Invited review

Health concerns and management of select veterinary drug residues

Ronald E. Baynes [a, *], Keith Dedonder [b], Lindsey Kissell [a], Danielle Mzyk [a], Tara Marmulak [c], Geof Smith [a], Lisa Tell [c], Ronette Gehring [b], Jennifer Davis [a], Jim E. Riviere [b]

[a] North Carolina State University, Raleigh NC 27607, USA
[b] Kansas State University, Manhattan, KS, USA
[c] University of California, Davis, CA 95616, USA

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ABSTRACT

The aim of this manuscript is to review the potential adverse health effects in humans if exposed to residues of selected veterinary drugs used in food-producing animals. Our other objectives are to briefly inform the reader of why many of these drugs are or were approved for use in livestock production and how drug residues can be mitigated for these drugs. The selected drugs include several antimicrobials, beta agonists, and phenylbutazone. The antimicrobials continue to be of regulatory concern not only because of their acute adverse effects but also because their use as growth promoters have been linked to antimicrobial resistance. Furthermore, nitroimidazoles and arsenicals are no longer approved for use in food animals in most jurisdictions. In recent years, the risk assessment and risk management of beta agonists, have been the focus of national and international agencies and this manuscript attempts to review the pharmacology of these drugs and regulatory challenges. Several of the drugs selected for this review can cause noncancer effects (e.g., penicillins) and others are potential carcinogens (e.g., nitro-imidazoles). This review also focuses on how regulatory and independent organizations manage the risk of these veterinary drugs based on data from human health risk assessments.

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* Corresponding author. College of Veterinary Medicine, North Carolina State University, 1060 William Moore Dr, Raleigh, NC, USA.
   E-mail address: Ronald_Baynes@ncsu.edu (R.E. Baynes).

1. Introduction

Risk assessment and regulation of veterinary drug residues in animal-derived food commodities, such as muscle, liver, kidney, fat, milk, and eggs, follow similar principles throughout the world. In the United States of America (USA), the Food and Drug Administration (FDA) is the regulatory body that sets maximum permitted concentrations for veterinary drug residues, known as tolerances. In the European Union (EU), the equivalent regulatory body is the European Medicines Agency (EMA), which publishes maximum residue limits (MRLs) that have been set by the Committee for Medicinal Products for Veterinary Use (CVMP). There are also independent risk assessment bodies, such as the Joint Food and Agricultural Organization/World Health Organization Expert Committee on Food Additives, (JECFA) which also recommends MRLs. JECFA advises the Codex Alimentarius Commission (CAC), which as risk manager, determines whether or not to establish international standards for residues of veterinary drugs in terms of MRLs. The term tolerance is used by the FDA while other countries and organizations use MRLs. Other developed countries that are not part of the EU develop their own MRLs. Most developing countries adopt EU or Codex MRLs. For these reasons, this review will focus on approaches adopted by the USA, EU, and Codex. Readers are advised to consult the guidance documents from these national and international agencies for details on how these tolerances and MRLs are derived. The safety evaluations of these compounds are described in public documentation provided by the USA and EU and through the JECFA reports and monographs. The FDA, EMA, and JECFA conduct similar risk assessments in their safety evaluation of veterinary drug residues as described in more detail in the next paragraph. The EU has since 2009 adopted MRLs established by CAC without requiring an additional MRL application and evaluation by EMA provided that the EU delegation at the CAC did not object to the MRLs. For the most part, the risk assessment methods are indeed very conservative by making allowance for the most sensitive member of the human population. However, when residue levels in the above food animal commodities exceed the tolerance or MRL, the consumer could develop adverse health effects. Potential adverse health effects can include allergic reactions to several antimicrobial drug classes, blood dyscrasias, carcinogenicity, and cardiovascular toxicity, to mention a few, but reflect several of the potential adverse health effects associated with exposure to the drugs selected for this review.

A residue at or below tolerance or MRL is considered safe when food at that level is consumed daily for a life-time. Derivation of the tolerance or MRL requires algorithms and several toxicological, pharmacological, and microbiological data packages which will be briefly described. This is a risk assessment process where a standard battery of safety studies in animals and/or humans as well as *in vitro* studies are used to determine the acceptable daily intake (ADI). The resulting toxicological ADI is often determined from the lowest no-observable-adverse-effect level (NOAEL) and/or lowest-observable-adverse-effect level (LOAEL) gleaned from the animal and/or human studies. These NOAELs and LOAELs are often adjusted by uncertainty factors to account for species differences (1—10 for animal to human extrapolations) and intra-species differences (1—10 for variability within a population). The ADI is then adjusted with food consumption values for various tissues (300 g for muscle, 100 g for liver, 50 g form kidney, 50 g for fat, and if a dairy approval, 1500 g for milk) to obtain MRLs or tolerance for each tissue. This requires kinetic data for each tissue and this is used to ensure that the total food basket of residues at each tissue MRL or tolerance results in less than the ADI. Different jurisdictions may use slight modifications such as allocations of ADIs in how MRLs and tolerances are calculated (Baynes et al., 1999), and a comparison is briefly discussed at the end of this review.

This paper focuses on several veterinary drugs that are (1) more likely to cause adverse health effects in humans consuming these drug residues in livestock products and/or (2) not approved or no longer approved for use in food producing animals because of their presence in food put human health at risk. We have focused on the antimicrobial drug class because they are among the most widely used drugs in the livestock industry. The drugs from this antimicrobial class that is the focus here include the penicillins, tetracyclines, aminoglycosides, sulfonamides, chloramphenicol, arsenicals, and nitroimidazoles. While there are several nonsteroidal anti-inflammatory drugs approved or used off label in food animals, this paper focuses on a nonsteroidal anti-inflammatory drug, phenylbutazone, because it is of high regulatory concern although not approved for use in food animals. The third drug class we focused on is the beta-agonists, which are known to have caused acute adverse health effects and deaths in humans following exposure to related residues in animal meat.

