Environmental Science and Pollution Research (2022) 29:15282–15302
https://doi.org/10.1007/s11356-021-18239-y

REVIEW ARTICLE

Current perspective on veterinary drug and chemical residues in food of animal origin

Attia H. Atta[1] · **Shimaa A. Atta**[2] · **Soad M. Nasr**[3] · **Samar M. Mouneir**[1]

Received: 16 July 2021 / Accepted: 16 December 2021 / Published online: 3 January 2022

Abstract
The marked increase in the demand for animal protein of high quality necessitates protecting animals from infectious diseases. This requires increasing the use of veterinary therapeutics. The overuse and misuse of veterinary products can cause a risk to human health either as short-term or long-term health problems. However, the biggest problem is the emergence of resistant strains of bacteria or parasites. This is in addition to economic losses due to the discarding of polluted milk or condemnation of affected carcasses. This paper discusses three key points: possible sources of drug and chemical residues, human health problems, and the possible method of control and prevention of veterinary drug residues in animal products.

Keywords Source of drug residues · Health hazards · Food pollutants · Residue avoidance

Introduction

The increasing population and increasing standard of living all over the world require an increased demand for the protein of animal origin (Weis 2013). Annual meat consumption at the world level is expected to increase by 70% up to 2050 (Hocquette et al. 2018). New efforts are necessary to produce the required quantities of the protein high quality (Boland et al. 2013). Protecting animals from infectious diseases requires increasing the use of veterinary therapeutics (Mitema 2009). The total global consumption of antibiotics, for example, in animals was estimated to be twice that of humans (Aarestrup 2012) which is expected to be increased 67% by 2030 compared to 2010 (Van Boeckel et al., 2015). A study (Vishnuraj et al., 2016) reported that 80% of all the antibiotics administered in the veterinary field are used as growth promoters. Some drugs are used through a part of animals or birds life and some of them such as growth promoters are often used throughout the entire life, although it has been advised that long-term use of antibiotics as growth promoters, for example, must be avoided to prevent the emergence of resistant strains of microorganisms (Singh and Bhunia 2019). Drugs are used to maintain animals' health; however, healthy food must be guaranteed. Generally, the safety of food has mainly been focused on preventing the transmission of zoonotic diseases, with less attention thus being paid to present chemical pollutants, probably because of the acute nature of the resulting disease. Moreover, drug residues generally may not generate a violation problem on public health. However, adverse effects of residues such as hypersensitivity reaction and occurrence of antibiotic resistance may appear on the human consumer after extensive use of drugs (Singh and Bhunia 2019). Therefore, the appropriate use of veterinary drugs in a manner to prevent feed contamination is necessary.

Drugs and chemicals used for protection against animal and crop diseases represent an important environmental source of residue in food and feed products (Klátyik et al. 2017). There are a large number of approved prescription and over-the-counter (OTC) medications to be used in farm animals. Several products of the approved drugs have significant human health hazards upon intentional or accidental exposure such as clenbuterol, ketamine, tilmicosin (Micotil), testosterone/estradiol, dinoprost, and cloprostenol. The severity of the adverse effects ranges from mild symptoms

Responsible Editor: Mohamed M. Abdel-Daim

✉ Attia H. Atta
attaattia52@yahoo.com

[1] Department of Pharmacology, Faculty of Veterinary Medicine, Cairo University, Giza 12211, Egypt

[2] Immunology Department, Theodor Bilharz Research Institute, Giza 12411, Egypt

[3] Department of Parasitology & Animal Diseases, National Research Centre, 33 Bohouth St., Dokki, Giza 12622, Egypt

to life-threatening effects (Lust et al. 2011). Therefore, several documents about drug residues and environmental pollutants have been discussed in the Joint FAO/WHO Expert Committee on Food Additives, and recommended maximum residue limits (MRLs) and acceptable daily intakes (ADIs) for various veterinary products have been established (Joint FAO/WHO 2018). This paper sheds light on the sources of drug and chemical residues in food of animal origin, their risks on human health, and suggested methods of control to minimize or to avoid the existence of drug residues.

Material and Methods

The following databases were searched for scientific literature; the National Library of Medicine's MEDLINE, the US Department of Agriculture's National Agricultural Library Catalog (known as AGRICOLA), and the Food and Agriculture Organization (FAO). The US Department of Agriculture's (USDA), Food Safety Inspection Service (FSIS), The European Food Safety Authority (EFSA), and The Codex Alimentarius Commission website were searched to identify research articles and policy documents about drug residues and food additives in food animals. The following keywords were used: residues, veterinary drug residues, chemical residues, chemical pollutants, antimicrobial residues, residues in meat, milk, eggs, fish, Growth promoters, feed additives, antiparasitic, hormones, steroids, beta 2-agonists, agricultural chemicals, environmental contaminants, insecticides, pesticides, herbicides, fungicides, fertilizers, and organic pollutants. We classified our search results into three main topics: from where chemical and drug residues can come, what are the health risk problems as a result of consuming contaminated food, and finally the suggested method of control to minimize or avoid the existence of residues aiming to produce food of high quality. Our search focused on the period from 2000 to 2019.

Results

From where do drug and chemical residues come?

Intentional use of animal drugs (direct additive)

Animal drugs are used intentionally for therapeutic, prophylactic purposes or as feed additives to improve performance and production. Food contamination by the residue of veterinary drugs is one of the major global issues of special concern (Beyene 2016). The most common drug groups are antimicrobials, antiparasitic, hormones, growth promoters, and feed additives. The diagram (Fig. 1) illustrates the relative use of different veterinary drug groups in the UK market through the year 2019 (https://www.noah.co.uk/about/industry-facts-and-figures/).

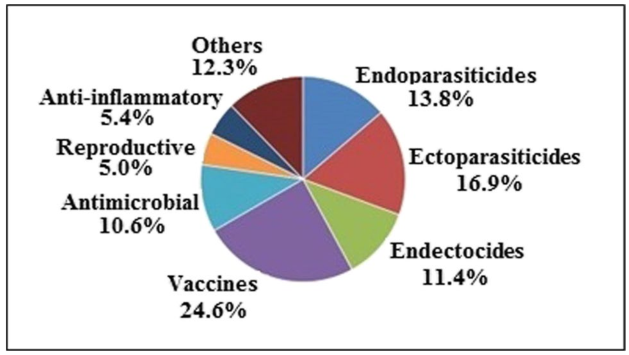

Fig. 1 UK market by product type, 12 months from June 2018 to June 2019

Antimicrobials Antimicrobial drugs are used for the treatment or prevention of bacterial diseases in humans, plants, and animals. Although their use for growth promotion of animals and poultry was banned in the European countries since long time ago, they still used in the USA and other countries for this purpose under the pressure of economic causes and its use is expected to continue until satisfactory alternative is provided (Costa et al., 2017). They perform growth promotion by changes in the levels of intestinal biochemical constituents, altering the intestinal metabolome and improving growth and feed efficiency (Gadde et al. 2018). Sometimes antimicrobials such as aminoglycosides and oxytetracyclines are used in the treatment of plant bacterial diseases and consequently enter the food chain either directly or through feeding animals on polluted plants (Wang et al. 2021).

In central Ethiopia for example, the most widely reported contaminants of food of animal origin are the antimicrobial drugs and the steroidal growth promoters (Beyene et al. 2015). In European countries, the prevalence of chemical and drug residues in animal products is less than 1%; however, in some African countries, it reaches up to 94%. The majority of residues confirmed in animals were antibiotic agents such as penicillin, streptomycin, polypeptides, macrolides, tetracyclines, chloramphenicol, sulfonamide, and quinolones (Bacanli and Başaran 2019; Rodrigues et al. 2021). Meat and meat products are still the first sources of antimicrobials drugs used for the treatment of animal diseases (Bacanli and Başaran 2019). Antimicrobials residues are reported, not only in the meat of food animals but also broilers (Gadde et al. 2018; Patel et al. 2018), Milk (Chirollo et al. 2018), eggs (Liu et al. 2021), aquaculture (Liu et al. 2017), beeswax and honey (Mitrowska and Antczak 2017), and even in freshwater and marine environments

(Suzuki et al. 2017). It has also been reported that the use of human excretions and animal manures as plant fertilizers, and inappropriate disposal of antibiotics either in the clinics, or direct disposal of the leftover antibiotics are one of the possible main sources of antibiotic pollutants in soil and water as it has been reported in Chinese rural community (Chen et al. 2018a). Although the violation rates of some antibiotics such as chlortetracycline and oxytetracycline decreased, some other antibiotics such as quinolones and penicillin detections increased in some countries such as in Korea (Kim et al. 2013). Recently, higher incidence of ciprofloxacin, enrofloxacin, tetracycline, amoxicillin, and chloramphenicol were reported in chickens and aquaculture food products (Hassan et al. 2021).

Antiparasitic drugs Antiparasitic drugs include anthelmintics, antiprotozoal, and insecticides (organophosphates, organochlorine) (Patel et al. 2018). Residues of the antiparasitic drugs are reported in several studies probably because of the unregulated and uncontrolled use either due to intentional use or unintentional contamination. However, after the application of a 28-day withdrawal period, moxidectin residues above the MRL were reported in muscle, fat, kidney, and liver of weaned lambs subjected to gastrointestinal parasite control using Moxidectin in Brazil (Fernandes et al. 2017). Albendazole sulfoxide and sulfone metabolites were quantified in eggs 7 days after albendazole single oral administration in Argentina (Moreno et al. 2018). In a study in Spain, albendazole metabolites reached their maximum concentration in goat's milk one day post-treatment and decreased to a level below the maximum residue limit on day 3 post-treatment (Romero et al. 2017). Similarly, benzimidazole residues were reported in 16% of the samples examined ovine and bovine milk in southern Greece (Tsiboukis et al. 2010). In a study in Brazil, albendazole and its metabolite residues were also reported in fish (Busatto et al. 2018). The ecto-endocidal anthelmintic drug, moxidectin (MOX), was reported with the highest concentrations in the fat as compared to other target tissues (muscle, liver, and kidney) in sheep (Cruz et al. 2018). Ivermectin was also reported in the edible tissues of broilers as reported by Mestorino et al. (2017) who suggested a withdrawal time for ivermectin to stay within the permitted residual levels of 0 days for muscle, 12 days for liver, 8 days for skin/fat, and 10 days for the kidney. Not only the residues of anthelmintics (Patel et al. 2018) but also coccidiostats (Bacila et al. 2017) were reported in meat.

Hormones Anabolics hormones are used as growth promoters in farm animals to increase meat production in addition to their widespread environmental and water contaminants. This leads to the international debate about the safety of products originating from such anabolics. Zeranol and diethylstilbestrol, for example, were reported in concentrations more than the acceptable limits in a considerable part of samples from food animals in the USA (Nachman and Smith 2015). Several hormonal drugs such as testosterone propionate, estradiol, and estradiol benzoate, and progesterone or hormone-like compounds have been approved by the FDA for use in food animal production. Some of these hormonal products such as trenbolone acetate, zeranol, and melengestrol acetate have a high affinity for natural hormone receptors (Nachman and Smith 2015). Other hormones such as bovine somatotropin are approved for increasing milk production in dairy cattle in the USA (Collier and Bauman 2014). Thyreostatic (Le Bizec et al. 2011) and corticosteroidal hormones are also used alone or in combinations to increase meat production. High concentrations of estradiol are reported in hen's eggs despite the total ban in the EU of all hormonal active growth promoters in livestock production (Stephany 2010). More interesting is that the residue of 17β-estradiol and estrogenic activities was reported in the water of the Hawkesbury River, Australia, in concentrations above the levels that have been linked to the adverse effects in fish and other aquatic organisms (Uraipong et al. 2018).

Growth promoter and Feed Additives The use of growth promoters and anticoccidials collectively constitutes about 30% of the total veterinary drug consumption. This class is used for long periods and sometimes for the entire lifespan as it occurs in poultry management. The most common growth promoters used in food-producing animals and poultry are the antibacterials, hormones, and β2-agonists (Aroeira et al. 2019). β2-adrenoceptor (β2-AR) agonists such as clenbuterol (Chen et al. 2017), zilpaterol (Loneragan et al. 2014), salbutamol (Zhang et al. 2017), and ractopamine (Aroeira et al. 2019) are used since the 1990s to improve growth and performance. Eighty-first reports of the Joint FAO/WHO Expert Committee on Food additives including β2-adrenoceptor agonists were evaluated (Joint FAO/WHO 2018). Arsenical feed additives are widely used in animal production and elevate arsenic levels in animal tissues (Halford, 2017). Moreover, their release through environmental transformation increases the risk to ecosystems (Hu et al. 2019). Colistin has also been used as a feed additive for a long time ago but recently it has been banned in China as well as in other countries (Walsh and Wu 2016). Diclazuril and nicarbazin feed additives were reported in egg and liver in concentrations above the MRL value in samples from Croatian farms (Bilandžić et al. 2013).

The unintentional residue (environmental pollutants)

Unintentional residue (environmental) pollutants include agrochemicals, dioxins and dioxin-like chemicals, heavy metals, food additives, and natural toxins. The environmental pollutants can be transmitted through animal feed, drinking water, and feedlot manure when used as organic fertilizer and unintentionally contaminates human food (Khan et al. 2008).

Agricultural chemicals Agrochemical products are the main source of toxicities in farm animals (Schediwy et al. 2015). The widely used polychlorinated, polybrominated biphenyls (PCBs), polychlorinated dibenzofurans (PCDFs), polycyclic aromatic hydrocarbons (PAHs), organophosphorus, and carbamate insecticides do not break down quickly in the environment. Those agrochemicals in addition to those that are released into air or water will end up in soils, and hence, animals feed and accumulate in animal's body and finally to the human consumer (Howard 2017; Chiesa et al. 2018b). Improper use of pesticides appeared to be the principal cause of contamination of food (Szpyrka 2015). High concentrations of the organochlorine pesticides and their metabolites have been found in soil, and water in Southwestern Nigeria, although it has been banned from agricultural and public health use during the past few decades (Adeleye et al. 2019). Moreover, organic honey from different production areas may contain a high concentration of organochlorine pesticides (Chiesa et al. 2018b). Not only animal feed but also surface and groundwater can be an important source of pollution by organochlorine pesticides (Navarrete et al. 2018). This is of particular importance and can account for the fish risk (Chiesa et al. 2019). The organochlorine pesticides, for example, dichlorodiphenyldichloroethylene, were detected in concentrations that exceeded the guidelines in sediments of the river's water in Nigeria (Unyimadu et al. 2019). Hexachlorocyclohexane isomers in freshwater can enter the food chain through worms and carp (Di et al. 2018). Feed and food-packing materials (Wang and Kannan 2018), milk, fish, and pork were reported to contain higher levels of organophosphorus pesticides (OPPs) that are correlated to the diet exposure and can account for risk to population (Liu et al. 2018). The presence of polychlorinated biphenyls, polybrominated diphenyl ether, and polycyclic aromatic hydrocarbons in organic honey was confirmed, not only in proximity to highly urbanized centers, where the concentrations were higher but in all environment contexts, confirming their ubiquity in Italy (Chiesa et al. 2018a). Organophosphorus flame retardants contamination may occur during industrial processing and manipulation of food, e.g., packaging, canning, and drying of food products since organophosphorus pesticides (OPPs) were reported in Belgian foodstuffs (fish, crustaceans, mussels, meat, milk, cheese, dessert, food for infants, fats and oils, grains, eggs, and potatoes) and derived products (Poma et al. 2018). Pyrethroids and chlorpyrifos were reported in animal and chicken origin food in Brazil (Dallegrave et al. 2018). Chlorpyrifos and cypermethrin were reported in high levels in beef and milk from animals fed on treated fruit/vegetable crops in Argentina (Ferré et al. 2018). Furthermore, children living in vineyard rural areas in France seem to be at higher risk of airborne pesticides such as dithiocarbamate, endosulfan, and lindane which were reported in the air, water, and soil and could be a problem of great concern (Raherison et al. 2019).

