Dietary supplements, harm associated with synthetic adulterants and potential governance solutions

Louise Manning*[1], Milena Bieniek[2], Aleksandra Kowalska[2] and Rachel Ward[3]

[1]Royal Agricultural University, Stroud Road Cirencester, Gloucestershire, GL7 6JS (UK)

[2]Faculty of Economics, Maria Curie-Skłodowska University, pl. M. Curie-Skłodowskiej 5, 20-031 Lublin, Poland

[3]R. Ward Consultancy Limited, Nottingham NG8 2SB, UK.

Louise Manning ORCID iD 0000-0002-9900-7303

Milena Bieniek ORCID iD 0000-0001-9686-7650

Aleksandra Kowalska ORCID iD 0000-0003-3854-951X

Rachel Ward

***Corresponding author: louise.manning@rau.ac.uk**

Abstract

Intentional adulteration of dietary supplements with undeclared synthetic drugs illegally enhances the supplement's purported efficacy and is a growing global crime issue that can cause actual harm to unsuspecting victims. The aim of this research is to identify the potential adulterants of interest in dietary supplement adulteration and then to consider what governance systems can be implemented to reduce the likelihood of such practices occurring. Firstly, existing academic and grey literature is iteratively reviewed to define and outline the challenge of dietary supplement adulteration. Three types of supplement are considered in particular, namely those supplements promoted for weight loss, sexual enhancement, and muscle building. Two regulatory databases (the European Union Rapid Alert System for Food and Feed database and the United States Food and Drink Administration database of Recalls, Market Withdrawals, & Safety Alerts databases) are used to determine the incidence of adulteration by product type and the nature of the adulterants being used. The role of pharmacovigilance governance systems that focus on dietary supplements is considered.

Keywords: dietary supplements, food supplements, synthetic adulterant, RASFF, US FDA, governance systems

Declarations

Funding (information that explains whether and by whom the research was supported)

There has been no funding.

Conflicts of interest/Competing interests (include appropriate disclosures)

There have been no conflicts of interest/competing interests.

Availability of data and material (data transparency)

Data available on request.

1. Introduction

Dietary supplements include dietary ingredients such as vitamins, minerals, botanical extracts or preparation, amino acids, enzymes and many others. Furthermore, dietary ingredients might be the components of finished food products other than dietary supplements, e.g. breakfast cereal (Wheatley & Spink, 2013). As specified in regulations such as the European Union (EU) General Food Law Regulation (EC) 178/2002 and the United States (US) Dietary Supplement Health and Education Act of 1994 (DSHEA), ingredients used in dietary supplements should be safe, effective and have no adverse side effects. The US DSHEA (1994) defines a dietary supplement as a product that: is intended to supplement the diet, contains one or more dietary ingredients, is intended to be taken by mouth as a pill, capsule, tablet or liquid and is labelled on the front panel as being a dietary supplement. As regulatory bodies use conflicting definitions for dietary supplements this impacts on the collation and comparison of

data from different sources. The term “dietary supplement” is used in the US and a clear distinction has been made in legislation between conventional food, dietary supplements, medical foods and drugs (Table 1). The US Food and Drug Administration (FDA) is responsible for all these types of products, operate a consolidated process for recalls, market withdrawals and safety alerts and define the products using an appropriate designation as per the legislation.

Take in Table 1

In the EU, food supplements are described in Directive 2002/46/EC as: “foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination…” Thus, as part of their registration process in the EU, food supplements are considered as foods and are not required to be tested, registered and checked as exhaustively as medicines or synthetic drugs (Rocha, Amaral & Oliveira 2016; Kowalska, Bieniek & Manning 2019). In the EU there is a clear distinction drawn between medicines, herbal medicinal products, conventional food and food supplements (Table 1). Food supplements are regulated in the EU as foods and are described in Directive 2002/46/EC with various amendments. A single collective category of “dietetic foods, food supplements, fortified foods” is used within the EU Product Rapid Alert System for Food and Feed (RASFF) database which collates and notifies Member States about food and feed product withdrawals, recalls and import failures. This collective category had the 4th highest number of RASFF alerts in 2017 and 5th highest in 2018, the latest report published (RASFF 2017; 2018). Dietetic foods are no longer a regulated product category in the EU per se. Previously the Regulation (EC) No 953/2009 on substances that may be added for specific nutritional purposes in foods for particular nutritional uses [PARNUTS] defined dietetic foods (Table 1). This has now been repealed and replaced with Regulation (EU) 609/2013 which covers food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control and terms them 'Food

for Specific Groups'. Regulation of meal replacement products for weight control was transferred to Regulation (EC) No 1924/2006 on nutrition and health claims. After considerable review, young child formulae and food intended for sports people were not considered sufficiently unique in role in the diet of a specific vulnerable group to require any specific regulatory definition or provision.

At the global level, the Codex Alimentarius CAC/GL 55 – 2005 Guidelines for vitamin and mineral food supplements also defines these products. Codex standards or guidelines do not address dietary supplements other than those providing solely vitamin and mineral supplementation to normal diet. The Codex Alimentarius Commission General Standard for the labelling of and claims for prepackaged foods for special dietary uses (CODEX STAN 146-1985) states that they “shall not be described or presented in a manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding their character in any respect”. These foods for special dietary uses can be labelled ‘special dietetic’ foods and include products intended for infants and young children. They are not dietary supplements.

Fortified foods are considered simply to be foods which have been ‘fortified’ by the addition of extra nutrients for the purpose of improving the nutritional status of a population and to decrease the occurrence of nutrient deficiencies. Regulation EU 1925/2006 controls the addition of vitamins and minerals and other substances to foods in the EU. In the USA, the FDA have published a fortification policy entitled “Nutritional Quality of Foods; Addition of Nutrients” which discourages indiscriminate addition of nutrients to foods (FDA 2015). There are no international definitions of fortification defined by the Codex Alimentarius Commission. The General Principles for the addition of essential nutrients to foods CAC/GL 9-1987 does define restoration as an activity. Thus, there is a multiplicity of terms in use when considering dietary supplement and this can create confusion when assessing such products across jurisdictions. In this paper, the term dietary supplement is used for simplicity, except where a

regulatory prescribed term is specifically used such as in the RASFF database. It is clear however, despite these differences, that regulatory authorities expect that dietary supplements are safe to consume, are not adulterated, and do not exert a pharmacological, immunological or metabolic action, or make misleading claims.

There is also a variance in the use of adulteration or contamination as terms in the datasets examined. Contamination is described as: "the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter…" (WHO 2007, 112). This definition of contamination is at odds with the definition in the Codex Alimentarius General Standard for Contaminants and Toxins in Food and Feed CXS 193-1995 (as amended in 2018) that states contamination as: "Any substance not intentionally added …." focusing on the mediating issue of intent with the term 'contamination' as opposed to 'adulteration'. Poor regulatory governance and weak market governance relating to contaminants can result from inadequate application of good manufacturing practice standards and quality control systems (Hachem et al. 2016) and from ineffective risk management across the supply chain by both commercial operators and regulators. Non-compliance of dietary supplements can also result from deliberate fraud including adulteration, either with natural and/or synthetic adulterants, and we consider both types of adulterants in this paper, but place particular emphasis on synthetic adulterants. Lord, Elizondo, & Spencer (2016, p. 606) rightly state that food fraud should be understood as an 'endogenous' phenomenon within the food system where criminal opportunities arise under conducive/facilitative conditions as part of legitimate actors' routine behaviours; where legitimate occupational actors and organisations are in some way necessarily involved.

Although there is no regulatory definition for 'adulterated food' in the EU, General Food Law Reg. (EC) 178/2002 applies to food and food supplements. In addition, EU Regulation 1169/2011 on the provision of food information to consumers specifies that food information

provided, (including labelling, claims and accompanying marketing and advertising materials), must not be misleading as to its characteristics, including its nature, identity, properties, composition etc., nor and claims made. The United States (US) Federal Food, Drug and Cosmetic Act Section 342 determines adulteration occurring from any poisonous or deleterious substance that could cause harm; if food is unfit for consumption; if any valuable constituent has been omitted, abstracted or substituted; if damage or inferiority has been concealed; or if any substance has been added to increase bulk or weight, or reduce quality or strength, or make it appear better or of greater value than it is. The US Federal Food, Drug and Cosmetic Act Section 343 considers food as misbranded, inter alia, when its labelling is false or misleading or the food is offered for sale under another name, when it is an imitation of another food or its container is so made, formed, or filled as to be misleading. There has been some confusion about the narrow FDA definition of adulterated food, particularly, given that there are local definitions of adulteration that due to the lack of consistency could influence collective approaches to determining the extent of, or addressing of, the problem of mislabelling, misrepresentation and misbranding as a form of adulteration (Kowalska, Soon & Manning 2018). Adulteration is usually economically motivated (Spink & Moyer 2011; Manning & Soon 2014; Kowalska, Soon & Manning 2018) denying informed choice and consumer rights (Lo & Shaw, 2018; Kowalska, Bieniek & Manning 2019) see Figure 1.

