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SCIENTIFIC OPINION

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Scientific Opinion on additional scientific data related to the safety of monacolins from red yeast rice submitted pursuant to Article 8(4) of Regulation (EC) No 1925/2006

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The declarations of interest of all scientific experts active in EFSA's work are available at https://open.efsa.europa.eu/experts

Abstract

The Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver a scientific opinion on the safety of monacolins from red yeast rice (RYR), which have been placed under Union scrutiny in Part C of Annex III in accordance with Article 8(4) of Regulation (EC) No 1925/2006. The NDA Panel reviewed the additional scientific data submitted during the period of scrutiny, which included analytical data on the composition of RYR supplements, the intake of monacolins from other dietary sources, in vitro bioaccessibility and cytotoxicity data of monacolins vs. other statins, nutrivigilance/post-marketing data, case reports and clinical studies. Based on the new nutrivigilance data provided, the NDA Panel reiterates the concerns of the ANS Panel (EFSA ANS Panel, 2018) that exposure to monacolin K from RYR at intake levels as low as 3 mg/day could lead to severe adverse effects on the musculoskeletal system, including rhabdomyolysis, and on the liver. The NDA Panel concludes that the data submitted by interested parties during the Union scrutiny period do not allow establishing the safety of monacolins in RYR supplements below 3 mg/day or to identify a daily intake of monacolins from RYR in food supplements that does not raise safety concerns for the general population or vulnerable subgroups thereof.

KEYWORDS

food supplements, lovastatin, monacolins, *Monascus purpureus*, red yeast rice

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1 | INTRODUCTION

1.1 | Background and Terms of Reference as provided by the requestor

1.1.1 | Background

Regulation (EC) No 1925/2006[1] establishes the rules governing the addition of vitamins and minerals and of certain other substances to foods and, in particular, Article 8 thereof defines the procedure to be followed for prohibiting, restricting, or placing under Community scrutiny a given substance.

1.1.2 | Terms of Reference

On 1 June 2022, pursuant to Article 1(2) of Commission Regulation (EU) 2022/860,[2] amending Annex III, Part C, of Regulation (EC) No 1925/2006, the Commission has placed under Union scrutiny 'Monacolins from red yeast rice'.

The European Commission (EC) requests the European Food Safety Authority's (EFSA) opinion on whether the scientific data contained in the files submitted or to be submitted for evaluation by food business operators or any other interested parties demonstrate the safety of substances placed under Union scrutiny mentioned above.

1.2 | Interpretation of the Terms of Reference

As safety concerns were raised in relation to the consumption of monacolins from red yeast rice (RYR) in food supplements at doses of 10 mg/day, and individual cases of severe adverse reactions had been reported at doses as low as 3 mg/day (EFSA ANS Panel, 2018), monacolins from RYR were placed under Union scrutiny (Commission Regulation (EU) 2022/860) and Annex III (Part B) to Regulation (EC) No 1925/2006 was amended to indicate that the individual portion of the product for daily consumption shall provide less than 3 mg of monacolins from RYR.

The main reasons for placing monacolins from RYR food supplements under Union scrutiny (Recital 18 of Commission Regulation (EU) 2022/860) were the scientific uncertainties in relation to the possibility of harmful effects on health associated with the use of monacolins from RYR and that EFSA (EFSA ANS Panel, 2018) could not identify a level of intake that does not give rise to concerns about harmful effects to health for the general population, and as appropriate, for vulnerable subgroups of the population.

In the context of the terms of reference and the reasons given in the recitals of Commission Regulation (EU) 2022/860 for placing monacolins from RYR under Union scrutiny, the Panel understands that EFSA is requested to assess whether the data provided by food business operators (FBO) or any other interested parties during the scrutiny period are sufficient to:

a. address the scientific uncertainties raised by the EFSA ANS Panel (2018) in relation to the safety assessment of monacolins from RYR; and
b. allow the identification of a daily intake of monacolins from RYR in food supplements[3] that does not raise safety concerns for the general population or vulnerable subgroups thereof.

Therefore, this assessment needs to be read in conjunction with the EFSA ANS Panel opinion (2018), where all the information and data available in relation to the safety of monacolins from RYR up to the scrutiny period is presented and assessed, including the chemical homology with the cholesterol-lowering medication lovastatin and a (comparative) assessment of the ADME and reported adverse effects in humans.

This assessment concerns the safety of monacolins from RYR in food supplements only. Potential beneficial health effects of monacolins from RYR and risk–benefit analyses are out of the scope of this mandate.

This assessment does not concern quality aspects of RYR products available in the market, such as the potential presence of contaminants (e.g. fungi and their mycotoxins such as citrinin) or adulterants (e.g. addition of synthetic statins).

1.3 | Previous EFSA assessments on monacolins from RYR

The EFSA NDA Panel has assessed two health claim applications on monacolin K from RYR and maintenance of normal blood LDL-cholesterol concentrations with a favourable outcome (EFSA NDA Panel, 2011, 2013). To obtain the claimed effect,

[1]Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. OJ L 404, 30.12.2006, p. 26–38.

[2]Commission Regulation (EU) 2022/860 of 1 June 2022 amending Annex III to Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards monacolins from red yeast rice. OJ L 151, 2.6.2022, p. 37–41.

[3]According to recital 6 of Regulation (EC) No 2022/860, the use of RYR preparations in other food categories is subject to an authorisation under Regulation (EC) 2015/2283 on novel foods.

10 mg of monacolin K from fermented RYR should be consumed daily. The target population was adults in the general population. In the framework of Regulation (EC) No 1924/2006, a safety assessment is not foreseen in health claim evaluations.

In relation to the restrictions of use, the NDA Panel referred to the opinion by the EFSA CONTAM Panel on citrinin (a nephrotoxic mycotoxin), which can be produced by some strains of *Monascus purpureus* (EFSA CONTAM Panel, 2012). The maximum level of citrinin (100 µg/kg) in food supplements based on rice fermented with the red yeast *Monascus purpureus* is regulated [Regulation (EU) 2023/915].

In relation to the restrictions of use, the NDA Panel also referred to the Summary of Product Characteristics (SmPC) for lovastatin-containing medicinal products available on the EU market, as monacolin K in lactone form is identical to lovastatin. The SmPC, among others, includes special warnings and precautions for use that refer to the risk of myopathy/rhabdomyolysis, which is increased by concomitant use of lovastatin with certain other medicinal products, and discourages the use of lovastatin by pregnant and lactating women [EFSA NDA Panel, 2011, 2013; Regulation (EU) 2022/860]. In that context, Member States raised potential safety concerns associated with the consumption of foods containing monacolins from RYR (ANSES, 2014; CSS, 2016; DFG, 2016).

Consequently, in 2017, the European Commission initiated the procedure under Article 8(2) of Regulation (EC) No 1925/2006 and asked EFSA to:

- review the existing scientific data on the possible link between the intake of monacolins from RYR and harmful effects on health.
- provide advice on a daily intake of monacolins from RYR that does not give rise to concerns about harmful effects to health, for the general population, and as appropriate, for vulnerable subgroups of the population.

