ANSES Opinion
Request No 2019-SA-0136

The Director General

Maisons-Alfort, 1 April 2020

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

on a case of fatal fulminant hepatitis associated with consumption of the food supplement Slim Metabol®

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
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 1 April 2020 shall prevail.

1. BACKGROUND AND PURPOSE OF THE REQUEST

Under the nutrivigilance scheme it set up in 2009, ANSES received a report of a severe adverse effect (Level 4 severity)[1] likely to be associated with consumption of the food supplement Slim Metabol® marketed by the Italian company Zuccari. Causality in this case, registered in the nutrivigilance database under the number 2019-214, was found to be likely.

Given the severity of the adverse effect described (fatal fulminant hepatitis), ANSES felt it necessary to bring this case to the attention of the public and health professionals, with a view to improving protection of consumer health.

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)".

This expert appraisal falls within the scope of the Expert Committee (CES) on "Human Nutrition". The draft opinion, validated by the Working Group on "Nutrivigilance" on 8 October 2019, was sent to the CES on 31 October 2019. The conclusions were adopted by the CES at its meeting on 14 November 2019.

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

[1] The scale of severity in nutrivigilance goes from Level 1 (low severity) to Level 4 (death).

3. ANALYSIS AND CONCLUSIONS OF THE WG AND THE CES

As part of its nutrivigilance scheme, ANSES received a report of fatal fulminant hepatitis likely to be associated with consumption of the food supplement Slim Metabol® marketed by the Italian company Zuccari. This case was registered under the number 2019-214.

3.1. Product composition

According to the package leaflet, 37 mL of Slim Metabol® contains 334 mg red yeast rice (including 10 mg monacolin K), 600 mg olive (*Olea europea*), 200 mg rhubarb (*Rheum palmatum*), 500 mg hibiscus (*Hibiscus sabdariffa*), 100 mg cola (*Cola acuminata*), 400 mg *Garcinia cambogia*, 50 mg moringa (*Moringa oleifera*), 1 mg nopal (*Opuntia ficus-indica*), 1 mg guggul (*Commiphora mukul*), 1 mg *Coleus forskohlii*, 1 mg green coffee (*Coffea arabica*), 1 mg shiitake (*Lentinula edodes*), 1 mg hawthorn (*Crataegus oxyacantha*), 1 mg rhodiola (*Rhodiola rosea*), 1 mg Siberian ginseng (*Eleutherococcus senticosus*), 1 mg cassia nomame (*Cassia mimosides*), 1 mg *Orthosiphon stamineus*, 1 mg caigua (*Cyclanthera pedata*), 1 mg maqui (*Aristotelia chilensis*), 2 mg blackcurrant (*Ribes nigrum*), 56.25 mg magnesium, 1.5 mg zinc, 40 µg chromium, 250 mg marine collagen and water.

3.2. Analysis of the product

The product Slim Metabol® was analysed by the Joint Laboratories Service (SCL) following a request from the French Customs' Observatory of Medicinal Products. The analysis revealed the presence of lovastatin and hydroxycitric acid (HCA), confirming the presence in the product of red yeast rice and *Garcinia cambogia*. No adulteration with any medicinal active substance was found.

3.3. Case description

This involved a 71-year-old woman (BMI 27.3 kg/m²) with high blood pressure, who had been treated with nebivolol for several years. She had no other known personal history, particularly regarding immune disorders.

In January 2019, she had started consuming the food supplement Slim Metabol®, taking 1 vial per day (37 mL of product to be diluted in 500 mL of water).

In April, she "felt unwell" and consulted her general practitioner. Biological examinations were carried out and revealed major abnormalities in liver biology.

On 21 April, the patient was hospitalised and would therefore have stopped the food supplement by this date at the latest.

On being hospitalised:

- liver biology showed acute hepatitis with predominant cytolysis: AST 1999 IU/L (normal: 5-35 IU/L), ALT 1792 IU/L (normal: 5-35 IU/L), GGT 72 IU/L (normal: < 35 IU/L), ALP 179 IU/L (normal: 35-100 IU/L), total bilirubin 269 µmol/L (normal: < 17 µmol/L), conjugated bilirubin 217 µmol/L (normal: 0 µmol/L), PT 44% (normal: 70-120%) and factor V normal;

- viral serologies were performed twice and were negative (hepatitis A, B, C, E, CMV, EBV, HIV, HSV, VZV);

- serum paracetamol levels were 2 mg/L (limit of quantification of the method);

- serum IgA and IgG were respectively 7 g/L (normal: 1-3.5 g/L) and 35 g/L (normal: 7-15 g/L);

- the autoantibody test found 1/320 positive anti-nuclear antibodies (ANAs), but no anti-smooth muscle antibodies (ASMAs) or other types of antibodies;

- a liver biopsy was performed. It suggested autoimmune hepatitis (AIH) with confluent hepatic necrosis, lymphoplasmacytic infiltrate, multinucleated hepatocytes, microvesicular steatosis and early-stage panlobular fibrosis;

- the thoracic-abdominal-pelvic computed tomography (CT) scan and hepatic Doppler ultrasound showed a dysmorphic liver and signs of portal hypertension. There was no evidence supporting a vascular or biliary disorder.

The diagnosis of AIH was initially accepted. The patient was placed on corticosteroids and azathioprine. Despite treatment, the situation deteriorated, resulting in a clinical picture of fulminant hepatitis (increased bilirubin, decreased factor V, encephalopathy).

