

The Director General

Maisons-Alfort, 14 February 2014

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

**on the risks associated with the presence of “red yeast rice” in food supplements**

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*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 made public. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 14 February 2014 shall prevail.*

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On 26 September 2012 ANSES issued an internal request to conduct the following expert appraisal: Risks associated with the presence of “red yeast rice” in food supplements.

### **1. BACKGROUND AND PURPOSE OF THE REQUEST**

“Red yeast rice” is a red mould grown on white rice. It is found in many food supplements designed to “maintain normal cholesterol levels”. 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). The term “lovastatin” is the international nonproprietary name of a substance that is pharmacologically active, in a pharmaceutical context. In this Opinion, the term “monacolin K” shall refer to the compound found in “red yeast rice”, while the name “lovastatin” shall apply only to the drug. “Red yeast rice” shall be referred to by the abbreviation RYR.

Consumers use RYR, with or without medical advice, as an adjuvant or as a substitute for statins. Thirty reports of adverse reactions potentially associated with the consumption of food supplements containing RYR have been brought to the attention of ANSES since the creation of its nutrivigilance system in 2009. Twenty-five of these reports are complete enough to be analysed.

In this context, ANSES issued an internal request to investigate the risks associated with the presence of RYR in food supplements. The expert appraisal was based on a review of the literature and clinical cases reported within the nutrivigilance system.

In the analysis carried out, the effect of RYR on lowering cholesterol levels, which had been examined by the European Food Safety Authority (EFSA), was not assessed.

### **2. ORGANISATION OF THE EXPERT APPRAISAL**

The expert appraisal was carried out in accordance with the French Standard NF X 50-110 “Quality in Expertise - General requirements of competence for expert appraisals (May 2003)”.

The expert appraisal fell within the sphere of competence of the Expert Committee (CES) on Human Nutrition. ANSES entrusted the expert appraisal to external rapporteurs and the permanent working group on nutriviigilance. The methodological and scientific aspects of the work were discussed by the working group at its meetings of 28 March 2013, 26 April 2013, 14 May 2013 and 11 June 2013. The conclusions were adopted by electronic means by the working group on nutriviigilance on 20 June 2013. The working group's conclusions were then presented to, discussed and validated by the CES on Human Nutrition at its meeting of 27 June 2013. The Opinion was submitted for public consultation between 17 October and 15 December 2013. The information that emerged during this consultation was then integrated.

ANSES analyses the links of interest declared by the experts prior to their appointment and throughout the work, in order to avoid potential conflicts of interest with regard to the matters dealt with as part of the expert appraisal.

The experts' declarations of interests are made public via the ANSES website ([www.anses.fr](http://www.anses.fr)).

### 3. CES ANALYSIS AND CONCLUSIONS

#### 3.1. Characterisation of the ingredient

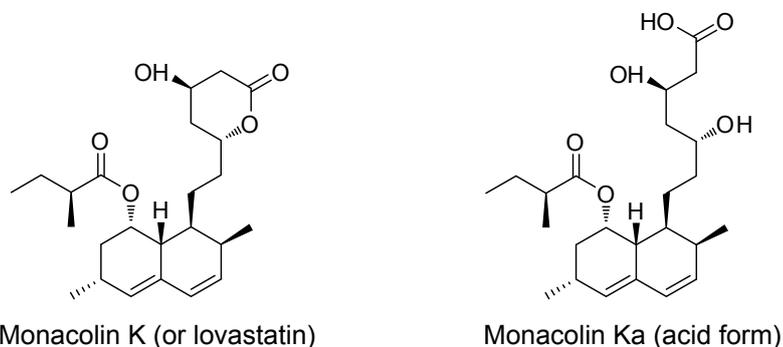
##### 3.1.1. "Red Yeast Rice"

RYR is traditionally used in China for culinary purposes as a food colouring or for therapeutic purposes to improve digestion and blood circulation. It is a microscopic fungus grown on cooked rice (Ma *et al.* 2000). Rice fermented in this way becomes red due to fungal pigments. This fungus belongs to the class Ascomycetes, order Eurotiales, family Monascaceae and genus *Monascus*.

Traditionally prepared RYR (*Hung-ch'u*, *Hongqu*, *Angkak* or *Beni Koji*) is the product of fermentation using a mixture of several species from the genus *Monascus*, the main one being *Monascus purpureus* Went, discovered in 1895. The other species represented are *Monascus ruber* van Tieghem, *Monascus fuliginosus* Sato, *Monascus pilosus* Sato and *Monascus albidus* Sato (Zhang *et al.* 1999). Sixty-five strains are currently deposited at the American Type Culture Collection (ATCC). Most of these belong to three species: *M. pilosus*, *M. purpureus* and *M. ruber* (Lin *et al.* 2008; Park *et al.* 2004). There are non-traditional RYR preparations currently on the market that may be present in food supplements aiming to reduce cholesterol.

##### 3.1.2. Monacolins

Fungi from the genus *Monascus* produce compounds called monacolins, among which monacolin K predominates. This occurs in two forms (Figure 1): the lactone form and the open acid form, with the conversion to either of these two forms being pH dependent (Ma *et al.* 2000; Nigović *et al.* 2013).



**Figure 1: Molecular structure of monacolin K and its acid form**

Monacolin K has the same pharmacological characteristics as statins. It inhibits an enzyme involved in cholesterol synthesis, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, which explains its cholesterol-lowering effect (Endo 1979; Gordon *et al.* 2010).

Several other monacolins have been identified in food supplements on the market containing RYR (see Annex 1), including monacolin J, monacolin L (precursor of monacolin J), dehydromonacolin K and dihydromonacolin K. Their pharmacological action is poorly documented (Ma *et al.* 2000).

### **3.1.3. Other compounds contained in RYR**

#### **3.1.3.1. Fatty acids**

The fatty acids found in RYR (2.84%) are saturated (palmitic, stearic and eicosanoic acids) and unsaturated (oleic, linoleic and linolenic) fatty acids in equal proportions (Ma *et al.* 2000).

#### **3.1.3.2. Pigments and citrinin**

The pigments produced by *Monascus purpureus* form a group of secondary metabolites belonging to the family of azaphilones. The main six are divided into three groups:

- orange pigments: monascorubrin and rubropunctatin;
- red pigments: monascorubramin and rubropunctamin;
- yellow pigments: ankaflavin and monascin (Feng *et al.* 2012; Juzlová *et al.* 1996; Patakova 2012; Sabater-Vilar *et al.* 1999).

These coloured metabolites also include citrinin (Figure 2), a mycotoxin produced by several species of fungi belonging to the genera *Aspergillus*, *Penicillium* and *Monascus* (Elsawi *et al.* 2012).

### **Figure 2: Molecular structure of citrinin**

Citrinin may be present in stored grain, as well as in other plant products such as beans, fruits, fruit or vegetable juices, plants used for medicinal or condiment purposes, spices and tainted dairy products (EFSA 2012).

#### **3.1.3.3. Other**

The overall composition of RYR includes starch, protein, fibre, minerals (phosphorus, sodium, calcium, iron, magnesium) and trace elements (aluminium, manganese, copper, silver). It also contains sterols, including  $\beta$ -sitosterol, campesterol and stigmasterol (Heber *et al.* 1999; Liu *et al.* 2006; Ma *et al.* 2000).

### **3.1.4. Amounts**

#### **3.1.4.1. Monacolins**

It is very difficult to know the exact amounts of monacolins present in food supplements containing RYR. They are rarely stated by manufacturers and are not standardised (Gordon *et al.* 2010).

It should be noted that there is no official method for measuring total monacolins. Furthermore, their presence in RYR depends on the strain of *Monascus* used and the fermentation conditions (Liu *et al.* 2006).

Gordon *et al.* (2010) measured and compared the concentrations of monacolin K, acid-form monacolin K and total monacolin contained in 12 food supplements based on RYR (600 mg of RYR per capsule). The results show great variability in monacolin concentration from one food supplement to another (from 0.10 to 10.09 mg/capsule for monacolin K, from 0 to 2.30 mg/capsule for acid-form monacolin K, and from 0.31 to 11.15 mg/capsule for total monacolins). This variability is even higher when considering the daily dose of monacolins consumed (from 0.20 to 14.54 mg/d for monacolin K, from 0 to 9.19 mg/d for acid-form monacolin K, and from 0.62 to 24.71 mg/d for total monacolins).

A recent article by the French Federal Union of Consumers (UFC-Que Choisir) reported results from the measurement of monacolin K (lactone and acid form) in 10 food supplements. Concentrations ranged from 1.39 to 11.59 mg/capsule and quantities consumed from 1.59 to 11.59 mg/d (Vennetier 2012).

The variability in the composition of food supplements containing RYR is also demonstrated by an acid-form monacolin K content that is sometimes higher than that of monacolin K, for example 1376 µg/mL and 486 µg/mL respectively (Mornar *et al.* 2013; Nigović *et al.* 2013).

#### 3.1.4.2. Citrinin

Citrinin has been measured in RYR at highly variable concentrations. The study by Gordon *et al.* (2010) shows that it was present in one third of the products tested, at levels ranging from 14.3 to 114.2 µg/capsule (standard deviation 38.2) and from 28.5 to 228.3 µg/d (standard deviation 76.3). In the article by UFC-Que Choisir, no citrinin was detected in eight of the ten samples analysed. However, for the other two samples, the concentrations measured were 310 and 1900 µg/kg. The detection limit of the method used was 15 µg/kg (Vennetier 2012).

Sabater-Vilar *et al.* (1999) detected the presence of citrinin in the 12 RYR samples tested, at concentrations ranging from 200 to 17,100 µg/kg.

In Japan, the maximum concentration of citrinin authorised in RYR is 200 µg/kg (Chen and Hu 2005).

It should be noted that concentrations of citrinin present in seeds intended for human dietary consumption may reach 420 µg/kg. Concerning other foodstuffs, reported concentrations vary up to 42 µg/kg in cereal products, 355 µg/kg in plants used for medicinal or condiment purposes and 0.2 µg/L in fruit and vegetable juices (EFSA 2012).

Food supplements containing RYR are not systematically tested for the absence of citrinin. It should be noted that not all strains of *Monascus* produce it. New approaches aim to reduce the citrinin concentrations without altering the monacolin K concentrations, but these require further study. Heat treatment, for example, can degrade citrinin, but one of the products obtained, citrinin H1, is ten times more cytotoxic than citrinin itself (Jia *et al.* 2010; Lee *et al.* 2007; Lin *et al.* 2008).

