Volume 5 • Issue 1 • 2023

Research Article

Archives of Nutrition and Public Health

Review on Antimicrobial Residue Occurrence in Cow Milk and its Public Health Importance in Ethiopia

Hussein Mohammed Roba*

Haramaya University, School of Veterinary Medicine, Ethiopia

***Corresponding Author:** Hussein Mohammed Roba, Haramaya University, School of Veterinary Medicine, Ethiopia.

Received: January 05, 2023; **Published:** February 08, 2023

Summary

The occurrence of Antimicrobial residues in the milk of lactating cows is a matter of public health concern, since dairy products are widely consumed by infants, children and many adults throughout the world. Antimicrobial residues are small amounts of drugs or their active metabolites which remain in the tissues or products such as meat, milk and eggs from treated animals. Antimicrobial residues in milk are unimportant amounts of drugs or chemicals, which are active metabolites and remain in milk after treating lactating cows. The regulation of illegal residues in foods is a cooperative effort of Food Safety and Inspection Services, Feed and Drug Administration and Environmental Protection Agency. However, in Ethiopia not yet attention is given regarding set standards, control measures and monitoring programs of antimicrobial residues in animal originated foodstuffs. Antimicrobial residues which could contaminants cow milk are antibiotic, chlorinated pesticides, organophosphates, herbicides, fungicides, anthelminthic drugs, hormones, detergents and disinfectants, nitrites, mycotoxins, heavy metals and somatotropin hormone. Antibiotics such as Oxytetracycline, beta lactams, aminoglycosides (e.g. streptomycin, neomycin and gentamicin), macrolides (e.g. erythromycin) and sulfonamides are the source of residues. Residues enter the milk through contaminated feed and water, improper use of veterinary drugs, negligent milk withdrawal or incorrect collection and processing of milk. These residues have important public health and economic implications for the following reasons: allergic reactions, selection of resistant pathogenic and non-pathogenic bacteria, toxicity, carcinogenicity and hindrance of certain food products. The most important cause for occurrence of antimicrobial residue in animal tissues is insufficient period of time given for the drug to be eliminated from food and must be considered a practical impossibility. Therefore, the maximum residue limits (MRL) set for each antimicrobial agent should be respected. Conducting appropriate screening tests to determine residue status can aid in maintaining a safe milk supply. The overall public health impact of antimicrobial residues in milk is a public health concern and policy makers' involvement is necessary to increase detection, quantification, and control by the contribution of farmers, producers, clinicians, researchers, consumers, legislative and other food safety authorities.

Key words: *Antimicrobial Residues; Milk; Public Health*

Introduction

Milk is widely consumed throughout the world by all age groups, particularly infants, children and elderly people (Vanga and Raghavan, 2017). Globally more than 6 billion people are the consumers of milk and milk products (Silva Meneguelli et al., 2020). Milk is regarded as a complete food and a basic component of various human diets. Since, it is a balanced source of essential nutrients including protein, fat, minerals etc.(Ojha et al, 2018). Despite high nutritional values and tremendous usage, milk is reported to be contaminated with a variety of adulterants, chemical and pharmaceutical compounds (Shaikh and Patil, 2020). The occurrence of drug residues affect the quality of milk and a higher concentration than maximum permissible limits can produce significant health hazards to the consumers (Shaikh and Patil, 2020).

The Food Safety and Standards Act, 2006, describes residues of a veterinary drug as the parent compounds or their metabolites or both in any edible portion of any animal product and include residues of associated impurities of the veterinary drugs concerned (P. T. Bhoomika et al., 2019). The term food safety generally applies to food quality that can cause harmful effects in mankind and includes zoonotic diseases and adverse effects produced by xenobiotic (Shaikh and Patil, 2020). Recently, the presence of residues in milk and dairy products and their impact on public health is recognized as a matter of serious concern. Antimicrobial residues could enter the human food chain and have toxicological effects on humans (D. Kumar et al, and S. Kumar, 2018a). Infants and growing children are more susceptible than other age groups to residues given their higher consumption of milk and milk products. Antimicrobial resistance (AMR) is also a human health concern (Nougadère et al., 2020). because humans will slowly develop resistance to antibiotics that could be needed to treat human ailments (Katakweba et al, 2012). Thus, ensuring that milk and milk products are safe from antimicrobial residues is critically important. Milk production is inextricably linked to the environment.

Animals may become exposed to chemical substances during their production cycle which have been identified to date could come from drugs aimed at treating diseases or application of chemicals for the control of weeds, insects, fungi and rodents has enabled agricultural productivity and intensity to increase. These chemicals are environmental contaminants linked to atmospheric pollution, feed, soil and/or water uncontrolled processes interfering with the food delivering ecological system or with its natural compounds that lead to residues in milk and result in risk to human and environmental health. (S. Aytenfsu, G. Mamo, & B. Kebede, 2016a). Antimicrobial residues which have been or are found in milk are antibiotics, chlorinated pesticides, organophosphates, herbicides, fungicides, anthelminthic drugs, detergents and disinfectants, nitrites, polychlorinated, polybrominated biphenyls, dioxins, mycotoxins, heavy metals and somatotropin hormone. Any of these compounds may persist at collection, preparation processes of dairy products and they considered as residues (Aytenfsu et al., 2016a).

The use of antibiotics therapy to treat and prevent udder infections in cows is a key component of mastitis control in many countries. Unauthorized antibiotic use may result in residues of these substances in milk and tissues (Almashhadany, 2021). Antimicrobial residues are small amounts of drugs or their active metabolites, which remain in milk after treating the cows (Syit, 2011). Because of the public health significance, milk and milk products contaminated with antibiotics beyond a given residue levels, is considered unfit for human consumption (Aytenfsu et al., 2016a). Problems associated with antibiotic residues in milk include the risk of allergic reactions, aplasia of the bone marrow, carcinogen and increased resistance of pathogens towards antibiotics (Aytenfsu et al., 2016a). Most of the foods produced for human consumption are grown using organochlorine pesticides. Organochlorine pesticides are substances containing chemically combined chlorine and carbon. Dairy herds are mainly exposed to these contaminating residues through their feed. The most common effects of organochlorine compounds in milk are birth effects, neurological effects and behavioral effects, reproductive and cancer (Naidu et al., 2021).

In Ethiopia, few research reports indicate the existence of chemical residue contamination in milk and meat such as Oxytetracycline and Penicillin G antibiotic residue in cow milk (Rana et al., 2019). Tetracycline residue levels in slaughtered beef cattle and organochlorine pesticide residues in human and cow's milk were some of the studies which highlight the significance of the problem of chemical residues in Ethiopia (Bedada et al., 2012) In order to safeguard human health the World Health Organization (WHO) and the Food Agriculture Organization (FAO) have set standards for acceptable daily intake and maximum residue limits in foods (Li, 2018). A regulatory limit for antibiotic residues and other chemical residues imposed on the dairy industry in many countries (Abebew et al, 2014). Current developments in the market economy are prompting the liberalization of the veterinary profession. The problem is that, in most African countries, there is no control over the distribution of veterinary pharmaceuticals and phytosanitary products (G. Jaime et al, 2020) Worse still, no appropriate legislation yet exists to guarantee the quality of the various products released onto the African market (G. L. M. Jaime et al, 2022). In the data from Africa, Nigeria stands out in particular. Most of the research on the African continent comes from the most populous country in West Africa, followed by Tanzania and other Eastern African countries (Treiber and Beranek-Knauer, 2021). North Africa is only represented with Egypt, Algeria, and Morocco with regard to investigations into antibiotic residues (El-Guendouz et al, 2019). The most frequently contaminated products in this evaluation group were milk, eggs, and beef. As raw or pasteurized, milk was a rich source of antibiotic residues above and below the permitted limit values (Treiber and Beranek-Knauer, 2021). However, Ethiopia has not yet adopted international standards or established specifications for chemical residue limits in the milk and other consumable animal products Aytenfsu, et al. (2016). The Ethiopian livestock industry has not established any control programs to ensure the safety of the milk. (S. Aytenfsu et al and. Kebede, 2016b). The chemical residue limits, which apply to both the parent chemicals and its metabolites, need to have strong legislations to be forced at all levels in Ethiopia livestock industry in order to protect the health of the consumers (Tadesse , 2017).