On 11 May, the patient experienced neurological deterioration and a < 50% drop in factor V, leading the medical team to suggest a liver transplant. This was rejected because of excessive haemodynamic instability (relating to identification during the pre-transplant tests of an obstructive cardiomyopathy with diastolic dysfunction).

The patient was transferred to life support. She was placed on MARS™ albumin dialysis at a rate of three 8-hour sessions combined with extracorporeal dialysis. Despite a transient improvement after each session, the liver failure progressed.

On 17 May, sepsis was detected (positive *E. Coli* blood culture). This was treated with Augmentin, but the haemodynamic and renal status deteriorated.

The patient died four days later.

Doctors finally concluded as to fulminant hepatitis, of autoimmune and toxic origin, complicated by sepsis and multiple organ failure.

3.4. Causality

The food supplement's causality in the occurrence of fulminant hepatitis was analysed by applying the method defined in the revised ANSES opinion of 10 July 2019 on updating the method for determining causality in reports of adverse effects in nutrivigilance (ANSES 2019). It was established by the Working Group (WG) on "Nutrivigilance".

3.4.1. Intrinsic score

The chronological score refers to the time taken for the adverse effect to appear, its progression and its recurrence if the products are reintroduced. In this case, the onset time for the effect was found to be "compatible". Because the adverse effect was irreversible, progression was described as "suggestive". The Slim Metabol® was not reintroduced. Based on this information, the chronological score is C3[2].

The aetiological score is determined after establishing a differential diagnosis for the observed effect. In this case, the female sex, biology (ALT more than ten times normal, IgG more than three times normal, 1/320 anti-nuclear antibodies) and histology were in favour of AIH. On the other hand, the absence of AIH-specific antibodies, lack of response to corticosteroid and immunosuppressive therapy, and grade 2 microvesicular steatosis were suggestive of toxic hepatitis. The hypothesis of an autoimmune type hepatitis induced or facilitated by the toxin is a possibility. The aetiological score is therefore E2[3].

[2] The chronological score ranges from C0 (zero) to C4 (high).

[3] The aetiological score ranges from E0 (another cause was identified) to E3 (all common causes were ruled out or the assessed product was formally incriminated).

The intrinsic score, which results from the combination of the chronological score and the aetiological score, is therefore I3, meaning that the food supplement was likely responsible for the occurrence of fatal fulminant hepatitis[4].

3.4.2.Extrinsic score

The extrinsic causality score assesses the quality of the science demonstrating a causal relationship between consumption of an ingredient or a product and an adverse effect. It is based on data from the literature, on a given date. In this case, the literature search focused on the potential hepatotoxicity in humans of each ingredient in the food supplement Slim Metabol®.

- **Red yeast rice (RYR)**

Red yeast rice is a red mould grown on white rice. It contains monacolin K, also known as lovastatin, which has the chemical characteristics and pharmacological activity of statins (inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, an enzyme involved in cholesterol synthesis).

In February 2014, ANSES published an opinion on the risks associated with the presence of red yeast rice in food supplements (ANSES 2014). A search for clinical cases reporting hepatic adverse effects was conducted during this work. Table 1 below is an excerpt from the 2014 opinion.

Table 1: Case studies of adverse reactions relating to food supplements containing RYR (from ANSES 2014)

Reported adverse reaction, sex and age of the patient (dose consumed)	Medical history or risk factors	Presence of other ingredients than RYR in the product consumed	Related products taken	Progression of the adverse reaction	Reference
hepatitis in a 62-year-old woman taking RYR for four months (two 600 mg capsules twice a day)	asthma, allergic rhinitis, depression	unknown composition	montelukast sodium, fluoxetine	complete regression of the adverse reaction several months after discontinuing	Roselle *et al.* (2008)
sharp increase in transaminases in a 63-year-old woman taking RYR for at least six months (one 30 mg tablet per day)	moderate increase in transaminases two years previously under lovastatin, reversible on discontinuation	guggulsterol, sitosterol, chlorogenic acid, policosanol, vitamins C, E and B6, niacin, coenzyme Q, RYR (1 to 17 g)	not reported	complete regression of the adverse reaction on symptomatic treatment	Grieco *et al.* (2009)

This opinion states that the molecular mechanisms of increased transaminases associated with statins are unknown. Liver damage following treatment with statins, and especially with lovastatin (0.1 to 2.3% of cases with a persistent increase in transaminases to more than three times the normal level, with a dose-effect relationship), is thus essentially idiosyncratic, with an immunoallergic mechanism only rarely being reported (Björnsson, Jacobsen, and Kalaitzakis 2012).

Several hypotheses have been put forward, including intra-hepatocyte accumulation of HMG-CoA or inhibition of the synthesis of mevalonate or an active metabolite. The biological presentation is

[4] The intrinsic score ranges from I0 (excluded) to I4 (very likely).

usually cytolytic or mixed (cytolytic and cholestatic hepatitis). Rare cases of association with granulomatous hepatitis, lupus or cholangiolitis have been described with lovastatin (Cadranel *et al.* 2009).

In order to supplement these data and identify new clinical cases, a literature search for the period 2014-2019 was initiated. Two articles of interest were identified.

Loubser, Weider, and Drake (2019) report the case of a 64-year-old woman, not taking any medication, who developed acute hepatitis six weeks after starting a food supplement containing red yeast rice. A liver biopsy validated the hypothesis of liver damage induced by an active substance. After the patient stopped the red yeast rice and started methylprednisolone therapy, her liver enzymes returned to normal.

Between 2002 and 2015, the Italian natural health product surveillance scheme recorded ten reports of adverse liver effects following consumption of food supplements containing red yeast rice (Mazzanti *et al.* 2017). These reports are shown in Table 2.