#### 3.1.5. Sources of variability

The inconsistency of the concentrations of different components of RYR is partly explained by the lack of a standardised production method. The levels of monacolin and citrinin vary considerably depending on the strain of *Monascus* (Chen and Hu 2005). The fermentation processes and growing conditions (medium, temperature) are variable. Levels of monacolin may also depend on degradation phenomena in the samples (Li *et al.* 2005).

As with substances derived from natural sources that have a complex chemical composition, standardising RYR is difficult (Gordon *et al.* 2010).

In addition, the control monograph for lovastatin appearing in the European Pharmacopoeia recommends assaying the lactone form by liquid chromatography with spectrophotometric detection, with the acid form considered as an impurity with a content limit of 0.3% in pure lovastatin. Even if manufacturers referred to this monograph, the monacolin K content in RYR would potentially be underestimated due to the fact that the acid form is not taken into account.

According to the European Food Safety Authority (EFSA), the preferred method for assaying citrinin is high-performance liquid chromatography coupled with fluorescence detection, with a detection limit of 0.1 µg/kg. However, analysis of citrinin is difficult because of its heat instability in several organic solvents (EFSA 2012). Methods for the simultaneous assaying of both forms of monacolin K and citrinin in RYR are in the process of being developed and need to be standardised (Mornar *et al.* 2013; Nigović *et al.* 2013).

It seems that the RYR traditionally consumed in Asia has low levels of monacolin because of the traditional fermentation process (Juzlová *et al.* 1996; Lin and Demain 1991; Seenivasan *et al.* 2008). In a recent study, the content of monacolin K in traditionally-made preparations, compared to food supplements, was very low (4.4 vs 510 µg/g) or even undetectable (Mornar *et al.* 2013). According to Zhang *et al.* (1999), traditional RYR relates to preparations containing less than 0.005% of monacolin K. A patent filed in 1999 concerned an "improved" RYR called Xuezhikang<sup>®</sup>, obtained by fermentation of the mutant strain *Monascus purpureus* Went CGMCC No. 0272, and claiming at least 0.05% of monacolin K in the final product, i.e. ten times more than the traditionally obtained product (Zhang *et al.* 1999). This "improved" RYR also claimed better triglyceride- and cholesterol-lowering properties than those of the traditional RYR.

### 3.2. Pharmacology

#### 3.2.1. Statins

The pharmacological action of the components of RYR, especially the monacolins, is poorly documented. However, the pharmacological class of statins to which monacolin K belongs has undergone extensive pharmacological studies.

Statins are a family of drugs that inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyses an early stage of hepatic cholesterol synthesis (Figure 3): the transformation of HGM-CoA into mevalonic acid, a precursor of terpenes and sterols (Chen *et al.* 2012).

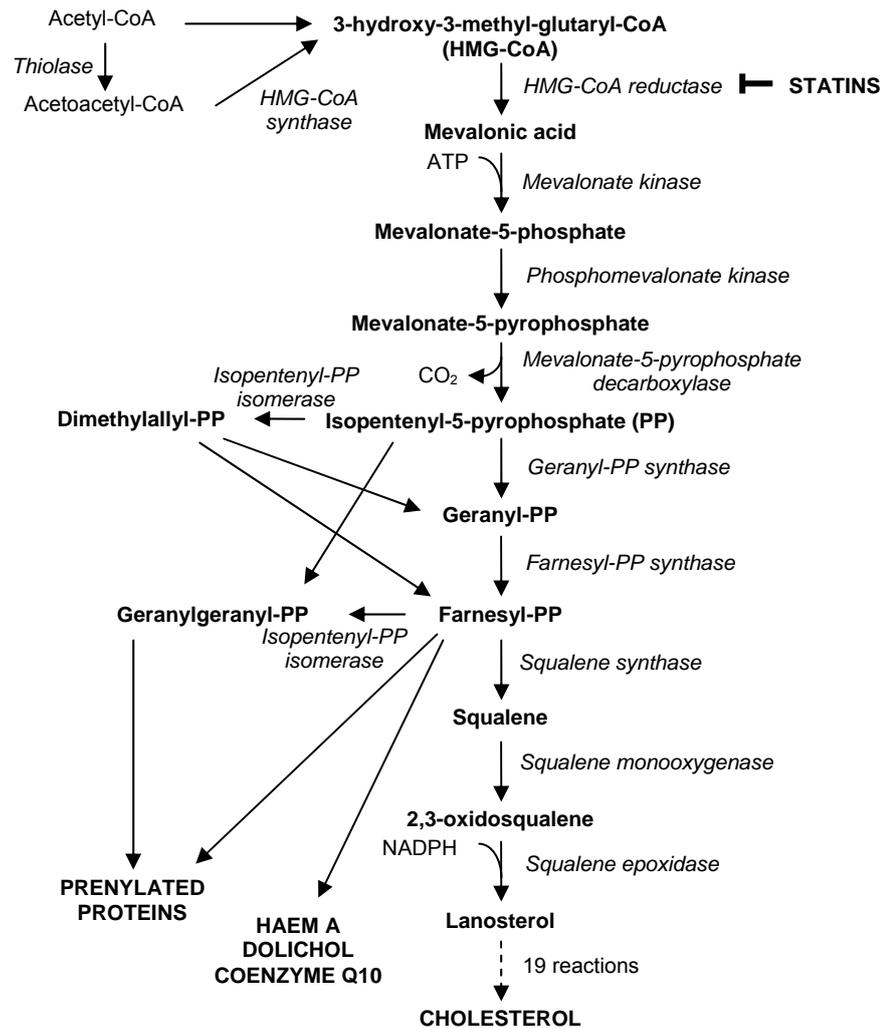


Figure 3: Pathway of cholesterol synthesis in humans

The lipid-lowering effect is due to competitive inhibition of HMG-CoA reductase, which results in a decrease in the synthesis of intracellular cholesterol. This induces the expression of Low Density Lipoprotein (LDL) receptors on the surface of the hepatocytes, which in turn results in decreased concentrations of circulating LDL-cholesterol (Schachter 2005). Statins also cause a decrease in plasma concentrations of apolipoprotein B, Very Low Density Lipoproteins (VLDLs) and triglycerides (Wierzbicki *et al.* 2003).

In a randomised double-blind placebo-controlled study, taking a food supplement containing RYR and providing about 5 mg of monacolin K significantly reduced cholesterol levels (reduction in LDL-cholesterol) compared to the placebo. The same effect was observed with 20 to 40 mg of lovastatin. These results suggest that some components of RYR, primarily the other monacolins, have additive or synergistic pharmacological effects (Heber *et al.* 1999).

### **3.2.2. Coenzyme Q10**

Coenzyme Q10 (or ubiquinone) is a ubiquitous lipophilic molecule located in the inner membrane of mitochondria and synthesised from mevalonic acid (Figure 3). It acts in the functioning of the mitochondrial respiratory chain. Its antioxidant properties are expressed by the inhibition of the oxidation of proteins, DNA and lipids.

Administration of statins may lead to a reduction in levels of coenzyme Q10. Some authors have suggested a link between this reduction and muscle damage associated with statins. In fact, several studies show a decrease in concentrations of coenzyme Q10 in serum and muscle tissue after administration of statins, but the effect of coenzyme Q10 supplementation on muscle damage remains controversial. It appears that aging causes a greater decrease in coenzyme Q10 concentrations than the statins themselves (Deichmann *et al.* 2010).

The absence of data in humans on concomitant administration of RYR with coenzyme Q10 means that this association is not proven as efficient for reducing adverse reactions, even though the food supplements combine these two ingredients.

### **3.2.3. Dolichol**

The decrease in mevalonic acid synthesis also causes the depletion of dolichol (Figure 3), which plays an important role in protein glycosylation. This glycosylation is essential for the formation of mature and functional proteins and receptors (Bektas and Rubenstein 2011).

## **3.3. Pharmacokinetics and interactions**

### **3.3.1. Pharmacokinetic data**

For each undocumented aspect of monacolin K pharmacokinetics, the pharmacokinetic data for lovastatin are provided for information.

The kinetics of monacolin K and its acid form are linear after administration of a single dose of RYR. No significant accumulation is observed after multiple doses (Chen *et al.* 2012). The maximum plasma concentration of both forms of monacolin K, strongly bound to human plasma proteins (over 95%), is reached two hours after administration.

The study by Chen *et al.* (2013) conducted on 14 healthy volunteers showed that intestinal absorption of monacolin K contained in RYR is greater than that of pure lovastatin. Moreover, when this monacolin K is ingested in the form of RYR, its maximum concentration and area under the curve are increased, and the time to peak concentration is decreased, compared to the parameters observed with lovastatin.

The bioavailability of lovastatin is estimated at less than 5% (Chen *et al.* 2013). It is a substrate for P-glycoprotein (P-gp) and is hydrolysed *in vivo* by an esterase in active acid form ( $\beta$ -hydroxy acid), which itself is metabolised by cytochrome P450 2C8 (CYP2C8). In addition to this hydrolysis, lovastatin is oxidised by CYP3A4 to give several metabolites: 6 $\beta$ -hydroxy-lovastatin, 6'-exomethylene-lovastatin and 3"-hydroxy-lovastatin (Chen *et al.* 2012; Wang *et al.* 1991).

It has a half-life of three hours and is excreted mainly in the faeces (only 10% in the urine) after oral administration in humans (Schachter 2005).

### **3.3.2. Interactions**

Due to the lack of data, most of the potential interactions with RYR are inferred from known interactions with statins (Chen *et al.* 2012). As RYR does not only contain monacolin K, these inferences should be treated with caution.

#### **3.3.2.1. Change in concentrations of certain drugs**

Chen *et al.* (2012) compared the pharmacokinetic parameters of extracts of RYR (Cholestin<sup>®</sup>, LipoCol Forte<sup>®</sup> and Xuezhikang<sup>®</sup>) and lovastatin, for the same concentration (25  $\mu$ M of monacolin K/lovastatin), on several cytochrome P450 monooxygenases (CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) and P-gp. The extracts inhibit the six cytochromes and P-gp

with higher activity than lovastatin. More specifically, two of the products tested (LipoCol Forte<sup>®</sup> and Xuezhikang<sup>®</sup>) appear to be potent inhibitors of CYP1A2 and CYP2C19, suggesting a potential risk of interaction with drugs primarily metabolised by these enzymes (for example verapamil and clopidogrel).

#### 3.3.2.2. Change in concentrations of monacolin K

The concomitant consumption of potent inhibitors of CYP3A4 or P-gp (fibrates, azole antifungals, macrolides, anti-arrhythmic drugs, protease inhibitors, grapefruit juice, etc.) and RYR can significantly increase plasma concentrations of both forms of monacolin K (Chen *et al.* 2012).

