Problems associated with drug residues in beef from feeds and therapy

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Summary

Drug residues in beef have been reported internationally. These include antimicrobials, anti-inflammatories, growth promotants, parasiticides and insecticides. The main factors associated with residues are animal age and use, and failure to observe withdrawal time for regular or extra-label use. Public health concerns include toxic and anaphylactic reactions, and development of drug-resistant strains of bacteria. The maximum residue level (MRL) is the current standard for residues in food adopted by the Codex Committees of the Food and Agriculture Organisation and World Health Organisation, but is not universally accepted or standardised.

Detection of residues at slaughter is a critical point in residue control. Several live animal tests are available, but these vary in reliability and usage. After slaughter, tissues sampled and tests used are more uniform. To prevent international trade barriers associated with drug residues in beef, the following conditions should be implemented:

- standardisation of testing methods used to detect drug residues
- standardisation of methods for determining MRLs
- establishment of active surveillance programmes to monitor residues.

Keywords


Introduction

The presence of detectable drug residues in beef has evoked concern in many countries over the years. This concern is centred on health hazards, both actual incidents of reactions and potential hazards perceived by the public. Both concerns are real and important: each country seeks to provide a safe food supply for residents, and fears about unwholesome foods from exporting countries may result in increasing (and possibly unnecessary) restrictions in international trade. While all countries may have the same basic goal of ensuring a safe food supply for the national population, farming and food production practices, acceptable levels of residues, and even methods of determining safe levels of residues in foods vary from country to country and change over time. Therefore, the objectives of this paper are to:

a) describe the types of drug residues found in beef, the frequency of occurrence, and the risk factors associated with the occurrence of residues

b) discuss the health hazards which have been associated with the consumption of beef with drug residues and how 'safe' levels of residues are determined

c) review some of the current methods of residue detection for beef

d) present suggestions for dealing with drug residues in beef on a global level in order to avoid health problems and international trade barriers.

Types of residues

The different types of drug residues found in beef can be broken down into five general categories: antimicrobials (antibiotics and sulfonamides), anti-inflammatories, growth promotants, 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, tranquillizers and anaesthetics (63).

Antimicrobials (antibiotics and sulfonamides) are a focal residue group. These drugs are among the most commonly used veterinary drugs (32, 33, 63) and are one of the primary forms of residues found in meats (17, 22, 23, 24, 25, 26, 35, 66, 70).

The major groups of antibiotics found as residues are as follows:
- penicillins (3, 13, 37, 38, 50, 51, 52, 66)
- cephalosporins and cephemycins such as cefixime (76)
- aminoglycosides, including streptomycin (38, 50, 66, 69, 71, 72, 73), dihydrostreptomycin (38), gentamicin (69), neomycin (71, 72, 73) and apramycin (75)
- tetracycline (69) and oxytetracycline (29, 38, 50, 58, 64, 65, 66)
- macrolides, including erythromycin (38), tylosin (38), and tilmicosin (38, 77)
- other miscellaneous antibiotics, such as chloramphenicol (29, 50, 69), flumequine (49), tinidazole (54)
- quinolones such as norfloxacin nicotinate (27) and sarafloxacin hydrochloride (42).

Among sulfonamides causing residue problems (22), sulfamethazine (1, 28, 56, 66, 71, 72, 73) and sulfadimidine (50, 56) 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 (67). Drugs used in this way include chlorotestosterone acetate, progesterone, nandrolone and stanozolol (67). These hormones are used often in combination to increase weight gain: estradiol and testosterone 'cocktails' are commonly used (61, 67). In addition to hormones, β-agonists are another class of drugs now being used for growth promotion. One β-agonist which has recently received much attention is clenbuterol (43, 53, 57, 60), a drug accepted for use 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 (30). Salbutamol (albuterol) is another β-agonist which can be used legally to treat respiratory problems, but also appears to be used illegally to promote growth (46). Antibiotics such as monensin (47) are also used primarily for growth promotion.

Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, dipyrene, flunixin, phenylbutazone, are commonly used drugs 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%), dipyrene (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 (36). Residues of the NSAID ketoprofen in milk and meat have been the focus of some attention (15, 39).

Dewormers and other antiparasitic drugs have also been found as residues in animal foods. Among dewormers, ivermectin (5, 6, 7, 22), benzimidazole (6, 22) (including fenbendazole [59]), levamisole (7, 55), and albendazole (21) have been reported as residues in beef. Other antiparasitic drugs with residue potentials include imidocarb (used to treat babesiosis) (11) and homidium (used for trypanosomes) (48).

Insecticides may enter food animals either intentionally or unintentionally. According to the results of surveys on feeds, pesticide residues do inadvertently get into forages (14) and feeds (41), 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 (31). 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 organochlorine, 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.

Frequencies of residues

While awareness and concerns about residues in foods have existed for decades, consumer awareness in the United States of America (USA) of potential health hazards of residues escalated in the 1980s to demand action to ensure a safer food supply. To address these concerns, the United States Department of Agriculture (USDA) launched a residue avoidance programme designed to increase awareness of residue prevention practices amongst food producers. In addition, producer groups worked with veterinarians and Government officials to develop quality assurance (QA) programmes for industries and to further educate members with regard to the reduction of residues in food products (34).
The Food Safety and Inspection Service (FSIS) Federal Meat and Poultry Inspection Program collects slaughter/processing plant data on domestic meat, poultry and meat products produced in the USA, as well as products imported from other countries. The information collected is not restricted to drug residues alone: any condition which would result in the condemnation or refusal of a product is tracked, and of these, drug residues constitute only a minor portion. Between 1989 and 1991, the percentage of cattle carcasses condemned for residues rose slightly from 0.0005% in 1989 to 0.0007% in 1991.