Herbicides are common soil and groundwater contaminants (Verma et al. 2017). The aquaculture organisms can be contaminated by several herbicides that are used to control aquatic weed growth in fish ponds, lakes, and canals (Tran et al. 2019) which can be of public health concern to human consumers (Chang et al. 2016). Arsenical herbicides were reported in meat, milk, poultry, and eggs (Bencko and Foong 2017). Moreover, pesticide residues in honey and pollen may lead to a negative impact on honeybees' health and hence great economic losses (Muli et al. 2018). Arsenic, cadmium, and iodine were identified as major hazards in the European seaweed chain (Banach et al., 2020).

Fungicides such as Malachite green have been widely used in commercial fish farms and can cause a wide range of toxicological effects on various fish species and mammals (Chang 2017). Plant protection products and their adjuvants and other co-formulants can have additive, synergistic, or antagonistic side effects with the active ingredients in the final products (Klátyik et al. 2017).

Food additives such as antioxidants, coloring agents, preservatives sweeteners, emulsifiers, and stabilizers are all added to human food during processing to improve the quality of the product. These additives may be risky when added in large amounts. A case of poisoning with sodium nitrite occurred recently, in three family members in Serbia after eating homemade sausages (Cvetković et al. 2019).

Other environmental contaminants Organic pollutants (POPs) such as dioxins and dioxin-like chemicals accumulate up in the animals, an effect is known as biomagnifications, and consequently meat and dairy products, fish, and shellfish are the main source (more than 90%) of human exposure to dioxins (Barone et al. 2019). In France, for example, dioxins, polychlorinated biphenyls, hexabromocyclododecane, etc., were measured at significantly higher levels in organic and conventional meat (Dervilly-Pinel et al. 2017). On the other hand, groundwater, surface water, sediment as well as aquatic flora can be contaminated by pharmaceutical industries, hospitals, sewage, and wastewater (Thai et al. 2018). Consequently, plants treated with wastewater and animal feed are an important sources of organic pollutants (POPs) (Khalid et al. 2018) and have been reported to contain high quantities of antibiotics (Tahrani et al. 2017) and psychoactive substances (Gao et al. 2017).

Animal feed can be contaminated with air-borne metals such as As, Cd, and Pb (Pandey et al. 2012). Plant fertilizers may contain heavy metals that are bioaccumulated in the soil and implicated in animal feed contamination (Dessalew et al. 2018). The widespread use of Cu, Zn, and phenyl arsenic compounds in intensive poultry farming is another source of environmental contamination (Hu et al. 2019). Meat and internal organs of broiler birds reared near the roadside/canal and waste disposal site/wastewater drains were reported to contain high concentrations of heavy metals in Pakistan (Abbas et al. 2019). Processed meat products in southeastern Brazil (de Souza Ramos et al. 2019) and seafood in Tianjin, China (Wang et al. 2019), near wastewater drains have also been reported to contain heavy metals and polycyclic aromatic hydrocarbons (PAHs) at levels higher than the MRL. In the EU the accepted MRLs for As, Cd, and Pb in feed materials with some exception are 2, 1, and 10 mg/kg (ppm) relative to a feed with a moisture content of 12% (European Commission 2013). In Vietnam, the USDA foreign agricultural services approved a level range of 0.01–1.0, 0.003–3.0, and 0.02–3.0 mg/kg (ppm) for As, Cd, and Pb in feed, respectively, depending on the type of food (Huong 2013). Nearly similar levels are approved in Australia (0.14–1.4, 0.1–2, and 1–6 mg/kg, respectively, Choi 2011).

Mycotoxins (e.g. aflatoxin, ochratoxins) and plant toxins in particular in food and feed are of growing concern because of their diverse potent pharmacological and toxic effects on human and animal health (Adegbeye et al. 2020). Mycotoxins have been reported in meat and meat products (Elghandour et al. 2019), in eggs and chicken tissues in China (Wang et al., 2018), and muscles and liver of broiler chickens and turkey poults (Tardieu et al. 2019). Representative examples for the unintentional residues in food are listed in Table 1.

Potential sources of residues in a disaster situation (emergency slaughtered animals) Emergency slaughtered animals, animals treated before a disaster, meat or milk of unidentified animals, and the slaughter of treating sick and debilitated animals should be suspected as risk points for existing drug residues. In this respect, the anthelmintic drug residues were high in the muscle of emergency slaughtered cattle (Cooper et al. 2012). Similarly, the level of antimicrobial drug residues was high in pork meat of sick animals under treatment and sold preferentially in a local abattoir in Madagascar (Rakotoharinome et al. 2014). Tetracycline or an unidentified microbial inhibitor residue was detected in culled dairy cows in California, USA (Aly et al. 2014). Moreover, large amounts of anesthetics either administered by inhalation (Lockwood 2010) or intrathecal injection (Aleman et al. 2016) remain in the body for days and their use for euthanasia is potentially harmful and may cause environmental impact and secondary toxicosis (Payne et al. 2015). A report of a panel meeting concerning euthanasia of animals intended for human or animal food has been published (AVMA, 2020). Figure 2 illustrates the possible hazards from drug residues in food of animal origin.

Risk Factors for violative residues in Food-producing Animals It is supposed that veterinary drug products and agricultural chemicals should not leave any residues at slaughter. However, residues can be found due to possible reasons such as extra-label use of drugs (Cramer et al. 2019), misuse and overuse (Ngumbi and Silayo 2017), failure to follow the recommended dose and or route, failure to apply the recommended withdrawal periods, incorrect mixing, and contamination of animal feed/water (Beyene 2016). Risk factors responsible for the development of residue include also animal factors such as age, species, and diseases of treated animals (Beyene 2016; Yang et al. 2019). However, the failure to observe the appropriate withdrawal time remains the critical risk factor for the development of unacceptable residue especially after using an overdose or the use of long-acting formulations (Riviere et al. 2017). Regulatory agencies (Code of Federal Regulations) prohibited the extra-label use of a list of drugs in food-producing animals including clenbuterol, chloramphenicol, diethylstilbestrol (DES), dimetridazole, ipronidazole, furazolidone, nitrofurazone, sulfonamide drugs in lactating dairy cattle, fluoroquinolones, and glycopeptides (Fajt 2007).

Hazards from drug residues Short-term and long-term hazards can occur due to drug residues in food. The short-term hazards include allergic hypersensitive reactions, mutagenicity, teratogenicity, and direct intoxication. The hazards after long-term use include carcinogenicity, reproductive effects, disruption of normal human intestinal microflora, and development of antibiotic-resistant mutant of bacteria in treated animals (Falowo and Akimoladun 2019). In addition to health hazards, there are important dairy technical problems or condemnation of residues containing carcasses.

Short-term health problems

Drug hypersensitivity reactions Drug hypersensitivity may occur in humans shortly after the consumption of food containing drug residues. Anaphylaxis, allergic skin reactions, or delayed hypersensitivity response are examples of allergic reactions to drugs (Ortelli et al. 2018; Bacanli and Başaran 2019). Hypersensitivity associated with antibiotics, especially β-lactam (Cardona et al. 2021) and macrolides (Darwish et al. 2013), is very common. Food additives generate IgE-mediated and non-IgE-mediated immune reactions and act as allergens and pseudo allergens and can generate direct clinical pictures or may exacerbate diseases such as

Table 1 Examples of the unintentional residue in food of animal origin

Pollutants	Sources	References
I. Agrochemicals: Polychlorinated biphenyls, Polychlorinated dibenzofurans, polybromodiphenyl ethers (PBDEs), polycyclic aromatic hydrocarbons, organophosphorus and carbamate insecticides	Polluted air or water ends up in animal feed and accumulate in animal's body, milk, fish, pork, and food-packing materials and finally to the human consumer	Wang and Kannan 2018), (Liu et al. 2018)
Organophosphorus flame retardants contamination	Occur during industrial processing of food (fish, crustaceans, meat, milk, cheese, dessert, eggs, etc.,	(Poma et al. 2018)
Glyphosate-based herbicide	Glyphosate, N-(phosphonomethyl)glycine, is a broad-spectrum herbicide used globally for plant protection and improve plant growth. It is commonly found in the environment and surface waters	Astiz et al. 2009; Jensen et al. 2016
Fungicides such as Malachite green	Widely used in commercial fish farms	Chang 2017
Food additives such as antioxidants, coloring agents, preservatives sweeteners, emulsifiers, stabilizers	Consumption of processed food	Cvetković et al. 2019)
II. Other environmental pollutants Dioxins and dioxin-like chemicals, Polychlorinated biphenyls, hexabromocyclododecane, etc.)	Animal feed, drinking water and feedlot manure when used as organic fertilizer, and then to meat and dairy products, fish and shellfish	Fung et al. 2018, Trevisani et al. 2017, Barone et al. 2019
Heavy metals: Cu, Zn, and arsenical herbicides	Plant fertilizers, seaweed and then to meat, milk, poultry, and eggs. Airborne arsenic can be taken via inhalation, drinking water, beverages, or from food and drugs	Banach et al., 2020, Bencko and Foong 2017)
Methyl mercury (organo-mercury)	Consumption of fishes and shellfishes containing methyl mercury that was generated during the production of acetaldehyde using mercury as a catalyst	Shimohata et al. 2015
Cadmium poisoning	Dietary cadmium intake in polluted areas. Cadmium was identified as major hazards in the European seaweed chain	Trevisani et al. 2014), Banach et al. 2020
Mycotoxins:	Consumption of mycotoxin-contaminated food products, such as meat, milk, or eggs, containing residues or metabolites of mycotoxins	Trevisani et al. 2014
Melamine	Melamine-tainted milk	El-Nezami et al. 2013

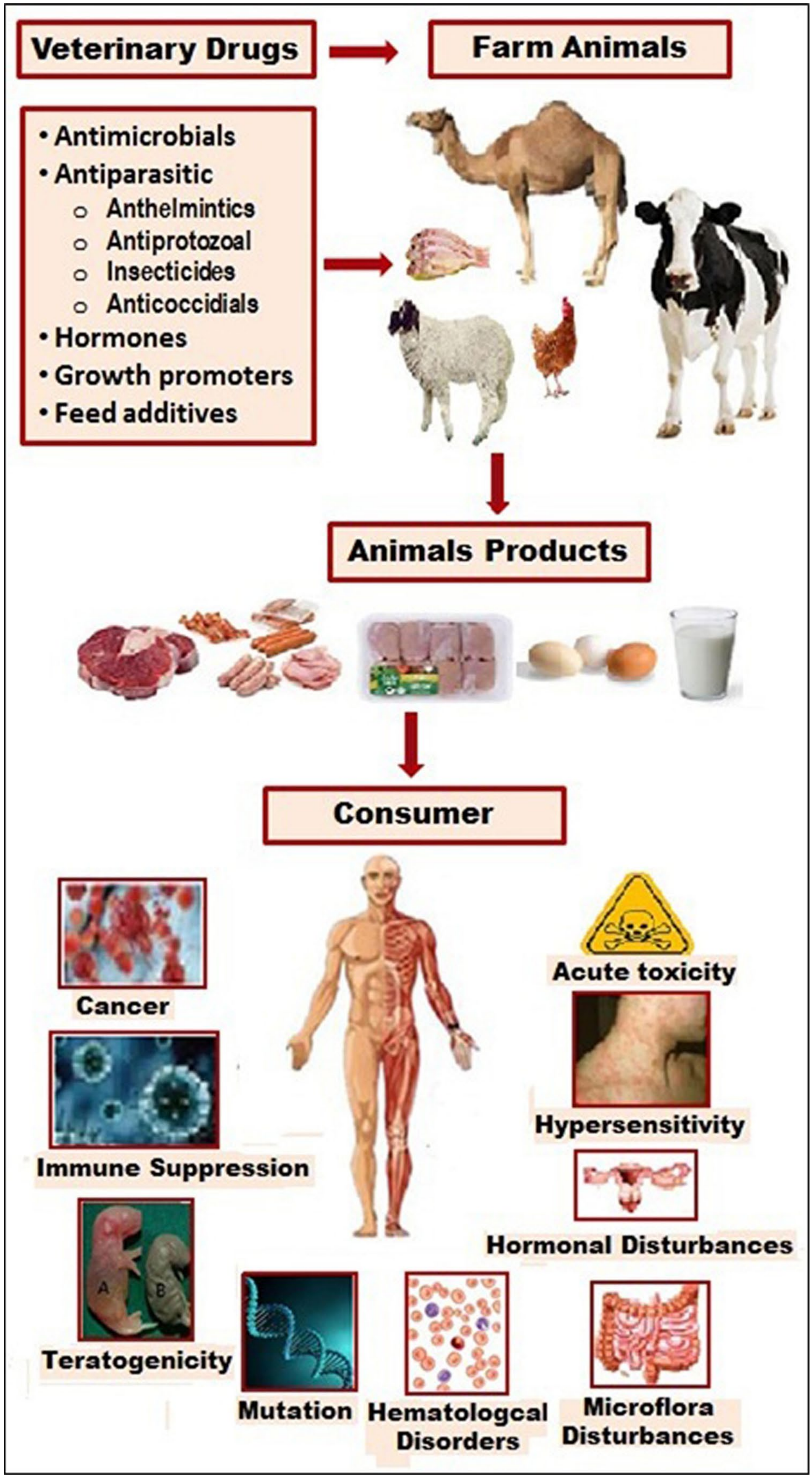

Fig. 2 Possible hazards from drug residues in food of animal origin

bronchial asthma, dermatitis, chronic urticaria, or anaphylaxis (Andreozzi et al. 2019).

Direct intoxication Direct intoxication due to consumption of drug residue-containing food is also an important issue of human health concern. Clenbuterol, a beta-agonist growth promoter, was suspected to cause direct intoxication after eating contaminated liver and non-liver beef meat (Zhang and Wu 2002). In Portugal, Barbosa et al. (2005) described four cases of acute food poisoning due to the ingestion of lamb and bovine meat containing residues of clenbuterol.

Hormonal disturbances There are a large number of pollutants known to be endocrine-disrupting agents such as pesticides, polychlorinated biphenyls, aromatic hydrocarbons, dioxins as well as phytoestrogens (Wilson et al. 2016). Furazolidone induces hormonal disturbances involving the thyroid, ovarian, and adrenal hormones (Ahmed et al. 2008). More recently, the exposure to the fungicide, difenoconazole elicited estrogenic endocrine disruption on the offspring in zebrafish (Teng et al. 2018). The presence of organochlorine pesticides in breast milk is reported to be associated with the exposure of Taiwanese women to OCPs in their diet and is considered a probable cause of infertility (Chen et al. 2018b). Several veterinary drugs have an affinity to the sexual hormone receptors and exhibit endocrine-disrupting effects (Lee et al. 2019).