With gemfibrozil, an inhibitor of CYP2C8, plasma concentrations of acid-form monacolin K can be increased without affecting those of monacolin K (Chen *et al.* 2012).

#### 3.3.2.3. Change in concentrations of lovastatin

When lovastatin is administered during a meal, its intestinal absorption is increased by about 50%, while pectins and oat bran decrease it (Lachenmeier *et al.* 2012).

### **3.4. Toxicology**

#### **3.4.1. “Red Yeast Rice”**

There is only one study in Wistar rats (n=5/sex/group for the acute toxicity study and n=6/sex/group for the subchronic toxicity study) receiving RYR supplementation in the diet containing 0.05% of monacolin K. No form of toxicity was observed in body weight or blood parameters. Histology performed on the studied organs (liver, lungs, brain, spleen, heart, testes, kidneys and ovaries) showed no significant difference compared with the controls (Kumari *et al.* 2009).

#### **3.4.2. Lovastatin**

The lack of toxicological data on RYR led to the studies on lovastatin being analysed. The toxicity of the other monacolins contained in RYR is unknown.

##### 3.4.2.1. Systemic toxicity

Few publications have included animal toxicity data. The available results come from studies conducted as part of the industrial development of statins.

MacDonald and Halleck (2004) examined the main preclinical toxicity data. The effects described were observed at high doses (more than 100 mg/kg/d) of lovastatin. The main target organs are:

- the liver, with centrilobular necrosis in rabbits, cellular damage and bile duct hyperplasia in rats, and increased transaminases in dogs;
- the kidney, with degeneration of proximal tubular epithelial cells in rabbits;
- the forestomach, with hyperplasia and hyperkeratosis of the non-glandular gastric mucosa in rats and mice (an anatomical part specific to the rodent);
- the skeletal muscles, with muscle degeneration in rats;
- the central nervous system and especially the vascular endothelial cells, with optic nerve lesions secondary to ischemia in dogs.

Lens opacities evolving into cataracts have also been reported in dogs, and more rarely testicular abnormalities (decreased weight of the testes, degeneration of seminiferous epithelial cells, a spermatocyte maturation disorder, etc.) without any changes in serum concentrations of sex hormones (MacDonald and Halleck 2004).

##### 3.4.2.2. Genotoxicity and carcinogenicity

In rats administered lovastatin, the appearance of spontaneous tumours, including lung adenomas and squamous cell papillomas of the forestomach, is increased. None of the data reported any genotoxic activity of lovastatin *in vitro* or *in vivo*, indicating the absence of mutagenic or clastogenic potential. The increased occurrence of tumours is therefore the result of a non-genotoxic mechanism (MacDonald and Halleck 2004).

#### 3.4.2.3. Reprotoxicity

Statins are classified by the US Food and Drug Administration (FDA) in Category X, which means that on the basis of animal studies and/or human data, a foetal risk has been observed (MacDonald 2004). This point should be qualified. Studies conducted with lovastatin in animals (rats and rabbits) have shown, for administration during the sensitive period of gestation, the occurrence of malformations, skeletal variations and delays in ossification at very high doses (400 and 800 mg/kg/day), which resulted in high maternal toxicity with a decrease in food consumption, a very significant decrease in weight of the treated mothers and the appearance of lesions of the forestomach in rats. It has been shown that the embryonic skeletal anomalies likely to appear from 100 mg/kg/day were not due to a direct teratogenic effect, but resulted from the pharmacological mechanism of action of statins (central role of cholesterol in the development of cell membranes), since mevalonate supplementation suppressed the embryonic effects (Lankas *et al.* 2004; MacDonald and Halleck 2004).

#### 3.4.3. Citrinin

##### 3.4.3.1. Systemic toxicity

A study conducted with dry lemon extract contaminated with different unspecified concentrations of citrinin in male Wistar rats (n=10/group) showed, after gavage, renal toxicity in treated animals on the basis of an increase in certain biomarkers (serum urea and creatinine) and histological damage (from atrophy of some renal corpuscles to tubular degeneration) but there is great imprecision in the doses of citrinin actually administered (Elsawi *et al.* 2012).

Another study involving 15 dogs (eleven females and four males) receiving a single intravenous dose of citrinin (5 or 20 mg/kg) showed kidney damage. Nephrotoxicity was manifested at a dose of 20 mg/kg by proteinuria, glucosuria and decreased phosphorus excretion, inulin clearance and renal circulation. The toxicity of citrinin was exerted on the proximal tubules through deterioration of mitochondria. *In vitro* studies showed that citrinin produced effects on the functioning of mitochondria and the biosynthesis of macromolecules leading to cell death (Krejci *et al.* 1996).

##### 3.4.3.2. Genotoxicity and carcinogenicity

Genotoxicity data show the absence of mutagenic properties of citrinin with the Ames test, with or without metabolic activation. However, after biotransformation in hepatocytes, citrinin induced a dose-dependent mutagenic response on strains TA 98 and TA 100 of *Salmonella typhimurium* (Sabater-Vilar *et al.* 1999).

The clastogenic property of citrinin is well documented *in vitro*, with a positive micronucleus test on V79 cells, human lymphocytes and HepG2 cells. The occurrence of chromosomal abnormalities (including chromatid breaks) was observed in male BALB/c mice receiving oral doses of 100 µg/kg bw twice a week for eight weeks. An aneugenic potential was also identified (Chang *et al.* 2011).

The occurrence of renal tumours (adenomas) has been reported in male F344 rats after oral administration of citrinin for 80 weeks (EFSA 2012; IARC 1986).

Within the regulatory framework for the drug, the level of genotoxic impurities should not cause intake to exceed the limit of 1.5 µg/d according to the principle of Threshold of Toxicological Concern (TTC) defined by the European Medicines Agency (EMA 2006; EMA 2013). In food supplements containing RYR, the citrinin content may lead to this value being exceeded (see Section 3.1.4.2).

##### 3.4.3.3. Reprotoxicity

The effects of citrinin on reproductive function have been the subject of various studies. It has been demonstrated *in vitro* on ICR mouse blastocysts that citrinin is an inducer of apoptosis, after treatment with a concentration of 15 or 30 µM for 24 h, leading *in vivo* to a decrease in embryo implantation and viability, according to an as yet unknown mechanism (Chan and Shiao 2007).

Foetotoxicity was reported in pregnant Wistar rats (n=10/group) receiving citrinin in feed at a dose of 10 mg/kg/day for 15 days. The foetuses had moderate liver damage (vacuolar degeneration observed in some hepatocytes) and severe renal damage (tubular degeneration and necrosis), confirming the existence of placental transfer (Singh *et al.* 2008).

Furthermore, in male mice receiving different doses of citrinin (0.0625, 0.625 and 6.25 mg/kg/d) via the intraperitoneal route for seven days, a significant relative increase in the weight of testes, epididymis, seminal vesicles and preputial glands was shown. At the same time, decreases in the production of sperm and serum testosterone were reported, leading to a decline in fertility and reproductive potential. These effects were observed after the first dose tested, meaning that a no-effect level could not be defined (Qingqing *et al.* 2012).

### **3.5. Clinical data**

#### **3.5.1. “Red Yeast Rice”**

##### **3.5.1.1. Cases from nutrivigilance**

Since the creation of the nutrivigilance system in 2009 and until 31 May 2013, ANSES received thirty reports of adverse reactions potentially associated with the consumption of food supplements containing RYR. Two were received in 2010, four in 2011, eighteen in 2012 and six in 2013. Five of these reports were considered incomplete due to missing information (for instance regarding the dates on which the individuals started/stopped taking the food supplement).

In order to identify the role of RYR in the reports received, ANSES analysed the causality of the twenty-five cases declared as complete by applying the method defined in ANSES’s Opinion of 11 May 2011 on the development of a method for determining causality in reports of adverse reactions in nutrivigilance (ANSES 2011).

Of the twenty-five cases examined (fifteen women and ten men, median age 59 years):

- causality was considered very likely in two cases (I4);
- causality was considered likely in ten cases (I3);
- causality was considered possible in eight cases (I2);
- causality was considered doubtful in four cases (I1);
- causality was excluded in one case (I0).

The cases, type of effect and causalities established are detailed in Table 1. The adverse reactions brought to the attention of ANSES were mainly muscle- (nine cases) and liver-related (eight cases). Two cases of allergic reaction were also reported.

The twelve cases where causality was very likely or likely (Figure 4) concern predominantly muscle damage, including one associated with joint pain, as well as three cases of liver damage (increased transaminases) whether or not associated with muscle damage, one dermatology case (Stevens-Johnson syndrome) and one gastroenterology case (colitis).

It should be noted that causality was likely or very likely in all nine cases of muscle damage.

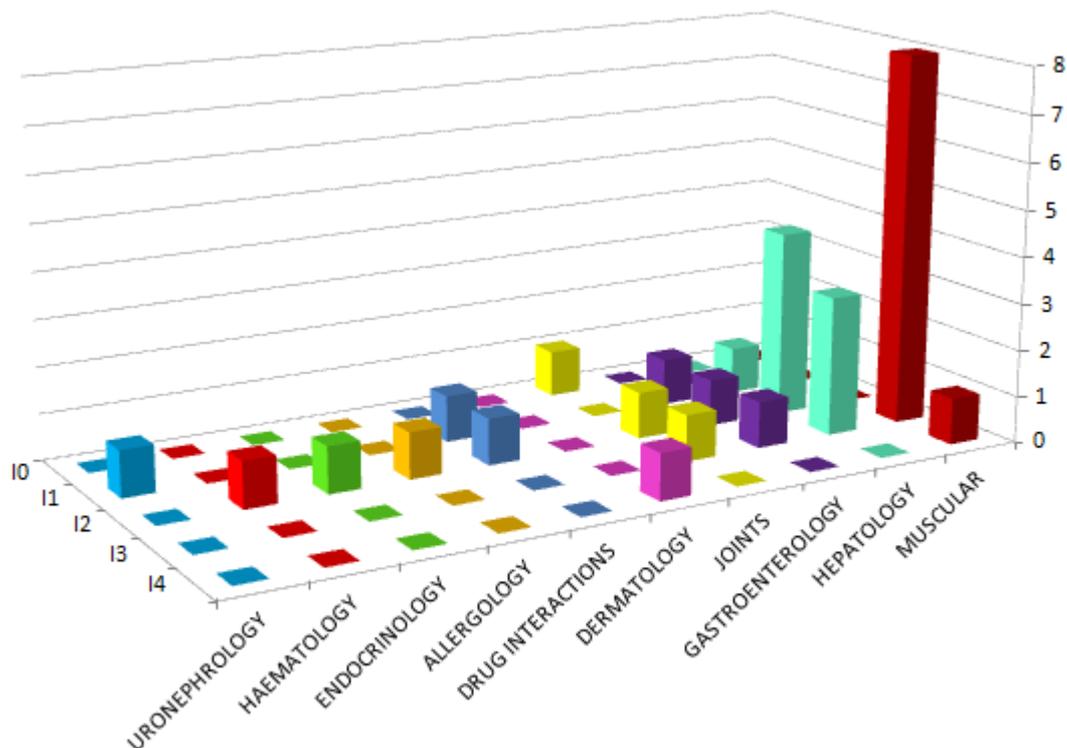


Figure 4: Diagram of nutriviigilance cases according to effect type and causality

