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Residues of veterinary drugs in fish and fish products: an analysis of RASFF data over the last 20 years

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Abstract

An analysis of the notifications in the European Union (EU) Rapid Alert System for Food and Feed (RASFF) portal due to residues of veterinary drugs in fish and fish products over the period 2001–2021 was conducted examining the following data: number and type of notifications; year of notification; notification basis; notifying country; country of origin; action taken; distribution status; risk decision; fish product type; residue found. A total of 292 notifications were found (mean number/year 9.8±13.8 SD), mostly information notifications (60.9%). The most common notification basis was “border control - consignment detained” (38.4%), followed by “official control on the market” (37.9%) and “border control - consignment released” (13.7%). Over half (54.1%) of the notifications were issued by the United Kingdom, Germany and Spain, dominant countries in the fish processing market. Thirty-one countries of origin were recorded, but 48.6% of the notifications were referred to products from Vietnam, followed by China (15.7%), that are among the leading fish producing countries. The most common actions taken were re-dispatch (23.3%), followed by recall from consumer (10.3%), withdrawal from recipients (9.9%), destruction (9.6%), and import not authorised (9.2%). Overall, 28.8% of the notifications involved fish products belonging to the Pangasiidae family (*Pangasius* spp. and *Pangasianodon* spp.), followed by tilapia (12.7%), trout (11.0%), eel (8.6%), catfish (7.9%) and salmon (3.4%). Triphenylmethane dyes and their metabolites were the most frequent category of residues found, accounting for 51.4% of the total notifications, followed by a wide range of antibiotics classes, of which nitrofurans and metabolites (19.5%) were the most common, while amphenicols (6.8%), quinolones and fluoroquinolones (6.5%), sulphonamides and potentiators (5.1%), tetracyclines and metabolites (3.4%) and other classes were less represented. Avermectins and unspecified residues were also found in a few cases (2.7%). The annual frequency of these issues varied and was probably influenced by dedicated monitoring plans, as well as by specific sanitary problems occurring in farms. Nevertheless, by providing historical trends and current issues, our analysis identified hazards to be closely monitored, through coordinated official controls especially in the most involved countries.

Keywords: chemical residues; notification; official control; triphenylmethane dyes; antimicrobials; aquaculture

1. Introduction

Global per capita fish consumption has risen in the last five decades, doubling from ~9 kg in the 1960s to 20.5 kg in 2018 (FAO, 2020a). Thus, many countries worldwide import a growing volume of seafood to fulfil consumers' demand. The European Union (EU) as a whole reported the highest total expenditure on fish in the world and it is recognized as a major trader country, both in the fishery and aquaculture sector. In 2019 extra-EU imports reached a ten-year high of 6.34 million tonnes, almost 8% more than in 2010. The European import market has for years been mainly supplied by Asian countries that, with the exception of the Norwegian dominance in importing some specific products (salmon and cod), still play a relevant role in the total volume of EU seafood imports from non-EU countries (EUMOFA, 2020). In fact, China is one of the main fish producers, accounting alone for 35% of the global fish production in 2018, when a significant share of production also came from other Asian countries (34%) (FAO, 2020a).

In order to guarantee food safety throughout the food chain, products traded and imported in the EU must fulfil specific hygienic requirements that are checked during official controls. The legal basis for these checks on food and animal feed both produced and imported in EU, which are conducted by competent authorities (CAs), is currently the Regulation (EU) No. 2017/625, and subsequent Delegated Regulations and Implementing Regulations. Import of animals and goods from third countries is only possible from countries which appear in a list drawn up by the European Commission, pursuant to Articles 126 and 127 of Regulation (EU) 2017/625 and Commission Delegated Regulation (EU) 2019/627. The recognition indicates that the country has a CAs, equivalent to those present in the EU, implementing official controls also on animal health standards as well as hygiene and public health requirements. The country of export must also be listed as having a residue monitoring plan (Commission Decision 2011/163/EU). In addition, a list of establishments eligible for export from each country is drawn up, kept up to date and directly accessible on Trade Control and Expert System (TRACES) database.

Control measures on imported food (e.g. documentation, identity, inspection, sampling and analysis) is based on the risk category, which are regularly reviewed and adjusted (FAO, 2016). On arrival in the EU, live animals and animal products, including fish and fish products, must be verified and checked by EU official veterinarians at a designated Border Control Posts (BCPs) (previously Border Inspection Post, BIP) (Commission Delegated Regulation (EU) No. 2019/1012; Commission Implementing Regulations (EU) No.

2019/1014, (EU) 2019/1873, (EU) 2019/2129). Further checks on the products may also be carried out at the point of destination (Regulation (EU) No. 2017/625). As regards specifically residues of pharmacologically active substances in food of animal origin, the EU, Codex Alimentarius Commission (CAC) and other regulatory authorities worldwide have set tolerable levels for veterinary drugs in animal products and banned harmful chemicals based on risk assessment (Kang et al., 2018). At EU level, Commission Regulation EU No 37/2010 classifies them on the basis of maximum residue limits (MRL), dividing allowed substances, for which MRL in target tissues and animal species are set (Annex, Table 1), from prohibited substances, for which MRL cannot be established. Products that have not been assessed as safe according to these requirements can neither be authorised nor used otherwise for food production animals. Moreover, the current legal framework for veterinary medicinal products and medicated feed have been recently integrated by Regulation (EU) 2019/6 and Regulation (EU) 2019/4 , respectively .