Therefore, the objective of this seminar paper are: -

- To review the type, source and detection method of antimicrobial residues in cow milk.
- To highlight the public health importance of antimicrobial residue occurrence in cow milk
- To forward potential recommendations for prevention and control of the risk of antimicrobial residues in cow milk.

Antimicrobial Residue

Source and types of Antimicrobial Residue

Contamination of milk starts right from the intake of contaminated pasture and drinking water by the animal (Shaikh & Patil, 2020). Further inappropriate use of antimicrobial drugs in dairy animals without considering the withholding periods causes drug residues in milk. Apart from these, the contaminants may also be introduced during milk collection, preservation, transport, processing and packaging (Shaikh & Patil, 2020). Therefore, the milk could be the potential source of drug residues and contaminants in the human diet (Shaikh & Patil, 2020). The extended and excessive usage of approved drugs or prolonged drug clearance and multiple dosing as the sources of antibiotics in milk (Mohamed, 2015).

Common causes of residues in milk can be attributed to extra-label drugs, over the counter antibiotics sale, poor farm records, non-compliance with the withdrawal period, among other (Akkou et al., 2018). Most of the residues in the milk and milk products are pharmaceutical drugs such as antimicrobials, anthelmintic agents, hormones etc. However, other compounds like pesticides, insecticides, herbicides, detergents, disinfectants, mycotoxins, nitrates, nitrites and heavy metals are also detected as mentioned below in Table 1 (Aytenfsu et al.,2016b). Amongst various pharmaceuticals, the antibiotics are most widely used in medical as well as veterinary practices (Chauhan et al.,2018). Therefore, consistent drug residues found in the milk are of antimicrobial agents (Teixeira et al, 2020). Antibiotics as feed additives are administered orally while intramammary route (gel, ointments, and infusions) is considered as the most effective for udder infections (Shaikh and Patil, 2020). During the treatment and after a certain time (withdrawal period) of discontinuation of drug therapy these drugs are continuously secreted into the milk (Shaikh and Patil, 2020).

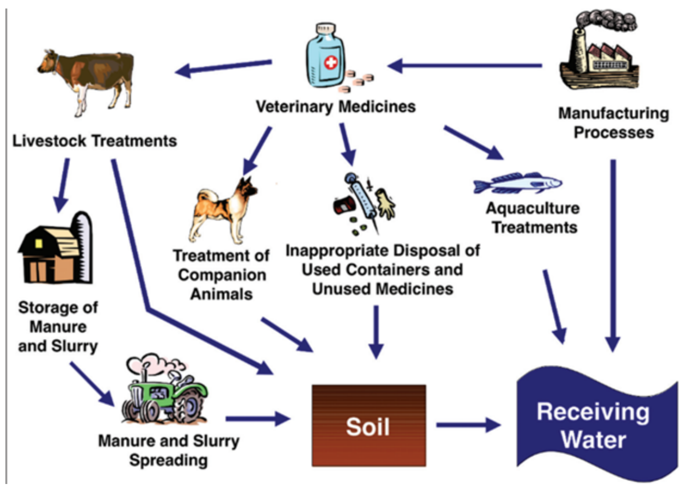

Figure 1: *Potential pathways for veterinary medicines in soil and water. Source:(Summaries, 2020)*

Antibiotics are used in therapeutics, and prophylaxis of infectious diseases or as a production aid in the food animals (Doron et al., 2021). The most commonly used antimicrobial classes in food animals include the beta-lactams, tetracycline, aminoglycosides, macrolides and sulphonamides as shown in Table 2 (Shaikh & Patil, 2020). Some other antibiotics like polymyxin B, colistin, tiamulin, novobiocin and carbadox are commonly used as growth promoters. (Shaikh and Patil, 2020).

Citation: Hussein Mohammed Roba. (2023). Review on Antimicrobial Residue Occurrence in Cow Milk and its Public Health Importance in Ethiopia. *Archives of Nutrition and Public Health* 5(1).

Common Antimicrobial	Reference
Penicillin, Oxytetracycline, streptomycin, neomycin, tetracycline, sulfamethazine, gentamicin, enrofloxacin, azithromycin	(Arsène et al., 2022)
Closantel, ivermectin, levamisole, albendazole,	(Shaikh & Patil, 2020)
Organochlorine, organophosphates, DDT, HCHs	(Ramezani et al., 2022)
Bovine somatotropin, progesterone, testosterone	(Shaikh & Patil, 2020)
Aflatoxin M1, aflatoxin B1	(Pandey et al., 2021)
Nitrate fertilizers, rodenticides	(Shaikh & Patil, 2020)
Lead (Pb), cadmium (Cd)	(Shaikh & Patil, 2020)

Table 1: *Common chemical and drug residues appearing in the milk (Motshakeri et al., 2022).*

Commonly Used Antibiotics	Group
Penicillin's	Benzyl penicillin, procaine penicillin, amoxicillin, ampicillin, cloxacillin
Cephalosporins	Ceftriaxone, ceftiofur, cefotaxime, ceftizoxime, cefoperazone, cephalexin
Aminoglycosides	Streptomycin, dihydrostreptomycin, gentamicin, neomycin, amikacin
Tetracycline	Oxytetracycline, tetracycline, chlortetracycline, doxycycline
Macrolides	Erythromycin, tylosin, azithromycin
Sulphonamides	Sulfadimidine, sulfamethoxazole, sulfadiazine, sulfanilamide
Fluoroquinolones	Enrofloxacin, ciprofloxacin, marbofloxacin, ofloxacin, levofloxacin
Other	Chloramphenicol, metronidazole, polymyxin B, colistin, tiamulin, bacitracin

Table 2: *Commonly used antibiotics in dairy animals (Lee et al, 2001).*

Antimicrobials are administered to animals through various routes including parenteral injections, orally through food and water, topically and by intramammary and intrauterine infusions. Antibiotics as feed additives are administered orally while intramammary route (gel, ointments, and infusions) is considered as the most effective for udder infections (Shaikh and Patil, 2020). During the treatment and after a certain time (withdrawal period) of discontinuation of drug therapy these drugs are continuously secreted into the milk (Shaikh and Patil, 2020). Theoretically, all of these routes may lead to residues which are appearing in the milk (Shaikh and Patil, 2020) but intramammary infusions cause a higher incidence of drug residues (Shaikh and Patil, 2020). Further, improper milking or milk collection, insufficient cleaning, poor hygienic conditions i.e. over all inappropriate management practices also contribute to contamination of milk by drugs and chemicals (Shaikh and Patil, 2020).

Following administration to cattle and sheep, albendazole is readily absorbed from the gut and rapidly transformed to various metabolites, the major metabolites being albendazole sulfoxide, albendazole sulfone and albendazole 2-amino sulfone (Aytenfsu et al., 2016b). Those metabolites can account for all residues found in milk and dairy products at any time point that are both bioavailable and of toxicological significance (Haben .,et al 2020). Residues of benzimidazole compounds can occur in milk and dairy products and it is necessary to observe withdrawal periods for milk therapy (Jeena., et al 2020). Ivermectin, a macrocyclic lactone, is exceptionally effective in very low dosages against nematodes and arthropod parasites in cattle and has been widely used for treating endo and ecto parasites in cattle; however, Ivermectin has a teratogenic effect in laboratory animals like rats, rabbits and mice (Aytenfsu et al., 2016b).

Bovine growth hormone

Bovine Growth Hormone or Bovine Somatotropin (BST), which is administered to animals, is a genetically engineered protein hormone either identical or similar to the natural bovine growth hormone produced by the pituitary gland. Its primary function is to increase milk production of dairy lactating cattle (Raux et al., 2022). Therefore, BST is a protein hormone that increases milk production in cows between 10 and 15% (Zahra et al., 2021). Bovine Growth Hormone is probably stimulating immunological responses of animals and hence increasing the milk cell count (D. Kumar et al., 2018b).