Table 1: Analysis of the causality of adverse reactions reported to ANSES involving food supplements containing “red yeast rice”

Reference <sup>1</sup>	Type of effect	Serious effect <sup>2</sup>	Chronological (C) and semiological (S) scores	Causality
2012-238	myalgia	no	C3: timeframe consistent and progression suggestive S3: no other aetiology	very likely
2013-063	Stevens-Johnson syndrome	no	C3: timeframe consistent and progression suggestive S3: no other aetiology	very likely
2010-068	increased creatine phosphokinase	no	C3: timeframe consistent and progression suggestive S1: another possible aetiology	likely
2011-070	myalgia and joint pain	no	C3: timeframe consistent and progression suggestive S2: another hypothetical aetiology	likely
2012-014	increased transaminases	no	C3: timeframe consistent and progression suggestive S2: another hypothetical aetiology	likely
2012-029	rhabdomyolysis	no	C3: timeframe consistent and progression suggestive S2: another hypothetical aetiology	likely

<sup>1</sup> The numbers correspond to the references of the reports of adverse reactions recorded in the nutritional vigilance database

<sup>2</sup> According to the definition of a serious adverse reaction given in Article R1323-3 of the French Public Health Code

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Reference <sup>1</sup>	Type of effect	Serious effect <sup>2</sup>	Chronological (C) and semiological (S) scores	Causality
2012-045	myalgia	no	C3: timeframe consistent and progression suggestive S2: another hypothetical aetiology	likely
2012-217	nausea, muscle weakness, increased transaminases	yes	C3: timeframe consistent and progression suggestive S1: another possible aetiology	likely
2012-225	colitis	no	C3: timeframe consistent and progression suggestive S1: another possible aetiology	likely
2012-226	muscle cramps	no	C3: timeframe consistent and progression suggestive S1: another possible aetiology	likely
2012-227	myalgia	no	C3: timeframe consistent and progression suggestive S1: another possible aetiology	likely
2013-062	increased transaminases and creatine phosphokinase	no	C3: timeframe consistent and progression suggestive S1: another possible aetiology	likely
2010-078	abnormal liver function tests, hepatosiderosis	no	C2: timeframe consistent and progression cannot be interpreted S1: another possible aetiology	possible
2011-046	acute pancreatitis	yes	C2: timeframe consistent and progression cannot be interpreted S2: another hypothetical aetiology	possible
2012-046	rheumatoid purpura, inflamed joints, hepatic cytolysis	no	C2: timeframe consistent and progression cannot be interpreted S1: another possible aetiology	possible
2012-223	decreased INR (International Normalised Ratio)	no	C1: timeframe not very consistent and progression cannot be interpreted S3: no other aetiology	possible
2012-224	increased transaminases, epigastric pain	no	C2: timeframe consistent and progression cannot be interpreted S1: another possible aetiology	possible
2013-061	thrombocytopenia	yes	C2: timeframe consistent and progression cannot be interpreted S2: another hypothetical aetiology	possible
2013-080	oedema, diffuse urticaria	no	C2: timeframe consistent and progression cannot be interpreted S2: another hypothetical aetiology	possible
2013-089	hepatic cytolysis	yes	C2: timeframe consistent and progression cannot be interpreted S2: another hypothetical aetiology	possible

Reference <sup>1</sup>	Type of effect	Serious effect <sup>2</sup>	Chronological (C) and semiological (S) scores	Causality
2011-053	Reduced blood levels of Depakine (valproic acid) (enzyme induction)	no	C1: timeframe unknown and progression cannot be interpreted S1: another possible aetiology	doubtful
2011-056	degraded dysautonomia with motility-related diarrhoea	yes	C1: timeframe not very consistent and progression cannot be interpreted S2: another hypothetical aetiology	doubtful
2012-016	decreased renal function	yes	C1: timeframe not very consistent and progression cannot be interpreted S1: another possible aetiology	doubtful
2012-044	acute hepatitis	no	C2: timeframe unknown and progression suggestive S0: other aetiology very probable	doubtful
2012-222	tendinitis	no	C0: timeframe incompatible	excluded

It should be noted that other Member States of the European Union in which food supplements containing RYR are marketed, especially Cyprus, Spain, Estonia, Finland, Poland and the Czech Republic, do not have schemes for compiling reports of adverse reactions potentially associated with the consumption of such products. Data on adverse reactions associated with the consumption of RYR are therefore not recorded in those countries.

In Italy, between April 2002 and May 2013, the surveillance system of natural health products collected 38 cases of adverse reactions occurring after the consumption of food supplements containing RYR. These cases related to muscular (13 cases), digestive (9 cases), liver-related (8 cases) or dermatological disorders (8 cases). Four cases of muscle damage were included in a publication, mentioned in Section 3.5.1.2.1 (Lapi *et al.* 2008). The causality of the other cases was not specified.

### 3.5.1.2. Cases from the literature

#### 3.5.1.2.1. *Isolated cases of adverse reactions*

Isolated cases of adverse reactions of a muscle, liver or neurological nature have been reported in the literature and are summarised in Table 2. In most cases, the reported adverse reactions can probably be attributed to RYR given similar medical histories with statin and the reversibility of the effects upon discontinuation of the product. These adverse reactions are the same as those observed with statins.

The case of peripheral neuropathy concerns a 63 year-old man who self-medicated with RYR (unknown dose) for four to six years after a statin intolerance. The patient had also been undergoing treatment with imatinib at a dose of 400 mg/day for three years. The neurological symptoms decreased three months after discontinuing RYR and did not reappear. The patient never stopped taking the imatinib. Peripheral neuropathies are a rare side effect of statins (Kumari *et al.* 2013).

The two cases of liver damage described in Table 2 were characterised by a sharp increase in transaminases (up to 24 times the normal value) (Grieco *et al.* 2009; Roselle *et al.* 2008). It should be noted that in the case described by Grieco *et al.* (2009), the patient had already presented a moderate increase in transaminases under lovastatin.

Prasad *et al.* (2002) reported a case of rhabdomyolysis in a 28 year-old female who self-medicated with RYR while taking cyclosporine after undergoing a kidney transplant. Cyclosporine, a potent

inhibitor of CYP3A4, probably caused increased serum concentrations of RYR by blocking its metabolism. An interaction between the two products was suspected.

The other cases of muscle damage reported under RYR involve patients who had already developed a myopathy with the same product or during statin therapy statine (Mullen *et al.* 2010; Polsani *et al.* 2008; Smith et Olive 2003; Vercelli *et al.* 2006).

**Table 2: Case studies of adverse reactions relating to food supplements containing RYR**

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
peripheral neuropathy in a man aged 63 years taking RYR for four to six years (unknown dose)	gastrointestinal tumour, statin intolerance (no details on the symptoms or the prescribed statin)	unknown composition	imatinib	complete regression of the adverse reaction three months after discontinuing	Kumari <i>et al.</i> (2013)
hepatitis in a woman aged 62 years 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 <i>et al.</i> (2008)
sharp increase in transaminases in a woman aged 63 years taking RYR for at least six months (one 30 mg tablet per day)	moderate increase in transaminases two years previously under lovastatin, reversible upon 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 <i>et al.</i> (2009)
myopathy in a man aged 50 years, taking RYR for 3 months (unknown dose)	AHT <sup>3</sup> , anxiety, smoking and occasional alcohol consumption	unknown composition	quinapril, clonazepam, rofecoxib, paroxetine, ginseng	complete regression of the adverse reaction upon discontinuation but recurrence of symptoms eight months later after reintroduction	Smith and Olive (2003)
myopathy in a woman aged 61 years taking RYR for one or two months (unknown dose)	myalgia under simvastatin four months earlier, reversible upon discontinuation	unknown composition	œstradiol, aspirin, vitamins	complete regression of the adverse reaction one month after discontinuing	Mueller (2006)

<sup>3</sup> AHT: arterial hypertension

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
myopathy in a man aged 46 years taking RYR for six to eight months (unknown dose)	depression, hyperactivity with attention deficit disorder, dyslexia in childhood, AHT, brucellosis in 2006, oral candidiasis, myalgias under simvastatin and niacin three years earlier, reversible upon discontinuation of simvastatin, cardiac catheterisation	unknown composition	duloxetine, valproic acid, niacin, clotrimazole, cayenne, guggulipid	complete regression of the undesirable effect 10 days after discontinuing	Polsani <i>et al.</i> (2008)
myopathy in a man aged 76 years taking RYR (unknown dose)	Type II diabetes, muscle weakness and increased CPK <sup>4</sup> under atorvastatin six months previously	unknown composition	not reported	complete regression of the adverse reaction three months after discontinuing	Vercelli <i>et al.</i> (2006)
rhabdomyolysis in a woman aged 28 years taking RYR for two months (unknown dose)	kidney transplant	unknown composition	cyclosporine	partial regression of the adverse reaction two weeks after discontinuing	Prasad <i>et al.</i> (2002)

Between April 2002 and December 2007, four cases of muscle-related adverse reactions implicating RYR were brought to the attention of the Italian surveillance system of natural health products. All were assessed as probable, according to the Naranjo probability scale (Naranjo *et al.* 1981). The four patients, three women and one man (median age 51 years), had increased creatine phosphokinase two to six months after beginning consumption of RYR, without having taken any other associated products. The adverse reactions regressed in three of the patients upon discontinuation of the products (Lapi *et al.* 2008).

No allergy-type adverse reactions after administration of RYR have been described in the literature. However, two cases of contact allergy were reported after occupational exposure to RYR as a food colouring<sup>5</sup> in Germany and Belgium.

A butcher aged 26 years had a severe anaphylactic reaction (sneezing, rhinitis, conjunctivitis, generalised pruritus followed by generalised urticaria and dyspnea) a few minutes after handling raw meat and spices containing RYR for the preparation of sausages. The subject had a history of allergic rhinoconjunctivitis, moderate allergic asthma and repeated dyspnea during work hours. The skin tests and leukocyte stimulation tests performed were strongly positive for RYR powder dissolved in water, as well as for *Monascus purpureus* at various concentrations, but negative for rice. The serological analysis revealed the presence of immunoglobulin E specific to *Monascus purpureus* (Wigger-Alberti *et al.* 1999).