Table 2: Cases of liver damage involving the consumption of red yeast rice identified by the Italian natural health product surveillance scheme (extract and translation from Mazzanti *et al.* 2017)

Sex, age	Product	Timeframe between ingestion and occurrence of symptoms	Clinical signs	Prior history/associated consumption	Progression of the adverse reaction
F, 68 years	Armolipid Plus	Around 2 weeks	Increase in liver enzymes	None	Recovery
M, 51 years	Policol 400	23 days	Acute cholestatic hepatitis	Also took Olivis, Nuovo 3D, Omega 3	Recovery
F, 42 years	Armolipid Plus	30 days	Acute hepatitis	Atenolol, levothyroxine, potassium canrenoate	Not specified
M, 35 years	Armolipid Plus	Around 60 days	Acute toxic hepatitis	None	Recovery
M, 36 years	Colest 500	76 days	Acute hepatitis	Omega 3 Modest alcohol consumption	Recovery
F, 49 years	Armolipid Plus	50 days	Acute hepatitis, epigastralgia, heartburn	None	Recovery
F, 68 years	Armolipid Plus	Around 1 year	Increase in transaminases	Statin intolerance and biliary lithiasis Levothyroxine, ursodeoxycholic acid	Recovery
F, 57 years	Armolipid Plus	60 days	Increase in ASTs	None	Recovery
F, 75 years	COLEX-MU	Not specified	Liver disorder	Indacaterol, mometasone furoate	Not specified
M, 53 years	Armolipid Plus	Not specified	Increase in transaminases	Not specified	Recovery

The extrinsic causality score for this component is B2[5].

- ***Garcinia cambogia* (Malabar tamarind)**

Garcinia cambogia (GC) extracts or products containing this plant are among the most popular food supplements on the weight-loss market. Its supposed properties are attributed to the hydroxycitric acid found in the pericarp of the fruit.

[5] The intrinsic causality score ranges from B0 to B2. A B2 score corresponds to a well-documented effect.

According to the ANSM, GC meets the definition of a medicinal product by function, because of its glucose-lowering and lipid-lowering properties. This plant is also monitored under the pharmacovigilance scheme. This led to the importation, preparation, prescription and dispensing of magistral, officinal and hospital preparations consisting of GC, as well as the prescription, dispensing and administration to humans of the GC plant being prohibited as of 12 April 2012, following a decision by the Director General of the ANSM (ANSM 2012).

Crescioli *et al.* (2018) described four cases of severe acute hepatitis in women who used this plant for weight loss. These cases came from the Italian vigilance scheme for natural health products. This article also provides a literature review of all clinical cases and series of cases of adverse effects involving oral consumption of GC extracts. Thirty-two articles were identified, of which 17 reported acute liver damage observed in fifty patients who had consumed food supplements containing GC or pure GC extracts. These different cases are listed in Table 3.

In a study of the long-term effects of GC in obese mice, Kim *et al.* (2013) observed that GC supplementation increased liver collagen accumulation, lipid peroxidation, transcription of genes related to oxidative stress (superoxide dismutase and glutathione peroxidase) and inflammatory responses (TNF-α and MCP-1), as well as plasma concentrations of liver enzymes.

The extrinsic causality score for this component is B2.

It is important to stress the major role of GC in the occurrence of fulminant hepatitis, similar to the clinical case reported in this opinion, with eleven cases collected. Only two cases involved another factor potentially responsible for hepatitis (hepatitis B and use of montelukast, a drug known for its hepatotoxicity). In the remaining cases, no alternative diagnosis to that of GC-induced hepatitis could be suggested, even though most of them involved a histological study of the liver. Eight cases had a context of autoimmune hepatitis but very atypical for this disease (isolated presence of anti-nuclear antibodies, no elevated gamma globulin, isolated presence of giant cells, etc.). It is therefore possible that the GC hepatotoxicity may involve an autoimmune mechanism, at least in some cases.

Table 3: Cases of liver damage involving consumption of *Garcinia cambogia* (adapted from Crescioli *et al.* 2018)

Bibliographic reference	Sex, age	Product Quantity	Duration of consumption	Clinical assessment	Prior history/ associated consumption	Progression of the adverse reaction	Comments
(Crescioli *et al.* 2018)	F, 61 years	Super Ananas Slim®[6] 1 dose/day	2 months	Cholestatic hepatitis	None	Recovery	-
	F, 39 years	Obless®[7] 1 capsule/day	1 month	Acute cholestatic hepatitis	High blood pressure, obesity, hiatus hernia Concomitant intake for 15 days of a magistral preparation (*Citrus aurantium*, *Rhodiola rosea*, *Orthosiphon stamineus*) Concomitant treatments: methyldopa, domperidone and omeprazole	Recovery	-
	F, 47 years	Thermo Giallo®[8] 2 capsules/day	1 month	Acute hepatitis	Hypothyroidism, high blood pressure, mild obesity Concomitant treatments: levothyroxine, enalapril	Recovery	-
	F, 52 years	Jill Cooper Be Slim®[9] 1 capsule/day	1 month	Acute hepatitis	none	Recovery	-
(Stevens, Qadri, and Zein 2005)	M, 27 years	Hydroxycut® 9 capsules/day	5 weeks	Acute hepatitis	None	Recovery	-
	M, 30 years	Hydroxycut® 9 capsules/day	5 days	Cholestatic hepatitis	none	Recovery	-

[6] Super Ananas Slim® contains GC, *Ananas comosus* and *Ilex paraguariensis*.
[7] Obless® contains *Citrus aurantium*, GC, *Orthosiphon stamineus* and *Griffonia simplicifolia*.
[8] Thermo Giallo® contains 50 µg chromium and 400 mg GC.
[9] Jill Cooper Be Slim® contains 400 mg of 60% GC extract and 400 mg of 50% green coffee extract.