In 2018, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) issued an opinion on the safety of monacolins in RYR (EFSA ANS Panel, 2018) within the framework of Article 8(2) of Regulation (EC) No 1925/2006.

In its opinion, the EFSA ANS Panel (2018) noted that monacolin K in lactone form is identical to lovastatin, the active ingredient of several medicinal products authorised for the treatment of hypercholesterolemia in the EU. Monacolin K from RYR is available in food supplements at varying recommended daily intakes for its effect on the maintenance of normal blood LDL cholesterol levels. The estimated exposure to monacolin K was within the range of therapeutic doses of lovastatin. The ANS Panel noted that the profile of adverse effects of RYR was similar to that of lovastatin. Based on case reports, the most important target organs/tissues for adverse events were musculoskeletal and connective tissues (including rhabdomyolysis), liver, nervous system, gastrointestinal tract, skin and subcutaneous tissue, in descending order of occurrence. The available information on the adverse effects reported in humans was judged to be sufficient to conclude that monacolins from RYR in food supplements were of significant safety concern at the use level of 10 mg/day. The ANS Panel further noted that individual cases of severe adverse reactions (rhabdomyolysis, hepatitis and skin disorders) to monacolins from RYR which required hospitalisation had been reported at intakes as low as 3 mg/day taken for periods of between 2 weeks and 1 year.

On the basis of the information available and the several uncertainties highlighted in its opinion, the ANS Panel was unable to identify a level of intake of monacolins from RYR in food supplements that does not give rise to concerns about harmful effects to health, for the general population, and as appropriate, for vulnerable subgroups of the population (EFSA ANS Panel, 2018).

In 2019, the European Commission asked EFSA to provide technical assistance on two scientific publications that were submitted to the Commission by an interested party following the adoption of the scientific opinion by the ANS Panel (2018). These were a systematic review and meta-analysis of randomised controlled trials (RCT) on the safety of RYR supplementation (Fogacci et al., 2019) and a narrative review and expert opinion aiming at weighing the risks and benefits of using RYR in food supplements and the drug lovastatin as blood cholesterol-lowering agents (Banach et al., 2019). EFSA noted that the RCTs provided were not designed to detect adverse effects as the sample size was not sufficient for that purpose, and that comparative risk–benefit analyses were not useful in addressing the safety concerns raised by the available case reports of adverse effects associated with the consumption of RYR in humans.

2 | DATA AND METHODOLOGIES

2.1 | Data

During the period of Union scrutiny, foreseen by Article 8(4) of Regulation (EC) No 1925/2006, four interested parties [Società Italiana di Scienze Applicate alle Piante Officinali e ai Prodotti per la Salute (SISTE), European Federation of Associations of Health Product Manufacturers (EHPM), Linneus Consulting Services and Hylobates Consulting srl as representative of Asociación Española de Complementos Alimenticios (AFEPADI)] submitted data. All the documents submitted by each interested party are listed in alphabetical order of the first author.

SISTE submitted:

- A narrative review including the analysis of serious adverse events (rhabdomyolysis and acute hepatitis), associated with the consumption of RYR reported to the US Food and Drug Administration (Banach & Norata, 2023), which included reference to post-marketing nutrivigilance safety data for specific food supplements containing RYR (Banach et al., 2021).
- An RCT on the effects (including adverse effects) of a food supplement containing RYR and providing total monacolins < 3 mg/day (Cicero et al., 2024).
- A narrative review on the occurrence of muscle symptoms and liver dysfunction associated with the consumption of RYR supplements, using available data from adverse event reporting systems and meta-analyses (Norata & Banach, 2024).

EHPM submitted:

- A final report of the Task Force for RYR of EHPM on nutrivigilance data (EHPM, 2024), including an update on post-marketing nutrivigilance safety data for a specific food supplement containing RYR (Banach et al., 2024, unpublished).
- A study about the phytochemical profile, pharmacological effects and safety of various RYR samples in comparison with lovastatin, using in vitro/in silico models (Rigillo et al., 2025).

Linneus Consulting Services submitted:

- A report including the monacolin content in commercially available RYR products (food supplements) and in vitro cytotoxicity assessments of RYR samples vs. lovastatin, and of monacolin K vs. simvastatin and atorvastatin, using a human HepG2 cell line model (Linneus Consulting Services, 2024).
- An analytical report of RYR metabolites in different ethanolic extracts (SUPPLEMENTARY_MATERIALS_TOT).

Hylobates Consulting srl, representative of AFEPADI, submitted:

- A summary report/document of the evidence for establishing a health-based guidance value (HBGV) for RYR (< 3 mg/day) (AFEPADI, 2024), including a scientific statement from the American Heart Association (AHA) on statin safety and associated adverse events (Newman et al., 2019) and reference to a food-borne outbreak in Japan linked to the consumption of RYR products (Hashimoto et al., 2024).
- A list of references included in the submission (AFEPADI20240703MonacolinReferenceProvided.pdf).
- A published article about the lovastatin content in *Pleurotus ostreatus*, or oyster mushroom (edible mushroom) (Alarcón et al., 2003).
- A published article about the influence of the gut microbiota on the conversion of monacolin K to its active β-hydroxy acid form (BBeltrán et al., 2019).
- A published article about the on-label and off-label uses of lovastatin as a drug (Duong & Bajaj, 2023).
- EFSA's external scientific report about the occurrence of citrinin in food (López Sánchez et al., 2017).
- A narrative review about the use of statins in children (Fiorentino & Chiarelli, 2023).
- A narrative review about statins (Hajar, 2011).
- A cover letter from AFEPADI (Hylo2024SignedLetter.pdf).
- A published article about a new analytical method [nuclear magnetic resonance (NMR) assay] for assessing total statin content and β-Hydroxy β-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibition in RYR supplements (Lachenmeier et al., 2012).
- A published systematic review and meta-analysis on the use of statins in children with familiar hypercholesterolaemia (Radaelli et al., 2018).
- A published article on the content of mycotoxins and natural statins in commercially available RYR food supplements (Righetti et al., 2021).
- A systematic review about the beneficial and adverse effects of Xuezhikang, a partially purified extract of fermented RYR, in the secondary prevention of coronary heart disease (CHD) combined with dyslipidaemia (Shang et al., 2012).
- An analytical guideline for RYR, as a basis to establish the specifications for the product [SIFITLab Laboratorio d'analisi di Siena et al. (2018b) (translation in English) and SIFITLab Laboratorio d'analisi di Siena et al. (2018a) (original document in Italian)].
- A narrative review about citrinin occurrence in food supplements (Silva et al., 2021).
- A published article about the quantification of lovastatin in *Agaricus bisporus* (mushroom species) (Tsiantas et al., 2021).
- A published article containing the evaluation of the quality profile of food supplements containing RYR marketed in Italy (Vitiello et al., 2023).
- A document about the first identification of *M. purpureus* (Went, 1895).