In addition to routine inspection at slaughter plants, the FSIS has also conducted a National Residue Program (NRP) since the late 1960s. Initially, the focus of the NRP was the detection of residues in meat and poultry at slaughter. The NRP uses two different types of residue testing: individual enforcement and population sampling (monitoring, exploratory and surveillance). Individual enforcement is the testing of animals or lots based on herd history (i.e. previous violations) or clinical signs at slaughter. Monitoring is population-based random sampling, using animal slaughter classes as the basis for sampling and established residue limits to determine violations. Exploratory programmes are designed to focus on residues for which there are no established limits. Surveillance, the newest of the population sampling programmes (established in 1990), focuses attention on a slaughter population after problems have been detected through monitoring (34). Table I shows the percentage of samples tested by the FSIS which contained violative residues for antibiotics, sulfonamides and parasiticides.

The Residue Violation Information System (RVIS) collects data from the FSIS surveillance programme, testing apparently healthy animals which are suspected of having exceeded the MRL. A total of 3,249 violative residues were found in 2,734 carcasses in 1991, 3,132 violative residues were found in 2,813 carcasses in 1992, and 2,317 residues were found in 2,051 carcasses in 1993. A total of 700 carcasses revealed multiple residues between 1991 and 1993. The FSIS NRP data were examined for specific residues found in specific slaughter classes. Of 3,095 violations recorded in 1988, evaluations were made of 954 bob-veal calves (calves of less than three weeks of age, which weigh less than 68 kg) which gave a positive reaction to the calf antibiotic and sulfonamide test (CAST). By carcass, the most common residue found was neomycin (44% of carcasses), followed by unidentified microbial inhibitors (UMI) (30.1%), streptomycin (8.9%), penicillins (8.4%), sulfamethazine (7.5%), tetracycline (6.1%), gentamicin (5.5%), oxytetracycline (3.5%), and chlorotetracycline (2.1%). Penicillin was the most common antimicrobial found in multiple residues (73). The order in which tests were run influenced overall results: antibiotics were screened first, and only a sample which gave negative results for antibiotics was then tested for sulfonamides. Consequently, levels of sulfonamides are probably higher than reported here. Since less than 10% of muscle samples had identifiable residues in them, this may imply that test-positive carcasses may have safe meat but contain violative residues in some tissues (71).

The Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) has also established a Tissue Residue Program to track residues. One aspect of the FDA CVM Tissue Residue Program was monitoring for sulfamethazine (SMZ). Phase I of the tissue residue programme involved an enhanced sampling programme, using sulfa on-site (SOS) to eliminate all violative residues of SMZ. One hundred of the largest swine slaughter plants had to submit two muscle samples per week for testing. A total of thirty violations were found, fifteen of which came from the FSIS Southeast Region, and five each from the Mid-Atlantic, Midwest, and Southwest Regions (28).

Data collected in these national-level programmes have been studied in conjunction with State-level residue tracking programmes. Residue data from the FDA CVM Tissue Residue Program between 1986 and 1987 (252 samples) and the Virginia Department of Agriculture and Consumer Services (VDACS) from 1983 to 1988 (99 samples) were examined. Tables II and III contain brief summaries of this information. The drugs responsible for the most common residue violations were streptomycin, penicillin, sulfamethazine and oxytetracycline.

### Table I

<table>
<thead>
<tr>
<th>Year (Ref.)</th>
<th>Animal class</th>
<th>Antibiotics</th>
<th>Sulfonamides</th>
<th>Parasiticides</th>
<th>All residues</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987 (22)</td>
<td>Cattle</td>
<td>1.98</td>
<td>1.01</td>
<td>0.05</td>
<td>NA</td>
</tr>
<tr>
<td>1988 (70)</td>
<td>Bob veal</td>
<td>1.00</td>
<td>1.10</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>1989 (70)</td>
<td>Cows</td>
<td>0.49</td>
<td>0.37</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1990 (5)</td>
<td>Dairy cull</td>
<td>1.70</td>
<td>0.48</td>
<td>0.00</td>
<td>0.97</td>
</tr>
<tr>
<td>1991 (6)</td>
<td>Dairy cull</td>
<td>0.00</td>
<td>0.66</td>
<td>0.00</td>
<td>0.23</td>
</tr>
<tr>
<td>1993 (7)</td>
<td>Bob veal</td>
<td>1.84</td>
<td>1.43</td>
<td>0.00</td>
<td>1.64</td>
</tr>
</tbody>
</table>

NA: not available

Source: United States Department of Agriculture/Food Safety and Inspection Service Monitoring Program

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Programmes similar to those in the USA are in operation in several other countries to track and control drug residues in food supplies. In the residue monitoring programme in Canada, less than 1% of carcasses of all species showed violative residues. The most common violations involved penicillin and tetracycline. In a surveillance programme conducted in 1991 and 1992, 2.3% (138/5,880) of cattle showed violative residues of antibacterials in kidney tissues. Antiparasitic drugs were rarely reported (68). In a surveillance programme conducted in Canada from February to May 1992 (which tested both carcasses giving positive results for swab test on-site (STOP) or CAST tests and those which gave negative results but seemed suspicious to the inspector), 54 beef muscle, 44 beef kidney, 95 pork muscle and 90 pork kidney samples were taken and tested. Positive results were identified from 15 (27%) beef muscle and 35 (79%) beef kidney samples (38).

Besides programmes for residue tracking through official Government sampling programmes, researchers have conducted independent studies in an effort to determine the levels of residues in beef and other food animal products. In one survey conducted in the USA, a prospective study found two of thirty cattle recumbent at slaughter with detectable antibiotic residues (17). In another independent study, fifty beef and thirty chicken samples were purchased from stores in Hermosillo, Sonora, Mexico, between June 1987 and April 1988, and were tested for five antibiotic families. Only 4% of samples were antibiotic-free, and all contaminated samples showed levels above the United States FDA acceptable limits (69).

