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ORIGINAL ARTICLES AND REVIEWS

Turmeric (*Curcuma longa* L.) food supplements and hepatotoxicity: an integrated evaluation approach

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Abstract

Introduction. Turmeric is the common name for the rhizome of *Curcuma longa* L. In the recent years, food supplements containing turmeric have been marketed and widely used by an increasing number of consumers. Spontaneous reports of suspected adverse reactions to food supplements are collected within the Phytovigilance system.

Methods. An ad hoc multidisciplinary group investigated the suspected cases of hepatotoxicity reported to the Italian Phytovigilance system associated with the assumption of turmeric food supplements with the methodology specific to pharmacovigilance as well as for the evaluation of the quality and safety of food supplements.

Results. A cluster of 28 spontaneous reports of acute hepatitis, mostly with cholestasis, associated with turmeric products were sent to the Italian Phytovigilance system in the first six months of 2019.

In all cases, except one, the causality assessment was at least possible. The suspected products were collected and analysed for the presence of drugs, heavy metals, aflatoxins, pesticides, synthetic dyes and pyrrolizidine alkaloids.

Conclusion. On the basis of the results of all the activities performed by multidisciplinary group, regulatory intervention was taken. This study highlights the importance of developing an integrated evaluation approach for the evaluation of the adverse effects associated with the use of food supplements.

Key words

- *Curcuma longa*
- food supplements
- adverse reactions
- food safety
- chemical analyses

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INTRODUCTION

Turmeric is the common name for the rhizome of *Curcuma longa* L. (*C. domestica* Valeton, Fam. *Zingiberaceae*). Its main chemical components are curcuminoids (3-5%), including curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-dien-3,5-dione] (77%), demethoxycurcumin (17%) and bisdemethoxycurcumin (3%). These compounds are part of a mixture of yellow-colored substances chemically derived from diferuloylmethane. Turmeric also contains carbohydrates, proteins, lipids, minerals and essential oils (5.8%). Essential oils and curcuminoids are pharmacological markers for drug quality control; indeed, the dry rhizome must contain at least 2% curcuminoids, calculated as curcumin, and at least 25 ml/kg of essential oil [1].

The powder of rhizome is most widely used as a spice to color and flavor food such as mustard, cheese and butter, it is incorporated into tea and it is a base component in many culinary spice blends, such as curry. Curcumin, is also used as food dye (E 100), authorized for specific purposes in food and beverage production. The European Union legislation has established specific characterization and purity requirements for this substance in Reg. 231/2012 and subsequent amendments [2]. In this context, the European Food Safety Authority (EFSA) established an Acceptable Daily Intake (ADI) for curcumin of 3 mg/kg/day, equal to 210 mg/day for an adult of 70 kg of body weight [3].

Moreover, turmeric based products are present on the market as food supplements, containing *Curcuma longa* extracts, often standardized up to 95% curcuminoids, obtained after extraction with organic solvents like ethanol, methanol, or ethyl acetate.

Since the bioavailability of curcumin, almost insoluble in water, is very low (1%) [4], various methods have been devised to enhance the bioavailability, including complexation with piperine (an alkaloid extracted from *Piper nigrum*). Recently, also complexes of curcumin with phospholipids, polymeric micellar formulations and curcumin-loaded solid lipid nanoparticles have been used to increase the absorption of curcumin improving its oral bioavailability [5].

Commercial food supplements containing *Curcuma longa* extracts, alone or in combination with other plants, are used in rheumatologic diseases (such as arthritis) for the reputed anti-inflammatory activity and for reduction of body weight [6-8]. In addition, curcumin is under clinical evaluation as neuroprotective agent in the management of cognitive disorders even if the results appear contradictory [9, 10].

The European Union herbal monograph [11] on *Curcuma longa* supports its traditional use for relief of mild digestive problems, such as feelings of fullness, slow digestion and flatulence. This means that, although there is insufficient evidence from clinical trials, the efficacy of these herbal products is plausible, according to traditional use, confirmed that they have been used safely for those mild conditions for at least 30 years (including at least 15 years within the EU). As undesirable effects the monograph lists: mild symptoms of dry mouth, flatulence and gastric irritation. The monograph lists mild symptoms of dry mouth, flatulence and gastric irritation as *Curcuma longa* and reports that it is not recommended in case of obstruction of the bile duct, cholangitis, liver disease, gallstones and any other biliary diseases, due to possible stimulation of bile secretion. In experimental animal models, turmeric stimulated the contraction of the gall bladder and the bile secretion, these effects are specific to choleretic activity. The chemical components responsible for choleretic activity are curcuminoids and sesquiterpenes (α-turmerone and β-turmerone) [12]. Human studies report an increased contraction of the gallbladder with various dosages of curcumin (from 20 to 80 mg) [13-15]. Turmeric is used as powdered herbal substance (posology is 0.5-1 g 2-3 times daily), herbal tea (0.5-1.0 g as an infusion 2-3 times daily), tincture (the dilution is 1:10 or 1:5 and the posology is respectively 0.5-1 ml 3 times daily and 10 ml once daily or 5 ml 3 times daily), and dry extract [11].

