Polyphenols and Functional Foods from the Regulatory Viewpoint

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Abstract

The aim of the present article is to give a bird's eye view about polyphenols in the European Legislation and its applications according to the European Food Safety Authority, in particular with reference to labelling for the consumer protection in the European market. Polyphenols are given much attention by consumers due to their health effects, and exploited by food producers. Consequently, a study on cases relating to claims about polyphenols cannot leave out of consideration a panoramic about the legal framework regarding European Regulations on nutrition claims. In this ambit, the general framework is the (EC) Regulation No 1924/2006 on nutrition and health claims made on foods: it sets the basic legal rules about nutrition claims in the European Union. Because of the possible allowed use of health claims about polyphenols, many applications have been made by food business operators. At present, the use of health claims related to polyphenols in the European market is limited only to olive oil polyphenols. All other formulations so far proposed relating to other foods have been rejected by the European Authority, being judged lacking of substantial scientific evidence.

Polyphenols in the European Union. The General Legal Framework

The (EC) Regulation No 1924/2006 of the European Parliament and of the Council of 20th December 2006 on nutrition and health claims made on foods, sets the basic legal rules about nutrition claims. This Regulation has to be held separated by other Regulations concerning distinct aspects on food labelling. In fact, general labelling provisions are contained in the Directive No 2000/13/EC of the European Parliament and of the Council of 20th March 2000 on the approximation of the laws of the Member States relating to the labelling presentation and advertising of foodstuffs. The principal aim of the cited Directive 2000/13/EC is to prohibit the use of information that would mislead the purchaser or attribute medicinal properties to food.

The (EC) Regulation No 1924/2006 covers all nutrition and health claims made in commercial communications, including generic advertising of food and promotional campaigns, also supported, both in whole and in part, by public authorities. Said Regulation has also a cross-road with intellectual property rights, given the fact that it does apply to trademarks and other brand names which may be construed as nutrition or health claims.

On the contrary, the Regulation does not apply to claims which are made in non-commercial communications, such as dietary guidelines, public health authorities advice, non-commercial communications, and information in the press and in scientific papers.

In addition, the Codex Alimentarius Commission formed by the Food and Agriculture Organization (FAO) and by the World Health Organization (WHO) has adopted General Guidelines on claims since 1991, followed by Guidelines for the use of nutrition claims in 1997, and amended in 1994. These Guidelines intend to consider nutrition and health claims made on foods at a broader and international level than the European Union (EU) legislation.

The (EC) Regulation No 1924/2006 on Nutrition and Health Claims Made on Foods. An in-Depth Analysis

According to EU legislation criteria, the (EC) Regulation No 1924/2006 gives definitions of the concepts used for regulating the matter of health and nutrition claims, sometimes directly giving a definition of the concepts, other times referring to other EU regulations.

As for the reference to other regulations, it states that the definition of "food", "food business operator", "placing on the market" and "final consumer" are laid down in the Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28th January 2002. Moreover, the definition of "food supplement" is laid down in Directive n° 2002/46/EC, definitions of "nutrition labelling", "protein", "carbohydrate", "sugars", "fat", "saturates", "mono-unsaturates" and "fibre" are laid down in Directive n° 90/496/EEC, while the definition of "labelling" is laid down in the Directive n° 200/13/EC. The term "Authority" has to be intended as a reference to the European Food Safety Authority established by Regulation (EC) No 178/2002.

As already said, other definitions are given directly in the text of (EC) Regulation n° 1924/2006. The "whereas n° 15" of the Regulation contains a reference to the notion of "average consumer" as extrapolated by the Court of Justice of the European Community's case law, which states that said average consumer is "reasonably well-informed and reasonably observant and circumspect, taking into account social, cultural and linguistic factors […] but makes provision to prevent the exploitation of consumers whose characteristics make them particularly vulnerable to misleading claims. Where a claim is specifically aimed at a particular group of consumers, such as children, it is desirable that the impact of the claim be assessed from the perspective of the average member of that group." It is important to highlight that the average consumer test is not a statistical test. Moreover, the Regulation contains a reference to the role of National courts and Authorities of Member States referring to the "average consumer", stating that they "will have to exercise their own faculty of judgement, having regard to the case-law of the Court of Justice, to determine the typical reaction of the average consumer in a given case".

