23 May 2025, 10:00-12:00 CET

Ad-hoc meeting with interested food business representatives on Art 8(4) Opinion related to MONACOLINS FROM RED YEAST RICE

EUROPEAN FOOD SAFETY AUTHORITY

WHO'S WHO

- **Nutrition and Food Innovation (NIF) Unit**: Ana Afonso (Head of Unit, Chair), Leng Heng (Team Leader), Leonard Matijević and Silvia Valtueña Martinez (Scientific officers in charge for this risk assessment)
- **Engagement & External Relations (ENREL) Unit:** Martina Liccardo
- **Legal Affairs Services (LA) Unit:** Citlali Pintado, Elvira Bacci
- **European Commission–SANTE A.1 Unit**: Fruzsina Nyemecz (observer)

WELCOME TO INTERESTED FOOD BUSINESS OPERATORS' REPRESENTATIVES

REPRESENTATIVE ORGANISATIONS OF PARTICIPANTS	
Anefp	**Italian Society of Nutraceuticals (SINut)**
ARKOPHARMA LABORATORIOS S.A.U.	**Laboratorios Normon**
Asociación Española de Complementos Alimenticios (AFEPADI) - *Submitter of studies during scrutiny period through Hylobates Consulting srl*	**Linneus Consulting Services** - *Submitter of studies during scrutiny period*
Association of the European Self-Care Industry (AESGP)	**SIFITLab, Italian Society of Phytotherapy**
European Federation of Associations of Health Product Manufacturers (EHPM) - *Submitter of studies during scrutiny period*	**Società Italiana di Scienze Applicate alle Piante Officinali e ai Prodotti per la Salute (SISTE)** - *Submitter of studies during scrutiny period*
Food supplements Europe (FSE)	**University of Bologna**

SCOPE

- In line with EFSA's Catalogue of services and commitment to engaging with its stakeholders and improving understanding of its work
- **The meeting objective**:
  - To explain the scientific rationale behind the EFSA assessment
  - To clarify the sources of evidence and the factors that influenced the outcome

AGENDA

1. WELCOME TO PARTICIPANTS
2. SCOPE OF THE MEETING
3. PRESENTATION OF THE SCIENTIFIC OPINION
   a) BACKGROUND & MANDATE
   b) ANALYTICAL DATA about characterisation of RYR preparations
   c) Data on the DIETARY INTAKE of monacolins from food sources other than RYR
   d) In vitro data of RYR/monacolin K vs. other statins
   e) NUTRIVIGILANCE/POST-MARKETING DATA on adverse events related to the use of RYR products
   f) CASE REPORTS of adverse events from the scientific literature
   g) New CLINICAL DATA including safety endpoints
   h) Overall conclusions
4. Q&A SESSION
5. CLOSING REMARKS

HOUSEKEEPING

- Questions pre-submitted are grouped and addressed in the presentation
- Additional questions will be addressed after the presentation
- Use “raise hand” function to ask the floor during Q&A session
- keep your microphone muted & camera off, unless you are given the floor
- Please do not write questions in the chat
- If you have problems with the connection, exit the meeting & rejoin
- Audio, video, or text recording — including the use of AI for such purposes — is not allowed.

POST MEETING - Publication on EFSA’s website: the presentation including the agenda, & list of participating organisations.

ART 8(4) OPINION

UNDER THE FRAMEWORK OF REG (EC) NO 1925/2006 ON THE ADDITION OF VITAMINS AND MINERALS AND OF CERTAIN OTHER SUBSTANCES TO FOODS:

MONACOLINS FROM RED YEAST RICE (RYR)

Leonard Matijević, Silvia Valtueña Martinez

EFSA, Nutrition and Food Innovation Unit

EUROPEAN FOOD SAFETY AUTHORITY

BACKGROUND & MANDATE

EFSA NDA PANEL (2011 & 2013) – HEALTH CLAIM OPINIONS

2011: monacolin K (MNK) from RYR and maintenance of normal blood LDL-cholesterol concentrations

- 2 RCTs proving a claimed effect at daily doses of 10 mg MNK (for adults)
- Restrictions of use: Summary of Product Characteristics (SmPC) for lovastatin which listed several adverse effects