In Europe, where the use of drugs for growth promotion is strictly controlled, and where several substances (e.g., hormones) commonly used in other parts of the world are illegal, much of the attention on monitoring and surveillance is focused on growth promotants. Over 2,000 injection sites were collected from cattle at slaughter from 1989 to 1994 in a monitoring programme in Belgium. The percentage of injection sites which gave positive results for hormones ranged from a low of 18.8% in 1989 to a high of 62.2% in 1990. There was also a steady switch in the presence of exogenous hormones to naturally-occurring hormones in injection sites over these years — this may be an effort to make it more difficult to detect abuse, as these hormones would be found naturally in animals (67). In addition to hormones, β-agonists are also an area of concern, particularly after outbreaks of human toxicity have been recorded (41, 53). Positive samples of clenbuterol were found in 9.9% of samples in Ireland in 1990 (19) and 1.3% from surveillance and monitoring programmes (18). Antiparasitic and insecticidal compounds can also be found as residues in foods of animal origin. Dewormers and antiparasitic drugs have been found in cattle carcasses in the USA (22, 25). One study in Mali found residues of lindane, p,p’-DDE (1,1-dichloro-2,2’-bis[p-chloro-phenyl] ethylene) and dieldrin in fat samples of cattle (31).

While considerable work is being conducted in drug residue surveillance and monitoring programmes, data collected in residue surveillance and monitoring programmes to compute actual rates of residue occurrence in the human food supply are not always available. The problem of inconsistency between testing programmes and the definition of acceptable levels of residues has been recognised and is being addressed (21).

### Factors associated with residue problems

#### Type of animal

The majority of residues detected by the FDA CVM and VDACS monitoring programmes were found in cows (46.1% and 47.6%, respectively) and bob veal (22.8% and 35.5%, respectively) (66). Bob veal has been identified as a problem.
group for residues (26, 28, 66), and has been the focus of efforts to prevent the occurrence of residues. Recently, reductions in the frequency of residues in bob veal have been recorded, and the formation of the Veal Quality Assurance Education Program (VQAEP) in 1988 is thought to have helped reduce residues in special-fed veal, from 3.3% in 1988 to 0.24% in 1991 (over 80% of all special-fed veal producers in the USA have participated in the VQAEP) (74). Cull dairy cows were identified as another problem group for residues (26, 28). This group was responsible for 1.7% of antibiotic residues found by the USDA National Residue Monitoring Program in 1990; over twice the level of residues found in beef cows (70).

In addition to age and usage, species may make a difference to drug pharmacology and, as a consequence; in residue potential. When both cattle and Indian buffalo (Bubalus bubalis) were fed similar doses of fenbendazole, the bioavailability of fenbendazole was lower in buffalo than in cattle (59).

**Age of animal**

Weaning status and, to a lesser extent, the age of the animal affect drug pharmacodynamics. Comparisons of the pharmacodynamics of norfloxacin nitocinate between weaned and unweaned calves were conducted. The distribution of the drug did not differ between the two groups of calves, but the total body clearance time was increased in weaned calves, possibly due to increased weight from the presence of rumen fluid (27). Calves fed grain had shorter clearance times (approximately four days) for sulfamethazine than unweaned calves (approximately ten days for bob veal and fancy veal). While adequate for weaned calves, the ten-day sulfamethazine withdrawal period for bob veal and fancy veal is not sufficient (1). The elimination half-life of tinidazole was 33.3% shorter in unweaned calves than in adult cows (54), while the elimination half-life of apramycin is longer in calves than in adult cattle, possibly due to the immaturity of the drug clearance system in calves (75).

**Feeding**

Diet can affect the bioavailability of drugs. To determine the effects of diet content of the bioavailability of orally-administered fenbendazole, cattle and Indian buffalo were given oral fenbendazole and fed dry hay either with or without fresh green herbage. Animals receiving feed containing fresh herbage had lowered bioavailability of the drug; fenbendazole stays in the rumen and is progressively released with digesta, and the presence of fresh herbage increases gut activity and the flow rate of digesta, which depletes the available stores of fenbendazole in the rumen (59).

In regard to feeds, actual gut contents can also affect drug uptake and pharmacodynamics. Oral dosing of ceftriaxone resulted in an elimination half-life of approximately 200 minutes for normal calves, and 263 minutes for fasted calves (76). In an in vitro model of the human gut, the activity of sarafloxacin hydrochloride was reduced five-fold in the presence of organic (faecal) material (based on bacterial inhibition testing). This work confirms earlier research, which showed a decrease in the bioavailability of quinolones in the presence of faecal material (42).

Another aspect of feed and residues is the inadvertent contamination of feedstuffs. An FDA CVM review of violations according to drug class (streptomycin, penicillin, tetracyclines, gentamicin, sulfamethazine and neomycin) and slaughter class for 1988 showed that 9% of residues occurred in calves fed milk and/or colostrum from cows receiving antibiotics (28). This data is supported by the findings of the USDA monitoring programmes in 1988-1990, where the third most common reason for residues was found to be the feeding of milk or colostrum to calves (9%) (70). Data from the FDA CVM Tissue Residue Program for sulfamethazine suggests that 25% of violations were due to inadequate cleaning of feed mixers – sulfamethazine residues left in the mixers were inadvertently added to ‘non-medicated’ feeds (28). A retrospective study examined samples of mixed feed rations (172 for cattle) for pesticides from a surveillance programme. Of the 545 samples collected, 88 did not reveal the presence of residues, and 457 samples revealed 804 different residues (654 quantifiable and 150 trace residues). All residues present fell below regulatory guidelines. The most common residue found was malathion (52.9%), followed by chlorpyrifos-methyl (25.2%), diazinon (8%), chlorpyrifos (5%), and pirimphos-methyl (3%) (41).

