out. This risk is even higher with subchronic use of the product, corresponding to a course of treatment of up to 3 months recommended by some companies.

- ***Special case of essential oils***

In 2019, the DGCCRF published a list of plants from which essential oils are extracted whose use in food is regarded as traditional. Essential oils of cinnamon are included in this list (*C. cassia and C. verum*), as well as those of true lavender, broadleaved lavender and lavandin.

The monograph on the genus *Cinnamomum* indicates relative coumarin levels ranging from 0.28% to 15.3% for the essential oil of *C. cassia* bark and an absence of coumarin in that of *C. verum* (Ravindran, Nirmal-Babu, and Shylaja 2003). The highest levels were found in an essential oil of *C. cassia* bark from Australia.

Different levels of coumarin in essential oils are also reported in the literature. For Chinese cinnamon bark essential oil, the coumarin content was between 1.5% and 4% (Bruneton 2016) and between 0% and 1.9% according to Tisserand and Young (2014). For Ceylon cinnamon bark essential oil, the presence of coumarin was not reported (Tisserand and Young 2014). For Chinese cinnamon leaf essential oil, the coumarin content was between 0.03% and 2.5% (Tisserand and Young 2014).

Although a German study reported 0.012% coumarin in lavender essential oil from *Lavandula angustifolia* (Rychlik 2008), coumarin was not mentioned as a constituent of the essential oils of true lavender or lavandin by Tisserand and Young (2014) or Salido *et al.* (2004), who reported the chemical analyses of six samples of *L. latifolia* essential oil from various sources.

The plant *Hierochloe odorata* var. *pubescens* Kryl. from China is particularly rich in coumarin. Ethanol extracts of the root and aerial parts have a coumarin content of 3.6% and 3.7%, and the essential oils of the same parts contain 10.3% and 24.9% respectively (Ueyama, Arai, and Hashimoto 1991).

According to the data presented in table 7, essential oil of Chinese cinnamon bark (*C. cassia*) has the highest coumarin content.

Table 7: Coumarin content of different essential oils

Plant essential oil	**Total coumarin content**		**References**
	mg/kg	%	
Anethum graveolens L. (fruits)	0.21	0.00002	(Rychlik 2008)
Cinnamomum cassia (L.) J.Presl (bark)	4370	0.44	(Rychlik 2008)
Cinnamomum cassia (L.) J.Presl (bark)	2800 – 153000	0.28 – 15.3	(Ravindran, Nirmal-Babu, and Shylaja 2003)
Cinnamomum cassia (L.) J.Presl (leaves)	0 – 19000	0 – 1.9	(Tisserand and Young 2014)
Cinnamomum cassia (L.) J.Presl (leaves)	300 – 25000	0.03 – 2.5	

Cinnamomum cassia (L.) J.Presl (leaves)	83	0.008	(EFSA 2004)
Cinnamomum cassia (L.) J.Presl (leaves and young twigs)	15000 – 40000	1.5 – 4	(Bruneton 2016)
Cinnamomum verum J.Presl (bark)	40	0.004	(Rychlik 2008)
Citrus limon (L.) Osbeck (fruits)	3.9	0.0004	(Rychlik 2008)
Coriandrum sativum L. (fruits)	0.3	0.00003	(Rychlik 2008)
Lavandula angustifolia Mill.	124	0.012	(Rychlik 2008)
Matricaria recutita L.	3.23	0.0003	(Rychlik 2008)
Mentha x piperita L. (leaves)	0.3	0.00003	(Rychlik 2008)

It should be noted that among the 28 reports of adverse effects likely to be associated with the consumption of food supplements containing coumarin and which underwent a causality analysis by the "Nutrivigilance" working group (table 8), 16 cases concerned products containing essential oils. Causality was found to be likely for seven cases, possible for three cases, and unlikely for six cases.

3.2.4.Coumarin in medicinal products

Coumarin had been used since the 1970s in the United States, Canada and various EU countries as a medicinal active ingredient to treat venous and lymphatic oedema, and as an adjuvant treatment for post-mastectomy lymphoedema. As mentioned in the section on "Adverse effects - cases from pharmacovigilance", this drug (Lysedem®) was withdrawn from the European and North American markets in the 1990s following the development of serious cases of hepatitis.

Coumarin was also used in the 1990s in clinical trials for the treatment of renal carcinomas, but no drug was subsequently developed for this indication. Currently, as mentioned below in the section on "Adverse effects - cases from pharmacovigilance", two herbal medicinal products containing sweet clover have a marketing authorisation in France: one for venotonic purposes (Esberiven Fort®) and the other as a sedative (Sedopal®).

3.2.5.Other uses of coumarin

Coumarin is used in many perfumes and cosmetic preparations, and in the flavouring of some tobacco. It is also used to neutralise the smell of certain synthetic products, such as detergents, insecticides, plastics, inks and paints (Lake 1999). According to Lake (1999), exposure to coumarin from these products, estimated taking into account dermal absorption, could reach 40% of the TDI of coumarin.

Exposure (inhalation and dermal) to coumarin used as an ingredient (fragrance) in numerous products was estimated with an aggregate exposure model (Creme RIFM model) to be 0.0057 mg/kg bw/day, in an adult population in Europe and the USA (Safford *et al.* 2015, Api *et al.* 2019).

In cosmetics, the presence of coumarin (90% of fragrances contain it) should be indicated in the list of ingredients when its concentration is higher than 0.001% (leave-on products) or 0.01% (rinse-off products) (Bruneton 2016).

The document "Recommendations on assessing the risks of essential oils in cosmetic products" (AFSSAPS 2010) points out that coumarin is included in the list of substances

subject to labelling requirements due to their allergenic potential. Coumarin is classified as a sensitising substance under the REACH Regulation.

These routes of exposure (respiratory and dermal) have not been considered in this risk assessment, which only examines oral exposure to coumarin.

3.3. Adverse effects associated with the consumption of coumarin

3.3.1. Cases from the nutrivigilance scheme

Between the establishment of the nutrivigilance scheme in 2009 and the month of April 2019, ANSES received 48 reports of adverse effects likely to be associated with the consumption of herbal supplements containing coumarin[10]. Of these 48 reports, 28 were analysed for their causality by the "Nutrivigilance" WG, according to the method defined in the ANSES opinion ANSES (2011). They are presented in table 8. The other cases were not sufficiently documented to allow an analysis.

The breakdown of the causality of the analysed cases by type of adverse effect is shown in Figure 3 (some products may have caused several different adverse effects).

For these 28 analysable cases, the most frequently reported adverse events were primarily hepatic (hepatic cytolysis), gastroenterological (nausea, vomiting and abdominal pain) or general symptoms (dizziness and headache). Causality was likely in 10 of these cases.

Plants with high levels of coumarin were rarely the only ingredients in the food supplements involved in these cases. However, the causality score applies to the food supplement as a whole and not to an ingredient. The role of another food supplement ingredient in the onset of the adverse effect cannot therefore be ruled out.

In addition, the occurrence of the adverse effects may have been facilitated by interactions between the different components of the food supplement, between several food supplements, or between the food supplement and any medicinal products consumed concomitantly.

[10] Plants containing coumarin and authorised in food supplements in France.

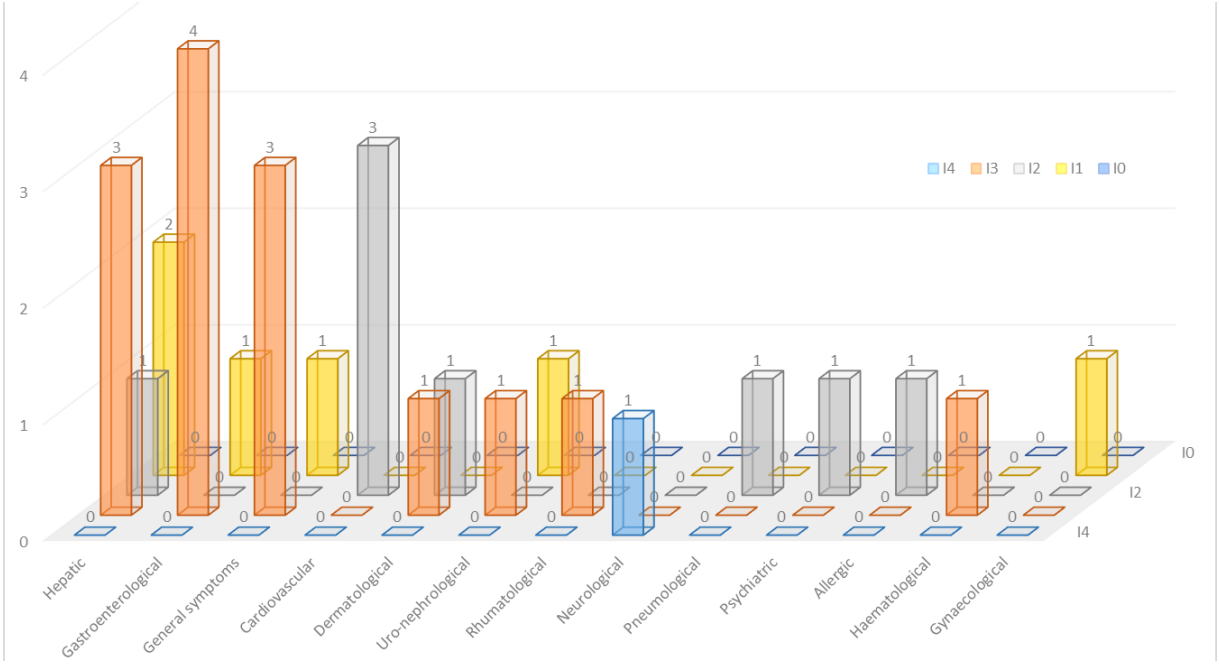

Figure 3 Breakdown of adverse effects reported to the nutrivigilance scheme and likely to be associated with the consumption of food supplements containing coumarin, according to their type and causality[11] (analysable cases)

[11] I0 = excluded, I1 = unlikely, I2 = possible, I3 = likely, I4 = very likely.

Table 8: Analysable nutrivigilance cases likely to be associated with the consumption of food supplements containing coumarin between 2009 and 2019.

NV number	Product Manufacturer Plant rich in coumarin (dose)	Sex and age of the consumer	Adverse effect(s) Onset time Dose ingested per day	Severity[12]	Intrinsic causality[13]	Comments
2011-013	Thermo Complete Herbalife *Cinnamomum verum* (50 mg)	F, 43 years	**Effect: metabolic encephalopathy** 6 days 2 tablets/d	3	**Very likely**	Associated consumption of food supplements (Multivitamin Complex and Cell-u-Loss)
2011-036	Aromaforce Synergie Multi-Usages Pranarôm Lavandin, EO (15%)	F, 54 years	**Effects: Nausea, vomiting, feeling of dizziness, very brief loss of consciousness and then intense asthenia** Within an hour 54 drops	1	**Likely**	
2011-039	Aromadoses Bronchi Phytosun Arôms Lavender, EO (30 mg)	F, 12 years	**Effects: sudden fainting, eyes rolling back, clenched hands** 3 days One capsule 3 times a day	1	**Likely**	
2012-068	Oleocaps 7 Pranarôm Lavandin, EO (60 mg)	F, 15 years	**Effects: fulminant hepatitis, hepatic encephalopathy, requiring a transplant** About 2 months 2 capsules/d	3	**Likely**	
2013-184	Cellulysse Santé Verte Sweet clover (unspecified), extract (60 mg - dried extract of aerial parts titrated to 2% coumarin)	F, 58 years	**Effect: appearance of numerous haematomas or bruises** About 1 month	1	**Likely**	Associated consumption of the drug ibuprofen

[12] The scale of severity in nutrivigilance goes from Level 1 (low severity) to Level 4 (death).
[13] The intrinsic causality score ranges from I0 (excluded) to I4 (very likely).

NV number	Product Manufacturer Plant rich in coumarin (dose)	Sex and age of the consumer	Adverse effect(s) Onset time Dose ingested per day	Severity[12]	Intrinsic causality[13]	Comments
2014-168	Détente Dieti Natura *Lavandula officinalis*, flower (62.5 mg) *Melilotus officinalis* (23.5 mg)	F, 69 years	**Effect: skin rash** 1 day unknown	1	**Likely**	Associated consumption of medication (atenolol, indapamide, fenofibrate and Eupantol)
2014-247	Gold Max Global Product Europe *Cinnamomum cassia*	M, 29 years	**Effect: acute kidney failure** 17 days unknown	3	**Likely**	Kidney transplant in 2007
2017-188	Physiomance DT2 Therascience Cinnamon (unspecified), extract (50 mg/tablet)	M, 57 years	**Effects: rhabdomyolysis and increased transaminases** 10 months Unknown	3	**Likely**	Associated consumption of food supplements (Physiomance Dimeol Q10, Fitolisat Chrysanthellum, Fitolisat Desmodium, Quantaphylle, Enzytonic, Equilibre Candida 2 and 3) and medication (Coaprovel, Glucor, Kardegic, Detensiel, paracetamol and Uvedose)
2017-277	SomActifs SynActifs Lavender, EO (100 mg/2 capsules)	F, 75 years	**Effect: nausea** 3 hours unknown	2	**Likely**	Associated consumption of medication (Azilect and Modopar)
2018-079	Phytosun Arôms Ampoules Tonus Omega Pharma *Cinnamomum verum*, EO (20%)	F, 65 years	**Effect: abdominal pain** 3 days 1 vial/d	1	**Likely**	Associated consumption of medication (Seroplex, esomeprazole and Levothyrox)
2018-723	LAPHT 086 Respiration Aisée Phytofrance Lavender (unspecified), extract	F, 52 years	**Effect: vomiting** Immediately 26 drops	1	**Likely**	

NV number	Product Manufacturer Plant rich in coumarin (dose)	Sex and age of the consumer	Adverse effect(s) Onset time Dose ingested per day	Severity[12]	Intrinsic causality[13]	Comments
2019-016	Aromasantis BTG Santis Lab *Lavandula latifolia*, EO	M, 18 years	**Effects: headache, difficulty concentrating, drowsiness** 20 minutes 3/d	1	**Likely**	
2019-022	Oleocaps 2 Pranarôm *Cinnamomum verum*, EO	F, 38 years	**Effect: hepatic cytolysis** 14 days 2/d	2	**Likely**	Associated consumption of food supplements (Curcuméga and Ristabil)
2013-140	Detox infusion Yogi Tea *Cinnamomum cassia* (17%)	F, 73 years	**Effect: aggravation of biliary cirrhosis and jaundice** About 5 months 1 infusion per day	3	**Possible**	Associated consumption of medication (Questran, propranolol, Utrogestan and Oestrodose)
2013-159	Ergyveine Nutergia *Melilotus officinalis* (440 mg/20 mL)	F, 59 years	**Effect: allergic reaction with redness and facial swelling** 30 minutes	1	**Possible**	Associated consumption of medication (Symbicort, Seretide and Ventolin)
2014-387	Physiomance Action Diète 4 Therascience Cinnamon (unspecified), extract (50 mg/tablet)	F, 62 years	**Effect: hypomanic syndrome** About 2 months ½ tablet/d for 1.5 months then 1 tablet/d for 1 month	2	**Possible**	Associated consumption of medication (Seroplex and Librax)
2016-007	PLZR+ Abo Factory Cinnamon (unspecified), extract (10 mg/capsule)	M, 21 years	**Effect: cardiocirculatory arrest** 14 days 2/d	3	**Possible**	
2017-129	Phytaroma G.A.E Naturactive *Cinnamomum verum*, EO (4.3 mg/1 capsule) Lavender, EO (4.3 mg/1 capsule)	F, 55 years	**Effect: bronchospasm** 1 day unknown	2	**Possible**	
2017-159	Régénérateur du Sommeil Nutrigénie	F, 72 years	**Effect: high blood pressure** 1 day	3	**Possible**	Associated consumption of the drug Nisis

NV number	Product Manufacturer Plant rich in coumarin (dose)	Sex and age of the consumer	Adverse effect(s) Onset time Dose ingested per day	Severity[12]	Intrinsic causality[13]	Comments
	Lavandula angustifolia		2 capsules/d			
2017-200	On Guard Protective Blend Beadlets doTERRA Cinnamon, EO	F, 60 years	**Effects: pruritic maculopapular facial and thoracic erythema and facial and cervical oedema** 10 hours 1 beadlet	2	**Possible**	Associated consumption of medication (Skenan, ondansetron, Emend, Primperan and Nordaz)
2017-289	Phytaroma G.A.E Naturactive *Cinnamomum verum*, EO (4.3 mg/1 capsule) Lavender, EO (4.3 mg/1 capsule)	M, 55 years	**Effects: pallor, hypertensive crisis, palpitations** A few hours 2 capsules	3	**Possible**	Associated consumption of medication (clopidogrel, Coaprovel and rosuvastatin)
2015-113	Phytaroma G.A.E Naturactive *Cinnamomum verum*, EO (4.3 mg/1 capsule) Lavender, EO (4.23 mg/1 capsule)	F, 41 years	**Effect: miscarriage** 2 hours 2 capsules	3	**Unlikely**	
2017-009	Colonpure Swiss Edilab Cinnamon, EO (2 mg/4 capsules)	F, 42 years	**Effect: hepatitis** 15 days Unknown	1	**Unlikely**	
2018-023	Lipocyte NHCO Nutrition *Melilotus officinalis*, flower (20 mg/20 mL)	F, 50 years	**Effect: increased transaminases** About 6 months	2	**Unlikely**	Associated consumption of food supplements (CelluStepper morning and evening capsules, Drain'Detox and Permaflore) and medication (esomeprazole, Fluoxetine, Amitriptyline, Meteospasmyl, Uvedose, Oestrodose, alprazolam, cromoglycate, paracetamol, Tiorfan, Ciclopirox, Mycoster and Telfast)

NV number	Product Manufacturer Plant rich in coumarin (dose)	Sex and age of the consumer	Adverse effect(s) Onset time Dose ingested per day	Severity[12]	Intrinsic causality[13]	Comments
2018-054	Phytaroma G.A.E Naturactive *Cinnamomum verum*, EO (4.3 mg/1 capsule) Lavender, EO (4.3 mg/1 capsule)	F, 70 years	**Effects: fever (39°C), chills** A few hours 3 capsules, twice a day unknown	1	**Unlikely**	
2018-260	Aromaforce Solution Natural defences Pranarôm Lavandin, EO (0.156 g/6 drops)	F, 49 years	**Effects: stomach and liver pain, asthenia, fungal infection of the tongue** 6 days	1	**Unlikely**	Associated consumption of medication (amoxicillin, prednisolone, Euphon, Humex spray and paracetamol)
2018-653	Urisanol Flash Naturactive *Cinnamomum verum*, EO (8.6 mg/2 capsules) Lavander, EO (8.6 mg/2 capsules)	F, 62 years	**Effects: blood clots in urine** 6 hours Twice a day	2	**Unlikely**	
2019-053	Complexe M+ Phase 2 Phytalliance Cinnamon (unspecified), EO	F, 34 years	**Effect: hepatic cytolysis, rhabdomyolysis** 18 days 23 drops, twice a day	3	**Unlikely**	Associated consumption of the food supplement Complexe CLA

3.3.2.Cases from toxicovigilance (in France)

Between January 2006 and February 2020, 66 reports associated with the oral ingestion of food supplements containing coumarin were registered in the national database of poisoning cases of the poison control centres' information system. Fifty-two of these reports concerned essential oils (mainly in pure form or in capsules), including 19 lavandin essential oils, 14 lavender essential oils and 19 cinnamon essential oils.

Almost 40% of the symptoms reported were digestive disorders such as abdominal pain, vomiting and diarrhoea; 18% of the symptoms concerned otorhinolaryngologic disorders, the vast majority of which were oropharyngeal pain or irritation; 13% were general symptoms such as headache or dizziness; and 11% concerned neurological disorders such as drowsiness or loss of consciousness. More sporadically, adverse effects such as a cough, respiratory pain or tachycardia have been reported. These adverse events were not analysed for causality using the nutrivigilance method (ANSES 2019).

3.3.3.Cases from other vigilance schemes

- ***In Canada***

Data were sought using the Canada Vigilance database for the period from 1 January 1965 to 31 December 2018. No reports were found with the keyword "coumarin". Using the keywords "*Cinnamomum verum*, *Cinnamomum cassia* and *Cinnamomum aromaticum*", 114 records were found. The most frequently reported adverse effects were allergic/dermatological (pharyngeal oedema, urticaria, pruritus), hepato-gastroenterological (diarrhoea, vomiting) or general symptoms (headache, malaise). Using the keywords "*Lavandula angustifolia* and *Lavandula* spp.", 19 reports were identified, but only seven were associated with oral exposure. The adverse events reported included diarrhoea, abdominal pain, anxiety and skin rash. Only two records were found with the keyword "*Melilotus*". They concerned a case of hypoesthesia and a case of foetal hypertension and hypokinesia. No cases were reported with other plants authorised in France and containing coumarin.

- ***In the United States***

On the FDA Adverse Events Reporting System (FAERS), 24 reports were found with the keyword "coumarin". Most of the adverse events reported were haematological (haemorrhage, anaemia, increased INR), pneumological and hepatic (hepatitis). Using the keywords "*Cinnamomum verum,* Cinnamon and Cinnamon oil", 41 reports were identified. No records were found with the keyword "Cassia". The most frequently reported adverse events were metabolic (blood sugar disturbance) and neurological (cognitive impairment). With the keyword "*Melilotus officinalis*", six reports were registered. The adverse events reported include one case of hepatitis, one case of rhabdomyolysis, one case of purpura, one case of pancreatitis, one case of asthenia and one case of angina pectoris.