Intentional adulteration of dietary supplements using undeclared synthetic drugs is a widespread global issue (Rocha, Amaral, & Oliveira 2016; Kim et al. 2017; Pascali et al. 2018), especially because of the high potential profits that can be made (Skalicka-Woźniak, Georgiev & Orhan 2017). Indeed, multiple instances of dietary supplement adulteration have been reported in the literature including in China (Li et al. 2012); Europe (RASFF reports 2009; 2013; 2014; 2015; 2016; 2017); India (Agrawal & Mishra 2016); Indonesia (Simaremare et al.

2018); Iran (Khazan et al. 2014); Italy (Pascali et al. 2018); and the United States (US) see Tucker et al. (2018).

Take in Figure 1

Therefore, authentication of dietary supplements is important to both validate their composition and to confirm that good manufacturing practices have been followed. The aim of this research has been to identify the potential adulterants of interest in dietary supplement adulteration, in particular synthetic adulterants, and then to consider what governance systems can be implemented to reduce the likelihood of such practices occurring.

2. Methodology

The methodological approach used in this research was to firstly review existing literature to define and outline the challenge of food supplement adulteration, and then to analyse data from regulatory databases to consider the incidence of adulteration by dietary supplement type and the nature of the adulterants being used. We searched the following databases: Science Direct, Google Scholar, Google (to include grey literature) to primarily consider current information on dietary supplement adulteration. The terms were used in a range of combinations with the search terms i.e. through an iterative literature review method (Kowalska & Manning, 2020). Iterative literature review is grounded by a foundational literature search using a series of iterative searches for a given combination of search terms the first 100 items in each search being considered for relevancy and any duplication. The papers were then read in full and screened for relevance and value in supporting a discursive primary narrative and argument.

Two databases are used in this secondary element of the research: the EU RASFF database and the US FDA Recalls, Market Withdrawals, & Safety Alerts database. When comparing data sets it became important to recognise and interrogate the lack of consistency in the definitions and requirements for dietary supplements within different countries regulations and this is taken

into account when the analysis is undertaken. There are other crucial differences: (1) the RASFF database covers all the notifications from members in the network checked by the European Commission for completeness, compliance with legal requirements, falling within the scope of the RASFF etc.; (2) The US FDA Recalls, Market Withdrawals, & Safety Alerts database provides information gathered from press releases and other public notices about certain recalls of FDA-regulated products (animal & veterinary, biologics, cosmetics, dietary supplements, drugs). Thus this database does not cover all recalls of FDA-regulated products. FDA seeks publicity about a recall only when it believes the public needs to be alerted to a serious hazard; so when a recalled product has been widely distributed, the news media including press releases is an effective way to reach a large number of people.

The quantitative analysis of the data collected in the RASFF dataset is based on time series analysis deriving index numbers along with a linear trend. Indexes are descriptive measures, but they can be used together with trend analysis to support the development of conceptual theory. An index number is displaying the level of a variable relative to its level in a given base period. The trend line is a line of best fit to the time series data and it is determined using the least square method. This method provides the best fit of a set of datapoints by minimisation of the sum of the squared residuals of points from the plotted curve. The main advantage of a trend study is that it is a simple form of analysis. As a rule, the number of estimated parameters (i.e. 2 for linear trend) has to be greater than the number of observations. For time series with a linear trend, the coefficient of determination r^2 sometimes may not evaluate the goodness of fitting of the model to the data well. However, if the coefficient of determination is close to 1, then it can be said that the regression line is of value in determining future trends (Aczel and Sounderpandian 2009).

3. Results

3.1 Literature review

A review of academic and grey literature shows that synthetic adulteration of dietary supplements to promote weight loss, sexual enhancement, and muscle building are the three current main areas of concern. The health implications of the presence of undeclared adulterants are explored in the following sections.

3.1.1 Weight loss

Pure and highly concentrated caffeine products are a significant risk to public health contributing to at least two deaths in the US and minor side effects include nervousness, tremors or headaches (FDA 2018b). Caffeine is thus of concern if it is found as an undeclared adulterant in weight loss products. Phenolphthalein has been shown for more than half a century to cause diarrhoea and bloody stools (French, Gaddie & Smith 1956) and there have been concerns about its carcinogenicity (Dunnick & Hailey 1996). Phenolphthalein is associated with multiple cancers including ovarian (Dunnick & Halley 1996) and colon cancer (Longnecker et al. 1997). However, a further study found no association with ovarian cancer (Cooper, Longnecker & Peters 2004). Even though phenolphthalein was banned in the 1990's in Europe and the US, it is still available in other countries e.g. India, where concerns are highlighted with regard to organ damage (Sharma et al. 2017). Thus, undeclared presence of phenolphthalein can have significant health risks to those consuming the adulterated supplement.

Sibutramine and its analogues are one of the most identified adulterants in dietary supplements sold to aid weight-loss purposes (Freitas et al. 2019). Mathon et al. (2014) found in their survey of weight loss supplements purchased from the internet (n=52) that 50% were adulterated with sibutramine. Sibutramine was withdrawn in the US and Europe in 2010 (Mathon et al. 2014) and is banned in many countries over concerns about associated side effects including hypertension, heart failure, insomnia, psychosis, panic attacks, suicidal tendencies, amnesia and manic episodes. (Morikawa et al. 2018; Örnek, Kani & Topçuoğlu 2018; Pascali et al. 2018; Saifuddin, Rahim & Mansor 2018). A series of example studies of

food supplement adulteration are listed in Table 2 from China, France, Iran and Italy. The studies demonstrate the widespread synthetic adulteration of products both in terms of number of products, geographic reach and the number of different types of synthetic chemicals used.

Take in Table 2

3.1.2 Sexual enhancement

Globally, there has been a long cultural history of using herbal aphrodisiacs, but these products been superseded in popular culture by the use of synthetic products for erectile dysfunction. Sildenafil, a phosphodiesterase-5 (PDE-5) inhibitor, is a commonly found synthetic adulterant of herbal aphrodisiac products (Nugroho et al. 2018). Whilst Sildenafil citrate, vardenafil hydrochloride and tadalafil are of benefit in addressing erectile dysfunction, multiple side effects such as nausea, facial flushing, headache, dyspepsia, and more concerningly interaction with nitrate drugs, can cause a rapid decrease in blood pressure (Skalicka-Woźniak, Georgiev & Orhan 2017).

3.1.3 Muscle building and performance enhancement

Consumption of anabolic androgenic steroids has been linked to severe psychological, neurological or psychiatric disorders, maladaptive behaviours, acute withdrawal symptoms, abnormal liver function, menstrual disorders, gynecomastia (non-cancerous increase in the size of male breast tissue), deepening of the voice in women, concerns for foetal development during pregnancy, and an increased risk of cardiovascular disease (Geyer et al. 2008; Eichner & Tygart 2016). Stimulants such as caffeine are often in performance based products and can increase blood pressure, emotional instability, nervousness, social withdrawal and lead to appetite loss (Eichner & Tygart 2016). DMAA (1,3-dimethylamylamine) is an amphetamine derivative used in illegal sports performance and weight loss products and consumption of DMAA can increase blood pressure and cardiovascular problems including heart attacks (FDA 2018c). da Justa Neves and Caldas (2015) suggest that the level of adulteration of bodybuilding supplements

may be subject to cultural norms. For example, in Brazil, despite DMAA being banned in 2012, two products (15% of the total seized) were identified as containing DMAA in 2013, and adulterated muscle building products represented 73% of all adulterated supplements in Brazil compared to 9.1% in the US and 4.4% in Europe. It is unclear however if this is due to the nature of the market sampling being different in each country. In a study to determine the undeclared presence of anabolic steroids in dietary supplements (n=30), multiple steroids were found (Odoardi et al. 2015). Baume et al. (2006) studied over the counter products (n=103) and found eighteen products that contained undeclared anabolic steroid adulterants. The presence of Selective Androgen Receptor Modulators, or SARMs in dietary supplements have been linked to severe reactions such as acute liver failure, heart attack and stroke. SARMs are chemically similar to anabolic steroids and can also stimulate muscle growth. However, they are not approved for human consumption.

3.2 US data for adulteration of food supplements

The reported adulteration cases linked to dietary supplements in the US from 2007 to 2016 have been analysed by Tucker et al. (2018) who considered FDA dietary supplement data for that time period (FDA, 2018). These products (n=776) originated from 146 companies with 157 adulterated products (20.2%) containing more than one unapproved ingredient. The details on the most common adulterants have been collated (Table 3).

