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VARIOUS PHARMACEUTICALS INCLUDING DRUGS AND INDUSTRIAL CHEMICALS AS ENVIRONMENTAL HEALTH HAZARDS

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ABSTRACT

This review describes the potential and, in particular, some relevant hazards associated with the use of veterinary drugs, various pharmaceuticals and industrial chemicals that have produced serious environmental risks and affected the life of people along with other animals by posing great health risks. Risk analysis regarding these problems has also been discussed with the measures to handle the problem at global level. The most contentious residues which occur in meat, milk and eggs along with the environment are antibacterial drugs, hormonal growth promoters, heavy metals and industrial chemicals that are producing potential toxic health effects that include systemic toxicity, mutations, cancer, birth defects and reproductive disorders. Systemic toxicity involves changes in the structure and function of organs and organ systems: weight change, structural alterations and changes in organ system or whole animal function. Functional effects may include changes in the lungs, liver, kidneys, cardiovascular function, brain, nervous system activity, behavior and in production of resistance to disease. Furthermore, continued monitoring and periodic reassessment of risks posed by these contaminants is needed to detect or anticipate new problems so that appropriate action can be taken in the interests of public safety.

INTRODUCTION: Environmental health is the branch of public health that is concerned with all aspects of the natural and built environment that may affect human health. Other terms that concern or refer to the discipline of environmental health include environmental public health and environmental health and protection. Environmental health addresses all human-health-related aspects of both the natural environment and the built environment. According to recent estimates, about 5 to 10 % of disability adjusted life years (DAILY) lost is due to environmental causes in Europe.

Environmental exposures have been estimated to contribute to 4.9 million (8.7%) deaths and 86 million (5.7%) deaths globally [1]. Environmental contamination of food refers to the presence in food of harmful chemicals and microorganisms which can cause consumer illness. A separate issue is genetically modified food, or the presence in foods of ingredients from genetically modified organisms, also referred to as a form of food contamination. Environmental contaminants include substances from natural sources or from industry and agriculture.

Many of the naturally occurring contaminants in food are of microbiological origin and consist of harmful bacteria, bacterial toxins and fungal toxins (Aflatoxin a contaminant of peanuts and grains is an example of a fungal toxin or mycrotoxin). The second category of environmental contaminants includes organic chemicals, metals and their complexes and radionuclides that are introduced into food as a result of human activities such as agriculture, mining and industry. The environmental contamination of food is a result of our modern, high-technology society. We produce and consume large volumes of a wide variety of substances, some of which are toxic.

Environmental contamination of food takes two forms; long-term low-level contamination resulting from gradual diffusion of persistent chemicals through the environment and relatively shorter term, higher level contamination stemming from industrial accidents and waste disposal. An example of low-level contamination is polychlorinated biphenyls (PCBs). This group of substances was widely used in transformers and capacitors, as heat- transfer fluids and as an additive in dyes, carbon paper, pesticides and plastics. An example of the second type of contamination is polybrominated biphenyls (PBBs) in dairy products and meat. PBBs, a fire retardant were accidentally mixed into animal feed.

Dairy cattle that were fed the contaminated food produced contaminated milk. The distinctions between the two types of food contamination are not exclusive. For example, PBBs have now become a long-term, low-level contaminant in Michigan because they are very stable and resistant to decay. Animals raised on farms affected by the original feed contamination are now contaminated by the PBB residues remaining in the pastures and farm buildings [2].

Microbial hazards like bacteria (*Salmonella*, *Campylobacter*, *Listeria*, *Clostridium botulinum*, *Escherichia coli* O157:H7); viruses (Calicivirus, Rotavirus, Hepatitis A virus); parasites (*Trichinella*, *Giardia*, *Sarcocystis*, *Cryptosporidium*); zoonosis (BSE, Campylobacteriosis, Salmonellosis) and natural toxins (Mycotoxins, Shellfish toxins, Glycoalkaloids, Lectins) can enter foods at many points from production to consumption [3].

The prevalence and concentration of hazard changes markedly at different points along the food production chain. Health risks are usually acute and result from a single edible portion of food. Individuals show a wide variability in health response to different levels of hazard. Chemical hazards like heavy metals (Pb, Cd, Hg); pesticide residues; veterinary drug residues; environmental pollutants; hazardous chemicals generated during cooking process (acrylamide, 3-MCPD, PAHs, HCAs, etc.); radionuclides usually enter foods in the raw food or ingredients, or through certain processing steps (e.g. acrylamide or packaging migrants).

The level of hazard present in a food after the point of introduction often does not significantly change. Health risks may be acute but are generally chronic. Types of toxic effects are generally similar from person to person, but individual sensitivity may differ. Foods from animals (principally meat, fish, milk and eggs) can potentially be contaminated with one or more of the thousands of man-made chemicals which are used in society. Relatively few of these occur with any regularity in foods from animals, and the most contentious residues (in terms of probability of occurrence and impact on human health, trade or consumer confidence) are antibacterial drugs, hormonal growth promoters or production adjuncts, polyhalogenated hydrocarbon pesticides, industrial chemicals and heavy metals.