Disruption of normal intestinal flora The broad-spectrum antimicrobials may adversely affect a wide range of intestinal flora and consequently cause gastrointestinal disturbances. Antimicrobials residues can reach humans not only through oral administration but may also be present and affect microbiota when administered parenterally (Cresci and Bawden 2016). Antibiotics may reduce the total number or selectively kill some important bacterial species (Mensah et al. 2014; Kim et al. 2017). Some drugs such as flunixin, streptomycin (Russell et al. 2015), and tylosin, vancomycin, nitroimidazole, and metronidazole in humans are known for this effect (Kim et al. 2017).

Mutagenic effect The potential mutagenic activity can be elicited by several chemicals, such as alkalizing agents, phenylurea herbicides, linuron and chlorbromuron (Federico et al. 2016), and the amyloid β-peptide aggregation inhibitor, morin, causing DNA damage (Mori et al. 2019). It has been reported that environmental chemicals may cause a complex gene-environment interaction predisposing to neurodegenerative diseases such as Alzheimer's and Parkinson's disease (Cicero et al. 2017) or may have an adverse effect on human fertility (Jeng, 2014). Although mutagenicity is usually associated with short-term exposure, an obvious DNA damage and DNA repair gene disorder in male workers engaged in e-waste recycling work for more than 1 year were reported in Tianjin, China (Wang et al., 2019).

Teratogenic effect Benzimidazole anthelmintics are reported to be embryotoxic and teratogenic when given during the early stage of pregnancy (El-Makawy et al. 2006). Glyphosate, the most widely used pesticide could be toxic at very low concentrations causing teratogenic, carcinogenic, and hepatorenal toxicity probably by GlyBH adjuvants of commercial formulations (Mesnage et al. 2015). Cytotoxic effects of oxytetracycline residues in the bones of broiler chickens following therapeutic oral administration of a water formulation were reported (Odore et al. 2015), suggesting potential human and animal health risks due to the entry of tetracycline residues contained in the bones of treated livestock into the food-chain.

Hematological disorders Enzymatic and hematological alterations have been reported in the African catfish, Clarias gariepinus exposed to diclofenac (Ajima et al. 2015), and zebrafish exposed to carbamazepine (da Silva Santos et al. 2018). However, organochlorine pesticides may exert adverse effects on hematopoietic tissue and liver in populations chronically exposed to high levels of these compounds (Freire et al. 2015). Chronic exposure to OTC products causes blood changes such as leucocytosis, toxic granulation of granulocytes and thrombocytopenia, atypical lymphocytes, lung congestion, and brown discoloration of the teeth (Praveena et al. 2019).

Long-term health problems

Carcinogenic effect Several drug residues are reported to be potentially carcinogenic such as metronidazole (Adil et al. 2018), steroid hormones, and bovine somatotropin which have been approved for use in food animals by the U.S. Food and Drug Administration (Nachman and Smith 2015). Estrogens have been listed as group 1 carcinogens in human and aquatic organisms by the World Health Organization (Bilal and Iqbal 2019). Some of the thyreostatic compounds are carcinogenic and teratogenic (Yang et al. 2018). Inorganic arsenic (Hu et al. 2019) and malachite green (MG) residues were reported to be toxic to mammals (Chu et al. 2013) causing carcinogenesis, mutagenesis, chromosomal fractures, teratogenicity, and respiratory toxicity (Pierrard et al. 2012). Taiwanese fish consumers have a greater risk of liver cancer due to exposure to leucomalachite green residues from fish products (Chu et al. 2013). Moreover, the illegal use of food additives may increase the formation of carcinogenic compounds during the processing of food containing such additives (Molognoni et al. 2019).

The emergence of resistant strains of pathogens One of the major problems of the existence of drug residues is the emergence of resistant strains of bacteria either affecting the animal itself or transmitted to the human population (Bacanli and Başaran 2019; Singh and Bhunia 2019). Resistant microorganisms can be transmitted to humans, either directly from the environment (Manaia 2017) or indirectly via milk, meat, and/or egg (Lee et al. 2018). Despite the recent significant decrease in antibiotic consumption, the resistance rate and distribution of multidrug-resistant bacteria are increasing (Ortelli et al. 2018). More interesting, the emergence of resistant strains of bacteria appears not only in milk-containing antimicrobial residues intended for human consumption (Ondieki et al. 2017) but also in waste milk for feeding calves (Pereira et al. 2018). Following acute and subchronic exposure to low concentrations of antimicrobial drug residue, the human intestinal microbiome structure and the resistance-gene profile were adversely affected (Jung et al. 2018). It appears that the transfer of resistance is encoded by genes rather than mutation as it was concluded from the results of the European Union surveillance program including the meat-producing animals and the antimicrobial resistance of zoonotic (Salmonella and Campylobacter) and indicator (Escherichia coli and enterococci) bacteria. Plasmids, transposons, and other mobile genetic elements contain resistance genes that can pass from one bacterium to another by horizontal transfer (Florez-Cuadrado et al. 2018). Resistance genes can also be spread and disseminated in the soil and environment from the waste of treated animals (Cheng et al. 2016). Not only is the resistance to the antimicrobial agents that can be transmitted but also the antiparasitic drugs (Liébano-Hernández et al. 2015).

Dairy technical problems Uncontrolled handling of veterinary drugs in lactating animals, lack of treatment records, use of unapproved drugs, and failure to observe withdrawal period cause release of these drugs into milk leading to major technical problems in the dairy industry. Residual quantities of antimicrobials in milk can interfere with starter culture activity and disruption of the manufacturing of milk products and may inhibit the growth of probiotics microorganisms during the manufacturing of yoghurt, cheese, acidophilus milk, etc. Antibiotic residues in milk can also cause underestimation of the microbial load in milk through interference with the methylene blue reduction test. Therefore, milk of inferior quality is released that may have to be discarded coupled with the disruption of the production schedule. The possible potential health hazards associated with antibiotic residues in milk are allergic reactions (penicillins and cephalosporins), carcinogenic effects (sulfamethazine and nitrofurazone), and nephrotoxicity and ototoxicity (aminoglycosides) (Patel and Walker 2004).

Economical influences The awareness about the potential risk of diseases such as cancer and impaired endocrine, nervous, reproductive, cardiovascular, and immune system functions results in a negative impact on individual productivity, the global economy, and international trade (Wilson et al. 2003). The US authorities have opposed restrictions adopted about antimicrobial use in food-producing animals (Maron et al. 2013). However, the EU has prohibited the importation of poultry processed with antimicrobial rinses resulting in a reduction of US poultry exports to the EU from $52 million in 1997 to only $13 million in 2011 (Johnson 2012). On the other hand, antibiotic contaminated milk has been estimated to cost the US dairy industry $50 million annually (Rice et al. 1984). Therefore, evidence strengthens the rationale for restricting antimicrobial use in food animals is mandatory (Ma et al. 2020).

How to control or minimize drug residues

Education

It is difficult to implement a good residue avoidance program without recruitment and retaining specialized scientific staff. The veterinarian must be aware of the pharmacological bases of many drugs such as the elimination half-life ($t_{1/2}$), the volume of distribution (Vd), total body clearance, rate of absorption of non-intravascularly administered drugs, and their withdrawal period. He must be aware of the factors which affect these estimates. Absorption of the nonparental administered drugs, for example, is influenced by the physiopathological state of the animal, the route of drug administration, and the physical characters of the drug. The maximum concentration and the time to peak concentration are indications of the rate of drug absorption (Sugano and Terada 2015). After reaching blood circulation, the drug has to be distributed through the body compartments. The physicochemical properties of the drug, the percent of binding to plasma protein, the local blood flow, and the drug affinity for the tissue constituents, volume of distribution, and others are the factors that affect the process of distribution (Fan and de Lannoy 2014). A veterinarian must know that most drugs undergo metabolism in the liver, although some drugs are eliminated from the body unchanged. Most drugs are inactivated, but some may be converted in the liver to an activated form. Some drugs can activate liver microsomal enzymes, which can terminate the effect of other drugs rapidly and vice versa (Fu et al. 2016). Moreover, the overall rate of elimination (metabolism and excretion) is very important to the residue of drugs in edible tissue (Busatto et al. 2018). It should be pointed out that there is a great variation among animals in their general ability to handle drugs (Toutain et al. 2010). Special attention should be directed to the depot and sustained-release preparations which are very important to residue avoidance (Chaccour et al. 2018). It should be noted that most of the pharmacokinetic parameters are derived from studies that have been carried out on healthy animals; however, the drugs target animal diseases, which can influence the pharmacokinetic parameters and the potential for residues (Yang et al. 2019). An increased Vd, for example, will reduce drug clearance and prolong the half-life. Decreased blood perfusion of the intestine in diseased animals may prolong the absorption half-life and alter gastrointestinal transit time and could influence the elimination profile than normal animals. On the other hand, ELDU must be taken into consideration since it refers to the use of an approved drug in a manner that is not indicated in the label. Ivermectin, for example, is used in dogs and cats despite its approval for use in cattle. Enrofloxacin solution is only approved for use as an injection, though it is used as a topical ear medication (Bae et al. 2013). Food producing staff must be aware of the restrictions on veterinary drugs prepared by regulatory agencies (Maron et al. 2013). The withdrawal time must be applied strictly to avoid illegal residues (Riviere et al. 2017). The staff must be aware of the prohibited drugs for dairy cattle. The veterinarian should pay attention to the fact that special formulations for dry cow mastitis can have 10 times the amount of drug found in a wet-cow mastitis treatment. Special attention should be paid to the identification of treated animals and avoid mistakes. Animal identification includes using treatment records for withholding periods, a numerical ID: ear tags, neck chains, or "Warning Sign" or leg bands, etc. Finally, treated animals can be segregated into a "hospital pen. Based on this simplified overview, the incidence of violative residues can be reduced.

Lab Spot

Analysis of drug residues Detection of residues must be carried out using sensitive tests with a low quantification level and a low rate of false-negative results. The detection strategy is based on two steps: (1) screening step followed by (2) confirmatory step for the positive results (Mensah et al. 2014). The animal identification and traceability, the lack of resources, and infrastructure for sample collection and transport are all constraints for sampling regimes that must be solved to establish accredited (ISO/IEC 17,025) screening laboratories' food safety. Sampling is conducted to identify possible areas of concern or when a violation has occurred (CFIA 2014). Directed samples are taken from animals or products which are suspected to have residues, or from groups of animals or types of products that are at higher risk. Several methods are developed for both general screenings and more sensitive quantitative measurements of drug residues.

Microbial screening method This method is used for the detection of an inhibitory substance in animal products. It is generally used for antibiotic testing. It is nonspecific and can cover a wide range of antimicrobials. It can be carried out in a test tube containing a growth medium or in a plate containing inoculated nutrient agar. Absence or delay of the color production by the acid produced by the growing bacterial colony in the test tube or the appearance of an inhibitory zone in the plate containing the inoculated nutrient agar indicates growth inhibition and positive antimicrobial drug residues. This method is still used for the rapid screening of antibiotic residues (Wu et al. 2019).

Immunological technique This test depends on antigen–antibody interactions and is used for the detection of antimicrobials, hormones, and β-agonists in meat, milk, or eggs. A colorimetric immunoassay, for example, was developed for the detection of amantadine residues in poultry at the ppb level (Yu et al. 2018). An indirect competitive enzyme-linked immunosorbent assay was developed using broad-spectrum monoclonal antibodies for the multi-residue detection of avermectins (Ni et al. 2019) and antibacterial drugs (Han et al. 2019) in animal tissues and milk. The immunoassay was also used for the determination of hormonal residues in food. A method for simultaneous determination of six zeranols by immunoaffinity solid-phase extraction in milk samples (Zhang et al. 2018), eggs (You et al., 2012), in foodstuffs of animal origin (Wang et al. 2014) was developed. A screening method for residues of diethylstilbestrol, dienestrol, hexestrol, and zeranol in bovine urine using immunoaffinity chromatography and gas chromatography/mass spectrometry was also validated (Dickson et al. 2003). The immunoaffinity chromatography was also used for the determination of beta-agonists in animal tissue samples (Mei et al. 2014), animal feed, and feed ingredients (Campbell and Armstrong 2007). A gold immunochromatographic strip is prepared to detect clindamycin, lincomycin, and pirlimycin residues simultaneously with a single monoclonal antibody was prepared (Guo et al., 2020).

Chromatographic method Liquid chromatography (Fidel and Milagro 2006), and recently the high-performance liquid chromatography (HPLC) and the ultra-performance liquid chromatography–quadrupole electrostatic field orbitrap mass spectrometry has been applied for the detection of multi-residue (Hou et al. 2020) within a short time. Coupling of HPLC with mass spectrometry (MS–MS) has been applied for confirmation in positive samples after initial screening (Chen et al. 2019). Chromatographic methods are used widely for determination a large number of veterinary drug residues in food of animal origin for example in beef (Zhao et al 2018), milk (Yao and Du 2020), eggs (Barreto et al. 2017), propolis (Wen et al., 2018), and aquatic products

(Kong et al. 2018). Recently, a simple screening procedure using liquid chromatography–tandem mass spectrometry was developed for the determination of polypeptide antibiotics (Bladek et al., 2020) and anthelmintic residues (Yoo et al., 2021).

Biosensors This method depends on the recognition of the target antimicrobial residue by a biological element called a bioreceptor, which converts the recognition event into a measurable signal (Velusamy et al. 2010). This method is simple, rapid, highly selective, and inexpensive (Gaudin 2017). A bioreceptor can be an antibody, enzyme, protein, nucleic acid or a living organelle (cells, tissues) or whole organisms (Gaudin 2017). It has been applied successfully for the detection of antimicrobials in animal-derived foods (Majdinasab et al. 2017)¶. Positive samples of the first screening step should be confirmed in the second step. The positive result of the positive samples should not exceed the MRL limit. The concentration is expressed in mg/kg or mg/L (Beyene 2016).

Rules and Regulations

Every country has an agency that oversees food safety. The safety of animal and poultry products in the USA for example is under the responsibility of the US Department of Agriculture's (USDA) and Food Safety Inspection Service (FSIS). Risk assessment regarding food and animal feed safety in the European Union's (EU) is the responsibility of the European Food Safety Authority (EFSA) (Silano and Silano 2017). The Codex Alimentarius Commission created by the FAO and WHO under the Joint FAO/WHO Food Standards Programme contains the food standards, guidelines, and related texts. For regulating the use of drugs in animal production activities, these organizations have proposed maximum residue levels (MRLs) for livestock products to minimize the risk to human health (Joint FAO/WHO, 2018) (council (EC) No 470/2009 and updated in line with Commission Implementing Regulation (EU) 2017/12]]. The European Commission (2010) in its current consolidated version: 07/12/2020 shows a list of approved drugs with their MRLs in foodstuffs of animal origin as well as a list of banned drugs. It should be noticed that the registered and approved veterinary uses may vary from country to country because of different efficacious use patterns, especially in regions with great differences in disease distribution, predominant parasites, production methods (e.g. 4 extensive or intensive), predominant animal breeds, climate and water temperature (Joint FAO/ WHO 2008), and consequently differences in their acceptable MRL. The residue limit for albendazole, for example, is 0.05 ppm (50 ug/kg) in meat in the USA and Canada (Canada gov, 2018), while in the EU, it is 100 ug/kg. The limit of doramectin in bovine muscles in Canada is 0.03 ppm (30 ug/kg), while in the EC it is 40 ug/kg (European Commission 2010) and in the Codex Alimentarius, it is 10 ug/kg (Joint FAO/WHO, 2018). The MRL for clenbuterol, for example, is 0.2 in cattle muscle and fat, 0.6 in liver and kidney, and 0.05 ug/kg in milk according to the Codex Alimentarius (Joint FAO/WHO, 2018), while in the EC it is 0.1 in bovine muscle and 0.5 in liver and kidney and 0.05 μg/kg in bovine milk, a fact that necessitates global standardization of the MRL values and harmonization of analytical methodology.