The Panel considers that the following documents submitted are not pertinent to the safety assessment of monacolins from RYR, which do not include quality aspects of RYR supplements in the market (see Section 1.3), and will not be considered further in this opinion:

- The publications by Went (1895), Beltrán et al. (2019) and Silva et al. (2021);
- Analytical guideline to establish the specifications for RYR products [SIFITLab Laboratorio d'analisi di Siena et al. (2018a) (original document in Italian) and SIFITLab Laboratorio d'analisi di Siena et al. (2018b) (translation in English)];
- Data related to a recent food intoxication outbreak in Japan that has been attributed to the contamination of RYR products during the fermentation stage with *Penicillium adametzoides*. This fungus produces puberulic acid, which can induce renal dysfunction (MHLW, 2024);
- Narrative reviews (Duong & Bajaj, 2023; Fiorentino & Chiarelli, 2023; Hajar, 2011), the systematic review (Radaelli et al., 2018) and the consensus statement from the AHA (Newman et al., 2019) on the safety of statins, which collectively address the trade-off between beneficial and adverse effects of the on-label and off-label use of statins for the treatment of hypercholesterolaemia and/or the prevention of cardiovascular diseases in different population groups, including children and adolescents and do not provide relevant information for the safety assessment of monacolins from RYR, including the identification of a daily dose of monacolin K from RYR in food supplements that does not raise safety concerns for humans.

In accordance with Article 38 of Regulation (EC) No 178/2002[4] and taking into account the protection of confidential information and of personal data in accordance with Articles 39, 39a to 39e of the same Regulation and of the Decision of EFSA's Executive Director laying down practical arrangements concerning transparency and confidentiality,[5] the non-confidential versions of the data submitted by the interested parties are published in OpenEFSA.[6]

According to Art. 32c (2) of Regulation (EC) No 178/2002 and according to the Decision of EFSA's Executive Director laying down the practical arrangements on the pre-submission phase and public consultations, EFSA carried out a public consultation (PC-1090) from 13 August to 03 September 2024 on the non-confidential version of the submissions by interested parties. No comments were received.

2.2 | Methodologies

The scientific evaluation was based on the data submitted during the period of scrutiny, and it was performed in line with the principles described in the EFSA Guidance on transparency in the scientific aspects of risk assessment (EFSA, 2009) and followed the relevant existing guidance documents from the EFSA Scientific Committee. The risk assessment was performed according to the EFSA Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (EFSA Scientific Committee, 2009).

3 | ASSESSMENT

The data submitted by interested parties to EFSA aim at addressing the uncertainties identified by the ANS Panel (2018), which precluded establishing a HBGV for monacolins in RYR food supplements. The NDA Panel considers as pertinent for that purpose:

- Analytical data about the characterisation of RYR preparations (Lachenmeier et al., 2012; Linneus Consulting Services, 2024; Righetti et al., 2021; Rigillo et al., 2025; Vitiello et al., 2023);
- Data on the dietary intake of monacolins from food sources other than RYR (AFEPADI, 2024);
- In vitro/in silico data of RYR/monacolin K vs. other statins (Linneus Consulting Services, 2024; Rigillo et al., 2025);
- Nutrivigilance/post-marketing data on adverse events related to the use of RYR products (Banach & Norata, 2023; Banach et al., 2021; Banach et al., 2024, unpublished; Norata & Banach, 2024; EHPM, 2024; AFEPADI, 2024);
- Case reports of adverse events from the scientific literature (Banach & Norata, 2023);
- New clinical data including safety endpoints (Shang et al., 2012; Cicero et al., 2024, unpublished).

3.1 | Analytical data about the characterisation of RYR preparations

The following uncertainties in relation to the characterisation of RYR preparations were highlighted by the ANS Panel (2018):

a. the composition and content of monacolins (and their relative abundance) in food supplements containing RYR;
b. monacolins in RYR are used in multi-ingredient botanical preparations, the components of which have not been fully evaluated individually or in combination; and
c. the ratio between monacolin K lactone and monacolin K hydroxy acid (HA) is variable in food supplements containing RYR.

[4]Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, pp. 1–48.

[5]Decision available online: https://www.efsa.europa.eu/en/corporate-pubs/transparency-regulation-practical-arrangements.

[6]The non-confidential version of the dossier, following EFSA's assessment of the applicant's confidentiality requests, is published on Open.EFSA and is available at the following link: https://open.efsa.europa.eu/questions/EFSA-Q-2023-00424.

Rigillo et al. (2025) analysed 14 commercial-grade RYR food supplements with a declared total monacolin K content ranging from < 0.15% to 5% w/w using a high-performance liquid chromatography with diode array detection (HPLC-DAD) method, which allows quantifying the content of total monacolin K (as the sum of monacolin K in lactone and HA forms) and the content of other monacolins (as the sum of monacolin M, monacolin L, monacolin L HA, monacolin X, compactin, dihydromonacolin K and dehydromonacolin K). Total monacolin K ranged from 0.05% to 5.25% w/w in the analysed samples, showing deviations from the declared amounts (from −5% to +20%), while other monacolins showed high variability, accounting for 3%–30% (mean 23%) of total monacolins. The ratio between monacolin K in lactone form and monacolin K in HA form ranged from approximately 1:1–34:1 in the tested samples. The average content of total polyphenols and total triterpenes was 0.92% and 3.63% w/w, respectively, and did not correlate with the total content of monacolins.

In the report by Linneus Consulting Services (2024), phytochemical analyses were conducted in 27 samples of RYR food supplements commercially available on the Italian market and supplied by different companies. The content of monacolin K in lactone (MK-L), HA (MK-HA) and dehydro- (DMK) forms and the content of other monacolins (M-SEC; the sum of monacolin L, compactin, monacolin J, monacolin L HA, monacolin X and monacolin M) were quantified using HPLC-DAD-MS/MS and high-resolution mass spectrometry (HRMS) methods. The measured content of total monacolins (from 0.45% to 7.84% w/w), including all forms of monacolin K and other monacolins, differed from the declared content (from –37% to +62% w/w) in most samples for which this information was available. The ratio MK-L:MK-HA varied from 2.5:1 to 114:1 across RYR samples. Based on the ratio between each monacolin measured (MK-L, MK-HA, DMK and M-SEC) and the sum of MK-L and MK-HA (MK-L/MK-L+MK-HA; MK-HA/MK-L+MK-HA; DMK/MK-L+MK-HA; M-SEC/MK-L+MK-HA), a hierarchical cluster analysis (HCA) was used to identify the different patterns of relative monacolin abundance across RYR samples. The four clusters identified on such bases were used to select six RYR samples that were representative of RYR supplements available on the market for untargeted analyses and in vitro cytotoxicity testing (see Section 3.3). The Panel notes that the four clusters identified widely differed in the relative abundance of MK-L, MK-HA, DMK and M-SEC. The six RYR samples selected underwent ethanol extraction at different concentrations (30%, 50% and 75%), followed by untargeted analysis by ultra-high-performance liquid chromatography-high-resolution mass spectrometry (UHPLC-HRMS) methodology. The major groups of compounds found in the ethanol extracts were monacolins (25%–30%), azaphilones (19%–23%) and polyketides (10%–15%), the amounts of which varied depending on the extract. Other compounds such as fatty acids, lignans, glycosides, steroids, amino acids, coumarins, decalins, terpenoids, alkaloids and flavonoids were also quantified.