Low levels of veterinary medicines have been detected worldwide in soils, surface waters, and ground waters. The most common pharmaceuticals detected during a survey conducted by the USA were steroids and nonprescription drugs; detergents, fire retardants, pesticides, natural and synthetic hormones, and an assortment of antibiotics and prescription medications. A study found detectable concentrations of 28 pharmaceutical compounds in sewage treatment plant effluents, surface water, and sediment [4].

The therapeutic classes included antibiotics, analgesics and anti-inflammatories, lipid regulators, beta-blockers, anti-epileptics, and steroid hormones. An increase in the use of veterinary drugs, including growth promoters, is a predictable consequence of expanded food animal production efforts.

In order to ensure a safe and saleable food product for both local consumption and international trade, developing countries require the capacity to operate quality assured testing programmes for detection of these regulated residues in food animals and their products. While assays for food contaminants (veterinary drug and pesticide residues, microbial pathogens, etc.) can be performed using a number of techniques at different stages of production, the ante-mortem or at slaughter testing of livestock or livestock products (milk, meat, cheese, etc.) provides the most practical avenue for large-scale analysis both for home consumption or for export purposes.

There have been incidents of illegal use of hormones in animal production, media reports of drug residues in milk, and considerable public debate about bovine somatotropin (BST) use in dairy cattle. The association of diethylstilbestrol (DES) with cancer in the daughters of women treated with this hormone raised questions about the safety of using DES as a growth promoter in animals [5]. Until very recently, the principal food safety issue in the mind of the public was chemical residue contamination and food additives [6].

Veterinary medicines are widely used to treat disease and protect the health of animals. Some drugs are considered feed additives, often improving and thereby allowing animals to be brought to market faster and at lower cost. Livestock farmers supplement their animal feed with a wide range of compounds from a number of therapeutic classes, including antimicrobials, antiprotozoals, ecto- and endo-parasiticides, and hormones. Many of the substances, such as cypermethrin, diazinon, and oxytetracycline, are used as pesticides or human medicines. Obtaining information on the usage of individual veterinary medicines is difficult, which makes the design of monitoring and experimental studies problematic.

However, limited data on the sale and usage of the different chemical classes in countries such as the United Kingdom, Denmark, Germany, and The Netherlands are available in the public domain [7]. Detailed data from the United Kingdom, The Netherlands, and Denmark indicate that antimicrobial substances are sold in the highest amounts followed by coccidiostats, sheep dip chemicals, growth promoters, endoparasitic wormers, antifungals, anti-inflammatory preparations, and enteric preparations. Several other groups of chemicals may also be potentially important because of their heavy usage, including antiseptics, steroids and other hormones, diuretics, cardiovascular and respiratory treatments, and immunological products. The impacts of selected compounds most notably anti-helmintics and selected antibacterial compounds have been extensively investigated but many other substances found in the environment are not well understood.

Veterinary medicines can enter the environment via different pathways, including emissions during the manufacture, formulation, and treatment processes, and as a result of the disposal of unused medicines and their containers. The most important routes of entry into the environment are excretion of substances in urine and feces of livestock animals, and the wash off of topical treatments from livestock animals as shown in **figure 1**.

Veterinary medicines may degrade biotically or abiotically in soils and water. Generally, these processes will reduce the potency of the veterinary medicines; however, some degradation products have similar toxicity to their parent compound. Daphnids and fish appear to be sensitive to the macrocyclic lactones. Earthworms appear to be sensitive to parasiticides, whereas, plants appear to be sensitive to many of the antimicrobial groups. The antimicrobial compounds are most toxic to soil microbes. Numerous studies suggest a link between antibacterial use in agriculture and antibacterial-resistant infections, and there is evidence that antibacterial resistance from agriculture can be transferred to humans.

Targeted ecotoxicological studies are needed to investigate the potential subtle and long-term effects of veterinary medicines in the environment, effects of degradation products, interactions of veterinary medicines and their mixtures with other classes of chemicals, and what, if any, role the environment plays in the transfer of antimicrobial resistance to humans and farm animals. In this review environmental health hazards particularly from the use of various veterinary drugs, pharmaceuticals and industrial chemicals have been discussed in relation to their adverse effects on human and animal health.

Impact of Pharmaceuticals and Personal Care Products on Environment: The environmental impact of pharmaceuticals and personal care products (PPCPs) is largely speculative. PPCPs are substances used by individuals for personal health or cosmetic reasons and the products used by agribusiness to boost growth or health of livestock. PPCPs have been detected in water bodies throughout the world. The effects of these chemicals on humans and the environment are not yet known, but to date there is no scientific evidence that they have an impact on human health. Pharmaceuticals", or prescription and over-the-counter medications made for human use or veterinary or agribusiness purposes, are common PPCPs found in the environment [8]. Antibiotics, nutraceuticals (e.g., vitamins), supplements, and sexual enhancement drugs are contained in this group. "Personal care products" may include cosmetics, fragrances, menstrual care products, lotions, shampoos, soaps, toothpastes, and sunscreen.