- ***In Australia***

A drug containing coumarin was used mainly to treat lymphoedema. After more than a year, in 1993, the Australian authorities had identified 10 cases of adverse effects, six of which concerned jaundice, with one case of fulminant hepatitis in a 49-year-old woman whose administered dose was around 400 mg/d for 1 to 4 months. No further cases were reported in other patients treated after discontinuation of the product (WHO 1995).

Because all the cases collected abroad involved many other compounds, interactions causing the reported adverse effects cannot be ruled out. Due to a lack of information, the nutrivigilance method for analysing causality (ANSES 2019) was not applied to these cases.

3.3.4.Cases from pharmacovigilance (in France)

ANSES approached the ANSM in February 2019 with a view to obtaining data on the adverse effects likely to be associated with the consumption of drugs containing coumarin. Two pharmaceutical products on the market containing coumarin were identified:

- Esberiven Fort[14]: 250 mg rutoside and 30 mg dried aqueous sweet clover extract titrated to 5 mg coumarin per tablet.
- Sedopal[15]: 120 mg powder of flowering tops of sweet clover, 120 mg powder of flowering tops of hawthorn and 120 mg powder of aerial parts of Eschscholtzia[16].

Among the 173 reports involving Esberiven Fort® registered by the pharmacovigilance scheme, the most frequently reported adverse effects were dermatological (skin rash), haematological (purpura, haematoma) and hepatic (hepatitis). The French National Authority for Health (HAS) ruled that the medical service provided by this product was insufficient to justify its reimbursement (HAS 2006).

No reports have been received for Sedopal®.

Lysedem®, a product containing 15 mg of synthetic coumarin per tablet, was marketed in France in the 1980s/90s and indicated in cases of lymphoedema with a dosage equivalent to 90 mg/day of coumarin but also with much higher dosages. The preliminary results of a French national survey in 1995 showed that 33 validated cases of adverse liver effects were reported to the pharmacovigilance system[17] or to the manufacturer. Cytolytic hepatitis was reported in 85% of cases and jaundice was observed in 13 cases. Three cases of major liver failure were observed; two were fatal and the third required a liver transplant. The incidence of severe liver reactions has been estimated at two cases per 10,000 per year. As mentioned above, following serious cases of hepatotoxicity, all products containing coumarin were withdrawn from the market in Europe and Canada during the 1990s, and Lysedem® in particular was withdrawn from the French market in 1997 (Marshall *et al.* 1994, Andréjak *et al.* 1998, Koch *et al.* 1997).

3.3.5.Drug interactions associated with coumarin

Contrary to the well-documented interactions involving coumarin derivatives of synthetic origin used as oral anticoagulant drugs (e.g. acenocoumarol, warfarin), there are no literature data indicating the existence of interactions between coumarin – or plants containing only coumarin – and drugs (Baxter, Driver, and Williamson 2013).

However, some authors recommend avoiding the oral intake of coumarin-rich essential oils in conjunction with monoamine oxidase inhibitor (MAOI) antidepressants, due to the risk of adverse effects: blood pressure changes, tremors, mental confusion (Tisserand and Young 2014).

[14] Esberiven Fort is used in the treatment of symptoms related to poor venous or lymphatic circulation (heavy legs, pain, restless legs when initially recumbent) and in the treatment of functional signs associated with haemorrhoidal crisis
[15] Sedopal is used in the symptomatic treatment of nervousness, especially in cases of mild sleep disorders.
[16] Eschscholtzia: California poppy.
[17] Medicines Agency, Rapid Alert – Pharmacovigilance, 29 November and 23 December 1996.

3.4. Estimate of exposure to coumarin from food

Based on data on consumption, individual body weights, available food composition and maximum authorised coumarin levels in certain foods, consumer exposure can be estimated and then compared with the health-based guidance value in order to assess the health risks (acute and chronic) associated with the presence of coumarin in food products, spices or food supplements. The exposure estimate concerns "coumarin" and not coumarin derivatives (the latter are often referred to as "coumarins" in the literature).

The Methodology and Studies Unit (UME) was asked (under the scientific and technical support request AST 2019-ASTDER-32) to estimate the exposure to coumarin of the population living in France, using data from the INCA3 study. The full report, including a detailed explanation of the methodology, is presented in Annex 4.

3.4.1. Calculation of individual exposure to coumarin

To calculate exposure, coumarin levels were assigned to the different foods or ingredients likely to contain it, using the regulatory levels of coumarin for food categories and the average maximum levels in plants described in the literature (Rychlik 2008, Fotland *et al.* 2012, Wang *et al.* 2013, Tisserand and Young 2014, Bruneton 2016) (table 9).

Table 9. Coumarin levels in foods and ingredients that may contain it, according to their type or regulatory category

	Food category/Ingredients	**Coumarin level in the products (mg/g)**
Regulatory categories	Traditional and/or seasonal bakery ware containing a reference to cinnamon in the labelling*	0.05
	Breakfast cereals including muesli	0.02
	Fine bakery ware, with the exception of traditional and/or seasonal bakery ware containing a reference to cinnamon in the labelling*	0.015
	Desserts	0.005
Plants containing coumarin listed in the INCA3 or OQALI database	Cinnamon	3
	Tonka bean	30
	Natural lavender flavouring	1
	Lavender essential oil	1.5
	Capers	1
	Fenugreek	0.004
Teas and infusions	Cinnamon tea/infusion	0.001

** For the regulatory categories, the regulatory levels were only applied in the case where the consumption act was identified as involving an industrial product containing coumarin. Otherwise, the level calculated from the percentage of the ingredient in the product and its coumarin level was used.*

The estimate of coumarin exposure was determined according to two scenarios:

- Scenario 1: "Regulatory approach": Foods or recipes belonging to a regulatory category contain the maximum coumarin level defined in the regulation. Other foods or recipes contain coumarin in proportion to the amount of ingredients containing it.
- Scenario 2: "Realistic approach": All foods or recipes contain coumarin in proportion to the amount of ingredients containing it, regardless of whether they belong to a regulatory category.

For each scenario, coumarin exposure was estimated separately for children (0-17 years) and adults (18-79 years).

In this risk assessment, exposure to coumarin was compared with the TDI of coumarin for the chronic risk estimate and with three times the TDI value for the acute risk estimate, as assessed by EFSA (2008). The rates at which these thresholds were exceeded were estimated for each scenario and for each population.

3.4.2. Identification of contributing foods

For each scenario, the main contributing foods were identified using the 44 groups in the INCA3 study nomenclature. The average contribution of each food group to total exposure was then estimated.

3.4.3. Results of the identification of foods, recipes and industrial products consumed, containing coumarin

There were 2788 consumption acts involving foodstuffs containing coumarin in the entire INCA3 database, broken down as follows:

- 262 "raw" foods;
- 2135 recipes with at least one ingredient containing coumarin;
- 391 industrial products with at least one ingredient containing coumarin.

In terms of "coumarin food categories", the consumption acts identified in INCA3 can be broken down as follows:

Coumarin food categories		**Children**	**Adults**
		Number of consumption acts	
Regulatory categories	1 Traditional bakery ware	72	127
	2 Breakfast cereals	9	3
	3 Other bakery ware	28	17
	4 Desserts	37	51
Cinnamon-rich product category	5 Spices	19	81
	6 Teas and infusions	8	93
Other categories	7 Other food products	1246	997
	Total	**1419**	**1369**

- ***Plants consumed directly as food***

The foods corresponding to plants consumed as food in the INCA3 study are listed in the report in Annex 4. Plants may appear in the name of the food directly or in the characteristic ingredients selected by the individual to describe it. The plants found among the foods corresponded to cinnamon (n = 194 citations), lavender (n = 37), capers (n = 29), fenugreek (n = 2) and tonka bean (n = 1).

- ***Plants consumed as food ingredients (home-made recipe database and OQALI database)***

In the recipe database and the OQALI database, cinnamon, fenugreek and capers were identified as being used as ingredients. Recipes incorporating one of these ingredients were selected and are detailed in the report in Annex 4.

3.4.4. Results of the estimate of coumarin exposure in the French population (excluding food supplements)

Using the data described above, exposure was estimated for children (0-17 years) and adults (18-79 years), according to the method of selecting consumption acts and the two exposure scenarios (1 and 2). Around 40% of adults and 43% of children are exposed to coumarin through their diet (excluding food supplements). table 10 shows the results for the total population and table 11 for those exposed to contributing foods only, corresponding to individuals whose estimated exposure is not zero.

- ***In the total population***

Table 10. Description of the exposure to coumarin (in mg/kg bw/day) of the total French population, estimated using consumption data from the INCA3 study, according to two exposure scenarios

	Number	Scenario	Mean	Median	P75	P95
Adults	2121	**1**	0.00161	0	0.00015	0.00766
		2	0.00155	0	0.00014	0.00766
Children	1993	**1**	0.00210	0	0.00028	0.00939
		2	0.00191	0	0.00028	0.00684

According to INCA3 data, the estimated exposure to coumarin for the French population was slightly higher with the scenario applying the regulatory levels to food (Scenario 1). In this scenario, it averaged $1.6 \cdot 10^{-3}$ mg/kg bw/day in adults and $2.1 \cdot 10^{-3}$ mg/kg bw/day in children.

The 95th percentile was $7.7 \cdot 10^{-3}$ mg/kg bw/day in adults for both scenarios, and was $9.4 \cdot 10^{-3}$ mg/kg bw/day for Scenario 1 and $6.8 \cdot 10^{-3}$ mg/kg bw/day for Scenario 2 in children.

- ***For exposed individuals only***

Table 11. Description of the exposure to coumarin (in mg/kg bw/day) of exposed individuals only, estimated using consumption data from the INCA3 study, according to two exposure scenarios

	Number	Scenario	Mean	Median	P75	P95
Adults	861	**1**	0.00404	0.00026	0.00199	0.01977
		2	0.00388	0.00025	0.00145	0.01977
Children	944	**1**	0.00482	0.00037	0.00128	0.01742
		2	0.00437	0.00036	0.00103	0.01743

In exposed individuals only, the average daily exposure to coumarin was:

- $4 \cdot 10^{-3}$ mg/kg bw/day in adults;
- $4.4 \cdot 10^{-3}$ and $4.8 \cdot 10^{-3}$ mg/kg bw/day in children.

The 95th percentile for coumarin-exposed individuals was 0.02 mg/kg bw/day in adults and 0.017 mg/kg bw/day in children. These estimates were of the same order of magnitude as those observed by Lake (1999).

In the exposed population, therefore, exposure to coumarin through food consumption can be assumed to reach as much as 20% of the TDI of 0.1 mg/kg bw/day.

3.4.5. Result of the estimate of the rates at which the thresholds set for chronic and acute risks are exceeded in the French population

Around 40% of adults and 43% of children are exposed to coumarin through their diet (excluding food supplements). However, about 0.2% of individuals reach the threshold for chronic or acute risk (table 12), regardless of the exposure scenario.

Table 12. Rates of exposed individuals and rates at which the thresholds determined for chronic risk (TDI) and acute risk (3xTDI) are exceeded in the French population, based on consumption data from the INCA3 study and according to two scenarios

	N	Rate of exposed individuals		Rate at which the "chronic risk" threshold (TDI) is exceeded		Rate at which the "acute risk" threshold (3xTDI) is exceeded	
		Scenario 1	Scenario 2	Scenario 1	Scenario 2	Scenario 1	Scenario 2
Adults	2121	39.9% [37.1-42.9]	39.9% [37.1-42.9]	0.2% [0.03-0.9] *(n = 4)*	0.2% [0.03-0.9] *(n = 4)*	0%	0%
Children	1993	43.6% [40.4-46.8]	43.6% [40.4-46.8]	0.2% [0.04-0.7] *(n = 3)*	0.2% [0.04-0.7] *(n = 3)*	0.04% [0.01-0.2] *(n = 2)*	0.04% [0.01-0.2] *(n = 2)*

3.4.6.Identification of foods contributing to coumarin exposure

The main food groups contributing more than 5% to coumarin intakes were, in descending order:

- condiments, herbs, spices and sauces: 60% for adults and 35% for children;
- croissant-like pastries, pastries, cakes and sweet biscuits: 19% in adults and up to 28% in children.

The average exposures and contributions associated with each food group are detailed in the report in Annex 4.

3.4.7.Characteristics of individuals exposed or not to coumarin

The breakdown of exposed and non-exposed individuals according to the two exposure scenarios is given in table 13 for adults and in ns (*not significant); *** (p<0.001)*

table 14 for children. The breakdowns of exposed and non-exposed populations were compared for each characteristic (age, sex and region) using bivariate Pearson Chi-square tests.

Table 13. Characteristics of adults exposed or not to coumarin in the population living in France, based on consumption data from the INCA3 study (2014-2015)

Variable	Categories	n	Exposed pop.	Non-exposed pop.	Difference
Age	18-44 years	783	56.2% [51.2-61.2]	39.0% [34.9-43.4]	***
	45-64 years	827	31.0% [26.5-35.9]	40.2% [35.5-45.1]	
	65-79 years	511	12.8% [10.3-15.6]	20.8% [18.3-23.5]	
Sex	Male	887	47.4% [43.2-51.6]	49.2% [45.8-52.7]	ns
	Female	1234	52.6% [48.4-56.8]	50.8% [47.3-54.2]	
Region	Ile-de-France	262	13.6% [10.6-17.3]	18.3% [15.0-22.0]	ns
	North West	466	19.1% [14.0-25.5]	20.3% [15.4-26.3]	
	North East	517	31.2% [25.5-37.5]	25.0% [20.0-30.7]	
	South East	473	19.4% [14.1-26.3]	18.1% [14.0-23.0]	
	South West	403	16.7% [12.0-22.7]	18.4% [13.9-24.1]	

ns (not significant); *** (p<0.001)

Table 14. Characteristics of children exposed or not to coumarin in the population living in France, based on consumption data from the INCA3 study (2014-2015)

Variable	Categories	n	Exposed pop.	Non-exposed pop.	Test
Age	0-11 months	59	1.5% [0.4-5.4]	7.2% [5.1-10.3]	**
	1-3 years	159	13.6% [9.9-18.4]	18.2% [14.3-23.0]	
	4-6 years	345	20.3% [17.0-24.0]	15.3% [12.9-18.1]	
	7-10 years	481	22.8% [19.3-26.9]	22.4% [19.2-26.0]	
	11-14 years	543	26.1% [21.8-30.9]	20.4% [17.6-23.5]	
	15-17 years	406	15.7% [12.8-19.1]	16.4% [13.6-19.7]	
Sex	Boy	1020	51.6% [46.8-56.3]	50.8% [46.3-55.3]	ns
	Girl	973	48.4% [43.7-53.2]	49.2% [44.7-53.7]	
Region	Ile-de-France	302	17.3% [12.9-22.7]	17.2% [14.0-20.9]	ns
	North West	455	19.0% [14.1-25.0]	20.7% [15.5-27.3]	
	North East	516	28.4% [22.5-35.3]	26.7% [21.2-33.2]	
	South East	416	18.5% [13.2-25.2]	20.5% [16.0-25.9]	
	South West	304	16.8% [12.2-22.9]	14.9% [11.2-19.4]	

ns (not significant); ** (p<0.01)

The results show that age is the only parameter for which there is a significant difference in exposure to coumarin. In particular, it appears that the age group most at risk in the adult population as a whole is the 18-44 year olds.

3.4.8.Exposure to coumarin via food supplements

According to the INCA3 study, around 40% of adults and 43% of children are exposed to coumarin through their diet (excluding food supplements). These results show that adults aged 18 to 44 years are the most exposed. For this population, exposure to coumarin through food consumption can be as much as 20% of the TDI of 0.1 mg/kg bw/day.

To avoid exceeding the TDI for the populations most exposed via food, therefore, the daily intake of coumarin from food supplements should be less than 80% of the TDI, i.e. a coumarin intake of 4.8 mg/d for a 60 kg adult. This dose can be reached through daily consumption of food supplements containing around 1.6 g[18] of cinnamon.

This daily intake should be even lower when considering other significant routes of exposure to coumarin, such as cosmetics (perfumes).

3.4.9.Limitations of the results

The data from the INCA3 study used for the exposure calculations came from observations over three days[19] of food consumption, which does not allow for an accurate estimate of habitual consumption, especially for foods that are rarely eaten. Moreover, the exposure estimate was based on a limited number of observations (2788). It may not therefore accurately reflect the population's habitual consumption over a long period of time and its usual level of exposure. While the average exposure value is *a priori* correct, the high percentiles estimated over three days of observation may be overestimated compared with those estimated over a long observation period. Similarly, given the small number of consumption acts, the results for contributing foods are also likely to be very sensitive to certain very high amounts found for a few individuals.

[18] Based on a content of 3 mg coumarin/g cinnamon (see Table 9 on page 30).
[19]three non-consecutive days (2 weekdays and 1 weekend day) spread over around three weeks, using the 24h recall method (R24) for individuals aged 15 to 79 years, and the 24h record method (using a food picture book) for individuals aged 0 to 14 years.

4. CONCLUSIONS AND RECOMMENDATIONS OF THE WG ON "PLANTS" AND THE CES ON "HUMAN NUTRITION"

The WG on "Plants" and the CES on "Human Nutrition" reiterate that lists of plants or plant parts, uses and doses authorised for food supplements, as well as restrictions and warnings governing their use, are not harmonised in the European Union. This is the case for the substance "coumarin" found in several plants authorised in food supplements and for which there are no restrictions in the current Italian or Belgian lists, and which was identified in France as a "substance to be monitored" in the Order of 24 June 2014. The WG feels that it is important to make the distinction between coumarin and coumarin derivatives (as the latter are often referred to as "coumarins" in the literature).

The WG and CES point out that there are EU regulations setting maximum levels for coumarin in certain food products (mainly bakery ware), where it occurs naturally in an ingredient. In addition, EFSA has established and confirmed a tolerable daily intake (TDI) of 0.1 mg/kg bw/day for coumarin. In the absence of specific regulations, this daily intake should be used to set the maximum levels and dosage of food supplements containing coumarin.

The results of the estimate of dietary exposure to coumarin according to the INCA3 study data show that condiments, herbs, spices and sauces, as well as croissant-like pastries, pastries, cakes and sweet biscuits are the main contributors to coumarin consumption. Around 40% of adults and 43% of children are exposed to coumarin through their diet (excluding food supplements). However, a small part of the French population studied (about 0.2%) exceeds the TDI.

The WG and the CES believe that there is a risk of the TDI of coumarin being exceeded by consumers of food supplements containing cinnamon or other plants containing coumarin, due to the high levels of coumarin in these plants and their essential oils. The risk of exceeding the TDI of coumarin is even greater if the products are derived from plants that are particularly rich in coumarin, such as Chinese cinnamon (*Cinnamomum cassia* (Nees & T.Nees) J.Presl), which is very often used in food supplements.

The WG and the CES stress that most of the reports of adverse effects associated with the consumption of food supplements containing coumarin relate to products containing essential oils (60% of cases analysed for causality).

The WG on "Plants" and the CES on "Human Nutrition" therefore conclude that it appears necessary to:

- clearly define the precise botanical identity of the plant containing coumarin – especially for cinnamon – as well as the part of the plant used, in the product ingredients;
- specify the coumarin content in the product;
- pay particular attention to the conditions of use (doses and frequency) of food supplements, especially in the case of essential oils that may contain coumarin.

In addition, given that the 95th percentile for individuals (adults and children) exposed to coumarin through food consumption is 0.02 mg/kg bw/day, the WG and the CES recommend that the daily intake of coumarin through food supplements should not exceed 80% of the TDI of 0.1 mg/kg bw/day, i.e. 0.08 mg/kg bw/day, corresponding to an intake of 4.8 mg/day of coumarin for a 60 kg adult.

However, other significant routes of exposure to coumarin, such as cosmetics, should also be taken into account. Coumarin exposure specific to these products should be assessed so as to be able to specify the maximum acceptable proportion of exposure through the consumption of food supplements.

In order to protect at-risk populations, the WG on "Plants" and the CES on "Human Nutrition" believe that foods rich in cinnamon or food supplements containing coumarin should not be consumed by individuals with a history of liver disease.

The WG on "Plants" and the CES on "Human Nutrition" reiterate that coumarin and plants containing it are not on the list of substances and foods for which health claims are permitted in Commission Regulation (EU) No 432/2012.

5. AGENCY CONCLUSIONS AND RECOMMENDATIONS

ANSES issued an internal request for an assessment of the risk of hepatotoxicity associated with the coumarin content of certain plants that can be consumed in food supplements – which are governed by a specific regulatory framework – or in other foodstuffs.

The Agency called on the WG on "Plants" for this expert appraisal; the WG helped draw up conclusions and recommendations which were then validated by the Expert Committee on "Human Nutrition".

ANSES endorses the conclusions and recommendations prepared by these expert groups.

It stresses that the liver toxicity of coumarin at high doses (> 25 mg/day in humans) has been confirmed by the available toxicological data.

In 2004, EFSA established a tolerable daily intake (TDI) of 0.1 mg/kg bw/day by the oral route for coumarin. This value was confirmed by EFSA in 2008 and has been used by ANSES for this expert appraisal.

ANSES emphasises that there is a risk of the TDI set by EFSA being exceeded by major consumers of food supplements containing coumarin. This risk is even higher for products containing plants rich in coumarin, such as Chinese cinnamon (*Cinnamomum cassia*).