Pesticides and Insecticides

The occurrence of persistent organochlorine compounds in the environment is changing relatively slowly over a span of years similar time trends are characteristic of contents in fish, meat, eggs, and dairy products, which are the foods with the greatest contributions to the intake of organochlorine compounds (Ray and Sen, 2019). As much as 20% of an ingested chlorinated hydrocarbon excretes in milk Chlorinated hydrocarbons adhere to milk fat and butter contains a much higher proportion of these insecticides (Aytenfsu et al., 2016b). Residues of such compounds may persist in the environment and cause contamination through the food chain Presented organochlorine pesticide residues or owing to their use in sanitary actions indicating a human exposure through milk and dairy products (Kumar et al., 2018b).

Mycotoxins

Those metabolites, which may be hazardous for human health, are called mycotoxins (Aytenfsu et al., 2016b). Aflatoxin M1 (AFM1) found in the milk of animals that are fed with aflatoxin B1 (AFB1) containing feed (Younis et al., 2016). Many researchers reported that there was a linear relationship between the amount of AFM1 in milk and AFB1 in feed consumed by the animals (Battacone et al., 2003). On the other hand, AFM1 levels in milk show a seasonal variation and the toxin amount has differences in the products, which produced from the toxin containing milk (Bahrami et al., 2016).

Nitrates and Nitrites

Nitrates and nitrites are chemicals used in fertilizers, in rodenticides (to kill rodents), and as food preservatives. The use of nitrate fertilizer on crops can result in higher concentrations in some crop residue of animal feed (Aytenfsu et al., 2016b).

Heavy Metals

Heavy metals enter the human and animal body mainly by the routes of inhalation and ingestion With increasing environmental pollution, a heavy metal exposure assessment study is necessary(Aytenfsu et al., 2016b). Heavy metals produce toxic effects by replacing essential metal ions existing in the chelates present in the body. Heavy metals can enter to milk and dairy products and affect the health of people who have consumed contaminate milk and dairy products (Licata et al., 2004).

Toxic Agents in an Organism

Living things are continuously exposed to external chemical substances, generically called xenobiotic, which can have adverse effects according to their chemical characteristics.(Rand et al, 2020). Oral, dermal and inhalation routes represent the commonest means of exposure to these substances, the risks to human health due to the consumption of foodstuff contaminated by potentially toxic substances. Chemicals in an organism go through a series of stages including absorption, distribution, metabolism and excretion, forming part of the pharmacokinetics or toxicokinetics according to the effects produced by a particular substance (Aytenfsu et al., 2016b).

Associated Risk Factors for Residue Occurrence

Disease Status

The disease status of an animal can affect the pharmacokinetics of drugs administered, which can influence the potential for residues. This can occur either when the disease affects the metabolic system and consequently drug metabolism, or when the presence of infection and/or inflammation causes the drug to accumulate in affected tissues. For example, cattle with acutely inflamed mastitis quarters, apramycin penetrates these areas of the body, and concentrations of the drug have been observed at ten times over the level recorded from cows without mastitis (Beyene, 2016).

Extra-label drug use

Extra-label drug use (ELDU) refers to the use of an approved drug in a manner that is not in accordance with the approved label directions. It occurs when a drug only approved for human use is used in animals, when a drug approved for one species of animal is used in another, when a drug is used to treat a condition for which it was not approved, or the use of drugs at levels in excess of recommended dosages. For instance, the use of enrofloxacin solution as a topical ear medication (Only approved for use as an injection) are the common ELDU in veterinary medicine (Średnicka-Tober et al., 2016).

Improper Withdrawal Time

Improper withdrawal time is another risk factor; the withdrawal time is the time required for the residue of toxicological concern to reach safe concentration as defined by tolerance. Based on the drug product, dosage form, and route of administration it may vary from a few hours to days or weeks. It is the interval from the time an animal is removed from medication until permitted time of slaughter for the production of safe foodstuffs (Kebede and Roba, 2021).

Public Health Impacts

Recently, food-borne diseases are emerging as serious issues because of their significant public health impacts. The food-borne illness occurs due of consumption of foodstuffs contaminated with pathogens (bacteria, protozoa, fungi, parasites) or chemicals (drugs, heavy metals, pesticides, hormones) usually as a result of mishandling of food and improper management practices (Shaikh and Patil, 2020). Majority of commonly used drugs are relatively safer even at higher concentration, but few of them can produce serious health impacts (Shaikh and Patil, 2020). In the same way, the residual amount of drugs consumed through animal origin food not necessarily toxic, except when exceeds a certain limit i.e. MRL (Shaikh and Patil, 2020). As far as our topic is concerned, the milk contaminated with antimicrobial residues particularly in a concentration higher than the MRL is harmful to health and should not be used for consumption (Shaikh and Patil, 2020). The infants and growing children are at high risk because they consume large quantities of milk and milk products on a body-weight basis (Thorning et al., 2016). The drug residue hazards are classified as a direct-short term and indirect-long term hazards based on the duration of exposure to residues and the time of onset of adverse effects (Shaikh and Patil, 2020).

The direct-short term hazards usually appear immediately following the drug exposure, for example, the occurrence of allergic and hypersensitivity reactions in sensitized individuals immediately after consumption of penicillin contaminated milk (Shaikh and Patil, 2020). On The Contrary, long term exposure to the residues provokes indirect and long-term hazards such as development of antimicrobial drug resistance, carcinogenicity, teratogenicity and reproductive effects (Rath et al., 2018).

Hypersensitive Reaction

The drug-mediated hypersensitivity reactions are of two types, one is IgE- mediated and the other Non-IgE mediated. The appearance of urticarial, anaphylaxis, bronchospasm and angioedema are some examples of IgE mediated reactions while, non-IgE-mediated reactions include hemolytic anemia, thrombocytopenia, acute interstitial nephritis, serum sickness and vacuities (Shaikh and Patil, 2020). However, unrecognized exposure through contaminated food (including milk) may result in sensitization and subsequently, the allergic reaction appears after the therapeutic administration of the drug. After exposure even in low amounts, the penicillin's reactive neoantigen produces hypersensitivity, mainly the Type I reaction i.e. urticaria. Approximately 10-15% of the human population is considered hypersensitive to penicillin and the reaction is also seen in the animals (Holmer et al., 2019).

Development of Antimicrobial Drug Resistance

It has been reported that the use of antibiotics in livestock practices are associated with the development of antimicrobial drug resistance (AMR) through farm-to-fork food chain. Especially, the use of antibiotics at sub therapeutic doses as growth promoters on a long-term basis is of more concern. The AMR not only affects directly causing untoward effects in consumers but also indirectly by spreading the antimicrobial resistance determinants to human pathogens (Shaikh and Patil, 2020). Although, all the drug-resistant bacterial strains are not pathogenic to the Humans can transfer their antibiotic resistance genes to other pathogenic bacteria making them also resistant (Shaikh and Patil, 2020). The resistant organisms get access to the human beings through direct contact or indirectly through the animal origin food including milk to produce serious infections which are very challenging to treat (Shaikh and Patil, 2020). Further, the indiscriminate use of avoparcin results in the development of vancomycin-resistant enterococci. In this regard, WHO has already raised concern about drug resistance due to indiscriminate use of penicillin, sulphonamides and tetracycline antibiotics, in the agriculture sector (Ma et al.2021).

Carcinogenicity

It is a cancer-producing ability of a drug or a chemical in the presence or absence of initiator or promoter (Rashid, 2017). The drugs like tetracycline, furazolidone, tamoxifen, phenobarbital and DDT act as a carcinogen and produce various types of cancers. Further, nitrofurans can react with nitrite to yield carcinogenic metabolite nitrosamines. Hence, Furazolidone and its metabolites have been banned by the US FDA (Gupta, 2019). The synthetic estrogen analogue diethylstilbestrol, on chronic exposure, leads to vaginal clear cell adenocarcinoma in female offspring and also causes benign structural abnormalities (Shaikh and Patil, 2020). Similarly, hormone related cancer, including cancer of breast, ovary, prostate, testes and colon have been reported following ingestion of milk with hormonal residues (P. T. Bhoomika, 2019A. and Patel, 2019).

