



Drug Residues in Milk and Milk Products: Sources, Public Health Impact, Prevention and Control

Junaid R. Shaikh^{1*} and M. K. Patil²

¹M.V.Sc. Scholar, Department of Veterinary Pharmacology and Toxicology, College of Veterinary and Animal Sciences, Udgir-413517, MAFSU, Nagpur, Maharashtra, INDIA

²Assistant Professor, Department of Veterinary Pharmacology and Toxicology, College of Veterinary and Animal Sciences, Udgir-413517, MAFSU, Nagpur, Maharashtra, INDIA

*Corresponding Author: dr.junaid084@gmail.com

How to cite this paper: Shaikh, J., & Patil, M. (2020). Drug Residues in Milk and Milk Products: Sources, Public Health Impact, Prevention and Control. *International Journal of Livestock Research*, 10(6), 24-36. doi: <http://dx.doi.org/10.5455/ijlr.20200410024336>

Received : Apr 10, 2020
Accepted : May 11, 2020
Published : Jun 30, 2020

Copyright © Shaikh *et al.*, 2020

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0). <http://creativecommons.org/licenses/by/4.0/>



Abstract

Milk is consumed everywhere throughout the world and it is having nutritional as well as economic importance. Although, milk and milk products are healthy and nutritious, may contain potentially harmful drug 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. Contamination of milk by certain drug residues not only deteriorates the quality but also make the milk unfit for the consumption. The overall public health impact of drug residues in milk and milk products can be minimized by the contribution of farmers, producers, clinicians, researchers, consumers, legislative and other food safety authorities. This review deals with the drug residues in milk and milk products with particular emphasis on sources, impact and their prevention and control.

Keywords: Drug Residues, Milk, Milk Products, Public Health Impact

Introduction

Milk is regarded as complete food and a basic component of various human diets. Since, it is a balanced source of essential nutrients including protein, fat, minerals etc. (Enb *et al.*, 2009). Milk is widely consumed throughout the world by all age groups, particularly infants, children and elderly people (Priyanka *et al.*, 2017). Globally more than 6 billion people are the consumer of milk and milk products (Luiz *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 (Kamthania, 2014; Kurjogi *et al.*, 2019). The occurrence of drug residues affect the quality of milk and milk products and a higher concentration than maximum permissible limits can produce significant health hazards to the consumers (Enb *et al.*, 2009; Priyanka *et al.*, 2017). 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” (FSSA, 2006). The term food safety generally applied to food quality that can cause harmful effects in mankind and includes zoonotic diseases and adverse effects produced by xenobiotics (Lee *et al.*, 2001). Recently, the presence of residues in milk and dairy products and their impact on public health is recognized as a matter of serious concern.

Along with the rise in demand of animal origin food, the need of intensified and well-organised livestock production practices are also increasing which ultimately augment the pharmacotherapy for treatment and prevention of diseases (Mitchell *et al.*, 1998, Lee *et al.*, 2001). India ranks first and contributes 22% of global milk production (FAO, 2020). The country is having a large population of milk-producing animals and the use of veterinary drugs for the treatment of sick animals is an integral part of such extensive husbandry practices (Priyanka *et al.*, 2017). The pharmaceutical products used in veterinary medicine have an extremely wide range which starting from teat dips to the hormones (Michel *et al.*, 1998). Therefore, it is not unlikely that the drug residues appear in the milk and milk products. In order to assure consumer’s safety and good-quality dairy products intended for export, raw milk should be regularly screened for drug residues (Priyanka *et al.*, 2017).

Terminologies and Indices of Drug Level in Food (Lee *et al.*, 2001; VaniPrasad and Koley, 2006)

Drug Residue

Quantity of the drug or pesticide or any other toxicant or their metabolites present in food at the time of ingestion having health hazards to the consumer.

Expressed in parts by weight viz. mg/kg or mg/L.

Unintentional Drug Residues

Drug residues occur in food as a result of circumstances not intended for treatment or protection of animals against diseases.

Target Animal

Species of animal in which the drugs are intended to be used or therapeutic claims have been made by the manufacturer.

Withdrawal Period (WDP)

It is the period in between the last exposure of drug and collection or harvesting of edible product or tissue from the treated animal.

Withdrawal Period = $1.44 \ln (C_0/\text{tolerance}) (t_{1/2})$

Where, C_0 = drug concentration in the target tissue at the end of administration; $t_{1/2}$ = half-life

Acceptable Daily Intake (ADI)

Quantity of chemical or drug that would not cause any harmful effect when consumed on a daily basis during the

entire life span on the basis of all the toxicological facts known at the time.

Expressed as mg per kg of body weight.

Maximal Residual Level (MRL)

The maximum concentration of a drug, toxicant or pesticide recommended by Codex Alimentarius Commission to be legally permitted in or on the food.

Expressed in percentage, µg/kg or µg/l.

No Observable Effect Dose (NOED)

It is the maximum dose of a chemical which does not cause any effect in the subject when administered over a given period of time.

Expressed as mg per kg of body weight.

