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RESEARCH ARTICLE

SAFETY OF DIETARY SUPPLEMENTS- A REVIEW ARTICLE

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ABSTRACT

This study aims to conduct a comparative analysis of the legislation in some countries regarding the composition and safety of dietary supplements, to alert the community for any potential risks of such products, as well as to offer some measures for their safe use. Harmonized requirements exist only for vitamins and minerals in dietary supplements. Any other substances that constitute the supplements lack regulation. Depending on the type of the substance and the dosage, a product may be defined as a pharmaceutical in one country while being labeled as a dietary supplement in another. On such grounds some traders, aiming to bypass the complicated registration norms, purposely label some products as dietary supplements instead of pharmaceuticals. To guarantee the safety of available dietary supplements, it is necessary for production standards to be established in Bulgaria as well as to incorporate a registration of the products into the Bulgarian Drug Agency. Coordination is necessary between the authorities, users and medical professionals to report any observed side effects resulting from the use of dietary supplements.

INTRODUCTION

Under normal conditions, a suitable and diverse diet can provide all of the necessary nutrients for optimal development of the organism and the maintenance of a healthy life. But under certain conditions people may use supplements as an addition to their diet. Some use them to compensate a deficiency of certain nutrients and others – to achieve a desired effect, some examples being body weight regulation or an increase in lean muscle mass. According to the Bulgarian legislation, these products are divided into two groups: dietary supplements and foods for particular nutritional uses. The similarities between the two groups are that both are offered as capsules, tablets, pills, vials, in powdered or liquid form; are an addition to a normal diet; may be used separately or combined; are intended to be used in previously established small quantities and reach the user in pre-packaged form. The differences on the other hand are, that dietary supplements are concentrated sources of vitamins, minerals and other substances with beneficial dietary or physiological effects (Ordinance 47, 2010), while the foods with special functions contain consituents, that are suitable for specific dietary use for a certain category of people (with impaired digestion or metabolism, in a specific physiological condition or healthy infants and small children) (Ordinance on the requirements for dietary foods for special medical purposes, 2013). Although it is a matter of different kinds of products on the market, they are commonly termed as "dietary supplements" amongst the average users. Most frequently used by healthy adults are foods intended for low-energy diets (aiming to decrease body weight) and foods suited for use during intensive muscle stress, especially by athletes. Whether dietary supplements are foods or pharmaceuticals is a frequently emerging question. Humane medicine defines any substance or a combination of such that is used to treat or prevent an illness. (Law on Medicinal Products in Human Medicine, SG, 2015) In the sense of the current legislation, dietary supplements are not intended for treatment and must not contain substances which define the product as a pharmaceutical. Their labels and packaging are not allowed to claim that the given product prevents, treats or cures diseases in people, as well as to imply such properties. (Ordinance 47, 2010, Directive 2002/46/EO, Ordinance on the requirements for dietary foods for special medical purposes, 2013) In that sense, despite being in tablet form dietary supplements are defined and labeled as foods and not as pharmaceuticals. (Ordinance 47, 2010, Directive 2002/46/EO) The supplements are viewed upon the same way in the EU and the USA. In Russia they are also defined as foods but are further subdivided as dietary supplements that

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are an addition to the diet and as parapharmacological products (parapharmaceuticals) which are used for prophylaxis. The latter contain small quantities of nutritional components (organic acids, bioflavonoids, glycosides, biogenic amines, regulatory peptides, oligosaccharides) that regulate the functional activity of different organs and systems. Those products contain the active substances in quantities that are under the therapeutic dose, and if the dose is exceeded they are viewed upon as pharmaceuticals (Shustov E, registrbad.ru.)

The borders of the therapeutic doses differ by country, which results in a certain product being labeled as a dietary supplement in one country, while being labeled as a pharmaceutical in another. The differences in those values are defined by the respective national regulations. The harmonized legislation in the EU member countries provides a notification regimen on demand form the authority for every dietary supplement which is marketed for the first time, regardless of the fact that it is produced within the EU. (Directive 2002/46/EO) Regarding the products imported by third parties such as the USA or Russia, notification of the authorities and evaluation of the product are mandatory conditions for its marketing. (Palova, 2009) In that case, the authority regarding dietary supplements in Bulgaria – Regional Food Safety Agency establishes via the presented documents and the labeled contents, whether the product in question fits the definition for a "dietary supplement" according to the current regulations. The purpose of this study is to conduct a comparative analysis of the legislation in some countries regarding the composition and safety of dietary supplements, to alert the community for any potential risks of such products, as well as to offer some measures for their safe use.