Teratogenicity

Teratogenicity is an ability of a drug or a chemical to produce harmful and toxic effects on developing embryos or fetuses during critical phases of pregnancy (Jamkhande et al, 2014). Developmental toxicity, embryo toxicity or teratogenic effects are reported due to the exposure of some pharmaceuticals during pregnancy. The teratogenic drugs include some chemotherapeutic agents (thalidomide), anthelmintic (albendazole), antibiotics (tetracycline, aminoglycosides), antiepileptic's (carbamazepine), hormones (diethylstilbestrol, misoprostol) and other drugs like ACE inhibitors, cyclophosphamide, methimazole etc. (Shaikh and Patil, 2020).

Mutagenicity

Mutagenicity refers to the ability of a chemical or drug to produce alteration in a DNA molecule or the genetic component of a cell in an organism (Kebede and Roba, 2021). Some of the drugs have the potential to cause DNA mutation or chromosomal damage subsequently leading to infertility in human beings (Sachi., et al 2019). The metronidazole, a nitro imidazole derivative, is reported to possess mutagenic and genotoxic activities. It has produced DNA strand breakdown and DNA fragmentation in human peripheral blood lymphocytes and the hepatocytes, respectively. Further, tinidazole and chloroquine drugs have also been found to be potentially mutagenic (Chin Chung.,et al 2011). Similarly, oxfendazole a benzimidazole anthelmintic also reported for its mutagenic activity (Prajwal et al., 2017).

Disruption of Normal Gut Flora

Normal gut flora acts as a barrier for the pathogenic bacteria to prevent the occurrence of disease by competing with them. Antibiotics like nitro imidazole, metronidazole, tetracycline, penicillin's, tocsin, streptomycin etc. as residues in milk, causes disruption of the normal gut flora and resulting in gastrointestinal disturbances (Kyuchukova, 2020). Disruption of the normal bacterial flora of gut may results in gastro-intestinal disturbances and allows pathogens to invade and multiply in the host. In some severe cases pseudomembranous colitis, Clostridium difficile associated diarrhea and other life-threatening infections may occur (Vaquero-Picado et al., 2018). But these effects are known to occur at therapeutic doses and there is little scientific data available regarding the effect of residue range concentration of antibiotics on human beings (Falowo et al., 2019).

Inhibition of Starter Culture

Presence of antibiotic residues in milk, even in very low concentration is of great concern in dairy industries. Antibiotic residues in the milk may alter the growth of starter cultures thus interfering with the fermentation process during the production of yogurt, cheese and other fermented dairy products (Kabrite et al., 2019).

Other Untoward Effects

Some studies have revealed the untoward effects like retinal detachment in individuals due to long-term exposure to fluoroquinolones and the optic neuropathy and brain abscesses associated with chloramphenicol (Jayalakshmi et al., 2017). Apart from these, various other harmful effects of drug residues have been reported such as immunodepression (tetracycline, chloramphenicol), endocrine disruption (HCHs), anemia's (chloramphenicol, sulphonamides), photosensitization (tetracycline), gastro-enteric disturbances (erythromycin, fluoroquinolones) acute and chronic toxicities of various tissues and body systems (Shaikh and Patil, 2020).

Safety Evaluation of Antimicrobial Residues

Acceptable Daily Intake

Acceptable daily intake (ADI) is the amount of substance that can be ingested daily over a lifetime without appreciable health risk (Fitch et al., 2021). The evaluation of the safety of residues is based on the determination of the ADI on which in turn maximum residues limits (MRL) is based. The ADI is determined by a consecutive estimate of a safe ingestion level by the human population on the lowest no effect level of toxicological safety studies (Asredie and Engdaw, 2015) . If the drug is not a carcinogen, the no observed effect level (NOEL) of the most sensitive effect in the most sensitive species divided by a safety factor is used to determine an ADI for drug residues. The FDA will calculate the safe concentration for each edible tissue using the ADI, the weight in kg of an average adult (60 kg), and the amount of the product eaten per day in grams as follows; Safe concentration = [ADI (μg/kg/day) x 60 kg]/[Grams consumed/ day] L.Moreno, (2017).

Amoxicillin	2***	4
Benzyl penicillin	30	4*
Procaine penicillin	30	4*
Gentamicin	0-20	100*
Tetracycline	0-30	100*
Oxytetracycline	0-30	100*
Chlortetracycline	0-30	100*
Tylosin	0-30	100
Ceftiofur	0-50	100*
Neomycin	0-60	1500
Sulphadimidine	0-50	25*
Ivermectin	0-10	10
Albendazole	0-50	100*
Thiabendazole	0-100	100*
Diminazene	0-100	150*
Deltamethrin	0-10	30
Progesterone	0-30	NS
Testosterone	0-2	NS
Bovine somatotropin	NS	NS
Porcine somatotropin	NS	NS
Clenbuterol	0-0.004	0.05*
Dexamethasone	0-0.015	0.3*
Lead	NS	20**
Aflatoxin M1	NS	0.5**

** = values are expressed in µg/L of milk; ** = values are Codex maximum level (ML) adapted from CAC (2011); *** = denotes Microbiological Acceptable Daily Intake (mADI); NS = Not specified*

Table 3: *Acceptable Daily Intake (ADI) and Maximum Residual Limits (MPL) of some chemicals and veterinary drugs, in cow milk Thrasyvoulou, (2018).*

Maximum Residue Level

A tolerance level (or maximum residue levels, MRLs) is the maximum allowable level or concentration of a chemical in feed or food at a specified time of slaughter or harvesting, processing, storage and marketing up to the time of consumption by animal or human Lee MH et al., (2001). The MRL in various foodstuffs (muscle, liver, kidney, fat, milk and eggs) is determined to minimize the risk of consumer exposure, considering dietary intake. Such considerations as food technology, good farming practices and the use of veterinary medicinal products may also be considered when setting the MRL Lee MH et al., (2001).

Calculating Withdrawal Period

The withdrawal period is determined when the tolerance limit on the residue concentration is at or below the permissible concentration. Withdrawal times are determined in edible, target tissues. Most commonly, they are liver or kidneys as they are primary organs of elimination and typically display a residue for the longest time. During withdrawal studies, the target organ is determined and animals are sampled at various times after drug administration is stopped. The withdrawal periods (WDPs) of commonly used drugs in dairy animals as per the Food Animal Residue Avoidance Databank, have been shown in Table 4 (Farad, 2020). But these established withdrawal periods may vary according to the policy of the country.

Techniques for Detection of Drug Residues in Milk

There are several techniques available for the determination of different classes of drug residues in milk and dairy products as listed below (Aytenfsu et al., 2016; Luiz et al., 2018). The methods for detecting antibiotic residues can be divided into two categories: screening method (Bacanlı, M. and Başaran, N. (2019) and confirmatory method Arsene et al., (2021). These two methods differ because the first one is globally qualitative or semi quantitative. In contrast, the second one ensures its determination with high precision of the type and concentration of the investigated residue.