Lowest Observable Effect Dose (LOED)

It is the minimal dose of a chemical which produces an effect in the subject when administered over a given period of time.

Expressed as mg per kg of body weight.

Tolerance Level

Maximal concentration of residue of a drug or chemicals in food animals that can be permitted at a specific period of harvesting, slaughter or processing; storage marketing up to the time of ingestion by the consumer.

Expressed in parts per million (ppm).

$$\text{Tolerance Level} = \frac{\text{ADI} \times \text{Average consumers body weight}}{\text{Food factor} \times 0.5 \text{ kg food}}$$

Where, ADI= acceptable daily intake; food factors= as recommended by the FDA (3 for cattle milk)

Action Level

Tolerance of unintentional drug residues due to environmental contamination including indirect additives and accidentally or incidentally introduced natural xenobiotics.

Sources of Milk Contamination

The production of milk and milk products is linked to the environment which is somehow designed by human beings (Shitandi and Sternesjo, 2004; Khaniki, 2007). Thus, contamination of milk starts right from the intake of contaminated pasture and drinking water by the animal (Akhtar and Ahad, 2017; Bedi *et al.*, 2018). Further, inappropriate use of veterinary 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 (Khaniki, 2007). Therefore, the milk could be the potential source of drug residues and contaminants in the human diet (Shitandi and Sternesjo, 2004). 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 (Khaniki, 2007). 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 (Luiz *et al.*, 2009).

Table 1: Common chemical and drug residues appearing in the milk

Class	Drugs/ chemicals	References
Antibiotics	Penicillin, oxytetracycline, streptomycin, neomycin, tetracycline, sulfamethazine, gentamycin, enrofloxacin, azithromycin	Brady and Katz (1988); Michel <i>et al.</i> , (1998); Aytenfsu <i>et al.</i> , (2016); Kurjogi <i>et al.</i> , (2019),
Anthelmintics	Closantel, ivermectin, levamisole, albendazole,	Waltner-Toews and McEwen, (1994);
Pesticides	Organochlorines, organophosphates, DDT, HCHs	Akhtar and Ahad, (2017); Bedi <i>et al.</i> , (2018)
Hormones	Bovine somatotropin, progesterone, testosterone	Rath <i>et al.</i> , (2018)
Mycotoxins	Aflatoxin M1, aflatoxin B1	Jawaid <i>et al.</i> , (2015)
Nitrates and Nitrites	Nitrate fertilizers, rodenticides	Aytenfsu <i>et al.</i> , (2016); Chamandust <i>et al.</i> , (2016)
Heavy Metals	Lead (Pb), cadmium (Cd)	Enb <i>et al.</i> , (2009); Chandrakar <i>et al.</i> , (2018)

Antibiotics are used in therapeutics, and prophylaxis of infectious diseases or as a production aid in the food animals (Chauhan *et al.*, 2018). The most commonly used antimicrobial classes in food animals include the beta-lactams, tetracyclines, aminoglycosides, macrolides and sulphonamides as shown in Table 2 (Michel *et al.*, 1998; Priyanka *et al.*, 2017). Some other antibiotics like polymyxin B, colistin, tiamulin, novobiocin and carbadox are commonly used as growth promoters (Lee *et al.*, 2001).

Table 2: Commonly used antibiotics in dairy animals

S. No.	Antibacterial class	Examples of drugs
1	Penicillins	Benzylpenicillin, procaine penicillin, amoxicillin, ampicillin, cloxacillin
2	Cephalosporins	Ceftriaxone, ceftiofur, cefotaxime, ceftizoxime, cefoperazone, cephalexin
3	Aminoglycosides	Streptomycin, dihydrostreptomycin, gentamicin, neomycin, amikacin
4	Tetracyclines	Oxytetracycline, tetracycline, chlortetracycline, doxycycline
5	Macrolides	Erythromycin, tylosin, azithromycin
6	Sulphonamides	Sulfadimidine, sulfamethoxazole, sulfadiazine, sulfanilamide
7	Fluoroquinolones	Enrofloxacin, ciprofloxacin, marbofloxacin, ofloxacin, levofloxacin
8	Other	Chloramphenicol, metronidazole, polymyxin B, colistin, tiamulin, bacitracin

(Sources: Lee *et al.*, 2001; Page and Gautier, 2012, Aytenfsu *et al.*, 2016)

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 additive are administered orally while intramammary route (gel, ointments, and infusions) is considered as the most effective for udder infections (Michel *et al.*, 1998; Page and Gautier, 2012). During the treatment and after a certain time (withdrawal period) of discontinuation of drug therapy these drugs are continuously excreted into the milk (Marth and Ellickson, 1959). Theoretically, all of these routes may lead to residues which are appearing in the milk (Michel *et al.*, 1998; Kurjogi *et al.*, 2019) but intramammary infusions cause a higher incidence of drug residues (Albright *et al.*, 1961). 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 (Priyanka *et al.*, 2017; Sachi *et al.*, 2019). Figure 1 reflects the sources of drug contaminants and chain of the entrance of various drug residues in milk and milk products.