Take in Table 3

The data from Tucker et al. (2018) highlighted the key supplement types where undeclared adulterants were found: sexual enhancement supplements (45.5% of cases); weight loss supplements (40.9%); muscle building supplements (11.9%) with adulterants including anabolic steroids and, supplements with other health claims (1.9%). Further analysis of the 2016-2019 FDA recalls database undertaken for this research highlights 76 (2016=21, 2017=20, 2018=22, 2019=13) dietary supplements products where non-compliance was noted

(FDA 2020). In the FDA recalls database, there was a strong trend in the identification of contamination and mislabelling issues such as undeclared allergens (22% of cases), pathogenic microorganisms (Salmonella, 6.5% of cases) and heavy metals with the presence of lead (3% of cases). It was observed also 17 recalls (22.4% of the cases) for the reason referred to as an unapproved new drug contamination (Table 4).

Take in Table 4

The biggest group of almost 24% of cases recalled in 2016-2019 consisted of the products containing sildenafil, tadalafil or vardenafil and analogues. This is a similar finding to the work of Tucker et al. (2018). Moreover, a range of stimulants including anabolic steroids, ephedrine, DMAA and SARMs were identified (13% of the cases) and products with the presence of sibutramine and its analogues (6.5%).

3.3 EU Data for adulteration of food supplements

There were 2529 RASFF notifications for the category “dietetic foods, food supplements, fortified foods” between 01/01/2004 and 31/12/2019, and there have been 2611 such notifications since the introduction of the RASFF System (between 18/08/1988 and 31/12/2019). Thus, almost 97% of the notifications relate to the period of analysis. The number of RASFF member states increased fundamentally in May 2004 due to EU enlargement. (For a wider discussion on this see Kowalska, Bieniek & Manning, 2018). The changes in the EU legislative framework for dietetic foods, food supplements and fortified foods in the early 2000’s are likely to influence the frequency of food control authorities actions that are taken in relation to this group of products (see Figure 2). Moreover, the dynamic development of the market and growing competition among producers and distributors of food supplements, dietetic foods and fortified foods could enhance the motivation of some to adulterate the products for economic gain.

Take in Figure 2

Analysis of the RASFF database demonstrates that there has been a growing trend in the number of RASFF incidents associated with dietetic foods, food supplements and fortified foods since 2004 (Figure 2). In our case study, the sampling approach that has given rise to the dataset is not probability-based or representative and the time series is short which is why using a trend analysis to draw objective conclusions may be questionable. However, the data considered demonstrates limited variation and a clear increasing linear tendency. Since the observations can be assumed not to be sequentially correlated, have little variation and $r^2 = 0.815$ (Figure 2), then the number of notifications for the next few years can be forecasted. These predictions cannot be too far from the considered interval of time as then the forecast will not be accurate. From estimated linear trend $Z_t = 16.671t + 16.55$ the determined forecast for 2020 is 300 RASFF notifications associated with "dietetic foods, food supplements and fortified foods" and the forecast for 2021 is 317 RASFF notifications.

We are interested in comparing the number of RASFF notifications associated with dietetic foods, food supplements and fortified foods in the individual years of the 2008-2019 period to the number of RASFF notifications associated with these foods in 2008. A given year is used as the first period but as times goes on, the relevance of any given based period in the past decreases in terms of comparison with values in the present (Aczel & Sounderpandian 2009). Thus, we consider 2008 as the base period, inter alia, as the new classes in RASFF classifications have appeared since then (namely information for follow-up and information for attention). Comparing the number of notifications in a given year to the number of notifications in 2008 the increase is as follows: 54% in 2009, 83% in 2010, 79% in 2011, 136% in 2012, 103% in 2013, 165% in 2014, 58% in 2015, 157% in 2016, 308% in 2017, 331% in 2018, and 339% in 2019. Thus, the number of notifications is still increasing and the growth in comparison to the base period is considerable, especially in recent years.

An alert notification is sent when food presenting a serious risk is on the market and when rapid action is or might be required in another country (Table 5); other notifications, i.e. border rejections and information notifications do not require rapid action because the risk to the general public is deemed to be lower (RASFF 2017). The RASFF risk decision was serious for 31.9% of all the notified incidents (n=807). The most reported issues concerned the **composition** of dietetic foods, food supplements and fortified foods. Thus, we are analysing this group of incidents in more detail.

Take in Table 5

The data for food supplements safety issues identified by RASFF for 2015/16 and 2017/18 has been considered (Figures 3 and 4). The most common adulterants identified by RASFF in 2015-2018 were Agmatine sulphate, DNP 2,4-diniprothenol and Synephrine. The problem of chemical and microbiological contamination (the term used by RASFF) in Europe is serious as seen with increasing amount of chemical contamination incidents in RASFF alert and non-alert notifications. A proportion of these incidents seem to be correlated with adulteration/fraud episodes (Parisi, Barone and Sharma 2016) and the term is thus used interchangeably in this section to reflect its usage in notifications rather than because the assertion here from an academic viewpoint that the terms are the same. Figure 3 identifies the contaminants (unintentionally present) and adulterants (intentionally added) identified in products that led to a notification; and Figure 4 the number of alert cases. The adulteration issues are analysed here.

Take in Figure 3

The number of food safety issues identified by RASFF notifications between 2015 and 2018 for the presence of DMAA and DMBA (nor-DMAA), caffeine, synephrine, lead and *Salmonella* all decreased, but issues relating to sildenafil, tadalafil, vardenafil and analogues; DNP 2,4-diniprothenol, allergens and zinc showed an increase. Vitamin B6 was also identified

as a cause for concern with a slight rise in the number of adulterated food supplement notifications (from n=12 in 2015/16 to n=17 in 2017/18). Synephrine is a substance that occurs naturally in citrus fruits (bitter orange) which is added to dietary supplements promoted for weight loss or muscle building (Rocha, Amaral & Oliveira 2016). Due to insufficient data on the safety of synephrine, no safe dose can be derived at present.

2,4-diniprothenol (DNP) was used as a weight-loss agent as long ago as the 1930s and is often targeted towards body builders. In 1938, DNP was taken off the market as a result of adverse effects including cataracts, liver failure, agranulocytosis, skin toxicity and death, but reappeared in 1980s as a slimming agent. The lethal dose is estimated to be 1-3 g taken orally but cases of death were reported even at the recommended dosage levels. In Europe the sale of DNP, including on-line sale, is illegal. Any sales of DNP must be reported to RASFF (Petroczi 2015).

Three additional adulterants were also identified in the RASFF as harmful issues for dietetic foods, food supplements, and fortified foods cases - Acacia rigidula, Agmatine sulphate and Yohimbine. Acacia rigidula was only involved with one adulteration incident in the FDA data (see Table 4), but there have been an increase in the number of notifications in the RASFF database (from n=5 in 2015/16 to n=23 in 2017/18) (Figure 3). Acadia rigidula has been shown to contain toxic amines and alkaloids (Clement, Goff and Forbes 1998; Garza et al. 2017). Extracts from Acacia rigidula leaves are used in weight-loss products. There is little or no published data about their potential effects on those who consume them or the extent to which products can be adulterated with synthetic compounds (Pawar et al. 2014).

Agmatine sulphate was found in 39 adulterated supplement notifications in the first period and for 90 products in the second time frame (Figure 3). The only human data on the use of agmatine available in the literature derives from studies of depressive illness (Halaris and Plietz 2007). Agmatine, produced during the fermentation of alcohol, is known to increase

histamine toxicity in humans and is used as a dietary supplement for promoting peripheral and central nervous system function (Halaris and Plietz 2007). However, its undisclosed use in dietary supplements is a risk to public health.

Yohimbine was the third major adulterant identified (n=18 in 2015/16, n=20 in 2017/18) (Figure 3). Yohimbine is an alkaloid found in the Corynanthe yohimbe tree and is used to promote weight loss and treat erectile dysfunction (Giampreti et al. 2009). However there are concerns over the effects associated with its use including acute neurotoxicity (Giampreti et al. 2009) and "increased blood pressure and heart rate, anxiety, dizziness, tremors, headache, nausea and sleep disorders" (Health Canada 2018).

Take in Figure 4

In Figure 4, the greatest number of alerts were related to the products for erectile dysfunction containing sildenafil, tadalafil, vardenafil and analogues (n=51). Moreover for such products the number of alert notifications increased from the period 2015/16 to the period 2017/18. Alert notifications were also registered for adulterated products with caffeine (n=28), DMAA or DMBA (n=25) and yohimbine (n=19). The smallest number of alert notifications were for the presence of acacia rigidula (n=1), agmatine sulphate (n=2) and zinc (n=4). Alert notifications increased in 2017/18 compared to 2015/16 for adulterated products containing sildenafil, tadalafil, vardenafil and analogues, undeclared allergens, DNP, zinc, vitamin B6. The number of alert notifications for products with caffeine, synephrine, yohimbine and DMAA or DMBA considerably decreased during the analysed period (Figure 4). This data shows the clear public health concern associated with adulterated dietary supplements.