A 36 year-old man working on a delicatessen-meat production site developed allergic symptoms (rhinoconjunctivitis and asthma) after handling RYR used as a food colouring mainly in the preparation of minced meat, salami and chorizo. The subject reported no allergic reaction after ingestion of delicatessen meat. The examinations conducted showed strong rhinoconjunctivitis and

<sup>4</sup> CPK: creatine phosphokinase

<sup>5</sup> Colouring not yet approved in Europe according to Directive 94/36/EC of the European Parliament and of the Council of 30 June 1994 on colours for use in foodstuffs

asthmatic reactions after exposure via inhalation for five minutes to RYR diluted in lactose. Skin tests showed a positive reaction to RYR diluted in phosphate-buffered saline solution and to extracts of *Monascus ruber* (Vandenplas *et al.* 2000).

#### 3.5.1.2.2. *Clinical studies*

There are few randomised placebo-controlled or statin-controlled clinical trials on RYR available in English in the scientific literature.

A study on secondary prevention of coronary events was performed on 4870 patients with a history of myocardial infarction, receiving a commercial preparation (Xuezhikang<sup>®</sup>) containing an extract of RYR (two 300 mg capsules containing 2.5 to 3.2 mg of monacolin K per capsule) or a placebo for 4.5 years. The number of adverse events occurring during the study was not significantly different in the two groups (Lu *et al.* 2008). It should be noted that the types of adverse events observed were not specified and they were not evidenced by enzymatic assays.

Two reviews of clinical studies, which were designed to assess the beneficial effects of RYR, were published in 2006 and 2012 (Liu *et al.* 2006; Shang *et al.* 2012). In the first, only two of the 92 studies analysed are in English, and in the second, which reports on 22 studies, only one study is in English, all the others being in Chinese.

In the 2006 review, adverse reactions were reported in 77 studies, the most common being dizziness and digestive problems (loss of appetite, nausea, stomach pain, abdominal distension and diarrhoea). There were no adverse reactions concerning muscle damage.

In the 2012 review, adverse reactions were only reported in 17 studies and related to increased levels of transaminases or creatine phosphokinase, or to digestive disorders.

The authors of these two reviews highlighted the lack of rigour in the clinical studies performed. It should be noted that no information on clinical monitoring and/or blood assays performed was reported in the majority of the studies cited.

### 3.5.2. Lovastatin

#### 3.5.2.1. Cases from pharmacovigilance

Lovastatin is marketed as a drug in several countries of the European Union (Germany, Austria, Spain, Greece and Portugal), and in the United States and Canada.

Data collected from 1993 to 2012 by the German pharmacovigilance system, the BfArM (*Bundesinstitut für Arzneimittel und Medizinprodukte*), show that the main reported adverse reactions potentially related to consumption of lovastatin are muscle- (myalgia, rhabdomyolysis, increased creatine phosphokinase, etc.) or liver-related (increased transaminases). The number of muscle disorders was three times higher than the number of liver disorders. A few cases of hypersensitivity, pruritus and rash were also reported.

The data available from Health Canada, collected from 1965 to 2012, show similar adverse reactions and in the same proportions (three times more muscle damage than liver damage), as well as a few cases of drug interactions.

#### 3.5.2.2. Clinical studies

The lack of clinical data on monacolin K present in RYR meant that it was necessary to analyse the clinical studies sponsored by the pharmaceutical company that developed lovastatin.

The randomised, double-blind EXCEL (Expanded Clinical Evaluation of Lovastatin) study involved 8245 patients (men and women) with moderate hypercholesterolemia and receiving lovastatin (20 to 80 mg/day) or a placebo for 48 weeks. It should be noted that individuals with co-morbidities or treated by another lipid-lowering agent were excluded from this study. The increased transaminase levels and the few cases of myopathy observed in this short study were rare and dose-dependent (Bradford *et al.* 1991).

The AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study), a randomised, double-blind cohort study for primary prevention of acute coronary events, involved 6605 individuals (men and women) with no history of cardiovascular disease, receiving lovastatin

(20 or 40 mg/d) or a placebo. After a follow-up of about five years, the results showed no more liver or muscle damage in the treated group than in the placebo group. One individual left the study after developing Stevens-Johnson syndrome after nine months of treatment with lovastatin. This adverse reaction declined upon discontinuation of lovastatin and under appropriate treatment (Downs *et al.* 1998).

The eight-week CURVES study, which aimed to compare the efficacy of several statins, including lovastatin, showed no difference in frequency of adverse reactions (muscle, liver or digestive) between the groups. However, as muscle and liver damage usually occurs two to five months after the start of statin therapy, this study was too short to detect such adverse reactions (Jones *et al.* 1998).

In general, statins are responsible for diverse adverse reactions of varying severity, including muscle damage that affects 10-20% of treated patients (Grundy 2013). The most common manifestation is myalgia, muscle pain with or without modification of creatine phosphokinase levels (Phillips *et al.* 2002). These symptoms are usually reversible upon discontinuation of treatment (Dirks and Jones 2006).

Rhabdomyolysis, which is very rarely observed (incidence of 0.3 cases per 10,000 patients treated with lovastatin), is characterised by a major increase in circulating levels of creatine phosphokinase and is sometimes complicated by impaired renal function related to myoglobinuria, with a mortality rate of 10% (Cziraky *et al.* 2013; Law and Rudnicka 2006; Mammen and Amato 2010).

Muscle damage is more common when statins are combined with drugs that interfere with their metabolism pathways (see Section 3.3.2). Liver damage, induced by statins more rarely than muscle damage, is reflected by increased transaminases (Grundy 2013).

### **3.6. Physiopathology data**

#### **3.6.1. Muscle damage from statins**

The molecular mechanisms of statin-induced myopathy are poorly understood. Most assumptions are based on the depletion of several metabolites due to the inhibition of HMG-CoA reductase (see Section 3.2).

The reduction in coenzyme Q10, which is a key component of the mitochondrial respiratory chain, may result in a malfunction of the mitochondria. However, the administration of statins leads to a reduction in this metabolite in serum, but not in muscle tissue (Kohro and Yamazaki 2009). In addition, coenzyme Q10 supplementation in patients with a history of myalgia attributed to statins did not change the onset of myalgia under simvastatin (Young *et al.* 2007). In another study, in patients treated with statins and under exercise conditions, a disruption of the mitochondrial respiratory chain that alters calcium homeostasis was observed (Sirvent *et al.* 2012).

It has also been shown that statins reduce protein prenylation (farnesylation and geranylgeranylation), which may affect the GTPases. The lack of prenylation of these enzymes causes vacuolisation of myofibrils, degeneration and swelling of organelles and ultimately apoptosis. Furthermore, the reduction in protein prenylation may cause an increase in cytoplasmic calcium leading to activation of caspase-3 and cell apoptosis (Abd and Jacobson 2011). It should be noted that the pro-apoptotic effects of statins on vascular smooth muscle cells are reduced with isoprenoid supplementation, especially farnesyl pyrophosphate and geranylgeranyl pyrophosphate (Guijarro *et al.* 1998).

Clearly, there are inter-individual differences in the risk of statin-induced myopathy. This susceptibility can be explained by the existence of genetic polymorphisms. Several have been identified in the *SLCO1B1* gene encoding the OATP1B1 transporter, responsible for the delivery of most statins to hepatocytes. Mutations have also been described in *CYP2D6*, which plays a major role in the metabolism of simvastatin. These phenomena contribute to increased plasma concentrations of statins, which could increase the risk of muscle damage (Scarpini *et al.* 2012).

Rare cases of autoimmune myopathies associated with statins have been described. They are characterised by the presence of anti-HMG-CoA reductase auto-antibodies. They are not reversible on discontinuation of the statin and require immunosuppressive therapy (Mohassel and Mammen 2013).

It should be noted that the muscle damage induced by statins affects striated skeletal muscles but not cardiac muscle. Simvastatin is a substrate of monocarboxylate transporter (MCT), especially type 4, which is extensively expressed in skeletal muscle and lacking in cardiomyocytes (Sirvent *et al.* 2005).

The study by Bouitbir *et al.* (2012) showed that atorvastatin causes an increase *in vitro* (53% compared to the control) in the production of reactive oxygen species (ROS) in cardiac muscle. In response, there is increased expression of messenger ribonucleic acid (mRNA) of peroxisome proliferator-activated receptor gamma co-activator (PGC-1 $\alpha$  and PGC-1 $\beta$ ), which are co-activators of the transcription of several genes encoding mitochondrial proteins, and of mRNA of superoxide dismutase (SOD1 in cytosol and SOD2 in mitochondria). This results in decreased production of ROS.

In contrast, in skeletal muscle, atorvastatin causes a much greater increase (368% compared to the control) in the production of ROS than in cardiac muscle, leading to oxidative stress from an imbalance between the antioxidant systems and the production of ROS, thus causing a malfunction of the mitochondria.

These results were also observed *in vivo* after two weeks of statin treatment (Bouitbir *et al.* 2012). The mechanism by which statins cause production of ROS has not yet been elucidated.

### **3.6.2. Liver damage from statins**

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 more than three times the normal level, with a dose-effect relationship) is thus essentially idiosyncratic, an immuno-allergic mechanism only rarely being reported (Björnsson *et al.* 2012). Cross-toxicity with other statins or other lipid-lowering agents (fibrates) is very rare.

Several hypotheses have been advanced, including the intra-hepatocyte accumulation of HMG-CoA or inhibition of the synthesis of mevalonate or an active metabolite. The biological presentation is usually cytolytic or mixed (cytolytic and cholestatic hepatitis). Rare cases of association with granulomatous hepatitis, lupus or cholangiolitis have been described with lovastatin (Cadranet *et al.* 2009).

## **3.7. Conditions under which RYR should not be consumed**

### **3.7.1. Pregnant women**

The available clinical data on the exposure of pregnant women to lovastatin are rare and contradictory. Nevertheless, as a precaution, pregnant or breastfeeding women are strongly advised not to take RYR (Kazmin *et al.* 2007). It should be noted that in France, statins are strictly contraindicated in pregnancy.

### **3.7.2. People with a history of adverse reactions with statins**

A personal and/or family history of myopathy (occurring during treatment with another cholesterol-lowering drug) or increased creatine phosphokinase are risk factors (Sikka *et al.* 2011).

