

Chemical Residues and Contaminants in Foods of Animal Origin

This factsheet is intended for food business operators and other interested parties, particularly in the sector of foods of animal origin. The factsheet provides information on:

- Chemical residues and contaminants that may occur in foods of animal origin
- The legislation setting the maximum limits for permitted substances and the listing of prohibited substances
- The legislation governing the monitoring of residues in foods of animal origin
- The National Residue Monitoring Plan, and
- Residue analysis and the risk-based approach to developing the National Residue Monitoring Plan

1. Introduction

Veterinary medicines are substances used to treat and prevent disease in animals and thus have the potential to enter the food chain through their occurrence as residues in food. Animals may also be exposed to a range of other chemicals such as pesticides and environmental contaminants (organohalogenes, chemical elements, mycotoxins, etc.) occurring in air, soil, water or in feed. A further category of substances of potential concern is growth promoting agents and non-approved veterinary medicines that are prohibited for use in food-producing animals. It is of critical importance that residues of veterinary medicines, contaminants and prohibited substances are either not present in animal products destined for the human food chain, or are present at such a level that adverse effects on the health of consumers cannot occur.

2. Residues, Contaminants and Food Safety

Consumers can potentially be exposed to residues via consumption of food from animals treated with veterinary medicines or exposed to chemical contaminants. This includes meat and meat products derived from the main food species (bovines, sheep/goats, pigs and poultry) as well as farmed fish, milk, eggs, honey and game. In the case of licensed veterinary medicines, these are approved for use in animal production to deal with animal diseases and to ensure that animals raised for food production are healthy. Some veterinary medicines, particularly antimicrobials, are also used as human medicines. Where veterinary medicines are used according to the licensed conditions of dose, period of treatment and withholding period specified before slaughter or use of milk for human consumption, residues should be at levels that will not cause any effect on consumer health. In the case of chemical contaminants, animals are only suitable for food production if the levels of residues of such contaminants in edible products are below levels that could pose a health risk for consumers.

Maximum residue limits/levels (MRLs) are specified under EU and national regulations for approved veterinary medicines and pesticides, and maximum levels (MLs) are similarly specified for contaminants in foods of animal origin. In the case of veterinary medicinal products, an assessment of the safety of residues is carried out by the Committee for Medicinal Products for Veterinary Use (CVMP) of the European Medicines Agency (EMA) and MRLs are specified for various foods of animal origin (different edible tissues and other food commodities). The MRLs for food products result from calculations based upon the Acceptable Daily Intake

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(ADI). The ADI is the estimated amount (extrapolated from animal studies) of a residue which can be consumed daily over a lifetime without a health risk to the consumer. Approved veterinary medicines must be authorised for use by the national licensing body in Ireland, the Health Products Regulatory Authority (HPRA), usually following the centralised evaluation by the CVMP of EMA.

In the case of pesticides, the European Food Safety Authority (EFSA) carries out a risk assessment and advises the European Commission on the appropriate MRLs to be assigned. In the case of chemical contaminants, again following risk assessments by EFSA, the European Commission sets MLs for certain contaminants with a view to reducing their presence in foods.

The setting of MRLs/MLs for veterinary medicines, pesticides and contaminants and the review of such MRLs/MLs is an ongoing activity by the European Commission through evaluations by the CVMP of the EMA and by EFSA, as appropriate.

3. Legislation

The legislation on residues of veterinary medicines and contaminants is harmonised at EU level. The key pieces of legislation are Council Directive 96/23/EC and Commission Regulation 37/2010/EU.

Directive 96/23/EC lays down measures to monitor certain substances and their residues in live animals and in animal products. In Annex IV of Directive 96/23/EC, the levels and frequencies of sampling are specified for bovine, porcine, ovine, caprine and equine animals, for poultry and for aquaculture products. In Commission Decision 97/747/EC, the levels and frequencies of sampling are specified for milk, eggs and honey and for rabbits and farmed and wild game. Other European legislation of importance in the implementation of the above legislation includes Commission Decision 98/179/EC which sets out rules relating to how sampling should be undertaken and Commission Decision 2002/657/EC which sets down standards for the performance of analytical methods and the interpretation of results.

Related national legislation includes the Animal Remedies Act, 1993 (S.I. No. 23/1993), the European Communities (Control of Animal Remedies and their Residues) Regulations, 2007 (S.I. No. 143/2007), and the European Communities (Animal Remedies) (No.2) Regulations, 2007 (S.I. No. 786/2007).

Regulation 37/2010/EU lists the MRLs for allowed pharmacologically active substances (veterinary medicines) in foodstuffs of animal origin and provides the list of prohibited substances. Prohibited substances are pharmacologically active substances for which an MRL cannot be established because of their toxicity; such substances include chloramphenicol, nitrofurans, nitroimidazoles and others. In addition to the prohibited substances listed in Regulation 37/2010/EU, Council Directive 96/22/EC prohibits the use in livestock of growth-promoting agents such as hormones, thyrostats and beta-agonists.