**Disease status**

The disease status of an animal can affect the pharmacology of drugs administered, which can influence the potential for residues. This can occur either when disease affects the metabolic system (and consequently drug metabolism), or when the presence of infection and/or inflammation causes the drug to accumulate in affected tissues. In cattle with acutely inflamed mastitic quarters, apramycin penetrates these areas of the body, and concentrations of the drug have been observed at ten times over the level recorded from cows without mastitis (75). Ketoprofen levels in milk increase during clinical mastitis where there is an influx of serum components into the udder (15).

In calves with experimentally-induced fasciolosis, the elimination half-life of antipyrine was slightly increased, but was slightly decreased for erythromycin and statistically significantly decreased for oxytetracycline. The proposed mechanisms for these changes were the changes in liver function by fasciolosis, which changed the processing of drugs through the liver (8). A study of cattle with and without trypanosomal infections, treated intramuscularly with homidium, found that uninfected cattle muscle showed higher levels of homidium at 14 and 21 days after treatment than did infected cattle muscle. The authors recommended...
bioavailability studies and studies on the effect of low-level intakes in humans to determine MRLs for this drug (48).

**Poor management**

Poor production practices were listed as one of the top five reasons for residues in a combined FDA CVM and VDACS study (66), and the fourth most common reason for residues found in USDA monitoring programmes between 1988 and 1990 was the lack of records on drug treatment (6%) (70).

**Extra-label drug use**

Extra-label drug use is commonly acknowledged to be present in veterinary medicine. Extra-label usage can be divided into two separate areas: use of drugs which have not been approved for the species in question (e.g. use of poultry antibiotics to treat cows), and use of approved drugs at levels which differ from the recommended dosage. The second most common reason for the occurrence of residues, found by the USDA monitoring programmes between 1988 and 1990, was the use of unapproved drugs (10%); the fifth most common reason was the use of drugs at levels in excess of recommended dosages (6%) (70). While this practice may occur commonly, a survey of 814 of 4,000 members of the AABP revealed that the use of approved drugs was significantly higher than that of non-approved drugs for lactating dairy cows (63). Based on results from the FDA CVM review of violations according to drug class (streptomycin, penicillin, tetracyclines, gentamicin, sulfamethazine and neomycin) and slaughter class for 1988, only 10% of violations were due to unapproved drug use (28). In the USDA residue monitoring programmes, extra-label drug use was not found to be a major problem (74). The regular occurrence of extra-label use for special-fedveal should be noted: this seems to occur because there are only three antibiotics (amoxicillin bolus/soluble powder, ampicillin bolus/injectable suspension, and decoquinate) approved for this animal type (74).

Drugs are frequently used above the label dosages to reach minimum inhibitory concentrations (MIC) levels (in µg/ml) in the animals being treated. Procaine penicillin G (51), trimethoprim (13) and sulfadoxine (13) do not reach MIC levels at recommended dosages.

There are occasions on which drugs are used above label doses for purposes other than the manufacturer-recommended uses. One example is the use of high doses of clenbuterol as a growth promotant (60). In trials where high levels of clenbuterol were administered to animals for growth promotion, clenbuterol was not detectable in muscle within 14 days, but was found at 10 ng/g in liver even at 16 days (60). When lambs were fed clenbuterol at 1, 10, and 25 times the recommended doses for 14 days, all doses were detectable in muscle at slaughter. The recommended dose was only detectable on the day of slaughter, the ×10 dose was detectable ten days after slaughter, and the ×25 dose was detectable until the end of the study at 15 days post slaughter (18).

High levels of drugs may or may not cause a potential residue problem, depending on the drug and dosage. When penicillin G (benzathine) is used above the label dose with procaine penicillin G, the drug is not detectable in muscle or kidney after 14 days, and is below the MRL in liver; at twice the recommended dosage residue, the drug is not detectable in muscle after 8 days, and is below the MRL in liver and kidney at 14 days (37). Oxytetracycline administered at twice the normal dosage was detectable in kidneys 42 days after dosing, and was not detectable in muscle after 21 days or in kidneys after 49 days (65).

**Withdrawal times**

Failure to follow recommended withdrawal times is often implicated in residue problems. The primary reason found for the presence of sulfamethazine residues detected by the FDA CVM Tissue Residue Program was the failure to observe withdrawal times (30% of positive violators). In addition, data collected in the 1989 review of violations according to drug class (streptomycin, penicillin, tetracyclines, gentamicin, sulfamethazine and neomycin) and slaughter class, showed that 61% of violations were due to the failure to observe withdrawal times (28). This is corroborated by findings of the USDA monitoring programmes between 1988 and 1990, which reported that the most common reason for the presence of residues was the failure to observe withdrawal times (61%) (70). Finally, a total of 105 FDA CVM samples and 30 VDACS samples gave no specified cause for residues. The most commonly identified reasons established in these studies for residue presence were: withdrawal time not known and not followed (38 and 41 samples, respectively); withdrawal time known and not followed (9 and 38 samples, respectively); and label instructions not followed (22 and 36 samples, respectively) (66).

When drugs are used in an extra-label fashion, recommended withdrawal times on the labels are often no longer valid. Procaine penicillin G used above the stated label dose for intramuscular administration has pre-slaughter withdrawal times which increase with dosage (51). After treatment of calves with clenbuterol twice a day for three weeks, detectable levels of clenbuterol above the MRL were found in eye, liver tissue and abdominal fat. A withdrawal period of one to two months is proposed to ensure that clenbuterol levels in all edible tissues fall below the MRL (45).