2013: monacolin K (MNK) from ”Sylvan Bio” RYR and maintenance of normal blood LDL-cholesterol concentrations

- The Panel reiterated the conclusions from the previous opinion
- In addition, the Panel referred to the CONTAM Panel’s opinion on citrinin (a nephrotoxic mycotoxin) which can be produced by some strains of RYR

"CITRININ REGULATION"

EC Regulation (EU) No 212/2014: of 6 March 2014 amending Regulation (EC) No 1881/2006 as regards maximum levels of the contaminant citrinin in food supplements based on rice fermented with red yeast *Monascus purpureus*

Repealed by the EC Regulation (EU) 2023/915: of 25 April 2023 on maximum levels for certain contaminants in food and repealing Regulation (EC) No 1881/2006

1.7	Citrinin	Maximum level (µg/kg)	Remarks
1.7.1	Food supplements based on rice fermented with red yeast *Monascus purpureus*	100	

Question: *why not to standardise RYR FS by establishing a concentration range for monacolins, as for citrinin?*

MEMBER STATES RISK ASSESSMENTS (1)

German research funding organisation DFG, 2012:

- *Red mould rice contains pharmacologically and toxicologically relevant constituents (including MNK, i.e. lovastatin). MNs are potent cholesterol lowering drugs to be administered under medical supervision. Hence, use of MN in FS is questionable*
- *No standardisation available, which precludes an adequate safety evaluation*
- ***Overall, red mould rice is not a safe food/FS***

ANSES, 2014:

- *"…due to the composition of RYR and in particular: the presence of MNK (also called lovastatin when marketed as a drug) that shares the adverse effects of statins; the presence at varying levels of the other monacolins, compounds whose safety has not been established,* ***consumption of "RYR" exposes some consumers to a health risk."***

MEMBER STATES RISK ASSESSMENTS (2)

Belgian Superior Health Council, 2016:

- **MNK in RYR includes adverse effects identical to those observed in patients taking statin drugs**
- the main toxic effect is muscular with a risk of renal failure in the case of rhabdomyolysis; functional digestive disorders are common; hepatotoxicity is relatively rare.
- certain vulnerable groups are at a higher risk of developing toxic effects, including pregnant women, people suffering from liver, kidney and muscle disorders, persons aged > 70 years and children and adolescents.

2018 ANS PANEL OPINION ON THE SAFETY OF MN IN RYR (1)

in accordance with **Article 8(2)** of Regulation (EC) No 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods

1.1.2. Terms of Reference

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002[8], the European Commission asks EFSA to:

- Review the existing scientific data on the possible link between the intake of monacolins from red yeast rice and harmful effects on health.
- Provide advice on a dietary intake of monacolins from red yeast rice 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.

Interpretation of the ToR:

- Focus on the safety endpoints previously identified by MSs
- MNK (in lactone form) and lovastatin are identical
- Dose for the health claim is 10 mg/day which overlaps with the lowest therapeutic dose for lovastatin
- The effect of other possible ingredients of FS on MN bioactivity is not considered

2018 ANS PANEL OPINION ON THE SAFETY OF MN IN RYR (2)

Conclusions:

- **MNK** identical to **lovastatin** (active ingredient in several medicinal products for the treatment of hypercholesterolemia)
- Summary of Product Characteristics (SmPC) for lovastatin listed several adverse effects
- RYR safety profile similar to lovastatin: case reports on adverse events: musculoskeletal and connective tissue (including rhabdomyolysis) > liver > nervous system > GI-tract > skin and subcutaneous tissue
- Intake of monacolins from RYR via food supplements (FS), could lead to estimated exposure to MNK within the range of the therapeutic doses of lovastatin
- monacolins from RYR when used as FS were of significant safety concern at the use level of **10 mg/day** (recommended dose), **but individual cases of severe adverse reactions were observed even at 3 mg/day**
- The Panel was **unable to identify a safe dietary intake** of monacolins from RYR

2018 ANS PANEL OPINION ON THE SAFETY OF MN IN RYR (3)

Uncertainties:

- The composition and content of MN in FS containing RYR
- MN in RYR are often used in multi-ingredients botanical preparations, without proper characterisation
- The ratio between MN-K lactone and MN-K HA forms is variable in FS containing RYR
- Lack of data on the bioactivity of components in RYR other than MNK
- Lack of data on certain groups of population (pregnant and lactating women, infants…)
- The effect of concomitant consumption of RYR-based FS with foods or drugs inhibiting CYP3A4
- In the majority of cases, RYR-based FS are multi-ingredients products. Interactions with other ingredients and the effect on the safety is unknown

"OTHER SUBSTANCES" UNDER UNION SCRUTINY (ARTICLE 8(4)) – MONACOLINS FROM RYR (1)

Article 1

Annex III to Regulation (EC) No 1925/2006 is amended as follows:

1. The following entry is added in the table in Part B 'Restricted substances' in alphabetical order:

Restricted substance	Conditions of use	Additional requirements
'Monacolins from red yeast rice	Individual portion of the product for daily consumption shall provide less than 3 mg of monacolins from red yeast rice.	The label shall provide the number of individual portions of the product for maximum daily consumption and a warning not to consume a daily amount of 3 mg of monacolins from red yeast rice or more. The label shall indicate the content of monacolins per portion of the product. The label shall include the following warnings: "Should not be consumed by pregnant or lactating women, children below 18 years old and adults above 70 years old". "Seek advice from a doctor on consumption of this product if you experience any health problems"; "Should not be consumed if you are taking cholesterol-lowering medication"; "Should not be consumed if you are already consuming other products containing red yeast rice".'

2. The following entry is added in the table in Part C 'Substances under Community scrutiny' in alphabetical order:
'Monacolins from red yeast rice'

"OTHER SUBSTANCES" UNDER UNION SCRUTINY (ARTICLE 8(4)) – MONACOLINS FROM RYR (2)

Question/comment:

- *Vulnerable subgroups (pregnant and breastfeeding women, neonates, children and adolescents under 18 years of age and adults over 70 years of age) are already excluded from taking RYR according to the restrictions prescribed by Regulation (EU) 2022/860.*

"OTHER SUBSTANCES" UNDER UNION SCRUTINY (ARTICLE 8(4)) – MONACOLINS FROM RYR (3)

EFSA task:

To assess **additional scientific data** submitted under Article 8(4) procedures (i.e. during the Community scrutiny period) and whether it is sufficient:

a) To address the **scientific uncertainties** raised by the ANS Panel (2018) in relation to the safety assessment of monacolins from RYR

b) To identify a daily intake of monacolins from RYR in FS that does not raise safety concerns for the general population or vulnerable subgroups thereof.

EFSA task was NOT:

To conduct a risk-benefit analysis

To consider socio-economic/regulatory aspects

"OTHER SUBSTANCES" UNDER UNION SCRUTINY (ARTICLE 8(4)) – MONACOLINS FROM RYR (4)

Questions/comments:

- *EFSA focused on hazard identification and not full risk assessment*
- *"no food is entirely safe"*
- *Traditional use (safe history of use) & international precedents not sufficiently weighted*

DATA SUBMITTED DURING THE SCRUTINY PERIOD (2 YEARS)

SISTE (Società Italiana di Scienze Applicate alle Piante Officinali e ai Prodotti per la Salute):

- 3 publications (1 manuscript)

EHPM (European Federation of Associations of Health Product Manufacturers):

- 2 documents

Linneus Consulting Services:

- 2 documents

Hylobates Consulting srl, representative of AFEPADI (Asociacion Espanola de Compementos Alimenticios):

- 19 documents

ANALYTICAL DATA about characterisation of RYR preparations

DATA SUBMITTED DURING THE SCRUTINY PERIOD

Analytical data about the characterization of RYR preparations:

- 5 studies on the analyses of commercial RYR products
  - Declared monacolin content vs. analysed (from -83% to +266%)
  - High variability in MN-K content (< 0.15% to 7.48% w/w)
  - Ratio MN-K lactone : HA forms from 1:1 to 114:1

EFSA conclusion(s):