Bibliographic reference	Sex, age	Product Quantity	Duration of consumption	Clinical assessment	Prior history/ associated consumption	Progression of the adverse reaction	Comments
(Actis *et al.* 2007)	F, 45 years	Topine®[10] Kalo®[11]	1 week	Fatal liver failure	Asthma, obesity Concomitant treatment: montelukast for 5 years	Death	The authors suspected GC to be the trigger for liver damage in a patient exposed to a hepatotoxic molecule, montelukast
(Elinav *et al.* 2007)	12 cases 11 F and 1 M Between 23 and 78 years of age	Herbalife products	11.9 months on average	Acute liver injury	1 patient with hepatitis B, 1 patient with primary biliary cirrhosis (PBC), 10 patients with no particular medical history A variety of medicinal products taken depending on the patients	11 recoveries 1 death following liver transplant (patient with hepatitis B)	3 patients resumed consumption of Herbalife products, leading to a reappearance of the liver disorders Liver biopsy performed in 4 patients Autoimmune antibodies detected in 3 patients
(Jones and Andrews 2007)	M, 19 years	Hydroxycut®	4 months	Acute liver injury	None	Recovery	-
(Schoepfer *et al.* 2007)	10 cases 6 F and 4 M Between 30 and 69 years of age	Herbalife weight-loss products	5 months on average	7 patients with hepatic necrosis, 1 patient with fulminant liver failure, 1 patient with hepatocellular damage, 1 patient with sinusoidal obstruction syndrome	1 patient positive for hepatitis A and B, 1 patient positive for hepatitis E, 1 patient with alcohol consumption Several patients were taking different medicinal products	8 recoveries 1 liver transplant 1 cirrhosis diagnosed	Not all implicated products contained GC Liver biopsy performed in 7 patients
(Dara, Hewett, and Lim 2008)	F, 40 years	Hydroxycut®[12] 6 capsules/day	1 week	Acute hepatitis	Hypothyroidism Concomitant treatment: levothyroxine	Recovery	-

[10] Topine® contains *Gymnema silvestris, GC*, bean pod, *Citrus aurantium*, chromium, carnitine and phenylalanine.
[11] Kalo® contains hydrolysed collagen, sodium hyaluronate, *Betula alba*, *Citrus aurantium*, *Magnolia officinalis, Bambusa vulgaris*, glutamine, L-Ornitine and magnesium pyruvate.
[12] Hydroxycut® contains calcium, chromium, potassium, GC, *Gymnema sylvestre*, phospholipids, *Rhodiola rosea*, green tea, white tea, oolong tea, caffeine.

Bibliographic reference	Sex, age	Product Quantity	Duration of consumption	Clinical assessment	Prior history/ associated consumption	Progression of the adverse reaction	Comments
	F, 33 years	Hydroxycut®12	2 weeks	Acute hepatitis	Pituitary adenoma Concomitant treatment: Ortho-Novum	Recovery	-
(McDonnell, Bhattacharya, and Halldorson 2009)	M, 25 years	Exilis®	One and a half weeks	Fulminant liver failure	None	Liver transplant	Liver biopsy performed
(Shim and Saab 2009)	M, 28 years	Hydroxycut®12 4 to 6 tablets/day	3 months	Hepatotoxicity	None Concomitant treatments: paracetamol, aspirin and caffeine 4 times a day for 10 days prior to admission	Recovery	The authors do not rule out a possible interaction between Hydroxycut® and paracetamol
(Stickel *et al.* 2009)	F, 78 years	Herbalife Formula Shake® (Strawberry and Cappuccino)	3 years	Cholestatic hepatitis, then lobular and portal hepatitis	High blood pressure, hip prosthesis, appendectomy, cholecystectomy, alcohol consumption (60-80 g/week)	Recovery	Not all products consumed contained GC Analysis of the products consumed by the two patients showed contamination by *Bacillus subtilis*, for which culture of the supernatant revealed hepatotoxicity
	F, 50 years	Herbalife products: RoseOx®, Multivitamin Complex®, Thermojetics Granules®, Tang Kuei Plus®, Vitamin C®, Personalized Protein Powder Mix Formula 3® and Herbalifeline Omega 3 fatty acid capsules® Daily consumption	1 year	Cirrhosis	Cholecystectomy, hysterectomy	Recovery	

Bibliographic reference	Sex, age	Product Quantity	Duration of consumption	Clinical assessment	Prior history/ associated consumption	Progression of the adverse reaction	Comments
(Chen *et al.* 2010)	F, 31 years	Hydroxycut® 2 tablets/day	1 year	Fulminant hepatitis	None	Recovery	Hydroxycut® also contains green tea, which is known to be hepatotoxic
	F, 37 years	Herbalife products (Formula One Nutritional Shake Mix®, Multivitamin Complex®, Cell Activator®, Cell-U-Loss®, Herbal Concentrate Original®, Total Control Formula®)	3 months	Acute hepatitis	None	Recovery	Many multi-ingredient products taken
	F, 53 years	Herbalife products (in the form of shakes, teas and capsules)	4 months	Cholestasis and hepatitis	None	Recovery	Names of consumed products not specified Many multi-ingredient products taken
(Fong *et al.* 2010)	8 cases 2 F and 6 M Between 17 and 54 years of age	Hydroxycut®	4, 6, 8, 52 or 104 weeks	Severe liver damage	None	5 patients recovered 3 liver transplants	Liver biopsy performed in 7 patients Autoimmune antibodies detected in 4 patients. One of these patients progressed to acute liver failure requiring a transplant. The explanted liver did not exhibit the characteristics of AIH.
(Vitalone *et al.* 2011)	F, 39 years	Magri XS®[13]	-	Acute hepatitis	None Associated consumption: Clarinol®, Bioperine®, Peso Stop®	Recovery	-

[13] Magri XS® contains pineapple, fennel, burdock, *Cassia nomame*, GC, banana, green tea, orthosiphon, jambul (Java plum).