To favour rapid communication and cooperation between CAs of the Member States (MSs) and also to promote CAs coordination in response to food and feed safety risks, an alert network, the Rapid Alert System for Food and Feed (RASFF) was set up through a Proposal for a Council Decision in 1979 (European Commission, 1979) followed by an Amended proposal in 1982 (European Commission, 1982) and Council Decision 84/133/EEC. Starting as a net of a few MSs, the RASFF currently comprehends all EU MSs, as well as Iceland, Liechtenstein, Norway, Switzerland, the European Commission (EC), the European Food Safety Authority (EFSA) and the European Free Trade Association (EFTA) (D'Amico et al., 2018; Kleter et al., 2009; Pigłowski, 2015). The RASFF was integrated in the food safety legislation framework developed in the EU in the past 20 years, as its legal basis were laid down in the Article 50 of the Regulation (EC) No. 178/2002 (the European General Food Law), while its implementing measures were set in the Commission Regulation (EU) No. 16/2011 (D'Amico et al., 2018). Over the years, the development of internet-based IT tools allowed speeding up data exchange on food and feed safety within the EU, making the RASFF more efficient and effective. The RASFF portal was set up in 2009, while the RASFF consumers' portal was launched in June 2014, to provide transparent information to consumers. It consists of an interactive searchable database including public health warnings issued by food safety authorities and food companies (European Commission, 2021a). Recently, Regulation (EU) No. 2017/625 established the information management system for official controls (IMSOC), and Commission Implementing Regulation (EU) 2019/1715 laid down implementing measures for the IMSOC and its components, including measures for the efficient operation of the RASFF within the IMSOC. According to the Regulation (CE) No. 178/2002, all the notifications are related to the presence of unsafe food and feed, defined as injurious to health or unfit for human consumption. In particular, the RASFF system includes four types of notifications: alerts, information (including information for attention and information for follow-up), border rejections, and news, in relation to the analysis of the risk related to food or feed subjected to control.

Several studies analysed RASFF data in the last decade, some investigating specific issues, such as food frauds (Marvin et al., 2016; Tähkäpää et al., 2015; Robson et al., 2020), presence of allergens (Pádua et al., 2019), recalls related to food contact materials (De Leo et al., 2021), veterinary drugs and plant protection products in food and feed (Klátyik et al., 2017), pathogenic microorganisms (Lüth et al., 2019; Piglowski, 2019; Somorin et al., 2021), while others had a more comprehensive approach, investigating all issues determining notifications for one or more categories of food products in a given time period (D'Amico et al. 2018; Kleter et al., 2009; Pigłowski, 2020). Furthermore, the Annual Reports by the European Commission, summarizing the main problems resulting from the RASFF notifications, are available. However, data are often presented in a simplified and general way, only relating to one year or few last years (Piglowski, 2020).

A large number of RASFF notifications involve food of animal origin and specifically seafood (D'Amico et al., 2018; Parisi et al., 2016; Pigłowski, 2015; Pigłowski, 2018; Pigłowski, 2020). Residues of veterinary medicinal products were identified as the seventh most represented hazard category between 1979 and 2017 (Piglowski, 2020), with crustaceans as the most frequently involved product category (35.1%), followed by meat (14.2%) and fish (13.3%).Similarly, this hazard ranked 6th among the hazard types in all notifications regarding seafood products reported in the RASFF portal between 2011 and 2015, accounting for 6% of the notifications (D'Amico et al., 2018). However, currently no study specifically analysed notifications regarding veterinary drugs residues in fish and fish products.

Veterinary drugs residues are historically associated to aquaculture products (GESAMP, 1997), as its worldwide growth has been accompanied by an increase in their use, mainly for the treatment or prevention of parasitic and microbial diseases (Uchida et al., 2016; Verdon and Andersen, 2017). However, veterinary drugs residues were also found in wild fish, especially if caught close to aquaculture plants (Heberer, 2011). Antibiotic residues in fishery products, which are influenced by the administration through feed in water and by environmental chemical and physical variables (e.g. sediment characteristics, water currents, temperature, light and pH) (Cabello et al., 2013; Kümmerer, 2009), can also contribute to the development of antibiotic resistance, a major concern for human and animal health worldwide (Cabello et al., 2016; GESAMP, 1997; Santos and Ramos, 2016; WHO, 2006). Besides antimicrobials, substances belonging to the triphenylmethane dyes group (e.g. green malachite, crystal violet and their metabolites) are the chemical substances most widely used in the treatment of fungal and protozoa infections in aquaculture (Verdon and Andersen, 2017; Verdon et al., 2015). However, they have risen concerns due to genotoxic and carcinogenic properties (Oplatowska et al., 2011; Verdon et al., 2015).

Misuse of veterinary drugs can result in high residue levels in fishery products (Okocha et al., 2018; Santos and Ramos, 2016). Thus monitoring plans have adapted over the time to regulatory changes and this might reflect in RASFF notifications, as observed for other issues (Pádua et al., 2019).

The present study was to analyse the RASFF notifications caused by residues of veterinary drugs in fish products entering or traded in the EU over the period 2001 to 2021. Considering that EU countries must implement residue monitoring plans to detect the illegal use or misuse of authorised veterinary medicines in food producing animals and investigate the reasons for residue violations, and that non-EU countries exporting to the EU must implement a residue monitoring plan which guarantees an equivalent level of food safety (European Commission, 2021b), a specific focus was given to the most common residues, fish products and countries of origin implicated, to highlight the most frequent chemical hazards, products particularly at risk, as well as historical and geographical trends.

2. Materials and methods

The RASFF portal search page was consulted on the 25th of April 2021 selecting "residues of veterinary medicinal products" as hazard category and "fish and fish products" as product categories, targeting the last 20 years (01/01/2001-25/04/2021). The following data were downloaded in an Excel file (supplied as SM 1) and further analysed:

- Number and type of notifications (alert, border rejection, information for attention, information for follow-up)
- Date (year) of notification
- Notification bases

- Notifying country
- Country of origin
- Action taken
- Distribution status
- Risk decision
- Fish product type (first listed as reported in the subject and subsequently grouped under one term when possible, in order to analyse together products deriving from the same species/genus or generally referred to with the same English commercial name, see Table 1. Association between species/genus and English commercial names were assessed on Frose and Pauly Editors, 2021)
- Residue found (as reported in the subject, subsequently grouped according to the chemical/ pharmacological classes)

The subjects of the notifications were screened and only those effectively referring to fish and fish products, and not to other type of seafood products (cephalopods, crustaceans, molluscs) were included.