- New analytical data were received
- Uncertainties highlighted by the ANS Panel in relation to the high variability in composition of RYR FS in relation to the MN content remained

DATA SUBMITTED DURING THE SCRUTINY PERIOD

Questions/comments:

- *Why considering "older" studies before Reg. 2022/860 came into force?*
- *Ratio MNK HA:MNK LA depends on many factors and should not be considered as standalone marker for variability of FS*
- *Why does the Panel consider that HA and LA forms are most likely responsible for adverse effects?*

DATA SUBMITTED DURING THE SCRUTINY PERIOD

Questions/comments:

- *Two samples in Rigillo et al. (2025) were lab. samples and not commercially available*
- *Some data indicates a clustering effect, suggesting that certain manufacturing processes result in more consistent compositions*

Data on the DIETARY INTAKE of monacolins from food sources other than RYR

DATA SUBMITTED DURING THE SCRUTINY PERIOD

Dietary intake of monacolins from other food sources than RYR

- One interested party argued that monacolins are present in edible mushrooms and that any risk assessment or risk management actions concerning monacolins from RYR should also consider (and be applicable to) other dietary sources

EFSA Conclusion(s):

- BVL/BfArM (2016) reviewed occurrence data from available literature and concluded that the reported monacolin content in edible mushrooms was not reliable (due to sample preparations and inadequate analytical methods used)
- BVL/BfArM conducted an in-house analytical study and concluded that, considering the monacolin K content, intakes per 100 to 200 g of fresh mushrooms would range from approx. 4 to 11 µg.
- Since this is several orders of magnitude lower than recommended daily doses of monacolins from RYR FS, monacolin K intake from other dietary sources was considered to be negligible

DATA SUBMITTED DURING THE SCRUTINY PERIOD

Questions/comments:

- *What is the specific scientific and procedural justification for prioritizing a single, unpublished, non-peer-reviewed study over the evidence submitted by AFEPADI and the broader body of available literature on monacolin exposure from diverse sources?*
- *Why full intake assessment was not conducted using EFSA's own methodology and guidance?*

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

DATA SUBMITTED DURING THE SCRUTINY PERIOD

In vitro comparison of toxicological profiles between the compounds of interest

- *In vitro* digestibility study (bioaccessibility rate of monacolins from RYR is higher than lovastatin, but variable among RYR products)
- variability in the cytotoxic effects (immortalized cells) between different statins and RYR preparations, as well as among the RYR samples themselves
- Gene expression and profiling to explain mode of action

EFSA conclusion(s):

- Variable *in vitro* cytotoxicity of RYR preparations (influenced by the composition) vs tested statins
- Several limitations of *in vitro* data to predict *in vivo* toxicity, hence this data was of limited value for the risk assessment

DATA SUBMITTED DURING THE SCRUTINY PERIOD

Question:

- *The Panel reported RYR preparations in µM from one cytotoxicity study submitted, why?*

NUTRIVIGILANCE/POST-MARKETING DATA on adverse events related to the use of RYR products

DATA SUBMITTED DURING THE SCRUTINY PERIOD

Nutrivigilance/post-marketing data about RYR products and AEs

- Data from nutri-/pharmacovigilance databases (FDA FAERS, CFSAN CAERS) for the number of reported muscle- and liver-related AEs and serious AEs (SAEs)
- Post-marketing information collected in a voluntary nutrivigilance system (spontaneous reporting by consumers, health professionals and health authorities) established by the manufacturing company of 2 RYR supplements with known composition, containing 3 mg MNK (recommended daily dose):
  - AEs and SAEs reported
  - Calculation of reporting rates (number of cases among total consumers); number of consumers estimated based on sales data
  - Claimed that most SAEs were due to off-label use + decrease in the reporting rate for SAEs in the last two years
- Nutrivigilance data used to compare the frequency of reported AEs for statins (e.g. lovastatin) and RYR supplements, concluding that SAEs are less frequently reported in relation to RYR supplement use.