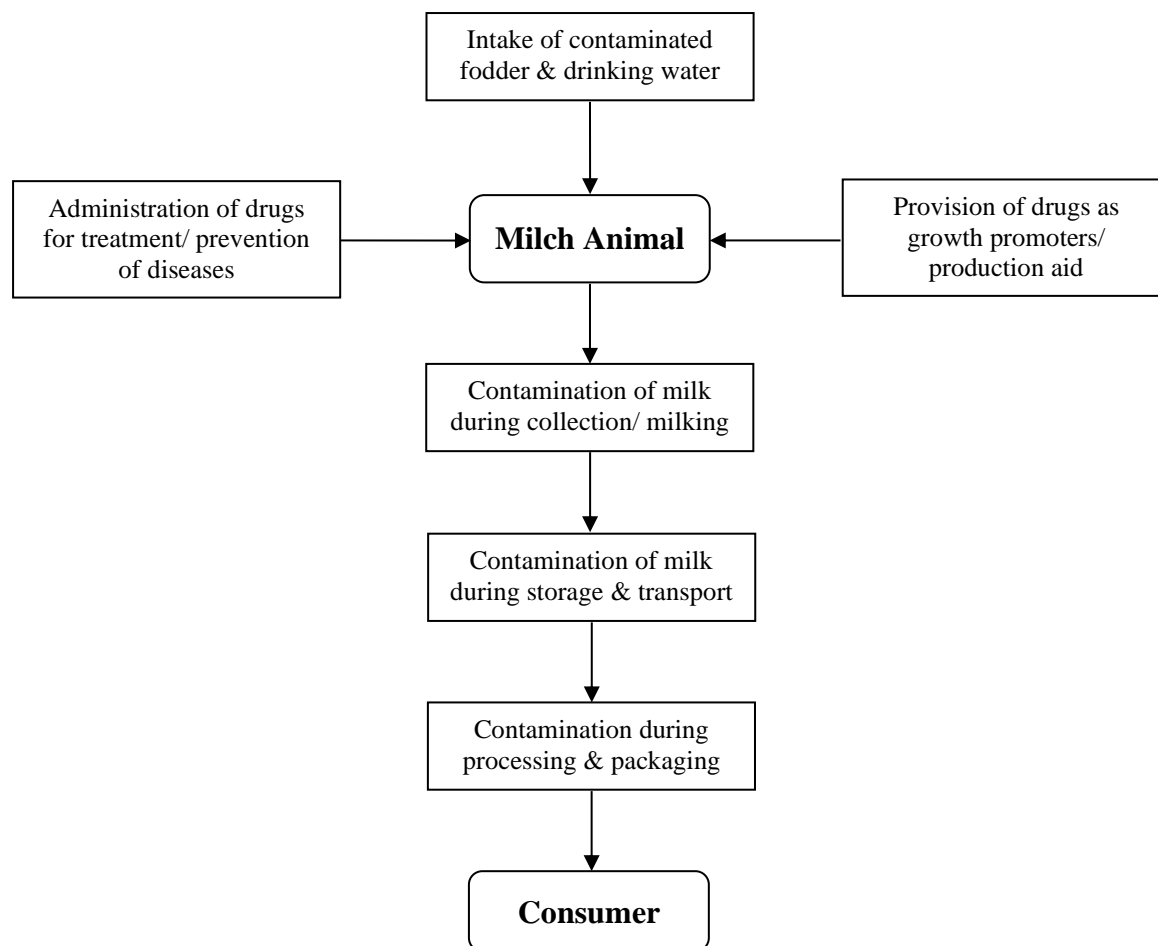


Figure 1: Chain of drug residue introduction in milk and milk products from stable to the table

Public Health Impacts

Recently, the food-borne diseases are emerging as the serious issues because of their significant public health impacts. The food-borne illness occurs due of consumption of food stuffs 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 (Padol *et al.*, 2015). Majority of commonly used drugs are relatively safer even at higher concentration, but few of them can produce serious health impacts (Jayalakshmi *et al.*, 2017). 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 (Gupta, 2019). As far as our topic is concerned, the milk contaminated with drug and chemical residues particularly in a concentration higher than the MRL is harmful to health and should not be used for consumption (Luiz *et al.* 2018). The infants and growing children are at high risk because they consume large quantities of milk and milk products on a body-weight basis (Shitandi and Sternesjo, 2004). The contamination of milk by antibiotics is usually not expressed by milk producer nor by consumer but dairy processors may express because of the inhibition of starter culture and altered dye reduction tests due to the contamination. Some contaminants like penicillins, tetracycline, chloramphenicol, streptomycin and oxytetracycline are not inactivated by the process of pasteurization and even drying cannot detoxify the penicillin residues in milk (Marth and Ellickson, 1995). 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 (Priyanka *et al.*, 2017). The direct-short term hazards usually appear immediately following the drug exposure, for example, the occurrence of allergic and hypersensitive reactions in sensitized individual immediately after consumption of penicillin-contaminated milk. On contrary, long term exposure to the residues provokes indirect and long-term hazards such as carcinogenicity, teratogenicity and reproductive effects (Padol *et al.*, 2015). Further, the presence of drug residues in milk and milk products itself is an aesthetic issue because these are not appealing for the consumers (Gupta, 2019).