Considering only data on dietary exposure (excluding food supplements) and in order to comply with the TDI, the Agency recommends keeping coumarin intake through the consumption of food supplements below 4.8 mg of coumarin per day, for a 60 kg person. In the absence of specific regulations for other products, this maximum daily intake should apply to food supplements containing coumarin. However, this value does not take into account other routes of exposure to coumarin, such as cosmetics, home fragrances and household products.

In this context, it may be worth considering a risk assessment of coumarin in these numerous products, to include all exposure routes (inhalation, dermal and oral).

In order to guarantee consumer safety, ANSES recommends precisely defining the botanical identity of the plant and its coumarin content in the product ingredients.

It also recommends exercising increased vigilance on the use of cinnamon essential oils in products intended for food and food supplements, because these essential oils have been responsible for most of the adverse effects associated with the consumption of products containing coumarin recorded by the nutrivigilance scheme.

Lastly, in order to protect at-risk populations, ANSES advises individuals with a history of liver disease or taking medicines known to cause adverse liver effects not to consume foods rich in cinnamon, or food supplements containing coumarin.

In general, ANSES recommends that consumers seek advice from a health professional before taking a food supplement, in order to assess whether it is appropriate with regard to their state of health and any medication they may be taking concomitantly.

Lastly, ANSES reminds healthcare professionals and manufacturers of the need to report to its nutrivigilance scheme any adverse effects likely to be associated with the consumption of food supplements about which they become aware.

Dr Roger Genet

KEYWORDS

Compléments alimentaires, plantes, préparation de plantes, huiles essentielles, coumarine, cannelle, hépatotoxicité.

Food supplements, plants, plant extracts, essential oils, coumarin, cinnamon, hepatotoxicity.

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ANNEX 1

Presentation of the participants

PREAMBLE: The expert members of the Expert Committees and Working Groups or designated rapporteurs are all appointed in a personal capacity, *intuitu personae*, and do not represent their parent organisation.

WORKING GROUP ON "PLANTS" (2019-2022)

Chair

Mr Fabrice NESSLANY – Research Director (Institut Pasteur de Lille) – Speciality: toxicology

Members

Ms Sabrina BOUTEFNOUCHET – University Lecturer (Paris-Descartes University) – Speciality: pharmacognosy

Mr Pierre CHAMPY – University Professor (Paris-Sud University) – Speciality: pharmacognosy

Ms Hanh DUFAT – University Lecturer (Paris-Descartes University) – Speciality: pharmacognosy

Ms Marion GIRARDOT – University Lecturer (University of Poitiers) – Speciality: pharmacognosy

Mr Thierry HENNEBELLE – University Professor (Lille University) – Speciality: pharmacognosy

Ms Marie-Aleth LACAILLE-DUBOIS – Emeritus University Professor (University of Bourgogne Franche-Comté) – Speciality: pharmacognosy

Mr Serge MICHALET – University Lecturer (Claude Bernard University, Lyon I) – Speciality: pharmacognosy

Ms Céline RIVIERE – University Lecturer (Lille University) – Speciality: pharmacognosy

Ms Florence SOUARD – University Lecturer (Grenoble Alpes University) – Speciality: pharmacognosy

Ms Dominique-Angèle VUITTON – University and Hospital Professor (University of Bourgogne Franche-Comté) – Speciality: internal medicine

Mr Bernard WENIGER – Retired, University Lecturer (Strasbourg University) – Speciality: pharmacognosy

RAPPORTEURS FROM THE WG ON "PLANTS"

Mr Serge MICHALET – University Lecturer (Claude Bernard University, Lyon I) – Speciality: pharmacognosy

Mr Bernard WENIGER – Retired, University Lecturer (Strasbourg University) – Speciality: pharmacognosy

EXPERT COMMITTEE

- CES on "Human Nutrition" (2018-2021)

Chair

Mr François MARIOTTI – Professor (AgroParisTech) – Specialities: metabolism of proteins, amino acids, nutritional requirements and recommendations, postprandial metabolism, cardiometabolic risk

Members

Mr Frédérik BARREAU – Research Manager (Inserm) – Specialities: chronic inflammatory intestinal diseases, microbiota, host-microbe relationships, barrier function of the intestinal mucosa

Ms Charlotte BEAUDART – Research Manager (University of Liège) – Specialities: epidemiology, public health, meta-analyses, sarcopenia

Ms Catherine BENNETAU-PELISSERO – Professor (Bordeaux Sciences Agro) – Specialities: phyto-oestrogens, isoflavones, endocrine disruptors, bone health, food supplements

Ms Clara BENZI-SCHMID – Federal Food Safety and Veterinary Office (FSVO), Switzerland – Specialities: revision and updating of legal bases of foodstuffs

Ms Marie-Christine BOUTRON-RUAULT – Research Director (CESP Inserm) – Specialities: nutritional epidemiology and cancer, digestive system

Ms Blandine de LAUZON-GUILLAIN – Research Director (INRA, CRESS) – Specialities: epidemiology, infant nutrition, nutrition of pregnant and breastfeeding women, public health

Ms Amandine DIVARET-CHAUVEAU – University Hospital Practitioner (Nancy Regional University Hospital) – Specialities: allergology, epidemiology, complementary feeding, breastfeeding

Ms Christine FEILLET-COUDRAY – Research Director (INRA, Montpellier) – Specialities: metabolism of minerals, oxidative stress

Ms Amandine GAUTIER-STEIN – INRA Research Manager (Inserm “Nutrition, diabetes and brain” unit) – Specialities: energy metabolism, neuroendocrinology, gut-brain axis

Mr Jacques GROBER – University Lecturer (AgroSup Dijon) – Specialities: nutrition, lipids, metabolism of lipoproteins

Ms Emmanuelle KESSE-GUYOT – Research Director (INRA, UMR Inserm U1153/INRA U1125/CNAM/University of Paris 13) – Specialities: epidemiology, nutrition and pathologies, nutrition and public health, food sustainability

Ms Corinne MALPUECH-BRUGERE – University Professor (University of Clermont Auvergne) – Specialities: human nutrition, metabolism of macro- and micro-nutrients

Ms Christine MORAND – Research Director (INRA Clermont-Ferrand) – Specialities: prevention of vascular dysfunctions and related diseases, micro-constituents of plants

Ms Anne-Sophie ROUSSEAU – University Lecturer (University of Côte d'Azur, UMR/INSERM 1065) – Specialities: nutrition and physical activity, oxidative stress, immunometabolism

Mr Stéphane WALRAND – University Professor-Hospital Practitioner (University of Clermont Auvergne and Gabriel Montpied University Hospital in Clermont-Ferrand) – Specialities: pathophysiology, protein metabolism, vitamin D, amino acids

ANSES PARTICIPATION

Scientific coordination

Mr Youssef EL OUADRHIRI – Nutritional Risk Assessment Project Leader – Risk Assessment Department

Scientific coordination of the project was carried out under the direction of Ms Irène MARGARITIS – Seconded University Professor (University of Nice Sophia-Antipolis), Head of the Nutritional Risk Assessment Unit and Mr Aymeric DOPTER – Deputy Head of the Nutritional Risk Assessment Unit – Risk Assessment Department

Scientific contribution

Mr Youssef EL OUADRHIRI – Nutritional Risk Assessment Project Leader – Risk Assessment Department

Ms Carine DUBUISSON – Deputy Head of Unit – Methods and Studies Unit – Risk Assessment Department

Ms Aurore COUDRAY – Scientific Project Leader – Food Observatory Unit – Risk Assessment Department

Ms Fanny HURET – Scientific Project Leader for Nutrivigilance – Risk Assessment Department

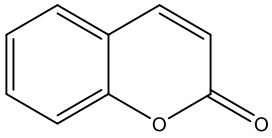
Administrative secretariat

Ms Virginie SADE – Risk Assessment Department

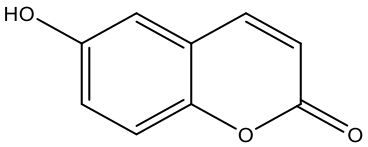
ANNEX 2

Structures of coumarin derivatives of natural and synthetic origin

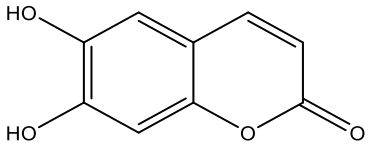
Simple coumarin



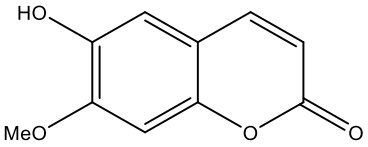
Coumarine



Ombelliférone

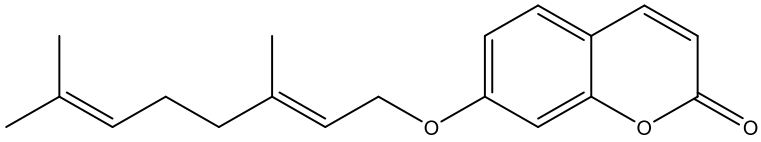


Esculétol



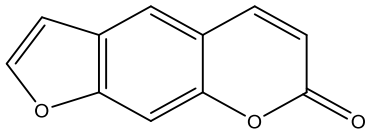
Scopolétol

Prenylated coumarins

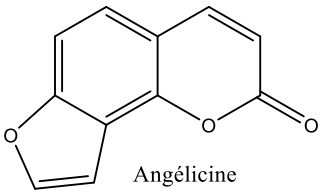


Auraptène

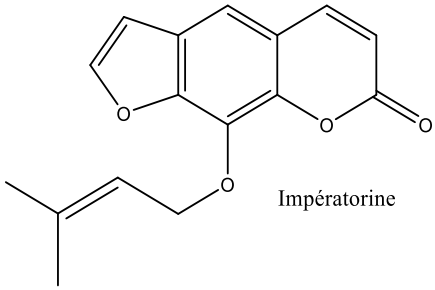
Furanocoumarins (= furocoumarins)



Psoralène

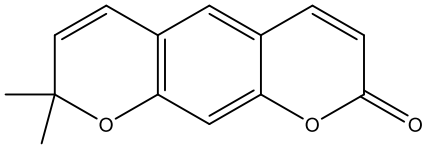


Angélicine

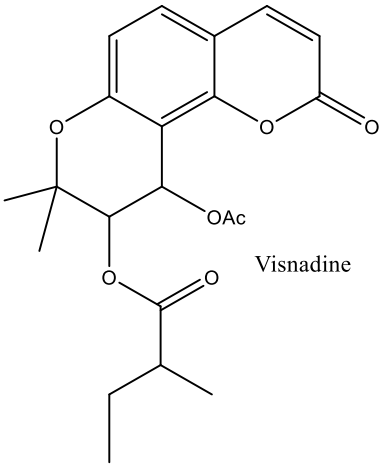


Impératorine

Pyranocoumarins

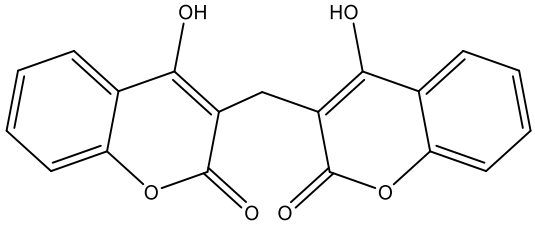


Xanthylétine

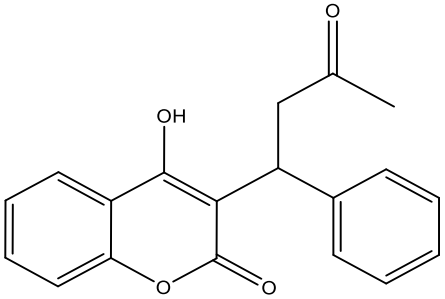


Visnadine

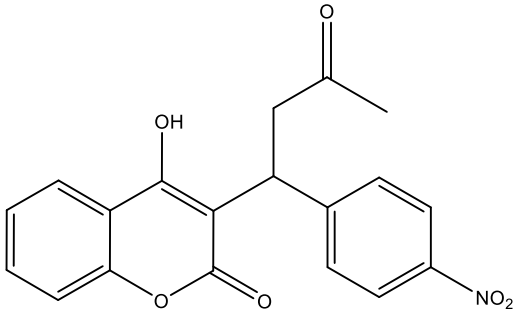
"Dimer" coumarins



Dicoumarol



Warfarine



Acénocoumarol

ANNEX 3

Scientific and technical support (AST) note of the French Agency for Food, Environmental and Occupational Health & Safety concerning an additional request for quantitative label data on ingredients containing coumarin, in the framework of Request No 2018-SA-0180 on the assessment of the risk of hepatotoxicity associated with the coumarin content of certain plants that can be consumed in food supplements or in other foodstuffs.

1. Background and purpose of the request

In the framework of Request No 2018-SA-0180 on the assessment of the risk of hepatotoxicity associated with the coumarin content of certain plants that can be consumed in food supplements or other foodstuffs, and under internal scientific and technical support request AST 2019-ASTDER-29, the Nutritional Risk Assessment Unit (UERN) asked the Food Observatory Unit (UOA) to provide data on the presence of certain ingredients in processed products available on the French market.

2. Organisation of the work

- **Sources of the data used**

The data came from the OQALI database.

The OQALI project, carried out jointly by ANSES and INRA, monitors over time the nutritional quality of the processed food products available on the French market. This monitoring concerns product references (branded products). The OQALI database, which includes lists of product ingredients, was therefore used to produce an inventory of the ingredients used in processed products available on the French market.

The research was conducted on 31,955 products labelled with a list of ingredients[20], divided into 30 food categories, and collected between 2009 and 2017. All the data presented were taken from the product packaging. To date, of all processed products, only the confectionery category is not yet covered by OQALI.

It is important to note that the OQALI database includes only one packaging type per recipe as long as all the information available on the packages is identical (apart from the barcode and the weight). For example, if the recipe for brand X yoghurt is available in both 4*100g and 8*100g formats (with the information provided being strictly identical), the OQALI database will contain only one record for just one of them. On the other hand, the market share according to Kantar Worldpanel data was calculated while including all possible packaging types for this brand X yoghurt.

It should also be noted that only the products considered in the most recent sectoral monitoring are presented below. This means that if certain products that were taken into account during the first sectoral monitoring are no longer available on the market, they have not been included in this inventory.

[20] In the particular case of cheese, all products in this category were considered, because lists of ingredients are not required if the products contain only milk products, food enzymes and micro-organisms.

- **Methodology**

The ingredient lists of the studied products were previously entered and structured in the OQALI database. A standard nomenclature was developed in order to be able to process them (since the same ingredient may be named in different ways).

A search for 15 ingredients was carried out in the codified ingredient lists and the list of requested ingredients:

- CINNAMON,
- CINNAMON EXTRACT,
- NATURAL_CINNAMON FLAVOURING,
- CINNAMON_FLAVOURING,
- NATURAL_CASSIA FLAVOURING,
- CAPERS,
- CAPER POWDER,
- LAVENDER,
- NATURAL_LAVENDER FLAVOURING,
- LAVENDER ESSENTIAL OIL,
- FENUGREEK,
- TONKA BEAN,
- TONKA BEAN POWDER,
- TONKA BEAN EXTRACT,
- NATURAL_TONKA BEAN FLAVOURING.

3. Analysis and conclusions

Of the 31,955 products included, divided into 30 categories, 516 had at least one of the ingredients listed above.

Thus, 22 categories had at least one product containing at least one of the ingredients searched for. These categories included Frozen snacking products (7.8%) and Condiments (5.6%).

At least one of the ingredients searched for was found in half or more of the products in the Speculoos (100%), Thin filled waffles (63.6%) and Gingerbreads (50%) subcategories of the Cakes and Biscuits category, as well as in the Seafood pizzas (68.4%) subcategory of the Frozen snacking products category and in the Cheesecakes (57.1%) subcategory of the Frozen pastries and desserts category. The ingredient found for these subcategories was cinnamon, except for the Seafood pizzas subcategory of the Frozen snacking products category for which it was capers.

ANNEX 4

Scientific and technical support (AST) note of the French Agency for Food, Environmental and Occupational Health & Safety concerning the "estimate of dietary exposure to coumarin of the population living in France based on data from the INCA3 study"

On 10 September 2019, the Nutritional Risk Assessment Unit (UERN) asked the Methodology and Studies Unit (UME) of the Risk Assessment Department (DER) to assess the exposure of the population living in France to coumarin, using data from the INCA3 study **(2019-ASTDER-32)**.

1. Background and purpose of the request

In the framework of Request No 2018-SA-0180 on the assessment of the risk of hepatotoxicity associated with the coumarin content of certain plants that can be consumed in food supplements or other foodstuffs, the UERN wished to obtain data on the consumption of foods containing coumarin and on exposure of the population to this substance, using data from the INCA3 study. The coumarin content of certain product categories has been set by Regulation (EC) No 1334/2008:

1. Traditional and/or seasonal bakery ware containing a reference to cinnamon in the labelling (50 mg/kg),
2. Breakfast cereals including muesli (20 mg/kg),
3. Fine bakery ware, with the exception of traditional and/or seasonal bakery ware containing a reference to cinnamon in the labelling (15 mg/kg),
4. Desserts (5 mg/kg).

The request to analyse the INCA3 study data focused specifically on the following tasks:

1. Identify foods and food supplements containing cinnamon, or likely to contain coumarin, consumed in the INCA3 study:
   For home-made recipes and spice mixes, identification concerned the ingredient "cinnamon". For food supplements, teas and herbal teas, the ingredients to be searched for were extended to the plants listed in Table 15. Industrial foodstuffs containing the plants listed in Table 15 were identified using the OQALI database.

Table 15: Plants containing coumarin and authorised in food supplements in France

Scientific name	Vernacular name	Parts used
Anthoxanthum odoratum	Sweet vernal grass	Not specified
Capparis spinosa L.	Caper bush	Not specified
Cerasus mahaleb (L.) Mill.	Saint Lucie cherry	Not specified
Cinnamomum cassia (Nees & T.Nees) J.Presl	Chinese cinnamon	Bark, leaf, twig
Cinnamomum verum J.Presl	Cinnamon, Ceylon cinnamon	Bark, leaf
Dipteryx odorata	Tonka bean	Not specified
Galium odoratum (L.) Scop.	Sweet woodruff, Sweet-scented bedstraw	Aerial parts
Hierochloe odorata (L.) Beauv.	Bison grass	Not specified
Jumellea fragrans (Thouars) Schltr.	Faham	Not specified
Justicia pectoralis Jacq.	Carpenter bush, freshcut	Not specified

Lavandula angustifolia Mill.	Lavender, True lavender	Aerial parts
Lavandula × intermedia Emeric ex Loisel.	Lavandin	Aerial parts
Melilotus altissimus Thuill.	Tall yellow sweet clover, Tall melilot	Aerial parts
Melilotus officinalis (L.) Pall.	Yellow sweet clover	Aerial parts
Melittis melissophyllum L.	Bastard balm	Not specified
Trigonella foenum-graecum L.	Fenugreek	Seed
Trigonella caerulea (L.) Ser.	Blue-white clover	Leaf

2. Calculate population exposure to coumarin separately for children and adults using the following two approaches:
   - "Regulatory" approach using:
     - The maximum level set by the regulations for the food products concerned
     - The average maximum level of the type of cinnamon used (where specified), or by default that of Chinese cinnamon, for food supplements and other products that include plants containing coumarin.
   - "Realistic" approach using for all products the maximum level of the ingredient and its percentage in the product
3. Identify contributing foods for both approaches
4. Compare observed exposures with reference values
5. Describe the exposed individuals according to their age, sex and region of residence

The reference value used was the Tolerable Daily Intake (TDI) defined by EFSA for children and adults. Several scenarios were considered:

- The scenario where individual exposure was compared with the TDI (0.1 mg/kg bw/day).
- The scenario where individual exposure was compared with three times the TDI value (0.3 mg/kg bw/day).

2. Data and methods

The internal scientific and technical support was provided by the Methodology and Studies Unit of ANSES's Risk Assessment Department according to the methodology presented below.

2.1 Data used: INCA3 study (2014-2015)

The Third Individual and National Study on Food Consumption (INCA3) was a cross-sectional survey designed to estimate the food consumption and eating habits of individuals living in France. The study was conducted between February 2014 and September 2015 with a representative sample of individuals living in metropolitan France (excluding Corsica).

The individuals were selected according to a three-stage random sampling method (geographical units, households and then individuals), from the 2011 annual census of the population, complying with a geographical stratification (region, size of the urban area) in order to ensure representativeness for the entire country. Two independent samples were established: a "Children" sample (from birth to 17 years of age) and an "Adults" sample (18 to 79 years).

The data collected in the study covered various topics related to the assessment of nutritional or health risks associated with food: consumption of food, beverages and food supplements, dietary habits, practices that are potentially risky to health, knowledge and behaviour in terms of food.

To ensure that the results presented were nationally representative, the data on participating individuals were adjusted. This was done separately for children and adults, taking into account geographical and socio-economic variables.

2.2 Data on detailed food consumption and ingredients

2.2.1 Method of collecting food consumption data

Information on the food consumption of individuals was collected over three non-consecutive days (2 weekdays and 1 weekend day) spread over around three weeks, using the 24h recall (R24) method for individuals aged 15 to 79 years, and the 24h record method (using a food picture book) for individuals from birth to 14 years. For the three selected days, the individuals were asked to describe their food consumption by identifying all the foods and beverages consumed during the previous day and night. They were invited to describe it in as much detail as possible and quantify it, mainly with the help of a picture book of food servings and household measures. Regardless of the individual's age, the interviews were conducted by telephone, using the GloboDiet standardised software package, by professional interviewers specifically trained in the methods and software used.

