The effect of antibiotic residues on the safety of food, water and agricultural products and the environment for human health

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Abstract

Animals are treated routinely with antibiotics to prevent, treat, or control disease. Even under the best conditions of agricultural management, crowding and stress can lead to disease. While historically there have also been nontherapeutic uses of antibiotics, typically as production tools to improve endpoints such as feed efficiency and weight gain, there is a call to diminish these uses worldwide, and concern for the development of resistance to antibiotics used in human medicine as a result of their use in animal agriculture has led to international efforts to evaluate that risk. The results of the therapeutic uses are healthy animalsthat contribute to a healthful and plentiful food supply. Measured concentrations of pharmaceuticals in water and crops in the studies described, typically result in exposures that are well below human therapeutic dose levels or acceptable daily intakes (ADIs). However, there is concern among the scientific and regulatory communities and the general public that exposure to pharmaceuticals, including antibiotics, in the environment may affect human health. Maximum residue limits (MRLs) also are linked directly to the ADI. Significantly, however, the MRLs are not derived from the ADI and do not represent a direct partitioning of the ADI. Rather, they are reflective of the concentrations of residues incurred under the evaluated conditions of use, determined using appropriately validated analytical methods.

Keywords: antibiotic residue“ food“ water

Introduction

Animals are treated routinely with antibiotics to prevent, treat, or control disease. Even under the best conditions of agricultural management, crowding and stress can lead to disease. While historically there have also been nontherapeutic uses of antibiotics, typically as production tools to improve endpoints such as feed efficiency and weight gain, there is a call to diminish these uses worldwide,[١،٢] and concern for the development of resistance to antibiotics used in human medicine as a result of their use in animal agriculture has led to international efforts to evaluate that risk.[٣،٤] The results of the therapeutic uses are healthy animalsthat contribute to a healthful and plentiful food supply.

However, one consequence of the use of the antibiotics in food-producing animals is the presence of residues of the drug, however minute, in the edible tissues of the treated animal. The residues of the antibiotic could be systemically toxic to the consumer, adversely affecting organ systems, leading to morbidity and even death. Residues of the antibiotic in consumed food could have direct adverse effects on the complex microflora that inhabit the human gastrointestinal system, with potentially disastrous consequences for the consumer.Another potential consequence is exposure of the human consumer to bacteria that, having been exposed to the drug through the treated animal and having survived the exposure, are less susceptible to that antibiotic. People who develop a human disease resulting from exposure to these bacteria may find that the causative organisms are resistant to antibacterials used in human medicine and the disease refractory to standard treatments.

HOW ALLOWABLE RESIDUECONCENTRATIONS ARE DETERMINED

Requirements to establish the safety of residues of veterinary drugs in food vary internationally. Table [٣،٧], later in the chapter, provides some of the national, regional, and international guidelines and online sources for these requirements.

TABLE 3.7 Online Sources[a] of Regulatory Requirements for ADI and MRL/Tolerance Development

Country/Regulatory Authority	Agency	URL for Requirements/Guidelines
Australia	Australian Pesticides and Veterinary Medicines Authority	http://www.apvma.gov.au/morag_vet/vol_4/index.php
Canada	Health Canada	http://www.hc-sc.gc.ca/dhp-mps/vet/legislation/guideld/vdd_pds_guide-eng.php
European Union	European Medicines Agency (EMA)	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000384.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002dd37
Japan	Ministry of Agriculture, Forestry and Fisheries of Japan (JMAFF)	http://www.mhlw.go.jp/english/topics/foodsafety/residue/d1/03.pdf
Trilateral Agreement between EU, Japan, and United States of America	International Cooperation on Harmonization Requirements for Registration of Veterinary Products (VICH)	http://www.vichsec.org/en/guidelines.htm 1
United Nations	FAO/WHO Joint Expert Committee on Food Additives (JECFA)	http://www.who.int/ipcs/food/principles/en/index1.html
United States of America	US Food and Drug Administration (USFDA)	http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm123817.htm

[a]URLs accessed October 23, 2010.

Toxicology—Setting Concentrations Allowed in the Human Diet

So, how do regulatory agencies address the concern to establish the safety of antibiotic residues of veterinary drugs in food? Numerous national regulatory authorities and international bodies have established guidelines for the toxicological evaluation of residues of veterinary drugs and pesticides. The toxicology studies are evaluated to characterize the toxicity of the antibiotic in various in vitroand in vivo animal models as well as any available human data to predict the potential toxicity of residues of the veterinary drug in food. In general, the approach [٥،٦]is to Evaluate the potential for short-term (acute, typically a single meal or a few meals) or long-term (chronic, months to years of exposure) dietary exposure to residues of the antibiotic (whether a Veterinary drug or a pesticide) to have adverse effects on the human consumer. This is typically done in orally exposed mammalian animal models (e.g., rodents, dogs and swine) but can include in vitro models and even human exposure data.