In Italy, no drug containing turmeric has been registered for traditional use to date.

In recent years, different types of food supplements containing turmeric have been marketed. In Italy, sales data of these products indicated an increase of 25% between 2018 and 2019 (from almost 4 million of packages in 2018 to almost 5 million in 2019) [16].

A first signal of hepatotoxicity of turmeric-based products arose by a cluster of spontaneous reports of liver damage associated with turmeric products consumption that arrived to the Italian Phytovigilance system in the first six months of 2019. The frequency of new cases of liver damage, the homogeneity of the diagnoses and of the products taken by the subjects, were in line with a risk signal of hepatotoxicity associated with the use of food supplements containing turmeric. Immediately, preventive actions have been taken, in particular the EFSA Focal Points of other European countries were contacted exchanging information, and at the same time, samples of suspected products were collected to perform analytical assays and rule out the presence of any hazard of concern.

The work describes the activities carried out by an ad hoc multidisciplinary group to evaluate the suspected cases of hepatotoxicity reported to the Italian Phytovigilance system associated with the assumption of turmeric food supplements and drive any decision to reduce the associated risk. In order to ascertain the presence of harmful substances and to substantiate the risk, the study was performed according to: i) the methodology specific to pharmacovigilance; as well as ii) the evaluation of the quality and safety of food supplements.

MATERIALS AND METHODS

Phytovigilance methodology

The Phytovigilance system, coordinated by the Italian National Institute of Health – NIH (Istituto Superiore di Sanità), collects spontaneous reports of suspected adverse reactions to food supplements and galenic preparations containing plants. The surveillance system was activated in 2002 as a research project and became in 2012 a national system to support the Ministry of Health in monitoring safety of products of its regulatory competence.

The Phytovigilance system activities are conducted

separately from the Pharmacovigilance system, which is coordinated by the Italian Medicines Agency (Agenzia Italiana del Farmaco – AIFA).

Anybody observing a suspected adverse reaction associated with the above-mentioned products can report the reaction. Online report is possible through the website VigiErbe (www.vigierbe.it). Diagnoses are coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Hospital physicians provide follow-up for hospitalized patients.

A request, for "exchange of information" on the presence of turmeric supplements and any adverse reactions to these supplements in the different EU countries was sent through the EFSA Italian Focal Point. Causality assessment was performed for all cases using an evaluation scale adapted from the World Health Organization causality categories [17]. It was not possible to apply Roussel Uclaf Causality Assessment Method (RUCAM) because important information was missing in the reports.

Analytical chemical methodology

To identify the substances potentially responsible for the adverse reactions observed, the suspected products were collected and analysed.

On one side, for the safety issue, the analyses were focused on the search of voluntary added drugs, accidental contaminants, residues, and intentional synthetic adulterants, on the other side the analysis of the curcuminoids was also carried out to characterize the quality of the product. In particular, the following classes of substances were checked: non-steroidal anti-inflammatory drugs (e.g. nimesulide), narcotic or psychotropic substances, heavy metals (cadmium and lead), aflatoxins (B1, B2, G1, and G2), pesticides, pyrrolizidine alkaloids (26 alkaloides plus 20 N-oxides), synthetic dyes.

The analytes previously indicated have been selected for the following aspects: substances used to fraudulently connote turmeric-based products, contaminants from the environment and substances known for their potential hepatotoxic effect.

Indeed, turmeric is often subject to adulteration with potentially toxic compounds such as synthetic dyes that mimic the colour appearance of curcumin as well as the mixing with lower-cost botanical ingredients such as other *Curcuma* species. The replacement of natural curcumin with synthetic curcumin, which is intended to serve a lower-cost substitute, is a deliberate practice also [18]. Moreover, anti-inflammatory drugs (e.g. nimesulide) and narcotic or psychotropic substances could be added to enhance the effectiveness of the supplements.