There are several other drug classes that are used in food-

producing animals that could result in residues but will not be presented in this review for several reasons. For example, the antiparasiticides are more widely used than many of the antimicrobials but they are very selective and their drug residues are least likely to affect human health compared to those drug classes selected for this review. The hormonal growth implants and their use in food-producing animals are a high regulatory concern and because of the disagreements between the regulators in the safety assessments (e.g., between the EU and USA), this will require a more detailed and separate review that documents the scientific merits and issues pertaining to their use, adverse effects, and risk assessment of these drugs. The EU has forbidden the use of hormonal substances as growth promoters in food producing animals and since the establishment of the EMA in 1995, there have been no request for authorization of such products (Grein and Duarte, 2014). In essence, the scope of this review is limited to those drugs and drug classes that were formerly approved or more widely used at the global level and for which there is growing scientific consensus about their judicious use in animal agriculture, potential adverse effects, and risk management steps. However, the reader should be aware that many of the adverse reactions reported in this manuscript are not from direct evidence of food related events or reported cases of consumption of food containing these drug residues. The literature is limited in relating drug exposure via food and adverse events; therefore, most of the adverse effects in the literature are from human exposure to the drug as a human medication and/or related animal and human testing.

For each drug class, we will review (1) current as well as former drug use in veterinary medicine in the US, (2) adverse health effects (cancer and non-cancer effects) in humans and specifically mention from the limited available literature where adverse events have been reported, and (3) risk management of these specific drug residues as described by the US, EU, and Codex. Our discussion on risk management of these selected drugs will be focused on regulatory status in predominantly the USA and EU with respect to its limited use in defined jurisdictions and special mention of withdrawal times where uniquely appropriate. Risk management measures can also include testing of meat and milk using screening and confirmatory tests and description of these tests for the various products is beyond the scope of this review. The reader should be aware that there are consequences in the event of residue violations; that is, residue levels that exceed the tolerance or MRL. Several of the drug classes discussed in this review are not approved or no longer approved for use in food animals in many jurisdictions although drug residue violations in livestock products have been reported.

2. Antimcirobials

2.1. Use in veterinary medicine

These antimicrobial drug classes are currently used and licensed in many jurisdictions for therapeutic indications in food animal veterinary medicine. However, some regulatory agencies no longer approve their use as growth promoters in food-producing animals. This highlights the distinction between therapeutic use which alleviates pain and suffering and growth promotion which aims to increase the rate of weight gain and improved feed efficiency thus achieving market weight in less time than if the antimicrobials were not in the feed. Because of antimicrobial resistance concerns, many countries, including those in the EU, have withdrawn approvals for their use for growth promotion since January 2006. In recent years, the FDA has also discouraged the use of these antimicrobials as growth promoters in livestock and have published plans to phase out the use of these antimicrobials as growth promoters as stated in the GFI #213 document (FDA, 2013). Because of antimicrobial resistance concerns, it is very likely in the future that only therapeutic use will be allowed in all jurisdictions and the veterinarian will be more involved in directly managing microbial infection on livestock farms to ensure the prudent use of antimicrobials. Effective Jan 1st 2017 in the USA, the veterinary feed directive (VFD) will be expanded to antibiotics used in feed for prevention control and treatment of disease and over-the-counter (OTC) sales of these drugs including those described below will not be allowed.

2.1.1. Penicillins

In the USA, there are about 27 approved penicillin products and only 6 of these require a veterinary prescription. There are currently 10 approvals available as OTC feed additives or OTC water additives. Many of these feed or water additives have therapeutic indications such as use for the treatment of erysipelas in turkeys (e.g., penicillin g potassium) or they may have indications for increased rate of weight gain and improved feed efficiency in poultry or swine (e.g., penicillin g).

2.1.2. Tetracyclines

There are approximately 122 tetracycline approvals in the USA which include various salts of tetracycline, oxytetracycline, and chlortetracycline with approximately 30 of these products approved for therapeutic use. The majority of these drugs are OTC products that may be combined with other antimicrobials such as sulfonamides and approved for use in almost all food animal species including fish and honey bees. In addition to bacterial infections, these drugs have been approved in some cases to treat *Mycoplasma* in poultry. Many of these drugs are used to control and/or treat bacterial enteritis or pneumonia and may be administered for as few as 3–5 days or as long as several weeks in feed or water.

2.1.3. Aminoglycosides

Gentamicin and neomycin make up the majority of aminoglycosides used in livestock production. In theUSA, there are about 15 gentamicin sulfate approvals and they are all OTC products. There is one product for treatment of infectious keratoconjunctivits caused by *Moraxella bovis* in cattle. Seven of the 15 products are OTC water additives for use in swine and poultry for several days, often to treat or control bacterial enteritis in piglets or young chickens and turkeys. There are also 15 neomycin approvals often used to control and treat for bacterial enteritis with about 14 approvals used as feed and water additives. One other aminoglycoside used in food animals, streptomycin, has 6 approvals, which are mostly used therapeutically in cattle and swine.

2.1.4. Sulfonamides

The sulfonamides are one of the oldest groups of antimicrobials and have been used in food animal production for over 60 years. Sulfonamides are still utilized in cattle, swine and poultry, however their use has somewhat declined in some jurisdictions in spite of this drug class being the third most commonly used antimicrobial used in food animals. A recent study across 25 European countries found that sulfonamides were the third most popular class of antimicrobials used in veterinary medicine (behind tetracyclines and penicillins) and that sulfonamides represented 11% of the total sales of veterinary antimicrobial drugs across Europe in 2011 (Grave et al., 2014). Resistance to sulfonamides has been reported for several of these drugs (Lanz et al., 2003; Gibbons et al., 2014). Oral sulfamethazine and sulfachlorpyridazine are commonly given to calves (including veal calves) with diarrhea, although there are limited efficacy data that would support this use. In the swine

industry, sulfamethazine is used in pigs as a treatment for septi-cemia and bacterial pneumonia (Riviere and Papich, 2009). Sulfa-methazine is also used in turkeys for the treatment of *Escherichia coli* and *Pasteurella multocida* (fowl cholera). Occasionally potenti-ated sulfonamides are used in very young chickens as well (for example a sulfadimethoxine/ormetroprim combination is approved in many countries). Sulfonamides are also utilized occa-sionally in the poultry industry to control coccidiosis. Use in broilers is rare as the growing cycle is generally too short to allow sufficient withdrawal intervals.

2.1.5. Chloramphenicol

Chloramphenicol is an older antibiotic that received approval from the US FDA for human use in 1950. It is not approved for use in any food producing animal and is prohibited from extra-label use in these species (FDA, 2012a). It is used in companion animal species and this antibiotic has broad-spectrum antimicrobial activity covering Gram-positive and negative organisms, anaerobes and rickettsiae. It is widely distributed into most tissues and fluids including penetrating the central nervous system, placental and mammary gland barrier (Riviere and Papich, 2009).