Adverse effects may range from systemic toxicity (e.g., damage to liver or kidney) to reproductive or developmental effects on offspring (e.g., increased stillbirths or abnormal limb development), immunological effects (e.g., decreased immune response), neurological effects (e.g., peripheral nerve damage), and cancer. Typically multiple doses of the antibiotic are orally administered to test animals to identify a dose that results in no observable change from background [a threshold dose, often called a no observable effect level (NOEL) or no observable adverse effect level

(NOAEL)] and ideally, higher doses that characterize the dose–response relationship.Responses across all of the models are considered and the most appropriate is selected as the basis for an acceptable daily intake (ADI).

Setting Residue Concentrations for Substances Not Allowed in Food

National and regional authorities responsible for the protection of public health must consider the concentration of residues of veterinary drug residues, pesticides, and other chemicals that may be in food regardless of whether the substance is allowed for that use. In many regions, in the absence of an approval for the substance, the concentration of residues allowed in food is considered to be zero. In practical terms, this is frequently defined by the technical capability of the analytical method. Attempts to improve on "zero" include the ALARA (as low as reasonably achievable) approach, which recognizes that absolute zero is unattainable, and describes an approach that considers what is technically achievable, the resources needed to achieve that technical goal, and the benefit gained.

Setting Residue Concentrations Allowed in Food

Residues are evaluated to determine the extent of uptake of the veterinary drug, its distribution throughout the body, and its elimination. Normally, contemporary residue depletion studies establish tissue concentrations in a radiolabeled drug study, in which total residues and parent compound are determined at several pre-determined times between zero time and a time beyond the proposed withdrawal time. As well as total residues, which include free and bound components, the study quantifies major metabolites. These are compounds contributing ١٠٪ or more of total radioactivity or those are present at a concentration of ≥٠.l٠ mg/kg. Metabolism studies enable identification of the marker residue and target tissue. The marker residue must give assurance that, when its concentration is at or below the MRL, total residues satisfy ADI requirements.

Maximum Residue Limits

Maximum residue limits (MRLs) also are linked directly to the ADI [٧]. Significantly, however, the MRLs are not derived from the ADI and do not represent a direct partitioning of the ADI. Rather, they are reflective of the concentrations of residues incurred under the evaluated conditions of use, determined using appropriately validated analytical methods. Because the MRLs reflect only those uses available for evaluation at the time they are established, the MRLs may not be fully reflective of the eventual spectrum of product development and may require reassessment as new uses for a particular druare realized. Inherent in relating MRLs back to the ADI is the assumption that all of the animal-derived edible products will be eaten at their maximum consumption values every day (i.e., no partitioning of the ADI), and quantifying human exposure to drug residues regulated through MRLs necessitates the assignment of MRLs for all appropriate edible products. Further, relating overall food safety regulated with MRLs to the ADI is often achieved using a theoretical maximum daily intake (TMDI) calculation: (tissue-specific MRL) × (marker: total ratio) × (tissue-specific consumption value) = tissue residue contribution to TMDI.Examples of calculations of MRLs and the related TMDI are given in Tables ٣،٥ and ٣،٦.

TABLE 3.5 Assumptions for Calculating an MRL

Assume an ADI of 0–0.8 μg/kg BW per day, corresponding to a total maximum acceptable exposure of 480 μg/person per day
Assume that incurred residues support MRLs as follows (tissue—MRL):
- Milk—200 μg/l
- Muscle—100 μg/kg
- Liver—1000 μg/kg
- Kidney—400 μg/kg
- Fat—100 μg/kg

Assume that there is no additional correction of marker : total (M : T) based on microbiological activity: marker residue = 100% of total residue (M : T factor = 1)

TABLE 3.6 Calculating Theoretical Exposure as Determined by the TMDI

Tissue	MRL (μg/kg)	M : T	Food Basket (kg)	TMDI (μg)
Muscle	100	1	0.3	30
Liver	1000	1	0.1	100
Kidney	400	1	0.05	20
Fat	100	1	0.05	5
Milk	200	1	1.5	300
TMDI	——	——	——	455

In summary, MRLs are derived following an assessment of incurred residues resulting from approved conditions of use and represent the maximum residue concentrations that are consistent with those label uses (e.g., dose and routes of administration). Residues in excess of the MRL are indicative of uses outside the approved conditions of use. Thus, the MRL approach is extremely effective in monitoring label compliance, focusing regulatory resourceson those residue cases that represent deviations from the labeled conditions of use. However, because not all extra label uses result in unsafe residues, the MRL approach may result in compliance cases that cannot claim to protect the public health [٢].

Uptake of Antibiotics into Crops

Antibiotics may also be taken up from soil into crops [٨,٩].The potential uptake of veterinary medicines into plantsis receiving increasing attention. Studies with a widerange of veterinary medicines showed that a number ofantibiotics are taken up by plants following exposureto soil at environmentally realistic concentrations of thecompounds, whereas other compounds were not observed to be accumulated.[٥٤] The lack of uptake observed may be due to the underlying properties of the compound or other factors such as high limits of detection or significant degradation during the study. These studies looked at uptake into carrots and lettuce following exposure to antibiotics at concentrations that might be found in the natural environment. Florfenicol and trimethoprim were detected in lettuce leaves, and enrofloxacin, trimethoprim, and florfenicol were detected in carrot tubers.