Comparative analysis of the legislation regarding the composition and safety of dietary supplements

Any foods produced within the limits of the EU may be sold freely in any member country. Dietary supplements are distributed in the same manner, the only difference being that the authorities may demand a notification before such products reach the market. The general requirements are listed in Directive 2002/46/EO of the European parliament and at the council of 10 June 2002 for rapprochement of the legislations of the member countries regarding dietary supplements. These requirements represent a partially harmonized set of rules, aiming to guarantee that dietary supplements are safe and correctly labeled. In the same time any EU member country, besides the general requirements, may introduce specific national requirements for dietary supplements, regarding some of their constituents. This leads to isolated cases of a given product being approved for marketing as food in some EU countries, while classified as a pharmaceutical by other. Constituents that may be used for the production of dietary supplements and foods with special functions are listed in specialized regulations. These are dietary substances – vitamins and minerals or other substances with nutritional or physiological effects, in a concentrated form. (Directive 2002/46/EO, Commission regulation No 953/2009)

Some substances (herbal extracts for example) are used in dietary supplements, as well as for the production of patented pharmaceuticals, with the difference being in the quantity of the respective substance.

Only substances that are proven to be safe through extensive scientific research are used for the production of dietary supplements. (Directive 2002/46/EO)

It is interesting however, that only vitamins and minerals, which are normally present in every individual's diet, are subjected to a principle of permission when used as supplement ingredients within the EU member countries. (Directive 2002/46/EO) The risk evaluation is conducted by a Panel on Food Additives and Nutrient Sources Added to Food (ANS Panel), authorized by the European Food Safety Authority (EFSA). The products are declared in a harmonized list of Directive 2002/46/EO but the requirements for their quantities are not uniform. (Duleva, 2013). The upper limits for safe daily intake are presented in our national Regulation № 47 of 28.12.2004 on the requirements for dietary supplements (Ordinance, 2010). The EFSA is still researching the safety of substances of plant origin that may be contained in dietary supplements which suggests that there are no precise requirements for their standardization. (Duleva, 2013) This is the reason why some products may be classified as foods in some EU countries while being defined as pharmaceutical products in other EU countries. In Bulgaria there is a prohibition list, including 120 plants which are not allowed for use as consituents in dietary supplements. (Ordinance 47, 2010) Respectively, any other plants that are not included in that list, may be used in supplements. In the same time, a positive list was published in the USA, including around 250 plants which are considered safe for use, based on scientific research results – termed Generally Reconized As Safe. (Duleva, 2013)

In Russia there is a list of medicinal plants and their products, which are forbidden for use in single-component dietary supplements, as well as a list of plants whose use as constituents in dietary supplements requires confirmation for the lack of a toxic effect. (Smed.ru) Regarding this matter, in Germany – also a member of the EU, representatives of the Federation and the federal provinces have made a list of substances that isn't legally bound, but provides guidance for the use of plants and parts of them as foods or food constituents. (Federal Office of Consumer Protection and Food Safety (BVL)) Before being marketed, the products containing plants are individually evaluated by the authority in foods, in cooperation with the Federal Institute for Drugs and Medical Products. Depending on the dosage of the substance in question, the products are defined as dietary supplements or pharmaceuticals. (BVL) In Russia the safety of dietary supplements is evaluated by the Center of the sanitary certification of food products Sanitary and Epidemiological Surveillance Ministry of Health of the Russian Department at the Institute of Nutrition. What is different in comparison to Bulgaria is that for the purpose of certification, besides the same documents which are viewed in Bulgaria (labels, packaging), the authorities may request experimental data for toxicological, physiological and metabolic effects, confirming the efficiency and safety of the supplements, as well as a clinical evaluation of their efficiency. (Ministry of Health of the Russian Federation order, 1997) Based on the presented documentation, the authorized individuals present their professional opinion in a certificate which has to include an evaluation of the composition, evaluation of the safety and a confirmation of the biological activity declared by the respective supplement's producer. The necessity for clinical

trials of the supplements is determined in the process of their evaluation. (Registrbad.ru) In order to guarantee the efficiency of their products, the producers may present a voluntary certification of dietary supplements to prove their health benefits. (Onischenko, G., 2006)

In the USA, an Office of Dietary Supplements (ODS) is established within the National Institutes of Health (NIH), whose purpose is a more thorough research on the benefits of dietary supplements for a healthy state and the prevention of chronic diseases. Regarding this matter, the DSHEA (Dietary Supplement Health and Education Act of 1994) is establishing separate standards for the safety of dietary supplements, by describing the conditions within which dietary supplements may be falsified thus becoming potentially dangerous. An independent organization - The US Pharmacopeia (USP) has taken up the issue of the safety of dietary supplements. USP started publishing standards for the quality, purity, packaging and labeling of dietary supplements back in 1997. The producers are not bound by law to follow the USP standards, but prefer to do so in order to guarantee the quality of their product (American Cancer Society, 2015 c).