2.1.6. Arsenicals

Roxarsone as 3-Nitro® was approved in 1944 as the first arsenical for use in food animals. Other arsenic-based feed and water additives were approved for use in food-producing animals to improve rate of weight gain, feed efficiency, and pigmentation, as well as control and treat bacterial and coccidial infections in chickens, turkeys and swine. These products contained nitarsone, arsanilic acid, or carbarsone. These organic arsenicals are no longer approved for use in food-producing animals in most jurisdictions.

2.1.7. Nitroimidazoles

Nitroimidazoles are a class of drugs that have both antibacterial and antiprotozoal activity. These drugs are no longer approved for use in food animals. Previously, some nitroimidazoles were labeled for the treatment of histomoniasis in turkeys, swine dysentery and recommended as a treatment for trichomoniasis in bulls. Members of this drug class include: metronidazole, dimetridazole, iproni-dazole, ronidazole and tinidazole. Metronidazole is the most commonly studied compound of this group.

2.2. Adverse health effects in humans

Drug residues above the regulatory concentration in food items established by the FDA (tolerances), EMA (MRLs), or JECFA (MRLs) for the above antimicrobials could result in either allergic reactions, disruption of normal intestinal human flora in the intestine, blood dyscrasias, cancer, and/or development of antimicrobial resistance making it difficult to treat human infections. The aminoglycosides can also cause ototoxicity and nephrotoxicity, however this typi-cally occurs only with high or frequent dosing and is unlikely to be a result of oral exposure from food residues. Of these potential adverse reactions, effects on human intestinal flora and allergic reactions are most likely following oral exposure. In this context, it is important to distinguish between initial sensitization that occurs in some individuals in a naïve population exposed to an allergen (with no symptomatic reaction) and subsequent, sometimes serious, allergic reactions that occur upon re-exposure of sensitized individuals.

2.2.1. Penicillins

Approximately 4—11% of the human population are believed to be allergic to penicillin and related drugs (Dayan, 1993), therefore exposure to this drug class via food animal residues puts them at risk for developing allergic reactions that may range from minor reactions, such as a skin rash, to severe anaphylaxis. Although the true incidence/prevalence and mortality associated with drug-induced anaphylaxis is unknown in western countries, several epidemiological studies investigating penicillin and anesthetic agents given during the perioperative period showed these drugs were associated with IgE-mediated allergic anaphylaxis (Thong and Tan, 2011). The immunogenicity of the penicillins is not based on the drug itself but based on the penicilloylation of proteins after the beta-lactam ring is open. Therefore human reactions are based on penicilloylated residues in meat and milk. It is believed that 10 IU (0.6 μg) or 6 ng/ml of drug in milk can cause this reaction (EMA, 2008). This is one of the reasons why the MRL and tolerance for this drug in milk is less than this concentration in many jurisdic-tions such EU and Codex (JECFA MRL = 4 ng/ml). These levels are also applicable to amoxicillin and ampicillin, and are applicable to the penicillin parent compound although the penicillin metabolites can also cause a hypersensitive reaction in humans. In theUSA, there is a zero tolerance established for residues of penicillin and its salts in milk or any processed food in which such milk is used. However, there is a "safe level" of 5 ng/ml "Safe levels" in the USA are not and cannot be transformed into tolerances that are estab-lished for animal drugs in milk, and a "safe level" does not super-sede the tolerance of zero. While there is no evidence that exposure to legal penicillin residues in food can cause sensitization to peni-cillin, there is sufficient evidence that consumption of beef or pork products containing violative penicillin residues has caused anaphylactic reactions (Dayan, 1993; Kanny et al., 1994; Raison-Peyron et al., 2001; Gomes and Demoly, 2005). In many of these cases, the investigators were able to confirm presence of the drug in the meat consumed, and that the hypersensitivity reactions were because of benzyl penicillin and not sensitivity to the consumed meat products. Further evidence of an adverse drug reaction was found by testing patient sensitivity to penicillin (Kanny et al., 1994). Some authors have proposed the inefficiency of oral exposure for immunization (Dayan, 1993), however, there are insufficient rigorous studies to support the claim that parenteral administra-tion tends to be more sensitizing than the oral route.

2.2.2. Tetracyclines and Aminoglycosides

The immunogenicity of these two antimicrobials has not been as well studied as that of the beta-lactams, but the amino sugars appear to be important epitopes for aminoglycosides. Anaphylaxis to tetracyclines is rare compared to the beta-lactam drugs described above, however, human exposure to minocycline (a tetracycline used to treat acne) has been associated with approxi-mately 13% adverse cases of which very few were anaphylactic reactions (Goulden et al., 1996; Jang et al., 2010). Furthermore, there is no reported evidence to date of human consumption of meat or milk products containing tetracyclines or aminoglycosides having resulted in adverse reactions related to what is associated with aminoglycoside or tetracycline toxicity (Doyle, 2006). The EMA MRLs for tetracyclines and gentamicin are based on microbi-ological ADIs. These were assessments of the impact of these drugs on human intestinal microbial flora from human volunteers for tetracyclines (no induction of resistant enterobacteriacea) and only from *in vitro* data for gentamicin (MIC_{50} for the most sensitive strain) as human data was not available.

2.2.3. Sulfonamides

The authors are not aware of any reports in the published literature reporting toxicity or other adverse reactions in humans associated with consumption of animal products containing trace amounts of sulfonamides. However, adverse drug reactions in humans to sulfonamide drug exposure are common.

Approximately half of the reported cases in humans are skin reactions which can range from a mild rash to a severe toxidermia and/or epidermal toxic necrolysis (Choquet-Kastylevsky, 2002). However blood dyscrasias including hemolytic anemia, neutropenia, thrombocytopenia and pancytopenia have also been described and represent about 15% of cases associated with sulfonamide use in humans. Acute liver injuries (hepatitis) are also frequently reported in humans, however these have primarily been associated with cotrimoxazole (Choquet-Kastylevskey et al., 2002). Although the mechanisms of these reactions in humans have not been fully elucidated, an immune-mediated reaction involving reactive metabolites has been suspected in most cases. Since the risk of severe hypersensitivity reactions is considered high, many of the long-acting sulfonamides are no longer available on the market for human use. In addition, topical sulfonamide creams are considered potent contact sensitizers and their use is generally discouraged. Another concern associated with the ingestion of sulfonamides is thyroid cancer. A chronic feeding study in mice done by the National Center for Toxicological Research (NCTR) found that sulfamethazine produced a dose-dependent increase in follicular cell adenomas of the thyroid gland in both male and female mice. This increase was noted after feeding moderate to high levels of sulfamethazine for 18–24 months (Littlefield et al., 1989).