An ^{1}H-NMR study (Lachenmeier et al., 2012) provided information about the monacolin content in five commercially available RYR products obtained from web-shops. Total monacolin content (the sum of the lactone and HA forms of monacolin K and other monacolins containing the hexahydronaphthalene moiety, including monacolins J, L, M or X) ranged between 1.5 and 8 mg/capsule (0.45%–1.33% w/w), leading to daily doses of 1.5–24 mg based on the manufacturer's recommendations.

In the study by Righetti et al. (2021), 37 RYR food supplements as mono- or multi-ingredient formulations available on the Italian market were analysed for their content of mycotoxins (e.g. citrinin), MK-L and MK-HA. Among these, nine RYR products had a total monacolin K content below the label statement (from −27 to −83%), with three products having a negligible content, while the content of total monacolin K was higher than reported (from 10% to 266%) in 25 products. In four products, the total monacolin K content would result in a daily intake below 3 mg following the manufacturer recommendations, while in 20 products, the daily dose would exceed 10 mg, reaching 36 mg in one product. The ratio MK-HA/MK-L+MK-HA across samples varied from 0.03 to 0.64. The authors noted that variable but small amounts of simvastatin (0.1–7.5 μg per daily dose) were also found in 30 RYR food supplements.

Vitiello et al. (2023) tested 14 RYR food supplements commercially available on the Italian market with a declared monacolin K content from 1.45 to 10 mg/unit of product (film-coated or uncoated tablets, hard-shell capsules, soft gels). The authors found that, in all products tested, the measured content of monacolin K deviated from the declared one (from –20.8% to +1.4%) and showed high variability across products (from 1.47 to 10.14 mg total monacolin K/unit of product).

The Panel acknowledges that some information has been provided regarding the identification and quantification of compounds other than monacolins in selected RYR samples and the identification and quantification of monacolins and their relative abundance (Linneus Consulting Services, 2024; Rigillo et al., 2025), including the total monacolins (Lachenmeier et al., 2012), the amount of total monacolin K (Vitiello et al., 2023) and the ratio between its lactone and HA form (Linneus Consulting Services, 2024; Righetti et al., 2021; Rigillo et al., 2025). The Panel also notes, however, that:

a. commercially available RYR food supplements show high variability in total monacolin K content (from < 0.15% to 7.48%, w/w), as well as in the amount of total monacolins/monacolin K measured vs. declared on the product label; and
b. the ratio between monacolin K in its lactone form (chemically identical to lovastatin) and its HA form shows significant variability in food supplements containing RYR, with reported ratios ranging from 1:1 to 114:1.

The Panel considers that, although the data provided contribute to the knowledge on the composition and total monacolin profile of commercially available RYR supplements, it also strengthens the concerns expressed by the EFSA ANS Panel (2018) about the uncertainties regarding the characterisation of these products, particularly in relation to the variability in content of total monacolin K and to the relative abundance of its lactone and HA forms, as these two forms of monacolin K are most likely responsible for the adverse health effects reported in relation to the consumption of RYR supplements.

3.2 | Data on the dietary intake of monacolins from food sources other than RYR

In the document by AFEPADI (2024), it is argued that monacolins (including monacolin K in lactone form) are naturally occurring substances found not only in RYR but also in various species of edible mushrooms (Alarcón et al., 2003; Chen et al., 2013; Kała et al., 2020; Lam & Okello, 2015; Lee et al., 2006; Lin et al., 2013; Lo et al., 2012; Tsiantas et al., 2021). Consequently, the interested party argued that any risk assessment or risk management actions concerning monacolins from RYR should also consider and apply to other dietary sources.

The Panel notes the opinion of the Joint Expert Committee BVL/BfArM (BVL/BfArM, 2016), which evaluated the occurrence of monacolins in food sources and provided intake estimates. Their review of the available literature on monacolin content in several edible mushroom species identified several methodological shortcomings, particularly concerning sample preparation and analytical methods used. To address these limitations, the Committee conducted an internal study using a validated method to measure the monacolin content in mushrooms. This study concluded that the intake of monacolin K lactone would range from approximately 4 to 11 µg per 100–200 g of fresh mushrooms consumed. The Panel notes that these intake levels are several orders of magnitude lower than the currently allowed maximum daily doses of monacolin K from RYR when consumed as food supplements [Regulation (EC) 2022/860]. Therefore, the Panel considers that the daily intake of monacolin K from RYR would greatly exceed the amount of monacolin K that would be reasonably expected to be consumed in the context of a balanced and varied diet.

3.3 | In vitro data of RYR/monacolin K vs. other statins

In the study by Rigillo et al. (2024), the pharmacokinetic differences between 1 mL of selected RYR solutions with a total monacolin K content between 1.55 and 5.25% w/w (see Section 3.1) and an equivalent concentration of pure lovastatin were evaluated in an in vitro model of simulated digestion. The median bioaccessibility rate of lovastatin, expressed as % of recovery after sample digestion compared to the initial (pre-digestion) amount used, was 65.23% ± 18.45%, which was explained by the poor solubility of lovastatin in the digestive environment. When replicating the simulated digestion without enzymes, but only changing the pH, a comparable recovery was obtained. Bioaccessibility of monacolin K from RYR samples varied, but it was higher than for lovastatin (only one sample had a slightly lower value), exceeding 80% in some samples and reaching 100% in one sample, with a total monacolin content of 3.5% w/w. The authors noted that the bioaccessibility of RYR samples was positively associated with the content of other monacolins and triterpenes and not with the content of monacolin K.

The in vitro cytotoxic effects of 14 RYR samples, differing in monacolin K content (from 0.05% to 5.25% w/w), total polyphenols, and triterpenes, as well as pure lovastatin, were assessed using the cell counting kit-8 (CCK-8) assay (Rigillo et al., 2025). Cytotoxicity was measured at concentrations ranging from 10 to 200 µg/mL in various immortalised or cancer-derived cell lines, including human intestinal (Caco-2), hepatic (HepG2), kidney (HEK293) cells and mouse muscle (C2C12) cells. The results were expressed as IC_{50} values, representing the concentration required to reduce 50% of cell viability. Most RYR samples showed IC_{50} values exceeding the highest concentration tested, i.e. 200 µg/mL in all cell lines. IC_{50} values above 100 µg/mL were shown in HEK293 cells by two samples and in C2C12 cells by four samples. When compared with lovastatin, the only remarkable difference was that the highest cytotoxicity of lovastatin was observed in the C2C12 myoblast cell line.