In general, patients who have presented a muscle disorder attributed to statins have a risk of developing the same side effect after taking RYR, sometimes even more intensely (see the case with rhabdomyolysis reported in the literature and in Section 3.3). Therefore, the trend that seems to be developing in both the medical literature and in the general public literature, to advise or even prescribe RYR in patients who are "statin-intolerant", is currently unfounded and presents a risk in the absence of any controls of the composition.

### **3.7.3. People with predisposing conditions**

Certain diseases (renal failure, muscle disease, untreated hypothyroidism, etc.) may contribute to the increased risk of muscle damage in patients receiving a food supplement containing RYR (Hansen *et al.* 2005).

#### **3.7.4. Situations presenting a risk**

All patients receiving drugs acting on lipid metabolism (statins, fibrates, etc.) or interfering with statin metabolism (gemfibrozil, cyclosporine, macrolides, niacin, azole antifungals, protease inhibitors, calcium channel blockers, cholestyramine, calcineurin inhibitors, serotonin reuptake inhibitors, amiodarone, anticonvulsants, erythromycin, clarithromycin) are exposed to a risk of muscle damage. Combining these drugs with consumption of RYR is likely to increase this risk (Hansen *et al.* 2005; Pasternak *et al.* 2002).

Excessive consumption of grapefruit juice (more than one litre per day) or alcohol associated with taking RYR can also increase the frequency of occurrence of muscle-related adverse reactions (ANSM 2002; Pasternak *et al.* 2002).

Intense physical activity may, by itself, cause an increase in creatine phosphokinase. This increase is higher when the physical exercise is associated with taking lovastatin, suggesting that lovastatin exacerbates muscle cell lesions potentially induced by the exercise (Pasternak *et al.* 2002). Statins, by altering the functioning of the mitochondrial respiratory chain and disrupting calcium homeostasis, may lead to the development of exercise intolerance in treated patients (Sirvent *et al.* 2012).

#### **3.7.5. Vulnerable populations**

Subjects aged over 70 years consuming food supplements containing RYR are more likely to develop muscle-related adverse reactions than the general population, especially if there are other muscle-related risk factors (ANSM 2002).

Regarding the specific case of children and adolescents, if there is hypercholesterolemia justifying a discussion on the need for drug treatment, it is most often a familial form. Given the lack of data on the exposure of this population to statins and the precautionary principle, children and adolescents should be strongly advised not to take RYR.

#### **3.7.6. Inter-individual variability in the general population**

Genetic polymorphisms have been identified in the *SLCO1B1* gene encoding the OATP1B1 transporter that delivers most statins, including lovastatin, to the hepatocytes. In carriers of these polymorphisms, plasma concentrations of statins are increased, which increases the risk of muscle damage (Scarpini *et al.* 2012).

### **3.8. Regulatory context**

#### **3.8.1. In Asia**

RYR is a remedy used in traditional Chinese medicine to promote digestion and blood circulation. Since 1982, it has also appeared on the list of food additives established by the Chinese health authorities. In Japan, *Monascus purpureus* pigments are authorised for food purposes (Ma *et al.* 2000).

#### **3.8.2. In North America**

In the United States, food supplements based on RYR, if they contain a substance claimed to have a cholesterol-lowering activity (except at trace levels), have been prohibited by the FDA since 1998. Otherwise, manufacturers must follow good manufacturing practices introduced in 2007 and bring to the FDA's attention any adverse reactions potentially related to the consumption of their RYR-based food supplements. In addition, no health claim should be mentioned. These measures, however, are not always complied with by the manufacturers (Childress *et al.* 2013).

Monacolin K in RYR is regarded as an unauthorised drug. In contrast, pure lovastatin, whose molecular structure is identical to that of monacolin K, is authorised as a drug subject to medical prescription and mandatory medical monitoring.

Like the United States, Canada authorises the marketing of lovastatin at doses of 10 to 80 mg/day.

### **3.8.3. In Europe**

In Europe, food supplements containing RYR are authorised and are entitled to make the claim appearing in Commission Regulation (EU) No 432/2012 of 16 May 2012: *“monacolin K from red yeast rice contributes to the maintenance of normal blood cholesterol levels”* under certain conditions of use. Indeed, the claim can only be authorised for a food that guarantees, in the indicated dosage, daily consumption of 10 mg of monacolin K from RYR and if the consumer is informed that the beneficial effect is obtained by consuming monacolin K from fermented red rice preparations (EFSA 2011).

Food supplements containing RYR are marketed in countries including Cyprus, Spain, Finland, Poland and the Czech Republic. However, the Icelandic and Swiss health authorities have not authorised the marketing of these food supplements, considering that they contain a pharmacologically active substance.

In France, the Directorate General for Competition, Consumer Affairs and Fraud Control (DGCCRF) authorises food supplements containing RYR provided that the product marketed allows a daily dose of monacolin K that does not exceed 10 mg. The contraindications and risks of interactions and adverse reactions mentioned on the packaging of food supplements found on the market vary from one product to another (Vennetier 2012).

Furthermore, pure lovastatin has medicinal product status in some Member States of the European Union, including Germany, Austria, Spain, Greece and Portugal. It has however never been marketed in France as a drug.

### **3.9. Additional information provided by the consultation**

In order to collect as much data as possible with which to refine its assessment, ANSES submitted a draft opinion for consultation between 17 October to 15 December 2013. A review of the information provided by the consultation is given in Annex 2.

The profiles of the respondents to the consultation were varied. One doctor and four consumers reported adverse effects possibly related to the consumption of food supplements containing RYR that had not been reported to the nutrivigilance system. These adverse effects are similar to those described in the cases analysed. A fifth consumer stated that they had not experienced any adverse effects after taking red yeast rice for two years whereas they had suffered from muscle pain when taking fibrates.

Two consumer associations (Italian and French) expressed their wish that food supplements containing RYR be reclassified as medicinal products subject to medical prescription, in order to obtain standardised manufacturing, labelling that specifies the exact name of the active substance, the composition, the adverse effects and contraindications, and medical monitoring.

Three industrial companies and the French Food Supplements Trade Association (Synadiet) related the number of known adverse effects to the number of boxes sold. They concluded, based on a risk/benefit analysis, that there were only a small number of cases compared to sales. However, this approach, which is common in the pharmaceutical field, cannot be applied to the food field without some adaptation. The testimony of the industrial companies showed a lack of uniformity in practices regarding analytical control, both with respect to the method used and the substances detected (for example, some only quantify monacolin K while others also screen for contaminants). On the other hand, the precautions for use displayed on the packaging from these manufacturers seem homogeneous, except for those relating to grapefruit consumption and statin intolerance. Most of the identified manufacturers advise against the consumption of their products by pregnant and breastfeeding women or children, in cases of liver or kidney disease, and when combined with cholesterol-lowering drugs. It was noted, however, that a recommendation to consult a doctor before consuming these supplements is not always given.

The National Academy of Pharmacy approved all of the concerns raised by the draft opinion submitted for consultation and ruled in favour of the inclusion of monacolin K in Annex III of Regulation (EC) No 1925/2006.

In addition, EFSA has issued warnings about the health claim associated with products containing RYR (“helps maintain normal cholesterol”) which must be made while respecting the precautions for use and contraindications of drugs containing lovastatin, and while taking into account EFSA’s Opinion on the risks related to the presence of citrinin in food ([EFSA 2012](#)).

### 3.10. Summary and conclusions of the Expert Committee on Human Nutrition

#### "Red yeast rice" contains a substance marketed as a drug in several countries

"Red yeast rice", obtained by a traditional process and used as a food additive, has been consumed for centuries in Asia. Some food supplements containing "red yeast rice" and claiming an effect on cholesterol levels are found on the French market and available on the Internet.

The claimed effect is based on the discovery in the late 1970s of the inhibitory activity with respect to 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase of several substances called monacolins, especially monacolin K. The latter has the pharmacological characteristics of statins. It is marketed under the international nonproprietary name "lovastatin" as a drug in the United States, Canada, Germany, Austria, Spain, Portugal and Greece.

#### The monocolin composition of "red yeast rice" is highly variable and there is no standardised measurement method

Monacolin levels in "red yeast rice" depend on the strain of microorganism, growing conditions implemented by manufacturers and production processes used. The composition declared by manufacturers lacks precision and the actual levels of monacolins are mostly unknown.

Several different methods are used to assay monacolins in finished products. Therefore it is currently impossible to determine unambiguously the levels of monacolin, including monacolin K, in a food supplement containing "red yeast rice".

#### "Red yeast rice" contains potentially toxic substances and causes adverse reactions

The toxicity of "red yeast rice" is poorly documented, while that of lovastatin is better known. Lovastatin has undergone some animal studies that show toxicity to the liver, kidneys and skeletal muscles. In humans, "red yeast rice" causes the same adverse reactions as those observed with statins, which are primarily muscle and liver related.

"Red yeast rice" may also contain citrinin, a genotoxic mycotoxin.

#### There are vulnerable populations and risk situations: in these cases "red yeast rice" should not be consumed

The vulnerable populations by whom "red yeast rice" should not be consumed are pregnant women, patients regarded as "statin-intolerant", people with predisposing conditions such as kidney failure, muscle disease or untreated hypothyroidism, subjects aged over 70 years, children, adolescents and carriers of genetic polymorphisms that may increase plasma concentrations of statins.

There are also risk situations in which "red yeast rice" should not be consumed, including when taking a drug that may interfere with the metabolism of lipids and statins, and high consumption of grapefruit juice or alcohol.

#### Conclusion

Due to the composition of "red yeast rice" and in particular:

- the presence of monacolin K (also called lovastatin when marketed as a drug) that shares the adverse effects of statins;
- the presence at varying levels of other monacolins, compounds whose safety has not been established,

consumption of "red yeast rice" exposes some consumers to a health risk.

Therefore, consumption of these products should be accompanied by:

- medical monitoring related to the muscle damage caused by statins;
- a prior liver function test and strict medical supervision related to the liver toxicity caused by statins;
- readily available information on the precautions for use and contraindications of statins relative to populations at risk (especially pregnant women and patients with hepatic impairment) and risk situations (drug and food interactions).

At the present time, the marketing as a food supplement of products containing "red yeast rice" is unable to guarantee compliance with these recommendations.

Moreover, regardless of the form of marketing of such products, the possible presence of citrinin, a genotoxic mycotoxin, calls for the systematic implementation of controls.

#### **4. AGENCY'S CONCLUSIONS AND RECOMMENDATIONS**

The French Agency for Food, Environmental and Occupational Health & Safety adopts the conclusions of the CES on "Human Nutrition" considering that the consumption of "red yeast rice" presents a health risk for some consumers.