Only certain dishes were regarded as recipes during the collection of food consumption data. A breakdown of ingredients was suggested to the individual, giving them the option of modifying the type and quantity of ingredients in this recipe (addition, substitution, exclusion). The ingredients in the other foods were not detailed at the time of collection, to avoid increasing the burden of responding to the study. These foods were therefore broken down into ingredients afterwards.

2.2.2 Database of recipes broken down into ingredients

In parallel with the INCA3 study, a recipe database was therefore created under a research and development agreement (CRD) with the Research Centre for the Study and Monitoring of Living Conditions (CREDOC). This recipe database contained:

1. the standard recipes suggested at the time of data collection,
2. the most frequently mentioned complex foods **reported as home-made** in the INCA3 study (e.g. apple tart = pastry dough, custard, apples), broken down after collection.

For the latter, the recipe corresponded to an average generic recipe resulting from a combination of the five most consulted recipes on the Internet. The choice of ingredients and their quantification in the generic recipe followed a precise methodology defined by ANSES, in order to standardise the recipe breakdown and ensure that the generic recipes obtained reflected the likely home-made recipes for these foods.

These generic home-made recipes were assigned to all corresponding complex foods, regardless of the declared origin (home-made, industrial or traditional production), so as to allow the ingredients of interest to be identified in all foods.

2.2.3 OQALI labelling database (see detailed AST notes from the UOA)

The UOA was asked to provide a list of industrial product subcategories that included, among their ingredients, the plants containing coumarin listed in Table 15. Out of 671 product subcategories, 142 had a product with at least one ingredient containing coumarin. Within these subcategories, the proportion of products mentioning at least one of the ingredients searched for varied between 0.3% and 100%, with the majority below 10%.

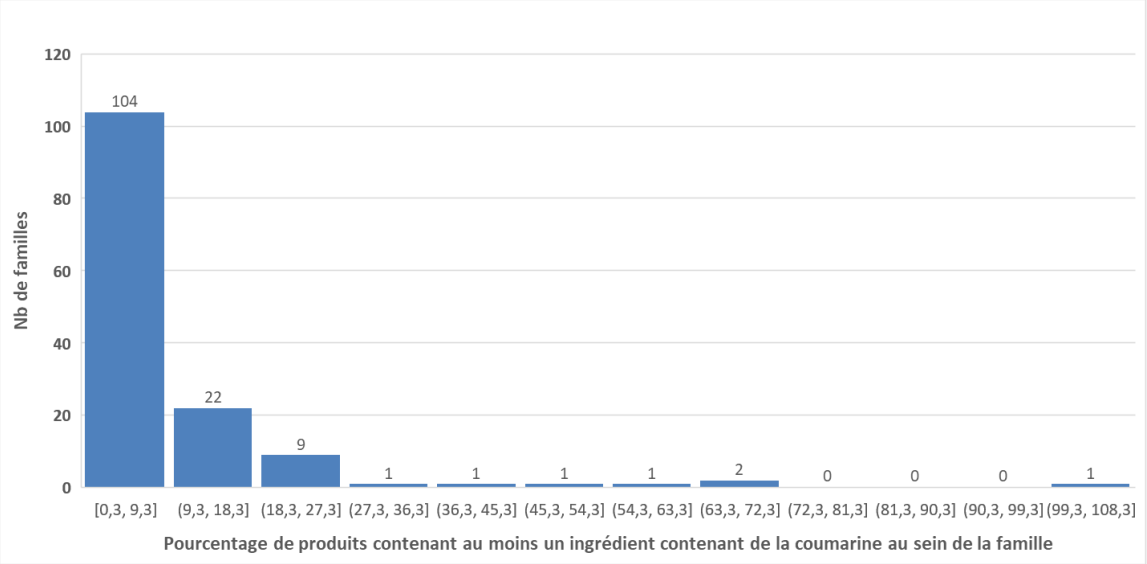


Figure 4. Breakdown of the 142 product subcategories according to the percentage of products with at least one ingredient containing coumarin

Five subcategories included more than 50% of products mentioning at least one of the ingredients searched for: Gingerbreads (50%), Cheesecakes (57.1%), Thin filled waffles (63.6%), Seafood pizzas (68.4%) and Speculoos (100%). Conversely, 12 subcategories included less than 1% of products containing at least one of the ingredients searched for: Meals with vegetables and/or starchy foods and meat/fish (0.3%), Non-carbonated fruit beverages with sugar > 2.5g/100ml (0.3%), Classic and wavy crisps (0.4%), Superior dry pork sausages (0.4%), Battered or breaded fish (0.5%), Smoked salmon and trout (0.5%), Dessert creams, jellied or curdled milks, chocolate custards topped with whipped cream (0.6%), Egg-based fresh dairy desserts (0.7%), Fish in sauce (0.7%), Plain white breads (0.8%), Artificially-sweetened yoghurts and fermented milks (0.8%) and Fruit desserts (0.9%)

Some subcategories had products with different ingredients. For example, within the "Ethnic soups" subcategory, six products contained exclusively cinnamon (15.4%), one product contained both cinnamon and fenugreek, and one product contained exclusively fenugreek.

Where available, the quantity of the ingredient was searched for. This was available for 29 subcategory-ingredient pairs. The average quantity of ingredient in the product varied according to the subcategories between 0.01 and 1% for cinnamon (n = 16 subcategories) and between 0.20 and 6.43% for capers (n = 11 subcategories), and was 0.29% for tonka bean (n = 1 subcategory) and 0.50% for lavender essential oil (n = 1 subcategory).

2.3 Data on food supplements

2.3.1 Data on consumption of food supplements

In the INCA3 study, the definition of "food supplement" did not strictly follow the regulatory definition, but also included drugs that can provide nutrients, and plant extracts. The definition provided to participants was as follows: "*Food supplements are products intended to supplement the diet and which are a concentrated source of micronutrients or other substances such as vitamins, minerals, amino acids, proteins, essential fatty acids, phyto-oestrogens, etc. Some medicines, whether or not prescribed by a doctor and whether or not they are reimbursed, may also contain these nutritional substances*. *In our study, they will be considered in the same way as food supplements. These products are intended to be taken orally and are packaged as pills, tablets to be swallowed, effervescent tablets, capsules, sachets of powder, syrups, ampoules, gums, etc.*" Long-term consumption of these products was assessed using a face-to-face questionnaire administered by the interviewer during the home visit. The questionnaire covered the five most frequently consumed products

during the questionnaire reference period (1 month for children aged 0-15 months and under, 3 months for children aged 16-24 months, 6 months for children aged 25-35 months and 12 months for individuals aged 3-79 years). For each product mentioned, the name, brand, form of presentation, place of purchase, frequency of consumption and quantity consumed were documented.

2.3.2 Data on composition of food supplements

The packaging of the food supplements consumed was collected by the investigators when they had the opportunity to do so. The information available on the packaging (name, brand, manufacturer, form of presentation, dosage, list of ingredients, list of constituents, etc.) was entered in an Access database by an external service provider. Information on products whose packaging could not be recovered was supplemented afterwards by searches on the internet or by contacting the manufacturers. A database containing 692 different products was compiled.

2.4 Study population and data on individuals

A total of 5855 individuals, broken down into 2698 children from birth to age 17 and 3157 adults between the ages of 18 and 79, participated in the study. Of these 5855 individuals, **4114** (2121 adults and 1993 children) validated the consumption part by taking part in at least two food interviews, and **1544** (949 adults and 595 children) reported consuming food supplements in the broad sense. This formed the basis for the results of this note.

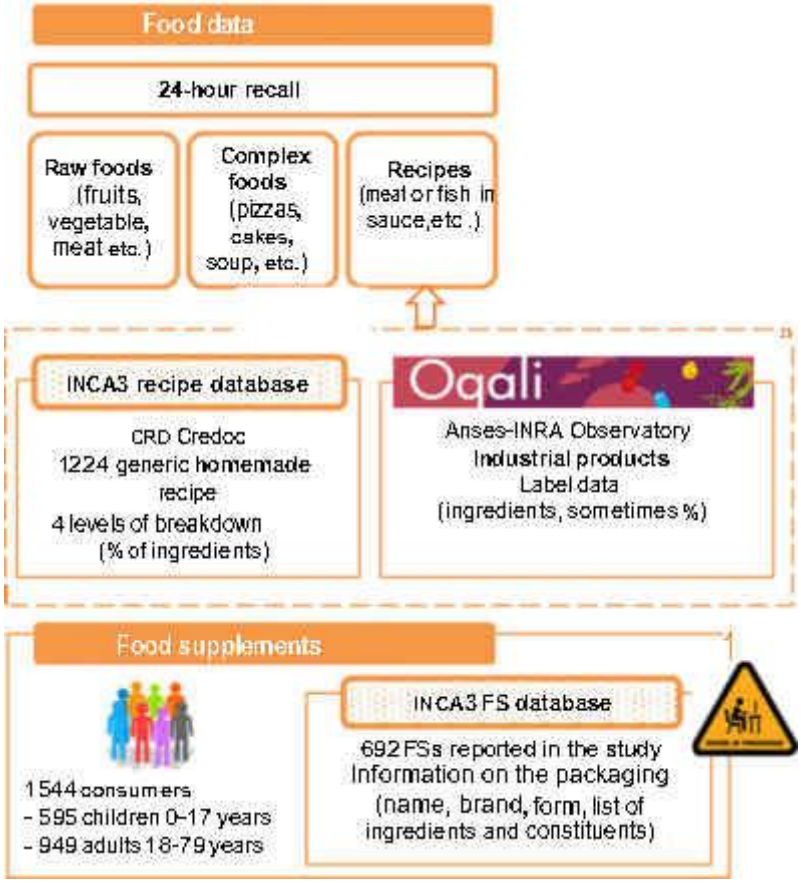
2.5 Methodology

2.5.1 Identification of foods and ingredients regarded as potentially containing coumarin

The list of plants provided by the UERN was compared with:

1. the lists of foods mentioned in the INCA3 study and their reported characteristic ingredients,
2. the ingredients used for the recipe breakdowns in the recipe database,
3. the labelled ingredients in the OQALI industrial product database (see the UOA's AST notes),
4. the lists of constituents[21] and ingredients of currently available food supplements.

[21] As long as the database is not completely cleaned, similar information may be found in both lists.

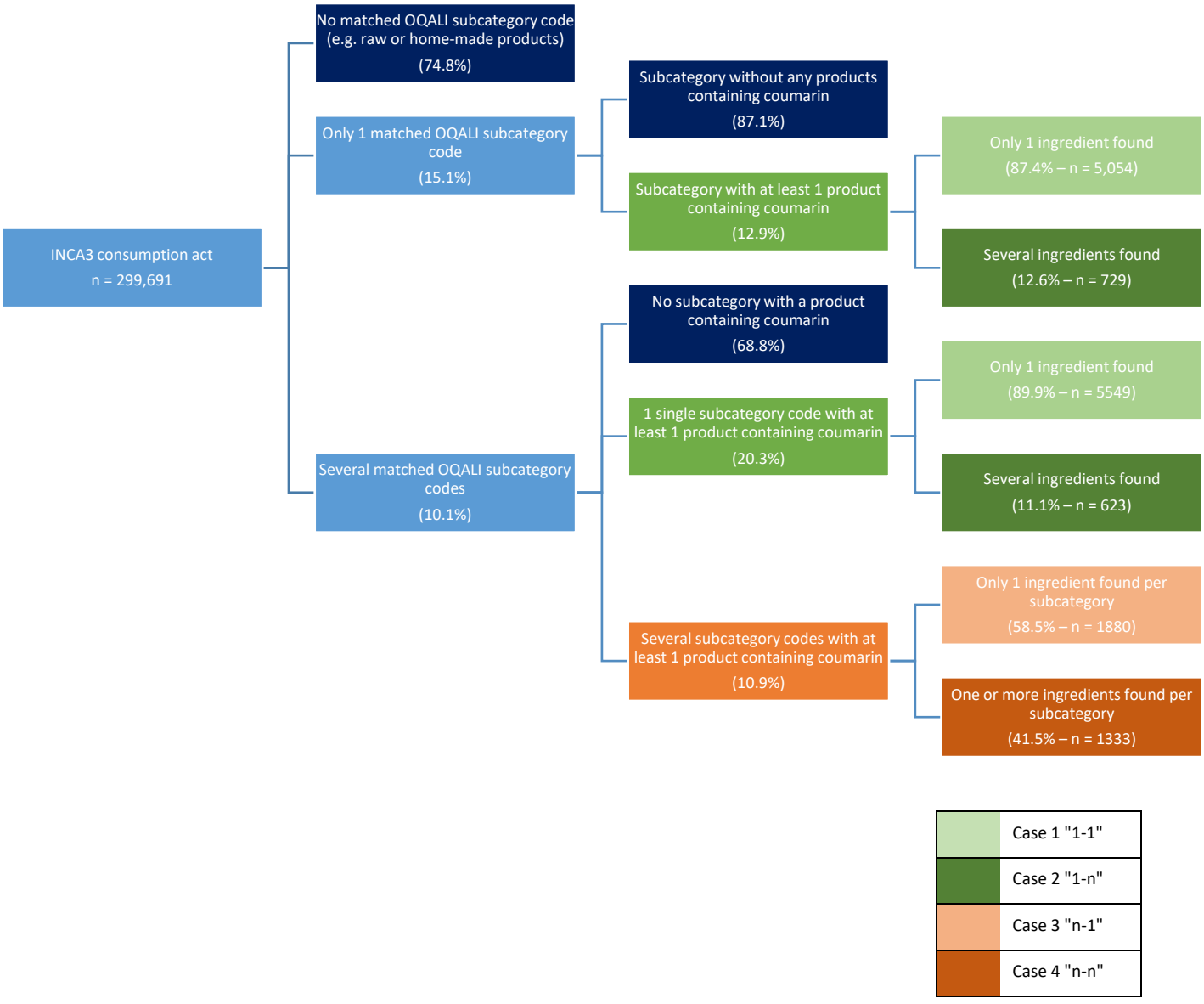


Where appropriate, foods and recipes were classified in the food categories defined by Regulation (EC) No 1334/2008, or in additional categories such as spice mixes, teas and infusions, or other products. These "coumarin food categories" were numbered as follows:

1. Traditional and/or seasonal bakery ware containing a reference to cinnamon in the labelling,
2. Breakfast cereals including muesli,
3. Fine bakery ware, with the exception of traditional and/or seasonal bakery ware containing a reference to cinnamon in the labelling,
4. Desserts,
5. Spices and spice mixtures,
6. Teas and infusions, hot chocolate,
7. Other food products.

2.5.2 Assignment of OQALI information for industrial products

After matching INCA3 consumption data to OQALI subcategories, it was found that 5.1% of consumption acts corresponded to subcategories of industrial products that may contain coumarin (n = 15,287). This matching refers to one or more subcategories and one or more ingredients containing coumarin, as shown in the figure below.



2.5.3 Choice of OQALI subcategories to be retained

Where there was only one product category for a given consumption act, it was retained (Case 1). For Cases 2 to 4, involving multiple choices of products for the same consumption act, selection rules were applied in order to retain only one subcategory/category of ingredient:

1. Priority was given to ingredients for which the quantity was labelled and was at the maximum => **maximisation of exposure**

2. *Regarding the lines with several equal quantities of ingredient and the remaining lines*: priority was given to subcategories with products containing cinnamon (ingredient containing the most coumarin) => **maximisation of exposure**
3. *Regarding the subcategories with products containing cinnamon*: the subcategories with the highest proportion of products containing coumarin were selected => **representativeness**
4. *Regarding the subcategories with the highest share of products containing coumarin*: the subcategories/ingredients with the highest relative proportion (%) of products containing coumarin were selected => **representativeness**
5. *Regarding the subcategories/ingredients with the highest relative proportion (%) of products containing coumarin*: the subcategories or ingredients with the largest number of products (absolute number) were selected => **representativeness**
6. Arbitrary selection of the few remaining cases

This selection enabled a single product subcategory x ingredient combination to be assigned to each of the 15,287 consumption acts corresponding to at least one product subcategory that may contain coumarin.

To avoid artificially overestimating exposure, given the small proportion of products that may contain coumarin within the identified OQALI subcategories, a second selection was then carried out to retain the consumption acts finally recorded as being consumption of a product containing coumarin. This selection was carried out using two methods (A and B).

Method A involved three steps:

1. selection of all consumption acts of industrial speculoos: the only product subcategory for which the proportion of product containing coumarin was equal to 100% => *selection of 117 consumption acts*;

2. when facet 06 was available and differed from "don't know": acts stating in facet 06 one of the ingredients searched for ("gingerbread", "speculoos", "cinnamon", "caper", "unspecified spices") were retained as consumption acts involving products containing coumarin => *selection of 79 consumption acts*;

2. when facet 06 was not available or entered as "don't know": consumption acts of each INCA3 food were randomly selected in proportion to the amount of products containing coumarin for that food. This proportion was calculated by summing all the product subcategories and/or ingredient categories concerned for cases 2 to 4 => *selection of 195 consumption acts*.

Method B did not take into account the information contained in facet 06 and included a single step of randomly selecting the consumption acts in proportion to the amount of products containing coumarin for that food. As with Method A, this proportion was calculated by summing all the product subcategories and/or ingredient categories concerned for cases 2 to 4 => *selection of 1205 consumption acts*.

Thus, of the 15,287 lines matched to an OQALI subcategory with products containing at least one of the ingredients searched for, only 391 in Method A and 1205 in Method B remained matched and counted as being consumption of products containing coumarin. This represented respectively around 2.6% and 7.9% of products containing coumarin across all product subcategories. Method A was closer to the rate observed from the data provided by OQALI (around 2.6%) than Method B. As a reminder, the OQALI data reflect supply, without weighting by actual consumption. There may therefore be a difference between the rates observed for supply and consumption.

2.5.4 Assigning ingredient quantities

As previously mentioned, very few products state the quantity of ingredients searched for on their labels in the OQALI database (29 subcategory x ingredient pairs out of 136). In order to maximise exposure, the ingredient quantities selected correspond to the maximum quantities noted for the pair. For the other subcategory x ingredient pairs for which the quantity was not available, there was a first attempt to fill in the missing values according to the following rules:

1. Extension to certain subcategory x ingredient pairs of data existing in other pairs, when these were similar in terms of recipe (see Table 16);
2. Assignment of the median quantity observed in the OQALI category for the ingredient;
3. Assignment of the ingredient quantities available for similar recipes in the home-made recipe database.