IV	IM	SC	PO	IMa	Top	
Procaine Penicillin G	–	5 D	–	–	–	–
Gentamicin	5 D	5 D	5 D	–	10 D	–
Tetracycline	–	–	–	–	–	1 D
Oxytetracycline	144 H	144 H	–	–	96-120 H	–
Florfenicol	–	–	–	–	120 H	–
Ceftiofur	0**					
Monensin	0*					
Ivermectin	–	–	47 D	28 D	–	53 D
Moxidectin	–	–	–	–	–	0
Morantel	0*					
Thiabendazole	4 D*					
Acepromazine	48 H	48 H	–	–	–	–
Detomidine	72 H	72 H	–	–	–	–
Xylazine	72 H	24-120 H	–	–	–	–
Guaifenesin	48 H	–	–	–	–	–
Ketamine	48 H	48 H	–	–	–	–
Flunixin meglumine	84 H	72-96 H	96 H	96 H	–	–
Epinephrine	0	0	–	–	–	–
Atropine	6 D	6 D	–	–	–	–

IV= Intravenous, IM= Intramuscular, SC= Subcutaneous, PO= Per os, IMa= Intramammary, Top= Topical, D=Day(s), H=Hour(s); * = Route is not specified (Adapted from Riviere and Papich, 2018); ** = Route is not specified (Adapted from Giguer et al., 2013).

Table 4: *Withdrawal periods (WDPs) of commonly used drugs in dairy animals (FARAD, 2020).*

Screening Method

All screening methods are essentially microbiological or immunological. The most well-known and earliest microbiological technique is the so-called "four plates" technique. This method inhibits the growth of Micrococcus luteus and Bacillus subtilis. Inhibitory zones lacking bacterial colonies around the sample deposit sites indicate the potential presence of antibiotics Zeghilet, N. and El Hadef, E.O.S. (2009). This method is widely used to investigate the presence of antibiotic residues in different meats, fish, and eggs Zeghilet, N. and El Hadef, E.O.S. (2009) Cantwell, H. and O'Keeffe, M. (2006) Kilinc, B. and Cakli, S. (2008) Rahimi et al., (2018). Similarly, acidification is also a well-known microbiological technique used to detect the presence of antibiotic residues in milk. This test uses a culture of a bacterium capable of degrading lactose into lactic acid and a colored indicator, bromocresol purple, which detects if the acidification of the medium has been done. The most suitable strain for this method is Bacillus stearothermophilus var. calidolactis C953 (strain C953, CIP 5281).

Furthermore, if the milk analyzed contains antibiotics, the bacteria will not degrade the lactose, and the color of the medium will remain unchanged. On the other hand, the absence of antibiotics results in a color change from blue to yellow, indicating acidification. However, despite these techniques being accessible, inexpensive, and performed by a non-professional, there is a lack of specificity and long incubation time. Thus, to overcome these disadvantages, several companies have manufactured different commercial kits under different trade names (e.g., BR test, Eclipse test, Copan test, Delvotest, Lumac, and Arla). Such tests detect numerous antibiotics at thresholds generally close to the MRL Cháfer-Pericás, et al., (2010). Compared with microbiological methods immunological methods such as enzyme-linked Immuno sorbent assay, fluoro immune assay, and time-resolved fluoro immunoassay are highly specific, highly sensitive, simple, and cost effective. In addition, rapid-detection immunochromatographic kits (on strips) have been developed (TwinSensor), allowing within one assay the simultaneous screening of penicillin and cephalosporins (TwinSensor KIT034) beta-lactam and tetracycline (TwinSensor KIT020); beta-lactam antibiotics tetracycline's, streptomycin, and chloramphenicol (4Sensor BSCT-KIT060); beta-lactam antibiotics, sulfonamides, tetracycline's, and (Fluoro) quinolones (4Sensor BSTQ-KIT072) Kyselková, et al., (2015). Dolenc. et al., (2018) ,Mensah.,et al., (2019), Broekaert.,et al ., (2020).

Confirmatory Methods

The main advantage of confirmatory methods is their high specificity, sensitivity, preciseness, accuracy, and reliability. But they are expensive, time-consuming, and require personnel and an adequate laboratory Bacanlı et al., (2019). Confirmatory methods are essentially chromatographic methods (mainly liquid chromatography) coupled to mass spectrometry or ultraviolet (UV) Bacanlı, M. et al., (2019). However, capillary electrophoresis (CE) CE–laser-induced fluorescence Khatibi et al., (2020), surface-enhanced Raman spectroscopy and high-performance liquid chromatography (HPLC) with spectroscopic fluorometric detection (HPLC–RF) or with a spectroscopic HPLC–photodiode array detector (Adesiyun, et al., 2021) are also shown to be effective detectors of antibiotic residues.

New Fully Automatic Approach

Fully automatic biosensors are becoming increasingly important in detecting antibiotics in food Bacanlı, M.et al., (2019). The biosensors can be classified according to the biological element enzymatic, neurosensory, and microbiological, transducer piezoelectric, electrochemical, optical, thermal, impedimetric, and calorimetric, and biological element immobilization procedure on solid support adsorption, covalent bonding, cross-linking, entrapment, and encapsulation Cháfer-Pericás, et al., (2010) in their work, reported most of the existing techniques for the rapid detection of antibiotic residues in foods. They concluded that fully automatic biosensors consist of a combination of biological element/transducer such as microbiological cell/electrochemical, antibody/impedimetric, and oligonucleotide/electrochemical with microbiological cell represent an interesting screening approach due to its quick and fully automated operability Cháfer-Pericás et al., (2010). They also reported the advantages of biosensors, specifically the bio recognition element used, which allows rapid, continuous control, and onsite applications. However, the main limitations of these instruments are the potential loss of stability of the biological detection component due to exposure to environmental stresses, such as pH, temperature, or ionic strength, and the limited size of the physicochemical transducers used.

Status of Antimicrobial Residues in Dairy Milk in Ethiopia

Globally, more than half of all medicines are prescribed, dispensed or sold improperly. This is more wasteful, expensive and dangerous, both to the health of the individual patient and to the population as a whole that magnifies the problem of misuse of anthelmintic agents Cupic V et al., (2011). In many African countries, antibiotics may be used indiscriminately for the treatment of bacterial diseases or they may be used as feed additives for domestic animals and birds. The ongoing threat of antibiotic contamination is one of the biggest challenges to public health that is faced by the human population worldwide (Sivaraman et al. 2008). Such residues are spreading rapidly, irrespective of geographical, economical, or legal differences between countries. In Ethiopia, few studies have indicated the existence of antibiotic residue in milk and other animal products. In Central Ethiopia the prevalence of Oxytetracycline and penicillin, G Residues in milk and meat showed higher than maximum residue limits. Abebaw, (2008). Antimicrobials pass into every tissue and fluids of the body before excreted. High levels of antibiotic residues were detected in milk and meat destined for human consumption.

In Ethiopia 70.58% of farms in DebreZeit and 83.33% of the farms in Nazareth the Oxytetracycline level is similarly, in 20.58% of the farms found in DebreZeit and 16.16% of the farms found in Nazareth, the penicillin G level were above the maximum residue limit established by FAO. Other studies were also conducted in Ethiopia in which Oxytetracycline and penicillin G from milk (Desalegne et al., 2014) and tetracycline from beef (Addisalem and Bayleyegn, 2012). Also, as study conducted in University of Gondar veterinary clinic revealed, anthelmintic drugs are quite commonly but improperly utilized in the clinic. Three group of anthelmintic namely benzimidazole (Albendazole, fenbendazole, mebendazole and triclabendazole), imidazothiazole (tetramisole and levamisole) and macrocyclic lactone (Ivermectin) were used. Utilization of a limited group of drugs for a long period may favor the development of resistance which is a risk factor for drug residues Kassahun C et al., (2016). Though the primary purpose of veterinary drugs is to safeguard the health and welfare of animals Cannavan A (2004), 44.3% anthelmintics were prescribed irrationally to treat diseases that were tentatively diagnosed as nonparasitic cases and 92.1% of anthelmintics were utilized to treat diseases that were tentatively diagnosed without getting correct laboratory supported diagnosis. This may be due to inadequate recognition of the disease, unavailability of diagnostic aids for confirmatory tests, and absence of a right drug and to make the treatment broader anthelmintics can be given in combination with other drugs residues, (Adem A et al.,2016).