Researchers found clenbuterol residues in cattle muscle at slaughter one week after withdrawal from medicated feeds (during which the maximum level had never exceeded 0.7 µg/kg), and levels were undetectable (below 2 µg/kg) in muscle 14 days after slaughter, even though residues in the eye were still detectable 35 days post slaughter. The
recommended four-week withdrawal period for the medicated feeds appears to have been adequate to ensure that meat was safe for consumption (20). However, when twelve veal calves were treated for 42 days with clenbuterol levels commonly used for growth promotion, all tissues tested (eye, liver, urine, kidney, brain and muscle) had levels of clenbuterol greater than the MRL of 0.5 µg/kg (2).

There are also situations in which the recommended withdrawal period is either incorrect or is not provided. While the recommended dosage for subcutaneously-administered penicillin G is adequate to reach MIC, the five-day withdrawal period is inadequate to prevent residues occurring (13). Care must be exercised when using imidocarb to prevent babesiosis, since a single dose is still detectable in liver even 224 days after administration (11).

When using combinations of slow-release (benzathine) and regular-release (procaine) penicillin G, the regular-release penicillin is absorbed first, followed by the slow-release form. The slow and incomplete absorption of slow-release penicillin when combined with regular-release forms may explain the increase in penicillin residues of the combination (52).

**Route of administration**

The way in which drugs are administered (orally, subcutaneously, intravenously, intramuscularly) and the site of administration (e.g., neck, gluteus maximus) do affect drug pharmacodynamics. In general, drugs administered intravenously are absorbed and distributed quickly through the bloodstream, while subcutaneous and intramuscular administration increase the potential for residues at the injection sites. Data from the 1989 review of violations according to drug class (streptomycin, penicillin, tetracyclines, gentamicin, sulfamethazine and neomycin) and slaughter class had 705 violations which reported a specific route of administration: 460 (60%) of these violations were caused by intramuscular administration (28). In the 103 FDA CVM records of residue violations with route of administration known, the majority of those routes were injections (51.3% from FDA CVM and 61.7% from VDACS), feed supplementation (21.4% from FDA CVM and 6.7% from VDACS) and bolus (15.4% from FDA CVM and 26.7% from VDACS) (66).

Once an injection has been administered, the injection site itself is a potential source of violative residues. In one study, cows were injected with a combination of chloramphenicol and oxytetracycline intramuscularly every 12 hours for three days. Neither oxytetracycline nor chloramphenicol were detectable in milk and edible tissues 14 days after treatment, but chloramphenicol was still present at the injection site 21 days after treatment, and oxytetracycline persisted at the injection site for 35 days. These levels in injection sites pose a problem for residue avoidance (29). In another study using pigs, the highest levels of ivermectin residues found at 7 and 14 days post injection were detected at the injection site (up to 59 mg/kg at 7 days compared to < 50 µg/kg in liver – the highest level for edible tissues), but by 21 days post injection, only traces were found both in body tissues and the injection sites (62).

When using benzathine penicillin G with procaine penicillin G at recommended levels (intramuscularly at 8,600 IU/kg in Canada, or subcutaneously at 8,800 IU/kg in the USA), all tested tissues were below the MRL (30 µg/kg) after the withdrawal time (14 days in Canada, 30 days in the USA), but injection sites were still 30 to 60 times in excess of the MRL. When administering only benzathine penicillin G intramuscularly at 24,000 IU/kg, penicillin was not detectable in muscle 8 days after injection, and was below the MRL in liver and kidney at 14 days, but was 24 times the MRL at the injection site 50 days after injection. When using benzathine penicillin G with procaine penicillin G intramuscularly at 12,000 IU/kg, penicillin was not detectable in muscle or kidney and was below the MRL in liver 14 days after injection, but was 156 times the MRL at the injection site. Consequently, the testing of organs and meat for penicillin residues will not safeguard against violative residues at the injection sites (37).

**Factors affecting residues after slaughter**

While much research has been focused on prevention and detection of residues, some research has been conducted on the performance of residues in tissues after slaughter. The optimal goal is to ensure a safe food supply which satisfies the demands of the consumer: these factors may be important when considering the potential health effects of foods with a known history of residue problems.

One simple factor which affects the stability of residues in tissues is the passage of time. For example, penicillin G degrades after time. It is fairly stable in plasma but degrades more rapidly in tissues: in muscle samples, nearly 50% was lost after 10 days at ~20°C, and the drug was undetectable after 60 days (3). However, penicillin G is fairly stable in serum and tissues when stored at -76°C, even at 189 days after slaughter (3).

Another factor which will affect the viability and presence of residues in tissues are the effects of chilling and cooking. Freezing would be expected to retard degradation of chemicals. Sulfonamides were found to be stable in long-term freezing conditions (56). In a study by O'Brien et al., calves received either ampicillin, chloramphenicol, oxytetracycline, streptomycin or, sulfadimidine, and were then slaughtered two hours after an intramuscular administration in the neck. The carcasses were hung and chilled for 5 to 7 days. The presence of biologically active residues was determined by measuring the zone of inhibition in microbiological assays. Both ampicillin and chloramphenicol levels were reduced by
cold storage, while minimal effects were seen in oxytetracycline, streptomycin and sulfadimidine (50).

The same study cut roasts and steaks from the prepared carcasses to examine the effects of cooking on residues in meats, and the level of residues was measured in the same way. Both ampicillin and chloramphenicol were definitely meats, and the level of residues was measured in the same way. Both ampicillin and chloramphenicol were definitely affected by cooking; the effect was weaker for oxytetracycline, and no effect of cooking was found for the sulfadimidine (50).

The effects of cooking on sulfonamides (sulfamethazine and sulfadimidine) in pork muscle, liver, and kidney, and oxytetracycline in beef muscle and liver were studied by Rose et al. The stability of sulfamethazine alone was checked in boiling water and frying; sulfamethazine is stable in boiling water (100°C), but not in hot oil at 180°C or 260°C. In general, sulfonamides are stable under normal cooking conditions, and some is leached from the tissues into cooking juices (56). Alone, oxytetracycline is unstable during boiling and frying conditions, and is unstable during cooking. The highest levels of oxytetracycline lost from meat occurred during roasting to well-done (94% loss), while the lowest levels of loss occurred during grilling (39%) and shallow frying (49%). However, oxytetracycline is stable when frozen at -20°C (58).