Considering that all data were referred to a single hazard category and a single product category, the non-homogenous distribution of notifications and their low numbers in relation to the different collected data, a descriptive approach was adopted to investigate trends and frequencies.

3. Results

A summary of the main results, focusing on the fish product type, in relation to the veterinary drug residue found and the country of origin is presented in Table 1. More detailed results are given in Table 2, focusing on the residue found and showing, beside the fish products concerned and the country of origin, also the notification year, the notifying country, notification type and information on the authorization or banning of the substances. Moreover, details on the exact residues found and concentration are reported as additional data in SM 2 and SM3. Detailed results for all the examined data are presented in the sections below.

3.1 Number and type of notifications.

A total of 297 notifications related to residues of veterinary medicinal products in fish and fish products were retrieved from 2001 to 2021. Five of them, referring to king prawn/prawns or shrimp skewers in the subject, were thus excluded from the analysis, which was finally conducted on a total of 292 notifications. In most of the cases the notification was classified as information notification (n=178, 61.0%). The specific type of information notification, however, was only indicated for 48 of them (38 information for attention and 10 information for follow-up). The other notification types were alert notifications (n=69, 23.6%) and border rejection notifications (n=45, 15.4%).

3.2 Year of notification

The mean number of notifications per year was 9.8 (±13.8 SD). The number of notifications varied widely among years, while a general increasing or decreasing tendency in the number of notifications was not observed. The highest frequency of records was observed for 2005 (n=62, 21.2%). It was followed by 2004 (n=30, 10.3%), 2006 and 2014 (n=26 each, 8.9%) and 2002 (n=21, 7.2%). The 2004, 2005 and 2006 peaks seem to be related to the presence of organic dyes, meaning different combinations of malachite green (MG), crystal violet (CV) and their metabolites, leucomalachite green (LMG) and leucocrystal violet (LCV). In fact, while overall organic dyes of the triphenylmethane family accounted for over half (51.4%, see section 3.10) of the overall notifications in the analysed period, in these years they contributed 60% (2004), 77.4% (2005) and 73% (2006) of notifications per year. On the contrary, in 2014 the percentage of organic dyes over the total annual notification was only 19.2% (n=5). In this case the highest number of notifications (n=20,76.9%) was due to the presence of nitrofurans, mainly in pangasius from Vietnam (n=19). The lowest number of notifications (n=3 each) was observed in 2003 and 2020, while no notifications were reported in 2001.

3.3 Notification bases

Several types of notification basis were reported. The most common were “border control - consignment detained” (n=112, 38.4%) and “official control on the market” (n=108, 37.0%), followed by “border control - consignment released” (n=40, 13.7%). However, border controls altogether (n=152) accounted for 52% of the notifications. Official control in non-member countries and company's own checks were far less frequent (n=5, 1.7% and n=4, 1.4% respectively). The notification basis was not specified in 23 notifications (7.9%), only in the years 2002 and 2003. To be noted that all “border control - consignment detained” before 2008 ended with an “information” (n=67), while since 2008 all of them (n=45) ended in a border rejection.

3.4 Notifying country

Overall, 22 countries issued notifications in the 20 year-period investigated. The highest number of notifications was issued by the United Kingdom (n=61, 20.9%), followed by Germany (n=53, 18.2%) and

Spain (n=44, 15.1%). Altogether, these three countries issued more than half (54.1%) of the total notifications. More details are given in Fig. 1.

3.5 Country of origin

Overall, 31 countries were found as origin of fish products notified for residues of veterinary drugs in the analysed period: 142 (48.6%) of the products came from Vietnam, followed by China (n=46, 15.8%), Indonesia (n=15, 5.1%), Denmark (n=11, 3.8%) and Thailand (n=11, 3.8%). All the remaining countries accounted for less than 10 notifications. Complete results on the number of notifications per country of origin are presented in Table 1, in relation with fish product and residues found, and in Fig. 2.

3.6 Action taken

The most common action taken was re-dispatch (n=68, 23.3%), followed by product recall from consumer (n=30, 10.3%) and withdrawal from recipients (n=29, 9.9%), destruction (n=28, 9.6%), import not authorised (n=27, 9.2%). Altogether, these categories account for 62.3% of the total notifications. Furthermore, in 21 cases (7.2%) the action taken was not specified, in 15 cases (5.1%) no action was taken, while in the 74 remaining cases a range of other actions were taken, of which the two most common were official detention (n=17, 5.8%) and return to consignor (n=11, 3.8%).

3.7 Distribution status

The following distribution status were most often recorded: no distribution (n=75, 25.7%), distribution restricted to notifying country (n=52, 17.8%), distribution on the market (possible) (n=40, 13.7%), product not (yet) placed on the market (n=33, 11.3%) and distribution to other member countries (n=29, 9.9%). These other status were less common: product (presumably) no longer on the market (n=7, 2.4%); product already consumed (n=6, 2.1%), information on distribution not (yet) available (n=6, 2.1%); no distribution from notifying country (n=3, 1.0%); product past use-by date (n=3, 1.0%); distribution to non-member countries (n=2, 0.7%); no distribution to other member countries (n=1, 0.3%); no stock left (n=1, 0.3%). In 34 cases (11.6%) the distribution status was not specified, all notifications from 2002 and 2004.

3.8 Risk decision

In most notifications the risk decision was undecided (n=221, 75.7%), less frequently serious (n=60, 20.5%) and not serious (n=11, 3.8%). Risk decision was always "undecided" until 2012 (n=193) and then undecided (n=28), serious and not serious. Moreover, since 2012 nitrofurans were always (with one exception) associated to a serious risk decision, and also notifications due to triphenyl-methane dyes were mainly (n=25, 75.8%) associated to "serious" risk decision.