Determination of pesticide residue in South-West Ethiopia (Asendabo, Serbo and Jimma) the mean estimated daily intake of DDT by infants from mother's milk and cow milk samples showed that 62.17 µg/kg body weight, which is about three times higher than the acceptable daily intake set by WHO/FAO for total DDT, 20 µg/kg of body weight. This alarmingly high daily intake value is cause for concern, since children are highly susceptible to effects from such environmental contaminants (Gebremichael et al., 2013). Another study on cow milk in Addis Ababa indicated the prevalence of toxic metals such as Cd, Pb, Fe and Zn are amongst the elements that have caused most concern in terms of adverse effects to human health (Table 4). (Dawd AG et al., 2012). In Ethiopia, the control of drugs from the government authorities and information on the actual rational drug use pertaining to veterinary drug use is very limited. In addition, misuses of drugs are common among the various sectors including veterinary and public health. In addition, there is lack of awareness and preparedness among the controlling authorities and producers in dealing with the risk of indiscriminate use of antibiotics to the livestock and to the consumers Tesfalem et al., 2017. No formal control mechanisms exist to protect the consumer against the consumption of milk products containing harmful drug residues in the country Addisalem, H et al., 2012. Therefore, an integrated management including cultural practices, plant-derived products and biological control has been experimented on a limited scale Sun H. (2016).

Comman antimicrobial residue	Study area	Factor	Referance
Oxytetracycline	Bishoftu Adama	Above residue limit	Abebaw (2008)
Penicillin G	Bishoftu Adama	Above residue limit	Abebaw (2008)
Benzimidazole	Gondar university	Prescribed irrationally	Cannavan (2004)
Pesticide	South west Ethiopia (Asendabo, Serbo and Jimma)	Higher than acceptable daily intake	Gabremichael et al., 2013
Toxic metal	Addis Abeba	adverse effects to human health	Dawd AG et al., 2012

Table 5: *Summary Status of Antimicrobial Residue in Dairy Milk in Ethiopia.*

Management of Antimicrobial Residue

Legislation and Regulations toward Drug Residue

The European Union has strictly regulated the use of veterinary drugs in food animal species. Some of these drugs can be permitted only in specific circumstances (therapeutic purposes) but under strict control and administration by a veterinarian, Peteghem VC et al., (2004). The availability of simple and useful screening techniques is really necessary for an effective control Fidel T. (2008). Establishment of a legislative framework and of an institutional structure is the first step in the assessment and management of drug related risk. A major tool for veterinarians to prevent and control drug borne risk is Pharmacovigilance Odore R. (2008). Pharmacovigilance is the post-marketing surveillance of antimicrobial drug and vaccine safety used for prevention, diagnosis and therapy and consists of the report of any adverse effects of a drug by veterinarians, pharmacists, farmers and other health care professionals, in the improvement of knowledge about the pharmacological action of a drug and hence, in the evaluation of the risk/benefit balance of a drug Veenhuizen MF et al., (2006). The main tasks of Pharmacovigilance can be summarized as Control of clinical safety of veterinary medicinal products, Control of potential reaction in man linked to user safety, Evaluation of decreased efficacy or lack of expected activity of a veterinary medicinal product, Control of maximum residue levels (MRL) of veterinary drugs in food products of animal origin, Assessment of risks for the environment related to the use of veterinary drugs, Control of the development of drug resistance, with particular concern to antibiotic resistance.

Control and Prevention of Antimicrobial Residue in Dairy Milk

The first step in residue prevention is to make individuals and organizations aware of the problem through education by means of scientific literature, computer databases, veterinary consultations and the efforts of national organizations (Riviere and Sundlof, 2009). Government is responsible for the preparation and implementation of the regulatory laws for food safety (Aytenfsu et al., 2016). The FSSAI monitors and regulates the production, processing, storage, distribution and sale of various foodstuffs including milk and milk products to ensure public health safety. The section 21 of FSS Act, 2016 specifies that "no article of food shall contain insecticides or pesticides residues, veterinary drugs residues, antibiotic residues, solvent residues, pharmacological active substances and microbiological counts in excess of such tolerance limits as may be specified by regulations". For this purpose, the FSSAI has recognized food testing laboratories (under section 43 of FSS Act, 2006) across various regions of the country and developed standard methods for food analysis and determination of antibiotics, hormones, pesticides in food material including milk and dairy products (FSSAI 2016a and 2016b). FSSAI also grants the licensing and registrations for manufacture and sell of the food articles including milk and milk products to ensure the availability of safe and wholesome milk and dairy products for human consumption. According to section 31 of the FSS Act, 2016, "no person shall commence or carry on any food business except under a license". Carrying out a food business without a license in India is punishable under section 63 of the FSS Act, 2016. For the protection of consumers, the Codex Alimentarius has established MRLs and ADI for various veterinary drugs in foods (including the milk) that have been presented in Table 3. According to the Codex few of drugs like chloramphenicol, chlorpromazine, furazolidone, dimetridazole, metronidazole, nitrofural and some others, have no safe levels of residue hence should not be used in food-producing animals (CAC, 2018). Food and Drug Authority (FDA) is the international body which ensures the safety of food products and has developed a risk assessment regarding animal drug residues in milk and milk products (FDA, 2015). The withdrawal periods (WDPs) of commonly used drugs in dairy animals as per the Food Animal Residue Avoidance Databank, have been shown in Table (FARAD, 2020). But these established withdrawal periods may vary according to the policy of the country (Riviere and Papich, 2018). As the pharmacokinetics of a drug is dependent on the vehicle or excipient used in a drug formulation the withholding time is valid for that specific drug formulation. Therefore, different withholding periods may be appropriate for the same drug in different veterinary preparation (Padol et al., 2005).

Conclusions and Recommendations

The contaminants as residues in the milk have significant public health importance since dairy products are widely consumed by infants, children and many adults throughout the globe on a daily basis. These residues in milk are often due to farmers failing to adhere to the specified milk withdrawal periods after antibiotic use to sick lactating cows, illegal or extra label use of drugs and incorrect dosage levels and route of administration. The contaminants as drug residues in the milk have significant public health and economic implications for the following reasons: allergic reactions, selection of resistant pathogenic and non-pathogenic bacteria, toxicity, carcinogenicity and inhibition of starter cultures used in production of different milk products. For this reason, to protect the consumer, safe limits have been established on residual amounts of antibiotics in milk in the form of maximum residue level. In order to safeguard human health, the WHO and FAO have set standards for acceptable daily intake and maximum residue limits in foods. However, Ethiopia has not yet adapted international standards or established specifications for residue limits in the milk. In reality, avoidance or complete elimination of chemical and drug residues from milk and milk product is not easy, however, adoption of certain safety measures and guidelines may help in minimizing the residues to non-toxic levels (Jones, 1999; Khaniki 2007; Priyanka et al., 2017; Sachi et al., 2019). By implementing proper food safety measures the drug residues can be minimized to a level that is safe. Therefore, based on the above conclusions the following recommendations are forwarded: -

- Avoid using antibiotics in the veterinary field pillars without a veterinarian's prescription.
- There should be reduction of unnecessary prophylactic treatment in animals.
- Reducing antimicrobial residues in animal foods by adequate management practices and careful use of antimicrobials.
- Until the withdrawal period has elapsed, the animal or its products must not be used for human consumption.
- Training of farmers, animal keepers and Milk producers should be aware about Hygienic and proper management practices, risks with antimicrobial residue as a result of failure to respect the withdrawal time.
- Implementation of regulatory laws at dairy farms and dairy industries. Encouraging use of safe alternate medicine and ethno-veterinary practices
- Adoption of programs such as Hazard Analysis Critical Control Point (HACCP), Quality Control (QC), Total Quality Management and Quality Assurance Programs in the livestock and dairy industry.
- Monitoring, screening and surveillance of milk residues by aforementioned methods
- In a similar manner inexpensive and easy-to-use tests should be developed to detect antibiotic residues in foods rapidly. Finally, healthier approaches such as probiotics and herbal remedies should be used.
- Strict national legislation passed on the livestock sector to avoid unnecessary use of chemicals.
- National chemical residues control and monitoring programs should be designed to set standards on the use of chemicals (antimicrobials, insecticides, pesticides, etc.)
- Further research on the effect of chemical residues on humans and alternative control systems should be encouraged. Because milk and milk products are essential foodstuffs for small children, attention has to be paid to the presence of drug residues in milk. In addition, the use of effective enforcement of their standards is essential to fulfill the objective of consumers providing them with safe and wholesome milk and milk products. Therefore, the overall public health impact of drug residues in milk and milk products can be minimized by the collaboration and contribution of farmers, clinicians, manufacturers, researchers, consumers and legislative and other food safety authorities.