In the case of pesticides, the MRLs for residues are regulated by Commission Regulation 396/2005/EC on maximum residue levels of pesticides in or on food and feed of plant and animal origin. Council Regulation 315/93/EC provides that MLs are set for certain contaminants in foodstuffs and the list is set out in Commission Regulation 1881/2006/EC; in the case of foods of animal origin, contaminants for which MLs apply include aflatoxin M1 (in milk and milk products), heavy metals such as cadmium, lead and mercury, dioxins and polychlorinated biphenyls (PCBs), and polyaromatic hydrocarbons (PAHs). It should be noted that most of this European legislation has been amended by subsequent pieces of legislation, which determines the up-to-date situation; these may be viewed in the legislation section of the FSAI website.

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4. Enforcement and Monitoring

Directive 96/23/EC requires national authorities to draw up and implement residue control plans, sets out key obligations for primary producers and processors of primary produce and deals with infringements and penalties. Also, it requires countries exporting to the EU to have equivalent controls including residue control plans that are approved by the EU. In Ireland, legislation is enforced by the Department of Agriculture, Food and the Marine (DAFM) under service contract to the Food Safety Authority of Ireland (FSAI). Official controls in this area must be performed in accordance with the requirements of Regulation (EC) No 882/2004 on official controls performed to ensure the verification of compliance with feed and food law, animal health and animal welfare rules.

The principal means of enforcement is sampling under the National Residue Monitoring Plan, following the guidelines as set out in Directive 96/23/EC and further elaborated by Commission Decisions 97/747/EC and 98/179/EC. These set out detailed rules on official sampling for the monitoring of certain substances and residues thereof in live animals and animal products. The National Residue Monitoring Plan, required by Directive 96/23/EC, covers all farmed food-producing species (bovines, sheep/goats, pigs, poultry, fish, horses and farmed deer) as well as food commodities such as milk, honey and eggs. Minimum levels and frequencies of sampling are laid down in the Directive, and depend upon the species, substance and on the number of animals of each species slaughtered in the previous year or on the overall volume of production of a food product. The matrix to be tested is also specified and is intended to represent the sample type for each substance where measurable residues are most likely to be detected.

Implementation of the plan involves taking samples from food producing species at both farm and primary processing plant levels. Samples are generally taken in accordance with criteria designed to target animals or products which are more likely to contain non-compliant residues, that is, for licensed animal remedies, pesticides or contaminants, at levels higher than the specified MRLs/MLs, and for prohibited substances, at any confirmed levels. Sampling is also conducted in specific cases where the presence of non-compliant residues is suspected by inspectors, for example, following ante or post-mortem examinations in slaughterhouses. Suspect animals or carcasses/food products are detained from entering the food chain and, should non-compliant results be found, the food products are excluded from entering the food chain. Residue breaches lead to follow-up investigations at the farms of origin with a view to taking enforcement measures, including legal action where appropriate.

The sampling strategy outlined in Commission Decision 98/179/EC is aimed at a) detecting illegal treatments b) controlling compliance with MRLs/MLs and c) surveying the reason for occurrence of residues in food of animal origin. Wherever official samples are taken, they should be unannounced and not undertaken at any particular fixed time or on any particular day of the week. The samples are taken at a range of points such as farms, slaughtering plants, dairies, border inspection posts (BIPs), etc. In addition, details on self-monitoring and co-responsibility on the part of the food business operators are included in Directive 96/23/EC (see Section 6).

The involvement of the various organisations in the National Residue Monitoring Plan is shown in Table 1.

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Under Directive 96/23/EC (Annex I), all substances to be covered by the National Residue Monitoring Plan are classified either into Group A or Group B (see Appendix I). Group A substances comprise prohibited substances: growth promoting agents, such as stilbenes, thyrostats, hormonal substances and beta-agonists, and prohibited animal remedies such as chloramphenicol and nitrofurans. Group B substances comprise approved veterinary medicines, such as antimicrobials, antiparasitics, sedatives, anticoccidials, etc., and contaminants such as pesticides, heavy metals, and persistent organohalogen compounds. Minimum levels of sampling are specified for each sub-group of Group A and Group B substances. In addition, the competent authority is mandated to allocate the remainder of the required sampling to those substances which experience suggests are most likely to occur as non-compliant residues. For example, intensified sampling for anthelmintics in sheep/goats, phenylbutazone in horses and dioxins in all species and food commodities, has been introduced to address the findings of non-compliant results relating to these substances. A risk-based approach to developing the National Residue Monitoring Plan is appropriate for allocating this discretionary sampling (see Section 8).

In relation to imports from third countries, a list is provided in European legislation of those countries from which Member States are authorised to import animals and animal products. Inclusion and retention on the list is subject to submission by the third country of a residue plan setting out guarantees as regards the monitoring of residues. These guarantees must have an effect equivalent to the monitoring within EU Member States as detailed in Directive 96/23/EC. Compliance with the requirements of, and adherence to, the guarantees offered by the plans submitted by third countries are verified by means of checks. The European Food and Veterinary Office (FVO) carries out these checks (see Section 7).