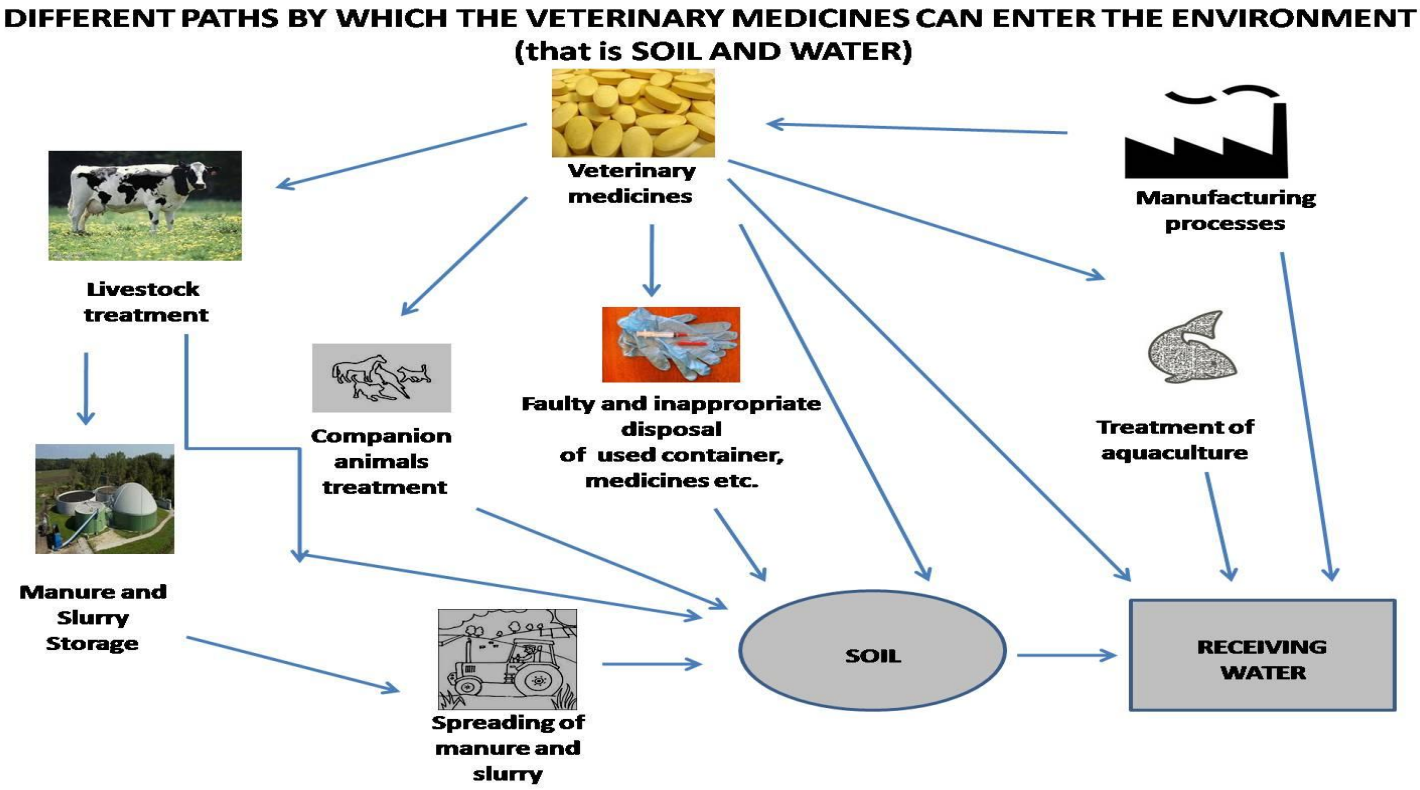

FIG. 1: PATHWAYS INTO THE ENVIRONMENT FOR VETERINARY MEDICINES [97]

These products typically enter the environment when passed through or washed off the body and into the ground or sewer lines, or when disposed of in the trash, septic tank, or sewage system. Illicit drugs such as methamphetamine and cocaine are another type of PPCP. The manufacturers of these products may accidentally spill or purposefully dump harmful byproducts directly into the environment. Drug users also introduce these substances into the environment when handling drugs and when the substances pass through their bodies and into a septic tank or sewage system [9]. Traces of illicit drugs can be found in waterways and may even be carried by money [10].

The use of pharmaceuticals and personal care products (PPCPs) is on the rise with an estimated increase from 2 billion to 3.9 billion annual prescriptions between 1999 and 2009 in the United States alone[4]. PPCPs enter into the environment through individual human activity and as residues from manufacturing, agribusiness, veterinary use, and hospital and community use.

Individuals may add PPCPs to the environment through waste excretion and bathing as well as by directly disposing of unused medications to septic tanks, sewers, or trash. Because, PPCPs tend to dissolve relatively easily and do not evaporate at normal temperatures, they often end up in soil and water

bodies. Some PPCPs are broken down or processed easily by a human or animal body and/or degrade quickly in the environment. However, others do not break down or degrade easily. The likelihood or ease with which an individual substance will break down depends on its chemical makeup and the metabolic pathway of the compound.