3.9 Fish product type

The fish products most frequently involved in notifications were members of the Pangasiidae family (mainly *Pangasius* spp. or *Pangasianodon* spp.), accounting alone for 28.8%of the notified fish products (n=84). Other fish products frequently involved in notifications were various types of tilapias (n=37, 12.7%), trout (32, 11.0%), eel (n=25, 8.6%), catfish (n=23, 7.9%), surimi (n=16, 5.5%) and salmon (n=10, 3.4%). The 65 remaining notifications referred to 25 different fish product types with less than 10 notifications each. All details are given in Table 1.

3.10 Residues found

All the residues found are listed in Table 2, together with the related notification years, the notifying countries, notification types and information on the authorization or banning of the substances. Triphenylmethane organic dyes and their metabolites were the most represented residue category found, accounting for over half of the notifications (n=150, 51.4%). In particular, 148 notifications were due to triphenylmethane dyes and their metabolites alone, and 2 notifications to the concurrent presence of organic dyes and antibiotics (MG and furazolidone; doxycycline and LMG, Table 2). Antibiotics of a wide range of classes accounted for 46.6% of the notifications. The most represented categories (defined as those for which more than 10 notifications were issued in the analysed timeframe) were nitrofurans and metabolites (19.9%), amphenicols (6.9%), quinolones and fluoroquinolones (6.5%), sulphonamides and potentiators (5.1%), tetracyclines and metabolites (3.4%), while aminoglycosides, macrolides, aminoglycosides and sulphonamides, and ß-lactams only accounted for a few (6-1) notifications each (Table 2). Ivermectine was found in 3 notifications and in other 3 cases the residues were only generically indicated as veterinary drug residues (Table 2). Thirty-four notifications reported values above LMR for quinolones, in the range 36-1340 and 138-830 μg/kg for ciprofloxacin and enrofloxacin, respectively. Neomycin, tetracyclines, sulfonamides, trimethoprim and amoxicillin were found in concentrations in the ranges of 656-1385, 110-365, 131-576, 76-790 and 394 μg/kg, respectively (Table SM3).

4. Discussion

The analysis of the RASFF notifications caused by residues of veterinary drugs in fish products entering or traded in the EU over the period 2001 to 2021 highlighted the frequent occurrence of nitrofuran metabolites, chloramphenicol, MG and LMG, as already reported in RASFF notifications related to fish and to other types of food (crustaceans, meat and honey) (Klátyik et al., 2017; Piglowski et al., 2020). The presence of these compounds, and in particular of MG, in fish was already reported in a study by Love et al. (2011) that evaluated the veterinary drug violations reported by Canada, the EU, Japan, and the United States from 2000–2009. The violations per 10000 tons of edible seafood presented variations depending on the countries of origin, with the highest rates of non-compliance for individual Asian countries (Love et al., 2011). However, it should be noted that the results might be influenced by the attention paid to specific categories of residues, following the issue of toxicological reports by international agencies, specific data collection by control authorities and guidelines on farms health management. In fact, imported food control measures is based on the risk category of the imported food and allows, if necessary, the possibility of strengthening or modifying the type, intensity and frequency of controls according to the exporting country risk profile and/or importer control (FAO, 2016).

The residues of veterinary drugs found in the present study will be discussed in the following sections, focusing on the annual distribution, fish product type, country of origin, and notifying countries. Particular emphasis will be given to triphenylmethane dyes and nitrofurans, accounting together for 71.0% of the total notifications.

4.1 Triphenylmethane dyes

Triphenylmethane dyes are a class of chemical substances with antimicrobial and antiparasitic properties, largely used in aquaculture worldwide, primarily against fungal and external parasitic infections. Their high affinity for different cellular components makes them excellent biological stains (Verdon and Andersen, 2017), and they are also widely used as colouring agents in the textile industry and as a food additives (Culp and Beland, 1996). Therefore, dyestuff discharged into streams without any pre-treatment may represent additional sources of accumulation in fish tissue (Singh et al., 2011). MG and CV are the most commonly used substances due to their handiness, low cost and effectiveness. After application as an aqueous solution, the dyes are absorbed through fish gills, skin or intestinal tract and metabolized to the reduced form (LMG and LCV). These metabolites persist in edible fish tissues for extended periods of time, mainly stored in fatty tissues due to their lipophilic nature and highly stability (Culp and Beland, 1996; Hurtaud-Pessel et al., 2013; Plakas et al., 1996; Sinha & Jindal, 2020).

Potential carcinogenic and teratogenic effects are associated to triphenylmethane dyes (Gammoh et al., 2019). Thus, they are not registered for use in food-producing animals neither in the EU, nor in the USA and Canada

(Gammoh et al., 2019; Singh et al., 2011). Despite this, residues of MG, CV and their metabolites have been detected in aquaculture products worldwide (Gammoh et al., 2019; Verdon and Andersen, 2017), including in monitoring programmes of EU Member States. In the EU, a minimum required performance limit (MRPL) was established for analytical methods, being 2 μg/kg for the sum of MG and LMG in meat of aquaculture products. This MRPL is used as a reference point for action (RPA) by food control authorities (EFSA CONTAM Panel, 2016). There is no MRPL set for CV and LCV (Dowling, 2007).