Several drugs such as chloramphenicol, metronidazole, and nitrofurans are prohibited for use in food animals are available (European Commission. 2010). Taking into consideration that antimicrobial residues in edible animal products have increased over the permissible level in developing countries (Odetokun et al. 2019), harmonization on residue definitions, methods of analysis, and evaluation of the MRLs and other issues relating to the use of chemicals both as veterinary drugs and as pesticides is a critical issue (Joint FAO/ WHO 2014). In continuation and to achieve this goal, the Codex Alimentarius Commission (Joint FAO/WHO 2014) established a strategic plan through the period 2014–2019. The plan objectives were 1. Establish international food standards that address current and emerging food issues. 2. Ensure the application of risk analysis principles in the development of Codex standards. 3. Facilitate the effective participation of all Codex Members. 4. Implement effective and efficient work management systems and practices. In 2020 the Codex Alimentarius Commission (Joint FAO/ WHO 2020) discussed the strategic plan during the period 2020–2025. The Codex Alimentarius Commission commits itself to work towards the achievement of the following five goals: 1. Address current, emerging, and critical issues in a timely manner. 2. Develop standards based on science and Codex risk-analysis principles. 3. Increase impact through the recognition and use of Codex standards. 4. Facilitate the participation of all Codex Members throughout the standard-setting process. 5. Enhance work management systems and practices that support the efficient and effective achievement of all strategic plan goals. The situation in the developing countries still needs more effort to achieve harmonization of MRL, withdrawal periods, and analytical procedure with the industrialized countries although there are some trade development programs in cooperation with the European Commission implemented through twinning projects with the EU.

Residue Avoidance

In general, the strategy is based on preventing the entry of violative residues in animal and poultry products intended for human consumption by proper and rational drug use.

A guide developed for use by each veterinarian and food animal (dairy and beef) producer embraces the following:

Herd health management Vaccination, nutrition, and stress management continues to be the crucial steps of a comprehensive herd health program. Alternatives to current antimicrobials, biosecurity guidelines, and management approaches are essential., Special care should be offered for the pregnant animals during the last third of pregnancy to ensure adequate colostrum both the amount and concentration of antibodies. Special attention should also be paid to avoid residue in aquaculture production systems residue in fish (Reimschuessel 2014).

The use of approved drugs Approved animal drug products only should be used by dairy and beef producers who must follow the guidelines in the Generic Animal Drug and Patent Restoration act regarding animal species, dose, route of administration, withdrawal periods, etc. The list of approved drugs known as the "Green Book" is now updated monthly. To ensure misunderstanding, dairy and beef producers should not keep or store unapproved drugs or products. The herd veterinarian should be sure that ELU involves only the approved products. A good veterinarian–client–patient relationship is critical to the health of animals. A veterinarian should be close with the owner to make judgments regarding the health of the patient by a timely examination, emergency coverage, and continuing care, treatment, and revise medication records. The veterinarian's recommendations and prescription should be accepted by the producer. The employees on the farm have to know the drugs approved for each animal species and are familiar with the approved dosage, route of administration, and withdrawal time. As of November 24, 2019, all Green Book reports are updated monthly and are located on the Animal Drugs @ FDA website: https://animaldrugsatfda.fda.gov/adafda/views/#/search. Farmers should keep written/electronic treatment records for all groups of animals. Included in these records are date, ID, the person administering treatment, indication for treatment, a drug used, dosage, route of administration, and withhold information for meat and milk (Vickroy et al. 2014). Treated animals should be identified clearly and isolated separately.

The use of alternatives to veterinary drugs The introduction of ethnoveterinary medicine is recently practiced and proved to be effective in minimizing the use of current drugs for combating animal diseases. Ethno-veterinary therapeutics are obtained mainly from medicinal plants due to their efficacy, availability, and ease of preparation particularly in areas where medical assistance is not available (Eiki et al. 2021). Ethno-veterinary medicine has been used successfully for compacting several animal and poultry diseases (Piluzza et al. 2015). Besides being effective and safe, ethno-veterinary medicines can be a good solution to the problem of antimicrobial resistance and drug residues in animal and poultry products (Ranganathan 2017, WHO 2017).

Identify risks for drug residues Handling and use of drugs, treatment records, number of treated individuals, culling decisions, identification of treated animals, storage, and accessibility of drugs should be reviewed periodically. Proper drug residue testing capabilities should be available on and off the farm. The objective of the residue avoidance program is based upon improving livestock management and keeping healthy animals with emphasis on avoidance of drug residues (Tufa et al. 2018). All of these activities can be achieved by implementing an employee training program.

Preslaughter testing of body fluids Treated animals intended for meat production should not be slaughtered before applying the appropriate withdrawal periods by government authorities or regulatory bodies (Vishnuraj et al. 2016). Preslaughter living monitoring of drug residues is very important not only for the protection of human health but also for the detection of the illegal use and violative residue in food animals. Body fluids such as blood, urine, and milk can be sampled and tested preslaughter for predicting residue levels in edible tissues (Zhang et al. 2017; Chirollo et al. 2018; Aroeira et al. 2019). Urine and hair were excellent for predicting ractopamine residues in tissues of pigs, whereas plasma and urine were satisfactory body fluids for the prediction of ractopamine concentrations in edible tissues of goats (Huang et al. 2016). Chloramphenicol was also reported in the urine of pigs (Trevisani et al. 2014). Hair analysis can be a useful target of sampling for residues testing of some drugs such as sulfamethazine as an alternative to edible tissues in animal farming (Gratacós-Cubarsí et al. 2006). A similar study was carried out for various nitroimidazoles in feathers and shanks in poultry (Církva et al. 2019).

Effect of food Thermal treatment on drug residue levels Previous studies have suggested that chloramphenicol, aminoglycosides, quinolones, clindamycin, novobiocin, trimethoprim, vancomycin, and azlocillin are heat-stable (Rana et al. 2019; Monir et al., 2021). Moreover, quinolones, Lincomycin, tylosin, and oxacillin are degradable by only 10% during thermal treatment (Rozanska and Osek, 2013; Heshmati, 2015). β-lactams, tetracyclines, erythromycin, florfenicol, and thiamphenicol were heat-labile (Hassani et al. 2008; Laszlo et al. 2018; Filazi et al. 2015; Rana et al. 2019; Kellnerova et al. 2015). Although a significant reduction of OTC concentration in meat by cooking was reported (Vivienne et al., 2018), microwaving meat had a limited. However, the food matrix composition and physicochemistry (e.g., pH, fat content), the cooking methods, and the presence of food additives could influence the degradation of antibiotics (Franje et al. 2010, Abou-Raya et al. 2013, Tian et al., 2017). No significant decrease in ampicillin concentration was observed during the first 3 months of storage monitoring at -20 and -75 degrees C. However, after 8 months of storage at -20 degrees C, a significant decrease arose and was never observed at -75 degrees C (Verdon et al. 2000). Sulfadiazine residues were slightly decreased during milk boiling while most sulfonamide residues are stable in animal tissues when frozen (Laszlo et al. 2018). Different cooking procedures have no net effect on clenbuterol residues in incurred tissues (Parr et al. 2016). The sedatives, azaperone, and azaperol residues are stable in pig kidneys and liver under frozen conditions (Aoki et al. 2009). Levamisole residues in fried muscle and rafoxanide in cooked muscle were decreased by only 11% and 17%-18%, respectively (Cooper et al. 2011), while carbadox was stable in muscle (Rana et al. 2019).

Future prospects International Feed Industry Federation and FAO are looking for new, safe proteins. Among the emerging sources of protein for food are edible insects (Van Huis et al., 2013). Moreover, improving agricultural production and food security are anticipated (FAO, 2017) and the use of natural products can be used as a safe replacement for synthetic agrochemicals (Ogunnupebi et al., 2020). The use of alternative animal therapeutics such as immune modulators, phages against specific bacterial strains, phytochemicals such as oregano and thyme, probiotics such as yeast, fungi, and bacteria, which helps control "bad" bacteria and creates a favorable environment in the gut. Vaccines are among the most promising alternative approaches to control a host of respiratory and digestive diseases, as well as a number of other health problems such as enhancing animal productivity (Hoelzer et al. 2018; Callaway et al. 2021). However, at the present time, prudent use of antibiotics for example and the establishment of scientific monitoring systems are the best and fastest ways to limit the adverse effects of the abuse of antibiotics and to ensure the safety of animal-derived food and the environment (Toutain et al., 2016; More, 2020).

Conclusion and Recommendations

The unregulated use of veterinary products in food-producing animals and poultry is the main cause of the occurrence of drug and chemical residues in food of animal origin leading to a health hazard to the human consumer. The most likely reason for drug residues may result from improper usage, including extra-label or illegal drug use and most importantly is the failure to observe a withdrawal period. Measures to reduce antibiotic residue in livestock products include the following: 1- Farmers should be encouraged to maintain herd health by applying the best hygienic measures to minimize drugs used. 2-Veterinary supervision is critical for the appropriate use of veterinary drugs and for keeping the safety of animals, fish, and chicken products. The veterinarian should use label dispensed drugs and should distinguish the difference between OTC, prescription, and 'extra-label drugs', as well as using alternatives to antibiotics such as vaccination, probiotics, phage therapy, and essential oils and develop a good veterinarian–client–patient relationship. 3- Research projects should be directed to find safe and effective alternatives to veterinary drugs for treating animal diseases. 4-Testing for the presence of residues must be carried on and off the farm using rapid, sensitive, and standardized laboratory tests. 5- Condemnation of meat, milk, or eggs proved to be polluted with drug residues is very essential. 6- Regulatory bodies should enforce to apply the appropriate withdrawal periods strictly and to set the harmonized MRLs and analytical methods. 7- Using proper processing techniques to avoid contamination is essential. 8- Researchers should be encouraged to develop new safe methods to inactivate and/or enhance clearance of animals ‘ bodies of residues. 9- Efforts to find out new sources of protein similar to and acceptable as animal protein should be encouraged.

Authors' contributions AHA created the idea for the article, SAA searched for the literature, SMM drafted the manuscripts, and SMN revised the manuscript critically.

Funding This work did not receive any specific grant from any funding agencies.

Declarations

Ethics approval and consent to participate Not applicable
Consent for publication Not applicable

Availability of data and materials Figure 1 is available at https://www.noah.co.uk/about/industry-facts-and-figures/

Competing interests The authors declare no competing interests.

References

Aarestrup F (2012) Sustainable farming: Get pigs off antibiotics. Nature 486(7404):465–466. https://doi.org/10.1038/486465a
Abbas M, Chand N, Khan RU, Ahmad N, Pervez U, Naz S (2019) Public health risk of heavy metal residues in meat and edible organs of broiler in an intensive production system of a region in Pakistan. Environ Sci Pollut Res 26(22):23002–23009. https://doi.org/10.1007/s11356-019-05639-4
Abou-Raya S, Shalaby AR, Salama NA, Emam WH, Mehaya FM (2013) Effect of ordinary cooking procedures on tetracycline residues in chicken meat. J Food Drug Anal 21(1):80–86. https://doi.org/10.6227/jfda.2013210110

Adegbeye MJ, Reddy PRK, Chilaka CA, Balogun OB, Elghandour MMMY, Rivas-Caceres RR, Salem AZM (2020) Mycotoxin toxicity and residue in animal products: Prevalence, consumer exposure and reduction strategies - A review. Toxicon 177:96–108. https://doi.org/10.1016/j.toxicon.2020.01.007

Adeleye AO, Sosan MB, Oyekunle JAO (2019) Occurrence and Human Health Risk of Dichlorodiphenyltrichloroethane (DDT) and Hexachlorocyclohexane (HCH) Pesticide Residues in Commonly Consumed Vegetables in Southwestern Nigeria. J Health Pollut 9(23):190909. https://doi.org/10.5696/2156-9614-9.23.190909

Adil M, Iqbal W, Adnan F, Wazir S, Khan I, Khayam MU, Kamal MA, Ahmad S, Ahmed J, Khan IN (2018) Association of Metronidazole with Cancer: A Potential Risk Factor or Inconsistent Deductions? Curr Drug Metab 19(11):902–909. https://doi.org/10.2174/1389200219666180329124130

Ahmed HH, El-Aziem SH, Abdel-Wahhab MA (2008) Potential role of cysteine and methionine in the protection against hormonal imbalance and mutagenicity induced by furazolidone in female rats. Toxicology 243(1–2):31–42. https://doi.org/10.1016/j.tox.2007.09.018

Ajima MN, Ogo OA, Audu BS, Ugwoegbu KC (2015) Chronic diclofenac (DCF) exposure alters both enzymatic and haematological profile of African catfish. Clarias Gariepinus Drug Chem Toxicol 38(4):383–390. https://doi.org/10.3109/01480545.2014.974108

Aleman M, Davis E, Knych H, Guedes A, Smith F, Madigan JE (2016) Drug Residues after Intravenous Anesthesia and Intrathecal Lidocaine Hydrochloride Euthanasia in Horses. J Vet Intern Med 30(4):1322–1326. https://doi.org/10.1111/jvim.14372

Aly SS, Rossow HA, Acetoze G, Lehenbauer TW, Payne M, Meyer D, Maas J, Hoar B (2014) Survey of beef quality assurance on California dairies. J Dairy Sci 97(3):1348–1357. https://doi.org/10.3168/jds.2013-6856

Andreozzi L, Giannetti A, Cipriani F, Caffarelli C, Mastrorilli C, Ricci G (2019) Hypersensitivity reactions to food and drug additives: problem or myth? Acta Biomed 90(3-S):80–90. https://doi.org/10.23750/abm.v90i3-S.8168

Aoki Y, Hakamata H, Igarashi Y, Uchida K, Kobayashi H, Hirayama N, Kotani A, Kusu F (2009) Simultaneous determination of azaperone and azaperol in animal tissues by HPLC with confirmation by electrospray ionization mass spectrometry. J Chromatogr B. Analyt Technol Biomed Life Sci 877(3):166–172. https://doi.org/10.1016/j.jchromb.2008.11.047

Aroeira CN, Feddern V, Gressler V, Molognoni L, Daguer H, Dalla Costa OA, de Lima GJMM, Contreras-Castillo CJ (2019) Determination of ractopamine residue in tissues and urine from pig fed meat and bone meal. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 36:424–433. https://doi.org/10.1080/19440049.2019.1567942

Astiz M, de Alaniz MJ, Marra CA (2009) Effect of pesticides on cell survival in liver and brain rat tissues. Ecotoxicol Environ Saf 72(7):2025–2032. https://doi.org/10.1016/j.ecoenv.2009.05.001

AVMA (2020) Guidelines for the Euthanasia of Animals: 2020 Edition. Copyright © 2020 by the American Veterinary Medical Association 1931 N. Meacham Road Schaumburg, IL 60173. https://www.avma.org/sites/default/files/2020-01/2020-Euthanasia-Final-1-17-20.pdf