Potential risks from the use of dietary supplements

Dietary supplements are considered safe, but there is evidence that in certain cases their use carries some risks (American Cancer Society, 2015 a.). The dangers related to the use of dietary supplements may be viewed in a couple of categories. Form the user's perspective; the risks are overdosing and adverse effects resulting from the interactions with other foods and pharmaceuticals. Overdosing is a possibility due to the sales without prescription and the quick access to the product. The users make additions to their treatment by themselves without consulting with a medical specialist, simply trusting the "helpful" effects declared on the packaging. More and more people are using dietary supplements. According to the data from research conducted between 2011 and 2015, the share of Americans who use supplements is almost constant – 68 %. (CRN, 2015) Usually, "abuse" of such products occurs as a result of the users' desire to achieve the desired effect as soon as possible. But the different supplements have an individual effect on every single person depending on his physiological characteristics, needs and illnesses; this is why even the seemingly harmless supplements should be used after consulting with a medical professional.

It is a proven fact, that in large doses some vitamins and minerals are dangerous, even toxic. For example, too much vitamin C may affect the organism's ability to utilize copper. The increased quantity of phosphorus may inhibit calcium absorption. The organism cannot metabolize high doses of the fat-soluble vitamins A, D and K which when accumulated, may have toxic effects. (American Cancer Society, 2015 a)
A lot of people presume that using dietary supplements in combination with pharmaceuticals is harmless and do so without consulting with a medical specialist. In that case instead of the desired effect, the exact opposite may occur. For example, some constituents of plant origin in dietary supplements may block or accelerate the absorption of some pharmaceuticals by the organism. (American Cancer Society, 2015 b) The constituents of some supplements can interact with pharmaceuticals, resulting in adverse side effects such as an increased toxicity of the respective pharmaceutical and a decreased favorable effect, which in turn results in health deterioration. Despite this, the percentage of adverse effects resulting from interactions between dietary supplements and pharmaceuticals is low – 2 % to 3 %. It is presumed that the interaction may be due to some impurities in the supplements – pesticides, bacteria, fungi, heavy metals, as well as some "inert" substances. (Supplements-and-health.com, 2012) The producer has to monitor these impurities on an annual basis using the integrated system for internal control, while the Food Safety Agency should be conducting laboratory control. In the exported report of the Agency for the first quarter of 2016, it is evident that dietary supplements have not undergone laboratory control. (BFSA, 2016 e) For the same timeline, the territorial authorities of Rospotrebnadzor in Russia reported 2579 laboratory samples of dietary supplements, of which 4,5 % do not meet the requirements for microbiological indicators, 0.2 % do not meet the requirements for chemical indicators and 7 % do not meet the requirements for physicochemical parameters including the presence of biologically active substances (Rospotrebnadzor, 2016). For the aforementioned timeline, there is a warning on the BFSA official web page, received via the Rapid Alert System for Food and Feed (RASFF), for a dietary supplement "organic barley" in tablet form (Bio Gerstehgras Tabletten), bearing the trademark Hanoju and originating from Germany, which was found to contain Shiga toxin-producing Escherichia coli.

The risk of an exceeded dosage or the presence of an unauthorized substance in the supplements also exists on the part of the producer/ distributor. The legislative frameworks allow marketing of supplements that contain certain constituents and are harmless for the consumers, but is this really achieved?

To evaluate the safety of dietary supplements, the Centers for Disease Control and Prevention (CDC) in USA conducts a survey in 63 emergency rooms for a period of ten years (2004 – 2013). It is established that there are 23 000 visits to a physician and 2 000 hospitalizations resulting from the use of dietary supplements. The most frequent complaints were increased heart rate and chest pains. (Geller and all, 2015, Murray, 2015) On the official web sites in Bulgaria, there are no reported registered cases of individuals who sought medical attention for complaints resulting from use of dietary supplements. Does that mean that all dietary products on the market in Bulgaria are harmless?

If we take a look at the BFSA web page we will encounter multiple warnings for the distribution of dietary supplements containing prohibited substances or exceeded dosages, for example:

- A dietary supplement "XM+ Energy Mix" from USA, that made its way to the EU through the Netherlands, which was found to contain the prohibited substance "Ephedrine". (BFSA, 2016 d)
- A dietary supplement "Assault XT 30 servings" bearing the trademark Musclepharm Assault and originating in the USA, for a risk of nicotinic acid overdose was established. (BFSA, 2016 a).
- A dietary supplement "Dragon Power" originating from China, which was found to contain the prohibited substance "Sildenafil" (BFSA, 2016 b).

- A dietary supplement "Oxy Elite Pro"- there are reports of acute hepatitis (BFSA, 2016 c).