Antibiotics in the Environment: Pharmaceuticals are designed to stimulate a physiological response in humans, animals, bacteria or other organisms. Among a number of potential sources for this antibiotic effluence, land application of livestock manure containing residual veterinary antibiotics (VAs) appeared to be the dominant pathway for the release of antibiotics to the environment [11]. Antibiotics are widely used in livestock production for disease prevention and growth promotion [12], with significant quantities of antibiotics used as a feed supplement for growth enhancement of food animals [13, 14].

The selection and development of antibiotic-resistant bacteria is one of the greatest concerns with regard to the use of antimicrobials [15, 16, 17]. Bacteria are able to survive because they have certain genetic material that is coded for resistance-allowing them to avoid the effects of the antibiotic. The surviving bacteria that are resistant to antibiotics will multiply and quickly become the dominant bacterial type. Bacteria that are susceptible to the effects of antibiotics may become resistant to such antibiotics after acquiring resistant genetic material from bacteria that are resistant through horizontal gene transfer.

Horizontal gene transfer is the movement of genetic material between bacteria, and can occur within a species of bacteria and can sometimes occur between certain species of bacteria [18]. It is difficult to explain the role of antibiotics and antibiotic resistance in natural environments from an anthropocentric point of view, which is focused on clinical aspects such as the efficiency of antibiotics in clearing infections and pathogens that are resistant to antibiotic treatment.

A broader overview of the role of antibiotics and antibiotic resistance in nature from the evolutionary and ecological prospective suggests that antibiotics have evolved as another way of intra- and inter-domain communication in various ecosystems. This signaling by non-clinical concentrations of antibiotics in the environment results in adaptive phenotypic and genotypic responses of microbiota and other members of the community [19]. A significant portion of the VAs given to livestock may be excreted with urine or feces [12], and the consequential treatment of soils with these wastes as an alternative organic fertilizer could result in environmental contamination.

Given that VAs are often found to be recalcitrant after excretion [20, 21], many previous investigations [22, 23] have shown that VAs can spread to the groundwater and the surface water by infiltration and runoff, respectively.Unused therapeutic drugs are sometimes disposed of into the sewage system. If the drugs are not degraded or eliminated during sewage treatment, in soil or in other environmental compartments, they will reach surface water and ground water, and, potentially, drinking water. Unmetabolized antibiotic substances are often passed into the aquatic environment in wastewater. Antibiotics used for veterinary purposes or as growth promoters are excreted by the animals and end up in manure. Manure is used as an agricultural fertilizer; thus, the antibiotics seep through the soil and enter ground water. Ciprofloxacin, for example, was found in concentrations of between 0.7 and 124.5 µg/L in hospital effluent [24].

Ampicillin was found in concentrations of between 20 and 80 µg/L in the effluent of a large German hospital [25]. Antibiotic concentrations calculated and measured in hospital effluents are of the same order of magnitude as the minimum inhibitory concentrations for susceptible pathogenic bacteria [26]. Tetracyclines have been detected in concentrations of up to 0.2 µg per kg in soil[27] whereas, others have been found in the sediment under fish farms. Some study may be at odds with the majority of other studies because their poultry was medicated with extremely high amounts of antibiotics, and this consequently resulted in higher concentrations of antibiotics being excreted with the manures [21].

Furthermore, in arid regions, wastewater containing resistant bacteria and antibiotics is used for irrigation, and sewage sludge serves as a fertilizer. This allows resistant bacteria to enter the food chain directly. Although antibiotic residues in foods can have a

detrimental effect on the processing of cultured products such as cheese, and are important in terms of consumer confidence, the public health significance of residue concentrations of some of these compounds in foods from animals appears to be low, based on substantial scientific assessment [28, 29].

Risk from Industrial Chemicals: Industrial chemical is a 'catch-all' phrase designed to cover all chemicals other than identified exceptions. Industrial chemicals include paints, dyes, pigments, solvents, adhesives, plastics, inks and laboratory chemicals. It also includes chemicals used in mineral and petroleum processing, refrigeration, printing, photocopying, household cleaning products, cosmetics and toiletries. Products designed to dispense industrial chemicals (e.g. ballpoint pens dispense ink), articles (e.g. plastic chairs, glow sticks and photographic film) and radioactive chemicals are not included. Industrial chemicals and heavy metals which are not used for agricultural purposes can contaminate animal feeds or the animal environment and thereby gain access to milk, meat or eggs.

Some contaminants in this category are fungicides (e.g., pentachlorophenol and hexachlorobenzene) which have been used as wood preservatives and seed grain fungicides, respectively. Wood preservatives, such as pentachlorophenol, may contaminate animals housed in pens made of treated wood or bedded on treated wood shavings. Seed grain fungicides may contaminate animals if treated grains are mistakenly used as animal feeds [30].