Bibliographic reference	Sex, age	Product Quantity	Duration of consumption	Clinical assessment	Prior history/ associated consumption	Progression of the adverse reaction	Comments
(Melendez-Rosado *et al.* 2015)	F, 42 years	-	1 week	Acute hepatitis	High blood pressure, chronic kidney disease, type II diabetes, chronic back pain, obesity, haemochromatosis Concomitant treatments: hydralazine, hydrocodone/ paracetamol every 4-6 h for the back pain, 3 days prior to admission	Recovery	-
(Corey *et al.* 2016)	F, 52 years	*Garcinia cambogia*®[14] (USA Nutra Labs) 2 capsules/day	About 25 days	Acute liver failure	None Concomitant use of cream with hormones (β-oestrogen, progesterone and DHEA), melatonin, dicyclomine and antifungal nail oil	Liver transplant	Liver biopsy performed The authors concluded that consumption of the food supplement was the most likely aetiology for the liver failure
(Lunsford *et al.* 2016)	M, 34 years	Garcinia Cambogia 5:1 Extract® 6 capsules/day	5 months	Fulminant liver failure	None	Liver transplant	Autoimmune antibodies detected Liver biopsy performed The authors put forward the hypothesis of a genetic predisposition or pre-existing liver damage
(Smith, Bertilone, and Robertson 2016)	M, 26 years	Weight-loss food supplement containing 70% *Garcinia cambogia*	Consumption for 1 week, 10 weeks prior to onset of symptoms	Liver failure, hepatic necrosis	None Concomitant consumption of whey protein	Liver transplant	Liver biopsy performed
(Kothadia *et al.* 2018)	F, 36 years	Food supplement containing 1000 mg GC extract (50% HCA) and 150 mg potassium	4 weeks	Hepatitis	Followed a 500-kcal diet for 4 weeks	Recovery	Liver biopsy performed

[14] *Garcinia cambogia*® contains 50 mg calcium, 200 µg chromium, 50 mg potassium, 936 mg GC extract (for 2 capsules).

- **Rhubarb**

A systematic review of the literature was published in 2019 on plants causing liver damage. The authors pinpointed 334 cases of liver damage where the plant was identified. Rhubarb (*Rheum officinale*) was responsible for 24 of these cases (Byeon *et al.* 2019).

In addition, experimental studies in rats have shown the hepatotoxic potential of rhubarb (Wang *et al.* 2011, Tu *et al.* 2018).

The extrinsic causality score for this component is B1[15].

- **Guggul**

Two clinical cases involving the consumption of guggul were found in the literature.

The first, published by Grieco *et al.* (2009), is presented in Table 3, as the implicated product also contained *Garcinia cambogia*.

The second reports the case of a 28-year-old woman with no previous history, who presented with liver failure leading to a liver transplant, one month after starting to take Lipolyz®[16] (three tablets a day) and Somalyz®[17] (one or two tablets a day). She also consumed calcium, fibre and caffeine. The aetiological profile was negative, especially for viral serologies and autoimmune markers. The authors suspected usnic acid as the main agent causing this hepatotoxicity, but did not rule out a role for green tea or guggul (Krishna *et al.* 2011).

The extrinsic causality score for this component is B1.

- **Green coffee**

Two clinical cases involving the consumption of green coffee were found in the literature.

The first, published by Crescioli *et al.* (2018), is presented in Table 3, as the implicated product also contained *Garcinia cambogia*.

The second reports the case of a 55-year-old woman who developed cholestatic hepatitis after consuming six tablets of a fat-burning product containing green coffee (Gavrić *et al.* 2018).

The extrinsic causality score for this component is B1.

- **Orthosiphon**

Three clinical cases involving the use of orthosiphon were found in the literature.

Two of these cases, published by Vitalone *et al.* (2011) and Crescioli *et al.* (2018), are presented in Table 3, as the implicated products also contained *Garcinia cambogia*.

The third reports the case of a 25-year-old woman with no previous history, who developed acute hepatitis two months after starting Ortosifón-Arkocápsulas®[18] (1.5 g/day) and Camilina-

[15] A B1 score corresponds to a poorly-documented effect.

[16] Lipolyz® contains usnic acid, propionyl-L-carnitine, green tea, Z-guggulsterone, E-guggulsterone, cAMP and vitamin E.

[17] Somalyz® contains usnic acid, propionyl-L-carnitine, phosphatidylcholine, phosphatidylethanolamine, gamma-aminobutyric acid and vitamin E.

[18] Ortosifón-Arkocápsulas® contains *Orthosiphon stamineus*.

Arkocápsulas®[19] food supplements. The authors attributed the hepatitis to the consumption of *Camellia thea* without ruling out the possible involvement of orthosiphon (García-Morán *et al.* 2004).