2.2.4. Chloramphenicol

Bone marrow suppression resulting in aplastic anemia is the most significant and widely recognized adverse effect associated with chloramphenicol use in humans (Eliakim-Raz et al., 2015). However, no dose relationship or threshold dose for the induction of aplastic anemia has been identified (Wongtavatchai et al., 2004). Since only a small exposure to chloramphenicol may lead to aplastic anemia, of particular importance in veterinary medicine, persons handling and administering the drug may also be at risk. A feed lot rancher died in 1981 from aplastic anemia acquired from exposure through an open wound on his hand when treating a herd of cattle for pneumonia (Settepani, 1984).

JECFA classifies chloramphenicol as genotoxic and a possible carcinogen. The limited studies available on the carcinogenicity of chloramphenicol do not allow a definitive classification of the drug.

Many animal-derived food products including milk, honey, meat from poultry, cattle and pork, fish and other seafoods have been identified as being contaminated with chloramphenicol presumably after use of chloramphenicol at therapeutic doses (EFSA, 2014). However, there are no data to implicate the presence of residues of chloramphenicol in food consumed by humans as a cause of aplastic anemia.

2.2.5. Arsenicals

While there are some organic forms of arsenic that have been found to be carcinogenic, it is the inorganic arsenic that is of greater concern in this respect. The latter is classified by the International Agency for Research on Cancer (IARC) as a known carcinogen in humans. Chronic exposure to inorganic arsenic in humans has been linked to non-cancer effects such as skin lesions, neurotoxicity, cardiovascular diseases, abnormal glucose metabolism and diabetes (EFSA, 2009). There is also a need for further evidence supporting the dose–response relationships for many of these adverse effects. EFSA also reported that the provisional tolerable weekly intake (PTWI) of 15 µg/kg b.w. established by JECFA was no longer appropriate as adverse effects had been reported at exposures lower than those reviewed by JECFA. The benchmark dose lower confidence limit values for a 1% extra risk ($BMDL_{01}$) for the relevant health endpoints, i.e. skin lesions, cancers of the skin, urinary bladder and lung, ranged from 0.3 to 8 µg/kg b.w. per day. In 2015, ESFA reported that for average and high level consumers in the EU,

exposure to inorganic arsenic in their diet is estimated to be within the range of the $BMDL_{01}$ values, and there is little or no margin of exposure, and the "*risk to some consumers cannot be excluded*" (EU, 2015). This report also lists the MRLs for inorganic arsenic in several rice products as ranging from 0.1 to 0.3 µg/kg, but no MRLs were reported for livestock products.

Until recently, it was thought that all organic arsenic consumed was excreted without transformation. Newer information has disproved this and inorganic arsenic has been detected in animals administered an organic arsenical, roxarsone (Conklin et al., 2012). Prior to this publication, the FDA performed a study in 2009 which detected higher inorganic arsenic in the livers of broiler chickens treated with the drug 3-Nitro® (roxarsone) than in untreated chickens, even after the 5 day withdrawal time associated with roxarsone (FDA, 2009). The levels of inorganic arsenic in these livers were very low (1.04 µg/kg wet weight of liver). While the actual concentration of inorganic arsenic in muscle tissue of these animals could not be determined due to technical limitations of the assay, total arsenic levels in muscle were much lower than in the liver, suggesting the amount of inorganic arsenic consumed in muscle tissue could be toxicologically insignificant. Inorganic arsenic is rapidly excreted from the body in humans, thereby decreasing adverse health potential even further. Furthermore, if humans consumed 0.1 kg of liver per day then exposure to 1.04 µg arsenic/kg liver would expose humans to 0.1 µg arsenic per day or 0.1 µg/70 kg per day or 0.0014 µg/kg b.w/day; this would be less than $BMDL_{01}$ of 0.3–9.0 µg/kg b.w. per day.

2.2.6. Nitroimidazoles

Although these drugs are no longer approved for use in food animals in the USA, Canada and the EU, they are still directly used in people without reports of cancer associated morbidity (Bendesky et al., 2002). According to the IARC, there is sufficient evidence to consider metronidazole as an animal carcinogen, but insufficient to do so for humans (Bendensky et al., 2002). Metronidazole is also used extensively in companion animal veterinary medicine for a variety of indications (Riviere and Papich, 2013).

2.3. Risk management

As described above, there are many antimicrobial approvals which can be broadly classified as therapeutic drugs, drugs used for control and prevention of disease, and until recently in theUSA, drugs that can be used as growth promoters which are often administered via water or feed additives. Many of the latter have very short withdrawal times and some may have as short as zero days withdrawal when used according to label. Irrespective of drug claims, residue violations are more likely to occur when these drugs are used (1) in an extra-label (or off-label) manner but use the withdrawal time on the label and/or (2) in a label manner but do not follow the approved withdrawal time. The dairy industries in all countries are very concerned about antimicrobial residues for the many reasons described above, therefore they employ very sensitive screening tests to ensure that the bulk tankers contain whole milk in which concentrations are below the established tolerances or MRLs for that drug in milk. Residue violations in milk for these antimicrobials have declined over last 3 decades and residue violations in meat and meat products have been declining in most western countries. In the FDA national Milk Drug Residue Sampling Survey of about 2000 dairy farms, half of the farms were a targeted group, based on history of drug residues, and the other half were the randomly selected group (FDA, 2015). Of the original 1918 milk samples that were tested for 31 different drug residues, only 1% of the samples from the targeted group had residue violations and 0.4% of the random group had residue violations. The antimicrobial

Table 1
U.S. tolerances, EU MRLs and US withdrawal times for selected drugs.