In addition, the notion of "claim" is explained in the definition of the article 2.2.1 which reads "claim means any message or representation, which is not mandatory under Community or National legislation, including pictorial, graphic or symbolic representation, in any form, which states, suggests or implies that a food has particular characteristics". This definition of "claim" should be taken into account, remembering that, the same definition is applied - according to art. 1.2 of Reg. No 1924/2006 - to "[…] nutrition and health claims made in commercial communications, whether

in the labelling, presentation or advertising of foods to be delivered as such to the final consumer, including foods which are placed on the market unpacked or supplied".

More specifically, art. 2.4 gives also a definition of "nutrition claim", intended as "any claim which states, suggests, or implies that a food has particular beneficial nutritional properties due to a) the Energy (calorific value) it: I) provides; II) provides at a reduced or increate increased rate, or III) does not provide; and/or B) the nutrients or other substances it: I) contains, II) contains in reduced or increate increased proportions, or III) does not contain".

Moreover, the Regulation gives a definition of "health claims" which, according to art. 2.5, may be defined as "any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health.", together with (art. 2.6) a definition of "reduction of disease risk claim" intended as "any health claim that states, suggests or implies that the consumption of a food category, a food or one of its constituents significantly reduces a risk factor in the development of a human disease".

The "use of nutrition and health claims" is authorized by art. 5.1 in labelling, presentation and advertising of foods placed on the market in the Community provided that are fulfilled the following general conditions (1):

a) "The presence, absence or reduced content in a food or category of food has shown a beneficial nutritional or physiological effect, as established by generally accepted scientific data";
b) "The nutrient or other substance is present in a quantity that will produce a nutritional or physiological effect or, according to the type of claim, is not present or is present in a reduced quantity that will produce such effects, in both cases as established by generally accepted scientific data";
c) "The nutrient or other substance is in a form available to be used by the body";
d) "The quantity of the product that can reasonably expected to be consumed provides a significant quantity of the nutrient or other substance about which the claim is made".

In any case, use of nutrition and health claims according to the provision of art. 6.1 has to be based on substantiated and generally accepted scientific data. The burden of proof in justifying the use of such claims weighs on the food business operator making a nutrition or health claim.

On the contrary, nutritional and health claims cannot be used, according to art. 3, if they are "false, ambiguous or misleading", or they "give rise to doubt about the safety and/or nutritional adequacy of other foods", or "encourage excess consume of food", or "suggest or imply that a balanced and varied diet cannot provide appropriate quantities of nutrients in general" or, last but not least, "refer to change in bodily functions which could give rise to or exploit fear in the consumer" (1). Another restriction in the use of nutrition and health claims is laid down in art. 4.2 referring to "beverages containing more than 1.2% by volume in alcohol" that cannot bear neither health claims nor nutrition claims other than those which refer to a reduction in the alcohol or energy content.

Having summarized the notions of "average consumer" and "nutritional and health claims", we have to highlight now that the Regulation joins both of them by stating in art. 5.2 that "the use of nutrition and health claims shall only be allowed if the average consumer can be expected to understand the beneficial effects expressed in the claim" (1). In this ambit, the demand for clarity and authenticity issues when speaking of functional foods concern also normal and traditional products on the one side, and new and well-known compounds (both natural and added substances) on the other side. In detail, the introduction or the fortification of foods and beverages with sugars, fructans, galacto-oligosaccharides, and some exopolisaccharide of microbial origin, is considered one of the most challenging areas in the coming years when speaking of research and analytical progress (2,3,4,5,6). Also, food hygiene and public safety (the worrying issue of allergens and ready analytical detection by consumers should be considered) are often associated with authenticity and the need to protect the average consumer (7,8,9,10). On the other side, may worrying risks concern the possible use of new antimicrobial strategies against certain menaces for human and animal beings (11,12). With reference to the EU legislation, the General rule about health claims on food is that they are prohibited unless they fulfil some conditions that may be summarized as follows:

a) Compliance with the general rules about the use of nutrition and health claims as stated above
b) Compliance with specific rules laid down in art. 10.2, that states the necessity of including in the information about the health claims to the consumer: a statement about the importance of "a

varied and balanced diet and a healthy style of life", "the quantity of the food and pattern of consumption requires to obtain the claimed beneficial effect", a statement addressed to people "who should avoid using the food" (if any), and a "warning for products that are likely to present a health risk if consumed in excess"

c) Authorization by the European Commission and inclusion in the list of authorised claims.

In any case, health claims cannot be used (art. 12) when they suggest that health can be affected by not consuming the food or when reference is made to the rate or amount of weight loss or when there is a reference to opinions of individual doctors or health professionals other than National medical associations and health related charities (1).

The procedure for including a certain health and nutrition claim in the list of authorized ones starts with the filing of an application submitted to the National Competent Authority of a Member State of the European Union. The National Competent Authority has to acknowledge receipt of the application, informing the European Food Safety Authority (hereinafter EFSA), and it has to make available the application and attached documents to the same EFSA that will provide to transfer it to the other Member States and to the Commission. A summary of the application will be made publicly available. Among other information about the applicant (name, address, etc.), the application has to be filed together with "a copy of studies, including, where available, independent peer-reviewed studies, which have been carried out with regard to the health claim and any other material which is available to demonstrate that the health claim complies with the criteria provided in the Regulation" as stated by art. 15. This obligation is a burden of the applicant who wants to protect proprietary information, subtracting it to publicity, to indicate them as such, providing a verifiable justification. Moreover, the applicant has to draft the "proposal for the wording of the health claim for which authorisation is sought including, as the case may be, specific conditions for use".

The EFSA has a time limit of no more than six months before issuing a pronunciation about the application. By the way, this time period can be extended if the same Authority seeks supplementary information from the applicant. In order to issue its opinion, EFSA has to verify that the proposed wording of the claim is substantiated by scientific data, considering whether or not the

wording of health claim complies with the criteria of the Regulation (e.g. on clarity) and give advice on whether the proposed wording of the health claim is understandable and meaningful to the average consumer. In case the opinion is favourable to authorise the health claim, it must include, among others: information about the nutrient or other substance in respect of which a claim is to be made and its particular characteristics, as well as the recommended wording of the health claim and, if any, conditions or restrictions of use or warning that could accompany the health claim. Opinions issued by the Authority are public, according to art. 38.1 of Regulation (EC) No 178/2002. Within three months after receiving the opinion of the Authority, the Commission submits to the Standing Committee on the Food Chain and Animal Health instituted by Article 58(1) of Regulation (EC) No 178/2002 a draft decision on the list of permitted health claims, taking into account said opinion. It is important to note that EFSA opinion is mandatory but not binding for the Commission; consequently, the same Institution can draft a decision not in accordance with the Authority, provided that the same Commission gives an explanation of the differences. The final decision is notified to the applicant and is also published in the Official Journal of the European Union. Authorized health claims may be used by any food operator, unless they are not restricted in the use being proprietary data, qualified as such in the application. This provision has the aim of protecting Intellectual Property Rights of the business firm (in the form of protected know-how) filing the application.

As to the relationship between civil and criminal liability from one side and the granting of an authorization to include the health claim in the list of the authorised ones on the other side, it must be said that the granting of authorisation does not lessen in any case civil or criminal liability of the business food operator. Moreover, EFSA opinions do not constitute an authorisation to marketing of a food or food constituent, nor a positive assessment of its safety and also it does not constitute a decision on whether a food or food constituent can be classified or not as foodstuff.