Hypersensitive Reaction

The drug-mediated hypersensitivity reactions are of two types, one is IgE-mediated and the other Non-IgE-mediated. The appearance of urticaria, anaphylaxis, bronchospasm and angioedema are some examples of IgE-mediated reactions while, non-IgE-mediated reactions include haemolytic anaemia, thrombocytopenia, acute interstitial nephritis, serum sickness and vasculitis (Bhoomika *et al.*, 2019). In this context, violent allergic reactions like anaphylaxis, serum sickness and cutaneous reaction may occur in response to the exposure of some drugs specially β -lactam antibiotics in sensitized individuals. For the development of penicillin mediated hypersensitive reaction, prior known exposure of penicillin is necessary. 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 amount, the penicillins form reactive neoantigen which produces hypersensitivity mainly the Type I reaction i.e. urticaria. Approximately 10-15% of the human population is considered hypersensitive to the penicillin and the reaction is also seen in the animals (Papich and Riviere, 2009; William and Petri, 2011; Kaplan *et al.*, 2013).

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 long-term basis is of more concern. The AMR not only affect directly causing untoward effects in consumers but also indirectly by spreading the antimicrobial resistance determinants to human pathogens (Prajwal *et al.*, 2017). Although, all the drug-resistant bacterial strains are not pathogenic to the humans, they can transfer their antibiotic resistance genes to other pathogenic bacteria making them also resistant (Bhoomika *et al.*, 2019). Continuous low dose intake of antibiotic for a long duration through contaminated milk and milk products result in antimicrobial resistance. The normal flora and pathogenic bacteria harbouring in the consumer, get unnecessarily exposed to antibiotic residue at sub-therapeutic concentration leading to the development of multi-drug resistant bacterial species such as *Salmonella*, *Staphylococcus* (MRSA), *Campylobacter*, *E. coli* and many other. Further, these organisms transfer the resistance genes to other species and to the next generation as well. The resistant organisms get access to the human beings through direct contact or indirectly through the animal origin food including milk to produces serious infections which are very challenging to treat (Beyene, 2016; Tilahun *et al.* 2016; Patnaik *et al.*, 2019). Antimicrobials like fluoroquinolones and avoparicin have become ineffective against various microbial species against whom these were quite effective. Further, the indiscriminate use of avoparicin 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 (Prajwal *et al.*, 2017, Bhoomika *et al.*, 2019).

Carcinogenicity

It is a cancer-producing ability of a drug or a chemical in the presence or absence of initiator or promoter (Lee *et al.*, 2001). 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 diethyl stilbestrol, on chronic exposure, leads to vaginal clear cell adenocarcinoma in female offsprings and also causes benign structural abnormalities (Bhoomika *et al.*, 2019). Similarly, hormone-related cancer, including cancer of breast, ovary, prostate, testes and colon have been reported following ingestion of milk with hormonal residues (Klaunig, 2013; Aytenfsu *et al.*, 2016).

Teratogenicity

Teratogenicity is an ability of a drug or a chemical to produce harmful and toxic effects on developing embryo or foetus during critical phase of pregnancy (Lee *et al.*, 2001). Developmental toxicity, embryotoxicity or teratogenic effects are reported due to the exposure of some pharmaceuticals during pregnancy. The teratogenic drugs include some chemotherapeutic agents (thalidomide), anthelmintics (albendazole), antibiotics (tetracyclines, aminoglycosides), antiepileptics (carbamazepine), hormones (diethylstilbestrol, misoprostol) and other drugs like ACE inhibitors, cyclophosphamide, methimazole etc. (Rogers, 2013; Tilahun *et al.*, 2016).

Mutagenicity

Mutagenicity refers to the ability of a chemical or drug to produce alteration in DNA molecule or the genetic component of a cell in an organism (Prajwal *et al.*, 2017). Some of the drugs have the potential to cause DNA mutation or chromosomal damage subsequently leading to infertility in human being (Sachi *et al.*, 2019). The metronidazole, a nitroimidazole derivative is reported to possess mutagenic and genotoxic activities. It has produced DNA strand break down and DNA fragmentation in human peripheral blood lymphocyte and the hepatocytes, respectively. Further, tinidazole and chloroquine drugs have also been found to be potentially mutagenic (Sahu *et al.*, 2016). 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 nitroimidazole, metronidazole, tetracyclines, penicillins, tylosin, streptomycin etc. as residues in milk, causes disruption of the normal gut flora and resulting in gastrointestinal disturbances (Beyene, 2016). Disruption of the normal bacterial flora of gut may result in gastro-intestinal disturbances and allows pathogens to invade and multiply in the host. In some severe cases pseudomembranous colitis, *Clostridium difficile*-associated diarrhoea and other life-threatening infections may occur (Ritter *et al.* 2020). 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 being (Prajwal *et al.*, 2017).