Based on the statistical data for June 2015, the number of notifications received via the RASFF under the category "Dietetic foods, dietary supplements and enriched foods" has decreased by 61 % compared to the same period during 2014, but despite this the number of products with inconsistencies available on Bulgarian territory for only a single month remains high – 9 notifications. (Kanakidis, 2015a). For March 2015, the number of recieved warning notifications for dangerous products on the market is slightly higher compared to March 2014 – from 19 to 20, which indicates that the percentage of dangerous products on the market varies for the different periods. There is no detailed information for every month and as a result, the share of dangerous supplements on the market for an entire year cannot be established. (Kanakidis, 2015b). The products with inconsistencies are mainly in the category of dietetic foods and dietary supplements intended for athletes. (Supplements-and-health.com, 2013 b). Prohibited substances are usually found as a result of filed complaints from users regarding specific side effects, which sometimes lead to lethality, as was the case with the prohibited chemical 2,4-dinitrophenol (DNP) found in weight loss products (so called fat burners) used mainly by athletes. The substance is not declared on the label and may lead to serious health complications, even death. In the database for 2,4-dinitrophenol poisonings up to 2015. The Federal Institute for Risk Assessment (BfR) has registered five cases, three of which having a lethal end. (Sertova, 2015)

Any products claiming to have healing properties should be registered in the Bulgarian Drug Agency (BDA). Regarding the producers, in order to evade the strict regimen for authorization (clinical trials, requirements for maintenance of the registration record, requirements for monitoring the quality, safety and efficiency of the products) they label the products as dietary supplements by not giving specific information regarding their composition. This is one of the reasons for the substantial growth of the market for supplements during recent years. According to data from the Bulgarian Food Safety Agency, 23 000 traders have submitted notifications for registration of dietary supplements, with 3 500 new notifications received only for 2015, with 500 more than those from 2014. The data suggests that such products are used by a large portion of the population, but the Bulgarian statistical database has no information for their use. In the same time, it would be difficult for the BFSA to keep track of the composition of all kinds of dietary supplements via laboratory analysis. For the detection of a prohibited substance or a substance which exceeds the dosage, it is necessary for the Agency to receive a specific complaint. In this case the specialist, after verification may request laboratory examination of the product. For that purpose however, it would be necessary for the specialist to identify the sought substance, based only on the adverse side effects it has caused, which in most cases is impossible. And is every adverse side effect reported? Maybe this is the place to pose the question regarding the coordination between the authorities and physicians. The authority regarding dietary supplements and foods with special functions is the Bulgarian Food Safety Agency under the Ministry of Agriculture and Food, and the one regarding the control of pharmaceutical products is the Bulgarian Drug Agency under the Ministry of Health.

Considering the thin line in certain cases between a dietary supplement and a pharmaceutical, it would be appropriate for the control to be tightly specialized and to be conducted by a single institution, to avoid having to redirect the cases between different authorities.

Recommendations

From the conducted analysis we may conclude, that there are flaws in the Bulgarian regulation of dietary supplement control, which aims to guarantee their safety. Not all of the used constituents have undergone scientific evaluation, there is a lack of certain standards for the production of supplements, there is no clear and precise limit for the contained amounts of the active substances, laboratory control is not conducted periodically. There are multiple notifications on the BFSA web site regarding dangerous dietary supplements on the Bulgarian market, which shows that the control over such products is loose not only in Bulgaria but in the entire EU altogether. Based on the aforementioned, the following recommendations may be made:

- Control over the composition of dietary supplements to be conducted by the BDA;
- Evaluation and certification of dietary supplements before their marketing, following the Russian model;
- To establish standards for the production of dietary supplements;
- To introduce a mandatory regimen for notification from every medical professional who establishes any side effects resulting from the use of dietary supplements, after a medical examination;
- The authenticity of the dietary supplements be checked by laboratory analysis conducted by the BDA;
- The sale of dietary supplements to take place only in pharmacies and drug stores;
- To conduct a communal survey regarding the use of dietary supplements.

Conclusion

The use of dietary supplements amongst the population is increasing with every passing year. The users' aim towards a healthy lifestyle and a suitable dietary regimen is logical. But the safety of the products in question is a responsibility of the national authorities. Sometimes, aiming to achieve the desired effect quickly, the user increases the listed dose or uses dietary substances while using pharmaceuticals without first consulting with a medical professional. And while that kind of risk are related to the population's lack of knowledge, purposeful alluding by the producers is also encountered, aiming to advertise the product and to increase its sales. Frequently, to avoid going through the complicated procedures of registering a given substance as a pharmaceutical product, the traders resort to its careless labeling as a dietary supplement. Sometimes these supplements may contain harmful substances. The multiple warning notifications posted on the BFSA web page are an evidence of that. Without a doubt, one of the reasons why such products are available on the market is the loose legal control. This is why it is crucial to make certain changes in the regulation, guaranteeing the safety of dietary supplements.

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