The effects of cooking on clenbuterol in cattle liver and muscle have also been studied. Initially, the stability of clenbuterol alone was checked in boiling water and frying; clenbuterol is stable in boiling water (100°C), but not in hot (smoking) oil at 260°C (half-life of five minutes). Clenbuterol in beef tissues was stable in grilling, frying and boiling, and was not leached from the tissues in cooking juices. Forty-four percent of the clenbuterol present in meat was lost in extreme deep frying, but the meat was rendered charred and inedible by this process (57).

The effects of cooking on residues from two different dewormers (levamisole and ivermectin) in muscle were evaluated in two different studies. The stability of levamisole alone was measured in boiling water and frying; levamisole is stable in boiling water (100°C), but not in hot (smoking) oil at 260°C (half-life of five minutes). Some loss of levamisole was seen in microwaving, but, in general, levamisole is stable under normal cooking conditions. Some levamisole is leached from the tissues in cooking juices (55). When evaluating the fate of ivermectin in minced beef tissue during cooking, there was a 45% decrease of ivermectin in boiling, and a 50% decrease in frying (62).

Testing for residues

Residue testing can occur either before or after slaughter. Whenever possible, testing animals before slaughter is desirable, as many drug residues are the result of improper withholding times, testing before slaughter provides the opportunity to hold the animal back until the withholding time is met, or until the animal gives negative test results for residues (4).

There are several tests marketed for ‘on-farm’ use, requiring test samples which do not involve the death of the animal. For procaine penicillin G with or without benzathine penicillin G, four on-farm tests have been found to be highly selective, and will reliably and correctly detect penicillin G residues in plasma. Tests can be conducted on live animals, provide same-day results, and produce no false positive results (4). For the testing of clenbuterol, a colour change test is being developed for hair and eyes. On-farm testing of hair can be performed on live animals, but the current test needs further refinement: the duration of the presence of clenbuterol residues in hair needs to be determined, and the issue of cross-contamination (urine, faeces, hair from other animals) must be addressed (19).

While there are ‘on-farm’ tests for residues which can be used, some caution must be exercised with test results. The accuracy of the Live Animal Swab Test (LAST) was checked in calf urine from 30 calves dosed with twice the normal dose, and confirmed by quantitative assays. LAST was 100% accurate in detecting oxytetracycline when concentrations were above 4.3 µg/ml. When oxytetracycline levels fell below 4.3 µg/ml, the drug was correctly detected in only 60% of samples; 20% gave false positive results, and 20% gave false negative results. While LAST was 100% accurate at detecting therapeutically effective levels of oxytetracycline in calves, this method is not effective when testing for lower levels of the drug, and should not be used for the purposes of residue avoidance testing (64).

Nine different enzyme-linked immunosorbent assay (ELISA) kits for testing clenbuterol in urine were evaluated. Researchers found the tests easy to use, rapid and capable of handling large numbers of samples at a time, but there were also remarkable quality defects. In addition, urine samples required cleaning with organics, which further complicates the procedure and creates disposal problems after testing (30).

Even with the use of ‘on-farm’ tests, testing on animal tissues at slaughter will still be an important part of residue monitoring and surveillance. These tests are being evaluated and improved, and alternative screening methods are being developed to improve efficiency, speed and cost-effectiveness. Work has been conducted on a commercially available on-site test for screening at packing plants for penicillin G, oxytetracycline, dihydrostreptomycin, streptomycin, erythromycin, tylosin and tilmicosin: the test gave false negative results for 5% of beef muscle and 27% of beef kidney samples, and false positive results for 19% of beef muscle. When muscle and kidney were paired by animal, 100% of
muscle samples with violative residues had kidneys which gave positive results when tested using a commercially available on-site test. Unfortunately, the sensitivity of the test was above the MRL for some drugs (38).

An evaluation of the USDA/FSIS multiple bioassay was conducted for the following groups of antimicrobials: tetracyclines, β-lactams, macrolides and aminoglycosides (sulfonamides were not detectable below 100 µg/ml). These tests were easy to use and a large number of samples could be run without the use of organic solvents. While unable to discriminate between specific drugs, the tests can be used as post-screening tests to identify groups of antimicrobials for more specific testing (9).

In Europe, the European Union currently uses a four-plate microbial inhibition test (4PT) to test for β-lactams, tetracyclines, chloramphenicol, macrolides, aminoglycosides, sulfonamides and quinolones. A one-plate test (1PT) has been used in Belgium (it is simpler and less expensive than the 4PT, and provides extensive information), and sensitivity was compared to the 4PT: results were comparable for β-lactams but the 1PT was less sensitive to the other drug groups. Kidney is the recommended tissue to test, since many drugs are excreted in urine, and will be found in the kidney. The test is less effective in meat, in which the possibility of detecting positive results is low. Despite the lack of sensitivity, the ease and cost of the 1PT makes this a useful tool, in conjunction with other screening methods, for testing kidneys for residues (35).

The usefulness of immunochemical tests (membrane-based quick test, microtitre plate routine test, immunophysico-chemical coupling) was examined. These tests were shown to be good for rapid screening or monitoring, and semi-quantitative analysis. There is a wide variety of tests which have high sensitivity, good performance and are cost-effective, but also show low specificity, give false positive results and require confirmatory testing before taking any regulatory action (44).