Acknowledgement

I would like to thank my advisor Dr. Mohammed Jafer for his constructive advices, guidance, material support and devotion of incalculable time in correction of this paper. In addition to this I would like to extend my thanks to all my friends and relatives who in one way or the other helped me during the review work.

References

1. Abebew, D., Belihu, K., & Zewde, G. J. E. V. J. (2014). Detection and determination of oxytetracycline and penicillin G antibiotic residue levels in bovine bulk milk from Nazareth dairy farms, Ethiopia. 18(1): 1-15.
2. Akkou, M., Bouchiat, C., Antri, K., Bes, M., Tristan, A., Dauwalder, O., . . . Vandenesch, F. J. V. m. (2018). New host shift from human to cows within Staphylococcus aureus involved in bovine mastitis and nasal carriage of animal's caretakers. 223: 173-180.
3. Almashhadany, D. A. (2021). Screening of antibiotic residues in raw milk of cows and buffalos by diffusion assays. Italian Journal of Food Safety. 10(3).
4. Arsène, M. M. J., Davares, A. K. L., Viktorovna, P. I., Andreevna, S. L., Sarra, S., Khelifi, I., & Sergueïevna, D. M. J. V. W. (2022). The public health issue of antibiotic residues in food and feed: Causes, consequences, and potential solutions. 15(3): 662.
5. Asredie, T., & Engdaw, T. A. J. W. J. D. F. S. (2015). Antimicrobial residues in cow milk and its public health significance. 10(2): 147-153.
6. Aytenfsu, S., Mamo, G., & Kebede, B. (2016a). Review on chemical residues in milk and their public health concern in Ethiopia. J Nutr Food Sci, 6(4): 524-524.
7. Aytenfsu, S., Mamo, G., & Kebede, B. J. J. N. F. S. (2016b). Review on chemical residues in milk and their public health concern in Ethiopia. 6(4): 524-524.
8. Bahrami, R., Shahbazi, Y., & Nikousefat, Z. J. F. C. (2016). Aflatoxin M1 in milk and traditional dairy products from west part of Iran: occurrence and seasonal variation with an emphasis on risk assessment of human exposure. 62: 250-256.
9. Battacone, G., Nudda, A., Cannas, A., Borlino, A. C., Bomboi, G., & Pulina, G. J. J. o. D. S. (2003). Excretion of aflatoxin M1 in milk of dairy ewes treated with different doses of aflatoxin B1. 86(8): 2667-2675.
10. Bedada, A. H., Zewde, B. M., & Zewde, B. J. G. V. (2012). Tetracycline residue levels in slaughtered beef cattle from three slaughterhouses in central Ethiopia. 8(6): 546-554.

11. Beyene, T. J. J. V. S. T. (2016). Veterinary drug residues in food-animal products: its risk factors and potential effects on public health. 7(1): 1-7.
12. Bhoomika, P. T., Kadwalia, A., Jaiswal, S., Rani, B., & Patel, P. K. (2019). Antibiotic residues in animal products and its effect on human health. The Pharma Innovation Journal, 8(4): 03-06.
13. Bhoomika, P. T., Kadwalia, A., Jaiswal, S., Rani, B., & Patel, P. K. J. T. P. I. J. (2019). Antibiotic residues in animal products and its effect on human health. 8(4): 03-06.
14. Chauhan, A. S., George, M. S., Chatterjee, P., Lindahl, J., Grace, D., Kakkar, M. J. A. R., & Control, I. (2018). The social biography of antibiotic use in smallholder dairy farms in India. 7(1): 1-13.
15. Chin Chung, M., Longhin Bosquesi, P., & Leandro dos Santos, J. J. C. p. d. (2011). A prodrug approach to improve the physico-chemical properties and decrease the genotoxicity of nitro compounds. 17(32): 3515-3526.
16. Doron, A., Broom, A. J. E., & Weekly, P. (2021). Chicken curry in the time of COVID-19: The industry of bugs and drugs. 56(17).
17. El-Guendouz, S., Lyoussi, B., Miguel, M. G. J. C., & biodiversity. (2019). Insight on propolis from mediterranean countries: Chemical composition, biological activities and application fields. 16(7): e1900094.
18. Falowo, A. B., Akimoladun, O. F. J. V. M., & Pharmaceuticals. (2019). Veterinary drug residues in meat and meat products: Occurrence, detection and implications. 3: 194.
19. Fitch, S. E., Payne, L. E., van de Ligt, J. L., Doepker, C., Handu, D., Cohen, S. M., . . . Wikoff, D. J. B. p. h. (2021). Use of acceptable daily intake (ADI) as a health-based benchmark in nutrition research studies that consider the safety of low-calorie sweeteners (LCS): a systematic map. 21(1): 1-11.
20. Gupta, P. (2019). Veterinary Drug Residue Hazards. In Concepts and Applications in Veterinary Toxicology (pp. 301-308): Springer.
21. Haben Fesseha, M., Aliye, S., Mathewos, M., & Fesseha, H. (2020). Chemical and Drug Use in Dairy Farms of Hawassa Town, Southern Ethiopia.
22. Holmer, I., Salomonsen, C., Jorsal, S., Astrup, L. B., Jensen, V. F., Høg, B. B., & Pedersen, K. J. B. v. r. (2019). Antibiotic resistance in porcine pathogenic bacteria and relation to antibiotic usage. 15(1): 1-13.
23. Jaime, G., Hobeika, A., & Figuié, M. (2020). Access to veterinary medicines in sub-Saharan Africa.
24. Jaime, G. L. M., Hobeika, A., & Figuié, M. J. F. i. V. S. (2022). Access to Veterinary Drugs in sub-Saharan Africa: Roadblocks and currents Solutions. 1612.
25. Jamkhande, P. G., Chintawar, K. D., & Chandak, P. G. J. A. P. J. o. T. D. (2014). Teratogenicity: a mechanism based short review on common teratogenic agents. 4(6): 421-432.
26. Jayalakshmi, K., Paramasivam, M., Sasikala, M., Tamilam, T., & Sumithra, A. J. J. E. Z. S. (2017). Review on antibiotic residues in animal products and its impact on environments and human health. 5(3): 1446-1451.
27. Jeena, S., Venkateswaramurthy, N., Sambathkumar, R. J. R. j. o. P., & Pharmacodynamics. (2020). Antibiotic Residues in Milk Products: Impacts on Human Health. 12(1): 15-20.
28. Kabrite, S., Bou-Mitri, C., Fares, J. E. H., Hassan, H. F., & Bou-mosleh, J. M. J. V. w. (2019). Identification and dietary exposure assessment of tetracycline and penicillin residues in fluid milk, yogurt, and labneh: A cross-sectional study in Lebanon. 12(4): 527.
29. Katakweba, A., Mtambo, M., Olsen, J. E., & Muhairwa, A. (2012). Awareness of human health risks associated with the use of antibiotics among livestock keepers and factors that contribute to selection of antibiotic resistance bacteria within livestock in Tanzania. Livestock Research for Rural Development, 24(10): 170.
30. Kebede, A., & Roba, M. J. I. J. V. H. S. R. (2021). Review On Antibiotics Residue In Beef: Its Risk Factors and Public Health Impacts. 9(1): 260-265.
31. Kumar, D., Rai, D., Porwal, P., & Kumar, S. (2018a). Compositional quality of milk and its contaminants on physical and chemical concern: a review. Int. J. Curr. Microbiol. App. Sci, 7(5): 1125-1132.
32. Kumar, D., Rai, D., Porwal, P., & Kumar, S. J. I. J. C. M. A. S. (2018b). Compositional quality of milk and its contaminants on physical and chemical concern: a review. 7(5): 1125-1132.
33. Kyuchukova, R. J. B. J. o. A. S. (2020). Antibiotic residues and human health hazard-review. 26(3): 664-668.
34. Lee, M., Lee, H., & Ryu, P. J. A.-A. J. o. A. S. (2001). Public health risks: Chemical and antibiotic residues-review. 14(3): 402-413.
35. Li, Z. J. J. o. e. m. (2018). Evaluation of regulatory variation and theoretical health risk for pesticide maximum residue limits in food. 219: 153-167.