The extrinsic causality score for this component is B1.

- **Cassia nomame**

A clinical case involving the consumption of Cassia nomame was found in the literature. It was published by Vitalone *et al.* (2011) and is presented in Table 3, as the implicated product also contained *Garcinia cambogia*.

The extrinsic causality score for this component is B1.

- **Rhodiola**

No data on the hepatotoxicity of rhodiola were found in the literature. However, cases of liver damage involving the consumption of rhodiola have been published because it is an ingredient in Hydroxycut®. These cases are described in Table 3.

The extrinsic causality score for this component is B1.

- **Other ingredients**

The literature search did not identify any cases of liver damage for olive, hibiscus, cola, moringa, nopal, coleus, shiitake, hawthorn, Siberian ginseng, caigua, maqui, blackcurrant, zinc gluconate or chromium picolinate.

The extrinsic causality score for these components is B0[20].

3.4.3. Other cases recorded in the nutrivigilance database

To date, no other reports concerning the food supplement Slim Metabol® have been recorded by the nutrivigilance scheme.

Table 4 lists cases of liver damage likely to be associated with the consumption of other food supplements containing, in particular, red yeast rice, *Garcinia cambogia*, rhubarb, guggul, green coffee, orthosiphon, rhodiola, olive, hibiscus, cola, moringa, nopal, coleus, shiitake, hawthorn, Siberian ginseng, cassia nomame, caigua, maqui, blackcurrant and marine collagen.

Due to the frequent presence of zinc, magnesium and chromium in food supplements, many cases are recorded in the database but they have not enabled any conclusions to be drawn as to the causality of these ingredients in the liver disorders.

[19] Camilina-Arkocápsulas® contains *Camellia thea*.

[20] A B0 score corresponds to a non-documented effect.

Table 4: Other cases of liver damage involving food supplements containing the ingredients of Slim Metabol®

Identification number	Food supplement	Composition	Effect(s)	Sex, age	Causality	Severity
2012-014	Levure de riz rouge - lovastatine naturelle 2.5 mg®	**Red yeast rice**	Increase in transaminases	F, 67	Likely	1
2012-044	Levure de riz rouge®	**Red yeast rice**	Acute hepatitis	F, 59	Unlikely	1
2012-046	Liposterol®	**Red yeast rice,** policonasol	Rheumatoid purpura, joint inflammation, hepatic cytolysis	F, 66	Possible	1
2012-217	Levure de riz rouge®	**Red yeast rice**	Nausea, muscle weakness, increased transaminases	F, 60	Likely	1
2012-224	Arterin®	**Red yeast rice**	Increased transaminases and epigastric pain	F, 74	Possible	1
2013-062	Levure de riz rouge®	**Red yeast rice**	Increase in transaminases and CPK levels	F, 65	Likely	1
2013-089	Levure de riz rouge®	**Red yeast rice**	Hepatic cytolysis, generalised urticaria	M, 45	Possible	2
2013-200	Levure de riz rouge®	**Red yeast rice**	Hepatic cytolysis and steatosis	M, 62	Likely	1
2016-018	Staticoncept Q10®	**Red yeast rice,** coenzyme Q10, **guggul**, sugar cane, policonasol	Increase in transaminases	F, 71	Likely	2

Identification number	Food supplement	Composition	Effect(s)	Sex, age	Causality	Severity
2017-188*	Physiomance DT2®	Green tea, **olive**, taurine, taurine, α-lipoic acid, cinnamon, vitamins C, E, B3, B5, B8, B12, B2, D3, B6, B1, B9, Zn, Cr, Mg	Increase in transaminases and rhabdomyolysis	M, 57	Likely	3
	Physiomance Dimeol Q10®	**Red yeast rice,** coenzyme Q10, garlic, pine, Cr, vitamins B3 and E				
	Equilibre Candida 3®	**Olive,** coriander, savory, alfalfa, feverfew, gum arabic				
2016-320*	Trioptec®	Fish oil, evening primrose oil, vitamins C, E, B6, B12, blueberry, coenzyme Q10, Zn, Cu, Se, lutein, orange, **olive**, zeaxanthin	Hepatic cytolysis	F, 69	Unlikely	2
2014-260	Revex-16®	***Garcinia cambogia*,** green tea, Cr, resveratrol, quercetin, black pepper	Hepatic cytolysis	F, 23	Possible	2
2018-193	Metaferrine®	***Garcinia cambogia,*** α-lipoic acid, lactoferrin, coenzyme Q10, vitamin D3	Hepatic cytolysis	F	Possible	1

Identification number	Food supplement	Composition	Effect(s)	Sex, age	Causality	Severity
2009-011*	Ménophytéa ventre plat®	Green tea, yam, caraway, angelica, **nopal**	Mixed hepatitis	F, 60	Unlikely	2
2010-043*	Minceur J-15®	Slim-data complex, cherry stem, heather, acacia, rosemary, **cola**, maté, green tea, chistosan	Hepatic cytolysis, abdominal pain, vomiting	M, 38	Possible	1
	Destockant Jour et Nuit®	**Nopal**, maté, ginger, **green coffee**				
2014-262	Skineance 3D Programme®	Artichoke, celery, **green coffee**, meadowsweet, cherry stem, black radish, prune, apple pectin, vitamin B3, Cr	Mixed hepatitis	F, 49	Excluded	2
2010-054	Ménophytéa ventre plat®	Green tea, yam, caraway, angelica, **nopal**	Hepatic cytolysis	F, 59	Likely	1
2010-055	Ménophytéa ventre plat®	Green tea, yam, caraway, angelica, **nopal**	Hepatitis	F, 44	Likely	1
	Ménophytéa rétention d'eau®	Yam, fucus, **hibiscus**				
2010-056*	Ménophytéa ventre plat®	Green tea, yam, caraway, angelica, **nopal**	Hepatic cytolysis	F, 59	Unlikely	1
2010-057	Ménophytéa ventre plat®	Green tea, yam, caraway, angelica, **nopal**	Hepatic cholestasis	F, 36	Possible	2
	4321 Minceur chrono Nuit®	Green tea, maté, barley, **cola**, fennel, celery				
	4321 Minceur chrono Nuit®	Lemon balm, grape, bean, **hawthorn**, chicory				