4. Discussion

The analysis of literature and secondary data in this research has shown the global challenge of adulteration of dietary supplements. There are many countries where current regulatory sampling identifies instances of adulteration (Kowalska et al. 2019; Grazina, Amaral & Mafra

2020) and this is of concern as such instances are a clear threat to consumer health. The advent of global on-line sales means that distribution network for these products are increasingly diverse so there needs to be more effective surveillance measures for monitoring for the marketing and sale of adulterated supplements (Wang et al. 2017). Governance can be delivered through more effective public regulatory controls, including improved surveillance practices (Grazina, Amaral & Mafra 2020) and also enhanced private market controls and practices, or indeed a hybrid form of governance built from both public and private policy instruments. The first approach is then via regulatory policy levers, but the evidence presented here shows there is a barrier resulting from lack of coherence of common definitions across various legislation jurisdictions or indeed through international standards such as Codex Alimentarius. The alternative is market based private mechanisms where organisations and sector bodies assist to improve market governance of dietary supplement safety. The role and purpose of dietary supplements as defined in EU legislation is 'to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect'. These products should deliver efficacious doses for the entire declared shelf-life to support their composition claims and justify their placing in the market. Regulatory standards using evidence on demand for such efficacy whether for pre-approval or through post-market surveillance, would improve current levels of governance. Similarly, greater attention to pre-market approval and post-marketing surveillance for dietary supplement product functional claims that impact the maintenance of health and disease prevention, and identify unpermitted claims such as those relating to disease treatment or superior physiological performance would be of value.

Safety of dietary supplements is crucial and the achievement of safety standards requires "better chains of custody and product characterisation" than currently exists, particularly in global markets (Dwyer, Coates, and Smith, 2018). Post-marketing surveillance is lacking for dietary supplements and the risk of adulteration means they should be included in national

pharmacovigilance programmes along with medicinal products (Shaw et al. 2012; Bhagavathula, Elnour and Shehab, 2016). Pharmacovigilance is not a new term, as it is applied routinely to medicinal products globally. Internationally recognised pharmacovigilance guidance and standards such as ICH Guideline E2E on Pharmacovigilance Planning (ICH 2004), created by the International Council for Harmonisation (ICH), are adopted by widely for medicinal products and deliver robustness and transparency and ensure a high level of public health (EC 2019). EC Directive 2001/83/EC requires inter-Member State pharmacovigilance systems and that each Member State establishes a pharmacovigilance system to collect information for surveillance and evaluation of medicinal products such as adverse reactions in human beings. Similar post-marketing systems should be developed for dietary supplements and should interface with national and international regulatory surveillance systems.

Specific and deliberate attention is needed to address the challenges relating to the on-line marketing of dietary supplements. In February 2019, the US Federal Trade Commission, for example, challenged the use of fake paid reviews on-line for a food supplement (FTC 2019). The defendants, Cure Encapsulations Inc, were said to have advertised and sold "Quality Encapsulations Garcinia Cambogia Extract with HCA" capsules on Amazon.com. They claimed the product was a weight-loss pill and paid a third party to post fake reviews with false claims on Amazon.com and were required to pay a fine of $50,000. Following another approach, some researchers suggest data mining techniques can be used to monitor on-line reviews to determine adverse reactions to supplements sold on-line and thus provide a low cost, reactive approach to monitoring dietary supplement safety (Sullivan et al. 2016). This could also include monitoring of forum posts (Akhtyamova, Alexandrov & Cardiff 2017), general on-line text (Wang et al. 2017); electronic health records (Fan & Zhang 2018) and text analytics (Tori et al. 2016). Paul et al. (2016) view this post-marketing public health surveillance approach as pharmacovigilance and reflect on Sullivan et al.'s work using Amazon.com as a

source. Similarly, Correia, Li and Rocha (2016) investigated the potential of Instagram, Twitter and Facebook to provide such data. Change such as the socialisation of e-commerce via sharing of knowledge, experiences, and information about products and services influences purchasing intention (Hajli 2014). On-line review manipulation is an increasing concern. Hu et al. (2012) identified a 10.3% manipulation of reviews for on-line book sales. There is no information available in the literature as to wider spread abuse of on-line reviews, but this is a social concern that needs further analysis.

5. Conclusion

Fraudsters often set-up operations in regions that lack governance and oversight where the risks of detection and enforcement are the least to hide the full extent of their operations (Manning, Smith & Soon 2016). The fundamental basis for reducing the fraud opportunity is to have capable guardians (including customs officials, federal and local law enforcement, trade associations, non-governmental organizations, companies themselves and even consumers) and hurdles (the components or systems that are in place to make fraud more difficult to perpetrate) see Cohen and Felson (1979). Although, the evolving nature of the marketplace and the adaptability of fraudsters create new gaps that are exploited by them (Spink, Rip & Moyer, 2016 and references therein).

The substantial disparities in the level of human health protection between countries and regions then provides opportunity for adulterated dietary/food supplements to be sold in more mature markets such as the US and EU. This vulnerability needs a strong societal response and in an age of rapid supply chain globalisation, harmonisation of terminology and regulatory controls concerning dietary/food supplements and their integrity is needed to enable effective monitoring and risk management. Mitigation of the risk will be enabled through better guidance and governance expectations relating to good manufacturing practices, labelling and

substantiation of claims. Embedding of these risk mitigation measures in a range of supply chain surveillance activities working alongside greater regulatory controls are both needed to prevent non-compliant practices and behaviours. Greater focus on this increasing health issue is essential, with more guidance given to consumers on the risks they take when purchasing dietary/food supplements from opaque marketing channels.

There are various food safety governance models in regions and individual countries, and in certain European countries, the producers of food supplements submit a quite extensive and detailed pre-market approval dossier. What is interesting is the universal model of Garcia Martinez et al. (2007) adapted by Wu et al. (2018) where government governance is divided into six stages in terms of intervention level: (1) no public intervention (doing nothing); (2) corporate self-governance (voluntary code of conduct; farm management system, corporate quality management system); (3) co-governance (regulation by law; governance by government policies and management measures); (4) information and education (communicating information on food safety governance to the public; providing information and guidance to consumers; publishing the identities of violating companies); (5) market incentives (rewarding companies for safe production; creating market incentives for investment in food safety), and (6) direct government command and control (direct regulation; law enforcement and inspection; sanctions and punishment for violating companies). Wu et al. (2018) suggest developing social co-governance which is a form of social innovation that integrates diverse resources and efforts from multiple stakeholders (rooted in government, company or society) for better and sustainable development of any food system. While addressing the risk of dietary/food supplement adulteration it seems to be reasonable to suggest developing public-private partnerships (PPPs) for the governance of the provision of safe and legal food underpinned with advanced technology (Blockchain or other Distributed Ledger Technologies) which is of value

in assuring product data traceability (Manning & Kowalska in press) and building food system resilience.

The aim of this research is to identify the potential adulterants of interest in dietary supplement adulteration and then to consider what governance systems can be implemented to reduce the likelihood of such practices occurring. Three types of supplement those promoted for weight loss, sexual enhancement, and muscle building emerge from the data as being vulnerable to synthetic adulteration. The development of pharmacovigilance governance systems that focus on dietary supplements is essential to ensure product safety and the maintenance of public health.

References

Aczel, A. D., & Sounderpandian, J. (2009). Complete business statistics. Boston: McGraw-Hill/Irwin.

Agrawal, S. S., & Mishra, G. (2016). Adulteration of synthetic PDE-5 inhibitors viz., sildenafil and tadalafil in marketed herbal aphrodisiacs. Current Medicine Research and Practice, 6(4), 152-156. doi: 10.22159/ijpps.2020v12i3.36527.

Akhtyamova, L., Alexandrov, M., & Cardiff, J. (2017). Review of trends in health social media analysis. In 2017 12th International Scientific and Technical Conference on Computer Sciences and Information Technologies (CSIT) (1, 413-416). IEEE. doi: 10.1109/STC-CSIT.2017.8098818.

Baume, N., Mahler, N., Kamber, M., Mangin, P., & Saugy, M. (2006). Research of stimulants and anabolic steroids in dietary supplements. Scandinavian Journal of Medicine & Science in Sports, 16(1), 41-48. doi: 10.1111/j.1600-0838.2005.00442.x.

Bhagavathula, A. S., Elnour, A. A., & Shehab, A. (2016). Pharmacovigilance on sexual enhancing herbal supplements. Saudi Pharmaceutical Journal, 24(1), 115-118. doi: 10.1016/j.jsps.2015.01.018.

CAC/GL 9-1987 (Codex Alimentarius Commission) General Principles for the addition of essential nutrients to foods Adopted in 1987. Amendment: 1989, 1991. Revision: 2015. http://www.fao.org/fao-who-codexalimentarius/sh-proxy/jp/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCAC%2BGL%2B9-1987%252FCXG_009e_2015.pdf. Accessed 19 December 2018.

CAC/GL 55 – 2005. (Codex Alimentarius Commission) Guidelines for vitamin and mineral food supplements. www.fao.org/input/download/standards/10206/cxg_055e.pdf. Accessed 19 December 2018.

Clement, B. A., Goff, C. M., & Forbes, T. D. A. (1998). Toxic amines and alkaloids from Acacia rigidula. Phytochemistry, 49(5), 1377-1380. doi: 10.1016/S0031-9422(97)01022-4.