The quali-quantitative analysis of the curcuminoids, the principal bioactive compounds of suspected products, including curcumin, demethoxycurcumin and bisdemethoxycurcumin and the presence of other Curcuma species such as *C. zedoaria* and *C. zanthorrhiza* was also carried out in order to evaluated and to investigate the content of curcumin and its natural origin.

The analytical techniques used for the determinations of the substances studied are listed below:

1) HPLC (High Performance Liquid Chromatography) with diode array detector (HPLC-DAD) used for the determination of synthetic dyes (2G yellow, fast yellow, naphthol yellow S, metanil yellow, oil orange S, orange 2, orange 6, sudan 1, yellow sudan, orange sudan G, red para). The chromatographic profile obtained by HPLC, was evaluated to investigate the content of curcumin and its natural origin;

2) HPLC (High Performance Liquid Chromatography) with fluorescence detector (HPLC-FLD) used for the determination of aflatoxins, namely aflatoxin (B1, B2, G1 and G2);

3) HPTLC (High-Performance Thin Layer Chromatography) was used to investigate the presence of other species of Curcuma (*C. zedoaria* and C. *zanthorrhiza*) as well as to compare the chromatographic profile of curcuminoids obtained by HPLC;

4) LC-MS/MS (Liquid Chromatography coupled with Tandem Mass Spectrometry) used for the determination of aflatoxins, confirmation of the presence of red dyes, narcotic or psychotropic substances, pyrrolizidine alkaloids, volatile pesticides, non-steroidal anti-inflammatory drugs and NSAIDs (e.g. nimesulide). In order to ensure the quality of the analytical data, the analyses performed by LC MS / MS were conducted, in collaboration between ISS and IZS, on the same samples;

5) GC/MS/MS (Gas Chromatography coupled with Tandem Mass Spectrometry) used for volatile pesticides;

6) ICP-MS (Inductively Coupled Plasma Mass Spectrometry) used for the determination of heavy metals (such as lead and cadmium).

Analyses were carried out by the NIH, the Istituto Zooprofilattico Sperimentale del Lazio e della Toscana (IZS LT) and the Istituto Zooprofilattico Sperimentale della Lombardia e della Emilia-Romagna (IZS LER).

RESULTS

Analysis of reports

From April 1st 2002 to July 15th 2019, 76 spontaneous reports of suspected adverse reactions to products, mainly food supplements, containing turmeric alone or in combinations with other ingredients were registered in the Italian Phytovigilance system. Thirty-nine of these reports (51%) indicated symptoms attributable to liver damage. We excluded eleven reports from the analysis because of lack of clinical documentation.

In the following, we refer to 28 reports associated with products containing turmeric, with date of onset between November 10th 2018 and June 17th 2019, reported to the Phytovigilance system between December and July (*see Table 1S in Supplementary Material available online*). In almost all cases, diagnosis, as described on the reporting form or derived from follow-up report, was acute hepatitis, mostly with cholestasis. For all included cases a diagnosis of viral hepatitis was ruled out. Negative tests for HAV, HBV, HCV, Epstein-Barr virus, cytomegalovirus were indicated.

The median age of patients was 55 years (range 27-71 years), mostly women (86%). Twenty-five patients (89%) were hospitalized. As for the products, 19 cases (67%) assumed food supplements containing high titre curcumin and various dosage of piperine; six cases assumed food supplements with turmeric and other ingre-

dients (2 with echinacea, 3 with boswellia and one with red yeast rice and berberine). One patient assumed a food supplement containing only *Curcuma longa* extract, one assumed a spice containing turmeric and ginger and one assumed two herbal teas containing turmeric, ginger and dandelion. In one case the assumed product was a galenic preparation containing curcumin and piperine. In one report, the name of the food supplement was not specified. Duration of use varied from 8 days to 8 months (median 2 months). As for the reason of using the food supplements, in 8 cases (29%) weight loss was indicated; in 4 pain associated to arthrosis, arthritis, joint pain and senile osteoporosis. In one report, the reason for use was "digestion". Other reasons for use were "detoxification", "as antioxidant" and hypercholesterolemia. In eight reports the reason for use was not indicated.

In 8 of the 28 reports, it was explicitly specified that no concomitant drugs were assumed. In ten cases (36%) concomitant use of drugs was reported, some of which with known or suspected hepatotoxicity. Two patients assumed in addition to drugs, other food supplements not containing turmeric. In 10 cases, the presence of concomitant drugs was not indicated: in these cases, it was not possible to determine if the information about concomitant drugs was missing or if there were not concomitant drugs.