Identification number	Food supplement	Composition	Effect(s)	Sex, age	Causality	Severity
2019-053*	Complexe M+ Phase 2®	Artichoke, **cola**, peppermint, mandarin and cinnamon essential oils	Rhabdomyolysis and hepatic cytolysis	F, 34	Unlikely	3
2010-060	Ménophytéa ventre plat®	Green tea, yam, caraway, angelica, **nopal**	Mixed hepatitis, intrahepatic jaundice	F, 47	Likely	2
2011-031	TurboDraine Minceur thé pêche®	Green tea, meadowsweet, **nopal, hibiscus**, cherry stem, guava, aosa, ginseng	Hepatic cytolysis	F, 47	Likely	1
2018-588*	Boisson instantanée à base de thé vert et plantes®	Green tea, caffeine, mallow, **hibiscus**, cardamom	Hepatitis, hypokalaemia, abdominal pain, nausea, diarrhoea	F, 41	Possible	1
2011-038	Ménophytéa ventre plat®	Green tea, yam, caraway, angelica, **nopal**	Mixed hepatitis	F, 48	Likely	1
2013-157	Nopal®	**Nopal**	Mixed hepatitis	F, 35	Likely	2
	Dépuratif interne®	Artichoke, burdock, *Aloe vera*, dandelion, lemon balm, *Chrisanthellum americanum*, couch grass, black radish, carqueja, **orthosiphon**, essential oils of basil, juniper, coriander, lemon, peppermint, grapefruit, thyme				

Identification number	Food supplement	Composition	Effect(s)	Sex, age	Causality	Severity
2013-213*	Speed Draineur®	Chicory, meadowsweet, ash, **orthosiphon**, caffeine, green tea, cherry stem, apple	Hepatic cytolysis	F, 60	Likely	1
2012-005*	Liquid cleanse®	Oats, lemon, coconut, pomegranate, raspberry, blueberry, cornflower, black elder, blackberry, cherry, cranberry, acerola, *Aloe vera*, chlorella, kombu, wakame, nori, endive, artichoke, liquorice, astragalus, barley, mung bean, wheat, **Siberian ginseng**, jasmine tea	Abdominal pain and hepatic cytolysis	F, 31	Likely	1
2014-392	Massive Sperm Optimizer®	Ginger, **Siberian ginseng**, vitamin	Acute hepatitis	M, 64	Unlikely	2
2018-104*	Gemo-chocs®	**Hawthorn**, alder, **blackcurrant**	Hepatic cytolysis	F, 56	Likely	2
	Karoshil®	*Saccharomyces cerevisiae,* **Siberian ginseng**, selenium, vitamins B1, B2, B3, B5, B6, B9, B12				
2019-022*	Ristabil®	**Siberian ginseng,** rosehip, blueberry, royal jelly, vitamins B1, B2, B6	Hepatic cytolysis and cholestasis	F, 38	Excluded	2

Identification number	Food supplement	Composition	Effect(s)	Sex, age	Causality	Severity
2016-040	Ymea Ménopause Jour&Nuit®	Black cohosh, **rhodiola**, lemon balm, vitamin B6, valerian, passion flower	Disruption of liver function	F, 52	Unlikely	2
2016-067*	Seriane Stress®	**Rhodiola**, vitamin B6, Mg	Cytolytic and cholestatic hepatitis	F, 63	Excluded	2
2016-102*	Phytostandard Rhodiole Safran®	**Rhodiola,** saffron	Hepatic cytolysis	F, 56	Possible	2
2010-016*	Formincil®	Guarana, green tea, bitter orange, **coleus**	Hepatic cytolysis	F	Unlikely	1
2010-026	Formincil®	Guarana, green tea, bitter orange, **coleus**	Acute hepatitis	F, 38	Possible	2
2018-404*	Shiitake Hericium LO®	**Shiitake,** *Hericium erinaceus*, aspen, essential oil of bay laurel and oregano	Hepatic cytolysis	F, 49	Possible	3

* Cases involving the consumption of other food supplements.

3.5. Conclusions of the WG and the CES

ANSES received a report of fatal fulminant hepatitis (whose severity level was therefore 4). According to the nutrivigilance method, the causality score for the food supplement Slim Metabol® is likely.

The food supplement is suspected of playing a role in triggering this hepatitis. It contains many ingredients, mostly plants. Some of these, including *Garcinia cambogia*, have been associated with fulminant hepatitis requiring liver transplantation, as reported in publications.

4. AGENCY'S CONCLUSION

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) received a report of fatal fulminant hepatitis involving consumption of the food supplement Slim Metabol®. This food supplement Slim Metabol® is authorised and marketed in Italy with the claimed aim of controlling body weight. According to the evidence collected in the context of the report, it appears that the patient, although adhering to the recommended doses, took the product for more than three weeks without seeking medical advice as recommended by the manufacturer**.** In this context, ANSES adopts the conclusions of the Working Group on "Nutrivigilance" and the Expert Committee on "Human Nutrition".