CODEX STAN 146-1985. (Codex Alimentarius Commission) General standard for the labelling of and claims for prepackaged foods for special dietary uses. http://www.fao.org/docrep/005/Y2770E/y2770e04.htm. Accessed 19 December 2018.

CODEX STAN 180-1991. (Codex Alimentarius Commission) Standard for the labelling of and claims for foods for special medical purposes www.fao.org/input/download/standards/294/CXS_180e.pdf. Accessed 19 December 2018.

Cohen, L. & Felson, M. (1979). Social change and crime rate trends: a routine activity approach. American Sociological Review, 44(4), 588-608. doi: 10.2307/2094589.

Commission Directive 1999/21/EC of 25 March 1999 on dietary foods for special medical purposes. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31999L0021&from=EN. Accessed 20 December 2018.

Commission Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 as the Community code relating to medicinal products for human use. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf. Accessed 20 December 2018.

Commission Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0128:en:PDF. Accessed 11 May 2019.

Commission Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32002L0046&from=EN. Accessed 20 December 2018.

Commission Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2004_24/dir_2004_24_en.pdf. Accessed 20 December 2018.

Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006R1881&from=EN. Accessed 19 February 2019.

Commission Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:404:0026:0038:EN:PDF. Accessed 20 December 2018.

Commission Regulation (EC) No 953/2009 of 13 October 2009 on substances that may be added for specific nutritional purposes in foods for particular nutritional uses. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R0953&from=EN. Accessed 20 December 2018.

Cooper, G. S., Longnecker, M. P., & Peters, R. K. (2004). Ovarian cancer risk and use of phenolphthalein-containing laxatives. Pharmacoepidemiology and drug safety, 13(1), 35-39. doi: 10.1002/pds.824

Correia, R. B., Li, L., & Rocha, L. M. (2016). Monitoring potential drug interactions and reactions via network analysis of Instagram user timelines. In Biocomputing 2016: Proceedings of the Pacific Symposium (pp. 492-503).

CXS 193-1995 (Codex Alimentarius Commission) GENERAL STANDARD FOR CONTAMINANTS AND TOXINS IN FOOD AND FEED Adopted in 1995 Revised in 1997, 2006, 2008, 2009. Amended in 2010, 2012, 2013, 2014, 2015, 2016, 2017, 2018. http://www.fao.org/fao-who-codexalimentarius/codex-texts/list-standards/pt/. Accessed 19 December 2018.

CEN Workshop Agreement (CWA) 17369:2019 Authenticity and fraud in the feed and food chain - Concepts, terms, and definitions. http://www.foodauthenticity.uk/blog/cwa-17369-2019-authenticity-and-fraud-in-the-feed-and-food-chain-. Accessed 11 May 2019.

da Justa Neves, D. B., & Caldas, E. D. (2015). Dietary supplements: International legal framework and adulteration profiles, and characteristics of products on the Brazilian clandestine market. Regulatory Toxicology and Pharmacology, 73(1), 93-104. doi: 10.1016/j.yrtph.2015.06.013.

Dunnick, J. K., & Hailey, J. R. (1996). Phenolphthalein exposure causes multiple carcinogenic effects in experimental model systems. Cancer Research, 56(21), 4922-4926.

Dwyer, J., Coates, P., & Smith, M. (2018). Dietary supplements: regulatory challenges and research resources. Nutrients, 10(1), 41. doi: 10.3390/nu10010041.

EC (European Commission) (2019). Medicinal Products. https://ec.europa.eu/health/human-use/pharmacovigilance_en. Accessed 12 May 2019.

Eichner, A., & Tygart, T. (2016). Adulterated dietary supplements threaten the health and sporting career of up-and-coming young athletes. Drug Testing and Analysis, 8(3-4), 304-306. doi: 10.1002/dta.1899.

EMA (European Medicines Agency) (2018). Human regulatory. https://www.ema.europa.eu/en/human-regulatory/herbal-medicinal-products. Accessed 20 December 2018.

Fakhri, S., Mohammadi, B., Jalili, R., Hajialyani, M., & Bahrami, G. (2018). Screening and confirmation of different synthetical adulterants in slimming products, Screening, 11(2), 260-264. doi: 10.22159/ajpcr.2018.v11i2.22516.

Fan, Y., & Zhang, R. (2018). Using natural language processing methods to classify use status of dietary supplements in clinical notes. BMC Medical Informatics and Decision Making, 18(2), 51. doi: 10.1186/s12911-018-0626-6.

FDA (Food and Drug Administration) (2015). Questions and Answers on FDA's Fortification Policy Guidance for Industry, U.S. Department of Health and Human Services Food and Drug Administration Center for Food Safety and Applied Nutrition November 2015.

FDA (Food and Drug Administration) (2018). Tainted products marketed as dietary supplements_CDER. https://www.accessdata.fda.gov/scripts/sda/sdnavigation.cfm?sd=tainted_supplements_cder. Accessed 28 February 2019.

FDA (Food and Drug Administration) (2018a). Dietary Supplement Products and Ingredients. https://www.fda.gov/Food/DietarySupplements/ProductsIngredients/default.htm. Accessed 20 December 2018.

FDA (Food and Drug Administration) (2018b). Pure and Highly Concentrated Caffeine. https://www.fda.gov/Food/DietarySupplements/ProductsIngredients/ucm460095.htm. Accessed 20 December 2018.

FDA (Food and Drug Administration) (2018c). DMAA in Products Marketed as Dietary Supplements. https://www.fda.gov/Food/DietarySupplements/ProductsIngredients/ucm346576.htm. Accessed 20 December 2018.

FDA (Food and Drug Administration) (2020). Recalls, Market Withdrawals, & Safety Alerts, Available at: https://www.fda.gov/Safety/Recalls/default.htm#additional-info. Accessed 2 June 2020.

Freitas, J. M., Oliveira, T. C., Santana, M. H., Banks, C. E., Munoz, R. A., & Richter, E. M. (2019). A simple and fast-portable method for the screening of the appetite-suppressant drug sibutramine in natural products and multivitamins supplements. Sensors and Actuators B: Chemical, 282, 449-456. doi: 10.1016/j.snb.2018.11.094.

French, J. M., Gaddie, R., & Smith, N. (1956). Diarrhoea due to phenolphthalein. The Lancet, 267(6922), 551-553. doi: 10.1001/archinte.1964.03860110104010.

FTC (Federal Trade Commission) (2019). FTC Brings First Case Challenging Fake Paid Reviews on an Independent Retail Website. https://www.ftc.gov/news-events/press-releases/2019/02/ftc-brings-first-case-challenging-fake-paid-reviews-independent. Accessed 11 May 2019.

Garza, B. A. A., Arroyo, J. L., González, G. G., González, E. G., de Torres, N. W., & Aranda, R. S. (2017). Anti-fungal and Anti-Mycobacterial activity of plants of Nuevo Leon, Mexico. Pakistan Journal of Pharmaceutical Sciences, 30(1), 17-21.

Garcia Martinez, M., Fearne, A., Caswell, J.A., & Henson, S. (2007). Co-regulation as a possible model for food safety governance: Opportunities for public–private partnerships. Food Policy, 32(3), 299-314. doi: 10.1016/j.foodpol.2006.07.005.

Geyer, H., Parr, M. K., Koehler, K., Mareck, U., Schänzer, W., & Thevis, M. (2008). Nutritional supplements cross-contaminated and faked with doping substances. Journal of Mass Spectrometry, 43(7), 892-902. doi: 10.1002/jms.1452.

Giampreti, A., Lonati, D., Locatelli, C., Rocchi, L., & Campailla, M. T. (2009). Acute neurotoxicity after yohimbine ingestion by a body builder. Clinical Toxicology, 47(8), 827-829. doi: 10.1080/15563650903081601.

Grazina, L., Amaral, J. S., & Mafra, I. (2020). Botanical origin authentication of dietary supplements by DNA‐based approaches. Comprehensive Reviews in Food Science and Food Safety, 19(3), 1080-1109. doi: 10.1111/1541-4337.12551.

Hachem, R., Assemat, G., Martins, N., Balayssac, S., Gilard, V., Martino, R., & Malet-Martino, M. (2016). Proton NMR for detection, identification and quantification of adulterants in 160 herbal food supplements marketed for weight loss. Journal of Pharmaceutical and Biomedical Analysis, 124, 34-47. doi: 10.1016/j.jpba.2016.02.022.

Hajli, M. N. (2014). The role of social support on relationship quality and social commerce. Technological Forecasting and Social Change, 87, 17-27. doi: 10.1016/j.techfore.2014.05.012.

Halaris, A., & Plietz, J. (2007). Agmatine. Metabolic Pathway and Spectrum of Activity in Brain. CNS Drugs. Drug Therapy in Neurology and Psychiatry, 21, 885-900. doi: 10.2165/00023210-200721110-00002.

Health Canada (2018). Unauthorized products may pose serious health risks (June 5, 2018 to November 7, 2018). http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2018/66890a-eng.php. Accessed 24 February 2019.