Annual distribution. As mentioned, triphenylmethane dyes were the residues most frequently responsible for notifications. It has to be remarked that 65.3% of these notifications occurred in the years 2004 (n=18, 12.0%), 2005 (n=50, 33.3%), 2006 (n=19, 12.7%) and 2007 (n=11, 7.3%) (Table 2). This may be attributed to the fact that in 2002 a MRPL of 2 µg/kg, as well as sampling procedures, were defined in Commission Decision 2002/657, later amended by Commission Decision 2004/25/EC10, recently implicitly repealed by Commission Implementing Regulation (EU) 2021/808. Reliable quantifying methods were developed since the set of a MRPL and probably contributed to the observed peak in the subsequent years. The presence of MG/LMG and of CV/LCV (which are included in the same group, B3e) in aquaculture is also monitored in the European Commission National Residue Monitoring Plans. In 2016 the prevalence of dyes (B3e) in aquaculture samples (1.6%) was within the range noted for the previous nine years (1.1%– 2.2%) (EFSA, 2018), and remained stable in the following years (1.1-1.8%) (EFSA, 2019; EFSA, 2020; EFSA, 2021).

Fish product type and country of origin. Interestingly, a very wide range of fish products (18 different types) was found to be associated to the occurrence of triphenylmethane dyes (Table 2). The most common products were pangasius (n=36, 24.0%), trout (n=24, 16.0%), eel (n=22, 14.7%), catfish (n=19, 12.7%), and tilapia (n=12, 8.0%), accounting altogether for 75.3% of the 150 notifications in which triphenylmethane dyes were found (including 148 in which they were the only class and 2 in the mixed class). As expected, these are all, except the trout, aquaculture species mainly farmed in Asian countries, which hold the undisputed world aquaculture production leadership (89% of the production volume) driven by China, India, Indonesia, Vietnam, and Bangladesh, followed by other Southeast Asian countries (FAO, 2020c). In particular, these countries are the largest producers of carps, tilapia and pangasius. In terms of production, tilapia (*Oreochromis niloticus*) and pangasius (*Pangasianodon hypophthalmus*) are among the mainly bred species, with constantly increasing production and export demand volumes (FAO, 2020c). For instance, pangasius farming, which is mostly concentrated in Vietnam in producing plants located in the Mekong delta, is responsible for the approximate production of 1.5 million tons per year, with an annual increase of 2.6% from 2010 to 2019 (https://www.aquaculturealliance.org/advocate/goal-2019-global-finfish-production-review-and-forecast/). This data would support the observed countries of origin of the notified products, as they were represented by Vietnam (n=73, 48.7%), followed by Indonesia (n=15, 10.0%) and China (n=12, 8.0%).

Trout and eel are fish species commonly exported in the world, as their export constantly increased from 2008 to 2018 (FAO, 2020a). In particular, the rainbow trout is the leading freshwater farmed species in Europe (EUMOFA, 2021). In this regard it is worth noting that 10 (41.7%) of the 24 notifications for triphenylmethane dyes in rainbow trout were reported from Denmark and Germany (5 notifications each). As regards eel, most of notifications were issued for products originating from China (n=9, 42.9%) and Indonesia (n=8, 38.1%).

The detection of triphenylmethane dyes in the above mentioned species suggests their common use in aquaculture mainly in countries where their use is not fully controlled (Chi et al., 2017), and alerts due to the presence of their residues in fish products had already been reported (Verdon et al., 2015). However, it should be noted that production in a country generally derives from many different companies and thus health management problems should not be referred to the whole nation, but rather to the level of training of individual Food Business Operators (FBOs) and to the surveillance system implemented by local authorities as also highlighted by European Union auditing activities carried out in Vietnam and China (European Commission, 2009; European Commission, 2012; European Commission 2017).

Although in a lower number of notifications, noteworthy is also the presence of MG, CV and their metabolites in caviar, salmon, carp, seabream and *Seriola* sp., most of them farmed, which again suggests the use of such substances in aquaculture practices worldwide (Adel et al., 2017; Chi et al., 2017; Pipoyan et al., 2020; Verdon and Andersen, 2017). In fact, the countries of origin of the notified products, besides Vietnam (n=73, 48.7%), Indonesia (n=15, 10.0%) and China (n=12, 8.0%) which contributed 66.7% of the total notifications, products also originated from other 25 countries, including the EU or neighbouring countries (Table 2). For instance, three recent notifications regarding farmed seabream from Malta and Greece were all issued in 2021 by Italy, where the high demand of this species is often satisfied by imports from other Mediterranean countries where farming is common (EUMOFA, 2019; EUMOFA, 2020).

Notifying countries. As regards the notifying country, this was most commonly the United Kingdom (n=43, 28.7%), followed by Germany (n=24, 16.0%), Poland (n=16, 10.7%), Belgium (n=13, 8.7%) and Spain (n=12, 8%) (Table 2). All of them are large EU importer countries of several fish species where triphenylmethane dyes were most frequently found (https://www.cbi.eu/market-information/fish-seafood).

4.2 Nitrofurans

Nitrofurans, including furazolidone, furaltadone, nitrofurantoin, nitrofurazone, nifursol and nifurpirinol, are a class of broad-spectrum synthetic antimicrobials with a 5-membered nitrofuran ring (Khan and Lively, 2020; Santos and Ramos, 2016; Vass et al., 2008) which were widely employed in the prophylactic and therapeutic treatment of bacterial and protozoan infections for food-producing animals, including fish and shrimps (Vass et al., 2008). However, due to concerns over the carcinogenicity of these compounds, a ban on nitrofurans (except furazolidone) was issued in the EU in 1993 (Council Regulation 2901/93) and extended two years later also to furazolidone (Council Regulation 1442/95). Since then, it has been forbidden to use any nitrofuran in food-producing animals within the EU, or in any animal destined to the EU (Commission Regulation EU No 37/2010). However, nitrofurans are rapidly transformed into tissue bound metabolites, thus testing for residues of the parent drugs is insufficient for the evaluation of the actual contamination of a tissue and the related public health risk (Santos and Ramos, 2016; Vass et al., 2008). Thus, defined metabolites of the drugs were established as marker residues (Vass et al., 2008). In particular, the compounds AOZ (3-amino-2-oxazolidinone), AMOZ (3-amino-5-morpholinomethyl-2-oxazolidinone), AHD (1-aminohydantoin) and SEM (semicarbazide) (Vass et al., 2008) are used as the marker residues of the nitrofuran banned parent drugs furazolidone, furaltadone, nitrofurantoin and nitrofurazone (Santos and Ramos, 2016).