DATA SUBMITTED DURING THE SCRUTINY PERIOD

EFSA conclusion(s):

- Neither the FAERS nor the CAERS databases allow concluding on causal relationships between the use of RYR-containing products and the reported adverse events.
- Nutrivigilance data confirms the reporting of AEs in relation to the consumption of RYR supplements after the implementation of Regulation (EU) 2022/860
- Post-market monitoring data confirm cases of SAEs at doses of 3 mg/day MNK in RYR FS
- Direct comparison of SAEs between RYR FS and lovastatin is not appropriate
- The information provided does not allow establishing a safe level of intake < 3 mg MNK/day

DATA SUBMITTED DURING THE SCRUTINY PERIOD

Questions/comments:

- *On the reporting of data from FAERS and CAERS databases, and the inability of these databases to establish causality between RYR FS consumption and AEs/SAEs*
- *EHMP nutrivigilance report contains data on products < 3 mg MNK/day only.*
- *SAEs at < 3 mg MNK/day are extremely rare and mostly in off—label users; decreasing reporting trends seen in the last 2 years.*
- *Panel's concerns about exposure estimation methods are noted, but calculating exposure from the total number of tablets manufactured and recommended usage is a widely accepted approximation in pharmacovigilance.*

CASE REPORTS of adverse events from the scientific literature

DATA SUBMITTED DURING THE SCRUTINY PERIOD

Newly published case-reports (after 2018)

- 3 case-reports: content of MNK of 10 mg/day or not reported

EFSA conclusion(s):

- Further confirmation of the occurrence of known SAEs
- These data do not contribute to the body of evidence considered to draw conclusions, i.e. in addition to cases of severe adverse events 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.

DATA SUBMITTED DURING THE SCRUTINY PERIOD

Question/comment:

- *The "new" case reports referenced by the Panel involve individuals consuming excessively high doses of RYR, exceeding safe limits. For instance, consumers in the Peterslund et al. (2019) case consumed 10 mg of monacolin K/day, and in the Loubser et al. (2019) case, 1200 mg/day of RYR was taken. These cases are not representative of typical or recommended usage. No severe adverse events have been definitively linked to intakes of 3 mg/day of monacolin K.*

New CLINICAL DATA including safety endpoints

DATA SUBMITTED DURING THE SCRUTINY PERIOD

New clinical data

- One RCT submitted, double-blind, placebo-controlled, cross-over design (unpublished manuscript)
- Several narrative and systematic reviews on RCTs designed to test efficacy of RYR products

EFSA conclusion(s):

- Vast majority of RCTs designed for efficacy, with sample sizes and duration, and methods to assess and report adverse events, inadequate to detect significant between-group differences for uncommon and rare adverse events.
- These data cannot be used to establish a safe level of intake for MNK in RYR FS

DATA SUBMITTED DURING THE SCRUTINY PERIOD

Questions/comments:

- *The purpose of Cicero et al. (2024, unpublished) was not to evaluate the safety of MN from RYR (at least 5,000 subjects would have been needed otherwise), but rather to detect potential biological effects using proteomics.*
- *The study was properly powered for that purpose and duration (6 weeks) was adequate*
- *The total content of MNK in the RYR supplement used in the study was 2.8 mg/day (as reported in the trials register and documents submitted to the Ethics Committee)*

OVERALL CONCLUSIONS

CONCLUSIONS FROM THE NDA PANEL OPINION (2025) (1)

- Uncertainties raised by the ANS Panel (2018) regarding characterisation and variability of commercially available RYR FS remain
- Available in vitro data may be useful for initial screening and understanding of potential cellular mechanisms of toxicity, otherwise is of limited value to predict in vivo toxicity
- Available RCTs were designed to assess efficacy, had short duration and small sample size to detect idiosyncratic and relatively rare AEs, typical for statins

CONCLUSIONS FROM THE NDA PANEL OPINION (2025) (2)

- New nutrivigilance data provided further confirmation on the occurrence of AEs in relation to the consumption of RYR FS at 3 mg MNK/day
- Exposure to monacolin K from RYR (at intake levels as low as 3 mg/day) could lead to severe AEs on the musculoskeletal system (including rhabdomyolysis) and on the liver
- **Submitted data is not sufficient to identify and establish a safe level of intake below 3 mg/day**

Q&A session

Thank you for your attention