Some industrial chemicals have become widespread environmental contaminants and as such can enter the food chain. Polychlorinated biphenyl is an example of a compound which was widely used in industry until, like dichlorodiphenyltrichloroethane (DDT), the tendency of this compound to persist in the environment and bioaccumulate became apparent and both were banned. Cadmium, mercury and lead occasionally contaminate meat and milk, particularly when these originate from animals pastured or housed in areas of industrial contamination, or in the case of cadmium, where soils naturally contain significant levels of the element. Iodine concentrations in milk have reached levels which cause concern in some countries and have resulted-at least in Canada-in the withdrawal of licensure of iodine-based medicines from feeds of food-producing animals [30].

Global chemical production is expected to double every 25 years for the foreseeable future [31, 32, 33], underscoring developed countries dependence on these chemicals to sustain and advance modern life. According to the US Environmental Protection Agency [34], which regulates hazardous waste disposal in the US, more than 20,000 companies, referred to as "hazardous waste generators" produce over 40 million tons of hazardous waste each year. These companies include chemical manufacturers, electroplating companies, petroleum refineries, dry cleaners, auto repair shops, hospitals, exterminators, and photo processing centers. Some hazardous wastes generated in homes, such as paint, mineral spirits, batteries, and used oil, are not regulated by the federal government.

Chemicals also enter the environment as a result of direct discharges from industrial processes, "leaching" from waste and landfill sites, or from use, such as emissions into indoor air from the materials and products that contain them. Pollutants released into the indoor air result in about 100 to 10 00 times greater human inhalation exposure than pollutants released into outdoor air. These pollutants also can settle on to dust.

As a result, these sources have a much larger effect on public health if their pollutants are emitted indoors rather than outdoors [35, 36]. In addition, many persistent, bio-accumulative, and endocrine disrupting chemicals substances can persist in the environment for long periods and transport long distances via the air and waterways, including migrating from the soil into underground aquifers. They also can get into the food chain, another primary source of exposure, and thus accumulate in living organisms and eventually in people [35].

The United Nations has classified 21 of the most damaging chemicals to the environment and human health as persistent organic pollutants (POP) [37].

In the US, there are more than 80,000 chemical compounds registered for use, with 62,000 compounds grandfathered under the Toxic Substances Control Act (TSCA) without mandatory testing. According to California Policy Research Center, about 2,000 new

compounds that may pose hazard to human health are introduced into commercial use each year [31].

In recognition of the growing evidence linking industrial chemicals to health risks, the US EPA, using its authority under the TCSA, took an unusually strong step in 2010 by establishing a Chemicals of Concern list and action plans. These plans are being used to prompt restrictions on four types of synthetic chemicals used widely in manufacturing and consumer products, including phthalates, polybrominated diphenyl ethers (PBDEs), long chain perfluorinated chemicals (PFCs), and short-chain chlorinated paraffins (SCCPs). Phthalates and PBDEs will be listed as chemicals of concern. The PFCs and SCCPs may be restricted under other TSCA provisions [38].

Risk from Exogenous Hormones: The use of hormones for growth promotion in meat animals, or for enhancement of milk production in dairy animals remains a very controversial issue. Two items continue to be debated:

- The effects of residues of these chemicals on human health
- The economic, social and political implications of banning
- The use of these compounds in agriculture.

The Scientific Committee on Veterinary Measures relating to Public Health (SCVPH) was invited to examine the use of hormones for growth promotion purposes in cattle. The Commission consequently requests the SCVPH to deliver an opinion on the potential for adverse effects to human health arising from the administration of the six hormones oestradiol-17β, progesterone, testosterone, zeranol, trenbolone acetate and melengestrol acetate used individually or in combinations for animal growth promotion. At present, these compounds are used legally to a varying degree in many countries; the European Union has considered a repeal of the ban on these compounds which was instituted a few years ago as a result of public and political pressure. In the context of food safety, the hormonal substances used in food animals can be usefully considered as belonging to two main groups: those which occur naturally in animals (and therefore also in humans) and those which are synthetic compounds and which do not occur naturally in animals (so-called steroidal and non-steroidal xenobiotics). Among the naturally-occurring compounds are testosterone, progesterone, oestrogen and somatotropin. There is clear evidence that hormones originating outside the body can interfere with our own hormone function [39].

In its first scientific statement issued in June 2009, the Endocrine Society, citing the Precautionary Principle [40], determined that "Results from animal models, human clinical observations, and epidemiological studies converge to implicate EDCs [endocrine disrupting chemicals] as a significant concern to public health." [41]. From FDA approval in 1954 until 1979, DES continued to be used as a growth-promoting synthetic estrogen in beef cattle production, even after its human uses were halted. Three natural steroid hormones (estradiol, testosterone, and progesterone), and 3 synthetic surrogates (zeranol, melengestrol, trenbolone) remain in widespread use by US and Canadian beef cattle producers to boost growth and production [42, 43]; concurrent use of more than 1 steroid is approved [44]. Trenbolone, is thought to have 8 to 10 times greater anabolic activity than testosterone [45].