To investigate the molecular mechanisms of statin-induced toxicity in muscle cells, the authors compared the effects of selected RYR samples and lovastatin on the expression of genes involved in muscle function and metabolism, including myoblast determination protein 1 (MyoD), muscle creatine kinase (MCK) and interleukin-6 (IL-6). The C2C12 muscle cells were treated for 24 h with lovastatin (1 µg/mL) or RYRs at the equivalent monacolin K concentration, corresponding to 1 µg/mL. The mRNA levels of the selected genes were measured by quantitative reverse transcription polymerase chain reaction (RT-qPCR) and in the case of IL-6, also at protein levels. Lovastatin treatment significantly downregulated MyoD and upregulated MCK and IL-6 compared to controls and RYR samples, suggesting targeted effects on muscle physiology. In contrast, RYR samples showed minimal or sporadic effects, indicating a more limited and variable impact. Additionally, the expression of autophagy- (Atg5 and Atg7) and atrophy-related genes (Fbxo32 and Trim63) was analysed. Lovastatin significantly upregulated Atg7 and Trim63 mRNA levels compared to control, while RYR samples did not affect the expression of these genes (Rigillo et al., 2025).

In the Linneus Consulting Services report (2024), an in vitro Alamar Blue cytotoxicity assay was conducted on liver HepG2 cells exposed for 24 h to various concentrations (0.1–100 µM) of simvastatin, atorvastatin, monacolin K and six RYR preparations with varying monacolin compositions (0.45–7.84% w/w; see Section 3.1). Simvastatin caused significant cytotoxicity at higher concentrations (97% at 100 µM, 70% at 50 µM), while atorvastatin was less cytotoxic (49% at 100 µM). Monacolin K caused 20% cell death only at 100 µM. RYR preparations exhibited higher cytotoxicity overall, with 72%–96% cell death at 100 µM and up to 95% at 50 µM. Notably, three RYR samples showed slight cytotoxicity (13%–18%) even at 0.1 µM. Increased cytotoxicity correlated with higher dehydromonacolin K content. These findings suggest that RYR preparations are more cytotoxic than pure monacolin under these conditions.

The Panel notes that, based on the submitted studies, RYR preparations (with total monacolin K content ranging from 0.05% to 5.25% w/w) demonstrate variable cytotoxic effects, which are generally less pronounced than those observed for lovastatin, particularly in muscle C2C12 cells. However, the IC_{50} values reported for RYR preparations are predominantly

threshold values (i.e. > 200 μg/mL), indicating no cytotoxicity within the tested concentration range. Consequently, the actual IC_{50} values could be any value higher than 200 μg/mL, rendering any definitive conclusion inappropriate. The analysis of transcriptional levels of target genes involved in muscle function and metabolism provides a plausible mechanism for the greater toxicity of lovastatin in muscle cells compared to RYR preparations. The Panel also notes the higher in vitro cytotoxicity of RYR samples as compared to monacolin K and other statins (Linneus Consulting Services report, 2024) in the HepG2 cell line, the same cell line that showed a lack of cytotoxic effects with both lovastatin and RYR samples up to 200 μg/mL in the Rigillo et al. (2024) study. These contrasting findings highlight the variability in RYR sample compositions, which may hamper cytotoxicity assessments. The Panel acknowledges that, while in vitro cytotoxicity studies may offer valuable mechanistic insights, their predictive value for in vivo toxicity is limited, especially when using immortalised cell lines, as in the submitted studies. The Panel considers that, given these limitations, these studies are of limited value for the safety assessment of monacolins in RYR for human consumption.

3.4 | Nutrivigilance/post-marketing data on adverse events related to the use of RYR products

A narrative review (Norata & Banach, 2024) reported on adverse events related to muscle and liver as target organs associated with the consumption of products containing RYR. The FDA Adverse Event Reporting System (FAERS) (as of September 2023) and CFSAN Adverse Event Reporting System (CAERS) (as of June 2023) were used as sources of data.

A total of 28 cases of adverse events, of which 25 were classified as serious events, were retrieved from FAERS. These included eight cases of musculoskeletal- and connective tissue-related adverse events, of which three were cases of rhabdomyolysis. Seven women and one man (from 51 to 78 years of age) were affected. In all cases, RYR was one among other active ingredients in the product suspected to be responsible for the adverse effects, and in three cases, the concomitant use of other products/medications was noted. Four cases of liver-related adverse events were reported, including three cases of hepatic cytolysis and one case of liver damage (not better specified). Only males (from 45 to 68 years of age) were affected. The concomitant use of other products/medications was noted in all cases.

The analysis of the CAERS database retrieved 223 cases of adverse events in relation to RYR supplement use. These included 53 cases of muscle-related adverse events, with myalgia and muscle spasms being the most common symptoms, and 29 cases of liver-related adverse events, with abnormal liver function tests being the most common finding. Multiple adverse effects were often reported by the same person. In 34 cases of muscle-related adverse events and 10 cases of liver-related adverse events, RYR was one among other active ingredients in the products suspected to be responsible for the adverse effects, while in all other cases, RYR was used in concomitance with the suspected product (other than RYR). When RYR was reported as the suspected product, adverse events were more frequent in women. The age of affected individuals ranged from 36 to 91 years (median age: 64 years).

The Panel notes that neither the FAERS nor the CAERS database allows concluding on causal relationships between the use of RYR-containing products and the reported adverse events. The Panel also notes that FAERS does not provide information on the doses of RYR consumed, while CAERS reports a dose of 600 mg of RYR in several cases but reports no information on the monacolin content of these products.

The paper by Banach et al. (2021) reports on post-marketing safety data for the RYR-containing food supplements Armolipid® (standard) and Armolipid® Plus (enhanced), at the recommended dose of one tablet/day for 1 year. One tablet of Armolipid (standard) contained RYR (200 mg, of which 3 mg of monacolin K), folic acid (0.2 mg), CoQ10 (2 mg), astaxanthin (0.5 mg) and, in some countries, policosanols (10 mg). One tablet of Armolipid Plus (enhanced) contained *Berberis aristata* extract (588 mg, of which 500 mg of berberine chloride), RYR (200 mg, of which 3 mg of monacolin K), policosanol (10 mg), folic acid (0.2 mg), CoQ10 (2.0 mg) and astaxanthin (0.5 mg).

Post-marketing information was collected in a voluntary nutrivigilance system established by the manufacturing company (Meda Pharma SpA, a Viatris Company, Monza, Italy) from 1 October 2004 to 31 December 2019. This system captured cases of suspected adverse effects spontaneously reported by consumers, healthcare professionals or health authorities, regardless of causality. A total of 542 notifications/cases reporting on 855 adverse events were received related to the use of Armolipid® (standard) and Armolipid® Plus (enhanced). The number of musculoskeletal adverse events (% of the total) was 148 (17.3%), and the number of hepatic adverse events was 26 (3%). Serious adverse events occurred in nine cases, two related to rhabdomyolysis and seven to serious hepatitis.