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 interfere with the fermentation process during the production of yoghurt, cheese and other fermented dairy products (Khaniki, 2007; Sachi *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 (tetracyclines, chloramphenicol), endocrine disruption (HCHs), anaemias (chloramphenicol, sulphonamides), photosensitization (tetracyclines), gastro-enteric disturbances (erythromycin, fluoroquinolones) acute and chronic toxicities of various tissues and body systems (Khaniki 2007; Aytenfsu *et al.*, 2016; Priyanka *et al.*, 2017).

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)-

- a) Bioassays
- b) Receptor assay
- c) Microbiological assays
- d) Enzymatic assays
- e) Enzyme-linked Immunosorbent Assay (ELISA)
- f) Thin Layer Chromatography (TLC)
- g) Paper chromatography
- h) Gas Chromatography-Mass Spectrometry (GC-MS)
- i) Liquid Chromatography-Mass Spectrometry (LC-MS)
- j) High-Performance Liquid Chromatography (HPLC)
- k) Fourier Transform Near-Infrared (FT-NIR) Spectroscopy
- l) Fourier Transform Medium-Infrared (FT-MIR) Spectroscopy

Control and Preventive Measures

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).

Table 3: Acceptable Daily Intake (ADI) and Maximum Residual Limits (MPL) of some chemicals and veterinary drugs, in cow milk (Codex Alimentarius, 2011 and 2018)

Category	Drugs	ADI ($\mu\text{g}/\text{kg bw}$)	MRL ($\mu\text{g}/\text{kg}$)
Antimicrobial Agents	Amoxicillin	2 ^{***}	4
	Benzylpenicillin	30	4 [*]
	Procaine penicillin	30	4 [*]
	Colistin	0-7	50
	Gentamicin	0-20	100 [*]
	Tetracycline	0-30	100 [*]
	Oxytetracycline	0-30	100 [*]
	Chlortetracycline	0-30	100 [*]
	Tylosin	0-30	100
	Ceftiofur	0-50	100 [*]
	Lincomycin	0-30	150
	Spectinomycin	0-40	200 [*]
	Dihydrostreptomycin/ Streptomycin	0-50	200
	Spiramycin	0-50	200 [*]
	Neomycin	0-60	1500
	Sulphadimidine	0-50	25 [*]
Monensin	0-10	2	
Anthelmintics	Ivermectin	0-10	10
	Doramectin	15	15
	Albendazole	0-50	100 [*]
	Febantel/ Fenbendazole/ Oxfendazole	0-7	100 [*]
	Thiabendazole	0-100	100 [*]
Antiprotozoal drugs	Imidocarb	0-10	50
	Diminazene	0-100	150 [*]
	Isometamidium	0-100	100 [*]
Insecticides	Deltamethrin	0-10	30
	Cyfluthrin	0-20	40 [*]
	Cypermethrin	0-20	100
	α -cypermethrin	0-20	100
Hormones (Production aids)	Estradiol-17 β	0-0.05	NS
	Melengestrol acetate	0-0.03	NS
	Progesterone	0-30	NS
	Testosterone	0-2	NS
	Bovine somatotropin	NS	NS
	Porcine somatotropin	NS	NS
Other drugs	Clenbuterol	0-0.004	0.05 [*]
	Dexamethasone	0-0.015	0.3 [*]
Heavy metals	Lead	NS	20 ^{**}
Mycotoxins	Aflatoxin M1	NS	0.5 ^{**}

* = values are expressed in $\mu\text{g}/\text{L}$ of milk; ** = values are Codex maximum level (ML) adapted from CAC (2011); *** = denotes Microbiological Acceptable Daily Intake (mADI); NS = Not specified

In India, the Food Safety and Standards Authority of India (FSSAI) is the regulatory and law enforcing body, established under The Food Safety and Standards Act, 2006. The FSSAI monitor and regulate the production, processing, storage, distribution and sale of various food stuffs 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 limit 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 etc. 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 licence". Carrying out a food business without a licence 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, nitrofur 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 4 (FARAD, 2020). But these established withdrawal periods may vary according to the policy of the country (Riviere and Papich, 2018).

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

Category	Drugs	Route of Drug Administration					
		IV	IM	SC	PO	IMa	Top
Antimicrobial Drugs	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	–
	Flofenicol	–	–	–	–	120 H	–
	Ceftiofur	0**					
	Monensin	0*					
Anthelmintics	Ivermectin	–	–	47 D	28 D	–	53 D
	Moxidectin	–	–	–	–	–	0
	Morantel	0*					
	Thiabendazole	4 D*					
Sedatives	Acepromazine	48 H	48 H	–	–	–	–
	Detomidine	72 H	72 H	–	–	–	–
	Xylazine	72 H	24-120 H	–	–	–	–
Anaesthetics	Guaifenesin	48 H	–	–	–	–	–
	Ketamine	48 H	48 H	–	–	–	–
Local anaesthetics	Lignocaine	24 H (Epidural); 72 H (Infiltration)					
NSAIDs	Flunixin meglumine	84 H	72-96 H	96 H	96 H	–	–
Other Drugs	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 Gieger *et al.*, 2013)