EFSA Decisions on Health Claims Concerning Polyphenols

The widespread knowledge of Mediterranean Diet (9), known for its beneficial effects on health, has led various food producers to file applications to EFSA, according to the aforementioned

Reg. (EC) No 1924/2006 for obtaining “health claims” about polyphenols which are deemed by the public opinion to be healthy natural substances that might have beneficial effects.

In the opinion published on EFSA Journal 2011; 9(4) 2033, the Authority compared seven different groups of health claims relating to alleged beneficial effects of polyphenols in olive oil for the health of consumers (13).

First of all, EFSA starts its analysis with the definition of polyphenols in olive oil with the following statement, according to its Panel on Dietetic Products, Nutrition and Allergies in the aforementioned opinion: “ […] The Panel considers that the food constituent, polyphenols in olive (olive fruit, olive mill waste waters or olive oil, Olea europaea L. extract and leaf) standardised by their content of hydroxytyrosol and its derivatives (e.g. oleuropein complex), which is the subject of the health claims, is sufficiently characterised in relation to the claimed effects” (13).

After the definition of Polyphenols, EFSA examines single health claims relating to beneficial effects of health claims.

An health claim scrutinized by EFSA was an alleged effect of polyphenols in the “Maintainance of normal blood pressure”. This alleged health effect was supported by several studies that were not deemed able to prove said effect for various reasons. An internal report by Moccetti and colleagues cited by the EFSA (13) describing an effect from the consumption of olive leaf extracts was deemed not proving the effect because it was judged not sufficient with regard to study design, methodology and statistical analysis. With concern to two other studies (14,15), the Panel came to the conclusion that evidence provided on animal studies and by intravenous administration cannot support claims relating to human beings. The EFSA Panel has not established a relationship between consumption of polyphenols by olive oil and maintenance of normal blood pressure.

EFSA was also designated to examine the “Maintenance of normal blood HDL-cholesterol concentrations” as an effect deriving from the use of polyphenols. Two studies (16,17) have been examined, but they were considered not proving effects of polyphenols, because: a) there was not evidence of a “biologically plausible mechanism by which olive oil polyphenols could exert the

claimed effect", and b) no data were available for other food sources of polyphenols like leaf tea or tea extract (13).

Other health claims were dismissed by the Authority because they are general and non-specific declarations, and do not refer to any specific health claim as required by Regulation (EC) No 1924/2006. In particular, the claims rejected with such a motivation were the following: "contributes to the upper respiratory tract health", "can help to maintain a normal function of gastrointestinal tract" and "contributes to body defences against external agents" (13).

Another dismissed health claim was referred to "Anti-inflammatory properties", in particular in the wording "a potent source of olive biophenols with anti-inflammatory properties". The aforementioned claim, in the reasoning of EFSA, refers specifically to diseases such as osteoarthritis or rheumatoid arthritis, in which reduction of inflammation can be a therapeutic target for the treatment of the disease. Following this reasoning, EFSA comes to the conclusion that the reduction of inflammation in the context of diseases is a therapeutic target for the treatment of diseases and so it is out of the scopes of the Regulation (EC) No 1924/2006.

In the same opinion, EFSA admitted only one health claim referring to "Protection of LDL particles from oxidative damage". The claim was presented in a variety of forms, that is to say: "reduces oxidative stress", "antioxidant properties", "lipid metabolisms", "antioxidant activity, protect body cells and LDL from oxidative damages" "antioxidant properties". In evaluating the claim, EFSA found that naturally occurring polyphenols in olive oil were shown to significantly decrease the amount of circulating oxidised low-density lipoprotein (LDL) particles in vivo in a dose-dependent manner in one large (200 subjects) and three small-scale human intervention studies (16,17,18,19). In other words, EFSA Panel took into account that a well conducted study and smaller scale studies showed a dose dependent and significant effect of polyphenol consumption from olive oil for at least three weeks on appropriate markers of LDL peroxidation (oxLDL) evidencing a biologically plausible mechanism that could explain the claimed effect. So, the EFSA Panel established that a cause and effect relationship has been proved between the consumption of olive oil polyphenols and protection of LDL particles from oxidative damages. For understanding the healthy effect of polyphenols by protecting LDL particles, it has to be considered that reactive