One case of rhabdomyolysis occurred in an elderly woman who took Armolipid® Plus (enhanced) while using sertraline and rosuvastatin. The second case was a consumer (unknown sex) with a history of rhabdomyolysis in response to simvastatin who developed rhabdomyolysis requiring hospitalisation after starting Armolipid® Plus (enhanced). The authors claim that, in both cases, the labelling warnings against concomitant use of RYR supplements and other statins without medical supervision were not respected by the consumers. As for the seven cases of serious hepatitis, causality was assessed as probable (in two cases), possible (in two cases) and unlikely (in three cases) by the reporter based on the WHO-UMC system criteria (WHO, 2018).

The authors (Banach et al., 2021) calculated the total reporting rate of adverse events and serious adverse events notified in relation to the consumption of Armolipid® (standard) and Armolipid® Plus (enhanced) by estimating the number of exposed consumers based on the number of tablets manufactured over 15 years, assuming a consumption of one tablet per day for 1 year ($n = 2{,}287{,}449$). The total reporting rate (number of cases among total consumers) was 0.0374% for any

adverse event, 0.0011% for potential serious adverse events, 0.0003% for confirmed serious adverse events, 0.0064% for musculoskeletal adverse events, 0.0001% for rhabdomyolysis, 0.0011% for hepatic adverse events and 0.0004% for acute hepatitis. The Panel notes the weaknesses of calculating the number of consumers based on the total of tablets manufactured and the instructions for use, which do not take into account varying individual consumption patterns, unsold products and product waste. The Panel considers that, in the absence of exposure data, the reporting rate of adverse events cannot be reliably estimated in this way.

The Panel notes that the updated analysis of Banach et al., 2024 (unpublished) includes the reporting of adverse events for the RYR-containing supplements Armolipid® (standard) and Armolipid® Plus (enhanced) up to 31 December 2023 (additional 4 years). The total number of notifications received mentioning these RYR-food supplements increased from 542 to 1186, in which 1904 adverse events were reported. A total of 28 notifications included suspected serious adverse events, of which nine (12 adverse events) were assessed by the manufacturer as serious and potentially related to the consumption of the RYR-containing supplements (3 mg monacolin K/day). The total number of exposed consumers was estimated to be 3,880,865 following the same methodology as in Banach et al. (2021). The estimated reporting rate was 0.049% for adverse events, 0.0007% for suspected serious adverse events and 0.0002% for confirmed serious adverse events. The Panel reiterates its considerations regarding the weaknesses of such calculations.

The 'Final Report of the EHPM Alliance for a Nutrivigilance System for Food Supplements Pilot Project: Red Yeast Rice' (EHPM, 2024) contains nutrivigilance data on RYR products collected from food supplement manufacturers within the EU from 12 December 2022 to 31 May 2024. A total of 148 reports of adverse events were collected. The cumulative number of consumers exposed ($n = 608{,}815$) was estimated based on product sales. The estimated reporting rate of adverse events and of serious adverse events was 0.02% ($n = 122$) and 0.0003% ($n = 2$), respectively. Serious adverse events were one case of pancreatitis and one case of so-called 'bladder congestion' leading to hospitalisation, which were deemed unlikely to be associated with the intake of an RYR supplement. The mean age of individuals who experienced the adverse events was 65.3 ± 13.3 years, with most adverse events affecting women (75.7%). Individuals over 70 years of age[7] accounted for over 58% of reports where age was specified, and for the only two cases of severe adverse events. The authors noted the off-label use of RYR supplements in individuals > 70 years of age in this period. In most cases, adverse events were gastrointestinal (45.9%), followed by arthromyalgia (16.9%) and cases of hypersensitivity (10.8%) and the time from the start of RYR supplementation to the occurrence of the adverse events was unknown. In accordance with the WHO-UMC causality assessment system (WHO, 2018), a certain cause–effect relationship between the supplement taken and the reported adverse events was established for 17 out of 148 cases (11.5%). Although this nutrivigilance study has been conducted after Regulation (EU) 2022/860 came into force, limiting the daily dose of monacolins from RYR to below 3 mg, the Panel notes that no information is available about the monacolin content of the RYR supplements for which adverse events were collected.

AFEPADI (2024) aimed at updating data on adverse events associated with the use of RYR-based products as reported in the EFSA ANS Panel opinion (2018). The databases searched, the time period covered by the searches and the findings were as follows:

a. Vigibase database maintained by the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring. Cut-off date: 31 January 2024. A total of 749 cases of adverse events with RYR supplements as suspected/interacting/concomitant products were retrieved for the European region. The number of cases peaked in 2021 with 226 reports, followed by 107 in 2022 and 53 in 2023.
b. CAERS database. Time period: January 2004 to August 2023. A total of 65 cases were identified in addition to those reported by the ANS Panel (2018).
c. The Canada Vigilance Adverse Reaction Online Database. Time period: 1965 to 30 September 2023. Four reports of adverse events were identified. The reports contained insufficient information about the product used or the individual experiencing the adverse event, or the RYR supplement was used in concomitance with drugs.

AFEPADI (2024) also contacted all nutrivigilance or pharmacovigilance authorities or entities in the EU and EEA to obtain further data. Only the Portuguese authority (out of 15 others) provided data and reported 30 adverse events linked to lovastatin, but none on RYR supplements.

The Panel notes that nutrivigilance data confirm the reporting of adverse events in relation to the consumption of RYR supplements after the implementation of Regulation (EU) 2022/860, which limits the amount of monacolins in RYR supplements to less than 3 mg per daily dose and restricts their use to individuals aged 18–70 years. The Panel also notes that Banach et al. (2021) and Banach et al. (2024) (unpublished) provide useful insights into the reported adverse events associated with the consumption of RYR supplements at 3 mg monacolin K/day and strengthen the previous considerations by the EFSA ANS Panel (2018) that individual cases of severe adverse effects have been reported at these levels of intake.

Regarding the estimated reporting rate of adverse events, the Panel notes that the total number of consumers is estimated based on the quantity of manufactured tablets (Banach et al., 2021; Banach et al., 2024 unpublished) or sale figures (EHPM, 2024), which overlook critical factors such as varying individual consumption patterns (including dose and duration of use) and product waste. It has been argued that spontaneous reporting of adverse effects (e.g. muscle symptoms) in relation to RYR use could be higher if consumers expect such types of adverse effects to occur (nocebo effect), as it has been

[7]According to Regulation (EU) 2022/860, food supplements containing monacolins from RYR should hold a labelling requirement stating: 'Should not be consumed by pregnant or lactating women, children below 18 years old and adults above 70 years old.'

observed for statins (Newman et al., 2019). However, underreporting of adverse events associated with the use of over-the-counter food supplements is well documented, possibly because these are presumed to be safe by consumers (Woo, 2007).

In this context, the publications submitted (AFEPADI, 2024; Banach et al., 2021; Banach et al., 2024, unpublished; Norata & Banach, 2024) used nutrivigilance data to compare the frequency of reported adverse events for statins (e.g. lovastatin) and for RYR supplements, concluding that serious adverse events are less frequently reported in relation to RYR supplement use. However, the Panel considers that direct comparisons between the frequency of adverse effects reported for statins at pharmacological doses under medical supervision and the estimated adverse event reporting rates for RYR supplements cannot be used to assess the safety of monacolins in RYR or establish a safe daily dose. The Panel notes the reported adverse events in relation to the consumption of RYR supplements at 3 mg monacolin K/day (Banach et al., 2021; Banach et al., 2024, unpublished).