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). Further, most of the countries mandate the drug manufacturer to provide a withdrawal time as a product label (Archimbault, 1983). In India, the rule 97 (sub-rule 3A) of Drugs and Cosmetics Rules, 1945, specifies that "the container of a medicine for treatment

of food producing animals shall be labelled with the withdrawal period of the drug for the species on which it is intended to be used". Further, it explains that if the specific withdrawal period has not been validated, the withdrawal period shall not be less than seven days for milk (DCR, 1945). The presence of disease processes, for example, nephritis, mastitis and hepatitis can substantially alter the normally accepted withdrawal times (Jenkins and Friedlander, 1983). Therefore, the veterinary practitioner should have a good knowledge of the various parameters which can influence the excretion of drugs to fix WDPs according to the particular cases he has on hand (Boisseau and Moretain, 1983)

Guidelines to Minimize Drug Residues in Milk and Milk Products

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). The guidelines are summarised as follow-

- a) Implementation of regulatory laws at dairy farms and dairy industries.
- b) Training of farmers and animal keepers for clean and contaminant-free milk production
- c) Hygienic and proper management practices at animal farms and dairy units.
- d) Well-planned drug use program, including rational antibiotic use, avoidance of drugs not meant for dairy animals and sticking-up with the label guidelines
- e) Withholding the milk from the animals on medication for a specific time (withdrawal period) as specified by the authority or manufacturer or should not be less than seven days for milk
- f) Encouraging use of safe alternate medicine and ethno-veterinary practices
- g) 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.
- h) Monitoring, screening and surveillance of milk residues by aforementioned methods.

Conclusion

Although milk is a nutritious, healthy and widely consumed food, it may be contaminated by various harmful drug residues. Along with the tremendous growth in the dairy industry in terms of adaption of modern techniques in processing and production, there is a huge need to regulate milk and milk product quality to ensure public safety. The contaminants as drug 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. Practically it is very difficult to completely prevent or eliminate the chemical and drug residues from milk and milk product. However, by implementing proper food safety measures the drug residues can be minimized to a level that is safe. 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.

Conflict of Interests

There is no conflict of interest.

Publisher Disclaimer

IJLR remains neutral concerning jurisdictional claims in published institutional affiliation.

References

1. Akhtar, S., & Ahad, K. (2017). Pesticides residue in milk and milk products: Mini review. *Pakistan Journal of Analytical & Environmental Chemistry*, 18(1), 37-45.
2. Albright, J. L., Tuckey, S. L., & Woods, G. T. (1961). Antibiotics in milk—a review. *Journal of Dairy Science*, 44(5), 779-807.