It is widely acknowledged that the use of these hormone growth promoters results in residues in meat [46, 47]. Residues of these hormone growth promoters also persist for weeks to months in manure and feedlot runoff, raising concerns about the added exogenous hormone load to the environment [48, 49]. Thus, even exposure to residual amounts of hormonally active compounds as present in meat and meat products needs to be evaluated in terms of potentially adverse effects to public health [50].

Hazards of Drug Residues, Chemicals and Antibiotics: The possible toxic effects of an environmental contaminant depend on its chemical nature, its concentration in food, and the type of toxic action involved. If the substance is highly toxic and/or is consumed in large quantity, acute toxic effects may occur and the onset of the symptoms would be rapid and severe. If a small amount of a highly toxic substance is consumed, or if the substance is of low toxicity, the health effects may not be seen for many months or years (or may not be observed at all). Potential effects of toxic environmental contaminants

in food include systemic toxicity, mutations, cancer, birth defects, and reproductive disorders.

Systemic toxicity involves changes in the structure and function of organs and organ systems: weight change, structural alterations, and changes in organ system or whole animal function.

Functional effects may include changes in the lungs, liver, and kidneys, in cardiovascular function, in brain and nervous system activity and behavior, and in resistance to disease [51]. Chemicals of most concern are identified as endocrine disruptors, including dioxins, polychlorinated biphenyls (PCBs), alkylphenols, bisphenol A (BPA), phthalate esters, and various pesticides [52, 53]. Flame retardants (BPDEs) also are suspected of being an endocrine disruptor. It has also been identified that a wide range of chemicals cause adverse reproductive, developmental, and neurotoxic effects [53].

These include metals (lead, mercury, manganese, arsenic, and cadmium); organic solvents (methylene chloride, glycol ethers, and trichloroethylene); pesticides (DDT, atrazine, chlorpyrifos, parathion, and lindane); environmental tobacco smoke (ETS) and nicotine; and PCBs.

The different types of drug residues found in animal feed can be broken down into five general categories: antimicrobials (antibiotics and sulfonamides), anti-inflammatories, growth promoters, anti-parasitic and insecticides, and analgesics and tranquilizers. According to a survey of members of the American Association of Bovine Practitioners (AABP), the drugs most commonly used by practitioners for dairy cows were antibiotics, followed by anti-inflammatories, tranquilizers and analgesics [54].

Antimicrobials (antibiotics and sulfonamides) are a focal residue group. These drugs are among the most commonly used veterinary drugs [54, 55] and are one of the primary forms of residues found in meats [56, 57].

The major groups of antibiotics found as residues are as follows: penicillins [58, 59], cephalosporins and cephamycins such as cefixime [60], aminoglycosides, including streptomycin [61, 62], dihydrostreptomycin [61], gentamicin [63], neomycin [62] and apramycin [64], tetracycline[63] and oxyttracycline [61, 65], macrolides, including erythromycin [61], tylosin [61], tilmicosin [60, 61], other miscellaneous antibiotics, such as chloramphenicol [63, 66], flumequine [67], tinidazole [68], quinolones such as norfloxacin nicotinate [69] and sarafloxacin hydrochloride [70].

Among sulfonamides causing residue problems [71], sulfamethazine [62, 65] and sulfadimidine [59] are specific drugs associated with residue problems. Drugs used for growth promotion are another source of residues in meat and poultry. Steroids and hormones can be used as growth promotants, but are illegal in many parts of Europe [72]. Drugs used in this way include chlorotestosterone acetate, progesterone, nadrolone and stanozolol [72]. These hormones are used often in combination to increase weight gain: estradiol and testosterone 'cocktails' are commonly used [72, 73].

In addition to hormones, ß-agonists are another class of drags now being used for growth promotion. One ß-agonist which has received much attention is clenbuterol [59, 74], a drag accepted for treatment of respiratory problems, but which has been finding use as a growth promotant in both North America and in Europe, where use for this purpose has been banned [75]. Salbutamol (albuterol) is another ß-agonist which can be used legally to treat respiratory problems, but also appears to be used illegally to promote growth [76]. Antibiotics such as monensin [77] are also used primarily for growth promotion.

Non-steroidal anti-inflammatories (NSAID), such as aspirin, dipyrone, flunixin, phenylbutazone, are commonly used drags which can be found as residues in foods of animal origin. In a survey of practitioners belonging to the AABP, 93% reported using NSAIDs, with the majority of use being on dairy cattle. The most commonly used NSAID in the survey was flunixin (95% of respondents), followed by butazolidin (69.5%), dipyrone (69%), and aspirin (66.8%). Most respondents who used NSAIDs did so in combination with antibiotics (88%), and followed withdrawal times for the antibiotic in those situations [78].

Residues of the NSAID ketoprofen in milk and meat have been the focus of some attention [79, 80].

Dewormers and other antiparasitic drags have also been found as residues in animal foods. Among dewormers, ivermectin [71, 81], benzimidazole [71],

levamisole [59, 81], and albendazole [82] have been reported as residues in beef. Other antiparasitic drags with residue potentials include imidocarb (used to treat babesiosis) [83] and homidium (used for trypanosomes) [84]. Insecticides may enter food animals either intentionally or unintentionally. According to the results of surveys on feeds, pesticide residues do inadvertently get into forages [85] and feeds [86], and can bioaccumulate when consumed. In rural Africa, where pest control is a large concern, the use of pesticides is not regulated in the same way as in more developed agricultural settings.