The outcome was "complete resolution" in 15 cases, "persistent" in 2 cases and "resolution with sequelae" in one case, in 10 cases the information was not reported; dechallenge was positive in 17 cases, in one case negative and in 10 cases the information was not reported; in one case the rechallenge was positive.

In 17 cases (61%) the causality assessment was "probable", in 10 cases (36%) was "possible" and in one case it was not possible to evaluate the causal relation because the hospital did not provide complete data.

Twenty-three reports were sent from hospital physicians or specialists, 4 from Poison Control Centre, and one from a hospital pharmacist. Results are synthetized in *Table 1*.

The correspondence between the recommended dose, reported on the label, and the assumed dose (taken from the reporting forms, where available) was verified. The assumed dose was equal or even higher than the recommended dose.

For 18 reports, the amount of curcuminoids/curcumin taken by patients (ranging from 40 to 1425 mg/die) was calculated considering what was declared by the patients or at the dose indicated by the manufacturer. In 67% of cases, the curcumin daily intake was 1.6 to 7 times higher than the daily reference value set by EFSA [19].

Of particular interest were the answers of EFSA focal points of Spain and Greece obtained following the Italian request for "exchange of information". Spain does not have a list of plants allowed in supplements and allows mutual recognition for turmeric supplements from other European Union countries. At national level, Spain has appointed the scientific committee of the Spanish Food Safety and Nutrition Agency to determine the maximum levels of curcumin that are eli-

Table 1
Summary of the reports

Variable		
Age (years)		
Mean (range)	55	(27-71)
Duration of use (months)	**n**	**%**
Median (range)	2	(0.25-8)
Sex		
Males	4	14.3
Females	24	85.7
Hospitalization		
Yes	25	89.3
No	3	10.7
Product components		
Curcumin+piperine	19	67.9
Turmeric+other	6	21.4
Turmeric+echinacea	*2*	*7.1*
Turmeric+boswellia	*3*	*10.7*
Turmeric+red yeast+berberine	*1*	*3.6*
Curcuma longa extract	1	3.6
Spice (Turmeric+ginger)	1	3.6
Herbal tea (Turmeric+ginger+dandelion)	1	3.6
Reasons for use		
Weight loss	8	28.6
Pain (arthrosis, arthritis, joint, senile osteoporosis)	4	14.3
Digestion	1	3.6
Other (detoxification, antioxidant, hypercholesterolemia)	7	25.0
Not reported	8	28.6
Concomitant drugs		
No	8	28.6
Yes	10	35.7
Not reported	10	35.7
Outcome		
Complete resolution	15	53.6
Persistent reaction	2	7.1
Resolution with sequelae	1	3.6
Not reported	10	35.7
Dechallenge		
Positive	17	60.7
Negative	1	3.6
Not reported	10	35.7
Rechallenge		
Positive	1	3.6
Not reported	27	96.4
Causality		
Probable	17	60.7
Possible	10	35.7
Indeterminable	1	3.6
Report from		
Hospital physicians or specialists	23	82.1
Poison Control Centre	4	14.3
Hospital pharmacist	1	3.6

gible for use in supplements, with reference to the ADI established by EFSA. The Greek National Medicines Agency suggests not to exceed the daily dose of 210 mg of curcumin, based on the EFSA opinion [19].

Analyses of the products

From May to June 2019, 18 samples related to 16 reports, identified by the product name and production batch, were collected and analysed, of these, six were products assumed by hospitalized patients and shipped directly from hospitals (*Table 2*).

In 13 (about 50%) of the 28 reports associated with the products containing turmeric (*see Table 1S in Supplementary Material available online*) no data on the production batch of the suspected products were reported. Only for three of these products a sample with a different production batch was collected and consequently analysed.

All the analysed products were food supplements with the exception of one food marketed as spice, containing turmeric and ginger powders and one galenic preparation containing curcuma Meriva®, *Curcuma longa* dry extract (titrated 95% in curcuminoids) and *Piper nigrum* (titrated 95% in piperine). With regard to the composition of the analysed food supplements, in most cases the ingredients declared on the label consisted of *Curcuma longa* dry extract (titrated 95% in curcuminoids) in association with *Piper nigrum* dry extract (titrated 95% in piperine), in some cases the dry extracts of *C. longa* were complexed with phospholipids (curcuma Meriva® phytosome).