3.5 | Case reports of adverse events from the scientific literature

Case reports of adverse effects related to the consumption of RYR supplements published in the scientific literature and for which causality was assessed, or where clinical data were sufficiently detailed, had been reviewed by the EFSA ANS Panel (2018).

A narrative review submitted (Banach & Norata, 2023) addressed published case reports of serious adverse events (rhabdomyolysis and acute hepatitis) associated with the consumption of RYR products. There were two cases of rhabdomyolysis (Prasad et al., 2002; Santos et al., 2023), three of acute hepatitis (Grieco et al., 2009; Loubser et al., 2019; Roselle et al., 2008) and one of acute renal failure, hepatitis and rhabdomyolysis (Peterslund et al., 2020). Out of these six case reports, three were already reviewed by the ANS Panel in 2018 (Grieco et al., 2009; Prasad et al., 2002; Roselle et al., 2008).

Peterslund et al. (2019) reported the case of a 65-year-old male who was hospitalised with acute renal failure, hepatitis and rhabdomyolysis. The authors concluded that the cause of these side effects was an RYR supplement consumed for 11 months (315 mg/day, containing 10 mg of monacolin K). Loubser et al. (2019) reported the case of a 64-year-old woman who was hospitalised with acute hepatitis after taking 1200 mg of RYR/day for 6 weeks before admission. The amount of monacolins in the RYR supplement was not reported. Liver biopsy results were consistent with acute drug-induced hepatitis. Finally, Santos et al. (2023) reported the case of a 50-year-old woman with comorbidities who was hospitalised with chest discomfort and generalised myalgia. Laboratory findings were consistent with the diagnosis of rhabdomyolysis. The publication does not contain information on the doses of RYR or monacolins consumed.

The Panel notes that these published case reports further confirm the occurrence of severe adverse events following the consumption of RYR supplements. The Panel considers that the new case reports do not address the concern raised by the EFSA ANS Panel that individual cases of severe adverse reactions had been reported for RYR supplements at intake levels of monacolin K as low as 3 mg/day consumed for a period between 2 weeks and 1 year (Mazzanti et al., 2017; EFSA ANS Panel, 2018, Tables 9 and 10).

3.6 | New clinical data including safety endpoints

The manuscript by Cicero et al. (2024, unpublished) reports on a randomised, double-blind, placebo-controlled, cross-over trial in which 40 participants (20 males and 20 females; ≥ 30 years and ≤ 70 years of age) with low-density lipoprotein cholesterol (LDL-C) levels between 115 and 130 (different values reported in different sections of the report) and 190 mg/dL were randomised to receive daily either a food supplement containing RYR (total monacolins < 3 mg; exact amount not reported) or placebo for 6 weeks. After a 2-week washout period, participants were assigned to the alternative treatment. Only the results for the first part of the trial (parallel intervention) were provided. Sample size was calculated based on the expected between-group differences with respect to changes in LDL-C concentrations during the study.

A fasting blood sample was taken at the beginning and end of the parallel intervention for the analysis of LDL-C, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, plasma glucose, alanine transaminase (ALT), aspartate transaminase (AST), Gamma-glutamyl-transferase (γ-GT) and creatine phosphokinase (CPK) followed by an extensive proteomic analysis. Safety and tolerability were evaluated through continuous monitoring of adverse events, clinical safety, laboratory findings, vital sign measurements and physical examinations. After 6 weeks of treatment, no significant differences between groups were observed in any of the parameters analysed in blood samples or the proteomic analysis. The manuscript does not provide further information on the safety or tolerability of the RYR supplement used.

The Panel notes that the total monacolin content in the RYR supplement used in this study is reported as < 3 mg per daily dose, but it is not further specified or quantified. The Panel also notes the small sample size and the short duration of the study, which limit the conclusions that can be drawn in relation to the safety of the RYR supplement tested.

The narrative review by Banach et al. (2024) summarised the findings of meta-analyses of RCTs designed to test the efficacy of RYR on the blood lipid profile and also reported on adverse effects (Fogacci et al., 2019; Gerards et al., 2015; Li et al., 2014; Peng et al., 2017). An additional systematic review of RCTs designed to test the efficacy of Xuezhikang (a partially purified extract of fermented RYR) in the secondary prevention of CHD combined with dyslipidaemia was also submitted (Shang et al., 2012). The RCTs included in these reviews and meta-analyses widely overlap. These reviews concluded that adverse effects of RYR supplementation were either not reported, or the frequency of reporting was not significantly different between RYR and placebo groups across trials.

As previously highlighted by EFSA [ANS Panel, 2018; Regulation (EU) 2022/860] and BfR (2020), the vast majority of RCTs reviewed in those publications were designed for efficacy, lasted < 6 months and included a number of subjects per intervention arm ($n < 100$) that is inadequate to detect significant differences between the intervention and placebo groups in adverse events that occur in < 1/100 or < 1/1000 participants, as reported for uncommon and rare adverse events in relation to the use of statins (SmPC for lovastatin, online). In addition, several trials did not report on adverse events (unclear whether these were specifically assessed or not), on the methodology used to assess adverse events, or on the dose of monacolins/monacolin K administered with RYR. In this context, the Panel reiterates that the results of the above-mentioned RCTs, including the new clinical trial submitted with an RYR food supplement providing < 3 mg/day total monacolins, do not address the safety concern raised by case reports of adverse events following consumption of RYR supplements at doses of 3 mg/day and above [ANS Panel, 2018; Regulation (EU) 2022/860] and do not allow establishing the safety of monacolins in RYR supplements at doses below 3 mg/day.

4 | DISCUSSION

The analytical studies submitted provide some information regarding the identification and quantification of monacolins and other compounds in selected RYR samples, including the relative abundance of monacolins, the amount of total monacolin K and the ratio between its lactone and HA forms. Although the data provided contribute to the knowledge on the composition and monacolin profile of commercially available RYR supplements, it also strengthens the uncertainties expressed by the EFSA ANS Panel (2018) regarding the characterisation of these products, particularly in relation to the variability in the content of total monacolin K (ranging from < 0.15% to 7.48% w/w) and to the relative abundance of its lactone and HA forms (ratio ranging from 1:1 to 114:1). These two forms of monacolin K are most likely responsible for the adverse health effects reported in relation to the consumption of RYR supplements (Section 3.1).

Comparative in vitro studies on the cytotoxicity of RYR preparations (total monacolin K content ranging from 0.05% to 7.84% w/w) in relation to statins in various immortalised or cancer-derived cell lines were submitted. These studies revealed variability in the cytotoxic effects between different statins and RYR preparations, as well as among the RYR samples themselves (Section 3.3). While in vitro data submitted may be useful for initial screening and understanding of potential cellular mechanisms of toxicity, they are of limited value to predict in vivo toxicity, and thus for the safety assessment of monacolins in RYR in vivo in humans (Section 3.3).