Table 16. List of OQALI subcategories for which an ingredient quantity was available and for which an extension was made (in italics) after regrouping (Subcategory_regroup)

OQALI category	Subcategory code	OQALI subcategory	Ingredient	Subcategory_regroup	Maximum quantity
Baby food	697	Meal with vegetables and/or starchy foods and meat/fish	*Cinnamon*		0.01
Cakes and biscuits	409	Other shortbreads	*Cinnamon*		0.35
Cakes and biscuits	728	Fruit biscuits	*Cinnamon*		0.40
Cakes and biscuits	404	Speculoos	*Cinnamon*		0.20
Soups and broths	647	Exotic soups	*Cinnamon*	Soups	0.30
Soups and broths	*627*	*Onion soups*	*Cinnamon*	*Soups*	*0.30*
Soups and broths	*633*	*Starchy soups*	*Cinnamon*	*Soups*	*0.30*
Soups and broths	*643*	*Pumpkin soups*	*Cinnamon*	*Soups*	*0.30*
Fruit purées, compotes and desserts	152	Low-sugar (light) fruit compotes	*Cinnamon*	Fruit compote	0.10
Fruit purées, compotes and desserts	*153*	*Fruit desserts*	*Cinnamon*	*Fruit compote*	*0.10*
Fruit purées, compotes and desserts	*155*	*Fruit compotes with specific added ingredients*	*Cinnamon*	*Fruit compote*	*0.10*
Ice-creams and sorbets	484	Luxury bulk ice-cream	*Cinnamon*	Ice-creams	0.05
Ice-creams and sorbets	*495*	*Sundae and frozen dessert*	*Cinnamon*	*Ice-creams*	*0.05*
Ice-creams and sorbets	*493*	*Ice-cream stick > or = 80ml*	*Cinnamon*	*Ice-creams*	*0.05*
Ice-creams and sorbets	*494*	*Ice-cream cone > or = 80ml*	*Cinnamon*	*Ice-creams*	*0.05*
Ice-creams and sorbets	*496*	*Ice-cream tub > or = 80ml*	*Cinnamon*	*Ice-creams*	*0.05*
Ice-creams and sorbets	*497*	*Frozen dessert for sharing*	*Cinnamon*	*Ice-creams*	*0.05*
Ready-to-eat canned meals	954	Canned mixed salads	*Capers*	Mixed_salads	2.80
Ready-to-eat canned meals	*1037*	*Canned Mexican salads*	*Capers*	*Mixed_salads*	*2.80*
Ready-to-eat canned meals	*1038*	*Canned Niçoise salads*	*Capers*	*Mixed_salads*	*2.80*
Ready-to-eat fresh meals	362	Meat_starchy_foods	*Capers*	Meat_starchy_foods	1.60
Ready-to-eat frozen meals	*758*	*Meat with starchy foods*	*Capers*	*Meat_starchy_foods*	*1.60*
Ready-to-eat frozen meals	775	Other starters	*Capers*		2.00
Ready-to-eat frozen meals	777	Vegetables	*Cinnamon*	Vegetables	0.08
Ready-to-eat frozen meals	777	Vegetables	*Capers*	Vegetables	01:50
Ready-to-eat canned meals	*553*	*Canned vegetables*	*Cinnamon*	*Vegetables*	*0.08*
Ready-to-eat canned meals	*553*	*Canned vegetables*	*Capers*	*Vegetables*	*01:50*

OQALI category	Subcategory code	OQALI subcategory	Ingredient	Subcategory_regroup	Maximum quantity
Ready-to-eat frozen meals	839	Starchy foods and vegetables	*Cinnamon*		0.07
Ready-to-eat frozen meals	759	Meat in sauce	*Capers*	Cooked meats	05:00
Ready-to-eat fresh meals	*605*	*Cooked meats*	*Capers*	*Cooked meats*	*05:00*
Ready-to-eat canned meals	*555*	*Canned cooked meats*	*Capers*	*Cooked meats*	*05:00*
Ready-to-eat frozen meals	760	Meat with vegetables	*Cinnamon*	Meat_vegetables	0.09
Ready-to-eat fresh meals	*363*	*Meat_vegetables*	*Cinnamon*	*Meat_vegetables*	*0.09*
Ready-to-eat frozen meals	762	Meat with vegetables and starchy foods	*Capers*		0.20
Dessert mixes	846	Mixes for dairy-based desserts without added sugar	*Lavender EO*	Mixes for dairy-based desserts	0.50
Dessert mixes	*219*	*Mixes for other dairy-based desserts*	*Lavender EO*	*Mixes for dairy-based desserts*	*0.50*
Dessert mixes	*225*	*Mixes for jellied dairy-based desserts*	*Lavender EO*	*Mixes for dairy-based desserts*	*0.50*
Fresh delicatessen products	453	Other spreads	*Capers*		09:00
Fresh delicatessen products	340	Desserts	*Cinnamon*		0.60
Fresh delicatessen products	818	Smoked_salmon_trout	*Capers*		04:30
Cold sauces	616	Emulsified sauces	*Capers*	Emulsified sauces	04:00
Cold sauces	*1005*	*Emulsified sauces_OOHC*	*Capers*	*Emulsified sauces*	*04:00*
Frozen snacking products	868	Crepes, pancakes and pastillas with meat or fish	*Cinnamon*		0.30
Frozen snacking products	870	Puff pastries with meat or fish, meat in pastry	*Capers*	Puff pastries	0.50
Crackers	*209*	*Puff pastries*	*Capers*	*Puff pastries*	*0.50*
Frozen snacking products	*948*	*Puff pastries with snails*	*Capers*	*Puff pastries*	*0.50*
Frozen snacking products	*869*	*Vegetarian puff pastries*	*Capers*	*Puff pastries*	*0.50*
Frozen snacking products	*866*	*Tarts with meat or fish*	*Capers*	*Puff pastries*	*0.50*
Frozen snacking products	952	Party loaves and cocktail canapés	*Cinnamon*		0.02
Frozen snacking products	952	Party loaves and cocktail canapés	*Capers*		0.70
Frozen pastries and desserts	851	Other brioches	*Cinnamon*		01:00
Frozen pastries and desserts	942	Other desserts	*Tonka bean*		0.29
Frozen pastries and desserts	862	Fruit desserts	*Cinnamon*		0.10
Frozen pastries and desserts	936	Apple and similar tarts	*Cinnamon*		0.10

In italics: subcategories to which quantities were extended

However, despite this filling in of missing values, not all the quantities were completed for all the subcategory x ingredient pairs. The missing quantities concerned:

- 126 consumption acts for cinnamon (out of 216 selected)
- 16 consumption acts for fenugreek (out of 16 selected)
- 11 consumption acts for capers (out of 54 selected)

These missing quantities were then processed more generally with all the "sources" of products containing coumarin (food, home-made recipes, industrial products).

2.5.5 Filling in missing ingredient quantities

In order to calculate exposure to coumarin, it is necessary to have the ingredient quantities for all the consumption acts identified as corresponding to products containing coumarin. The quantities were calculated as follows:

- ingredients consumed as is => quantity of the ingredient consumed
- ingredients of a home-made recipe => quantity of food consumed x percentage of ingredient in the recipe
- ingredients of an industrial product => quantity of food consumed x percentage of ingredient in the product

For recipes and industrial products, it was therefore imperative to have the ingredient percentages. For home-made recipes, this percentage was available in the INCA3 recipe database. For industrial products, this percentage was sometimes available in the OQALI database, or the missing values were partly filled in (see above). However, there were still percentages to be completed for:

- foods identified as containing coumarin through facet 06
- OQALI industrial products for which information was still lacking after the first attempt to fill in missing values

The missing percentages were then filled in according to the following rules:

1. Assignment of the median percentage observed for the INCA3 food and the ingredient concerned;
2. Assignment of the median percentage observed for the OQALI category for the ingredient concerned;
3. Assignment of the median percentage observed for the INCA3 food group for the ingredient concerned;
4. In the total absence of any information on the food, the OQALI category or the INCA3 food group, arbitrary percentages were assigned, taking into account quantities observed elsewhere:
    - Proportion of cinnamon in white bread set at 0.02%
    - Proportion of cinnamon in breakfast cereals set at 0.05%
    - Proportion of cinnamon in yoghurts set at 0.05%
    - Proportion of cinnamon in fruit beverages and fruit juices set at 0.1%.

2.5.6 Calculation of individual exposure to coumarin

To calculate exposure, coumarin levels were assigned to the different foods or ingredients likely to contain it, using the levels provided by the UERN and described in Table 17.

Table 17. Coumarin levels in foods and ingredients that may contain it, according to their type or regulatory category

	Food category/Ingredients	**Coumarin level (in mg/g of product)**
Regulatory categories	Traditional and/or seasonal bakery ware containing a reference to cinnamon in the labelling*	0.05
	Breakfast cereals including muesli	0.02

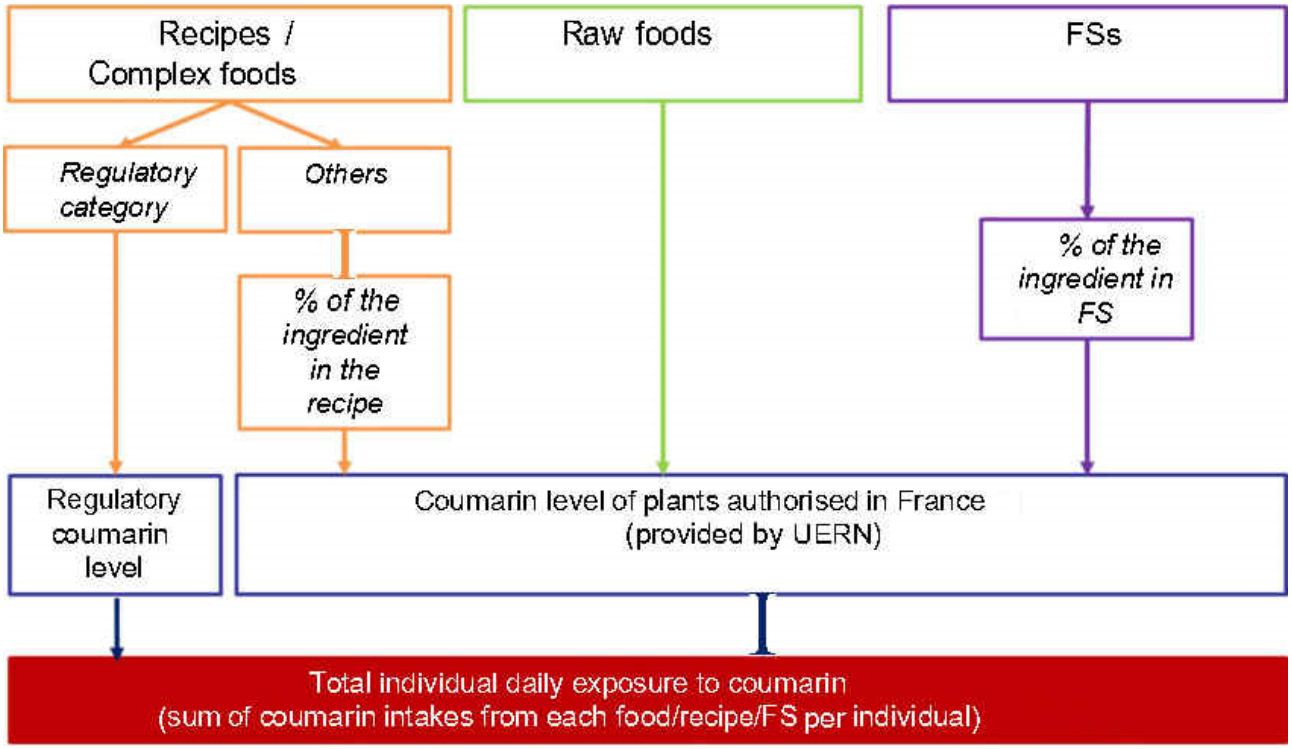
	Fine bakery ware, with the exception of traditional and/or seasonal bakery ware containing a reference to cinnamon in the labelling*	0.015
	Desserts	0.005
Plants containing coumarin listed in the INCA3 or OQALI database	Cinnamon	3
	Tonka bean	30
	Natural lavender flavouring	1
	Lavender essential oil	1.5
	Capers	1
	Fenugreek	0.004
Teas and infusions	Cinnamon tea/infusion	0.001

** For categories 1 and 3, the regulatory levels were only applied in the case where the consumption act was identified as involving an industrial product containing coumarin (see selection of OQALI products according to Method A or B). Otherwise, the level calculated from the percentage of the ingredient in the product and its coumarin level was used.*

Two exposure scenarios were then defined:

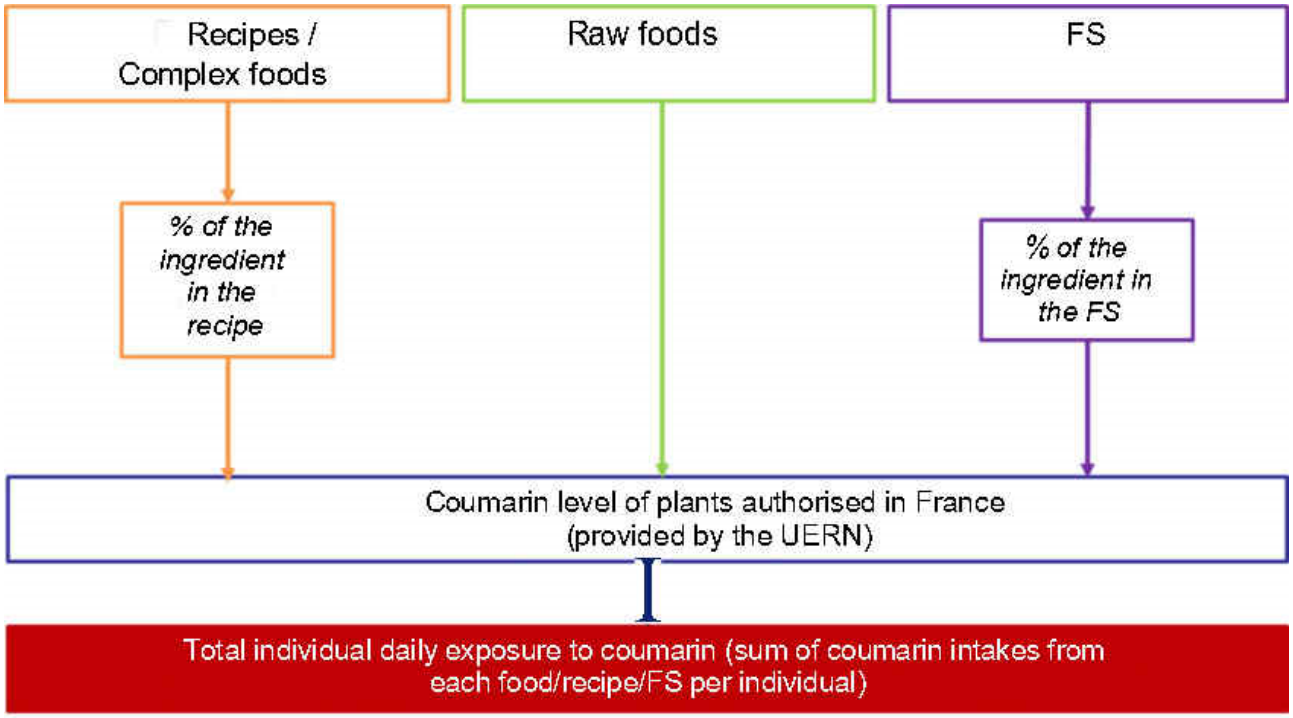
- **SCENARIO 1: Regulatory approach**

Foods or recipes belonging to a regulatory category contain the maximum coumarin level defined in the regulations, regardless of the amount of ingredient containing coumarin in the product. Other foods or recipes contain coumarin in proportion to the amount of ingredients containing it.



- **SCENARIO 2: Realistic approach**

All foods or recipes contain coumarin in proportion to the amount of ingredients containing it, regardless of whether they belong to a regulatory category.



For each scenario, exposure to coumarin was estimated separately for children (0-17 years) and adults (18-79 years). The rate of exposed individuals was also provided.

Note: Due to the low number of food supplements containing coumarin in the INCA3 study (n = 5), the intake from FSs was ultimately not taken into account to estimate the average daily exposure to coumarin. This is because it seemed more relevant to consider the "background" exposure from food estimated below and apply assumptions about consumption of FSs containing coumarin to be added to this background exposure.

2.5.7 Identification of contributing foods

For each scenario, the main contributing foods were identified using the 44 food groups in the INCA3 study nomenclature. The average contribution of each food group to total exposure was then estimated.

3. Results

3.1 Identification of foods, recipes, industrial products and food supplements consumed in the INCA3 study, corresponding to or including plants likely to contain coumarin

The number of consumption acts identified as corresponding to foods containing coumarin in the entire INCA3 consumption database was 2788 for Method A and 3578 for Method B, broken down as follows:

- "raw" foods: 262 for Method A and 285 for Method B;
- recipes with an ingredient containing coumarin: 2135 for Method A and 2088 for Method B;
- industrial products with an ingredient containing coumarin: 391 for Method A and 1205 for Method B.

In terms of "coumarin food categories", the identified consumption acts were broken down as follows:

Coumarin food categories	Children		Adults	
	Method A	Method B	Method A	Method B
1	72	73	127	127
2	9	98	3	20
3	28	43	17	22
4	37	72	51	74
5	19	19	81	82
6	8	461	93	200
7	1246	1266	997	1021
Total	**1419**	**2032**	**1369**	**1546**

The selection of acts according to Method B yielded a higher number of industrial products and, in particular, food categories No. 6 (mainly "hot chocolate") and No. 2 ("breakfast cereals").

3.1.1 Plants consumed directly as food

The foods corresponding to the plants in Table 15 consumed in the INCA3 study as food are listed in Annex AST 1 of annex 4. Plants may appear in the name of the food directly or in the characteristic ingredients (facet 06) selected by the individual to describe it.

The plants found among the foods corresponded to cinnamon (n = 194 mentions), lavender (n = 37), capers (n = 29), fenugreek (n = 2) and tonka bean (n = 1).

3.1.2 Plants consumed as food ingredients (home-made recipe database)

In the recipe database, the following plants were identified as being used as ingredients: cinnamon, fenugreek and caper. Each one is a direct ingredient in the recipes listed in Table 18 and as such they are included in all the recipes listed in Annex AST 2.

Table 18. List of recipes including as a direct ingredient plants that may contain coumarin, according to the INCA3 study recipe database

INGREDIENT	DIRECT RECIPE
cinnamon	BAKLAVA
cinnamon	CRUNCHY BROWN-SUGAR BISCUIT SUCH AS SPECULOOS
cinnamon	LAMB BRIOUAT
cinnamon	PEAR COMPOTE (WITHOUT ADDED SUGAR)
cinnamon	APPLE COMPOTE (REDUCED SUGAR CONTENT)

INGREDIENT	DIRECT RECIPE
cinnamon	APPLE COMPOTE (SWEETENED WITH A NATURAL SWEETENER SUCH AS STEVIA)
cinnamon	GAZELLE HORN
cinnamon	MEAT PUFF PASTRY
cinnamon	KING'S CAKE WITH APPLE
cinnamon	MILK TEA
cinnamon	MAKROUT
cinnamon	MASSALE SPICE
cinnamon	COUSCOUS SPICE MIX
cinnamon	4-SPICE MIX
cinnamon	5-SPICE MIX
cinnamon	TANDOORI SPICE MIX
cinnamon	NONETTE
cinnamon	GINGERBREAD
cinnamon	CHICKEN PASTILLA
cinnamon	DATE PASTE
cinnamon	COCONUT PUNCH
cinnamon	RAS-EL-HANOUT (SPICE MIX)
cinnamon	RATATOUILLE (COURGETTE, TOMATO, POTATO)
cinnamon	VEGETABLE SAMOSA
cinnamon	BOLOGNESE SAUCE (WITHOUT FAT)
cinnamon	WORCESTERSHIRE SAUCE
cinnamon	CANE SUGAR SYRUP SUCH AS CANADOU
cinnamon	MOROCCAN CHORBA SOUP
cinnamon	MOROCCAN HARIRA SOUP
cinnamon	LAMB TAGINE WITH PRUNES
cinnamon	BEEF TAGINE
cinnamon	APPLE TARTE TATIN
cinnamon	POULTRY TERRINE
cinnamon	CARAMELISED PORK RIBS
caper	GRIBICHE SAUCE
caper	OLIVE TAPENADE
caper	TARTAR SAUCE (MAYONNAISE, HERBS, CAPERS)
fenugreek	BSISSA
fenugreek	MASSALE SPICE

Note: As the recipe database only includes recipes reported as home-made, it could not be used to identify industrial foods that may include plants containing coumarin. These were therefore identified from the OQALI database. However, by default, home-made recipes were also applied to industrial recipes to ensure that all possible sources of coumarin were covered.

3.1.3 Plants consumed as industrial food ingredients (OQALI database)

In the OQALI industrial product database, the following plants were identified as being used as ingredients: cinnamon, fenugreek, caper and lavender, alone or in combination. The list of industrial product subcategories containing these ingredients and consumed in the INCA3 study is provided in Annex AST 3.

3.1.4 Plants that may contain coumarin used as ingredients in food supplements (food supplements database)

Lastly, from the data available in the food supplement composition database, 52 different ingredients and constituents were identified that may correspond to the list of plants in Table 15. Of these, 29 were selected by the expert rapporteurs responding to the request. They are listed in Table 19. These ingredients and constituents are included in the five products listed in Table 20, reported as consumed in the INCA3 study. Each product was mentioned only once in the INCA3 study.

Table 19. List of food supplement ingredients likely to contain coumarin selected as part of the request for scientific and technical support

INGREDIENT DESCRIPTION	SELECTED by the experts
FLAVOURING: CINNAMON	X
NATURAL FLAVOURING: LEMON BALM	
CINNAMON	X
CINNAMON	X
CINNAMON TINCTURE	X
CINNAMOMUM ZEYLANICUM	X
CINNAMON EXTRACT	X
FENUGREEK EXTRACT	X
LEMON BALM LEAF EXTRACT (MELISSA OFFICINALIS)	
LEMON BALM LEAF EXTRACT (MELISSA OFFICINALIS) (MALTODEXTRIN)	
TONKA BEAN EXTRACT	X
SWEET CLOVER EXTRACT	X
LEMON BALM EXTRACT (MELISSA OFFICINALIS)	
HYDROGLYCERIN PLANT EXTRACTS: FENUGREEK, SPIRULINA, TURMERIC, GINGER, CHICORY, WATERCRESS	X
CINNAMON, DRIED BARK EXTRACT (CINNAMOMUM ZEYLANICUM): MALTODEXTRIN CARRIER	X
LEMON BALM, DRIED EXTRACT	
FENUGREEK	X
LEMON BALM LEAF	
CINNAMON ESSENTIAL OIL	X
CEYLON CINNAMON ESSENTIAL OIL	X
CEYLON CINNAMON ESSENTIAL OIL	X
LAVENDER ESSENTIAL OIL	X
LAVENDER	X
BLEND OF ESSENTIAL OILS: PEPPERMINT ESSENTIAL OIL, CLOVE ESSENTIAL OIL, THYME ESSENTIAL OIL, LAVENDER ESSENTIAL OIL, CINNAMON ESSENTIAL OIL	X
SWEET CLOVER, DRIED EXTRACT	X
LEMON BALM	
LEMON BALM (PURIFIED LEAF)	
FENUGREEK SEED POWDER TRIGONELLA FOENUM-GRAECUM	X
HERBAL TINCTURE (ALCOHOL, SAGE, THYME, LAVENDER)	X
3 P-COUMAROYLQUINIC ACID	
4 P-COUMARIC QUINIC ACID	
4 P-COUMAROYLQUINIC ACID	
5 P-COUMARIC QUINIC ACID	
7 P-COUMAROYL GLUCOSE ACID	
CINNAMOYL GLUCOSE ACID	
COUMARIC QUINIC ACID	
COUMAROYL GLUCOSE ACID	
P-COUMARIC ACID	
TRANS CINNAMIC ACID	
CEYLON CINNAMON	X
CEYLON CINNAMON (BARK)	X
COUMARIN AND COUMARIN DERIVATIVES	X
COUMARINS AND COUMARIN DERIVATIVES	X
COUMAROYLQUINIC DERIVATIVES	

INGREDIENT DESCRIPTION	SELECTED by the experts
COUMARIC ACID DERIVATIVES	
CINNAMON EXTRACT	X
FENUGREEK EXTRACT (TRIGONELLA FOENUM-GRAECUM)	X
LEMON BALM LEAF EXTRACT, DRIED PLANT EQUIVALENT	
LEMON BALM EXTRACT	

INGREDIENT DESCRIPTION	SELECTED by the experts
LEMON BALM EXTRACT (DRIED PLANT EQUIVALENT) FOR BLUE NIGHT CAPSULE	
TOTAL HYDROXYCINNAMATES (DERIVATIVES)	X
LAVENDER	X
LEMON BALM	
LEMON BALM LEAF POWDER	

Table 20. Food supplements consumed in the INCA3 study and including a plant ingredient that may contain coumarin

Product type	Product code	Product name	Manufacturer's name	Ingredients used in the product
Food supplement	308	AROMA VITAL TONUS AMPOULES	OMEGA PHARMA N.V.	CINNAMOMUM ZEYLANICUM
Food supplement	59	BLOOD SUGAR COMPLEX, CINNAMON CHROMIUM ZINC	FLEURANCE NATURE	CEYLON CINNAMON DRIED BARK EXTRACT (CINNAMOMUM ZEYLANICUM): MALTODEXTRIN CARRIER; FENUGREEK SEED POWDER (TRIGONELLA FOENUM-GRAECUM)
Food supplement	301	OLEOCAPS WITH ESSENTIAL OILS	PRANAROM INTERNATIONAL	CEYLON CINNAMON (BARK)
Food supplement	71	PEDIAKID APPETIT-TONUS RASPBERRY FLAVOUR SYRUP	INELDEA	FENUGREEK
Food supplement	103	SOOTHING WINTER SYRUP WITH ORGANIC PROPOLIS	_	LAVENDER

Given the small number of consumption acts, coumarin intakes from FSs were not taken into account to estimate population exposure.