Annual distribution. Overall, 58 notifications for nitrofurans were issued (57 of nitrofurans alone, 1 for furazolidone and MG, see Table 2). The annual number of notifications ranged from 1 to 5 notifications, except for 2014, where a higher number of reports (n=20, 34.5%) was notified, mainly in pangasius (n=19) from Vietnam. Repeated detections of residues of banned substances in fishery products from Vietnam, had prompted the EU to put in place a number of active re-enforced checks on products from this country (European Commission, 2017). Thus, specific auditing activities by the European Commission (DG SANTE), were conducted in Vietnam to verify the effectiveness of the monitoring plans implemented to control of residues and contaminants in live animals and animal products eligible for export to the European Union (EU)

(European Commission, 2009; European Commission, 2017). In this respect, the 2017 audit report mentioned before specifically attributed the high number of non-compliances and the repeated RASFF notifications for Vietnamese aquaculture products exported in EU to the failure of official pre-export testing and the application, within the residue monitoring plan, of analytical methods with arbitrarily decreased sensibility (European Commission, 2017).

Fish product type and country of origin. The most common fish product type associated to the presence of nitrofurans and metabolites was by far pangasius, accounting alone for almost 57.9% of the notifications (n=33), followed by tilapia (n=6) contributing to another 10.5%. As mentioned in section 4.1, these species are the most commonly farmed in some Asian countries (FAO, 2020c). Pangasius in particular refers to the main aquaculture species in Vietnam, including *P. hypophthalmus* and *Pangasius bocourti* (http://www.fao.org/fishery/countrysector/naso_vietnam/en). In Vietnam, the production of pangasius rose from a few tonnes in 1990 to more than 1200000 tonnes in 2010 (Rico et al., 2013). In fact, the countries of origin were mainly Vietnam (n=35), China (n=6) and Thailand (n=6), contributing over 82% of the notifications. Detection of nitrofurans in aquaculture products imported from China to the United States was also reported by the Food and Drug Administration (Burridge et al., 2010; Love et al., 2011).

Notifying countries. Most of the notifications were issued by Spain (n=20, 35.1%), Germany (n=10, 17.5%), Italy (n=7, 12.3%) and United Kingdom (n=7, 12.3%). This aspect is possibly related to the fact that, as previously mentioned, Spain and Germany are large importers of pangasius and tilapia. More specifically Spain is the largest EU importer of frozen tilapia fillets and products (https://www.cbi.eu/market-information/fish-seafood/tilapia).

4.3 Other residues

4.3.1 Amphenicols, quinolones and fluoroquinolones

The subsequent most represented categories in the analysed period were amphenicols and quinolones/fluoroquinolones, accounting together for another 13.4% of the notifications. Chloramphenicol, the most representative of the class, was the only amphenicol reported. Chloramphenicol is one of the first broad spectrum antibiotics, widely used since the 1950s as a veterinary and human drug (Hanekamp and Bast, 2015; Santos and Ramos, 2016). However, its use is currently limited in the USA, EU, Japan, China, Canada and Australia, due to possible toxic effects, such as bone marrow depression, fatal aplastic anemia, and genetic carcinogenicity (Hanekamp and Bast, 2015; Santos and Ramos, 2016). Due to the absence of safe residue levels, in the EU chloramphenicol may be used in human medicine and in treatments for non-food-producing animals (EFSA Contam Panel, 2014), but it is not authorised for use in food-producing animals (Commission Regulation No 37/2010) and a MRPL of 0.3 μg/kg was established for food of animal origin (Commission Decision 2003/181/EC; Co). However, the Commission Decision 2003/181/EC has been recently implicitly repealed by the Commission Implementing Regulation (EU) No. 2021/808 repealing the Commission Decision (EC) No. 2002/657 from which the Decision followed. Nevertheless, the MRPLs established pursuant to Decision (EC) No. 2003/181 remain in application until 27 November 2022 pursuant to Implementing Regulation (EU) No. 2021/810 (Article 1), pending the publication of a further Implementing Regulation containing new specific MRPLs for residues listed in the repealed Annex II.

Quinolones are a group of synthetic antibiotics used as human and veterinary drugs. The introduction of quinolones with a fluorine atom (second generation), known as fluoroquinolones and including among others ciprofloxacin, enrofloxacin, flumequine, marbofloxacin, norfloxacin, ofloxacin, and sarafloxacin, provided important therapeutic advantages due to a higher antibacterial activity against Gram-negative and Gram-positive bacteria (Santos and Ramos, 2016). Their extensive administration to fish destined for human consumption has become a serious problem as their residues can persist in edible animal tissues (Santos and Ramos 2016). Based on their individual properties, some of the molecules, such as ciprofloxacin, enrofloxacin and oxolinic acid, can be used and an MRL was set (Commission Regulation (EU) No. 37/2010), while others, such as norfloxacin and ofloxacin, are not authorized.

Both categories were mainly found in pangasius and surimi (a multispecies seafood product, whose production can imply the use of an extremely wide range of species)(Giusti et al., 2017) imported from Vietnam and China. Chloramphenicol was already detected by the EU in seafood imported from China, Indonesia, Taiwan, Thailand and Vietnam (Cabello et al., 2013). Also, the finding of enrofloxacin is not surprising as it is one of the most frequently detected veterinary drug residues in fishery products in East Asian countries including Thailand, Vietnam, Indonesia, and South Korea (Pham et al., 2015; Rico et al., 2013; Sapkota et al., 2008). Control authorities from the USA and the EU already showed that enrofloxacin and ciprofloxacin were the most commonly detected approved drugs in imported fish products (Love et al., 2011).