Risks of Antibiotics in the Environment to Human Health

Measured concentrations of pharmaceuticals in water and crops in the studies described, typically result in exposures that are well below human therapeutic dose levels or acceptable daily intakes (ADIs)[٨,٢١]. However, there is concern among the scientific and regulatory communities and the general public that **exposure to** pharmaceuticals, including antibiotics, in the environment may affect human health. These concerns arise from the following facts:

Individual antibiotics do not occur in the environment on their own but occur as a mixture, which introduces the possibility of synergistic or additive interactions or environmental contraindications between an environmental residue and a medicine taken by a patient for an existing condition.

Non-therapeutic uses of antibiotics in food-producing animals to improve production, but this practice are falling out of favor. A consequence of the use of veterinary drugs (including Antibiotics) in food-producing animals is the production of residues of the drug in the edible tissues.

Regulatory agencies address the safety of antibiotic residues of veterinary drugs in food by evaluating the toxicity of the antibiotic and establishing an acceptable daily intake (ADI) or an acute reference dose (ARFD).

Both ADI and ARFD represent the quantity of residue that may safely be consumed (daily or from a single exposure, respectively) in the human diet. Following the establishment of the ADI (or ARFD), the maximum concentration of residues permitted in edible tissues (meat, milk, eggs, etc.) is determined, following an evaluation of the nature and extent of the residues in the treated animal. The value is termed either the maximum residue limit (MRL) or tolerance (used in the United States). Whether an MRL or tolerance is used, either approach ensures that people consuming products derived from the animal treated with the antibiotic veterinary drug will not ingest quantities of residue that exceed the acceptable daily intake.

Transport to and Occurrence in Surface Waters and Ground waters

Contaminants applied to soil can be transported to surface waters in surface runoff, subsurface flow, and drainflow or to groundwaters via leaching. The extent of transport via any of these processes is determined by a range of factors, including: the solubility, sorption behavior, and persistence of the contaminant; the physical structure, pH, organic carbon content, and cation exchange capacity of the soil matrix; and climatic conditions such as temperature and rainfall volume and intensity. A number of studies have explored the fate and transport of veterinary antibiotics by these different pathways [١٠,١١,١٢–١٣]. Field and semi-field studies have shown that sulfonamide, macrolide, and phenicol antibiotics have the potential to leach to groundwaters, probably because of their low sorption coefficients in soils, whereas the tetracyclines and fluoroquinolones do not leach [١٤,١٥,١٦]. Transport of veterinary medicines via runoff and drainflow has been observed for tetracycline antibiotics (i.e., oxytetracycline) and sulfonamide antibiotics (sulfadiazine, sulfamethazine, sulfathiazole, sulfachloropyridazine) [١٧, ١٨]. Just as with leaching, the transport of these substances is influenced by the sorption behavior of the compounds, the presence of manure in the soil matrix, and the nature of the land to which the manure is applied. Runoff of highly sorptive substances, such as tetracyclines, was observed to be significantly lower than that of the more mobile sulfonamides [١٧]. However, even for the relatively water-soluble sulfonamides, total mass losses to surface are small (between ٠,٠٤٪ and ٠,٦٪ of the mass applied) under actual field conditions[١٩]. Once in the water column, substances may be degraded abiotically via photodegradation and/or hydrolysis or biotically by aerobic or anaerobic organisms. Highly sorptive substances may partition to the bed sediment. A significant amount of information is available on the fate and behavior of many veterinary antibiotics in sediment due to their use as aquaculture treatments [٢٠]. while many compounds degrade very quickly (e.g., chloramphenicol, florfenicol, ormethoprim), others persist in the sediment for months to years (e.g., oxolinic acid, oxytetracycline, sarafloxacin, sulfadiazine, trimethoprim).

SUMMARY

Animals are routinely treated with antibiotics to prevent, treat, or control disease. There have been historicnon-therapeutic uses of antibiotics in food-producing animals to improve production, but this practice is falling out of favor. A consequence of the use of veterinary drugs (including antibiotics) in food-producing animals is the production of residues of the drug in the edible tissues. Regulatory agencies address the safety of antibiotic residues of veterinary drugs in food by evaluating the toxicity of the antibiotic and establishing an acceptable daily intake (ADI) or an acute reference dose (ARFD). Both ADI and ARFD represent the quantity of residue hat may safely be consumed (daily or from a single exposure, respectively) in the human diet. Following the establishment of the ADI (or ARFD), the maximum concentration of residues permitted in edible tissues (meat, milk, eggs, etc.) is determined, following an evaluation of the nature and extent of the residues in the treated animal. The value is termed either the maximum residue limit (MRL) or tolerance (used in the United States). Whetheran MRL or tolerance is used, either approach ensures that people consuming products derived from the animal treated with the antibiotic veterinary drug will not ingest quantities of residue that exceed the acceptable daily intake.

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References must be numbered and be listed in the list of references in the order that they are referred to in the text.
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[۱] Assembly Jobs, Economic Development, and the Economy Committee, ۲۰۰٦. ۲۰,Years of California Enterprise Zones: A Review and Prospectus, Sacramento,California, April ۱۲, ۲۰۰٦.

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