Hu, N., Bose, I., Koh, N. S., & Liu, L. (2012). Manipulation of online reviews: An analysis of ratings, readability, and sentiments. Decision Support Systems, 52(3), 674-684. doi: 10.1016/j.dss.2011.11.002.

ICH (2004). ICH Harmonised Tripartite Guideline E2E Pharmacovigilance Planning, November 2004. https://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html. Accessed 31 May 2019.

Khazan, M., Hedayati, M., Kobarfard, F., Askari, S., & Azizi, F. (2014). Identification and determination of synthetic pharmaceuticals as adulterants in eight common herbal weight loss supplements. Iranian Red Crescent Medical Journal, 16(3). e15344. doi: 10.5812/ircmj.15344.

Kim, E. H., Seo, H. S., Ki, N. Y., Park, N. H., Lee, W., Do, J. A., Park, S., Baek, S. Y., Moon, B., Oh, H. B., & Hong, J. (2017). Reliable screening and confirmation of 156 multi-class illegal adulterants in dietary supplements based on extracted common ion chromatograms by ultra-high-performance liquid chromatography-quadrupole/time of flight-mass spectrometry. Journal of Chromatography A, 1491, 43-56. doi: 10.1016/j.chroma.2017.02.032.

• Kowalska, A., & Manning, L. (2020). Using the rapid alert system for food and feed: potential benefits and problems on data interpretation. *Critical Reviews in Food Science and Nutrition*, 1-14. https://doi.org/10.1080/10408398.2020.1747978

Kowalska, A., Bieniek, M.,& Manning, L. (2019) Food supplements' non-conformity in Europe – Poland: a case study. Trends in Food Science and Technology, 93, 262-270. doi: 10.1016/j.tifs.2019.09.022.

Kowalska, A., Soon, J. M., & Manning, L. (2018). A study on adulteration in cereals and bakery products from Poland including a review of definitions. Food Control, 92, 348-356. doi: 10.1016/j.foodcont.2018.05.007.

Li, Y., Zhang, H., Hu, J., Xue, F., Li, Y., & Sun, C. (2012). A GC–EI-MS-MS Method for Simultaneous Determination of Seven Adulterants in Slimming Functional Foods. Journal of Chromatographic Science, 50(10), 928-933. doi: 10.1093/chromsci/bms092.

Lo, Y. T., & Shaw, P. C. (2018). DNA-based techniques for authentication of processed food and food supplements. Food Chemistry, 240, 767-774. doi: 10.1016/j.foodchem.2017.08.022.

Lord, N., Elizondo, C. J. F., & Spencer, J. (2017). The dynamics of food fraud: The interactions between criminal opportunity and market (dys)functionality in legitimate business. Criminology & Criminal Justice, 17(5), 605-623. doi:10.1177/1748895816684539.

Longnecker, M. P., Sandler, D. P., Haile, R. W., & Sandler, R. S. (1997). Phenolphthalein-containing laxative use in relation to adenomatous colorectal polyps in three studies. Environmental Health Perspectives, 105(11), 1210. doi:10.1289/ehp.971051210.

Manning, L., & Kowalska, A. (in press). The role of technology in crisis management/recall in food supply chains in Manning L. Ed. Developing smart agri-food supply chains: using technology to improve safety and quality. Burleigh Dodds. Due for Publication December 2021.

Manning, L., & Soon, J. M. (2014). Developing systems to control food adulteration. Food Policy, 49(1), 23-32. doi:10.1016/j.foodpol.2014.06.005.

Manning, L., Smith, R., & Soon, J. M. (2016). Developing an organizational typology of criminals in the meat supply chain. Food Policy, 59, 44-54. doi:10.1016/j.foodpol.2015.12.003.

Mathon, C., Ankli, A., Reich, E., Bieri, S., & Christen, P. (2014). Screening and determination of sibutramine in adulterated herbal slimming supplements by HPTLC-UV densitometry. Food Additives & Contaminants: Part A, 31(1), 15-20. doi:10.1080/19440049.2013.861934.

Morikawa, Y., Shibata, A., Sasajima, Y., Suenami, K., Sato, K., Takekoshi, Y., Endo, S., Ikari, A., & Matsunaga, T. (2018). Sibutramine facilitates apoptosis and contraction of aortic smooth muscle cells through elevating production of reactive oxygen species. European Journal of Pharmacology, 841, 113-121. doi: 10.1016/j.ejphar.2018.10.009.

Nugroho, A., Febriana, Y., Septiwi, M., & Pratiwi, D. A. (2018). Rapid analysis of adulterated sildenafil citrate in marketed herbal aphrodisiacs using infrared spectroscopy. In AIP Conference Proceedings (2026(1), 020003). AIP Publishing. doi: 10.1063/1.5064963.

Odoardi, S., Castrignanò, E., Martello, S., Chiarotti, M., & Strano-Rossi, S. (2015). Determination of anabolic agents in dietary supplements by liquid chromatography-high-resolution mass spectrometry. Food Additives & Contaminants: Part A, 32(5), 635-647. doi: 10.1080/19440049.2015.1014868.

Örnek, E., Kani, A. S., & Topçuoğlu, V. (2018). Manic episodes with psychotic features triggered by the use of slimming pills containing sibutramine. Klinik Psikofarmakoloji Bulteni, 28, 177-177.

Pascali, J. P., Fais, P., Vaiano, F., and Bertol, E. (2018). Application of HRAM screening and LC–MS/MS confirmation of active pharmaceutical ingredient in “natural” herbal supplements. Forensic Science International, 286, e28-e31. doi: 10.1016/j.forsciint.2018.03.014.

Parisi S., Barone C., & Sharma R. K. (2016). Chemistry and Food Safety in the EU: The Rapid Alert System for Food and Feed (RASFF). Springer Briefs in Chemistry of Foods.

Petróczi, A., Vela Ocampo, J. A., Shah, I., Jenkinson, C., New, R., James, R.A., Taylor, G.,& Naughton, D. P. (2015). Russian roulette with unlicensed fat-burner drug 2,4-dinitrophenol (DNP): evidence from a multidisciplinary study of the internet, bodybuilding supplements and DNP users. Substance Abuse Treatment, Prevention, and Policy, 10:39. doi: 10.118/s13011-015-0034-1.

Paul, M. J., Sarker, A., Brownstein, J. S., Nikfarjam, A., Scotch, M., Smith, K. L., & Gonzalez, G. (2016). Social media mining for public health monitoring and surveillance. In Biocomputing 2016: Proceedings of the Pacific symposium (pp. 468-479). doi: 10.1142/9789814749411_0043.

Pawar, R. S., Grundel, E., Fardin-Kia, A. R., & Rader, J. I. (2014). Determination of selected biogenic amines in Acacia rigidula plant materials and dietary supplements using LC–MS/MS methods. Journal of Pharmaceutical and Biomedical Analysis, 88, 457-466. doi: 10.1016/j.jpba.2013.09.012.

RASFF (2009). The Rapid Alert System for Food and Feed: 2009 Annual Report. https://ec.europa.eu/food/sites/food/files/safety/docs/rasff_annual_report_2009_en.pdf. Accessed 20 December 2019

RASFF (2013). The Rapid Alert System for Food and Feed: 2013 Annual Report. https://ec.europa.eu/food/sites/food/files/safety/docs/rasff_annual_report_2013.pdf. Accessed 20 December 2019.

RASFF (2014). The Rapid Alert System for Food and Feed: 2014 Annual Report. https://ec.europa.eu/food/sites/food/files/safety/docs/rasff_annual_report_2014.pdf. Accessed 20 December 2019.

RASFF (2015). The Rapid Alert System for Food and Feed: 2015 Annual Report. https://ec.europa.eu/food/sites/food/files/safety/docs/rasff_annual_report_2015.pdf. Accessed 20 December 2019].

RASFF (2016). The Rapid Alert System for Food and Feed: 2016 Annual Report. https://ec.europa.eu/food/sites/food/files/safety/docs/rasff_annual_report_2016.pdf. Accessed 20 December 2019.

RASFF (2017). The Rapid Alert System for Food and Feed: 2017 Annual Report. https://ec.europa.eu/food/sites/food/files/safety/docs/rasff_annual_report_2017.pdf. Accessed 20 December 2019.

RASFF (2018). The Rapid Alert System for Food and Feed: 2018 Annual Report. https://ec.europa.eu/food/sites/food/files/safety/docs/rasff_annual_report_2018.pdf. Accessed 31 May 2020.

Rocha, T., Amaral, J. S., & Oliveira, M. B. P. (2016). Adulteration of dietary supplements by the illegal addition of synthetic drugs: a review. Comprehensive Reviews in Food Science and Food Safety, 15(1), 43-62. doi: 10.1111/1541-4337.12173.

Saifuddin, T. M., Rahim, N., & Mansor, N. Z. (2018). Psychosis Associated with Weight-loss Product Containing Sibutramine: A Case Report. Malaysian Journal of Psychiatry, 26(2). 1-4.