Bacanli M, Başaran N (2019) Importance of antibiotic residues in animal food. Food Chem Toxicol 125:462–466. https://doi.org/10.1016/j.fct.2019.01.033

Bacila DM, Feddern V, Mafra LI, Scheuermann GN, Molognoni L, Daguer H (2017) Current research, regulation, risk, analytical methods and monitoring results for nicarbazin in chicken meat: A perspective review. Food Res Int 99(Pt 1):31–40. https://doi.org/10.1016/j.foodres.2017.07.011

Bae S, Choi S, Kim B, Lee Y, Oh T (2013) Efficacy of enrofloxacin and silver sulfadiaznine topical otic suspension for the treatment of canine otitis externa. J Vet Clin 30(3): 172–177. https://www.koreascience.or.kr/article/JAKO201321353692498.page

Banach JL, Hoek-van den Hil EF, van der Fels-Klerx HJ (2020) Food safety hazards in the European seaweed chain. Compr Rev Food Sci Food Saf 19(2):332–364. https://doi.org/10.1111/1541-4337.12523

Barbosa J, Cruz C, Martins J, Silva JM, Neves C, Alves C, Ramos F, Da Silveira MI (2005) Food poisoning by clenbuterol in Portugal. Food Addit Contam 22(6):563–566. https://doi.org/10.1080/02652030500135102

Barone G, Storelli A, Quaglia NC, Dambrosio A, Garofalo R, Chiumarulo R, Storelli MM (2019) Dioxin and PCB residues in meats from Italy: Consumer dietary exposure. Food Chem Toxicol 133:110717. https://doi.org/10.1016/j.fct.2019.110717

Barreto F, Ribeiro C, Hoff RB, Costa TD (2017) A simple and high-throughput method for determination and confirmation of 14 coccidiostats in poultry muscle and eggs using liquid chromatography - quadrupole linear ion trap - tandem mass spectrometry (HPLC-QqLIT-MS/MS): Validation according to European Union 2002/657/EC. Talanta 168:43–51. https://doi.org/10.1016/j.talanta.2017.02.007

Bencko, V, & Foong, F Y L (2017) The history of arsenical pesticides and health risks related to the use of Agent Blue. Ann Agric Environ Med 24(2):312–316. https://doi.org/10.26444/aaem/74715

Beyene T (2016) Veterinary Drug Residues in Food-animal Products: Its Risk Factors and Potential Effects on Public Health. J Veterinar Sci Technol 7(1):285. https://doi.org/10.4172/2157-7579.1000285

Beyene T, Kemal A, Jibat T, Tadese F, Ayana D, Feyisa A (2015) Assessment on Chemicals and Drugs Residue in Dairy and Poultry Products in Bishoftu and Modjo. Central Ethiopia J Nutr Food Sci S13:S13002. https://doi.org/10.4172/2155-9600.1000S13002

Bilal M, Iqbal HMN (2019) Persistence and impact of steroidal estrogens on the environment and their laccase-assisted removal. Sci Total Environ 690:447–459. https://doi.org/10.1016/j.scitotenv.2019.07.025

Bilandžić N, Dolenc J, Gačnik KŠ, Varenina I, Kolanović BS (2013) Feed additives diclazuril and nicarbazin in egg and liver samples from Croatian farms. Food Addit Contam Part b, Surveill 6(2):90–97. https://doi.org/10.1080/19393210.2012.727474

Bladek T, Szymanek-Bany I, Posyniak A (2020) Determination of Polypeptide Antibiotic Residues in Food of Animal Origin by Ultra-High-Performance Liquid Chromatography-Tandem Mass Spectrometry. Molecules 25(14):3261. https://doi.org/10.3390/molecules25143261

Boland MJ, Rae AN, Vereijken JM, Meuwissen MPM, Fischer ARH, van Boekel MAJS, Rutherfurd SM, Gruppen H, Moughan PJ, Hendriks WH (2013) The future supply of animal-derived protein for human consumption. Trends Food Sci Technol 29(1):62–73. https://doi.org/10.1016/j.tifs.2012.07.002

Busatto Z, de França WG, Cyrino JEP, Paschoal JAR (2018) Assessment of elimination profile of albendazole residues in fish. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 35(1):77–85. https://doi.org/10.1080/19440049.2017.1400186

Callaway R, Lillehoj H, Chuanchuen R, Gay CG (2021) Alternatives to antibiotics: a symposium on the challenges and solutions for animal health and production. Antibiotics 10(5):471. https://doi.org/10.3390/antibiotics10050471

Campbell HM, Armstrong JF (2007) Determination of zearalenone in cereal grains, animal feed, and feed ingredients using immunoaffinity column chromatography and liquid chromatography: Interlaboratory study. J AOAC Int 90(6):1610–1622. https://doi.org/10.1093/jaoac/90.6.1610

Canada gov (2018) List of Maximum Residue Limits (MRLs) for Veterinary Drugs in Foods - https://www.canada.ca/en/health-canada/services/drugs-health-products/veterinary-drugs/maximum-residue-limits-mrls/list-maximum-residue-limits-mrls-veterinary-drugs-foods.html

Cardona R, Santamaría L, Guevara-Saldaña L, Calle A (2021) Hypersensitivity to β-lactam antibiotics: algorithms of management and desensitization as a vital therapeutic alternative. Rev Alerg Mex. 68(1):35–47. Spanish. https://doi.org/10.29262/ram.v68i1.892 .

CFIA (Canadian Food Inspection Agency) (2014) Chemical residues. In: Meat hygiene manual of procedures: chapter 5-sampling and testing procedures. Meat Hyg. Dir. Canada: Russell A. Farrow Limited. http://www.inspection.gc.ca/food/meat-and-poultry-products/manual-of-procedures/chapter-5/eng/1395150894222/1395150895519?chap=2.

Chaccour CJ, Ngha'bi K, Abizanda G, Irigoyen Barrio A, Aldaz A, Okumu F, Slater H, Del Pozo JL, Killeen G (2018) Targeting cattle for malaria elimination: marked reduction of *Anopheles arabiensis* survival for over six months using a slow-release ivermectin implant formulation. Parasit Vectors 11:287. https://doi.org/10.1186/s13071-018-2872-y

Chang GR (2017) Surveys on Banned Veterinary Drugs Residues in Marine Bivalves and Gastropods in Taiwan between 2010 and 2015: A Mini Review. J Aquat Pollut Toxicol 1(1):16. http://www.imedpub.com/aquatic-pollution-and-toxicology

Chang GR, Chen HS, Lin FY (2016) Analysis of banned veterinary drugs and herbicide residues in shellfish byliquid chromatography-tandem mass spectrometry (LC/MS/MS) and gaschromatography-tandem mass spectrometry (GC/MS/MS). Mar Pollut Bull 113:579–584. https://doi.org/10.1016/j.marpolbul.2016.08.080

Chen D, Liu S, Zhang M, Li S, Wang J (2018a) Comparison of the occurrence of antibiotic residues in two rural ponds: implication for ecopharmacovigilance. Environ Monit Assess 190(9):539. https://doi.org/10.1007/s10661-018-6883-0

Chen L, Wang B, Diao Z, Zhao M, Xie K, Zhang P, Wang X, Zhang T, Wang J (2019) Development and Validation of an HPLC-ESI/MS/MS Method for the Determination of Amoxicillin, Its Major Metabolites, and Ampicillin Residues in Chicken Tissues. Molecules 24(14):2652. https://doi.org/10.3390/molecules24142652

Chen M, Liu C, Wang M, Wang H, Zhang K, Zheng Y, Yu Z, Li X, Guo W, Li N, Meng Q (2017) Clenbuterol Induces Cell Cycle Arrest in C2C12 Myoblasts by Delaying p27 Degradation through β-arrestin 2 Signaling. Int J Biol Sci 13(10):1341–1350. https://doi.org/10.7150/Fijbs.17948

Chen MW, Santos HM, Que DE, Gou YY, Tayo LL, Hsu YC, Chen YB, Chen FA, Chao HR, Huang KL (2018b) Association between Organochlorine Pesticide Levels in Breast Milk and Their Effects on Female Reproduction in a Taiwanese Population. Int J Environ Res Public Health 15(5):931. https://doi.org/10.3390/ijerph15050931

Cheng W, Li J, Wu Y, Xu L, Su C, Qian Y, Zhu YG, Chen H (2016) Behavior of antibiotics and antibiotic resistance genes in eco-agricultural system: A case study. J Hazard Mater 304:18–25. https://doi.org/10.1016/j.jhazmat.2015.10.037

Chiesa LM, Nobile M, Ceriani F, Malandra R, Arioli F, Panseri S (2019) Risk characterisation from the presence of environmental contaminants and antibiotic residues in wild and farmed salmon from different FAO zones. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 36(1):152–162. https://doi.org/10.1080/19440049.2018.1563723

Chiesa LM, Panseri S, Nobile M, Ceriani F, Arioli F (2018a) Distribution of POPs, pesticides and antibiotic residues in organic honeys from different production areas. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 35(7):1340–1355. https://doi.org/10.1080/19440049.2018.1451660

Chiesa LM, Shih-Kuo L, Ceriani F, Panseri S, Arioli F (2018b) Levels and distribution of PBDEs and PFASs in pork from different European countries. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 35(12):2414–2423. https://doi.org/10.1080/19440049.2018.1540889

Chirollo C, Vassallo A, Dal Piaz F, Lamagna B, Tortora G, Neglia G, De Tommasi N, Severino L (2018) Investigation of the Persistence of Penicillin G and Dihydrostreptomycin Residues in Milk of Lactating Buffaloes (Bubalus bubalis) Using Ultra-High-Performance Liquid Chromatography and Tandem Mass Spectrometry. J Agric Food Chem 66(25):6388–6393. https://doi.org/10.1021/acs.jafc.8b00229

Choi YY (2011) International/national standards for heavy metals in food Government Laboratory (Australia), pp 1–13. https://www.govtlab.gov.hk/g/texchange/Stds%20for%20heavy%20metals.pdf

Chu YL, Chimeddulam D, Sheen LY, Wu KY (2013) Probabilistic risk assessment of exposure to leucomalachite green residues from fish products. Food Chem Toxicol 62:770–776. https://doi.org/10.1016/j.fct.2013.10.002

Cicero CE, Mostile G, Vasta R, Rapisarda V, Signorelli SS, Ferrante M, Zappia M, Nicoletti A (2017) Metals and neurodegenerative diseases. A Systematic Review Environ Res 159:82–94. https://doi.org/10.1016/j.envres.2017.07.048

Církva A, Málková I, Rejtharová M, Vernerová E, Hera A, Bureš J (2019) Residue study of nitroimidazoles depletion in chicken feathers in comparison with some other selected matrixes. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 36(8):1206–1217. https://doi.org/10.1080/19440049.2019.1627000

Collier RJ, Bauman DE (2014) Update on human health concerns of recombinant bovine somatotropin use in dairy cows. J Anim Sci 92(4):1800–1807. https://doi.org/10.2527/jas.2013-7383

Cooper KM, Whelan M, Danaher M, Kennedy DG (2011) Stability during cooking of anthelmintic veterinary drug residues in beef. Food Addit Contam 28(2):155–165. https://doi.org/10.1080/19440049.2010.542775

Cooper KM, Whyte M, Danaher M, Kennedy DG (2012) Emergency slaughter of casualty cattle increases the prevalence of anthelmintic drug residues in muscle. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 29(8):1263–1271. https://doi.org/10.1080/19440049.2012.685893

Costa MC, Bessegatto JA, Alfieri AA, Weese JS, Filho JAB, Oba A (2017) Different antibiotic growth promoters induce specific changes in the cecal microbiota membership of broiler chicken. PLoS ONE 12(2):e0171642. https://doi.org/10.1371/journal.pone.0171642

Cramer G, Solano L, Johnson R (2019) Evaluation of tetracycline in milk following extra-label administration of topical tetracycline for digital dermatitis in dairy cattle. J Dairy Sci 102(1):883–895. https://doi.org/10.3168/jds.2018-14961

Cresci GA, Bawden E (2016) Gut microbiome: what we do and don't know. Nutr Clin Pract 30(6):734–746. https://doi.org/10.1177/0884533615609899

Cruz MDBA, Fernandes MÂM, Monteiro ALG, Teles JA, Anadón A, Reyes FGR (2018) Tissue residue depletion of moxidectin in lambs (*Ovis aries*) following subcutaneous administration. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 35(7):1278–1285. https://doi.org/10.1080/19440049.2018.1465207

Cvetković D, Živković V, Lukić V, Nikolić S (2019) Sodium nitrite food poisoning in one family. Forensic Sci Med Pathol 15(1):102–105. https://doi.org/10.1007/s12024-018-0036-1

da Silva Santos N, Oliveira R, Lisboa CA, Pinto ME, J, Sousa-Moura, D, Camargo, NS, Perillo, V, Oliveira, M, Grisolia, CK Domingues, I, (2018) Chronic effects of carbamazepine on zebrafish: Behavioral, reproductive and biochemical endpoints.

Ecotoxicol Environ Saf 164:297–304. https://doi.org/10.1016/j.ecoenv.2018.08.015

Dallegrave A, Pizzolato TM, Barreto F, Bica VC, Eljarrat E, Barceló D (2018) Residue of insecticides in foodstuff and dietary exposure assessment of Brazilian citizens. Food Chem Toxicol 115:329–335. https://doi.org/10.1016/j.fct.2018.03.028

Darwish WS, Eldaly EA, El-Abbasy MT, Ikenaka Y, Nakayama S, Ishizuka M (2013) Antibiotic residues in food: the African scenario. Jpn J Vet Res 61:Suppl:S13–S22. http://hdl.handle.net/2115/52350

de Souza RB, Pestana IA, Caldas D, Azevedo LS, Almeida MG, de Souza CMM (2019) Exposure to toxic and essential trace elements through the intake of processed and meat cuts (beef and chicken) in southeastern Brazil. Environ Monit Assess 191(8):477. https://doi.org/10.1007/s10661-019-7618-6

Dervilly-Pinel G, Guérin T, Minvielle B, Travel A, Normand J, Bourin M, Royer E, Dubreil E, Mompelat S, Hommet F, Nicolas M, Hort V, Inthavong C, Saint-Hilaire M, Chafey C, Parinet J, Cariou R, Marchand P, Le Bizec B, Verdon E, Engel E (2017) Micropollutants and chemical residues in organic and conventional meat. Food Chem 232:218–228. https://doi.org/10.1016/j.foodchem.2017.04.013

Dessalew G, Beyene A, Nebiyu A, Astatkie T (2018) Effect of brewery spent diatomite sludge on trace metal availability in soil and uptake by wheat crop, and trace metal risk on human health through the consumption of wheat grain. Heliyon 4(9):e00783. https://doi.org/10.1016/j.heliyon.2018.e00783

Di S, Liu R, Chen L, Diao J, Zhou Z (2018) Selective bioaccumulation, biomagnification, and dissipation of hexachlorocyclohexane isomers in a freshwater food chain. Environ Sci Pollut Res Int 25(19):18752–18761. https://doi.org/10.1007/s11356-018-2044-9

Dickson LC, MacNeil JD, Reid J, Fesser AC (2003) Validation of screening method for residues of Sypecka using immunoaffinity chromatography and gas chromatography/mass spectrometry. J AOAC Int 86(4):631–639. https://doi.org/10.5740/jaoacint.16-0377

Eiki N, Sebola NA, Sakong BM, Mabelebele M (2021) Review on Ethnoveterinary Practices in Sub-Saharan Africa. Vet Sci 8(6):99. https://doi.org/10.3390/vetsci8060099