The causality of consumption of this product in the occurrence of the serious adverse event – in this case death – was considered likely (I3, on a scale of I0 = excluded to I4 = very likely). This food supplement contains many ingredients: mainly plants including *Garcinia cambogia*, and red yeast rice (RYR). Other reports of liver damage associated with the consumption of *Garcinia cambogia*, some of them severe, have been identified in the literature and observed in other countries. This led the experts to view the link between this consumption and the liver effects as being well documented (score of B2, on a scale of B0 to B2). In addition, red yeast rice, which is another ingredient in this supplement, has a similar bibliographical score for liver damage.

Moreover, ANSES notes that *Garcinia cambogia* is the subject of an ANSM decision prohibiting the importation, preparation, prescription and dispensing of magistral, officinal and hospital preparations, as well as the prescription, dispensing or administration to humans of this same plant.

Lastly, from a regulatory point of view, ANSES notes on the one hand that the product Slim Metabol® is not among the food supplements declared in France, and on the other hand that the plant *Garcinia cambogia* is not listed in the Order of 24 June 2014 establishing the list of plants other than fungi authorised in food supplements, as well as the conditions of their use. However, it does appear under the name *Garcinia gummi-gutta* (L.) Roxb in the list of plants that can be used in food supplements, in the January 2019 version published by the DGCCRF on its website (commonly known as the "Plant List"), without any health recommendation or restriction.

In view of all these points, and although this is the first report to the nutrivigilance scheme of a case associated with this food supplement:

- ANSES strongly advises against consumption of the food supplement Slim Metabol® marketed outside France;
- Since *Garcinia cambogia* appears to be a common ingredient in food supplements on the weight-loss market, ANSES reiterates that according to its expert appraisal published in 2010, seeking to lose weight without a formal medical indication involves risks and requires support from a health professional (ANSES 2010);
- ANSES has issued an internal request to determine whether safe conditions for the use of food supplements containing *Garcinia cambogia* can be identified.

Lastly, ANSES reiterates its usual recommendations concerning food supplements:

- Consumers should:
  - notify a healthcare professional of any adverse effect occurring after consumption of a food supplement;
  - comply with the conditions of use specified by the manufacturer;
  - avoid taking food supplements on a multiple, prolonged or repeated basis throughout the year without having sought the advice of a healthcare professional (doctor, dietician, etc.);

- exercise great vigilance with regard to improper claims;
- exercise great vigilance regarding the purchase of products sold through alternative channels (internet, gyms, etc.) and without personalised advice from a healthcare professional.

- Healthcare professionals should communicate cases of adverse effects they suspect of being associated with the consumption of food supplements, and the Agency invites them to report these to the nutrivigilance scheme.

Dr Roger Genet

KEYWORDS

Hépatite fatale, complément alimentaire, Slim Metabol®, levure de riz rouge, *Garcinia cambogia*

Fatal hepatitis, food supplement, Slim Metabol®, red yeast rice, *Garcinia cambogia*

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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

- "Nutrivigilance" WG 2018-2021

Chair

Mr Pascal CRENN – University Professor – Hospital Practitioner (AP-HP/Paris-Saclay University) – Specialities: hepato-gastroenterology, nutrition

Members

Ms Catherine ATLAN – Head of Department (Luxembourg Hospital Centre) – Specialities: metabolic diseases, nutrition and endocrinology

Mr Alain BOISSONNAS – Retired, University Professor – Hospital Practitioner (University Hospital Paris-Sud) – Speciality: internal medicine

Ms Patricia BOLTZ – Hospital Practitioner (Poison Control and Monitoring Centre of Nancy University Hospital) – Speciality: clinical toxicology, toxicovigilance

Mr Nicolas DANEL BUHL – Medical Nutritionist (Artois Regional Hospital Grouping, GHT) – Speciality: nutrition

Mr Michel GERSON – Practitioner – Speciality: endocrinology, nutrition

Mr Raymond JIAN – Retired, University Professor – Hospital Practitioner (Georges Pompidou European Hospital) – Speciality: hepato-gastroenterology

Mr Pascal PLAN – Substitute Doctor – Speciality: general medicine, geriatrics, palliative care

Mr Jean-Marie RENAUDIN – Hospital Practitioner (Emilie Durkheim Hospital Centre) – Specialities: allergology, occupational medicine

Mr Philippe SCHERER – Retired – Speciality: allergology, occupational medicine

Mr Claude SICHEL – Retired, General Practitioner – Speciality: general medicine

Mr Jean-Fabien ZAZZO – Retired, Hospital Practitioner (Antoine Béclère Hospital – AP-HP) – Specialities: anaesthesia and resuscitation, nutrition

EXPERT COMMITTEE

The work that is the subject of this report was monitored and adopted by the following 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

Mr Jean-François HUNEAU – Professor (AgroParisTech) – Speciality: human nutrition

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, plant micro-constituents

Ms Beatrice MORIO-LIONDORE – Research Director (INRA Lyon) – Specialities: human nutrition, lipid and energy metabolism

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

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Scientific contribution

Ms Gwenn VO VAN-REGNAULT – Nutrivigilance Project Officer – Risk Assessment Department

Ms Irène MARGARITIS – Head of the Nutritional Risk Assessment Unit – Seconded University Professor (University of Nice Sophia Antipolis) – Risk Assessment Department

Administrative secretariat

Ms Isabelle PIERI – Risk Assessment Department