U.S. Approved drugs	U.S. Tolerance[a]	EU MRL[b]	U.S. Milk withdrawal time[a]	U.S. Meat withdrawal time[a]
Penicillins				
Benzylpenicillin (PEN-G-MAX®)	0 ppb (milk)	4 ppb (milk)	48 h (cattle)	10 days (cattle)
	5 ppb (milk safe level[c])	50 ppb (edible tissue)		
	50 ppb (meat)			
Tetracyclines				
Oxytetracycline (Liquamycin®)	300 ppb (milk)	100 ppb (milk)	96 h	28 days
	12,000 ppb (kidney)	600 ppb (kidney)	(cattle)	(cattle)
	6000 ppb (liver)	300 ppb (liver)		
	2000 ppb (meat)	100 ppb (muscle)		
Aminoglycosides				
Gentamicin (Garacin® Piglet Injection)	30 ppb (milk safe level)	100 ppb (milk)	NA	40 days (pigs)
(Gentocin® Pink Eye Spray)	400 ppb (kidney)	750 ppb (kidney)	0 days (cattle)	0 days (cattle)
	300 ppb (liver)	200 ppb (liver)		
	400 ppb (fat)	50 ppb (fat)		
	100 ppb (meat)	50 ppb (muscle)		
Sulfonamides				
Sulfamethazine (Sulmet®)	100 ppb (Edible Tissues))	100 ppb (all tissues)	NA	15 days (pigs)

[a] Obtained from Food Animal Residue Avoidance Databank; www.FARAD.org.
[b] Obtained from European Medicines Agency://www.ema.europa.eu/ema/.
[c] Safe levels are not and cannot be transformed into tolerances that are established for animal drugs and do not have the force of law of tolerances, or of binding rules.

florphenicol, was the most frequently confirmed along with 11 other drugs which were also antimicrobials. Unfortunately, none of these 12 drugs (except for gentamicin) are approved for use in lactating dairy cows. Of the antimicrobials relevant to this review, one sample contained the aminoglycoside, gentamicin.

Finally, very little is known about the partitioning of these antimicrobial drugs into the various milk fractions (e. g., whey proteins, butter fat) following processing, and whether cooking can influence the stability of these antimicrobials. Older studies have reported that chlortetracycline can be converted to iso-chlortetracyline which lacks sensitizing properties (Shirk et al., 1956) and that oxytetracyline is converted to α- and β-apooxyte-tracyclines (Katz et al., 1973) which may reduce the risk of adverse health effects to tetraccylines.

2.3.1. Sulfonamides

Historically, tissue residues from sulfonamide use in food animal species have been a major regulatory concern (Bevill, 1989). In fact, for many years this class of antimicrobial was responsible for more violative residues than any other drug. For example in 1977, 13.1% of pigs had violative sulfonamide residues detected at slaughter in the USA (Bevill, 1984). The primary reasons for the occurrence of sulfonamide residues are failure to observe the proper withdrawal time, improper feed mixing, and improper cleaning of feeding and/ or feed mixing equipment that allowed cross-contamination of feed. The electrostatic nature of sulfamethazine when used in a powdered form caused particles to adhere to contact surfaces. Therefore carryover of drug into later batches of unmedicated feed was common and resulted in residues (Cordle, 1989). Excretion of sulfamethazine in the feces and urine could also cause recontamination of the environment in swine and poultry houses and result in residues in the next group of animals when cleaning was not properly done between groups.

Regardless of no reported cases of sulfonamide-related adverse effects from food containing sulfonamides, sulfonamides remain a drug of great regulatory concern worldwide. In the United States, the extra-label use of sulfonamides have been prohibited from use in adult dairy cows, which are defined as any female greater than 20 months of age regardless of milking status (Davis et al., 2009). This prohibition was instituted due to the concern over carcinogenicity noted in rodents, coinciding with reports of sulfonamide residues detected in up to 73% of commercial milk samples. In the

swine and poultry industries, granulated forms of sulfamethazine have been developed that are less electrostatic and thus are less likely to cling to feed mixing equipment. However extreme caution is still utilized when making feeds with sulfonamides or following administration in the water. Extended withdrawal times, beyond that on the product label are also commonly used in the industry to avoid any residue issues; this is especially the case for meat and dairy products targeted for export. Pharmacometric studies in our laboratory (Buur et al., 2006; Mason et al., 2015) suggest that the labeled withdrawal time of 15 days for sulfamethazine in the USA (Table 1) should be extended at least 5—6 days to account for population variability in a swine herd.

2.3.2. Chloramphenicol

The JEFCA (JECFA, 1994; Wongtavatchai et al., 2004) was unable to determine an ADI for chloramphenicol because there was insufficient information available to establish a threshold dose for the development of aplastic anemia, assess its carcinogenicity, or reproductive toxicity. They also noted that they were unable to identify a suitable marker residue in cattle and pigs, for which the radio-depletion studies were considered inadequate. Codex (CAC, 2014) indicated in their risk management recommendations that as "*there is no safe level of residues of chloramphenicol or its metabolites in food that represents an acceptable risk to consumers, competent authorities should prevent residues of chloramphenicol in food by not using chloramphenicol in food producing animals*".

In the USA, there are no approved chloramphenicol drugs for use in livestock and the extra-label use of chloramphenicol in any food-producing animal is prohibited. There is no approved tolerance for chloramphenicol in food products and any residue detected is considered violative.

Similarly, in the EU, chloramphenicol is listed in Annex IV of Council Regulation No. 2377/90 (EEC, 1990) and revised more recently listed in Table 2 of EU documents 470/2009 and 37/2010 (EU, 2010) as a list of prohibited substances; although this list appears to be a limited list of 10 substances. Until 2005, the zero tolerance policy lead to the rejection of a number of crustacean and honey imports into the USA and the EU in the early to mid-2000s impacting international trade (Love et al., 2011; Tran et al., 2012; Wongtavatchai et al., 2004). Subsequently, the European Commission published a decision in January 2005 (Commission Decision, 2005) to no longer regulate chloramphenicol at a zero tolerance

Table 2
Chemical subcategory for each β-adrenergic agonist as defined by its aromatic substitution group. Substitution group determines the biotransformation pathway and ultimately the pharmacokinetic properties of each drug.

Category	Drug	Aromatic substitution	Biotransformation Pathway
Phenol	Ractopamine	4-OH	Conjugation
Haloaniline	Clenbuterol	3-,5-Cl; 4-NH$_2$	Conjugation and oxidation
Catechol	Zilpaterol	4-, 5-OH	Catecholamine O-methyl transferases

level. The European Commission set a minimum required performance limit (MRPL) or/reference point for action (RPA) for chloramphenicol at 0.3 µg/kg. Foods of animal origin containing residues at or above the RPA are considered to be noncompliant with EU legislation and should not be marketed. The source of contamination is then investigated. For foods containing chloramphenicol below the RPA, the cause of the contamination is investigated, but the product may still be marketed. EFSA (2014) determined that exposure to animal-derived food products contaminated with chloramphenicol at or below 0.3 µg/kg are unlikely to be a health concern for aplastic anemia or reproductive or hepatotoxic effects. It should be noted that EU 470/2009 states that setting RPAs should in no way serve as a pretext for supporting the illegal use of prohibited drugs such as chloramphenicol.