intermediates, generated during biochemical processes (as, for example, in the respiratory chain) and/or exposure to exogenous factors like radiation and pollutants, can be held responsible of genetic diseases and modifications concerning proteins and lipids, unless they are not intercepted by antioxidant substances that include also antioxidant nutrients such as polyphenols. Finally, EFSA opinion has authorised the health claim with the following wording: "Olive oil polyphenols contribute to the protection of blood lipids from oxidative stress". However, this use is not always allowed, being limited by the following conditions: "The claim may be used only for olive oil which contains at least 5 mg of hydroxytyrosol and its derivatives (e.g. oleuropein complex and tyrosol) per 20 g of olive oil. In order to bear the claim information shall be given to the consumer that the beneficial effect is obtained with a daily intake of 20 g of olive oil."

EFSA Opinions on Polyphenols Deriving from Food Other than Olive Oil

EFSA opinions have also considered the possibility of using health claims on other foods different from olive oil. For example, an EFSA opinion in 2011 (20) on health claims relating to "Polyphenols from processed fruits and vegetables and juices", consisting of various wording such as "Polyphenols contained in this product ensure antioxidant action; - Protects the cells; - Antioxidant properties, with natural fruit antioxidants; - Polyphenols contained in this product ensure protective effect on the organism; - Antioxidant/s" did not authorize the use of such claims. In the same opinion, the health claim about "polyphenols (general and from grape, olive and cacao in particular)" was rejected also in the following wording "Polyphenols contained in this product ensure antioxidant action; - help prevent tissue oxidation; - helps guard against oxidation caused by free radicals; - have an antioxidant effect; - help mop up free radicals in cells/ antioxidants". Moreover, the mention of "polyphenols from tea" in wording such as "Polyphenols contained in this product ensure antioxidant action; - polyphenols contained in this product ensure protective effect on the organism; - contains antioxidant/s; - is a source of antioxidant/s; - with antioxidant/s" were rejected. In all three cases, the EFSA denied use of health claims based on scientific literature submitted by business food producers, because there was "a non compliance with the Regulation because on the basis of the scientific evidence assessed, this claimed effect for this food has not

been substantiated" adding sometimes that "the food is not sufficiently characterised for a scientific assessment".

The same motivations were almost used to reject health claims of "Pyrus malus (Common Name Apple) extract powder containing polyphenols" in the two wordings "Can help to moderate the postprandial blood glucose level. Can help to decrease the blood glucose level." (21).

However, the list of health claims rejected by EFSA is very long, and among them there is also the "Aronia melanocarpa (Common Name : Chokeberry)" and its alleged "protection of DNA, proteins and lipids from oxidative damages" with the wordings "Contains antioxidant/s. Is a source of antioxidant/s. With antioxidant/s. Natural source of beneficial bioactive compounds: polyphenols (anthocyanins, flavonols, tannins), that help maintain optimum antioxidant status of the body" (21).

Another alleged "protection of lipids from oxidative damages" due to "chocolate" in the following complex wording, was rejected as a health claim: "Cocoa beans naturally contain polyphenols. Cocoa polyphenols are known for their antioxidant properties. Examples of any alternative wording that may be used in relation to claim: "Cocoa flavonols show antioxidative effects and help protect the cells against oxidative stress, help protect you from radicals which cause cell damage, help strengthen our body's natural defences againist oxidative stress." (22).

Attempts of exploiting polyphenols which are contained in "honey" had the same result of the others above-listed claims. EFSA did not authorised the claim "Helps maintain your natural defences. Honey antioxidants contribute to the total antioxidative capacity of the body. Honey contains naturally occurring antioxidants. Honey helps to support the digestion with a natural antimicrobial action. Honey helps contribute to the natural defences of the body. Honey helps to support the digestion. Honey polyphenols help ensure our antioxidant capacity. Honey has a natural antimicrobial action" (21).