Elghandour MMY, Khusro A, Adegbeye MJ, Tan Z, Abu Hafsa SH, Greiner R, Ugbogu EA, Anele UY, Salem AZM (2019) Dynamic role of single-celled fungi in ruminal microbial ecology and activities. J Appl Microbiol 128(4):950–965. https://doi.org/10.1111/jam.14427

El-Makawy A, Radwan HA, Ghaly IS, El-Raouf AA (2006) Genotoxical, teratological and biochemical effects of anthelmintic drug oxfendazole Maximum Residue Limit (MRL) in male and female mice. Reprod Nutr Dev 46(2):139–156. https://doi.org/10.1051/rnd:2006007

El-Nezami H, Tam PK, Chan Y, Lau AS, Leung FC, Chen SF (2013) Impact of melamine-tainted milk on foetal kidneys and disease development later in life. Hong Kong Med J. 19:S34–S38. https://pubmed.ncbi.nlm.nih.gov/24473527/

European Commission (EU) (2013) Commission Regulation (EU) No 1275/2013 of 6 December 2013 Amending Annex I to Directive 2002/32/EC of the European Parliament and of the Council as Regards Maximum Levels for Arsenic, Cadmium, Lead, Nitrites, Volatile Mustard Oil and Harmful Botanical Impurities. Official Journal of the European Union 328:86–92. http://data.europa.eu/eli/reg/2013/1275/oj

European Commission. (2010) Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin. Official Journal of the European Union 15:1–72. ELI: http://data.europa.eu/eli/reg/2010/37(1)/oj

Fajt VR (2007) Regulation of drugs used in feedlot diets. Vet Clin North Am Food Anim Pract 23(2):299–307. https://doi.org/10.1016/j.cvfa.2007.03.001

Falowo AB, Akimoladun OF (2019) Veterinary Drug Residues in Meat and Meat Products: Occurrence, Detection and Implications. In: Veterinary Medicine and Pharmaceuticals. IntechOpen, pp:1–18. https://doi.org/10.5772/intechopen.83616

Fan J, de Lannoy IA (2014) Pharmacokinetics. Biochem Pharmacol 87(1):93–120. https://doi.org/10.1016/j.bcp.2013.09.007

FAO, F. (2017) The future of food and agriculture–Trends and challenges. Annual Report, 296. http://www.fao.org/3/i6583e/i6583e.pdf

Federico C, Palmieri C, Pappalardo AM, Ferrito V, Pappalardo M, Librando V, Saccone S (2016) Mutagenic properties of linuron and chlorbromuron evaluated by means of cytogenetic biomarkers in mammalian cell lines. Environ Sci Pollut Res Int 23(17):17018–17025. https://doi.org/10.1007/s11356-016-6867-y

Fernandes MAM, Gilaverte S, Bianchi MD, da Silva CJA, Molento MB, Reyes FGR, Monteiro ALG (2017) Moxidectin residues in tissues of lambs submitted to three endoparasite control programs. Res Vet Sci 114:406–411. https://doi.org/10.1016/j.rvsc.2017.07.010

Ferré DM, Quero AAM, Hernández AF, Hynes V, Tornello MJ, Lüders C, Gorla NBM (2018) Potential risks of dietary exposure to chlorpyrifos and cypermethrin from their use in fruit/vegetable crops and beef cattle productions. Environ Monit Assess 190:292. https://doi.org/10.1007/s10661-018-6647-x

Fidel T, Milagro R (2006) Methods for rapid detection of chemical and veterinary drug residues in animal foods. Trends Food Sci Technol 17(9):482–489. https://doi.org/10.1016/j.tifs.2006.02.002

Filazi A, Sireli UT, Dikmen BY, Aydin FG, Kucukosmanoglu AG. (2015) The effect of cooking and storage on florfenicol and florfenicol amine residues in eggs. Ital J Food Sci. 27(3):351–356. https://doi.org/10.14674/1120-1770/ijfs.v278

Florez-Cuadrado D, Moreno MA, Ugarte-Ruíz M, Domínguez L (2018) Antimicrobial Resistance in the Food Chain in the European Union. Adv Food Nutr Res 86:115–136. https://doi.org/10.1016/bs.afnr.2018.04.004

Franje CA, Chang SK, Shyu CL, Davis JL, Lee YW, Lee RJ, Chang CC, Chou CC (2010) Differential heat stability of amphenicols characterized by structural degradation, mass spectrometry and antimicrobial activity. J Pharm Biomed Anal 53(4):869–877. https://doi.org/10.1016/j.jpba.2010.06.013

Freire C, Koifman RJ, Koifman S (2015) Hematological and hepatic alterations in Brazilian population heavily exposed to organochlorine pesticides. J Toxicol Environ Health A 78(8):534–548. https://doi.org/10.1080/15287394.2014.999396

Fu G, Zhou C, Wang Y, Fang W, Zhou J, Zhao S, Ma L (2016) Effects of inducers of cytochrome P450s on enrofloxacin N-deethylation in crucian carp Carassius auratus gibelio. Environ Toxicol Pharmacol 46:188–193. https://doi.org/10.1016/j.etap.2016.07.015

Fung F, Wang HS, Menon S (2018) Food safety in the 21st century. Biomedical Journal 41(2):88–95. https://doi.org/10.1016/j.bj.2018.03.003

Gadde UD, Oh S, Lillehoj HS, Lillehoj EP (2018) Antibiotic growth promoters virginiamycin and bacitracin methylene disalicylate alter the chicken intestinal metabolome. Sci Rep 8(1):3592. https://doi.org/10.1038/s41598-018-22004-6

Gao T, Du P, Xu Z, Li X (2017) Occurrence of new psychoactive substances in wastewater of major Chinese cities. Sci Total Environ 575:963–969. https://doi.org/10.1016/j.scitotenv.2016.09.152

Gaudin V (2017) Advances in biosensor development for the screening of antibiotic residues in food products of animal origin–A comprehensive review. Biosen Bioelectron 90:363–377. https://doi.org/10.1016/j.bios.2016.12.005

Gratacós-Cubarsí M, Castellari M, Valero A, Diaz I, García-Regueiro JA (2006) Novel approach to control sulfamethazine misuse in food-producing animals by hair analysis. Food Addit Contam 239(10):981–987. https://doi.org/10.1080/02652030600781813

Guo L, Wu X, Liu L, Kuang H, Xu C (2020) Gold Immunochromatographic Assay for Rapid On-Site Detection of Lincosamide Residues in Milk, Egg, Beef, and Honey Samples. Biotechnol J 15(1):e1900174. https://doi.org/10.1002/biot.201900174

Halford B (2017) Arsenic poultry feed additive may be more problematic than believed. Chemical & Engineering News, 95(20):1–2. https://www.cheric.org/research/tech/periodicals/view.php?seq=1547928

Han X, Sheng F, Kong D, Wang Y, Pan Y, Chen M, Tao Y, Liu Z, Ahmed S, Yuan Z, Peng D (2019) Broad-spectrum monoclonal antibody and a sensitive multi-residue indirect competitive enzyme-linked immunosorbent assay for the antibacterial synergists in samples of animal origin. Food Chem 280:20–26. https://doi.org/10.1016/j.foodchem.2018.12.040

Hassan MM, El Zowalaty ME, Lundkvist Å, Järhult JD, Khan Nayem MR, Tanzin AZ, Badsha MR, Khan SA, Ashour HM (2021) Residual antimicrobial agents in food originating from animals. Trends Food Sci Technol 111:141–150. https://doi.org/10.1016/j.tifs.2021.01.075

Hassani M, Lazaro R, Perez C, Condon S, Pagan R (2008) Thermostability of oxytetracycline, tetracyclines, and doxycycline at ultrahigh temperatures. J Agric Food Chem 56(8):2676–2680. https://doi.org/10.1021/jf800008p

Heshmati A (2015) Impact of cooking procedures on antibacterial drug residues in foods: A review. J Food Qual Hazards Control 2(2):33–37. http://jfqhc.ssu.ac.ir/article-1-142-en.html

Hocquette JF, Ellies-Oury MP, Lherm M, Pineau C, Deblitz C, Farmer L (2018) Current situation and future prospects for beef production in Europe - A review. Asian-Australas J Anim Sci 31(7):1017–1035. https://doi.org/10.5713/ajas.18.0196

Hoelzer, K., Bielke, L., Blake, D. P., Cox, E., Cutting, S. M., Devriendt, B., ... & Van Immerseel, F. (2018). Vaccines as alternatives to antibiotics for food producing animals. Part 1: challenges and needs. Vet Res 49(1):1–10. https://doi.org/10.1186/s13567-018-0560-8

Hou X, Xu X, Xu X, Han M, Qiu S (2020) Application of a multiclass screening method for veterinary drugs and pesticides using HPLC-QTOF-MS in egg samples. Food Chem 309:125746. https://doi.org/10.1016/j.foodchem.2019.125746

Howard P (2017) Handbook of environmental fate and exposure data: for organic chemicals, volume III pesticides, Routledge. http://www.taylorandfrancis.com

Hu Y, Cheng H, Tao S, Schnoor JL (2019) China's Ban on Phenylarsonic Feed Additives, A Major Step toward Reducing the Human and Ecosystem Health Risk from Arsenic. Environ Sci Technol 53(21):12177–12187. https://doi.org/10.1021/acs.est.9b04296

Huang L, Shi J, Pan Y, Wang L, Chen D, Xie S, Liu Z, Yuan Z (2016) Elimination and Concentration Correlations between Edible Tissues and Biological Fluids and Hair of Ractopamine in Pigs and Goats Fed with Ractopamine-Medicated Feed. J Agric Food Chem 64(9):2012–2020. https://doi.org/10.1021/acs.jafc.6b00456

Huong B (2013) Technical regulations on mycotoxin and heavy metals MRLs in foods. GAIN Report Number: VM3070, USDA Foreign Agricuitural Service. https://apps.fas.usda.gov/newgainapi/api/report/downloadreportbyfilename?filename=Technical%20Regulations%20on%20Mycotoxin%20and%20Heavy%20Metals%20MRLs%20in%20Foods%20_Hanoi_Vietnam_12-10-2013.pdf

Jeng HA (2014) Exposure to endocrine disrupting chemicals and male reproductive health. Front Public Health 2:55. https://doi.org/10.3389/fpubh.2014.00055

Jensen PK, Wujcik CE, McGuire MK, McGuire MA (2016) Validation of reliable and selective methods for direct determination of glyphosate and aminomethylphosphonic acid in milk and urine using LC-MS/MS. J Environ Sci Health B 51(4):254–259. https://doi.org/10.1080/03601234.2015.1120619

Johnson R. (2012) U.S.-EU Poultry Dispute on the Use of Pathogen Reduction Treatments (PRTs)., Washington, DC: Congressional Research Service. https://fas.org/sgp/crs/misc/R40199.pdf

Joint FAO/WHO (2014) Codex Alimentarius Commission (CAC) Strategic plan2014–19. http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https:// workspace.fao.org/ sites/codex/Shared% 20Documents/Publications/Strategic% 20Framework/Strategic%20Plan%202014–2019/Strategic_plan_2014_2019_EN.pdf

Joint FAO/WHO (2018) Expert Committee on Food Additives, Evaluation of certain veterinary drug residues in food: eighty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives. World Health Organization. https://apps.who.int/iris/bitstream/handle/10665/259895/9789241210171-eng.pdf

Joint FAO/WHO (2020) Codex Alimentarius Commission (CAC) Strategic plan 2020–2025. http://www.fao.org/3/ca5645en/CA5645EN.pdf

Jung JY, Ahn Y, Khare S, Gokulan K, Piñeiro SA, Cerniglia CE (2018) An in vitro study to assess the impact of tetracycline on the human intestinal microbiome. Anaerobe 49:85–94. https://doi.org/10.1016/j.anaerobe.2017.12.011

Kellnerova E, Navratilova P, Borkovcova I (2015) Effect of pasteurization on the residues of tetracyclines in milk. Acta Vet Brno 83(10): 21–26. https://actavet.vfu.cz/static/images/screen/content.png?188f0546ad2e

Khalid S, Shahid M, Natasha Bibi I, Sarwar T, Shah AH, Niazi NK (2018) A Review of Environmental Contamination and Health Risk Assessment of Wastewater Use for Crop Irrigation with a Focus on Low and High-Income Countries. Int J Environ Res Public Health 15(5):895. https://doi.org/10.3390/ijerph15050895

Khan SJ, Roser DJ, Davies CM, Peters GM, Stuetz RM, Tucker R, Ashbolt NJ (2008) Chemical contaminants in feedlot wastes: concentrations, effects and attenuation. Environ Int 34(6):839–859. https://doi.org/10.1016/j.envint.2007.10.007

Kim M, Cho BH, Lim CM, Kim DG, Yune SY, Shin JY, Bong YH, Kang J, Kim MA, Son SW (2013) Chemical residues and contaminants in foods of animal origin in Korea during the past decade. J Agric Food Chem 61(10):2293–2298. https://doi.org/10.1021/jf3046297

Kim S, Covington A, Pamer EG (2017) The intestinal microbiota: antibiotics, colonization resistance, and enteric pathogens. Immunol Rev 279(1):90–105. https://doi.org/10.1111/imr.12563

Klátyik S, Bohus P, Darvas B, Székács A (2017) Authorization and Toxicity of Veterinary Drugs and Plant Protection Products: Residues of the Active Ingredients in Food and Feed and Toxicity Problems Related to Adjuvants. Front Vet Sci 4:146. https://doi.org/10.3389/fvets.2017.00146

Kong C, Wang Y, Huang Y, Yu H (2018) Multiclass screening of >200 pharmaceutical and other residues in aquatic foods by ultrahigh-performance liquid chromatography-quadrupole-Orbitrap mass spectrometry. Anal Bioanal Chem 410(22):5545–5553. https://doi.org/10.1007/s00216-018-1124-5

Laszlo N, Lanyi K, Laczay P (2018) LC-MS study of the heat degradation of veterinary antibiotics in raw milk after boiling. Food Chem 267:178–186. https://doi.org/10.1016/j.foodchem.2017.11.041

Le Bizec B, Bichon E, Deceuninck Y, Prevost S, Monteau F, Antignac JP, Dervilly-Pinel G (2011) Toward a criterion for suspect thiouracil administration in animal husbandry. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 28(7):840–847. https://doi.org/10.1080/19440049.2011.565483

Lee HJ, Cho SH, Shin D, Kang HS (2018) Prevalence of Antibiotic Residues and Antibiotic Resistance in Isolates of Chicken Meat in Korea. Korean J Food Sci Anim Resour 38(5):1055–1063. https://doi.org/10.5851/kosfa.2018.e39

Lee HS, Kim NY, Song Y, Oh GY, Jung DW, Jeong DH, Kang HS, Oh HS, Park Y, Hong JS, Koo YE (2019) Assessment of human estrogen receptor agonistic/antagonistic effects of veterinary drugs used for livestock and farmed fish by OECD in vitro stably transfected transcriptional activation assays. Toxicol in Vitro 58:256–263. https://doi.org/10.1016/j.tiv.2019.02.003