Sharma, S., Gadpayle, A. K., Gupta, H. K., Kumar, N., & Sharma, N. (2017). Phenolphthalein abuse presenting as reversible renal failure. Asian Journal of Pharmacy and Pharmacology, 3(2), 58-60.

Shaw, D., Graeme, L., Pierre, D., Elizabeth, W., & Kelvin, C. (2012). Pharmacovigilance of herbal medicine. Journal of ethnopharmacology, 140(3), 513-518. doi: 10.1016/j.jep.2012.01.051 .

Simaremare, E. S., Susilowati, R. A., Astuti, Y. D., Hermawan, R., & Gunawan, E. (2018). Analysis of acetaminophen, mefenamic acid, sibutramine hydrochloride, and sildenafil citrate. Journal of Applied Pharmaceutical Science, 8(11), 48-56. doi: 10.7324/JAPS.2018.81107.

Skalicka-Woźniak, K., Georgiev, M. I., and Orhan, I. E. (2017). Adulteration of herbal sexual enhancers and slimmers: The wish for better sexual well-being and perfect body can be risky. Food and Chemical Toxicology, 108, 355-364. doi: 10.1016/j.fct.2016.06.018 .

Spink, J., & Moyer, D. C. (2011). Backgrounder: Defining the Public Health Threat of Food Fraud, in Research Grants, National Center for Food Protection and Defense (NCFPD), Minneapolis, MN, p. 7.www.ncfpd.umn.edu. Accessed 20 December 2018.

Spink, J., Rip, M., & Moyer, D. C. (2016). New Perspective for Addressing Public Health Threat of Counterfeit Medicines: A Review of the Nigerian Combating Counterfeiting and Sub-Standard Medicines Initiatives. Journal of Forensic Science & Criminology, 4(2), 1-13.

Sullivan, R., Sarker, A., O'Connor, K., Goodin, A., Karlsrud, M. A. R. K., & Gonzalez, G. (2016). Finding potentially unsafe nutritional supplements from user reviews with topic modeling. In Biocomputing 2016: Proceedings of the Pacific Symposium (pp. 528-539).

Torii, M., Tilak, S. S., Doan, S., Zisook, D. S., & Fan, J. W. (2016). Mining health-related issues in consumer product reviews by using scalable text analytics. Biomedical Informatics Insights, 8, BII-S37791. doi: 10.4137/BII.S37791.

Tucker, J., Fischer, T., Upjohn, L., Mazzera, D., and Kumar, M. (2018). Unapproved pharmaceutical ingredients included in dietary supplements associated with US Food and Drug Administration warnings. JAMA Network Open, 1(6), e183337-e183337. doi: 10.1001/jamanetworkopen.2018.3337.

US (United States) Federal Food, Drug and Cosmetic Act, Section 342 https://www.law.cornell.edu/uscode/pdf/uscode21/lii_usc_TI_21_CH_9_SC_IV_SE_343. Accessed 20 December 2018.

Wang, Y., Gunashekar, D. R., Adam, T. J., & Zhang, R. (2017). Mining Adverse Events of Dietary Supplements from Product Labels by Topic Modeling. Studies in Health Technology and Informatics, 245, 614.

Wheatley, V. M., & Spink, J. (2013). Defining the Public Health Threat of Food Supplement Fraud. Comprehensive Reviews in Food Science and Food Safety, 12, 599-613. doi: 10.1111/1541-4337.12033.

WHO (World Health Organisation) (2007). WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues. Geneva: World Health Organisation; 2007. http://apps.who.int/medicinedocs/documents/s14878e/s14878e.pdf. Accessed 19 December 2018.

Wu, L., Liu, P., Lv, Y., Chen, X., & Tsai, F-S. (2018). Social Co-Governance for Food Safety Risks. Sustainability, 10(11), 4246. doi: 10.3390/su10114246.

903 **Table 1. Regulatory definitions by region**

904

Country/ region	Regulation/ Code	Definition
EU	Directive 2001/83/EC	*Medicinal product:* "Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis."
	Directive 2004/24/EC	*Herbal medicinal product*: "Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations."
	Regulation (EC) 178/2002	*Food* "includes drink, chewing gum and any substance, including water, intentionally incorporated into the food during its manufacture, preparation or treatment. It includes water after the point of compliance as defined in Article 6 of Directive 98/83/EC and without prejudice to the requirements of Directives 80/778/EEC and 98/83/EC. 'Food' shall not include ... medicinal products within the meaning of Council Directives 65/65/EEC and 92/73/EEC; ... residues and contaminants."
	Directive 2002/46/EC	*Food supplements*: "Foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities."
	Regulation (EC) No 953/2009	*Dietetic foods* "Foods for particular nutritional uses including foods for special medical purposes but excluding infant formulae, follow-on formulae, processed cereal-based foods and baby foods intended for infants and young children."
	Regulation (EC) 609/2013*	*Food for special medical purposes* "means food specially processed or formulated and intended for the dietary management of patients, including infants, to be used under medical supervision; it is intended for the exclusive or partial feeding of patients with a limited, impaired or disturbed capacity to take, digest, absorb, metabolise or excrete ordinary food or certain nutrients contained therein, or metabolites, or with other medically-determined nutrient requirements, whose dietary management cannot be achieved by modification of the normal diet alone;"
USA	21 USC §321 (g)	*Drug* "means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)."
	21 U.S.C. §360ee (b) (3)	*Medical food* "means a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."
	21 USC §321 (f)	*Food* "means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article."
	21 U.S.C. §321 (ff)	*Dietary supplement* "(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)"
International	CODEX STAN 146-1985	*Foods for special dietary uses*: "Foods which are specially processed or formulated to satisfy particular dietary requirements which exist because of a particular physical or physiological condition and/or specific diseases and disorders and which are presented as such."
	CODEX STAN 180-1991	*Foods for special medical purposes*: "A category of foods for special dietary uses which are specially processed or formulated and presented for the dietary management of patients and may be used only under medical supervision".
	CODEX CAC/GL 55-2005	*Vitamin and mineral food supplements* "sources in concentrated forms of those nutrients alone or in combinations, marketed in forms such as capsules, tablets, powders, solutions etc., that are designed to be taken in measured small-unit quantities but are not in a conventional food form and whose purpose is to supplement the intake of vitamins and/or minerals from the normal diet."

905

906

907 **Table 2. Example case studies for synthetic adulteration of weight loss supplements**

Country	Details	Source
China	Undeclared sibutramine found in five out of six weight loss branded products.	(Li et al. 2012)
France	160 herbal weight loss supplements (n=160) were tested and 56% included an active pharmaceutical ingredient (API) which was undeclared on the label. Sibutramine was found in a quarter of samples (n=43); phenolphthalein (n=9) and a mixture of both (n=23). Sildenafil was found either as a single adulterant (n = 5) or in combination with sibutramine (n = 3), phenolphthalein (n = 3) and with both sibutramine and phenolphthalein (n = 1). Fluoxetine was present in four products, as a single adulterant (n = 3) or in combination with sibutramine and orlistat (n = 1). Lorcaserine was detected in one product.	(Hachem et al. 2016)
Iran	Studies found the undeclared presence of sibutramine an anorectic or appetite suppressant; phenolphthalein a potential carcinogen, bumetanide (diuretic), and phenytoin (anti-epiletic drug); caffeine (stimulant), pseudoephedrine (stimulant), theobromine (diuretic) and amfepramone (stimulant and appetite suppressant). Fakhri et al. (2018) analysed weight loss products (n=15) in Iran and the most common adulterant was phenolphthalein (n=11); caffeine (n=7); sibutramine (n=7); protryptyline, a tricyclic anti-depressant (n=3); phendimetrazine an appetite suppressant (n=2); fenbutrazate an appetite suppressant (n=1); docusate sodium and docusate potassium a purgative (n=1) and sildenafil (n=1).	(Khazan et al. 2014; Fakhri et al. 2018)
Italy	Five “natural herbal” weight loss supplements were screened for APIs known for their anorectic (appetite suppressing) action. One sample of tea was found to contain caffeine and sibutramine, a second tea contained sibutramine only, the third tea sample contained Caffeine only and the fourth and fifth sample contained theophylline (a bronchodilator).	(Pascali et al. 2018)

908

Table 3 Analysis of adulteration cases linked to dietary supplements in the US 2007-2016 (Adapted from Tucker et al. 2018)