When testing cattle for clenbuterol at slaughter using ELISA and a colour change test for hair and eyes, 950 surveillance and 250 monitored cattle were tested. Fifteen positive results were found by the ELISA and colour change test, and all were confirmed by gas chromatograph/mass spectrometry (GC/MS). When testing hair samples from a farm where clenbuterol use was suspected, 24 of 70 samples gave positive results which were confirmed by GC/MS (18).

Finally, regardless of the efficiency of the test, there may be an extra level of interpretation necessary to determine whether residues occur naturally or arise as a result of the misuse of drugs. When testing cattle for estradiol-testosterone 'cocktails' used for growth promotion, plasma concentrations between the genders should not be held equal, but should be judged according to the sex of the animal being tested. Taking bio-active levels of hormone in edible tissues into consideration, heifers should be tested for serum concentrations of 20 pg/ml for estradiol and 125 pg/ml for testosterone, and bulls for 28 pg/ml for estradiol and 1,500 pg/ml for testosterone (61).

Health safety aspects of residues

Residues have many implications for public health: there is the possibility of direct reaction to the residues (toxic, anaphylactic, etc.); there is the likelihood of developing drug-resistant strains of bacteria both in the food supply and in the gut; and the presence of residues in the human body may have legal as well as physical implications.

Some of the most dramatic examples of reactions to drug residues in foods have come from the ingestion of clenbuterol-contaminated foods. In the late 1980s, there were two outbreaks of human poisoning cases in Spain which resulted from the consumption of beef liver containing high levels of clenbuterol. A total of 134 individuals from 43 different families were affected: the attack rate among family members was 97%, and there were no cases of toxicity in family members who had not eaten the liver. Latency of the poisoning was approximately 101 minutes, with a duration of 40 hours. Clenbuterol was found in the urine of affected patients, in levels as high as 160-291 ppb (43). Later, there was a separate outbreak of 22 cases of human reaction to clenbuterol in France in 1990. Symptoms in these cases included tremors, headache, tachycardia and dizziness, with an onset of 1 to 3 hours after the consumption of veal liver. Clenbuterol was found in the veal liver, at concentrations ranging from 375,000 to 500,000 ppb (53).

The development of drug resistance in foodborne bacteria is another area of great concern. During a survey of antibiotics in beef and chicken in Mexico, a concurrent microbiological analysis was conducted. The predominant micro-organisms found in beef were:

- Staphylococcus epidermidis (94%)
- Enterobacter agglomerans (92%)
- Citrobacter freundii (70%)
- Escherichia coli (58%)
- Salmonella spp. (42%)
- E. aerogenes (42%).

Resistance to penicillin was found in isolates of:

- S. epidermidis (100%)
- Salmonella spp. (100%)
- C. freundii (100%)
- E. aerogenes (100%)
- E. agglomerans (98%)
- E. coli (90%).

The development of drug resistance in foodborne bacteria is another area of great concern. During a survey of antibiotics in beef and chicken in Mexico, a concurrent microbiological analysis was conducted. The predominant micro-organisms found in beef were:
Resistance to tetracyclines was found in isolates of:
- *C. freundii* (86%)
- *E. coli* (76%)
- *E. agglomerans* (74%)
- *Salmonella* spp. (57%)
- *E. aerogenes* (52%)
- *S. epidermidis* (45%).

Resistance to streptomycin was found in isolates of:
- *E. coli* (52%)
- *C. freundii* (46%)
- *E. aerogenes* (43%)
- *Salmonella* spp. (38%)
- *S. epidermidis* (32%)
- *E. agglomerans* (26%).

While penicillin residues were not found in these samples, the drug had been commonly used earlier. This suggests that resistance to antibiotics in bacteria extends beyond the period in which the drug is used (69).

Determination of ‘safe’ levels of residues

When determinations of acceptable levels of residues are made, basic questions need to be answered, as follows:

a) what is the maximum quantity of a residue at which no adverse effects are seen (the NOAEL: ‘no observed adverse effect level’)?

b) in what quantities are foodstuffs consumed?

c) based on the NOAEL and the quantities of food eaten, what is the maximum residue level at which residues can be present in food and not exceed safety levels when consumed at normal levels?

These issues are relevant not only within each country, but on a global level. Joint efforts for global food safety are being made by the Food and Agriculture Organisation (FAO), the WHO, the United Nations Environmental Programme (UNEP), the United Nations Development Programme (UNDP), the Codex Alimentarius Commission (CAC), the Codex Committee on Food Additives and Contaminants (CCFAC) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (10).

Different countries may take different approaches to food safety. Canada takes two different risk assessment approaches to food safety, as follows:
- biological monitoring examines humans for contamination
- foods are examined for residues.

The levels of residues are combined with information from a total diet programme to estimate intake. The total diet programme identifies commonly consumed foods and estimates the amount of foods consumed (12).

The MRL is the measure currently used in the USA to determine safe residue levels in foods. There is a proposal recommending the use of toxicologically determined acceptable daily intake (ADI) levels for drugs in place of the MRL. The ADI is dependent both on levels of residues in foods and on the quantities of food consumed. Instead of using the estimated maximum daily intake (EMDI) of a residue (which is computed using the MRL), a better estimator is the estimated daily intake (EDI), which is computed using known residue levels rather than MRL. Since both the EMDI and EDI will vary with dietary custom from country to country, each country should compute equivalencies for EMDI and EDI based on the MRLs in other countries, assess whether these levels violate national ADIs, and then develop ‘equivalent’ MRLs under which they will accept imports (21).

Even when differences between governmental agencies are taken into consideration, there are still areas in food safety which are open to discussion and suggested improvement. As an example, an alternative methodology for the development of MRLs and ADIs from most current systems involves the use of in vitro simulations. The four basic steps of the simulations are as follows:

a) to determine MIC of the drug in question for selected bacteria

b) to incorporate the drug into food and to test for drug stability under gut-like conditions in the *in vitro* simulation

c) to add the selected bacteria to the fluids in the *in vitro* gastrointestinal fluids

d) to confirm the MIC of the drug by counting bacterial growth in the presence of the gastrointestinal fluids.