In none of the analysed samples the presence of drugs, NSAIDs, synthetic dyes and pyrrolizidine alkaloids was detected. The presence of heavy metals, aflatoxins, pesticides, where determined, were found to be close to limit of quantification.

As regard to the analysis performed to evaluate the quali-quantitative composition in curcuminoids of turmeric extract, used as ingredient in the food supplements, the obtained results showed that:

a) in 100% of analysed sample (11/18) other species of curcuma were not found (e.g. *C. zedoaria* and *C. zanthorrhiza*);
b) the concentration in curcuminoids of the analysed samples was in compliance with the declaration on the label;
c) in about 60% of samples the turmeric demethoxylated compounds were not detected.

In *Table 2* the results of the qualitative composition in curcuminoids of the analysed products are shown. The "patient ID" in *Table 1S in Supplementary Material available online* and in *Table 2* represents the same cases.

Table 2
Experimental data on composition in curcuminoids of the analysed products

		Curcuminoids	
Patient ID	**Product**	**Curcumin**	**Demethoxylated forms of curcumin**
1	Supplement	Detected	Detected
3	Supplement	Detected	Detected
8	Spice	Detected	Detected
9	Supplement	Detected	Not detected
9*	Supplement	Detected	Not detected
10	Supplement	Detected	Not detected
10*	Supplement	Detected	Not detected
11*	Galenic preparation	Detected	Detected
12	Supplement	Detected	Detected
13	Supplement	Detected	Not detected
15	Supplement	Detected	Not detected
16	Supplement	Detected	Not detected
17*	Supplement	Detected	Not detected
18*a	Supplement	Detected	Detected
18 b	Supplement	Detected	Detected
20	Supplement	Detected	Not detected
21*	Supplement	Detected	Not detected
22	Supplement	Detected	Not detected

*find (product assumed by hospitalized patients and shipped from hospital).
a, b: different products from the same report.

DISCUSSION

Based on the frequency of new cases of liver damage, the homogeneity of the diagnoses and of the products taken by the subjects, a risk signal associated with the use of food supplements containing turmeric was pointed out. The signal arose through a cluster of 28 spontaneous reports of suspected cholestatic hepatitis associated with turmeric containing food supplements sent to the Italian Phytovigilance system between December 2018 and June 2019. The seven reports from Tuscany Region were described in detail in a paper recently published [20].

This system, almost unique among European countries, has shown during the years its value for monitoring the safety profile of dietary supplements, as a guarantee for protection of citizens' health considering the wide use of these products in Italy (Italy is the first country for consumption of supplements in Europe) [21].

Considering that, for their nature, food supplements fall under the regulatory framework of food control, the signal was managed using both methodologies specific to pharmacovigilance and food safety control.

With regard to pharmacovigilance strategies and considerations applied in this context, it has to be underlined that spontaneous reports of suspected adverse reactions provide a qualitative signal, thus do not allow the quantification of a risk. The good reporting level of the Italian Phytovigilance system in comparison with other European countries and the quality of the reported data, with the possibility of follow-up in serious cases, should be underlined.

The evaluation of the possible causal association in individual cases (causality assessment) was the first step of signal validation, to which further investigations (disproportionality analysis, observed/expected analysis) should follow, when feasible and appropriate. Further-

more, an important consideration to be taken into account when trying to estimate the entity of the potential risks associated with food supplements is under-reporting of adverse reactions to the so-called "natural" products. This under-reporting is partly showed in our situation by the geographical variability of the number of reports: the reports were received mostly from Tuscany and Lombardy, where it is known that there is a greater sensitivity to pharmaco- and phyto-vigilance activities. Cannot be excluded that the increase in reports could also be due to the "notoriety bias" (increase in reports following the spread of a problem), indeed the spread of the news occurred between January and May 2019.

Another important element in the evaluation of risk signals in the pharmacovigilance field is the possible biological plausibility of the reaction observed with regard to the substance assumed. Regarding the mechanisms at the basis of suspected hepatotoxicity from turmeric, many hypotheses can be formulated.

The choleretic and cholecystokinetic action of curcumin may be also considered. Curcumin is excreted through the bile and excretion is mediated by ATP-dependent efflux pumps called Mrp2 (multidrug resistance-associated protein 2) [22]. These pumps are also physiologically responsible for the transport of bile acids from the liver to the bile canaliculi to form bile. At the level of these transporters a competition can be created between curcumin and bile acids which therefore accumulate in the liver inducing cholestasis. Therefore, the cholecystokinetic effect of curcumin, possibly enhanced by piperine, could be a risk factor for hepatotoxicity [23-25].