In an EFSA opinion of 2010, both "Natural Grape Extract From red grape skin" and "Natural Grape Extract From white grape skin Solvent free" were rejected in their alleged "Protection of DNA, proteins and lipids from oxidative damage" that was represented by the wording "In healthy balanced diet natural Grape antioxidants help to protect body's cells against free-radicals, and so

make a contribution towards reinforcing body's defences With natural grape antioxidants With natural grape polyphenols" (23).

Not a different fate was that of "Polyphenols and vitamins from pomegranate extract" and its presumed "antioxidant and antiaging properties" that, at least in the opinion of a food-maker should "Make smoother and softer skin. Diminish appearance of fine lines and wrinkles. Increase skin hydration and suppleness. Give skin wellness and youthful appearance. Stimulate cell repair." This health claim was rejected by the EFSA (24).

The EFSA opinion of 2011 rejected health claims regarding various types of "berries (lingonberry, cloudberry, blueberry, currants, raspberry and strawberry)" and their presumed "protection of DNA, proteins and lipids from oxidative damage" in the wording "Natural berries contain plenty of natural antioxidants (polyphenolic compounds, vitamin C, and carotenoids) and fibre but only a small amount of energy and sodium. For this reason they are very suitable for a heart-friendly diet" (21).

Other health claims such as "polyphenols" in general and their "protection of lipids from oxidative damage" (22), "polyphenols from French maritime pine bark" and their effect as an "antioxidant" (23), and "Polyphenols from red wine" (20) were also all rejected.

Conclusions

At present, the use of health claims related to polyphenols in the EU market and in the "case-law" of EFSA opinion is limited only to "olive oil polyphenols" with the following wording "Olive oil polyphenols contribute to the protection of blood lipids from oxidative stress". All other formulations so far proposed relating to other foods has been rejected by the European Authority, being judged lacking of substantial scientific evidence.

References

1. European Parliament and Council (2006) *Off. J. Eur. Union* **L404**, 9-40
2. Austin, S., van Gool, M., Parisi, S., Bhandari, S., Haselberger, P., Jaudzems, G., & Sullivan, D. (2018) *J. AOAC Int.* **101**,1270-1271. doi: 10.5740/jaoacint.SMPR2014.003
3. Dentali, S.J., Amarillas, C., Blythe, T., Brown, P.N., Bzhelyansky, A., Fields, C., Johnson, H.E., Krepich, S., Kuszak, A., Metcalfe, C., Monagas, M., Mudge, E., Parisi, S., Reif, K., Rimmer, C.A., Sasser, M., Solyom, A.M., Stewart, J., Szpylka, J., Tims, M.C., Van Breemen, R., You, H., Zhao, H., Zielinski, G., & Coates, S.G. (2018) *J. AOAC Int.* **101**, 1256-1260. doi: 10.5740/jaoacint.SMPR2018.005
4. Popping, B., Allred, L., Bourdichon, F., Brunner, K., Diaz-Amigo, C., Galan-Malo, P., Lacorn, M., North, J., Parisi, S., Rogers, A., Sealy-Voyksner, J., Thompson, T. & Yeung, J. (2018). *J. AOAC Int.* **101**, 1-5 . doi: 10.5740/jaoacint.17-0425
5. Sharma, R.K., & Parisi, S. (2016) *Toxins and Contaminants in Indian Food Products*. Springer International Publishing, Cham, Switzerland. doi: 10.1007/978-3-319-48049-7
6. Spanò, A., Laganà, P., Visalli, G., Maugeri, T., & Gugliandolo, C. (2016) *Curr. Microbiol*.**72**, 518-528. doi:10.1007/s00284-015-0981-9
7. Parisi, S. (2018) *J. AOAC Int.* **101**, 914-915. doi: 10.5740/jaoacint.17-0444
8. Mania, I., Barone, C., Pellerito, A., Laganà, P., & Parisi, S. (2017) *Ind. Aliment*. **56**, 18-22
9. Delgado, A.M., Vaz Almeida, M.D., & Parisi, S. (2016) *Chemistry of the Mediterranean Diet*. Springer International Publishing, Cham, Switzerland. doi: 10.1007/978-3-319-29370-7
10. Zaccheo, A., Palmaccio, E., Venable, M., Locarnini-Sciaroni, I., & Parisi, S. (2016) *Food Hygiene and Applied Food Microbiology in an Anthropological Cross Cultural Perspective*. Springer International Publishing, Cham, Switzerland. doi: 10.1007/978-3-319-44975-3
11. Laganà, P., Melcarne, L., & Delia, S. (2015) *Int. J. Cardiol.* **187**, 678–679. doi:10.1016/j.ijcard.2015.04.019
12. Casella, S., Ielati, S., Piccione, D., Laganà, P., Fazio, F., & Piccione, G. (2012) *Cell. Biochem. Funct*. **30**, 406–410. doi:10.1002/cbf.2814
13. EFSA (2011) *EFSA J.* **9**, 2033-2058