ANSES recommends therefore that consumption of these products be accompanied by:

- medical monitoring including a liver function test prior to the consumption of these products, and monitoring of liver and muscle toxicity associated with statins;
- readily available information on the precautions for use and contraindications of statins relative to populations at risk (especially pregnant women and patients with hepatic impairment) and risk situations (drug and food interactions).

It also considers that the status of these products should be clarified at European level and that their marketing channels should ensure compliance with these recommendations.

Furthermore, ANSES reiterates that hypercholesterolaemia is not a disease but a factor that increases the risk of occurrence of cardiovascular disease, and that the "maintaining of normal cholesterol levels" claimed for products containing "red yeast rice" depends above all on following a suitable diet and taking regular physical exercise.

Because of the existing marketing channels for these products, the Agency recommends that consumers:

- seek advice from a healthcare professional before consuming food supplements containing "red yeast rice";
- avoid consuming these food supplements if they fall into the following categories:
  - o pregnant and breastfeeding women;
  - o children and adolescents;
  - o subjects aged over 70 years;
  - o people with predisposing conditions such as kidney failure, muscle disease, untreated hypothyroidism, or people suffering from progressive liver disease;
  - o heavy grapefruit (juice or fruit) or alcohol consumers.
- refrain from consuming these food supplements if they are being treated with cholesterol-lowering drugs containing statins, or if they have been obliged to stop taking these drugs following the occurrence of adverse effects (patients known as "statin-intolerant"), except on specific medical advice.

ANSES also reminds healthcare professionals of the following:

- food supplements containing "red yeast rice" are not an alternative to treatment with cholesterol-lowering medication;
- subjects treated with drugs that may interfere with lipid metabolism and statins must not consume food supplements containing "red yeast rice";
- any adverse effect occurring after consumption of food supplements containing "red yeast rice" must be reported to the Agency.

Marc Mortureux

## KEY WORDS

"Red Yeast Rice", *Monascus purpureus*, food supplement, monacolins, lovastatin, citrinin, nutritional vigilance, muscle damage, rhabdomyolysis, liver damage, vulnerable populations

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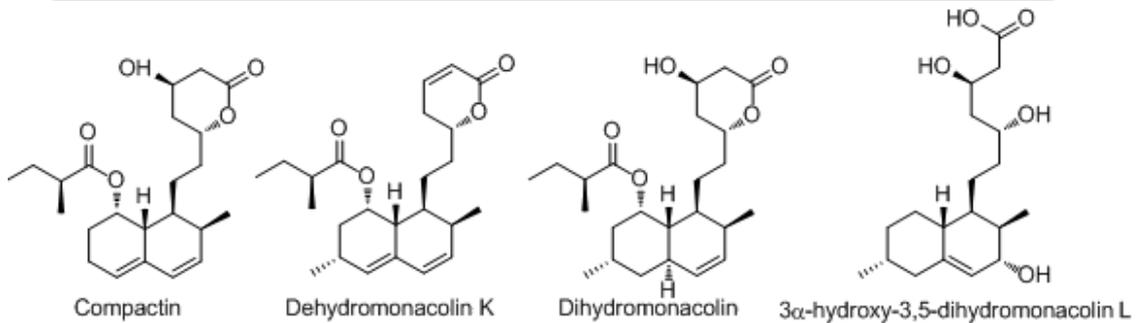
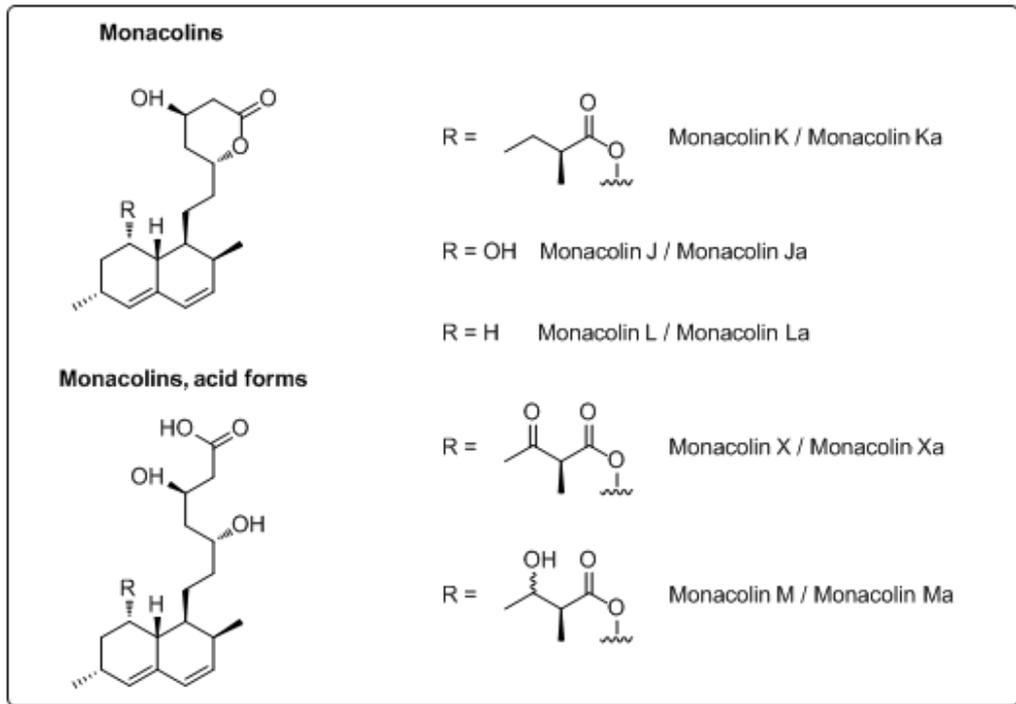


**ANNEXES**

Annex 1: Structure of monacolins identified in food supplements containing “red yeast rice”

Annex 2: Review of responses received from the consultation on the draft opinion on the risks associated with the presence of “red yeast rice” in food supplements

ANNEX 1: STRUCTURE OF MONACOLINS IDENTIFIED IN FOOD SUPPLEMENTS CONTAINING “RED YEAST RICE”



**ANNEX 2: REVIEW OF RESPONSES RECEIVED FROM THE CONSULTATION ON THE DRAFT OPINION ON THE RISKS ASSOCIATED WITH THE PRESENCE OF “RED YEAST RICE” IN FOOD SUPPLEMENTS**

The draft opinion on "red yeast rice" submitted for consultation between 17 October and 15 December 2013 drew responses from six categories of stakeholders:

**1. Individuals**

Five consumers of red yeast rice (four women and one man) wrote to share their experiences. Except in one case (43 years), their ages were not specified.

Four of them described muscle pain, associated with joint pain in two cases. In two of them, these adverse effects had already appeared when taking statins: Staltor® (cerivastatin) for one; Crestor® (rosuvastatin) for the other. The other two consumers had not previously received any cholesterol-lowering therapy. Of these four consumers, only two stated the time until appearance of adverse effects (two months for one and five months for the other). In all the cases, the pain ceased when the subjects stopped taking the red yeast rice.

The fifth consumer had no adverse effects after two years of taking red yeast rice, whereas they had suffered from muscle pain when taking fibrates.

**2. A physician**

One doctor reported a case of increased creatine phosphokinase (CPK) in a 77-year old man who had taken medically-prescribed red yeast rice for about 10 years. This statement, which followed the information in the *Quotidien du Médecin* journal of 28 October 2013, was the subject of a request for further information, which has remained unanswered to date.

**3. Consumer associations**

*a. In Italy*

An Italian consumers' association (*Altroconsumo*) expressed its views about the safety of food supplements containing red yeast rice. It forwarded a letter sent to Italian and European institutions (including EMA and EFSA). In the letter, the association requests the reclassification of these food supplements as medicinal products, to ensure that the manufacturing process is standardised, the exact name of the active substance and the composition is displayed on the packaging, together with the adverse effects and contraindications, and to ensure that they are subject to medical prescription.

An article was published on this subject in July 2013. The arguments set out in this article are the same as those given in the draft opinion (presence of a pharmacologically-active substance, less stringent manufacturing procedures and controls than for drugs, extremely variable monacolin K quantities from one food supplement to another, presence of other active substances from the same family whose mechanism of action and adverse effects are still unknown, over-the-counter product that is presented as a natural remedy, which may lead patients to consume it in addition to their statins thereby potentiating the adverse effects).

*b. In France - UFC-Que Choisir*

The association stressed the discrepancy between the claim (maintains cholesterol at a normal level) and the actual effect of these food supplements (reduces hypercholesterolaemia). It added that the draft opinion confirms that these products containing red yeast rice do indeed have a pharmacological action (effect type, effect intensity and adverse effects comparable to that of a statin drug) and not a physiological action. In this context, UFC-Que Choisir believes that the over-the-counter marketing of these substances, which can be consumed without any medical monitoring whatsoever, seems dangerous for consumers. UFC-Que Choisir requested that future recommendations address the issue of the inclusion of these products in regulations on food supplements.

#### **4. Industry**

##### *a. Synadiet*

Synadiet collected the sales figures of 23 member companies and five non-member companies through a survey: more than one million boxes of food supplements containing RYR were sold in France in the last 12 months. Out of 26 members, seven declared that they were aware of adverse effects (27 cases, "i.e. 1 case per 45,500 boxes sold"). The adverse effects reported were "minimal, infrequent (1/45,500 boxes = 0.002%) and reversible". They related mainly to muscle problems (cramps and pain) or digestive disorders (diarrhoea, constipation, heartburn). Only one case related to liver damage. "In comparison, statins have the disadvantage of causing adverse effects such as muscle pain in 15% of treated patients. The proportion of adverse effects with RYR food supplements is therefore far lower."

It seems that 17 members have an assaying method for monacolin K but not all use the same method (HPLC/UV mainly). Among them, 11 members systematically screen for possible adulterations (the methods used differ). Furthermore, nine of the 10 members who answered the question also screen for undesirable substances (citrinin and aflatoxin B1). Nevertheless, it seems that for some members this screening is not carried out on each batch for both substances.

Synadiet also collected data from members of foreign trade bodies. In Italy, it would appear that only one industrial company responded to the survey. It was aware of 73 cases of adverse effects since first marketing its RYR food supplement (4 years), "i.e. one case per 67,100 boxes sold". The daily dose of monacolin K in this food supplement is 3 mg. In Belgium, five members responded to the survey. The daily doses contained in their products are higher (6.75 to 12 mg). Annual sales for these members are 77,000 boxes. The adverse effects reported (muscle pain in the lower back) were derived from a clinical study of one of the products and relate to four of the 142 patients included in the study. These four patients belong to the subgroup of 37 statin-intolerant patients.