For example, some of the chemicals used in Government-run tick dips in the northern Côte d'Ivoire include dicrotophos (until 1985), chlorfenvinphos (until 1986), deltamethrin, flumethrin and lindane [87]. Of the chemicals listed, chlorfenvinphos is an organophosphate suspected of mutagenesis, pre-natal damage and reproductive system effects. Deltamethrin is a synthetic pyrethroid classified by the World Health Organisation (WHO) as a moderately hazardous compound. Lindane is a moderately toxic organo-chlorine, suspected of causing aplastic anaemia, carcinogenesis and pre- and. post-natal damage. The disposal of these dips is not well-controlled, and animals may ingest these chemicals through direct contact with other animals or contaminated dust or dirt, drinking water from sources contaminated by the dip, or eating forage directly contaminated with dip or growing in contaminated soils.

Concentrations of antibiotics below therapeutic levels may play a role in the selection of resistance and its genetic transfer in certain bacteria. Exposure of bacteria to sub-therapeutic antimicrobial concentrations is thought to increase the speed at which resistant strains of bacteria are selected. Resistance can be transferred to other bacteria living in other environments such as ground water or drinking water. Pathological effects produced by antibiotic residues in food include: Transfer of antibiotic resistant bacteria to the human, immunopathological effects, autoimmunity, carcinogenicity (Sulphamethazine, Oxytetracycline, Furazolidone), mutagenicity, nephropathy (Gentamicin), hepatotoxicity, reproductive disorders, bone marrow toxicity (Chloramphenicol).

Potentially, there are two types of hazards relating to drug residues;

i) Direct and short term hazards, and

ii) Indirect and long term hazards.

Direct and Short Term Hazards: Drugs used in food animals can affect the public health because of their secretion in edible animal tissues in trace amounts usually called residues. For example, oxytetracycline [88] and enrofloxacin residues [89] have been found above the maximun residual level in chicken tissues. Similarly, diclofenac residues were reported to be the cause of vulture population decline in India and Pakistan [90]. Some drugs have the potential to produce toxic reactions in consumers directly; for example, clenbutarol caused illness in 135 peoples as a result of eating contaminated beef in Spain in 1990. Other types of drugs are able to produce allergic or hypersensitivity reactions. For example, 2-β lactam antibiotics can cause cutaneous eruptions, dermatitis, gastro-intestinal symptoms and anaphylaxis at very low doses. Such drugs include the penicillin and cephalosporin groups of antibiotics [91].

Indirect and Long Term Hazards: Indirect and long term hazards include microbiological effects, carcinogenicity, reproductive effects and teratogenicity. Micro-biological effects are one of the major health hazards in human beings. Antibiotic residues consumed along with edible tissues like milk, meat and eggs can produce resistance in bacterial populations in the consumers.

This is one of the major reasons of therapeutic failures amongst such peoples. Certain drugs like 3-nitrofurans and nitroimidiazoles can cause cancer in human population. Similarly, some drugs can produce reproductive and teratogenic effects at very low doses consumed for a prolonged period of time. One such example is vaginal clear cell adenocarcinoma and benign structural abnormalities of uterus with diethyl stilbesterol [92].

Risks Analysis: Much has been written about the theory, importance and practice of risk analysis (including risk assessment, risk management and risk communication) for food safety [5, 93]. Risk assessment principles were first applied explicitly to food safety in

the context of chemical residues. The successes achieved in this area have contributed significantly to the international adoption of risk analysis. Risk assessment is a process which has evolved over the last two decades to assist in the characterization of risks due to low-level exposure to environmental contaminants and other hazards. Used in this context, the term 'risk' connotes both the probability of occurrence and the magnitude (or impact) of the negative health outcome from exposure to the chemical residue in food.

The impact may also involve outcomes other than health, such as lost sales or international trade, or loss in public confidence. Hazard identification and hazard characterization [5] entail description of the negative outcomes (types of disease, e.g., cancer, allergic reaction) which can be attributed to the chemical and the dose (threshold) at which toxic effects begin to be observed. These determinations have been based on evidence from case reports or epidemiological studies in people, when such data are available. Most of the relatively few incidents of foodborne disease convincingly linked with exposure to chemical contaminants in foods have been acute in nature, involving relatively high concentrations of chemicals. One such example involved high levels of clenbuterol in liver from illegally treated calves [74].

Low doses of residues in foods, if these have any negative health effects at all, are likely to produce chronic effects after rather long-term exposure [6]. Exposure assessment is sometimes achieved by measuring the quantities of residues within people (e.g., measurements of organochlorines in blood or body fat), or by measuring residue levels in foods and then estimating the amounts of the food eaten by people in society [6, 93, 94].