2.3.3. Arsenicals

Despite the low levels of arsenicals and the low risk for adverse human health events, drug manufacturers in the USA suspended production of these drugs for use in food animals. This is due to the Delaney Clause for new animal drugs of the US Federal Food, Drug, and Cosmetic Act, which states that the FDA cannot approve drug use in food-producing animals if the drug or its metabolites can cause cancer. There is an exception to this clause, known as the DES (diethylstilbestrol) proviso, which allows cancer-causing compounds (or compounds with cancer-causing metabolites) to be used in food-producing animals if (1) the drug does not harm the animal, and (2) tests approved by FDA do not detect residues of the drug in any food from the animal (FDA, 2012b). In 2015, the drug company voluntarily withdrew all new animal drug approvals and supplements for roxarsone, as well as arsanilic acid and carbarsone. That left only nitarsone containing products on the market in the USA. The approvals and marketing for this drug was phased out and withdrawn in Fall 2015. There is no evidence that the EU has ever approved the use of arsenicals in animal feed based on list in their Annex (EMA, 2009), which may be related to lack of science supporting health or safety standards for such use. This substance is not listed in Prohibited Substance list of Table 2 of the EU document 37/2010, however, it is left to be assumed that these substances are were and are not approved for use in food animals. Similarly, JECFA has not recommended MRLs for these arsenical substances for use in food animals; this organization has provided recommendations for contaminants in its safety assessment (CAC, 2011).

2.3.4. Nitroimidazoles

JECFA first evaluated (JECFA, 1989) heuse of nitroimidazoles in food-producing animals and there have been no major changes in their risk assessment since the first evaluation in 1989. JECFA was unable to evaluate the toxicological and residue depletion studies in food-producing animals for nitroimidazoles because relevant data were not made available to the committee. Therefore, no ADIs or MRLs were recommended by JECFA for metronidazole, dimetridazole and ipronidazole due to specific human health concerns. Thus no acceptable level of risk to the consumer could be identified and use of nitroimidazoles in food-producing species could pose significant health concerns to the consumer. The risk management recommendations from Codex are that "*competent authorities

should prevent residues of metronidazole in food, which can be accomplished by not using metronidazole in food producing animals" (CAC, 2013). In the EU, these drugs are listed as Prohibited Substances in Table 2 in the Annex of Regulation (EU) 37/2010 and indicates that MRLs cannot be established. Similarly, in the USA, no tolerance has been established for any nitroimidazole compound because there are no approved products for use in food-producing animal species and any extra-label use is strictly prohibited. In summary, there are no approvals for use of nitroimidazoles in food-producing animals in theUSA, EU, and many other OECD countries due to the risk for carcinogenesis. No ADI, tolerance limit or MRL has been established for any nitroimidazole drugs and as a result any detectable concentration would be consider a violation.

2.3.5. Tolerances and MLRs

Table 1 provides a list of drugs along with their respective US tolerance, EU MRL, and meat and milk withdrawal time for selected drugs. Sulfamethazine represents an example where there are harmonized MRLs and tolerances. However, for many drugs, there are notable differences between tolerances and MRLs for reasons related to how the risk assessment was conducted. Because of these differences, there may be differences in approved milk and/or tissue withdrawal times across jurisdictions. The reader should be reminded that there are many different formulations of any given antimicrobial drug and therefore the withdrawal times listed in Table 1 for, say, penicillin cannot be applied to all formulations of penicillin although the MRLs or tolerances apply to penicillin. These regulatory standards are used in the management of antimicrobial residues at the farm level before milk, slaughter, and further food processing.

3. Phenylbutazone

3.1. Use in veterinary medicine

Phenylbutazone (PBZ) was introduced into human medicine in 1949 as a non-steroidal anti-inflammatory drug (NSAID) for use in the treatment of acute and chronic inflammatory pain. In veterinary medicine, PBZ is currently approved for use in horses and dogs to treat pain and reduce inflammation, particularly when associated with musculoskeletal conditions including chronic laminitis and degenerative joint disease. It is not approved for use in any food-producing animal, and its labeled use in horses is limited to those not intended for food. Although PBZ is not approved, the pharmacokinetics of this drug has been described in several veterinary species, including cattle, llamas, sheep, goats, pigs, donkeys and rats (Lees et al., 2004; Lees and Toutain, 2013). Ruminant species demonstrate a prolonged elimination half-life (207 h in neonatal calves and 42–65 h in cows), allowing for prolonged dosing intervals (Arifah and Lees, 2002; Cheng et al., 1997, 1998; de Veau et al., 2002). Every other day or every third day dosing makes this an attractive drug to use for chronic pain issues in these species, but also leads to the need for prolonged withdrawal times (Smith et al., 2008). The plasma half-life is short in the horse (4.0–6.0 h), and the plasma:tissue ratio is very high (25:1 to 64:1), which suggest that for horses treated with this drug at therapeutic doses and

slaughtered for meat, the meat products are very unlikely to cause serious adverse effects described below (Lees and Toutain, 2013).

3.2. Adverse health effects in humans

There is considerable evidence in the clinical and scientific literature that indicate the most common side-effects of NSAID use, including PBZ, relate to inhibition of cyclooxygenase (COX) enzymes in the inflammatory cascade. These effects include perforation, ulceration and bleeding of the gastrointestinal tract, and uncontrolled hemorrhage leading to internal or external bleeding. Renal damage has also been reported in humans (Cuthbert, 1974; Smolinske et al., 1990).