3. Archimbault, P. (1983). Persistence in milk of active antimicrobial intramammary substances, In: Veterinary Pharmacology and Toxicology (Ruckebusch, Y., Toutain, P. L., & Koritz, G., D.), Edn 1, MTP press limited, Lancaster, pp 647-657.
4. Aytenfsu, S., Mamo, G., & Kebede, B. (2016). Review on chemical residues in milk and their public health concern in Ethiopia. *Journal of Nutrition & Food Sciences*, 6(4), 1-11.
5. Bedi, J.S., Gill, JPS, Kaur P, Aulakh RS (2018). Pesticide residues in milk and their relationship with pesticide contamination of feedstuffs supplied to dairy cattle in Punjab (India). *Journal of Animal Feed Science*. 27(1),18-25.
6. Beyene, T. (2016). Veterinary Drug Residues in Food-animal Products: Its Risk Factors and Potential Effects on Public Health. *Journal of Veterinary Science and Technolgy* 7, 285.
7. 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.
8. Boisseau, J., & Moretain, J. P. (1983). Drug excretion by the mammary gland, In: Veterinary Pharmacology and Toxicology (Ruckebusch, Y., Toutain, P. L., & Koritz, G., D.), Edn 1, MTP press limited, Lancaster, pp 193-202.
9. Brady, M. S., & Katz, S. E. (1988). Antibiotic/antimicrobial residues in milk. *Journal of food protection*, 51(1), 8-11.
10. Chamandust, S., Mehresebi, M. R., Kamali, K., Solgi, R., Taran, J., Nazari, F., & Hosseini, M. J. (2016). Simultaneous determination of nitrite and nitrate in milk samples by ion chromatography method and estimation of dietary intake. *International Journal of food properties*, 19(9), 1983-1993.
11. Chandrakar, C, Jaiswal SK, Chaturvedani AK, Sahu SS, Monika WU (2018). A Review on Heavy Metal Residues in Indian Milk and their Impact on Human Health. *International Journal of Current Microbiology and Applied Sciences*, 7(05), 1260-1268.
12. Chauhan, A. S., George, M. S., Chatterjee, P., Lindahl, J., Grace, D., & Kakkar, M. (2018). The social biography of antibiotic use in smallholder dairy farms in India. *Antimicrobial Resistance & Infection Control*, 7(1), 60.
13. Codex Alimentarius (FAO/WHO): International Food Standard (2015). General Standard for Contaminants and Toxins in Food and Feed (CODEX STAN 193-1995), Retrieved from: http://www.fao.org/input/download/standards/17/CXS_193e_2015.pdf
14. Codex Alimentarius (FAO/WHO): International Food Standard (2018). Maximum Residue Limits (MRLS) and Risk Management Recommendations (RMRS) for Residues of Veterinary Drugs in Foods, Retrieved from: <http://www.fao.org/fao-who-codexalimentarius/codex-texts/maximum-residue-limits/en/>.
15. DCA (1945). The Drugs and Cosmetics Rules, 1945, Retrieved from: <http://vbch.dnh.nic.in/pdf/Rules%20and%20regulations%20of%20Drug%20and%20Cosmetics%20act.pdf>
16. Enb, A., Abou Donia, M. A., Abd-Rabou, N. S., Abou-Arab, A. A. K., & El-Senaity, M. H. (2009). Chemical composition of raw milk and heavy metals behavior during processing of milk products. *Global Veterinaria*, 3(3), 268-275.
17. FAO (2020). Milk production. Retrieved from: <http://www.fao.org/dairy-production-products/production/en/>.
18. FARAD (2020). Food Animal Residue Avoidance Databank, Retrieved from: <http://www.farad.org/>
19. FDA (2015). Multicriteria-based Ranking Model for Risk Management of Animal Drug Residues in Milk and Milk Products. Retrieved from: <https://www.fda.gov/food/cfsan-risk-safety-assessments/multicriteria-based-ranking-model-risk-management-animal-drug-residues-milk-and-milk-products>.
20. FSSA (2006). The Food Safety and Standards Act, 2006. Retrieved from: <https://fssai.gov.in/cms/food-safety-and-standards-act-2006.php>.
21. FSSAI (2016a). Manual of Methods of Analysis of Foods: Antibiotics and Hormone Residues. Retrieved from: <https://fssai.gov.in/cms/manuals-of-methods-of-analysis-for-various-food-products.php>
22. FSSAI (2016b). Manual of Methods of Analysis of Foods: Pesticide Residues. Retrieved from: <https://fssai.gov.in/cms/manuals-of-methods-of-analysis-for-various-food-products.php>
23. Giguere, S., Prescott, J. F., & Dowling, P. M. (2013). Antimicrobial Therapy in Veterinary Medicine. Edn 5, John Wiley & Sons, Inc, Iowa.
24. Gupta P. K. (2019). Concepts and Applications in Veterinary Toxicology: An Interactive Guide. Springer Nature Switzerland AG, Cham, pp. 301-308.
25. Jawaaid, S., Talpur, F. N., Nizamani, S. M., & Afridi, H. I. (2015). Contamination profile of aflatoxin M1 residues in milk supply chain of Sindh, Pakistan. *Toxicology reports*, 2, 1418-1422.