14. Khayyal, M., El-Ghazaly, M., Abdallah, D., Nassar, N., Okpanyi, S., & Kreuter, M.H. (2002) *Arzneimittel-Forschung* **52**, 797-802 . doi:10.1055/s-0031-1299970

15. Hassan Gilani, A., Khan, A.U., Jabbar Shah, A., Connor, J., & Jabeen, Q. (2005) *Int. J. Food Sci. Nutr.* **56**, 613–620. doi:10.1080/09637480500539420

16. Marrugat, J., Covas, M.I., Fitó, M., Schröder, H., Miró-Casas, E., Gimeno, E., López-Sabater, M.C., de la Torre, R., & Farré, M. (2004) *Eur. J. Nutr.* **43**, 140–147. doi:10.1007/s00394-004-0452-8

17. Covas, M.I., de la Torre, K., Farré-Albaladejo, M., Kaikkonen, J., Fitó, M., López-Sabater, C., Pujadas-Bastardes, M.A., Joglar, J., Weinbrenner, T., Lamuela-Raventos, R.M. & de la Torre, R. (2006) *Free Rad. Biol. Med.* **40**, 608–616. doi:10.1016/j.freeradbiomed.2005.09.027

18. Weinbrenner, T., Fitó, M., Torre, R. de la, Saez, G. T., Rijken, P., Tormos, C., Coolen, S., Albaladejo, M.F., Abanades, S., Schroder, H., Marrugat, J., & Covas, M.I. (2004) *J. Nutr.* **134**, 2314-2321. doi:10.1093/jn/134.9.2314

19. De la Torre-Carbot, K., Chávez-Servín, J. L., Jaúregui, O., Castellote, A. I., Lamuela-Raventós, R. M., Nurmi, T., Poulsen, H.E., Gaddi, A.V., Kaikkonen, J., Zunft, H.F., Kiesewetter, H., Fito, M., Covas, M.I., & López-Sabater, M. C. (2010) *J. Nutr.* **140**,501-508. doi:10.3945/jn.109.112912

20. EFSA Panel on Dietetic Products, Nutrition and Allergies (2011) *EFSA J.* **9**, 2082-2120. doi: 10.2903/j.efsa.2011.2082

21. EFSA Panel on Dietetic Products, Nutrition and Allergies (2011) *EFSA J.* 9, 2243-2276. doi: 10.2903/j.efsa.2011.224

22. EFSA Panel on Dietetic Products, Nutrition and Allergies (2010) *EFSA J.* **8**, 1792-1813. doi: 10.2903/j.efsa.2010.1792

23. EFSA Panel on Dietetic Products, Nutrition and Allergies (2010) *EFSA J.* **8**, 1489-1552. doi:10.2903/j.efsa.2010.1489

24. EFSA Panel on Dietetic Products, Nutrition and Allergies (2010) *EFSA J.* **8**, 1750-1772 doi: 10.2903/j.efsa.2010.1750