In 2013, the presence of horse meat in beef burgers and other foods labeled as beef in Europe raised concerns that PBZ, which is widely used in horses, may be present in horses destined for slaughter and human consumption. Lees and Toutain (2013) recently reviewed the pharmacokinetics and toxicology of PBZ in humans and in horses and have estimated that daily intake for the worst case exposure scenario would result in 1/400 of a single therapeutic dose for humans. However, this review and others (Inman, 1977) described that at high doses this drug is capable of causing blood dyscrasias, including aplastic anemia, leukopenia, agranulocytosis and thrombocytopenia, and in some cases leading to death in humans. The US National Toxicology Program, part of the National Institute of Health, has demonstrated some evidence of carcinogenic activity in mice. The mice in these studies showed a chemical-related increased incidence of neoplasms (National Toxicology Program, 2015). However, IARC stated that there was inadequate evidence for a carcinogenic effect in humans (IARC, 1987).

3.3. Risk management

Although a thorough risk assessment has not been completed for PBZ due to limited data, there are public health risks (albeit not yet quantifiable) and therefore PBZ is prohibited from use in horses entering the food chain by the USA, the United Kingdom, Canada and the EU (Dodman et al., 2010; Mariani et al., 2012). The primary reasons are related to reported adverse health effects described above in adults and children since this drug was approved more than 50 years ago for humans. In 1984, the FDA began to seriously examine the use of this drug in humans and in 2003, the FDA issued an order prohibiting the extra-label use of animal and human PBZ products in female dairy cattle 20 months of age or older, due to evidence that residues of these drugs in milk could likely cause an adverse event in humans and present a significant public health risk (CFR530.41). The Food Animal Residue Avoidance Databank (FARAD) strongly discourages the use of PBZ in other dairy animals. Any extra-label use of PBZ in animals intended for human consumption in the USA carries a greatly extended withdrawal time (40—50 days after a single dose) due to a zero tolerance policy for residues in the United States (Smith et al., 2008; Mariani et al., 2012). EFSA and the EMA identified the main risks for the consumer as idiosyncratic blood dyscrasias and the genotoxic/carcinogenic potential for which no maximum residue limits could be established (EFSA, 2013). PBZ therefore should not be used in animals destined to enter the food supply.

4. Beta agonists

4.1. Use in veterinary medicine

Adrenergic agonists are sympathomimetic drugs that mimic the action of epinephrine and norepinephrine (Riviere and Papich,

2009). They act on the target cell via membrane-bound G-protein coupled receptors, and are categorized based on whether they bind to α- or β-adrenergic receptors. The adrenergic receptors are further be divided into several subclasses depending on whether they are post-synaptic (α_1) or pre-synaptic (α_2), or the tissue in which they are located (β_1, β_2). Most adrenergic drugs have some activity at both α and β receptors, however the ratio of activity varies between drugs and species.

Many tissues contain both subclasses of β receptors, however, one subtype usually predominates and provides that particular tissue with its functional classification. An over-simplification relevant to this review can be appreciated by thinking of β_1 receptors as being the most predominant receptor subtype in the heart and β_2 as being the most predominant receptor subtype present within the pulmonary and vascular smooth muscle. This fact makes the physiological outcome of potential toxicities from consuming meat containing β-adrenergic agonists (BAA) residues somewhat obvious, as will be presented later in this review.

In production agriculture systems, BAAs are used as partitioning agents in food animals, whereby they cause a modification of growth by increasing accretion of skeletal muscle and decreasing fat stores (Mersmann, 1998). Use of BAAs late in the feeding period results in consistent increases in the rate of weight gain without an increase in feed consumption, thereby increasing feed efficiency (Loneragan et al., 2014). The mechanism of action of BAAs in repartitioning of fat and muscle have been best explained as agonist action on β_2 receptors that are present in both skeletal muscle and adipocytes (Peters, 1989). The most considerable evidence supports a fat-reducing effect on the size of the adipocytes and an increase in the rate of lipolysis. Additionally, BAA use appears to cause muscle hypertrophy largely by reducing the rate of protein degradation and an increase in nitrogen retention.

Ractopamine hydrochloride was the first BAA approved by the FDA for use in theUSA, followed by zilpaterol hydrochloride. One other BAA, clenbuterol hydrochloride, is not approved for use in food animals and its extra-label use is prohibited in the USA (FDA, 2012a). Additionally, clenbuterol has been prohibited from use as a growth promoting agent worldwide (Wu et al., 2013), however, clenbuterol does have approval in some countries as a tocolytic agent in cows and as an adjunct therapeutic in respiratory disease (Rose et al., 1995; Wu et al., 2013).

4.2. Adverse health effects in humans

The first report of a drug residue contamination in animal tissue causing human harm was reported in Europe in 1990 (Martinez-Navarro, 1990). Symptoms reported included muscle tremors, cardiac palpitations, nervousness, headache, muscular pain, dizziness, nausea, vomiting, fever, and chills. Two similar outbreaks occurred the following year in Spain where 43 families were affected following consumption of liver tainted with clenbuterol residues (160—290 ppb in cooked liver samples). Sporadic outbreaks of clenbuterol toxicity have been and continue to be reported around the world, including reports from Spain, Italy, France, Portugal, and China from 1999 to 2011 (Wu et al., 2013).

In toxicology studies, the primary side effects of zilpaterol and ractopamine are those classically related to BAA, such as dose-dependent increases in heart rate and decreases in diastolic blood pressure, and they are unlikely to be carcinogenic (FDA, 1999, 2003, 2006a; WHO, 2004, 2014). In studies performed in human participants, zilpaterol exhibited a dose-dependent increase in heart rate, airway caliber, and systolic blood pressure (WHO, 2014). Ractopamine is approved for use in swine with a withdrawal time (WDT) of 0 days. All formulations of ractopamine are approved for use in cattle with a 0 day WDT, and when approved, zilpaterol had a WDT
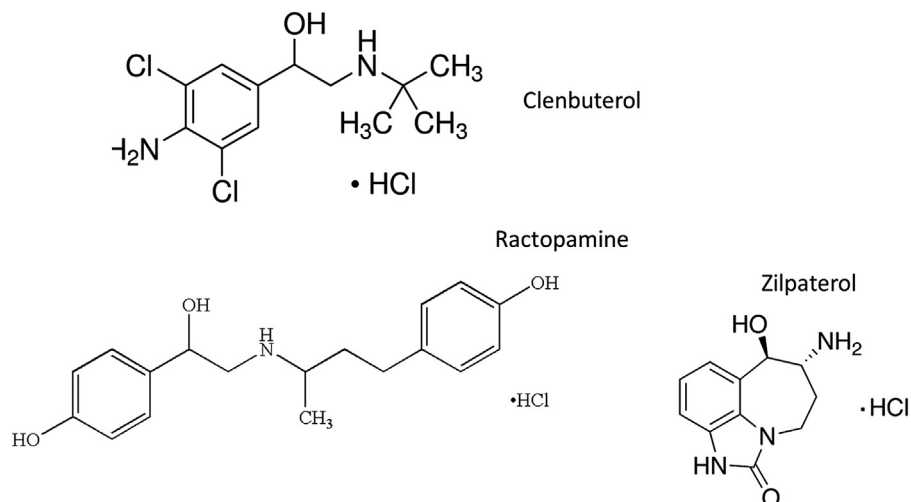
Fig. 1. Chemical structures of three β-adrenergic agonists.

of 3 days in cattle. It should be noted that there have been no reported cases of adverse health effects in humans exposed to livestock products containing zilpaterol or ractopamine residues.