36. Licata, P., Trombetta, D., Cristani, M., Giofre, F., Martino, D., Calo, M., & Naccari, F. J. E. i. (2004). Levels of "toxic" and "essential" metals in samples of bovine milk from various dairy farms in Calabria, Italy. 30(1): 1-6.
37. Ma, F., Xu, S., Tang, Z., Li, Z., Zhang, L. J. B., & Health. (2021). Use of antimicrobials in food animals and impact of transmission of antimicrobial resistance on humans. 3(01): 32-38.
38. Mohamed, A. (2015). Assessment of microbial loads and antibiotic residues in milk supply in Khartoum State. UOFK,
39. Motshakeri, M., Sharma, M., Phillips, A. R., Kilmartin, P. A. J. J. o. A., & Chemistry, F. (2022). Electrochemical methods for the analysis of milk. 70(8): 2427-2449.
40. Naidu, R., Biswas, B., Willett, I. R., Cribb, J., Singh, B. K., Nathanail, C. P., . . . Barclay, A. J. E. I. (2021). Chemical pollution: A growing peril and potential catastrophic risk to humanity. 156: 106616.
41. Nougadère, A., Sirot, V., Cravedi, J.-P., Vasseur, P., Feidt, C., Fussell, R. J., . . . Rivière, G. J. E. i. (2020). Dietary exposure to pesticide residues and associated health risks in infants and young children–results of the French infant total diet study. 137: 105529.
42. Ojha, S., Argade, A., Raje, K., Kumar, D., & Ahlawat, S. (2018). Importance of bovine milk in human diet and effect of adulterated milk on human health. Pharma Innov. J, 7: 453-457.
43. Pandey, A. K., Shakya, S., Patyal, A., Ali, S. L., Bhonsle, D., Chandrakar, C., . . . Hattimare, D. J. M. R. (2021). Detection of aflatoxin M1 in bovine milk from different agro-climatic zones of Chhattisgarh, India, using HPLC-FLD and assessment of human health risks. 37(3): 265-273.
44. Prajwal, S., Vasudevan, V., Sathu, T., Irshad, A., Nayankumar, S., & Pame, K. J. T. P. I. J. (2017). Antibiotic residues in food animals: Causes and health effects. 6(12): 01-04.
45. Ramezani, S., Mahdavi, V., Gordan, H., Rezadoost, H., Conti, G. O., & Khaneghah, A. M. J. E. R. (2022). Determination of multi-class pesticides residues of cow and human milk samples from Iran using UHPLC-MS/MS and GC-ECD: A probabilistic health risk assessment. 112730.
46. Rana, M. S., Lee, S. Y., Kang, H. J., & Hur, S. J. J. F. s. o. a. r. (2019). Reducing veterinary drug residues in animal products: A review. 39(5): 687.
47. Rand, G., Wells, P., & McCarty, L. (2020). Introduction to aquatic toxicology. In Fundamentals of aquatic toxicology (pp. 3-67): CRC Press.
48. Rashid, S. (2017). Cancer and chemoprevention: An overview: Springer.
49. Rath, A. P., Panda, S., Pandey, R., Routray, A., & Sethy, K. J. P. I. J. (2018). Hormone residues in milk and meat products and their public health significance. 7(1): 489-494.
50. Raux, A., Bichon, E., Benedetto, A., Pezzolato, M., Bozzetta, E., Le Bizec, B., & Dervilly, G. J. F. (2022). The Promise and Challenges of Determining Recombinant Bovine Growth Hormone in Milk. 11(3): 274.
51. Ray, P., & Sen, C. J. I. J. A. H. (2019). Biochemical residues in milk and milk products-A review. 58(2): 145-152.
52. Sachi, S., Ferdous, J., Sikder, M. H., Hussani, S. A. K. J. J. o. a. v., & research, a. (2019). Antibiotic residues in milk: Past, present, and future. 6(3): 315.
53. Shaikh, J. R., & Patil, M. (2020). Drug Residues in Milk and Milk Products: Sources, Public Health Impact, Prevention and Control.
54. Sharma, C., Rokana, N., Chandra, M., Singh, B. P., Gulhane, R. D., Gill, J. P. S., . . . Panwar, H. J. F. i. v. s. (2018). Antimicrobial resistance: its surveillance, impact, and alternative management strategies in dairy animals. 4: 237.
55. Silva Meneguelli, T., Viana Hinkelmann, J., Hermsdorff, H. H. M., Zulet, M. Á., Martínez, J. A., & Bressan, J. (2020). Food consumption by degree of processing and cardiometabolic risk: a systematic review. International Journal of Food Sciences and Nutrition, 71(6): 678-692.
56. Średnicka-Tober, D., Barański, M., Seal, C. J., Sanderson, R., Benbrook, C., Steinshamn, H., . . . Eyre, M. J. B. J. o. N. (2016). Higher PUFA and n-3 PUFA, conjugated linoleic acid, α-tocopherol and iron, but lower iodine and selenium concentrations in organic milk: a systematic literature review and meta-and redundancy analyses. 115(6): 1043-1060.
57. Summaries, M. C. J. M. C. S. (2020). US Geological Survey, 2020.
58. Syit, D. A. (2011). Detection and determination of oxytetracycline and penicillin g antibiotic residue levels in bovine bulk milk from debrezeit and nazareth dairy farms. Paper presented at the Proceedings of the 1st International Technology, Education and Environment Conference African Society for Scientific Research.
59. Tadesse, T., & Tadesse, T. J. P. H. (2017). Public health impacts of antibiotic residues in foods of animal origin: A review. 7(10).

60. Teixeira, R. C., Luiz, L. C., Junqueira, G. M. A., Bell, M. J. V., & Anjos, V. C. J. J. o. M. S. (2020). Detection of antibiotic residues in Cow's milk: A theoretical and experimental vibrational study. 1215: 128221.
61. Thorning, T. K., Raben, A., Tholstrup, T., Soedamah-Muthu, S. S., Givens, I., Astrup, A. J. F., & research, n. (2016). Milk and dairy products: good or bad for human health? An assessment of the totality of scientific evidence. 60(1): 32527.
62. Treiber, F. M., & Beranek-Knauer, H. J. A. (2021). Antimicrobial Residues in Food from Animal Origin—A Review of the Literature Focusing on Products Collected in Stores and Markets Worldwide. 10(5): 534.
63. Vanga, S. K., & Raghavan, V. (2017). Processing effects on tree nut allergens: A review. Critical reviews in food science and nutrition, 57(17): 3794-3806.
64. Vaquero-Picado, A., & Rodríguez-Merchán, E. C. (2018). Antibiotic Prophylaxis to Prevent Infection in Total Knee Arthroplasty. In The Infected Total Knee Arthroplasty (pp. 35-46): Springer.
65. Younis, G., Ibrahim, D., Awad, A., & El Bardisy, M. J. A. A. V. S. (2016). Determination of aflatoxin M1 and ochratoxin A in milk and dairy products in supermarkets located in Mansoura City, Egypt. 4(2): 114-121.
66. Zahra, N., Mahnoor, S., Ahad, A., & Ishfaq, R. J. L. G. U. J. o. L. S. (2021). Preamble of Steroids Types and Presence of Androgenic Anabolic Steroids (AAS) in Humans and Animals. 5(02): 110-122.