26. Jayalakshmi, K., Paramasivam, M., Sasikala, M., Tamilam, T. V. and Sumithra A. (2017). Review on antibiotic residues in animal products and its impact on environments and human health. *Journal of Entomology and Zoology Studies*; 5(3), 1446-1451.
27. Jenkins, W. L., & Friedlander, L. G. (1983). Oral antibacterial therapy in pre- and post-weaning calves, In: *Veterinary Pharmacology and Toxicology* (Ruckebusch, Y., Toutain, P. L., & Koritz, G., D.), Edn 1, MTP press limited, Lancaster, pp 141-150.
28. Jones, G. M. (1999). On-farm tests for drug residues in milk. *Virginia Cooperative Extension*, 404-401. Retrieved from: <https://www.pubs.ext.vt.edu/404/404-401/404-401.html>
29. Kamthania, M., Saxena, J., Saxena, K., & Sharma, D. K. (2014). Milk Adulteration: Methods of Detection & Remedial Measures. *International Journal of Engineering and Technical Research*, 1, 15-20.
30. Kaplan, B. L. F., Sulentic, C. E. W., Holsapple, M.P., Kaminski, N. E. (2013). Toxic Responses of the Immune System In: Casarett and Doull's *Toxicology: The Basic Science of Poisons* (Klaassen, C. D.), Edn. 8, McGraw Hill Education, New York. pp 559-638.
31. Khaniki, G. R. J. (2007). Chemical contaminants in milk and public health concerns: a review. *International Journal of Dairy Science*, 2(2), 104-15.
32. Klaunig, J. E. (2013). Chemical Carcinogenesis, In: Casarett and Doull's *Toxicology: The Basic Science of Poisons* (Klaassen, C. D.), Edn. 8, McGraw Hill Education, New York. pp 393-443.
33. Kurjogi, M., Mohammad, Y. H. I., Alghamdi, S., Abdelrahman, M., Satapute, P., & Jogaiah, S. (2019). Detection and determination of stability of the antibiotic residues in cow's milk. *PloS one*, 14(10), 1-14.
34. Lee, M. H., Lee, H. J., & Ryu, P. D. (2001). Public health risks: Chemical and antibiotic residues-review. *Asian-Australasian Journal of Animal Sciences*, 14(3), 402-413.
35. Luiz, L. D. C., Bell, M. J. V., Rocha, R. A. D., Leal, N. L., & Anjos, V. D. C. D. (2018). Detection of Veterinary Antimicrobial Residues in Milk through Near-Infrared Absorption Spectroscopy. *Journal of Spectroscopy*, 1-6.
36. Marth, E. H., & Ellickson, B. E. (1959). Antibiotic residues in milk and milk products—A review. *Journal of Milk and Food Technology*, 22(8), 241-249.
37. Mitchell, J. M., Griffiths, M. W., McEwen, S. A., McNab, W. B., & Yee, A. J. (1998). Antimicrobial drug residues in milk and meat: causes, concerns, prevalence, regulations, tests, and test performance. *Journal of food protection*, 61(6), 742-756.
38. Padol, A. R., Malapure, C. D., Domple, V. D., Kamdi B. P. (2015). Occurrence, Public Health Implications and Detection of Antibacterial Drug Residues in Cow Milk. *Environment & We an International Journal of Science & Technolog*, 10, 7-28.
39. Page, S. W., & Gautier, P. (2012). Use of antimicrobial agents in livestock. *Revue Scientifique et Technique-OIE*, 31(1), 145-188.
40. Papich, M. G., Riviere, J. E. (2009). β -Lactam Antibiotics: Penicillins, Cephalosporins, and Related Drugs, In: *Veterinary Pharmacology and Therapeutics* (Riviere, J. E., Papich, M. G. & Adams, H. R.), Edn. 9, Wiley-Blackwell. pp 865-893.
41. Patnaik, N. M., Das, A., & Mandi, K. (2019). Antimicrobial Use and Resistance Issues in Livestock Sector: A Review. *International Journal of Livestock Research*, 9(12), 1-7.
42. Prajwal, S., Vasudevan, V. N., Sathu, T., Irshad, A., Nayankumar, S. R., & Pame, K. (2017). Antibiotic residues in food animals: Causes and health effects. *The Pharma Innovation Journal*, 6, 1-4.
43. Priyanka, P. S., Sheoran, M. S., & Ganguly, S. (2017). Antibiotic residues in milk—a serious public health hazard. *Journal of Environment and Life Sciences*, 2(4), 99-102.
44. Rath, A. P., Panda, S., Pandey, R., Routray, A., Sethy, K. (2018). Hormone residues in milk and meat products and their public health significance. Conference proceeding. Retrieved from : <https://www.semanticscholar.org/paper/Hormone-residues-in-milk-and-meat-products-and-Rath-Panda/d96ce7e3e92edc406eb654d299b247872c982432>.
45. Ritter, J. M., Flower, R., Henderson, G., Loke, Y. K., MacEwan, D., Rang, H. P. (2020). Rang and Dale's *Pharmacology*. Edn. 9, Elsevier Ltd.
46. Riviere, J. E., & Papich, M. G. (2018). *Veterinary Pharmacology and Therapeutics*. Edn 10. John Wiley & Sons, Inc., Hoboken.
47. Riviere, J. E., Sundlof, S. F. (2009). Chemical Residues in Tissues of food Animals In: *Veterinary Pharmacology and Therapeutics* (Riviere, J. E., Papich, M. G. & Adams, H. R.), Edn. 9, Wiley-Blackwell. pp 1453-1462.
48. Rogers, J. M. (2013). Developmental Toxicology, In: Casarett and Doull's *Toxicology: The Basic Science of Poisons* (Klaassen, C. D.), Edn. 8, McGraw Hill Education, New York. pp 481-523.

49. Sachi, S., Ferdous, J., Sikder, M. H., & Hussani, S. A. K. (2019). Antibiotic residues in milk: Past, present, and future. *Journal of advanced veterinary and animal research*, 6(3), 315-332.
50. Sahu, R., Kashyap, P., Tripathi, A. K., Pradhan, D. K., & Kashyap, P. Genotoxic and Mutagenic Effects of Three Commonly Used Antiamoebic Drugs: Meteronidazole, Tinidazole and Chloroquine. *Indian Journal of Pharmaceutical Science & Research*, 6(2), 78-86.
51. Shitandi, A., & Sternesjo, A. (2004). Factors contributing to the occurrence of antimicrobial drug residues in Kenyan milk. *Journal of food protection*, 67(2), 399-402.
52. Tilahun, A., Jambare, L., Teshale, A., & Getachew, A. (2016). Review on chemical and drug residue in meat. *World J. Agric. Sci*, 12, 196-204.
53. VaniPrasad, V., Koley, K. M. (2006). Synopsis of Veterinary Pharmacology and Toxicology. Edn 1, Vahini Publications, Parbhani, pp 312-317.
54. Waltner-Toews, D., & McEwen, S. A. (1994). Residues of antibacterial and antiparasitic drugs in foods of animal origin: a risk assessment. *Preventive Veterinary Medicine*, 20(3), 219-234.
55. William A, Petri Jr. (2011). Penicillins, Cephalosporins, and other β -Lactam Antibiotics, In: Goodman & Gilman's - The Pharmacological Basis of Therapeutics (Brunton, L. L., Chabner, B. A. & Knollmann, B. C.). Edn. 12, The McGraw-Hill Companies, Inc., pp 1477-1503.