While clenbuterol displays a very similar toxicity profile in humans and animals, it has physiochemical differences that have conributed to it being not approved for use in food animals in many jurisdictions. There are differences among the BAAs based on the chemical moiety substitution at the aromatic ring which can greatly affect their metabolism, distribution, and longevity within tissue (WHO, 2014; Smith, 1998). Ractopamine and zilpaterol have phenolic and catecholic moieties, respectively, whereas clenbuterol is a substance with an anilinic moiety (Table 2 and Fig. 1). Due in part to these chemical differences, residues of clenbuterol are present for longer and in a relatively higher parent compound percentage as compared to ractopamine. Catechols and phenols are rapidly deactivated by metabolism pathways and halogenated BAAs such as clenbuterol are resistant to this rapid deactivation. Clenbuterol undergoes oxidative and conjugative pathways of metabolism and has a longer plasma half-life as compared to ractopamine, which is metabolized by conjugation only, displaying a relatively shorter half-life. Furthermore, clenbuterol has displayed a relative insensitivity to heat degradation in a range of cooking processes (boiling, roasting, frying, and microwaving) (Rose, Shearer et al., 1995). Clenbuterol was stable under normal cooking conditions, remaining unaltered in cooked edible tissues with little or no leaching into external medium. Only the most extreme cooking conditions resulted in any appreciable loss of clenbuterol from cooked meat (deep frying at 160 °C for 3 min, resulting in inedible charred tissue).

4.3. Risk management

Zilpaterol was voluntarily pulled from the market by Merck Animal Health in 2013 due to animal welfare concerns and remains off the market at the time of this publication. Codex adopted MRLs for clenbuterol in 2003 and ractopamine in 2012 (CAC, 2012). At the time of this publication, Codex has not formally adopted an MRL for zilpaterol, as can be seen in Table 3; however, JECFA (2015) recently recommended MRLs for zilpaterol for liver (3.5 ppb), kidney (3.3 ppb), and muscle (0.5 ppb) while the FDA has established a tolerance for liver (12 ppb).

Clenbuterol has a long history of illegal use in theUSA, primarily in livestock show animals (Mitchell and Dunnavan, 1998). Anecdotal evidence of its use first came to the attention of meat inspection officials in 1988 and methodology development research began to detect it in liver tissue (Mitchell and Dunnavan, 1998). Following these reports, in 1991, the FDA began investigating the domestic use of clenbuterol and shortly thereafter its approval was revoked in the USA. The use of clenbuterol as a growth promoting agent in food-producing animals is not approved in almost all jurisdictions (Rose, Shearer et al., 1995; Wu et al., 2013).

5. Comparison of EU and US risk management guidance

Despite recent efforts toward harmonization of regulatory systems, there remain significant differences between how risk assessment principles are put into practice across the world. Some jurisdictions, such as Japan, monitor chemical residues in food products primarily based on limits of analytical detection rather than attempting to quantitate or classify chemical risks in food in relation to the consumer health. The focus of this brief discussion will be on the USA and EU approaches, which have been extensively reviewed elsewhere (Baynes and Riviere, 2015; Fink-Gremmels, 2012; IOM, 2012). The basis of much of this is rooted in differences between jurisdictions in applying quantitative risk allocation algorithms, as done by the USA, versus the EU's application of the precautionary principle to avoid all risk of harm when specific outcomes are possible (e.g. reproductive endpoints), or as a function of the nature of the product (e.g. hormones, growth promoters), or the technology used to create the product (e.g.

Table 3
Maximum residue limits (MRLs) for β-adrenergic agonists associated with food animal production as approved by Codex Alimentarius. All values are parts per billion (ppb).

Drug	Muscle	Kidney	Fat	Liver	Comment
Ractopamine	10	90	10	40	–
Clenbuterol	0.2	0.6	0.2	0.6	MRLs are applicable only when associated with a nationally approved therapeutic use.
Zilpaterol	0	0	0	0	–

recombinant DNA biotechnology, Genetically Modified Organisms (GMO)). These result in complete banning of certain products or significant differences in how a product is used (e.g. therapy versus prevention or growth promotion) or what concentrations are deemed safe for human consumption.

Differences in assumptions relative to dietary intake patterns (e.g. percent of diet consumed as meat or milk) modify these safe and thus allowable food concentrations. Differences exist in how slaughter withdrawal times for exposed food animals are established even after a target tissue concentration, such as a tolerance in the USA or an MRL in the EU, has been determined. For the same formulation and dosage of a drug, the concept of good veterinary practices may be applied in the EU if judged important to further adjust withdrawal times. Similarly, the FDA Guidance for Industry #3 states that the recommended withdrawal periods, if followed, should provide a high degree of assurance to the producer that the animals treated will be in compliance with applicable regulations, and be compatible with livestock management practices (FDA, 2006b).

Small differences in how a specific animal is classified may further affect regulatory processes and level of surveillance, as seen when a species such as sheep is variously regulated as a minor species in the USA and a major species in parts of the EU. In the USA, state governments do not regulate veterinary drugs since all regulations are promulgated by the FDA. In the EU, some drugs are similarly uniformly regulated across the continent, while other are restrictively regulated by individual member states.

These philosophical and procedural differences result in different MRLs and tolerances for drugs that are approved for use, and often result in certain drugs being not approved for use in different jurisdictions. Recent incidents where significant regulatory differences exist between the USA and the EU include the use of beta—agonists, such as ractopamine, hormonal growth promoters, such as zeranol, recombinant bovine somatotropin, and use of food produced using GMO. Current and future debates surround use of certain antimicrobials compounds and the emerging field of nanotechnology-derived medicines.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Transparency document

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