3.2 Estimate of coumarin exposure in the French population (excluding food supplements)

Using the data described above, exposure was estimated for children and adults, according to the two methods for selecting consumption acts (A and B) and the two exposure scenarios (1 and 2). Table 10 shows the results for the total population and Table 11 for exposed individuals only.

- **For the total population:**

Table 21. Description of coumarin exposure (in mg/d/kg bw) of the total French population, estimated using consumption data from the INCA3 study, according to the two exposure scenarios and the two methods for selecting consumption acts

	Number	Method	Scenario	Mean	Median	P75	P95
Adults	2121	**A**	**1**	0.00161	0.00000	0.00015	0.00766
			2	0.00155	0.00000	0.00014	0.00766

		B	**1**	0.00215	0.00000	0.00041	0.01207
			2	0.00205	0.00000	0.00033	0.01041
Children	1993	**A**	**1**	0.00210	0.00000	0.00028	0.00939
			2	0.00191	0.00000	0.00028	0.00684
		B	**1**	0.00413	0.00009	0.00284	0.01666
			2	0.00304	0.00009	0.00159	0.01277

The method of selecting the consumption acts had an effect on the estimate of the average daily exposure to coumarin, which was higher with Method B. On the other hand, the exposure varied little with the exposure scenario: it was slightly higher when applying the regulatory levels. Thus, the estimated average daily exposure to coumarin varied between:

- $1.6 \cdot 10^{-3}$ mg/d/kg bw (Method A) and $2.2 \cdot 10^{-3}$ mg/d/kg bw (Method B) in adults;
- $1.9 \cdot 10^{-3}$ mg/d/kg bw (Method A) and $4.1 \cdot 10^{-3}$ mg/d/kg bw (Method B) in children.

In adults, the 95th percentile was around 0.008 mg/d/kg bw for Method A and 0.012 mg/d/kg bw for Method B. In children, the 95th percentile varied according to the scenario between 0.007 and 0.009 mg/d/kg bw for Method A and between 0.013 and 0.017 mg/d/kg bw for Method B.

- **For exposed individuals only:**

Table 22. Description of coumarin exposure (in mg/d/kg bw) of exposed individuals only, estimated using consumption data from the INCA3 study, according to two exposure scenarios and two methods of selecting consumption acts

	Number	Method	Scenario	Mean	Median	P75	P95
Adults	861	**A**	**1**	0.00404	0.00026	0.00199	0.01977
			2	0.00388	0.00025	0.00145	0.01977
		B	**1**	0.00484	0.00073	0.00288	0.01977
			2	0.00463	0.00053	0.00277	0.02127
Children	944	**A**	**1**	0.00482	0.00037	0.00128	0.01742
			2	0.00437	0.00036	0.00103	0.01743
		B	**1**	0.00756	0.00213	0.00724	0.02521
			2	0.00556	0.00112	0.00515	0.02006

For exposed individuals only, the average daily exposure was:

- around $4.0 \cdot 10^{-3}$ mg/d/kg bw (Method A) and $4.7 \cdot 10^{-3}$ mg/d/kg bw (Method B) in adults;
- between $4.4 \cdot 10^{-3}$ and $4.8 \cdot 10^{-3}$ mg/d/kg bw (Method A) and $5.6 \cdot 10^{-3}$ and $7.6 \cdot 10^{-3}$ mg/d/kg bw (Method B) in children.

The 95th percentile for exposed individuals only was a maximum of 0.021 mg/d/kg bw in adults and 0.025 mg/d/kg bw in children.

3.3 Estimate of the rates at which the thresholds set for chronic and acute risks are exceeded in the French population

With Method A, around 40% of adults and 43% of children are exposed to coumarin via their diet (excluding food supplements). Exposure rates are higher with Method B: 44% in adults and 55% in children. In contrast, less than 0.5% of individuals reached the thresholds for chronic or acute risk (Table 12), regardless of the selection method or exposure scenario.

Table 23. Rates of exposed individuals and rates at which the thresholds determined for chronic risk and acute risk are exceeded in the French population, based on consumption data from the INCA3 study and according to two scenarios

	N	Method	Rate of exposed individuals		Rate at which the "chronic risk" threshold (TDI) is exceeded		Rate at which the "acute risk" threshold (3xTDI) is exceeded	
			Scenario 1	Scenario 2	Scenario 1	Scenario 2	Scenario 1	Scenario 2
Adults	2121	A	39.9% [37.1-42.9]	39.9% [37.1-42.9]	0.2% [0.03-0.9] *(n = 4)*	0.2% [0.03-0.9] *(n = 4)*	0%	0%
		B	44.3% [41.3-47.2]	44.3% [41.3-47.2]	0.2% [0.03-0.9] *(n = 4)*	0.2% [0.03-0.9] *(n = 4)*	0%	0%
Children	1993	A	43.6% [40.4-46.8]	43.6% [40.4-46.8]	0.2% [0.04-0.7] *(n = 3)*	0.2% [0.04-0.7] *(n = 3)*	0.04% [0.01-0.2] *(n = 2)*	0.04% [0.01-0.2] *(n = 2)*
		B	54.7% [51.2-58.1]	54.7% [51.2-58.1]	0.4% [0.2-1.1] *(n = 7)*	0.2% [0.05-0.7] *(n = 3)*	0.04% [0.01-0.2] *(n = 2)*	0.04% [0.01-0.2] *(n = 2)*

3.4 Identification of foods contributing to coumarin exposure

The main food groups contributing more than 5% to coumarin intakes were, in descending order:

- In adults:
  - **Condiments, herbs, spices and sauces**, from 50% (Method B) to 60% (Method A);
  - **Croissant-like pastries, pastries, cakes and sweet biscuits**, from 15% (Method B) to 19% (Method A);
  - **Meat dishes**, up to 10% (Method B only);
  - **Hot beverages**, up to 10% (Method B only);
  - **Soups and broths**, up to 5% (Method B only).
- In children:
  - **Condiments, herbs, spices and sauces**, from 19-25% (Method B) to around 35% (Method A);
  - **Hot beverages**, up to 21-28% (Method B only);
  - **Croissant-like pastries, pastries, cakes and sweet biscuits**, from 15% (Method B) to 21-28% (Method A);
  - **Breakfast cereals**, up to 10% (Method B – Scenario 1 only);
  - **Seeds and nuts** up to 8% (Method A) and 5% (Method B);
  - **Infant milks and drinks** (Method B, Scenario 1 only) up to 13%.

The average exposures and contributions associated with each food group are detailed in Annexes AST 4 (adults) and AST 5 (children).

Method B for selecting consumption acts had a strong impact on the groups identified, with a much higher contribution from hot beverages (hot chocolate), as well as from breakfast cereals in children. Method A, taking into account the information collected on the type of food, seemed to be closer to the reality of the foods contributing to the coumarin intake of the population.

3.5 Description of exposed individuals

The characteristics of exposed individuals according to the two methods of selecting consumption acts (A and B) and the two exposure scenarios (1 and 2) are described in Table 13 for adults and in ns *(not significant);* *** *(p<0.001)*

Table 1425 for children.

It should be noted that the exposed individuals are the same regardless of the exposure scenario. They differ only in the method of selecting the consumption acts.

The results show that only age was associated with the fact of being exposed to coumarin:

- In adults: there was a higher proportion of individuals aged 18-44 and a lower proportion of individuals aged 45-64 or 65-79 among those exposed;
- In children: there was a higher proportion of individuals aged 4 to 6 years among those exposed.

Table 24. Characteristics of adults exposed to coumarin in the population living in France, based on consumption data from the INCA3 study and according to two scenarios

Variable	Categories	n	Method A (Scenario 1 or 2)			Method B (Scenario 1 or 2)		
			Exposed pop.	Non-exposed pop.	Test	Exposed pop.	Non-exposed pop.	Test
Age	18-44 years	783	56.2% [51.2-61.2]	39.0% [34.9-43.4]	***	57.5% [52.7-62.2]	36.7% [32.8-40.8]	***
	45-64 years	827	31.0% [26.5-35.9]	40.2% [35.5-45.1]		31.2% [26.9-35.8]	40.8% [36.4-45.4]	
	65-79 years	511	12.8% [10.3-15.6]	20.8% [18.3-23.5]		11.4% [9.2-13.9]	22.5% [19.9-25.4]	
Sex	Male	887	47.4% [43.2-51.6]	49.2% [45.8-52.7]	ns	48.5% [44.4-52.6]	48.5% [44.8-52.3]	ns
	Women	1234	52.6% [48.4-56.8]	50.8% [47.3-54.2]		51.5% [47.8-55.6]	51.5% [47.8-55.2]	
Region	Ile-de-France	262	13.6% [10.6-17.3]	18.3% [15.0-22.0]	ns	14.2% [11.4-17.6]	18.1% [14.4-22.6]	ns
	North-West	466	19.1% [14.0-25.5]	20.3% [15.4-26.3]		19.4% [14.3-25.8]	20.1% [15.2-26.2]	
	North-East	517	31.2% [25.5-37.5]	25.0% [20.0-30.7]		30.4% [24.9-36.6]	25.1% [20.0-31.0]	
	South-East	473	19.4% [14.1-26.3]	18.1% [14.0-23.0]		18.7% [13.5-25.4]	18.5% [14.3-23.7]	
	South West	403	16.7% [12.0-22.7]	18.4% [13.9-24.1]		17.2% [12.7-22.9]	18.2% [13.4-24.2]	

Table 25. Characteristics of children exposed to coumarin in the population living in France, based on consumption data from the INCA3 study and according to two scenarios

Variable	Categories	n	Method A (Scenario 1 or 2)			Method B (Scenario 1 or 2)		
			Exposed pop.	Non-exposed pop.	Test	Exposed pop.	Non-exposed pop.	Test
Age	0-11 months	59	1.5% [0.4-5.4]	7.2% [5.1-10.3]	**	1.3% [0.4-4.3]	8.9% [6.3-12.5]	***
	1-3 years	159	13.6% [9.9-18.4]	18.2% [14.3-23.0]		14.1% [10.8-18.2]	18.8% [14.1-24.6]	
	4-6 years	345	20.3% [17.0-24.0]	15.3% [12.9-18.1]		21.1% [18.2-24.4]	13.0% [10.5-16.1]	
	7-10 years	481	22.8% [19.3-26.9]	22.4% [19.2-26.0]		23.3% [20.1-26.8]	21.8% [18.1-26.1]	
	11-14 years	543	26.1% [21.8-30.9]	20.4% [17.6-23.5]		24.1% [20.3-28.3]	21.4% [18.0-25.3]	
	15-17 years	406	15.7% [12.8-19.1]	16.4% [13.6-19.7]		16.2% [13.4-19.3]	16.0% [13.0-19.6]	
Sex	Boy	1020	51.6% [46.8-56.3]	50.8% [46.3-55.3]	ns	50.6% [46.5-54.7]	51.8% [46.5-57.0]	ns
	Girl	973	48.4% [43.7-53.2]	49.2% [44.7-53.7]		49.4% [45.3-53.5]	48.2% [43.0-53.5]	
Region	Ile-de-France	302	17.3% [12.9-22.7]	17.2% [14.0-20.9]	ns	18.9% [14.8-23.9]	15.2% [11.5-19.8]	ns
	North West	455	19.0% [14.1-25.0]	20.7% [15.5-27.3]		20.0% [15.2-26.0]	19.9% [14.5-26.7]	
	North East	516	28.4% [22.5-35.3]	26.7% [21.2-33.2]		27.2% [21.7-33.6]	27.8% [21.6-35.0]	
	South East	416	18.5% [13.2-25.2]	20.5% [16.0-25.9]		17.9% [13.2-23.9]	21.7% [16.8-27.6]	
	South West	304	16.8% [12.2-22.9]	14.9% [11.2-19.4]		16.0% [11.5-21.7]	15.4% [11.4-20.6]	

4. Limitations of the results

The data used to calculate exposure were those observed from just three days of food consumption. Moreover, the exposure estimate was based on a limited number of observations (2788 for Method A and 3578 for Method B). It may not therefore accurately reflect the population's habitual consumption over a long period of time and its usual level of exposure. While the average exposure value is *a priori* robust, it is very likely that the high percentiles are overestimated. Similarly, given the small number of consumption acts, the results for contributing foods are also likely to be very sensitive to certain very high amounts found in a few individuals.

Annex AST 1: Foods mentioned in the INCA3 study that correspond to plants that may contain coumarin

COUMARIN FOOD CATEGORY	INCA3 FOOD CODE	INCA3 FOOD DESCRIPTION	CHARACTERISTIC INGREDIENT (FACET 06)	STANDARD RECIPE CODE	STANDARD RECIPE DESCRIPTION	NB CITATION A	NB CITATION B
1	2896	cheesecake	**speculoos**			2	2
1	1382	filled macaroon	salted butter caramel; **speculoos**			-	1
1	1843	vitamin-fortified **gingerbread**				-	1
2	587	unspecified breakfast cereal	**cinnamon**	2917	milk-based hot chocolate	1	1
2	587	unspecified breakfast cereal	**cinnamon**			4	4
2	597	unspecified muesli	honey; banana; kiwi; **cinnamon**			1	1
2	3432	muesli flakes such as special muesli	unspecified chocolate; chocolate chip; hazelnut; vanilla; honey; **cinnamon**			1	1
3	4244	cupcake	**speculoos**			1	1
4	416	cream dessert such as Danette	**speculoos**			1	1
4	416	cream dessert such as Danette	vanilla; **speculoos**			1	1
4	443	rice cake	**cinnamon**			3	3
4	1292	fruit tart (fruit only without cream)	damson plum; **cinnamon**			1	1
4	1292	fruit tart (fruit only without cream)	unspecified plum; **speculoos**			1	1
4	1345	unspecified dry biscuit	**cinnamon**			1	1
4	1921	sweet doughnut with fruit compote filling	apple; **cinnamon**			1	1
4	1953	unspecified sweet cake	**cinnamon**; carrot			3	3
4	1953	unspecified sweet cake	orange; vanilla; hazelnut; **cinnamon**; carrot; nutmeg			1	1
4	2140	ice-cream such as a log	damson plum; **cinnamon**			1	1
4	2296	frozen yoghurt	pistachio; **speculoos**			1	1
4	3343	unfilled macaroon	almond; **cinnamon**			1	1
4	4012	unspecified fruit tart	apple; **cinnamon**			1	1
4	4039	fruit tiramisu	lemon; **speculoos**			1	1
4	4039	fruit tiramisu	strawberry; **speculoos**			2	2
4	4039	fruit tiramisu	raspberry; **speculoos**			1	1
4	4039	fruit tiramisu	**speculoos**			1	1
4	2953	(fruit) compote	apple; fig; **cinnamon**			-	1
4	3004	ice-cream in a tub or pot	coffee; **speculoos**			-	1
4	3004	ice-cream in a tub or pot	caramel; **speculoos**			-	2
4	3004	ice-cream in a tub or pot	strawberry; **speculoos**			-	1

COUMARIN FOOD CATEGORY	INCA3 FOOD CODE	INCA3 FOOD DESCRIPTION	CHARACTERISTIC INGREDIENT (FACET 06)	STANDARD RECIPE CODE	STANDARD RECIPE DESCRIPTION	NB CITATION A	NB CITATION B
4	3004	ice-cream in a tub or pot	**speculoos**			-	3
4	3004	ice-cream in a tub or pot	**speculoos**; cookie			-	1
4	3004	ice-cream in a tub or pot	vanilla; **speculoos**			-	1
4	3023	jellied flan	**speculoos**			-	2
5	2468	**cinnamon**		6060	tomato stuffed with minced meat	1	1
5	2468	**cinnamon**		9014	beef tagine	1	1
5	2468	**cinnamon**		9032	lamb tagine with prunes	1	1
5	2468	**cinnamon**		9033	lamb tagine with vegetables	1	1
5	2468	**cinnamon**		9052	coconut chicken curry	1	1
5	2468	**cinnamon**		9055	turkey and mushroom stir-fry	1	1
5	2468	**cinnamon**		9524	tajine with vegetables	1	1
5	2468	**cinnamon**		9561	potato and vegetable gratin with meat/poultry	2	2
5	2468	**cinnamon**				46	46
6	1492	black tea	**cinnamon**			1	1
6	1492	black tea	orange; **cinnamon**			15	15
6	1492	black tea	orange; unspecified spices; **cinnamon**			1	1
6	1496	infusion	**cinnamon**			1	1
6	1496	infusion	**cinnamon**; unspecified chocolate			1	1
6	1496	infusion	**cinnamon**; unspecified candied fruit or peel; ginger			3	3
6	1496	infusion	lemon; **cinnamon**; clove			1	1
6	1496	infusion	orange blossom; **cinnamon**			1	1
6	1496	infusion	unspecified fruit; apple; **cinnamon**			3	3
6	1496	infusion	mint; **cinnamon**			3	3
6	1496	infusion	mint; rosehip; orange; **cinnamon**			1	1
6	1496	infusion	mint; rosehip; liquorice; orange; **cinnamon**			1	1
6	1496	infusion	mint; unspecified spices; **cinnamon**			1	1
6	1496	infusion	honey; orange; **cinnamon**; ginger			1	1
6	1496	infusion	lemon balm; **cinnamon**; cardamom			1	1
6	1496	infusion	lemon balm; orange; **cinnamon**; almond; clove; cardamom			3	3

COUMARIN FOOD CATEGORY	INCA3 FOOD CODE	INCA3 FOOD DESCRIPTION	CHARACTERISTIC INGREDIENT (FACET 06)	STANDARD RECIPE CODE	STANDARD RECIPE DESCRIPTION	NB CITATION A	NB CITATION B
6	1496	infusion	lemon balm; linden; blackberry; **cinnamon**; unspecified plant; flower; liquorice			1	1
6	1496	infusion	orange; **cinnamon**			5	5
6	1496	infusion	orange; **cinnamon**; unspecified plant			1	1
6	1496	infusion	apple; **cinnamon**			20	20
6	1496	infusion	verbena; fennel; camomile; rose petal; orange blossom; **cinnamon**			1	1
6	1496	infusion	verbena; unspecified plant; fennel; camomile; rose petal; orange; **cinnamon**			2	2
6	2455	green tea	unspecified citrus; **cinnamon**			3	3
6	2455	green tea	**cinnamon**			9	9
6	2455	green tea	lemon; **cinnamon**; ginger			1	1
6	2500	unspecified tea	**cinnamon**			4	4
6	2500	unspecified tea	honey; lemon; **cinnamon**			1	1
6	2500	unspecified tea	orange; **cinnamon**			5	5
6	4032	white tea	**cinnamon**			1	1
6	4033	red tea	**cinnamon**			1	1
6	4033	red tea	unspecified red fruit; **cinnamon**			1	1
7	1414	fruit or herbal syrup to be diluted such as Teisseire	**cinnamon**	4256	mint type syrup with water	2	2
7	4256	mint type syrup with water	**cinnamon**	4256	mint type syrup with water	2	2
7	1676	unspecified hot sauce	tomato; green olive; tuna; **caper**	6037	pasta other sauce	1	1
7	51	**caper**		9018	veal blanquette	1	1
7	5012	**fenugreek**		9086	fish salad	1	1
7	51	**caper**		9183	tuna pasta salad with raw vegetables	1	1
7	1756	tartar sauce (mayonnaise, herbs, capers)	mayonnaise; unspecified herb; **caper**	9240	filet o fish	6	6
7	1756	tartar sauce (mayonnaise, herbs, capers)	mayonnaise; unspecified herb; **caper**	9257	curry veggie burger	1	1
7	51	**caper**		9389	Greek salad	1	1
7	51	**caper**		9399	chicken Caesar salad	1	1
7	51	**caper**		9517	ham pasta salad	2	2
7	51	**caper**		9519	raw vegetable salad	1	1
7	51	**caper**		9566	surimi salad	1	1