What should be done to handle these above problems: Such problems can be resolved by taking into consideration three steps i.e. risk assessment, risk management and risk communication. Basically, risk assessment is a systematic scientific characterization of potential adverse health effects following exposure to hazardous agents. Results from the risk assessment are used to inform risk management, who work with factors like social importance of risk, social acceptability of the risk, economic impacts etc. Finally, risk communication involves making the risk assessment and risk management information comprehensible to lawyers, politicians, judges, environmentalists and community groups. One basic step to build this foundation is the determination of residue levels in our foods.

When the animal is slaughtered or its edible products are collected, there is a legal requirement that drug concentrations in these products are not at levels greater than those established as safe by the relevant regulatory authority in the country of origin. In many countries of the world, this upper level is referred to as the MRL, while in United States it is termed as tolerance [95]. MRLs and tolerances are established by regulatory authorities based on many factors primarily relating to the safety of the animal product to the consumer, the usage pattern of the compound (pesticide in the field), and analytical methodology. The major determining factor is food safety.

The emission of antibiotics into the environment should be reduced as an important part of the risk management. For this reason, unused therapeutic drugs should not be flushed down the drain and physicians must be made aware that antibiotics are not completely metabolized by patients. On the contrary, antibiotics and other pharmaceuticals are often excreted largely unchanged, i.e. as active compounds. Doctors and patients as well as pharmacists play an important role in reducing the release of antibiotics, other pharmaceuticals, and disinfectants into the environment.

The environmental significance of therapeutic drugs, disinfectants and diagnostics should be included in the undergraduate curricula of medical students and pharmacists. Patients should be made aware that antibiotics help against bacterial diseases but not against the common cold, which is caused by viruses. These issues should be addressed as part of a sustainable development in medicine and for the environment. This holds also for the agricultural use of antibiotics as well as their use in fish farming and elsewhere, e.g. as pesticides or for pets. Because of the timescales involved in acquiring the necessary knowledge, in the reaction times of ecological systems [96], in getting people to react, and also the socio-economic timescales involved we have to act now-at

least for precautionary reasons and sustainable development. This is especially important in respect of the effects of antibiotics, i.e. the promotion of resistance. In order to establish a firm base to resolve the above mentioned issues, certain aesthetic considerations, risks perceived by the public, sensitive populations and issues, international relations and trade barriers have to be considered. There is an urgent need for comprehensive anthropological studies to prioritize the issues and their solutions.

Limitations in Residue Analysis and Toxicological Testing: Given the range of possible adverse health impacts, it is clear that newly discovered environmental contaminants must be subjected to the best available toxicological testing techniques so that any harmful effects can be uncovered. Furthermore, regulators must have information on the possible toxic effects of ingesting small amounts of a substance in food over an extended period of time, perhaps over a lifetime. It would also be desirable to know what effects other toxic substances already present in our air, water, and food may have on the metabolism and toxicity of a new contaminant.

One basic limitation to conduct residue and risk analysis is the detection of chemical residues in edible animal products. Without accurate detection, exact risk is impossible to assess. This process needs highly qualified expertise, sensitive instruments and modern analytical techniques. High Performance Liquid Chromatography (HPLC), Gas Chromatography (GC) and Mass Spectrometry (MS) are sensitive instruments while Solid Phase Micro-extraction (SPME) and Microdialysis are modern analytical techniques used for residue analysis.

CONCLUSION: Although there have been many concerns in the past several decades regarding the presence of chemical residues in meat, milk and eggs, considerable progress has been achieved in reducing the probability of occurrence of these residues. In general, chemical contaminants in foods from animals are infrequently found at concentrations which could be hazardous to the consumer, and there is a temptation to conclude that these are not very significant from the public health standpoint. Nevertheless, such contaminants remain very significant from the perspective of consumer confidence and international trade.

Livestock farmers supplement their animal feed with a wide range of compounds from a number of therapeutic classes, including antimicrobials, antiprotozoals, ecto- and endo-parasiticides and hormones. Several other groups of chemicals may also be potentially important because of their heavy usage, including antiseptics, steroids and other hormones, diuretics, cardiovascular and respiratory treatments, and immunological products.

Veterinary medicines can enter the environment via different pathways, including emissions during the manufacture, formulation, and treatment processes, and as a result of the disposal of unused medicines and their containers.

The most important routes of entry into the environment are excretion of substances in urine and feces of livestock animals, and the wash off of topical treatments from livestock animals. Veterinarians must be well aware of the importance of drug/chemical residues in the food animals and their possible risk to the general public.

They must have updated information about the proper withdrawal times of all the drugs chemicals used in their areas of practice. They must extend this information to the livestock and poultry farmers for the production of residue free edible animal products like milk, meet and eggs.

For residue analysis, trained manpower is needed. In this regard, the availability of sensitive equipment and modern analytical techniques are of paramount importance. As tariffs are removed and goods flow freely between countries, importing countries must be confident that the goods available for purchase are safe, and in addition to this, there is, from time to time, pressure to use chemical residues as non-tariff barriers to importation. Continued vigilance is required to ensure that hazardous residues do not contaminate the international food supply.

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