The nutrivigilance data submitted have been used to compare the frequency of reported adverse events for statins (e.g. lovastatin) and for RYR supplements, suggesting that serious adverse events are less frequently reported in relation to RYR supplement use. However, direct comparisons between the frequency of adverse effects reported for statins at pharmacological doses under medical supervision (derived from preclinical studies and pharmacovigilance reports) and the estimated adverse event reporting rates for RYR supplements are of limited value. The Panel notes the occurrence of reported adverse events in relation to the consumption of RYR supplements at 3 mg monacolin K/day (Section 3.4).

Three newly published case reports further confirm the occurrence of severe adverse events following the consumption of RYR supplements, but do not modify the conclusions drawn from the existing body of evidence. The EFSA ANS Panel concluded that individual cases of severe adverse events had been reported for RYR supplements at intake levels of monacolin K as low as 3 mg/day consumed over periods between 2 weeks and 1 year (Section 3.5).

The vast majority of RCTs testing RYR supplements, including a new clinical study submitted, were designed to assess efficacy, lasted < 6 months and included less than 100 subjects per intervention arm, a sample size that is inadequate to detect significant differences in uncommon (< 1/100) or rare (< 1/1000) adverse events as reported for statins. Furthermore, several trials did not report on adverse events (unclear whether these were specifically assessed or not), on the methodology used to assess adverse events, or on the dose of monacolins/monacolin K administered with RYR (Section 3.6).

The Panel notes the variable composition and lack of standardisation of commercially available RYR products, particularly regarding the type and relative abundance of monacolins, including monacolin K and its forms. Severe adverse reactions, for which causality has been assessed and for which detailed clinical data are available, have been reported for RYR supplements at intake levels of monacolin K as low as 3 mg/day. Recent nutrivigilance data confirm reports of adverse events, including rhabdomyolysis, at this level of intake. The Panel also notes that daily doses of monacolin K from RYR, when consumed as food supplements following manufacturers recommendations, would greatly exceed the amount of monacolin K that would be reasonably expected to be consumed from a balanced and varied diet (Section 3.2). In this context, the additional data submitted on the composition of RYR supplements, their in vitro bioaccessibility and cytotoxicity, estimated adverse event reporting rates, case reports and clinical studies do not allow establishing the safety of monacolins in RYR supplements below 3 mg/day or to identify a daily intake of monacolins from RYR in food supplements that does not raise safety concerns for the general population or vulnerable subgroups thereof.

5 | CONCLUSIONS

Based on the additional nutrivigilance data provided, the NDA Panel reiterates the concerns of the ANS Panel (EFSA ANS Panel, 2018) that exposure to monacolin K from RYR at intake levels as low as 3 mg/day could lead to severe adverse effects on the musculoskeletal system, including rhabdomyolysis, and on the liver.

The NDA Panel concludes that the data submitted by interested parties during the Union scrutiny period do not allow establishing the safety of monacolins in RYR supplements below 3 mg/day or identifying a daily intake of monacolins from RYR in food supplements that do not raise safety concerns for the general population or vulnerable subgroups thereof.

6 | STEPS TAKEN BY EFSA

1. The files submitted by SISTE, EHPM, Linneus Consulting Services, and Hylobates Consulting srl pursuant to Article 8(4) of Regulation (EC) No 1925/2006 were received by EFSA within 24 months from the date on which the substances had been listed in Part C of Annex III to Reg (EC) No 1925/2006.
2. The scientific evaluation started on 27 June 2024.
3. In line with EFSA's policy on openness and transparency, a public consultation on non-confidential data submitted by interested parties was launched from 13 August to 03 September 2024. No comments were received.
4. EFSA informed the European Medicines Agency's (EMA) Committee on Herbal Medicinal Products (HMPC) about the ongoing risk assessment on monacolins from RYR during their meeting on 20 January 2025.
5. During its meeting on 29 January 2025, the NDA Panel, having reviewed the data, adopted an opinion on additional scientific data related to the safety of monacolins from red yeast rice submitted pursuant to Article 8(4) of Regulation (EC) No 1925/2006.

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, excretion
AFEPADI	Asociación Española de Complementos Alimenticios
AHA	American Heart Association
ALT	Alanine transaminase
ANS	EFSA Panel on Food Additives and Nutrient Sources added to food
ANSES	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail
AST	Aspartate Transaminase
Atg	Autophagy
BfR	Bundesinstitut für Risikobewertung
BVL/BfArM	Expert Committee of the Federal Office of Consumer Protection and Food Safety/Federal Institute for Drugs and Medical Devices
CAERS	CFSAN Adverse Event Reporting System
CCK	Cell Counting Kit-8
CHD	Coronary heart disease
CFSAN	Centre for Food Safety and Applied Nutrition
CONTAM	EFSA Panel on Contaminants in the Food Chain
CoQ10	Coenzyme Q10
CPK	Creatine phosphokinase
CSS	Conseil Supérieur de la Santé
DFG	Deutsche Forschungsgemeinschaft
DMK	Dehydro-monacolin K
EEA	European Economic Area
EHPM	European Federation of Associations of Health Product Manufacturers
FAERS	FDA Adverse Event Reporting System
FBO	Food business operators
FDA	U.S. Food and Drug Administration
Gamma-GT	Gamma-glutamyltransferase
HA	Hydroxy acid
HBGV	Health-based guidance value
HCA	Hierarchical cluster analysis
HDL-C	High-density lipoprotein cholesterol
HMG-CoA	β-Hydroxy β-methylglutaryl-CoA
H-NMR	Proton Nuclear Magnetic Resonance
HPLC-DAD	High-Performance Liquid Chromatography with Diode-Array Detection
HRMS	High-Resolution Mass Spectrometry
IC_{50}	Half maximal inhibitory concentration
IL-6	Interleukin-6
LDL-C	Low-density lipoprotein cholesterol
M.	*Monascus*
MCK	Muscle creatine kinase
MHLW	Ministry of Health, Labour and Welfare
MK	Monacolin K

MK-HA	Monacolin K in hydroxy acid
MK-L	Monacolin K in lactone
mRNA	messenger ribonucleic acid
MS	Mass Spectrometer
M-SEC	The sum of monacolins
MyoD	myoblast determination protein 1
NDA	EFSA Panel on Dietetic Products, Nutrition, and Food Allergies
NIF	Nutrition and Food Innovation
PC	Public consultation
RCT	Randomised controlled trials
RT-qPCR	Quantitative Reverse Transcription Polymerase Chain Reaction
RYR	Red Yeast Rice
SISTE	Società Italiana di Scienze Applicate alle Piante Officinali e ai Prodotti per la Salute
SmPC	Summary of Product Characteristics
UHPLC-HRMS	Ultra-high-performance liquid chromatography - high-resolution mass spectrometry
US	United States
WHO	World Health Organization
WHO-UMC	World Health Organization – Uppsala Monitoring Centre
w/w	Weight per weight

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APPENDIX A

Documentation as provided to EFSA

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