COUMARIN FOOD CATEGORY	INCA3 FOOD CODE	INCA3 FOOD DESCRIPTION	CHARACTERISTIC INGREDIENT (FACET 06)	STANDARD RECIPE CODE	STANDARD RECIPE DESCRIPTION	NB CITATION A	NB CITATION B
7	51	**caper**				5	5
7	1134	fruit jam	apple; **cinnamon**			1	1
7	1371	chewing gum	**cinnamon**			1	1
7	1676	unspecified hot sauce	tomato; onion; cumin; **cinnamon**			1	1
7	1756	tartar sauce (mayonnaise, herbs, capers)	mayonnaise; unspecified herb; **caper**			5	14
7	1885	milk chocolate bar	**speculoos**			2	2
7	3402	lavender honey				37	37
7	3790	unspecified cold sauce	garlic; vinegar; anchovy; **caper**			1	1
7	4097	fruit wine	vanilla; **cinnamon**; nuts			1	1
7	4349	pizza	mozzarella; button mushroom; red pepper; black olive; **caper**			1	1
7	4349	pizza	tomato; mozzarella; unspecified mushroom; ham; yellow pepper; green pepper; red pepper; **caper**			1	1
7	4350	savoury cake	unspecified squash; ginger; **cinnamon**			2	2
7	5012	**fenugreek**				1	1
7	5018	**tonka bean**				1	1

Annex AST 2. List of home-made recipes consumed in the INCA3 study, and including as a direct or indirect ingredient plants that may contain coumarin, according to the INCA3 study recipe database

COUMARIN FOOD CATEGORY	INCA3 FOOD CODE	INCA3 FOOD DESCRIPTION	RECIPE CODE	RECIPE DESCRIPTION	INGREDIENT SEARCHED FOR	NB CITATION A	NB CITATION B
1	1274	gingerbread	CL00516	GINGERBREAD	**cinnamon**	22	44
1	1913	crunchy brown-sugar biscuit such as speculoos	AF00514	BISCUIT SUCH AS SPECULOOS	**cinnamon**	2	2
1	3457	nonette	CL00514	NONETTE	**cinnamon**	3	3
4	1293	fruit tart such as tatin	DM00550	APPLE TARTE TATIN	**cinnamon**	16	16
4	1296	baklava	ME00711	BAKLAVA	**cinnamon**	1	1
4	2194	gazelle horn	ME00689	GAZELLE HORN	**cinnamon**	3	3
4	2953	(fruit) compote	ES00573	APPLE COMPOTE (SWEETENED WITH A NATURAL SWEETENER SUCH AS STEVIA)	**cinnamon**	2	2
4	2953	(fruit) compote	JG00545	PEAR COMPOTE (WITHOUT ADDED SUGAR)	**cinnamon**	6	6
4	3350	makrout	ME00695	MAKROUT	**cinnamon**	3	3
4	3540	speculoos spread	MB00569	SPECULOOS SPREAD	**cinnamon**	10	10
4	4242	king's cake with fruit	JG00502	KING'S CAKE WITH APPLE	**cinnamon**	9	9
5	3383	tandoori spice mix	ES00554	TANDOORI SPICE MIX	**cinnamon**	4	4
5	3385	couscous spice mix	ME00772	RAS-EL-HANOUT (SPICE MIX)	**cinnamon**	20	20
5	3390	5-spice mix	JRETY00499	5-SPICE MIX	**cinnamon**	4	4
5	3391	4-spice mix	SC00500	4-SPICE MIX	**cinnamon**	17	18
6	5022	milk tea	ES00574	MILK TEA	**cinnamon**	1	1
7	898	unspecified sausage	ES00536	SAUSAGE (PORK)	**cinnamon**	230	227
7	898	unspecified sausage	ES00537	SAUSAGE (PORK, BEEF)	**cinnamon**	4	4
7	898	unspecified sausage	ME00769	SAUSAGE (POULTRY)	**cinnamon**	12	12
7	898	unspecified sausage	ME00770	SAUSAGE (BEEF)	**cinnamon**	6	6
7	899	sausage meat	ES00580	SAUSAGE MEAT	**cinnamon**	155	153
7	919	galantine	MB00510	GALANTINE	**cinnamon**	4	4
7	920	breaded ham knuckle	ME00775	BREADED HAM KNUCKLE	**cinnamon**	5	5
7	922	mortadella	ME00776	MORTADELLA	**cinnamon**	25	24
7	937	unspecified pâté	ES00530	PATE (PORK, DUCK)	**cinnamon**	55	55

COUMARIN FOOD CATEGORY	INCA3 FOOD CODE	INCA3 FOOD DESCRIPTION	RECIPE CODE	RECIPE DESCRIPTION	INGREDIENT SEARCHED FOR	NB CITATION A	NB CITATION B
7	938	meat terrine	ME00567	pork terrine	**cinnamon**	1	1
7	938	meat terrine	ME00567	pork terrine	**cinnamon**	15	15
7	938	meat terrine	ME00568	POULTRY TERRINE	**cinnamon**	7	7
7	942	liver pâté with mushrooms	ME00537	LIVER PÂTÉ WITH MUSHROOMS	**cinnamon**	2	1
7	942	liver pâté with mushrooms	ME00537	LIVER PÂTÉ WITH MUSHROOMS	**cinnamon**	1	1
7	943	pâté en croûte	ME00604	PÂTÉ EN CROÛTE	**cinnamon**	63	63
7	950	garlic sausage	ES00535	GARLIC SAUSAGE	**cinnamon**	64	63
7	1227	cane sugar syrup such as Canadou	JG00538	CANE SUGAR SYRUP SUCH AS CANADOU	**cinnamon**	8	8
7	1731	ketchup	ME00665	KETCHUP	**cinnamon**	940	878
7	1761	gribiche sauce	MVB00507	GRIBICHE SAUCE	**caper**	1	1
7	1860	meat puff pastry	ME00590	MEAT PUFF PASTRY	**cinnamon**	4	4
7	1860	meat puff pastry	ME00590	MEAT PUFF PASTRY	**cinnamon**	9	9
7	1867	chicken samosa	ME00572	CHICKEN SAMOSA	**cinnamon**	7	7
7	1888	pork kebab	CL00511	PORK KEBAB	**cinnamon**	10	10
7	1906	meatball	ME00509	PORK AND BEEF MEATBALL	**cinnamon**	9	9
7	1906	meatball	ME00510	PORK MEATBALL	**cinnamon**	11	11
7	2363	barbecue sauce	MVB00506	BARBECUE SAUCE	**cinnamon**	46	46
7	2414	ravioli	DM00507	CHEESE RAVIOLI	**cinnamon**	2	2
7	2414	ravioli	DM00507	CHEESE RAVIOLI	**cinnamon**	24	24
7	2781	Caribbean blood sausage	ME00648	CARIBBEAN BLOOD SAUSAGE	**cinnamon**	5	5
7	2839	whole lacquered duck	ME00551	WHOLE LACQUERED DUCK	**cinnamon**	4	4
7	3083	chestnut stuffing	ME00650	CHESTNUT STUFFING	**cinnamon**	2	2
7	3430	whole-grain mustard	MB00509	WHOLE-GRAIN MUSTARD	**cinnamon**	88	88
7	3653	caramelised pork ribs	ME00569	CARAMELISED PORK RIBS	**cinnamon**	4	4
7	3695	purée (vegetables)	MB00518	BROCCOLI PUREE	**cinnamon**	14	14
7	3722	ratatouille	ME00552	RATATOUILLE (COURGETTE, TOMATO, POTATO)	**cinnamon**	7	7
7	3783	beef samosa	ME00570	BEEF SAMOSA	**cinnamon**	16	16

COUMARIN FOOD CATEGORY	INCA3 FOOD CODE	INCA3 FOOD DESCRIPTION	RECIPE CODE	RECIPE DESCRIPTION	INGREDIENT SEARCHED FOR	NB CITATION A	NB CITATION B
7	3785	vegetable samosa	ME00573	VEGETABLE SAMOSA	**cinnamon**	4	3
7	3807	cocktail sauce (mayonnaise and ketchup)	MB00577	COCKTAIL SAUCE	**cinnamon**	9	9
7	3807	cocktail sauce (mayonnaise and ketchup)	MB00577	COCKTAIL SAUCE	**cinnamon**	9	9
7	3822	mushroom cream sauce	MB00651	MUSHROOM CREAM SAUCE	**cinnamon**	52	52
7	3823	onion cream sauce	MB00651	ONION CREAM SAUCE	**cinnamon**	4	4
7	3830	Worcestershire sauce	JG00543	WORCESTERSHIRE SAUCE	**cinnamon**	11	11
7	3918	Moroccan harira soup	ME00621	MOROCCAN HARIRA SOUP	**cinnamon**	3	3
7	3928	Moroccan chorba soup	CL00564	MOROCCAN CHORBA SOUP	**cinnamon**	12	12
7	4008	black olive tapenade	MB00562	OLIVE TAPENADE	**caper**	25	25
7	4295	planter's punch	DM00499	ORANGE PLANTER'S PUNCH	**cinnamon**	10	10
7	4296	coconut punch	DM00563	COCONUT PUNCH	**cinnamon**	2	2
7	4299	ti punch	JR00514	TI PUNCH	**cinnamon**	2	2
7	4363	Alsatian pie (pork, egg, mushroom and onion)	JR00521	ALSATIAN PIE (PORK, EGG, MUSHROOM AND ONION)	**cinnamon**	2	2
7	5078	meatloaf	JR00501	MEATLOAF	**cinnamon**	1	1
7	5085	liver mousse	JR00510	LIVER MOUSSE	**cinnamon**	1	1
7	5119	bsissa	ES00539	BSISSA	**fenugreek**	2	2
7	5189	lamb briouat	JR00502	LAMB BRIOUAT	**cinnamon**	1	1
7	5200	fried vegetable spring roll	DM00508	FRIED VEGETABLE SPRING ROLL	**cinnamon**	1	1
7	5201	chicken pastilla	JR00517	CHICKEN PASTILLA	**cinnamon**	1	1
7	898	unspecified sausage	ES00536	SAUSAGE (PORK)	**cinnamon**	-	1

Annex AST 3. List of industrial products consumed in the INCA3 study, and including as an ingredient plants that may contain coumarin, according to the OQALI database

COUMARIN FOOD CATEGORY	INCA3 FOOD CODE	INCA3 FOOD DESCRIPTION	OQALI SUBCATEGORY CODE	OQALI SUBCATEGORY DESCRIPTION	INGREDIENT SEARCHED FOR	NB CITATION A	NB CITATION B
1	1274	gingerbread	23	Gingerbreads	cinnamon	50	28
1	1382	filled macaroon	854	Frozen macaroons	cinnamon	1	-
1	1843	vitamin-fortified gingerbread	23	Gingerbreads	cinnamon	1	-
1	1913	crunchy brown-sugar biscuit such as speculoos	404	Speculoos	cinnamon	117	117
1	2896	cheesecake	861	Cheesecakes	cinnamon	-	1
1	3457	nonette	23	Gingerbreads	cinnamon	1	1
2	587	unspecified breakfast cereal	6	Chocolate-flavoured cereals	cinnamon	-	2
2	620	Nesquik-type chocolate cereal	6	Chocolate-flavoured cereals	cinnamon	-	9
2	2317	chocolate powder (classic) such as Nesquik	279	Sweetened cocoa powders	cinnamon	4	3
2	2430	Filled cereals such as Trésor	8	Filled cereals	cinnamon	-	3
2	2822	cocoa powder such as Van Houten	279	Sweetened cocoa powders	cinnamon	-	1
2	2866	chocolate cereal such as Crunch	6	Chocolate-flavoured cereals	cinnamon	-	8
2	2868	chocolate cornflake cereal	6	Chocolate-flavoured cereals	cinnamon	-	3
2	2869	chocolate wheat flake cereal such as Chocapic	6	Chocolate-flavoured cereals	cinnamon	-	32
2	2870	chocolate puffed rice cereal such as Coco Pops	6	Chocolate-flavoured cereals	cinnamon	-	22
2	2873	chocolate cereal	6	Chocolate-flavoured cereals	cinnamon	-	16
2	2917	milk-based hot chocolate	279	Sweetened cocoa powders	cinnamon	-	5
2	2919	unspecified hot chocolate	279	Sweetened cocoa powders	cinnamon	-	1
2	2920	water-based hot chocolate	279	Sweetened cocoa powders	cinnamon	-	1
2	5114	cereal chocolate powder such as Banania	279	Sweetened cocoa powders	cinnamon	-	2
2	6004	hot chocolate made from baby milk	695	Instant cereals	cinnamon	-	1
2	6007	baby milk and baby flour	695	Instant cereals	cinnamon	1	2
3	522	unspecified white bread	260	Plain white breads	cinnamon	-	1
3	707	(plain) white bread	260	Plain white breads	cinnamon	4	4
3	1273	meringue	387	Assorted biscuits	cinnamon	2	2
3	1302	unspecified waffle	342	Thin filled waffles	cinnamon	22	22
3	1305	ordinary brioche	851	Other brioches	cinnamon	-	1
3	1340	Alsatian chinois type cream-filled brioche	851	Other brioches	cinnamon	-	3

COUMARIN FOOD CATEGORY	INCA3 FOOD CODE	INCA3 FOOD DESCRIPTION	OQALI SUBCATEGORY CODE	OQALI SUBCATEGORY DESCRIPTION	INGREDIENT SEARCHED FOR	NB CITATION A	NB CITATION B
3	1343	unspecified biscuit	409	Other shortbreads	cinnamon	-	1
3	1345	unspecified dry biscuit	728	Fruit biscuits	cinnamon	-	4
3	1357	unspecified chocolate biscuit	22	Chocolate-filled wafers	cinnamon	-	4
3	1366	madeleine with filling	28	Moist cakes with fruit filling	cinnamon	-	1
3	1380	unspecified wafer	22	Chocolate-filled wafers	cinnamon	-	1
3	1822	Tropézienne tart	851	Other brioches	cinnamon	1	1
3	2371	Saint Genix type praline brioche	851	Other brioches	cinnamon	-	1
3	2450	chocolate-filled wafer	22	Chocolate-filled wafers	cinnamon	-	2
3	2643	unspecified dry sweet biscuit	728	Fruit biscuits	cinnamon	-	2
3	3166	waffle with brown sugar filling	342	Thin filled waffles	cinnamon	11	10
3	3168	waffle ice-cream cone, plain	342	Thin filled waffles	cinnamon	-	1
3	3176	chocolate coated wafer such as Schoks	22	Chocolate-filled wafers	cinnamon	-	1
3	3490	(plain) white crustless bread	260	Plain white breads	cinnamon	4	2
4	213	plain yoghurt	465	Artificially-sweetened yoghurts and fermented milks	cinnamon	-	1
4	217	yoghurt drink such as Yop	465	Artificially-sweetened yoghurts and fermented milks	cinnamon	-	1
4	438	dessert mousse	340	Desserts	cinnamon	2	4
4	445	semolina cake	219	Mixes for other dairy-based desserts	cinnamon	-	1
4	1229	unspecified ice-cream (ice-cream)	497	Frozen dessert for sharing	cinnamon	-	1
4	1230	unspecified ice-cream (ice-cream, sorbet, water ice)	497	Frozen dessert for sharing	cinnamon	-	1
4	1238	ice-cream cone such as Cornetto	494	Ice-cream cone > or = 80ml	cinnamon	-	3
4	1585	chocolate fondant	340	Desserts	cinnamon	-	1
4	1953	unspecified sweet cake	234	Mixes for plain cakes	cinnamon	1	1
4	2140	ice-cream such as a log	497	Frozen dessert for sharing	cinnamon	-	1
4	2154	fruit crumble	936	Apple and similar tarts	cinnamon	-	1
4	2953	(fruit) compote	153	Fruit desserts	cinnamon	1	9
4	2953	(fruit) compote	152	Low-sugar (light) fruit compotes	cinnamon	-	8
4	3004	ice-cream in a tub or pot	484	Luxury bulk ice-cream	cinnamon	9	1
4	3004	ice-cream in a tub or pot	496	Ice-cream tub > or = 80ml	cinnamon	-	12
4	3009	ice-cream with dark chocolate coating such as Magnum	493	Ice-cream stick > or = 80ml	cinnamon	-	1
4	3015	ice-cream with chocolate centre such as Mystère	495	Sundae and frozen dessert	cinnamon	-	1

COUMARIN FOOD CATEGORY	INCA3 FOOD CODE	INCA3 FOOD DESCRIPTION	OQALI SUBCATEGORY CODE	OQALI SUBCATEGORY DESCRIPTION	INGREDIENT SEARCHED FOR	NB CITATION A	NB CITATION B
4	3023	jellied flan	225	Mixes for jellied dairy-based desserts	cinnamon	2	2
4	3053	ice-cream with biscuit such as Viennetta	497	Frozen dessert for sharing	cinnamon	-	1
4	3156	moist cake	340	Desserts	cinnamon	1	1
4	4012	unspecified fruit tart	936	Apple and similar tarts	cinnamon	-	1
4	4018	fruit tart with pastry cream	936	Apple and similar tarts	cinnamon	-	2
4	4158	flavoured yoghurt	465	Artificially-sweetened yoghurts and fermented milks	cinnamon	-	3
4	4159	fruit yoghurt	465	Artificially-sweetened yoghurts and fermented milks	cinnamon	-	2
4	4161	stirred fruit yoghurt, such as Velouté Fruix	465	Artificially-sweetened yoghurts and fermented milks	cinnamon	-	1
4	4166	flavoured yoghurt with bifidus such as Activia Saveur	465	Artificially-sweetened yoghurts and fermented milks	cinnamon	-	1
6	2917	milk-based hot chocolate	756	Capsules	cinnamon	6	562
6	2920	water-based hot chocolate	756	Capsules	cinnamon	-	4
7	1	potato	555	Canned cooked meats	cinnamon	1	-
7	1	potato	830	Fish with vegetables and starchy foods	lavender	1	-
7	18	endive salad	363	Meat_vegetables	cinnamon	-	1
7	38	green bean	777	Legumes	caper	-	1
7	53	carrot	362	Meat_starchy_foods	caper	1	1
7	53	carrot	830	Fish with vegetables and starchy foods	lavender	-	1
7	74	button mushroom	363	Meat_vegetables	cinnamon	-	1
7	88	broad bean	840	Cooked cereals and pulses	cinnamon	2	-
7	102	unspecified mixed vegetables	777	Legumes	caper	-	4
7	105	mixed garden vegetables	777	Vegetables	caper	-	1
7	107	flageolet	1024	Canned pulses and cereals	cinnamon	1	1
7	107	flageolet	840	Cooked cereals and pulses	cinnamon	-	1
7	111	dry kidney bean	1024	Canned pulses and cereals	cinnamon	1	-
7	478	unspecified pasta	362	Meat_starchy_foods	caper	-	1
7	493	tortellini	666	Other pasta with meat/fish	cinnamon	-	1
7	500	wonton	969	Exotic fried products	cinnamon	-	1
7	504	long-grain white rice	362	Meat_starchy_foods	caper	1	-
7	507	fragrant rice	362	Meat_starchy_foods	caper	1	1
7	509	polenta	840	Cooked cereals and pulses	cinnamon	4	2

COUMARIN FOOD CATEGORY	INCA3 FOOD CODE	INCA3 FOOD DESCRIPTION	OQALI SUBCATEGORY CODE	OQALI SUBCATEGORY DESCRIPTION	INGREDIENT SEARCHED FOR	NB CITATION A	NB CITATION B
7	627	puff-pastry salted cracker	209	Puff pastries	lavender	1	1
7	652	unspecified cocktail puff	871	Assortments and other cocktail snacks	cinnamon	4	4
7	678	Potato crisps (classic)	662	Classic and wavy crisps	cinnamon	2	-
7	765	veal cutlet	363	Meat_vegetables	cinnamon	-	1
7	788	unspecified cut of pork	362	Meat_starchy_foods	caper	-	1
7	808	unspecified lardon	363	Meat_vegetables	cinnamon	1	-
7	823	plain lardon	362	Meat_starchy_foods	caper	-	1
7	847	chicken breast	362	Meat_starchy_foods	caper	1	1
7	850	chicken nugget	761	Breaded meat	cinnamon	1	-
7	895	blood pudding	757	Meat without sauce	cinnamon	1	1
7	897	Lyon sausage	410	Cooked sausages	cinnamon	1	-
7	898	unspecified sausage	362	Meat_starchy_foods	cinnamon	1	-
7	898	unspecified sausage	435	Emulsified sausages (pork)	cinnamon	-	3
7	903	Strasbourg sausage	435	Emulsified sausages (pork)	cinnamon	2	4
7	915	saveloy	410	Cooked sausages	cinnamon	2	1
7	921	Aosta raw-cured ham	538	Raw-cured ham	cinnamon	4	3
7	922	mortadella	410	Cooked sausages	cinnamon	-	1
7	929	unspecified ham and meat cuts	538	Raw-cured ham	cinnamon	-	1
7	934	Bayonne raw-cured ham	538	Raw-cured ham	cinnamon	4	3
7	941	liver pâté	549	Pork liver pâtés or mousses	caper	2	-
7	942	liver pâté with mushrooms	549	Pork liver pâtés or mousses	cinnamon	-	1
7	950	garlic sausage	410	Cooked sausages	cinnamon	1	2
7	957	unspecified raw-cured ham	538	Raw-cured ham	cinnamon	7	2
7	1060	surimi stick	607	Filled Surimi	caper	11	10
7	1062	savoury shrimp fritter	969	Exotic fried products	cinnamon	-	3
7	1063	breaded fish	773	Breaded fish	caper	-	2
7	1091	sunflower oil	362	Meat_starchy_foods	caper	-	1
7	1091	sunflower oil	839	Starchy foods and vegetables	cinnamon	-	1
7	1099	unsalted butter	759	Meat in sauce	caper	1	-
7	1191	chocolate bar with nougat such as Toblerone	298	White chocolate with inclusions	cinnamon	-	1