Liébano-Hernández E, González-Olvera M, Vázquez-Peláez C, Mendoza-de-Gives P, Ramírez-Vargas G, Peralta-Lailson M, Reyes-García ME, Osorio J, Sánchez-Pineda H, López-Arellano ME (2015) Benzimidazole-resistant gastrointestinal nematodes in indigenous Chiapas and Pelibuey sheep breeds from Chiapas. Mexico J Helminthol 89(1):80–85. https://doi.org/10.1017/S0022149X13000618

Liu B, Xie J, Zhao Z, Wang X, Shan X (2021) Simultaneous determination of 11 prohibited and restricted veterinary drugs and their metabolites in animal-derived foods by ultra performance liquid chromatography-tandem mass spectrometry coupled with solid phase extraction. Se Pu (chinese Journal of Chromatography) 39(4):406–414. https://doi.org/10.3724/SP.J.1123.2020.05012

Liu J, Lu W, Cui R, Sun X, Li J, Chen L (2018) Determination of organophosphorus and carbamate insecticide residues in food and water samples by solid phase extraction coupled with capillary liquid chromatography. Se Pu 36(1):30–36. https://doi.org/10.3724/SP.J.1123.2017.09023

Liu Z, Wang Y, Walsh TR, Liu D, Shen Z, Zhang R, Yin W, Yao H, Li J, Shen J (2017) Plasmid-mediated Novel blaNDM-17 Gene Encoding a Carbapenemase with Enhanced Activity in a ST48 *Escherichia coli* Strain. Antimicrob Agents Chemother 61(5):e02233-e2316. https://doi.org/10.1128/AAC.02233-16

Lockwood G (2010) Theoretical context-sensitive elimination times for inhalational anaesthetics. Br J Anaesth 104(5):648–655. https://doi.org/10.1093/bja/aeq051

Loneragan GH, Thomson DU, Scott HM (2014) Increased mortality in groups of cattle administered the β-adrenergic agonists ractopamine hydrochloride and zilpaterol hydrochloride. PLoS ONE 9:e91177. https://doi.org/10.1371/journal.pone.0091177

Lust EB, Barthold C, Malesker MA, Wichman TO (2011) Human health hazards of veterinary medications: information for emergency departments. J Emerg Med 40(2):198–207. https://doi.org/10.1016/j.jemermed.2009.09.026

Ma, F, Xu S, Tang, Z, Li Z, Zhang L (2020) Use of antimicrobials in food animals and impact of transmission of antimicrobial resistance on humans. Biosafety and Health, pp 1–7 Available online 16 September 2020 (In Press) https://doi.org/10.1016/j.bsheal.2020.09.004

Majdinasab M, Yaqub M, Rahim A, Catanante G, Hayat A, Marty JL (2017) An Overview on Recent Progress in Electrochemical Biosensors for Antimicrobial Drug Residues in Animal-Derived Food. Sensors (basel, Switzerland) 17:1947. https://doi.org/10.3390/s17091947

Manaia CM (2017) Assessing the risk of antibiotic resistance transmission from the environment to humans: non-direct proportionality between abundance and risk. Trends Microbiol 25(3):173–181. https://doi.org/10.1016/j.tim.2016.11.014

Maron DF, Smith TJ, Nachman KE (2013) Restrictions on antimicrobial use in food animal production: an international regulatory and economic survey. Global Health 9:48. https://doi.org/10.1186/1744-8603-9-48

Mei L, Cao B, Yang H, Xie Y, Xu S, Deng A (2014) Development of an immunoaffinity chromatography column for selective extraction of a new agonist phenylethylamine A from feed, meat and liver samples. J Chromatogr B Analyt Technol Biomed Life Sci 945–946:178–184. https://doi.org/10.1016/j.jchromb.2013.11.057

Mensah SE, Koudandé OD, Sanders P, Laurentie M, Mensah GA, Abiola FA (2014) Antimicrobial residues in foods of animal origin in Africa: public health risks. Rev Sci Tech 33(3):987–996, 975–986. http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.1077.2075&rep=rep1&type=pdf

Mesnage R, Defarge N, De Vendômois JS, Seralini GE (2015) Potential toxic effects of glyphosate and its commercial formulations below regulatory limits. Food Chem Toxicol 84:133–153. https://doi.org/10.1016/j.fct.2015.08.012

Mestorino N, Buldain D, Buchamer A, Gortari L, Daniele M, Marchetti ML (2017) Residue depletion of ivermectin in broiler poultry. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 34(4):624–631. https://doi.org/10.1080/19440049.2016.1278307

Mitema ES (2009) Improved management of drugs, hormones and pesticides in Africa. Onderstepoort J Vet Res 76(1):155–159. https://doi.org/10.4102/ojvr.v76i1.80

Mitrowska K, Antczak M (2017) Transfer of nitroimidazoles from contaminated beeswax to honey. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 34(4):573–581. https://doi.org/10.1080/19440049.2016.1260166

Molognoni L, Daguer H, Motta GE, Merlo TC, Lindner JD (2019) Interactions of preservatives in meat processing: Formation of carcinogenic compounds, analytical methods, and inhibitory agents. Food Res Int 125:108608. https://doi.org/10.1016/j.foodres.2019.108608

Monir HH, Fayez YM, Nessim CK, Michael AM (2021) When is it safe to eat different broiler chicken tissues after administration of doxycycline and tylosin mixture? J Food Sci 86(3):1162–1171. https://doi.org/10.1111/1750-3841.15640

More SJ (2020) European perspectives on efforts to reduce antimicrobial usage in food animal production. Ir Vet J 73:2. https://doi.org/10.1186/s13620-019-0154-4

Moreno L, Bistoletti M, Fernández H, Cantón L, Ceballos L, Cantón C, Lanusse C, Álvarez LI (2018) Albendazole treatment in laying hens: Egg residues and its effects on fertility and hatchability. J Vet Pharmacol Ther 41(5):726–733. https://doi.org/10.1111/jvp.12675

Mori Y, Kato S, Fujisawa Y, Ohnishi S, Hiraku Y, Kawanishi S, Murata M, Oikawa S (2019) Mechanisms of DNA damage induced by morin, an inhibitor of amyloid β-peptide aggregation. Free Radic Res 53(1):115–123. https://doi.org/10.1080/10715762.2018.1562179

Muli E, Kilonzo J, Dogley N, Monthy G, Kurgat J, Irungu J, Raina S (2018) Detection of Pesticide Residues in Selected Bee Products of Honeybees (Apis melllifera L.) Colonies in a Preliminary Study from Seychelles Archipelago. Bull Environ Contam Toxicol 101(4):451–457. https://doi.org/10.1007/s00128-018-2423-4

Nachman KE, Smith TJ (2015) Hormone use in food animal production: assessing potential dietary exposures and breast cancer risk. Curr Environ Health Rep 2(1):1–14. https://doi.org/10.1007/s40572-014-0042-8

Navarrete IA, Tee KAM, Unson JRS, Hallare AV (2018) Organochlorine pesticide residues in surface water and groundwater along Pampanga River. Philippines Environ Monit Assess 190(5):289. https://doi.org/10.1007/s10661-018-6680-9

Ngumbi AF, Silayo RS (2017) A cross-sectional study on the use and misuse of trypanocides in selected pastoral and agropastoral areas of eastern and northeastern Tanzania. Parasit Vectors 10:607. https://doi.org/10.1186/s13071-017-2544-3

Ni T, Peng D, Wang Y, Pan Y, Xie S, Chen D, Wang Y, Tao Y, Yuan Z (2019) Development of a broad-spectrum monoclonal antibody-based indirect competitive enzyme-linked immunosorbent assay for the multi-residue detection of avermectins in edible animal tissues and milk. Food Chem 286:234–240. https://doi.org/10.1016/j.foodchem.2019.02.011

Odetokun IA, Akpabio U, Alhaji NB, Biobaku KT, Oloso NO, Ghali-Mohammed I, Biobaku AJ, Adetunji VO, Fasina FO (2019) Knowledge of Antimicrobial Resistance among Veterinary Students and Their Personal Antibiotic Use Practices: A National Cross-Sectional Survey. Antibiotics (basel) 8(4):243. https://doi.org/10.3390/antibiotics8040243

Odore R, De Marco M, Gasco L, Rotolo L, Meucci V, Palatucci AT, Rubino V, Ruggiero G, Canello S, Guidetti G, Centenaro S, Quarantelli A, Terrazzano G, Schiavone A (2015) Cytotoxic effects of oxytetracycline residues in the bones of broiler chickens following therapeutic oral administration of a water formulation. Poult Sci 94(8):1979–1985. https://doi.org/10.3382/ps/pev141

Ogunnupebi TA, Oluyori AP, Dada AO, Oladeji OS, Inyinbor AA, Egharevba GO (2020) Promising Natural Products in Crop Protection and Food Preservation: Basis, Advances, and Future Prospects. Int J Agro 2020:8840046. https://doi.org/10.1155/2020/8840046

Ondieki GK, Ombui JN, Obonyo M, Gura Z, Githuku J, Orinde AB, Gikunju JK (2017) Antimicrobial residues and compositional quality of informally marketed raw cow milk, Lamu West Sub-County, Kenya. Pan Afr Med J 28(Suppl 1):5. https://doi.org/10.11604/pamj.supp.2017.28.1.9279.

Ortelli D, Spörri AS, Edder P (2018) Veterinary Drug Residue in Food of Animal Origin in Switzerland: A Health Concern? Chimia (aarau) 72(10):713–717. https://doi.org/10.2533/chimia.2018.713

Pandey R, Shubhashish K, Pandey J (2012) Dietary intake of pollutant aerosols via vegetables influenced by atmospheric deposition and wastewater irrigation. Ecotoxicol Environ Saf 76(2):200–208. https://doi.org/10.1016/j.ecoenv.2011.10.004

Parr MK, Blokland MH, Liebetrau F, Schmidt AH, Meijer T, Stanic M, Sterk SS (2016) Distinction of clenbuterol intake from drug or contaminated food of animal origin in a controlled administration trial - The potential of enantiomeric separation for doping control analysis. Food Addit Contam Part A 34(4):525–535. https://doi.org/10.1080/19440049.2016.1242169

Patel D, Walker M (2004) Semi-solid cultured dairy products: Principles and applications. In: Hui Y.H., (editor), Chandan R.C., Clak S., Cross N., Dobbs J., Hurst W.J., Nollet L.M., Shimoni E., Sinha N., Smith E.B., Suripat S., Tilchenal A., Toldra F. (Associate editors). Handbook of Food Products Manufacturing John Wiley & Sons, Inc., New York, NY, Volume 2, Chapter 6, pp. 113–124.

Patel T, Marmulak T, Gehring R, Pitesky M, Clapham MO, Tell LA (2018) Drug residues in poultry meat: A literature review of commonly used veterinary antibacterials and anthelmintics used in poultry. J Vet Pharmacol Ther 41(6):761–789. https://doi.org/10.1111/jvp.12700

Payne J, Farris R, Parker G, Bonhotal J, Schwarz M (2015) Quantification of sodium pentobarbital residues from equine mortality compost piles. J Anim Sci 93(4):1824–1829. https://doi.org/10.2527/jas.2014-8193

Pereira RVV, Carroll LM, Lima S, Foditsch C, Siler JD, Bicalho RC, Warnick LD (2018) Impacts of feeding preweaned calves milk containing drug residues on the functional profile of the fecal microbiota. Sci Rep 8:554. https://doi.org/10.1038/s41598-017-19021-2

Pierrard MA, Kestemont P, Delaive E, Dieu M, Raes M, Silvestre F (2012) Malachite green toxicity assessed on Asian catfish primary cultures of peripheral blood mononuclear cells by a proteomic analysis. Aquat Toxicol 114–115:142–152. https://doi.org/10.1016/j.aquatox.2012.02.020

Piluzza G, Vrdis S, Serralutzu F, Bullitta S (2015) Uses of plants, animal and mineral substances in Mediterranean ethno-veterinary practices for the care of small ruminants. J Ethnopharmacol 168:87–99. https://doi.org/10.1016/j.jep.2015.03.056

Poma G, Sales C, Bruyland B, Christia C, Goscinny S, Van Loco J, Covaci A (2018) Occurrence of organophosphorus flame retardants and plasticizers (PFRs) in Belgian foodstuffs and estimation of the dietary exposure of the adult population. Environ Sci Technol 52(4):2331–2338. https://doi.org/10.1021/acs.est.7b06395

Praveena SM, Rashid MZM, Nasir FAM, Yee WS, Aris AZ (2019) Occurrence and potential human health risk of pharmaceutical residues in drinking water from Putrajaya (Malaysia). Ecotoxicol Environ Saf 180:549–556. https://doi.org/10.1016/j.ecoenv.2019.05.051

Raherison C, Baldi I, Pouquet M, Berteaud E, Moesch C, Bouvier G, Canal-Raffin M (2019) Pesticides Exposure by Air in Vineyard Rural Area and Respiratory Health in Children: A pilot study. Environ Res 169:189–195. https://doi.org/10.1016/j.envres.2018.11.002

Rakotoharinome M, Pognon D, Randriamparany T, Ming JC, Idoumbin JP, Cardinale E, Porphyre V (2014) Prevalence of antimicrobial residues in pork meat in Madagascar. Trop Anim Health Prod 46(1):49–55. https://doi.org/10.1007/s11250-013-0445-9

Rana MS, Lee SY, Kang HJ, Hur SJ (2019) Reducing Veterinary Drug Residues in Animal Products: A Review. Food Sci Anim Resour. 39(5):687–703. 10.5851%2Fkosfa.2019.e65

Ranganathan V (2017) Ethno veterinary practices for combating antimicrobial resistance. Int J Sci Environ Technol (Tehran) 6(1):840–844. http://www.ijset.net/journal/1613.pdf

Reimschuessel R (2014) Residue Avoidance in Aquaculture Production Systems. In: Baynes, R.E. (ed.) & Riviere, J.E. (ed.) Strategies for Reducing Drug and Chemical Residues in Food Animals. John Wiley & Sons, Inc., Hoboken, New Jersey, pp:161–191, 1st Publisher 11 August 2014. https://doi.org/10.1002/9781118872819.ch10

Rice D N, Wallen S, Nitzel D (1984) Nebraska's residue avoidance program report: reducing antibiotic residues in meat and milk. In Annual meeting-National Mastitis Council, Inc (USA). https://agris.fao.org/agris-search/search.do?recordID=US8628558

Riviere JE, Tell LA, Baynes RE, Vickroy TW, Gehring R (2017) Guide to FARAD resources: historical and future perspectives. J Am Vet Med Assoc 250(10):1131–1139. https://doi.org/10.2460/javma.250.10.1131

Rodrigues G, Maximiano MR, Franco OL (2021) Antimicrobial peptides used as growth promoters in livestock production. Appl Microbiol Biotechnol 105(19):7115–7121. https://doi.org/10.1007/s00253-021-11540-3

Romero T, Althaus R, Moya VJ, Beltrán MDC, Reybroeck W, Molina MP (2017) Albendazole residues in goat's milk: Interferences in microbial inhibitor tests used to detect antibiotics in milk. J Food Drug Anal 25(2):302–305. https://doi.org/10.1016/j.jfda.2016.08.007

Rozanska H, Osek J (2013) Stability of antibiotics in milk samples during storage. Bull Vet Inst Pulawy 57(3):347–349. https://doi.org/10.2478/bvip-2013-0060