Health claim category	Number (percentage of cases identified by FDA)	Adulterant	Number (percentage of cases within a category)
Sexual enhancement (Viagra, Levitra and Cialis are pharmaceuticals manufactured to address erectile dysfunction)	353 (45.5%)	Sildenafil (active ingredient in Viagra) or structural analogues. These are synthetic phosphodiesterase (PDE-5) inhibitors.	Sildenafil 166/353 (47.0%) Structural analogues 134/353 (38.0%).
		Tadalafil (active ingredient in Cialis)	72/353 (20.4%)
		Vardenafil (active ingredient in Levitra)	5/353 (1.4%)
		Other analogues	27/353 (7.6%)
		Dapoxetine (unapproved anti-depressant)	14/353 (4.0%)
		Sibutramine (appetite suppressant)	2/353 (0.5%)
Weight loss	317 (40.9%)	Sibutramine or analogues	Sibutramine 269/317 (84.9%) Analogues 20/317 (6.3%)
		Phenolphthalein (laxative)	75/317 (23.7%)
		Fluoxetine (antidepressant)	17/317 (5.4%)
		Sildenafil or structural analogues (erectile dysfunction)	12/317 (3.8%)
		Ephedrine	2/317 (0.6%)
		Other including bumetanide, cetilistat, diclofenac, dimethylamylamine, fenfluramine, fenproporex, furosemide, lorcaserin, orlistat, phenytoin, propranolol, rimonabant, and an unspecified diuretic	16/317 (5.0%)
Muscle building	92 (11.9%)	Synthetic anabolic steroids or steroid-like ingredients	82/92 (89.1%) 73 undeclared/ 9 declared on the label
		Aromatase inhibitors (block estrogens used in breast cancer treatment	10/92 (10.9%)
Other Marketed for multiple ailments	14 (1.8%)	Diclofenac, prescription non steroidal anti-inflammatory drug	7/14 (50%)
		Dexamethasone, a corticosteroid commonly used to treat inflammatory conditions	5/14 (35%)
		Chlorpheniramine, an antihistamine,	3/14 (21.4%)
		Indomethacin, a prescription nonsteroidal anti-inflammatory drug	3/14 (21.4%)
		10 of 14 adulterated supplements in the "other" category (71.4%) contained at least 1 of 11 other drug ingredients that were identified in 1 or 2 products each: chlorpromazine, chlorzoxazone, cyproheptadine, doxepin, furosemide, phenylbutazone, ibuprofen, methocarbamol, naproxen, nefopam, and terazocin hydrochloride.	10/14 (71.4%)

Table 4. Analysis of adulteration cases linked to dietary supplements in the US 2016-2019 (Adapted from FDA 2018d)

Category (number/percentage of cases identified by FDA)	Adulterant	Number of cases
Undeclared allergens (24/22%)	Milk	11
	Cassein	1
	Fish	2
	Almonds	1
	Crustaceans	1
	Eggs	1
	Soy	5
	Peanuts	2
Pathogenic microbiological organisms (7/6.5%)	Salmonella	5
	Other microbial contaminations	2
Heavy metals (3/3%)	Lead	3
Phenolphthalein (2/2%)	Phenolphthalein	2
Sibutramine and analogues (7/6.5%)	Sibutramine	5
	Sibutramine analogues	2
Sildenafil, Tadalafil, Vardenafil and analogues (26/24%)	Sildenafil	13
	Tadalafil	8
	Sildenafil analogues	3
	Vardenafil	2
Stimulants (14/13%)	Anabolic steroids	4
	Ephedrine alkaloids	3
	Acacia Rigidula	1
	DMAA	1
	Ligandrol	1
	Ostarine	2
	Andarine	2
Other recalled for various reasons (25/23%)	Undeclared active pharmaceutical ingredient	2
	Mislabelling	1
	Potential choking hazard	1
	No compliance with GMPs	1
	Undissolved ingredient	1
	Tablets are thicker and darker	1
	Unapproved drugs	1
	Unapproved new drug	17

Table 5 RASFF notifications for non-compliant dietetic foods, food supplements and fortified foods per notification type in 2004-2019 (Source: Own elaboration based on https://webgate.ec.europa.eu/rasff-window/portal/)

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Alert	11 52%	35 65%	59 66%	60 49%	20 26%	36 30%	30 21%	40 29%	55 30%	33 21%	57 28%	46 38%	83 42%	76 24%	116 45%	136 40%
Border rejection	-	-	-	-	13	21	39	26	52	54	50	22	16	9	13	11
Information	10	19	31	63	44	62	72	-	-	-	-	-	-	-		-
Information for attention	-	-	-	-	0	0	0	23	42	19	34	16	32	51	75	120
Information for follow-up	-	-	-	-	0	0	0	49	33	50	63	38	67	178	51	71
Total	**21**	**54**	**90**	**123**	**77**	**119**	**141**	**138**	**183**	**156**	**204**	**122**	**198**	**314**	**255**	**338**

supplements in 2015/16 and

Figure 1. CWA 17369:2019 Authenticity and fraud in the feed and food chain — Concepts, terms, and definitions" standard developed by the #H2020 Authent-Net project

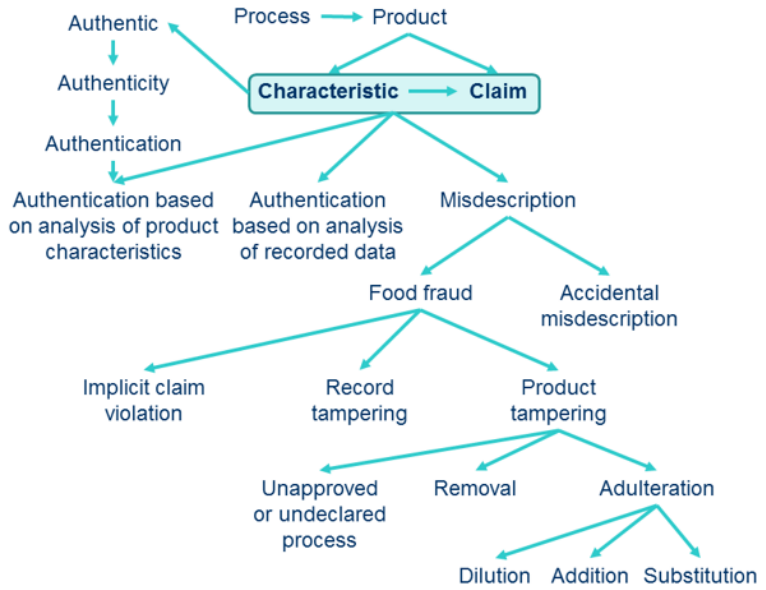

Figure 2 Food safety issues for dietetic foods, food supplements, fortified foods notified in RASFF in 2004-2019 (Source: Own elaboration based on https://webgate.ec.europa.eu/rasff-window/portal/)

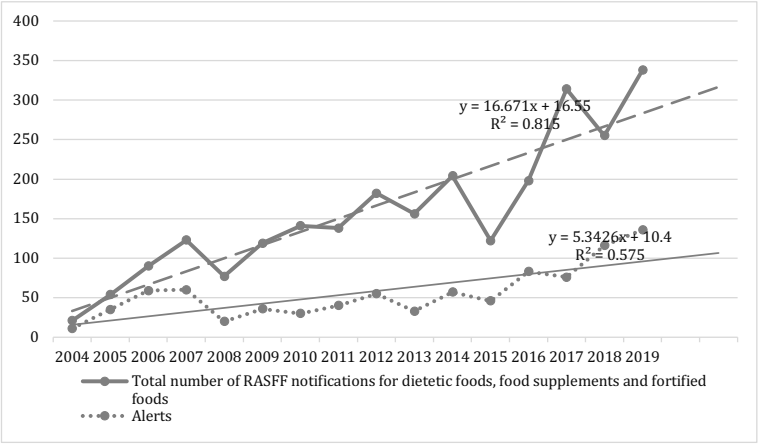

Figure 3 RASFF notifications linked to dietetic foods, food supplements and fortified foods per type of adulterant (Source: Own elaboration based on https://webgate.ec.europa.eu/rasff-window/portal/)

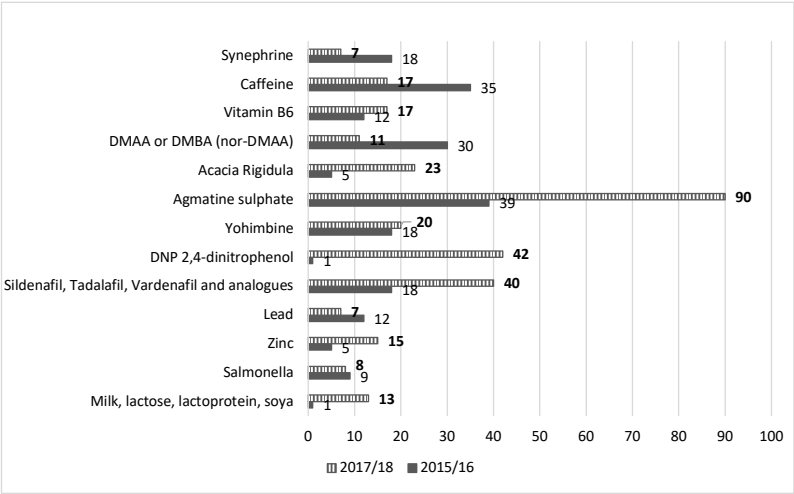

Figure 4. Alert cases in RASFF notifications linked to dietetic foods, food supplements and fortified foods per type of adulterant (Source: Own elaboration based on https://webgate.ec.europa.eu/rasff-window/portal/)