"Synadiet and its members share the desire to see the precautions for use and recommendations on product consumption appear on the labelling." Synadiet recommends that its members provide the following warnings on the labelling of food supplements containing RYR:

- not recommended for pregnant or breastfeeding women, or for young people under 18 years;
- not recommended in patients with liver or kidney disease, in patients with hypersensitivity to statins or in cases of abnormally high levels of transaminases;
- not recommended in patients undergoing medical treatment with statins: seek the advice of your doctor.

##### *b. Monin-Chanteaud Laboratory*

The laboratory states that the products it sells are mainly recommended by doctors, more rarely by pharmacists. For about three years it has marketed a commercial product providing a daily dose of 8.2 mg of monacolin K. Each batch of raw material undergoes self-inspection in addition to the supplier's data sheet with regard to pesticides, heavy metals, screening for citrinin and determination of monacolin K by HPLC. The sales volume is about 45,000 boxes/year. The finished product is assayed by HPLC.

Besides archiving for classical nutrivigilance, the laboratory has developed a more specific monthly report form since RYR was added to its product range. This form is used to record any adverse effects experienced by the patient and reported to their prescribing physician. More than 1000 physicians are questioned each month. The laboratory thus implemented a statistical study of the results obtained and of any possible adverse effects related to taking this product. This study is now finished and the analysis of its results will soon be completed (the results have not to date been disclosed). The analysis of classical nutrivigilance data showed that the few cases of muscle cramps and, occasionally, of increased CPK were always related to the daily dose (whether or not recommended by a doctor) being exceeded.

The laboratory believes that RYR is a sensitive product on which a further ruling would seem necessary. It challenges the decision of the European Commission regarding the efficacy above 10 mg, adding that it prefers to not make any claim and to remain at 8 mg based on the assumption that above 8 mg there is already the possibility of some minor adverse effects.

Regarding labelling, the laboratory already mentions the precautions for use: do not use in patients with kidney failure or liver disease; do not use in pregnant women; do not use in combination with any drug to combat cholesterol; do not use in cases of proven allergy to statins; reserved for adults.

*c. Omega Pharma Laboratory (Belgium)*

The Omega Pharma laboratory answered the summary points one by one.

- *RYR contains a compound that is classified as a drug in many countries.*

The laboratory makes three arguments for continuing the marketing of food supplements containing red yeast rice: RYR can be regarded as an "other substance with a nutritional or physiological effect" in the regulatory definition of a food supplement; RYR is not a novel food because it was used before 1997; EFSA issued a favourable opinion on the relationship between consumption of monacolin K and maintaining normal cholesterol levels, and accordingly a beneficial physiological effect. The laboratory reiterates that the coexistence of two regulatory statutes is legally possible, citing the example of vitamins or plants authorised both in medicinal products and in food supplements. It added that the mere presence of monacolin K is not sufficient in itself to conclude that RYR is a drug. Finally, "products containing more than 10 mg of monacolin K may be classified as medicinal products by function, but not products containing lower doses".

- *Monacolin composition in RYR is highly variable and there is no standardised assaying method.*

The laboratory quantifies monacolin K in the raw material and the finished product by LC/MS-MS, "which enables the two forms (acid and lactone) to be separated". The laboratory supports the validation of this analytical method and is willing to provide data to guarantee its reproducibility.

- *RYR contains potentially toxic substances and causes adverse effects.*

The presence of citrinin cannot be excluded, as the limit currently applied by the laboratory is 50 µg/kg ("significantly below the EU limit of 2000 µg/kg"). Moreover, reference is made in the draft opinion to 12 cases collected by the French nutriviigilance system, whose causality was likely to very likely. "Only 1 case in 12 is considered serious (nausea, muscle weakness, increased transaminases). The number of incidents (12 cases in 4 years, or 3 cases/year) corresponds to a percentage of 0.0008 (based on a total of 1,085,991 boxes sold in the last three years in France, as reported by IMS Health)". Reference was also made to cases collected by the Italian surveillance system for natural health products, with possible causality in 4 cases of muscle damage. These cases were reported between April 2002 and May 2013, i.e. over an 11-year period. "Taking into account the total number of sales over the last three years (9,359,276 boxes, reported by IMS Health) and 0.4 cases/year (4 cases in 11 years equates to 1.1 cases in 3 years), the number of incidents corresponds to 0.00001%. In the period preceding the acquisition of Arterin by Omega Pharma (2006 until early 2013, or about 7 years), four adverse effects with possible causality were reported in Belgium. With an average of 107,503 boxes sold per year by Arterin (322,510 over the last three years) and not more than one case per year, the number of incidents is equal to 0.0009%". The laboratory concludes by showing that these incident percentages are extremely low, "especially since consumers do not just buy a single box. Tests with a placebo probably lead to a greater number of adverse effects, and statins are responsible for adverse effects in 10-20% of patients treated".

Justification by the laboratory for the low number of incidents: "the use of RYR is not commonly associated with myopathy, and the risk of occurrence of typical effects induced by statins is low. Statin-intolerant patients who presented muscle pain after taking statins tolerate red yeast rice well. The fact that the dose of monacolin K in RYR is lower than the threshold necessary to trigger the muscle pain associated with statins is one possible explanation. Blaming drugs for various perceived side effects is a natural tendency, given that statins are known to have triggered muscle pain and that everyone feels muscle or joint pain from time to time. Products containing red yeast rice are therefore more likely to lead to biased reports of adverse effects."

- *There are vulnerable populations and risk situations where red yeast rice must not be consumed.*

"Risk managers in France are particularly cautious about warnings on the labelling of food supplements containing red yeast rice. The labelling of Arterin clearly indicates that it should not be used during pregnancy or breastfeeding, that the product is not recommended if the consumer is taking cholesterol-lowering medication or has liver or kidney disease, and that the product is not recommended with the consumption of grapefruit (juice or fruit). If the need for additional warnings is demonstrated, risk managers can change the labelling accordingly. Omega Pharma always recommends consulting a health professional before taking Arterin."

*d. Phacobel Laboratories (Belgium)*

The laboratory states that a list of precautions for use based on those of lovastatin is given on the information leaflet for their product (Artechol). This product is standardised at 3% (400 mg of red yeast rice per capsule, i.e. 12 mg of monacolin K guaranteed in each capsule). Each batch is tested by another laboratory using the Chinese method (ultrasound extraction of monacolin K in 75% ethanol followed by analysis by HPLC with UV detection at 238 nm) to determine the exact amount of monacolin K present in the raw material and in the finished product. The HPLC method allows them "to visualise the other forms of monacolin present in the sample and to distinguish the acid form from the lactone form of monacolin K". The strain of *Monascus purpureus* selected by the laboratory "produces a large quantity of monacolin K with a ratio of acid/lactone forms of 75%/25%, while producing very little citrinin, which is inevitably produced during the fermentation process." The laboratory states that the certificate of analysis provided by the supplier of the red yeast rice "guarantees an absence of citrinin in the samples" but that systematic checks are carried out "a second time on each delivery of the raw material, to verify the amount of citrinin that may be present, by HPLC as recommended by EFSA."

The product marketed by Phacobel Laboratories was the subject of a European clinical study, the Mona Lisa study. This was a prospective study conducted in 123 hypercholesterolaemic patients (86 patients who had never received statin therapy and 37 patients intolerant to synthetic statins). The treatment time was six weeks. The study was able to "demonstrate the effectiveness of Artechol but also the fact that it is well tolerated". A decrease in levels of total cholesterol and LDL-C of between 19 and 21% was observed while no significant changes in levels of HDL-C, blood triglycerides and creatine phosphokinase (CPK) were identified. The 86 patients who had never received any prior treatment with statins showed good tolerance. Among the 37 patients intolerant to synthetic statins, four cases of myalgia (muscle pain in the back) were reported. The laboratory concluded that Artechol showed 89% tolerability in this patient group.

A second randomised double-blind (placebo vs Artechol) clinical study is currently under way. This study aims to assess the effectiveness of Artechol in a population of patients at high cardiovascular risk but intolerant to synthetic statins. The treatment time in this study is 12 weeks. The results are not yet known.

In the patient information leaflet, consumption is not recommended: in pregnant or breastfeeding women, in patients with hepatic and renal impairment, in combination with grapefruit juice, or in children. A daily intake of 12 mg of monacolin K is recommended, which according to the laboratory, satisfies the health claims imposed by EFSA.

Apart from citrinin, the laboratory also systematically tests for the presence of arsenic in each batch. The supplier tests the levels of cadmium, lead, mercury, aflatoxin B1, *Salmonella* and *E. coliform*.

In conclusion, the laboratory admits that "the use of a food supplement made from red yeast rice of inferior quality that is insufficiently controlled and not standardised can expose consumers to a health risk". This is why the laboratory "supports the establishment of stricter controls on the quality of products containing red yeast rice on the EU market, in order to ensure patient safety."

## **5. The National Academy of Pharmacy**

The National Academy of Pharmacy approved the concerns raised in the draft opinion submitted for consultation, in particular the variability in monacolin composition, the presence of potentially

toxic substances, the observation of adverse effects and the lack of a standardised assaying method. It ruled "in favour of the inclusion of monacolin K in Annex III of Regulation (EC) No 1925/2006 and the prohibition in France of all food supplements containing RYR, unless they contain only trace amounts of monacolins and citrinin and subject to arranging suitable labelling that must mention the assaying method and its sensitivity."

## **6. EFSA**

EFSA expressed its satisfaction with the draft opinion, "which provides well-documented cases of adverse events potentially associated with food supplements containing red yeast rice from the nutriviigilance system and the literature."

EFSA reiterates, as explained in the draft opinion, that the health risks associated with citrinin in food are addressed in its opinion published in March 2012. Moreover, as Regulation (EC) No. 1924/2006 does not provide for risk assessment but rather an assessment of the scientific justification of the health claims (assessment of the effectiveness), EFSA has not conducted an assessment of the risks associated with the consumption of red yeast rice, despite being aware of the potential adverse effects and interactions with other products (mainly statins). In this context, it was very important to alert risk managers by issuing warnings in the EFSA opinions about the health claims associated with products containing red yeast rice, i.e. with the following clarification in the section on "Conditions and restrictions on use": regarding the restrictions on use, reference is made to the SPC for medicinal products containing lovastatin available on the European market and EFSA's opinion on citrinin, a nephrotoxic mycotoxin that can be produced by certain strains of *Monascus purpureus*.

In conclusion, "EFSA is responsible for providing scientific opinions on food safety for risk managers in the European Union, but EFSA is not involved in the entire legislative process launched on the basis of an EFSA opinion. The authorisation to use health claims in the EU, including the final conditions for use, the wording of the claim as well as any restrictions on use ultimately falls within the competence of the European Commission and the Member States".