The ADI can be computed from these data (49). To satisfy European Union registration requirements, work is under way to develop an *in vitro* model of the human gut to test the effect of residues on gut flora. Data generated using the model can be used to compute ADIs in the future (42).

The biotransfer factor (residue concentration in tissues divided by the daily intake of the chemical) is a figure used to help estimate MRLs for drugs. One proposed improvement in comparison to the simple computation of the biotransfer factor is to use polar-corrected first order molecular connectivity indices for chemicals to predict the biotransfer factor. A first order molecular connectivity index is an index of the structure of a molecule, correlated with molecule size, branching, molar volume and area. The polar correction is performed to account for polar compounds. This is a way of measuring the physical-chemical properties of a molecule, which can then be used to predict biotransfer of chemicals.
This is a more reliable estimator of the chemical processes, and gives more realistic estimates of the actual biotransfer factor (16).

The NOAEL (no observed adverse effect level) is used for setting exposure levels for residues, but is controversial. The NOAEL has been criticised in terms of sensitivity to sample size, high sample variability from experiment to experiment, and the fact that the level does not take dose-response relationships into consideration. The impact of distribution of the NOAEL on dose-response curves showed that the average risk levels associated with the NOAEL may be substantial (3%-21%). The implication is that NOAEL may be set at unacceptably high risk levels to ensure safety (40).

Suggestions for handling residue issues at the international level

To prevent international trade barriers associated with the presence of drug residues in beef, the following issues should be addressed:

- standardisation of testing methods used to detect drug residues in cattle before and after slaughter
- establishment of active surveillance programmes to monitor drug residues in beef.

The determination of rates of residue occurrence using standardised methods will enable comparisons to be made between different countries. This will allow international trade organisations to make informed decisions concerning restrictions of beef (and other foods of animal origin), which will be beneficial to both the exporter and the importer. In addition, this information can help participating countries to identify problems (of which there may be no awareness) which have an impact on international trade and public health. Once these problems have been identified, affected countries can make changes to national residue monitoring, control and prevention programmes. This will allow each country to provide internationally acceptable food products for export and, at the same time, improve the safety of foods for the national population. Standardisation of methods and co-operative efforts in the detection and reduction of drug residues in beef will result in an improved international trading environment, and ultimately in a safer food supply for global consumption.

Problèmes liés à la présence de résidus médicamenteux dans la viande des bovins, résultant de leur alimentation ou de leur traitement thérapeutique

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Résumé
La présence de résidus médicamenteux dans la viande bovine a été observée dans tous les pays. Il s’agit, entre autres, d’antimicrobiens, d’anti-inflammatoires, d’activateurs de croissance, de parasiticides et d’insecticides. Les principaux facteurs associés aux résidus sont l’âge de l’animal, le mode d’utilisation et le non-respect des délais d’attente pour une utilisation ordinaire ou hors label. Les problèmes de santé publique qui se posent sont, notamment, des réactions toxiques et anaphylactiques et le développement de souches de bactéries résistantes aux médicaments. La limite maximale de résidus (LMR) est la norme adoptée par les Comités du Codex de l’Organisation des Nations Unies pour l’alimentation et l’agriculture et par l’Organisation mondiale de la santé, actuellement applicable pour les produits alimentaires, mais elle n’est pas universellement acceptée ou normalisée.
La détection à l’abattage constitue un point critique de contrôle des résidus. Il existe plusieurs épreuves applicables aux animaux vivants, qui diffèrent par leur fiabilité et leur utilisation. Pour les épreuves réalisées après l’abattage, les tissus prélevés et les tests pratiqués sont plus uniformes. Pour éviter que la présence de résidus médicamenteux dans la viande bovine ne constitue une entrave aux échanges internationaux, il conviendrait de:

- normaliser les épreuves utilisées pour déceler les résidus de médicaments;
- normaliser les méthodes permettant de déterminer la LMR;
- mettre en œuvre des programmes de surveillance active des résidus.

Mots-clés

Problemas ligados a la presencia en la carne vacuna de residuos de medicamentos administrados en los piensos o durante un tratamiento terapéutico

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Resumen
La presencia de residuos de medicamentos en la carne vacuna es un fenómeno de dimensión internacional, que abarca desde antimicrobianos o antinflamatorios hasta promotores del crecimiento, parasiticidas o insecticidas. Los principales factores que vienen asociados a la presencia de residuos son la edad y el uso del animal y la no observancia del período de suspensión. Entre los principales problemas de salud pública que plantean los residuos figuran las reacciones tóxicas y anafilácticas y el desarrollo de cepas bacterianas resistentes a los medicamentos. Aunque no esté universalmente aceptado ni normalizado, el límite máximo de residuos (LMR) es el criterio de uso común para el monitoreo de residuos en los alimentos, adoptado por los Comités del Codex de la Organización de las Naciones Unidas para la Agricultura y la Alimentación y por la Organización Mundial de la Salud. La detección de residuos en el momento del sacrificio es un punto crítico de control. Existen diversas pruebas aplicables a los animales vivos, pero su fiabilidad y modo de empleo son variables. Más homogeneidad presentan las técnicas de muestreo de tejidos y de detección de residuos que se aplican tras el sacrificio. Para evitar que la presencia de residuos en la carne vacuna se traduzca en una barrera a los intercambios internacionales, es necesario crear las condiciones siguientes:

- normalización de los métodos de prueba utilizados para detectar residuos de medicamentos;
- normalización de los métodos empleados para fijar los LMR;
- creación de programas de vigilancia activa para el monitoreo de residuos.

Palabras clave
References