Some studies show that curcumin, as well as piperine, modulates the activity of different enzymes involved in the metabolism of some drugs. Curcumin has been shown to inhibit the activity of cytochrome P450, glutathione-S-transferase and UDP-glucuronosyl transferase. Inhibition of these enzymes in subjects taking curcumin can lead to an undesirable increase in blood concentrations of some drugs causing toxicity [26]. In this context, it was shown that CYP3A4 inhibitors could alter the metabolism of numerous drugs commonly used in the elderly, e.g. amiodarone and quinidine, increasing the risk of dangerous ventricular arrhythmias [27]. Piperine inhibits both the drug trasporter P-glycoprotein and the CYP3A4: these proteins are expressed in enterocytes and hepatocytes and contribute to a major extent to first-pass elimination of many dugs [28]. Therefore, the metabolic effect of curcumin, especially if associated with piperine, could be a risk factor for numerous drug interactions especially in patients undergoing polytherapy.

Many weaknesses and limitations emerged. In the first place, as already stated, spontaneous reports provide qualitative information and, in some cases, not all the necessary information were reported, such as the name of the product, batch, concomitant drugs or food supplements, follow-up of the patient. Thus, spontaneous report only can generate signals for further investigations.

During the qualitative and quantitative analysis phases, several aspects arose related, in particular, to the quantities of curcumin and other curcuminoids contained in the products. Many of the extracts analysed contained high concentrations of curcumin, but in about 60% of these, the other curcuminoids normally contained in the extracts of *Curcuma longa* were not present. For this reason, it was hypothesized that the different raw materials could not be totally of natural origin (and therefore derived from a normal extraction process) but consisted of synthetic substances added to enrich the finished product. However, this adulteration reduces turmeric quality, but should not impact its safety.

EFSA established the ADI of curcumin as safe considering the low bioavailability of this substance due to the negligible absorption in gastrointestinal tract [3]. However, this ADI is not referring to cases in which substances that increase the bioavailability of curcumin are added. Almost all the products indicated in our reports contained high titre curcumin associated with substances such as piperine to increase bioavailability. In these cases, the products no longer comply with the conditions examined by EFSA, therefore the benefit/risk ratio must necessarily be reassessed. All the aspects that emerged from the analyses need further investigation. In conclusion, the emerged problems can potentially be observed for any other product or substance available on the market, therefore it is appropriate to understand the need to plan interventions that may be reproducible for each situation. The detailed analysis of spontaneous reports represents the first step to face these problems and adopt appropriate intervention measures aimed at guaranteeing the safety of food supplements widely used by the population. During the first months of 2019 the Ministry of Health published a list of products implicated in the adverse reactions. The companies have autonomously withdrawn the products from the trade.

Spontaneous reports were the starting points for qualitative and quantitative analyses of the substances contained in some of the samples of the products. On the basis of the results of all the activities performed by the multidisciplinary group, regulatory intervention was taken, and further actions have been planned in the immediate future. The Ministry of Health has decided, to adopt a specific warning for the labelling of turmeric-based food supplements, aimed at discouraging their use for subjects with alterations of the hepato-biliary function. Moreover, the Ministry of Health invited to seek doctor's advice when using concomitant drugs.

CONCLUSION

Considering the results of the above investigations, it is concluded that the ADI established by EFSA (3mg/kg /day) for curcumin is a toxicological value that represents the quantity of the substance that can be taken daily for life without recognizable adverse effects. ADI was set by EFSA for curcumin as such and not in association with a molecule that increases its availability or biological effects. Therefore, this value cannot be used directly to assess the safety of the substance taken for limited periods. No illegal substances added voluntarily to the user have been detected by the analytical chemis-

try activity currently carried out. The levels of contaminants detected were always lower or close to the quantification limits. These supplements are formulated with associations of substances that increase the absorption of curcumin. Most of the supplements indicated on the label have a dosage which determines the exceeding of the ADI.

At the current state of knowledge and on the basis of the evidence collected so far, in the reported cases a cause-effect link of the dosage and formulation of the supplements in question with the hepatitis might not be excluded.

In order to investigate further interpretative scenarios of the phenomenon in the period under study, such as the increased exposure of the population to turmeric supplements and the presence of harmful substances, unidentified to date it is desirable to acquire further information on the various formulations present on the market over time for a better characterization of the supplement production chain (origin of raw materials, traceability, formulation, marketing).

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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