COUMARIN FOOD CATEGORY	INCA3 FOOD CODE	INCA3 FOOD DESCRIPTION	OQALI SUBCATEGORY CODE	OQALI SUBCATEGORY DESCRIPTION	INGREDIENT SEARCHED FOR	NB CITATION A	NB CITATION B
7	1301	blini	871	Assortments and other cocktail snacks	cinnamon	-	1
7	1468	non-carbonated fruit beverage such as Oasis	328	Non-carbonated fruit beverages (sugar > 2.5g/100ml)	cinnamon	-	2
7	1674	unspecified sauce	616	Emulsified sauces	caper	1	3
7	1674	unspecified sauce	969	Exotic fried products	cinnamon	1	-
7	1692	pepper sauce (flour, fat, water, pepper)	616	Emulsified sauces	caper	-	2
7	1706	curry sauce with coconut milk	616	Emulsified sauces	caper	-	1
7	1713	bearnaise sauce (egg, water, butter, wine, tarragon, shallot)	616	Emulsified sauces	caper	-	4
7	1714	hollandaise sauce (egg, water, butter)	616	Emulsified sauces	caper	-	2
7	1731	ketchup	617	Ketchups	cinnamon	-	62
7	1755	aioli (mayonnaise, garlic)	616	Emulsified sauces	caper	-	1
7	1756	tartar sauce (mayonnaise, herbs, capers)	616	Emulsified sauces	caper	9	-
7	1763	rouille sauce	616	Emulsified sauces	caper	1	-
7	1778	ordinary mustard	362	Meat_starchy_foods	caper	-	1
7	1857	sausage roll	870	Puff pastries with meat or fish, meat in pastry	caper	-	1
7	1864	cheese puff pastry	869	Vegetarian puff pastries	caper	-	1
7	1866	fried pork spring roll	968	fried spring rolls with fish sauce	cinnamon	-	1
7	1875	ham and cheese puff pastry	870	Puff pastries with meat or fish, meat in pastry	caper	-	1
7	1886	white chocolate bar	298	White chocolate with inclusions	cinnamon	-	1
7	1906	meatball	605	Cooked meats	cinnamon	1	-
7	1906	meatball	757	Meat without sauce	cinnamon	3	3
7	1908	snail	775	Other starters	caper	-	1
7	1917	gougère	951	Choux pastries and gougères	cinnamon	-	2
7	1990	cocktail petit four	871	Assortments and other cocktail snacks	cinnamon	1	-
7	1990	cocktail petit four	876	Cocktail aumonière bundles	cinnamon	1	-
7	1990	cocktail petit four	952	Party loaves and cocktail canapés	cinnamon	7	2
7	2124	cordon bleu	761	Breaded meat	cinnamon	3	-
7	2124	cordon bleu	972	Cordons bleus	cinnamon	3	1
7	2173	sweet and sour sauce	619	Non-emulsified sauces	cinnamon	1	-
7	2363	barbecue sauce	619	Non-emulsified sauces	cinnamon	2	2
7	2402	fruit juice with milk such as Danao	328	Non-carbonated fruit beverages (sugar > 2.5g/100ml)	cinnamon	-	1

COUMARIN FOOD CATEGORY	INCA3 FOOD CODE	INCA3 FOOD DESCRIPTION	OQALI SUBCATEGORY CODE	OQALI SUBCATEGORY DESCRIPTION	INGREDIENT SEARCHED FOR	NB CITATION A	NB CITATION B
7	2411	single cream	759	Meat in sauce	caper	-	1
7	2414	ravioli	570	Canned raviolis	cinnamon	-	2
7	2461	parsley	839	Starchy foods and vegetables	cinnamon	-	1
7	2493	unspecified soup	647	Ethnic soups	cinnamon	-	1
7	2763	unspecified chocolate confectionery	320	Chocolate assortments	cinnamon	1	6
7	3000	semi-thick fresh cream	759	Meat in sauce	caper	-	1
7	3205	French gruyère	570	Canned raviolis	cinnamon	-	1
7	3206	unspecified gruyère	570	Canned raviolis	cinnamon	1	-
7	3207	guacamole	453	Other spreads	caper	-	2
7	3239	Italian raw-cured ham	538	Raw-cured ham	cinnamon	1	2
7	3322	green lentil	840	Cooked cereals and pulses	cinnamon	-	1
7	3374	vegetable mix for couscous	553	Canned vegetables	caper	-	1
7	3374	vegetable mix for couscous	777	Vegetables	caper	-	1
7	3447	fried crab and shrimp spring roll	774	Ethnic fried products	cinnamon	-	1
7	3447	fried crab and shrimp spring roll	968	fried spring rolls with fish sauce	cinnamon	-	1
7	3448	fried chicken spring roll	968	fried spring rolls with fish sauce	cinnamon	-	1
7	3476	unspecified onion	757	Meat without sauce	cinnamon	1	-
7	3546	pasta (classic)	362	Meat_starchy_foods	caper	2	-
7	3593	unspecified soy-based ready-to-eat meal	840	Cooked cereals and pulses	cinnamon	-	2
7	3595	commercial baby meal	697	Meals with vegetables and/or starchy food and meat/fish	cinnamon	-	1
7	3720	cooked quinoa	840	Cooked cereals and pulses	cinnamon	-	1
7	3722	ratatouille	777	Vegetables	caper	-	2
7	3723	ravioli	775	Other starters	caper	-	1
7	3785	vegetable samosa	969	Exotic fried products	cinnamon	-	1
7	3790	unspecified cold sauce	616	Emulsified sauces	caper	2	1
7	3793	Mexican sauce (for snack biscuits)	616	Emulsified sauces	caper	1	1
7	3805	sauce for burgers	616	Emulsified sauces	caper	2	3
7	3806	sauce for chips	616	Emulsified sauces	caper	-	1
7	3809	white sauce for kebabs	616	Emulsified sauces	caper	2	1
7	3824	curry cream sauce	616	Emulsified sauces	caper	-	3

COUMARIN FOOD CATEGORY	INCA3 FOOD CODE	INCA3 FOOD DESCRIPTION	OQALI SUBCATEGORY CODE	OQALI SUBCATEGORY DESCRIPTION	INGREDIENT SEARCHED FOR	NB CITATION A	NB CITATION B
7	3832	sweetened soy sauce	362	Meat_starchy_foods	caper	1	-
7	3849	cooked semolina	1024	Canned pulses and cereals	cinnamon	3	1
7	3878	(vegetable) soup	633	Starchy soups	cinnamon	-	8
7	3878	(vegetable) soup	643	Pumpkin soups	cinnamon	-	1
7	3882	miso soup	647	Ethnic soups	cinnamon	-	1
7	3883	minestrone soup	633	Starchy soups	cinnamon	-	1
7	3885	Chinese soup	647	Ethnic soups	cinnamon	2	3
7	3912	Thai soup	647	Ethnic soups	cinnamon	-	2
7	4007	green olive tapenade	453	Other spreads	caper	-	1
7	4063	breaded veal cutlet	761	Breaded meat	cinnamon	1	-
7	4133	vegetable sauté	777	Vegetables	caper	-	1
7	4136	cabbage for sauerkraut	553	Canned vegetables	caper	1	2
7	4228	smoked salmon	818	Smoked_salmon_trout	caper	3	1
7	4228	smoked salmon	871	Assortments and other cocktail snacks	cinnamon	1	-
7	4324	samurai sauce (mayonnaise, ketchup, chilli paste)	616	Emulsified sauces	caper	-	1
7	4332	country-style sauté (potato, beef, onion)	839	Starchy foods and vegetables	cinnamon	1	-
7	4345	4-season pizza (tomato, ham, cheese, vegetable)	478	Vegetable/vegetarian pizzas	caper	-	1
7	4349	pizza	476	Other meat-based pizzas	cinnamon	1	-
7	4349	pizza	480	Cheese and ham pizzas	cinnamon	1	1
7	4349	pizza	477	Seafood pizzas	caper	-	12
7	4357	unspecified savoury quiche	866	Tarts with meat or fish	caper	1	-
7	5063	cereal steak	840	Cooked cereals and pulses	cinnamon	2	-
7	5159	Hannibal sauce	616	Emulsified sauces	caper	-	1
7	6039	petit salé with lentils	758	Meat with starchy foods	caper	1	1
7	6062	avocado and tuna salad	954	Canned mixed salads	caper	1	1
7	9013	chili con carne	362	Meat_starchy_foods	caper	2	-
7	9018	veal blanquette	759	Meat in sauce	caper	1	1
7	9034	pork with caramel	362	Meat_starchy_foods	caper	1	1
7	9090	tuna salad with carrot and sweetcorn	954	Canned mixed salads	caper	1	-
7	9091	tuna and pasta salad with sweetcorn and tomato	954	Canned mixed salads	caper	1	-

COUMARIN FOOD CATEGORY	INCA3 FOOD CODE	INCA3 FOOD DESCRIPTION	OQALI SUBCATEGORY CODE	OQALI SUBCATEGORY DESCRIPTION	INGREDIENT SEARCHED FOR	NB CITATION A	NB CITATION B
7	9146	tabbouleh tomato onion lemon pepper mint	927	Tabbouleh	cinnamon	2	2
7	9147	tabbouleh tomato onion lemon chicken	927	Tabbouleh	cinnamon	2	1
7	9148	tabbouleh carrot sweetcorn tomato onion chickpea	927	Tabbouleh	cinnamon	1	-
7	9159	lasagne Bolognese	768	Pasta Bolognese	cinnamon	-	1
7	9181	surimi pasta salad	926	Pasta salads	fenugreek	1	-
7	9223	chicken mayonnaise salad sandwich	686	Chicken and raw vegetable sandwiches	caper	-	1
7	9280	ham and cheese crepe with bechamel sauce	868	Crepes, pancakes and pastillas with meat or fish	cinnamon	2	-
7	9328	cauliflower gratin with bechamel sauce	450	Other gratins	cinnamon	1	-
7	9342	tomato stuffed with sausage meat	363	Meat_vegetables	cinnamon	-	2
7	9348	moussaka	450	Other gratins	cinnamon	1	-
7	9375	gratin dauphinois	362	Meat_starchy_foods	caper	1	-
7	9400	Piedmontese salad	954	Canned mixed salads	caper	4	2
7	9402	lentil salad with lardons	369	Other starchy salads	cinnamon	1	-
7	9547	pancake with ham/lardon	868	Crepes, pancakes and pastillas with meat or fish	cinnamon	1	-

Annex AST 4. Contribution of food groups from the INCA3 nomenclature to coumarin exposure (mg/d/kg bw and %) according to the scenario, for adults in the INCA3 study

		Method A				Method B			
		Scenario 1		Scenario 2		Scenario 1		Scenario 2	
	INCA3 groups	Mean exp.	% expo	Mean exp.	% expo	Mean exp.	% expo	Mean exp.	% expo
1	Refined bread and dried bread products	0.000003	0.2%	0.000000	0.0%	0.000002	0.1%	0.000001	0.1%
2	Wholegrain or semi-wholegrain bread and dried bread products	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
3	Breakfast cereals and cereal bars	0.000004	0.3%	0.000000	0.0%	0.000051	2.4%	0.000004	0.2%
4	Refined pasta, rice, wheat and other cereals	0.000005	0.3%	0.000005	0.3%	0.000001	0.0%	0.000001	0.0%
5	Wholegrain and semi-wholegrain pasta, rice, wheat and other cereals	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
6	Croissant-like pastries, pastries, cakes and sweet biscuits	0.000305	18.9%	0.000245	15.8%	0.000311	14.5%	0.000279	13.6%
7	Milk	0.000001	0.0%	0.000001	0.0%	0.000001	0.0%	0.000001	0.0%
8	Yoghurt and fromage blanc	0.000000	0.0%	0.000000	0.0%	0.000004	0.2%	0.000001	0.1%
9	Cheeses	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
10	Dairy-based and cream desserts	0.000004	0.3%	0.000007	0.5%	0.000007	0.3%	0.000019	0.9%
11	ice-creams, frozen desserts and sorbets	0.000003	0.2%	0.000001	0.1%	0.000007	0.3%	0.000002	0.1%
12	Animal fats	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
13	Vegetable fats	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
14	Eggs and egg dishes	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
15	Meat (excl. poultry)	0.000005	0.3%	0.000005	0.3%	0.000006	0.3%	0.000006	0.3%
16	Poultry	0.000002	0.1%	0.000002	0.1%	0.000002	0.1%	0.000002	0.1%
17	Delicatessen meats	0.000039	2.4%	0.000039	2.5%	0.000037	1.7%	0.000037	1.8%
18	Fish	0.000004	0.2%	0.000004	0.2%	0.000001	0.0%	0.000001	0.0%
19	Crustaceans & molluscs	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
20	Offal	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
21	Vegetables	0.000007	0.4%	0.000007	0.4%	0.000040	1.9%	0.000040	1.9%
22	Pulses	0.000000	0.0%	0.000000	0.0%	0.000002	0.1%	0.000002	0.1%
23	Potatoes and other tubers	0.000001	0.0%	0.000001	0.0%	0.000000	0.0%	0.000000	0.0%
24	Fresh and dried fruit	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
25	Fruit purees and fruits in syrup	0.000003	0.2%	0.000004	0.3%	0.000010	0.5%	0.000008	0.4%
26	Seeds and nuts	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%

		Method A				Method B			
		Scenario 1		Scenario 2		Scenario 1		Scenario 2	
INCA3 groups		**Mean exp.**	**% expo**	**Mean exp.**	**% expo**	**Mean exp.**	**% expo**	**Mean exp.**	**% expo**
27	Confectionery and chocolate	0.000001	0.0%	0.000001	0.1%	0.000003	0.1%	0.000003	0.2%
28	Sugar and sweeteners	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
29	Bottled water	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
30	Tap water	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
31	Soft drinks	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
32	Fruit and vegetable juices	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
33	Alcoholic beverages	0.000002	0.1%	0.000002	0.1%	0.000002	0.1%	0.000002	0.1%
34	Hot beverages	0.000053	3.3%	0.000053	3.4%	0.000211	9.8%	0.000198	9.6%
35	Soups and broths	0.000040	2.5%	0.000040	2.6%	0.000111	5.2%	0.000111	5.4%
36	Meat dishes	0.000057	3.5%	0.000057	3.7%	0.000210	9.8%	0.000210	10.2%
37	Fish dishes	0.000007	0.4%	0.000007	0.4%	0.000019	0.9%	0.000019	0.9%
38	Vegetable dishes	0.000010	0.6%	0.000010	0.7%	0.000013	0.6%	0.000013	0.6%
39	Potato, cereal or pulse dishes	0.000017	1.1%	0.000017	1.1%	0.000012	0.6%	0.000012	0.6%
40	Sandwiches, pizzas, pies, savoury pastries and biscuits	0.000054	3.4%	0.000054	3.5%	0.000061	2.8%	0.000061	3.0%
41	Condiments, herbs, spices and sauces	0.000985	61.1%	0.000985	63.6%	0.001021	47.6%	0.001021	49.7%
42	Replacements for animal products made from soy and other plants	0.000002	0.1%	0.000002	0.1%	0.000000	0.0%	0.000000	0.0%
43	Prepared dishes and desserts for infants	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
44	Infant milks and drinks	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
	TOTAL	**0.001613**	**100%**	**0.001549**	**100%**	**0.002146**	**100%**	**0.002054**	**100%**

Annex AST 5. Contribution of food groups from the INCA3 nomenclature to coumarin exposure (mg/d/kg bw and %) according to the scenario, for children in the INCA3 study

		Method A				Method B			
		Scenario 1		Scenario 2		Scenario 1		Scenario 2	
	INCA3 groups	Mean exp.	% expo	Mean exp.	% expo	Mean exp.	% expo	Mean exp.	% expo
1	Refined bread and dried bread products	0.000021	1.0%	0.000001	0.0%	0.000020	0.5%	0.000001	0.0%
2	Wholegrain or semi-wholegrain bread and dried bread products	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
3	Breakfast cereals and cereal bars	0.000026	1.2%	0.000001	0.1%	0.000392	9.5%	0.000028	0.9%
4	Refined pasta, rice, wheat and other cereals	0.000018	0.9%	0.000018	1.0%	0.000006	0.2%	0.000006	0.2%
5	Wholegrain and semi-wholegrain pasta, rice, wheat and other cereals	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
6	Croissant-like pastries, pastries, cakes and sweet biscuits	0.000584	27.8%	0.000403	21.1%	0.000635	15.4%	0.000473	15.5%
7	Milk	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
8	Yoghurt and fromage blanc	0.000000	0.0%	0.000000	0.0%	0.000029	0.7%	0.000009	0.3%
9	Cheeses	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
10	Dairy-based and cream desserts	0.000007	0.4%	0.000019	1.0%	0.000006	0.1%	0.000014	0.5%
11	ice-creams, frozen desserts and sorbets	0.000001	0.1%	0.000000	0.0%	0.000007	0.2%	0.000002	0.1%
12	Animal fats	0.000000	0.0%	0.000000	0.0%	0.000002	0.0%	0.000002	0.1%
13	Vegetable fats	0.000000	0.0%	0.000000	0.0%	0.000001	0.0%	0.000001	0.0%
14	Eggs and egg dishes	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
15	Meat (excl. poultry)	0.000006	0.3%	0.000006	0.3%	0.000010	0.2%	0.000010	0.3%
16	Poultry	0.000032	1.5%	0.000032	1.7%	0.000011	0.3%	0.000011	0.4%
17	Delicatessen meats	0.000059	2.8%	0.000059	3.1%	0.000065	1.6%	0.000065	2.1%
18	Fish	0.000000	0.0%	0.000000	0.0%	0.000145	3.5%	0.000145	4.8%
19	Crustaceans & molluscs	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
20	Offal	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
21	Vegetables	0.000000	0.0%	0.000000	0.0%	0.000038	0.9%	0.000038	1.2%
22	Pulses	0.000001	0.0%	0.000001	0.0%	0.000002	0.0%	0.000002	0.1%
23	Potatoes and other tubers	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
24	Fresh and dried fruit	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
25	Fruit purees and fruits in syrup	0.000034	1.6%	0.000054	2.8%	0.000090	2.2%	0.000088	2.9%

		Method A				Method B			
		Scenario 1		Scenario 2		Scenario 1		Scenario 2	
INCA3 groups		**Mean exp.**	**% expo**	**Mean exp.**	**% expo**	**Mean exp.**	**% expo**	**Mean exp.**	**% expo**
26	Seeds and nuts	0.000168	8.0%	0.000168	8.8%	0.000168	4.1%	0.000168	5.5%
27	Confectionery and chocolate	0.000027	1.3%	0.000054	2.8%	0.000028	0.7%	0.000055	1.8%
28	Sugar and sweeteners	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
29	Bottled water	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
30	Tap water	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
31	Soft drinks	0.000000	0.0%	0.000000	0.0%	0.000008	0.2%	0.000008	0.2%
32	Fruit and vegetable juices	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
33	Alcoholic beverages	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
34	Hot beverages	0.000004	0.2%	0.000004	0.2%	0.000874	21.1%	0.000856	28.1%
35	Soups and broths	0.000003	0.1%	0.000003	0.1%	0.000066	1.6%	0.000066	2.2%
36	Meat dishes	0.000009	0.4%	0.000009	0.5%	0.000002	0.1%	0.000002	0.1%
37	Fish dishes	0.000202	9.6%	0.000202	10.6%	0.000051	1.2%	0.000051	1.7%
38	Vegetable dishes	0.000008	0.4%	0.000008	0.4%	0.000013	0.3%	0.000013	0.4%
39	Potato, cereal or pulse dishes	0.000061	2.9%	0.000061	3.2%	0.000021	0.5%	0.000021	0.7%
40	Sandwiches, pizzas, pies, savoury pastries and biscuits	0.000085	4.0%	0.000085	4.4%	0.000124	3.0%	0.000124	4.1%
41	Condiments, herbs, spices and sauces	0.000718	34.2%	0.000718	37.7%	0.000775	18.7%	0.000775	25.5%
42	Replacements for animal products made from soy and other plants	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%	0.000000	0.0%
43	Prepared dishes and desserts for infants	0.000000	0.0%	0.000000	0.0%	0.000002	0.0%	0.000002	0.1%
44	Infant milks and drinks	0.000027	1.3%	0.000000	0.0%	0.000545	13%	0.000008	0.3%
	TOTAL	**0.002100**	**100%**	**0.001906**	100.0%	**0.004134**	**100%**	**0.003042**	**100%**