Russell SL, Gold MJ, Reynolds LA, Willing BP, Dimitriu P, Thorson L, Redpath SA, Perona-Wright G, Blanchet MR, Mohn WW, Finlay BB, McNagny KM (2015) Perinatal antibiotic-induced shifts in gut microbiota have differential effects on inflammatory lung diseases. J Allergy Clin Inmunol 135(1):100–109. https://doi.org/10.1016/j.jaci.2014.06.027

Shimohata T, Hirota K, Takahashi H, Nishizawa M (2015) Clinical aspects of the Niigata Minamata disease. Brain Nerve 67(1):31–38. https://doi.org/10.11477/mf.1416200084

Schediwy M, Mevissen M, Demuth D, Kupper J, Naegeli H (2015) New causes of animal poisoning in Switzerland. Schweiz Arch Tierheilkd 157(3):147–152. https://doi.org/10.17236/sat00011
Silano M, Silano V (2017) Food and feed chemical contaminants in the European Union: Regulatory, scientific, and technical issues concerning chemical contaminants occurrence, risk assessment, and risk management in the European Union. Crit Rev Food Sci Nutr 57(10):2162–2217. https://doi.org/10.1080/10408398.2015.1059313
Singh AK, Bhunia AK (2019) Animal-Use Antibiotics Induce Cross-Resistance in Bacterial Pathogens to Human Therapeutic Antibiotics. Curr Microbiol 76(10):1112–1117. https://doi.org/10.1007/s00284-019-01744-2
Stephany RW (2010) Hormonal growth promoting agents in food producing animals. Handb Exp Pharmacol Volume 195:355–367. Springer, Berlin, Heidelberg.https://doi.org/10.1007/978-3-540-79088-4_16
Sugano K, Terada K (2015) Rate- and Extent-Limiting Factors of Oral Drug Absorption: Theory and Applications. J Pharm Sci 104(9):2777–2788. https://doi.org/10.1002/jps.24391
Suzuki S, Pruden A, Virta M, Zhang T (2017) Antibiotic Resistance in Aquatic Systems Front Microbiol 8:14. https://doi.org/10.3389/fmicb.2017.00014
Szpyrka E (2015) Assessment of consumer exposure related to improper use of pesticides in the region of southeastern Poland. Environ Monit Assess 187(1):4140. https://doi.org/10.1007/s10661-014-4140-8
Tahrani L, Van Loco J, Anthonissen R, Verschaeve L, Ben Mansour H, Reyns T (2017) Identification and risk assessment of human and veterinary antibiotics in the wastewater treatment plants and the adjacent sea in Tunisia. Water Sci Technol 76(11):3000–3021. https://doi.org/10.2166/wst.2017.465
Tardieu D, Travel A, Metayer JP, Le Bourhis C, Guerre P (2019) Fumonisin B1, B2 and B3 in Muscle and Liver of Broiler Chickens and Turkey Poults Fed with Diets Containing Fusariotoxins at the EU Maximum Tolerable Level. Toxins (basel) 11(10):590. https://doi.org/10.3390/toxins11100590
Teng M, Qi S, Zhu W, Wang Y, Wang D, Dong K, Wang C (2018) Effects of the bioconcentration and parental transfer of environmentally relevant concentrations of difenoconazole on endocrine disruption in zebrafish (Danio rerio). Environ Pollut 233:208–217. https://doi.org/10.1016/j.envpol.2017.10.063
Thai PK, Binh VN, Nhung PH, Nhan PT, Hieu NQ, Dang NT, Tam NKB, Anh NTK (2018) Occurrence of antibiotic residues and antibiotic-resistant bacteria in effluents of pharmaceutical manufacturers and other sources around Hanoi. Vietnam Sci Total Environ 645:393–400. https://doi.org/10.1016/j.scitotenv.2018.07.126
Tian L, Khalil S, Bayen S (2017) Effect of thermal treatments on the degradation of antibiotic residues in food. Crit Rev Food Sci Nutr 57(17):3760–3770. https://doi.org/10.1080/10408398.2016.1164119
Toutain PL, Ferran A, Bousquet-Mélou A (2010) Species differences in pharmacokinetics and pharmacodynamics. In: Comparative and Veterinary Pharmacology, Springer, Berlin, Heidelberg, pp. 19–48. https://doi.org/10.1007/978-3-642-10324-7_2
Toutain PL, Ferran AA, Bousquet-Melou A, Pelligand L, Lees P (2016) Veterinary medicine needs new green antimicrobial drugs. Front Microbiol 7:1196. https://doi.org/10.3389/fmicb.2016.01196
Tran M, Malarvannan G, Hoang TL, Nguyen VH, Covaci A, Elskens M (2019) Occurrence of organochlorine pesticides and polychlorinated biphenyls in sediment and fish in Cau Hai lagoon of Central Vietnam: Human health risk assessment. Mar Pollut Bull 141:521–528. https://doi.org/10.1016/j.marpolbul.2019.03.006
Trevisani M, Diegoli G, Fedrizzi G (2014) Public Health Hazards: C. Chemical Hazards and their Control. Meat Inspection and Control in the Slaughterhouse, Chichester, Wiley Blackwell 2014:354–384. https://doi.org/10.1002/9781118525821.ch13c
Tsiboukis D, Sazakli E, Gortzi O, Hadjichristodoulou C, Matara C, Leotsinidis M (2010) Assessing quality of raw milk in southern Greece in the aspect of certain benzimidazole residues. Food Addit Contam Part b, Surveill 3(2):73–79. https://doi.org/10.1080/19440049.2010.487877
Tufa TB, Gurmu F, Beyi AF, Hogeveen H, Beyene TJ, Ayana D, Woldemariyam FT, Hailemariam E, Gutema FD, Stegeman JA (2018) Veterinary medicinal product usage among food animal producers and its health implications in Central Ethiopia. BMC Vet Res 14(1):409. https://doi.org/10.1186/s12917-018-1737-0
Unyimadu JP, Osibanjo O, Babayemi JO (2019) Concentration and Distribution of Organochlorine Pesticides in Sediments of the Niger River. Nigeria J Health Pollut 9:190606. https://doi.org/10.5696/2156-9614-9.22.190606
Uraipong C, Allan RD, Li C, Kennedy IR, Wong V, Lee NA (2018) 17β-Estradiol residues and estrogenic activities in the Hawkesbury River, Australia. Ecotoxicol Environ Saf 164:363–369. https://doi.org/10.1016/j.ecoenv.2018.08.013
Van Boeckel TP, Brower C, Gilbert M, Grenfell BT, Levin SA, Robinson TP, Teillant A, Laxminarayan R (2015) Global trends in antimicrobial use in food animals. Proc Natl Acad Sci USA 112:5649–5654. https://doi.org/10.1073/pnas.1503141112
Van Huis, A., Van Itterbeeck, J., Klunder, H., Mertens, E., Halloran, A., Muir, G., & Vantomme, P. (2013). Edible insects: future prospects for food and feed security (No. 171). Food and Agriculture Organization of the United Nations. http://www.fao.org/3/i3253e/i3253e.pdf
Velusamy V, Arshak K, Korostynska O, Olivia K, Adley C (2010) An overview of foodborne pathogen detection: In the perspective of biosensors. Biotechnol Adv 28(2):233–254. https://doi.org/10.1016/j.biotechadv.2009.12.004
Verdon E, Fuselier R, Hurtaud-Pessel D, Couëdor P, Cadieu N, Laurentie M (2000) Stability of penicillin antibiotic residues in meat during storage. Ampicillin J Chromatogr a 882(1–2):135–143. https://doi.org/10.1016/S0021-9673(00)00065-0
Verma NP, Dhannidevi Sinha B, Patry AS (2017) Role of microorganisms for the sustainable use of soil pollution abutment in agriculture lands. Int J Curr Microbiol App Sci 6(11):335–350. https://doi.org/10.20546/ijcmas.2017.611.038
Vickroy TW, Baynes RE, Tell L, Riviere JE (2014) The Food animal residue avoidance databank: an example of risk management of veterinary drug residues. In: Baynes, R.E. (ed.) & Riviere, J.E. (ed.) Strategies for Reducing Drug and Chemical Residues in Food Animals. John Wiley & Sons, Inc., Hoboken, New Jersey, pp: 289–301, 1st Publisher 11 August 2014. https://doi.org/10.1002/9781118872819.ch14
Vishnuraj MR, Kandeepan G, Rao KH, Chand S, Kumbhar V (2016) Occurrence, public health hazards and detection methods of antibiotic residues in foods of animal origin: A comprehensive review. Cogent Food Agric 2(1):1235458. https://doi.org/10.1080/23311932.2016.1235458
Vivienne EE, Josephine OO, Anaelom NJ (2018) Effect of temperature (cooking and freezing) on the concentration of oxytetracycline residue in experimentally induced birds. Vet World. 11(2):167–171. https://doi.org/10.14202/vetworld.2018.167-171
Walsh TR, Wu Y (2016) China bans colistin as a feed additive for animals. Lancet Infect Dis 16(10):1102–1103. https://doi.org/10.1016/S1473-3099(16)30329-2
Wang JH, Wang Y, Du LQ, Xu C, Liu Q (2019) Study on genomic stability of male workers in an e-waste dismantling area in Tianjin. Zhonghua Yu Fang Yi Xue Za Zhi [chinese Journal of Preventive Medicine] 53(4):371–375. https://doi.org/10.3760/cma.j.issn.0253-9624.2019.04.008

Wang L, Zhang Q, Yan Z, Tan Y, Zhu R, Yu D, Yang H, Wu A (2018) Occurrence and quantitative risk assessment of twelve mycotoxins in eggs and chicken tissues in China. Toxins 10(11):477. https://doi.org/10.3390/toxins10110477

Wang M, Ren P, Liu H, Dai X (2021) Investigating antibiotics, antibiotic resistance genes in soil, groundwater and vegetables in relation to agricultural field - Applicated with lincomycin mycelial residues compost. Sci Total Environ 777:146066. https://doi.org/10.1016/j.scitotenv.2021.146066

Wang Q, Wang G, Xi C, Li X, Chen D, Tang B, Zhang L, Zhao H (2014) Simultaneous determination of zeranols and chloramphenicol in foodstuffs of animal origin by combination immunoaffinity column clean-up and liquid chromatography-tandem mass spectrometry. Se Pu 32(6):640–646. https://doi.org/10.3724/sp.j.1123.2014.01031

Wang Y, Kannan K (2018) Concentrations and dietary exposure to organophosphate esters in foodstuffs from Albany, New York. United States J Agric Food Chem 66(51):13525–13532. https://doi.org/10.1021/acs.jafc.8b06114

Weis T (2013) The meat of the global food crisis. J Peasant Stud 40(1):65–85. https://doi.org/10.1080/03066150.2012.752357

Wen J, Wu F, Cao Y, He J, Huang Z, Huang Y, Tan W, Luo W, Lai Y (2018) Determination of chloramphenicol in propolis and propolis-derived dietary supplements by high performance liquid chromatography-tandem mass spectrometry. Se Pu 36(12):1284–1289. https://doi.org/10.3724/SP.J.1123.2018.08012

WHO, World Health Organization (2017) Guidelines on Use of Medically Important Antimicrobials in Food-producing Animals. Available from: http://apps.who.int/iris/bitstream/handle/10665/258970/9789241550130-eng.pdf;jsessionid=FD58B9CED3B23E51C59F325F08A89DEF

Wilson JS, Otsuki T, Majumdsar B (2003) Balancing food safety and risk: do drug residue limits affect international trade in beef? J Int Trade Econ Dev 12(4):377–402. https://doi.org/10.1080/0963819032000154810

Wilson J, Berntsen HF, Zimmer KE, Verhaegen S, Frizzell C, Ropstad E, Connolly L (2016) Do persistent organic pollutants interact with the stress response? Individual compounds, and their mixtures, interaction with the glucocorticoid receptor. Toxicol Lett 241:121–132. https://doi.org/10.1016/j.toxlet.2015.11.014

Wu Q, Peng D, Liu Q, Shabbir MAB, Sajid A, Liu Z, Yulian Wang Y, Yuan Z (2019) A novel microbiological method in microtiter plates for screening seven kinds of widely used antibiotics residues in milk, chicken egg and honey. Front Microbiol 10:436. https://doi.org/10.3389/fmicb.2019.00436

Yang J, Lv Y, Zhang Y, Li J, Chen Y, Liu C, Zhong J, Xiao X, Liu J, Wen G (2018) Decreased miR-17-92 cluster expression level in serum and granulocytes preceding onset of antithyroid drug-induced agranulocytosis. Endocrine 59(1):218–225. https://doi.org/10.1007/s12020-017-1481-4

Yang Q, Liu X, Zhang C, Yong K, Clifton AC, Ding H, Liu Y (2019) Pharmacokinetics and Pharmacodynamics of Gamithromycin Treatment of Pasteurella multocida in a Murine Lung Infection Model. Front Pharmacol 10:1090. https://doi.org/10.3389/fphar.2019.01090

Yao T, Du K (2020) Simultaneous determination of sulfonamides in milk: In-situ magnetic ionic liquid dispersive liquid-liquid microextraction coupled with HPLC. Food Chem 331:127342. https://doi.org/10.1016/j.foodchem.2020.127342

Yoo KH, Park DH, Abd El-Aty AM, Kim SK, Jung HN, Jeong DH, Cho HJ, Hacimüftüoğlu A, Shim JH, Jeong JH, Shin HC (2021) Development of an analytical method for multi-residue quantification of 18 anthelmintics in various animal-based food products using liquid chromatography-tandem mass spectrometry. J Pharm Anal 11(1):68–76. https://doi.org/10.1016/j.jpha.2020.03.008

You L, Li X, Xi C, Tang B, Wang G, Zhang L, Yuan Z, Zhao H (2012): Simultaneous determination of residues of six zeranols in eggs by high performance liquid chromatography with immunoaffinity cleanup column]. Se Pu 30(10):1021–1025]. https://doi.org/10.3724/sp.j.1123.2012.08016

Yu W, Zhang T, Ma M, Chen C, Liang X, Wen K, Wang Z, Shen J (2018) Highly sensitive visual detection of amantadine residues in poultry at the ppb level: A colorimetric immunoassay based on a Fenton reaction and gold nanoparticles aggregation. Anal Chim Acta 1027:130–136. https://doi.org/10.1016/j.aca.2018.04.035

Zhang K, Tang C, Meng Q, Du W, Bo T, Zhao Q, Liang X, Liu S, Zhang Z, Zhang J (2017) Residues of salbutamol and identification of its metabolites in beef cattle. J Agric Food Chem 65(13):2867–2875. https://doi.org/10.1021/acs.jafc.7b00189

Zhang L, Sun J, Wang Y, Wu H, Yu S (2018) Simultaneous determination of six zeranols in milk samples by immunoaffinity solid phase extraction coupled with ultra-performance convergence chromatography-tandem mass spectrometry. Se Pu 36(6):566–572. https://doi.org/10.3724/SP.J.1123.2018.02008

Zhang, Y, Wu, Y (2002) Toxicological effects of clenbuterol in human and animals. Wei Sheng Yan Jiu (Journal of hygiene research), 31(4):328–330. https://europepmc.org/article/med/12600052

Zhao X, Wang B, Xie K, Liu J, Zhang Y, Wang Y, Guo Y, Zhang G, Dai G, Wang J (2018) Development and comparison of HPLC-MS/MS and UPLC-MS/MS methods for determining eight coccidiostats in beef. J Chromatogr B Analyt Technol Biomed Life Sci 1087–1088:98–107. https://doi.org/10.1016/j.jchromb.2018.04.044