As regards the annual distribution, for chloramphenicol most notifications occurred in 2002 (n=10; 50%), then 1 to 2 notifications per year were reported, but only until 2011. The peak observed in 2002 might be due to a food safety incident related to the detection of high level of this residue in shrimps imported to Europe from Asian countries, which led to a tightening of official control activities and chloramphenicol testing in a wider spectrum of matrices imported from the countries involved (EFSA Contam Panel, 2014). In this regard, taking into account the need to apply a “zero tolerance principle” (Hanekamp et al., 2003; Verdon & Andersen, 2017), numerous chromatography-mass spectrometry methods have been developed for determination of chloramphenicol in a wide range of sample types to verify the compliance with the MRLs established by law (Council Regulation (EEC) No 2377/90, later repealed by Regulation (EC) No 470/2009 and Commission Regulation (EU) No 37/2010), in accordance with the criteria established for confirmatory methods by Commission Decision 2002/657/ EC. The absence of notifications after 2011 may suggests a positive impact of implemented controls, although the use in some Asian countries still occurs (XX).

For quinolones and fluoroquinolones, the highest number of notifications occurred in 2004 (n=6, 31.6%), followed by 2005 and 2018 (n=3 each, 15.8%), no notifications were observed in 2003 and between 2010 and 2018, while 1 or 2 notifications occurred in the remaining years.

4.3.2 Sulfonamides and potentiators

The 5th class in order of number of notifications were sulfonamides. Substances in this group are characterized by a p-aminobenzene sulfonamide functional group and include sulfadiazine, sulfamethizole, sulfamethoxazole, sulfasalazine, sulfisoxazole and various combinations. They are widely used for therapeutic and prophylactic purposes in both humans and animals, including fish (Santos and Ramos, 2016). Sulfonamides are typically used in aquaculture against enteric redmouth, furunculosis, haemorrhagic septicaemia, and vibriosis, often used in combination with the aminopyrimidine trimethoprim due to synergistic effects (Mo et al., 2017). An MRL for total sulfonamide concentration in fish at 100 µg/kg and of 50 µg/kg for trimethoprim was set in the EU (Commission Regulation (EU) No. 37/2010).

In the analysed period, the presence of sulfonamides was mainly associated with tilapia (n=12, 80%), all imported from China (n=8) and Vietnam (n=4). The annual distribution showed a peak in 2013 (n=5), although cases occurred throughout the 20 years. As already discussed for other residue classes, the frequent association of this issue with tilapia from Asian countries may indicate a possible use of a wide range of antimicrobials in Asian fish farms.

4.3.3 Tetracyclines

Tetracyclines, the 6^{th} class in order of number of notifications, represent another important class of human and veterinary antibiotics, targeting a variety of diseases in fish and shrimp (Dinh et al. 2020; Mo et al., 2017; Santos and Ramos 2016). Oxytetracycline for instance is widely used in aquaculture (Mog et al., 2020), resulting in antibiotic resistance among bacterial species (Santos and Ramos, 2016). The EU established an MRL for oxytetracycline at 100 μg/kg for muscle (and skin in natural proportions) of finfish (Commission Regulation (EU) No. 37/2010).

Interestingly, the fish product type most frequently affected by tetracyclines and metabolites in the present survey was salmon (n=5, 50%), probably due to the fact that these substances are known to be used in salmon farming (Miranda et al., 2018; Santos and Ramos, 2016). The country of origin of these cases was always Chile (n=5) and they were all quite recent, as they were reported in 2017 (n=4) and 2018 (n=1). In Chile, exported farmed salmonids (comprising species grouped as "salmon" and "trout" in this study) increased from approximately 200 000 tonnes in 2000 to almost 400 000 tonnes in 2007 (Cabello et al., 2013) and to over 725 000 tonnes in 2019 (Fishfarming expert, 2021). In contrast to the United States, Norway and Canada, Chile, the second largest producer of cultured salmon after Norway, permits aquacultural use of oxytetracycline and of several other antimicrobials (Cabello et al., 2016). Oxytetracycline is in fact one of the most frequently used antibiotics in Chilean aquaculture to contrast high mortality attributed to bacterial infections and particularly *Piscirickettsia salmonis*, currently considered the main bacterial threat to this industry (Miranda et al., 2018).

4.4. Public health and environmental issues due to the illegal or misuse of veterinary drugs in fish production

Veterinary drugs residues in fish products are a well-known relevant public health and environmental issue, that has been addressed by international bodies for several years (GESAMP, 1997). The use of veterinary drugs in aquaculture, a food producing sector growing worldwide, is often aimed at fighting parasitic and microbial diseases favoured by stressful conditions and high farming density (Cabello et al., 2013; Uchida et al., 2016). Such conditions are often associated with efforts to increase productivity, but on the contrary, they may favour development and epizootic dissemination of infections (Cabello et al., 2013).

The residues found in fish products may be the active substances of the medicine itself, related metabolites or other ingredients of the drug (http://vet.eudrapharm.eu/vet/mrlhelp.do?NOCOOKIE=NOCOOKIE&NEW_SESSION=true). Among the most relevant public health and environmental concerns are their persistence in the aquatic environment, toxicity or residues in non- target species, stimulation of resistance, and the presence of residues in seafood. In fact, while many chemicals degrade rapidly in aquatic systems, others, such as oxytetracyclin may persist for months, especially if incorporated in sediments. Besides accumulation in the environment, the use of chemicals in aquaculture may result in the accumulation of residues in non-target organisms and in seafood, which could have toxic effects on such organisms (GESAMP, 1997; Mog et al., 2020; WHO, 2006).

Furthermore, antimicrobials might contribute to a development of resistant bacteria in the aquatic environment. Several genetic elements and resistance determinants for quinolones, tetracyclines, and ß-lactamases are shared between aquatic bacteria, fish pathogens, and human pathogens, and appear to have originated in aquatic bacteria (Cabello et al., 2013). Significant concentrations of antimicrobials remaining in the aquatic environment for long periods of time are the principal selective pressure for antimicrobial resistance in sediments and the overlying water column, also leading to a major alteration of the sediment and water biodiversity by replacing susceptible communities of bacteria and other microorganisms with resistant ones (Cabello et al., 2013). The rise of antimicrobial and multi-antimicrobial resistances were claimed as impacting aquaculture production itself by selecting more virulent pathogens strains, lowering drug efficacy and decreasing the animal's immune system, affecting animal growth by causing the suppression of food conversion efficiency and directly altering animals intestinal microbial flora, thus also impacting on the production revenues (Azzam et al., 2017; Reverter et al., 2020; Sun et al., 2020).The problem of antimicrobial use in aquaculture and development of resistances is also influenced by the fact that: i) antimicrobials in aquaculture are administered mostly by feed, affecting both diseased and healthy fish; ii) unconsumed medicated food is deposited in sediments around aquaculture sites; iii) a large part of the ingested antimicrobials is released into the environment after passing in the faeces as unabsorbed form or as secreted forms in urine and other secretions (Cabello et al., 2013). All this raises numerous questions with regard to the establishment of antibiotic resistance phenomena. The consequent impact on the environment and on public health are both to be closely monitored through the implementation of antibiotic resistance surveillance programs and complementary initiatives to reduce the rate of increase of resistance in this industry (Miranda et al., 2018).

Major concerns over the presence of antimicrobial residues in animal-derived foodstuffs is also related by the plausible occurrence of allergic reactions, as some antibiotics can evoke allergy even following ingestion of small amounts or exposition by parenteral routes (Lee et al., 2001; Liu et al., 2017). For instance, well described hypersensitivity reaction are associated with penicillin, oxytetraciclines and macrolides residues (Graham et al., 2014; Treiber et al., 2021). Moreover, many pathogens can affect humans in the consumption of raw or undercooked fish, or even by direct contact. For instance, *Aeromonas* sp. are associated with gastroenteritis in healthy humans and can be fatal for immunocompromised individuals. Besides consumption, they can be transmitted through contact with mucus or infected fish tissue, especially in the case of wounds or cuts on consumers' hands. If these pathogens exhibit resistance to antimicrobials, the resulting infection with resistant bacteria cannot be treated with antimicrobials (Gazal et al., 2020).

Other veterinary drugs used in fish farming, such as the triphenylmethane dyes used as antifungal agents, also have potential adverse environmental effects due to the long-term persistence of active substances and their metabolites in the aquatic environment, in wastewater and at the outlet of aquaculture plants, to the detriment of not-target aquatic organisms (Tkaczyk et al., 2020). In addition, triphenylmethane dyes may also have negative effects on the workers' health, especially if used in a concentrated form (GESAMP, 1997), thus proper training and safety equipment are needed (GESAMP, 1997).

This urged governments to set drug residue tolerance levels and inspect seafood for violations of these standards (Love et al., 2011). The European Commission in this respect, more recently, in 2016, directly requested EFSA to verify if the MRPL set for MG and LMG at 2 μg/kg was adequate to protect public health. EFSA assessment was set on a hypothetical dietary exposure calculated on the basis of a mean dietary exposure across different European dietary surveys. The dietary was set, including all types of fish, fish products and crustaceans in a range from 0.1 to 5.0 ng/kg body weight (bw) per day and from 1.3 to 11.8 ng/kg bw per day for frequent fish consumers. Specifically, the European Commission asked EFSA to evaluate whether a reference value of 2 micrograms (μg) of malachite green per kilogram of food would adequately protect public health. EFSA's panel concluded that it is unlikely that exposure to food contaminated with malachite green up to 2μg/kg would represent a health concern. Nevertheless, the final recommendation of collecting further data on the fate of MG and LMG during food processing and on the generation of additional Malachite green metabolites in fish and shrimps was clearly stressed out. (EFSA, 2016)

Therefore, a reassessment by EFSA might be reasonably requested by the European Commission in a near future. However, the present survey confirms the widespread presence of such substances in fish products.

5. Conclusions

Considering the increase of global fish consumption and of fish farming production, the presence of veterinary drugs residues should be strictly monitored for a correct evaluation of risks and benefits of fish products consumption and possible needs to adapt production strategies.. In fact, despite the lack of accurate information, especially for developing countries, it is clear that an uncontrolled use of veterinary drugs is common for both therapeutic and prophylactic purposes.

RASFF notifications are issued for infringements of current regulations on food safety and hygiene, and do not indicate the underlying sampling efforts involved. Thus, the main limit of the current study is that the notification countsa, while demonstrating a particular issue with a product or country, cannot adequately reflect the scale of the problem, which could be amplified as a result of increased vigilance (Morris et al., 2012). In addition, despite being a legal obligation for all RASFF members, non-compliant products may not always be notified. Despite these limits, the analysis of RASFF data, as conducted in this study, explored previous and current trends and thus provides a basis to identify hazards that should be closely monitored. The highlighted non-conformities are an indication of sanitary problems affecting particular fish products and countries, where intensive farming and environmental conditions may favour disease spread. Data could be used to implement interventions and target coordinated plans and audits in the most involved countries, also promoting adequate FBOs training. In fact, efforts to prevent veterinary drugs misuse must include education of all stakeholders about negative impacts on the aquatic ecosystem and especially fish as well as human health in a One Health perspective, as well as promotion of alternative measures of disease prevention, including vaccines and lower farming densities.

Figure captions

Fig. 1 Map of countries issuing notifications for veterinary drugs in fish and fish products over the years 2001 to 2021 (created with mapchart.net).

Fig. 2 Map of countries of origin of fish and fish products notified for veterinary drugs over the years 2001 to 2021 (created with mapchart.net).

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