Table 1. National Residue Monitoring Plan

Co-ordination of Food Control	The FSAI is responsible for co-ordination of food control activities relating to the National Residue Monitoring Plan, through service contract arrangements with various agencies such as the Department of Agriculture, Food and the Marine (DAFM), local authorities, the Sea Fisheries Protection Authority (SFPA) and the Marine Institute (MI).
Development and Implementation	DAFM is responsible for developing and implementing the annual National Residue Monitoring Plan, in consultation with FSAI, SFPA, MI and local authorities.
Sampling	DAFM inspectors, local authority veterinary officers and MI sampling officers (farmed fish) are responsible for sampling.
Sample Testing Laboratories (see Appendix II)	DAFM Veterinary Public Health Regulatory Laboratory, the State Laboratory, Teagasc Ashtown Food Research Centre, the Marine Institute, DAFM Pesticides Control Laboratory and some other laboratories are responsible for analyses.
Follow-up Investigations	DAFM and the SFPA are responsible for follow-up investigations.

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5. Residue Analysis

Commission Decision 2002/657/EC specifies the performance criteria and the interpretation of results for analytical methods that are used for residue monitoring under Directive 96/23/EC. In addition, the validation parameters required to demonstrate that each analytical method is fit for purpose, such as detection and decision limits (or decision limit and detection capability), precision, selectivity/specificity, trueness/recovery and applicability/ruggedness/stability, are specified.

Screening methods which are designed to identify those samples which may contain non-compliant residues, include methods such as enzyme-linked immunosorbent assays (ELISAs), biosensor methods, receptor assays, biomarkers for the presence of residues, and gas- and liquid-chromatography. In the particular case of antimicrobials, microbiological or inhibitory substance tests in various formats are widely used for screening, allowing a high sample throughput but limited information about the substance identification or its concentration in the sample. When a screening test indicates a potential residue-positive sample, a confirmatory test, providing full information on identity and concentration of residue in the sample, is undertaken.

Confirmatory methods are largely based on mass spectrometry (MS), using triple quadrupole, ion trap, and other MS techniques. More efficient sample extraction/clean-up methods are an integral part of the advances in confirmatory methods. Indeed, with current methodology in a modern residue laboratory with good MS capability, much of the two-step approach of screening followed by confirmatory testing has been replaced by single confirmatory testing, allowing for unequivocal, quantitative determination of a broad spectrum of substances using a single analytical method.

Laboratories providing testing of samples within the National Residue Monitoring Plan are required to be accredited to the ISO 17025 standard. Details of the national reference laboratories designated for the National Residue Monitoring Plan testing are given in Appendix II.

6. Responsibilities of Food Business Operators

In addition to the overall responsibility placed on food business operators by the General Food Law (Directive 178/2002) to supply safe food, Directive 96/23/EC places responsibility upon farmers and processors of primary products of animal origin to ensure that animals or produce supplied or accepted for processing do not contain harmful residues and that their food products comply with the legislative limits for residues of veterinary medicines and contaminants as laid down in legislation.

In addition to the official testing carried out under the National Residue Monitoring Plan, primary processors in the red and white meat sectors and also in the milk sector are required to carry out residue testing. Processors are required to submit annual residue monitoring plans to DAFM for approval. Where animals or milk from certain suppliers are found to contain non-compliant levels of residues, the processors are required to apply an increased scale of testing to further supplies of animals or milk from those suppliers. Within the legislative framework, farmers or veterinarians, as appropriate, are required to enter in a register kept on the farm, the date and nature of any treatment prescribed or administered, the identification of the animals treated and the corresponding withdrawal periods.

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7. The European Food and Veterinary Office

The European Food and Veterinary Office (FVO) located in Grange, Co. Meath, is responsible for monitoring the compliance of Member States and third countries with European Union legislation in areas such as public, veterinary and plant health. The FVO monitors control systems for foodstuffs of animal origin in Member States and third countries, including control measures, sampling and analysis.

8. Risk-based Approach to Developing the National Residue Monitoring Plan

The sampling to be undertaken in residue monitoring under Directive 96/23/EC is 'targeted', meaning that the animals and sample matrices selected for sampling for particular substances should be those where non-compliant results are most likely to be found. A further refinement of this targeted approach to sampling is the development of a ranking system for substances to underpin the application of a risk-based approach to the residue testing programme.

At a national level, the FSAI published a Report of the Scientific Committee entitled *Risk-Based Approach to Developing the National Residue Sampling Plan* (FSAI, 2014). This document provides a ranking system for veterinary medicinal products and medicated feed additives and it has been developed as a tool to be applied in a risk-based approach to the residue testing programme for foods of animal origin in the National Residue Monitoring Plan. Three characteristics of substances that may occur as residues in food are included in the developed risk-ranking system: *Potency*, as measured by the ADI value assigned to each substance; *Usage*, as measured by the three factors of (a) number of doses sold for use on each species of animal, (b) use on individual animals or for group treatment, and (c) withdrawal period; *Residue Occurrence*, as measured by non-compliant results in the National Residue Monitoring Plan. For both number of doses and non-compliant results, data for the five-year period 2008 to 2012 were used.

The risk-ranking system for substances has been developed for beef cattle, sheep and goats, pigs, poultry and dairy cattle using a scoring system applied to the various parameters described above to give a Ranking Score = Potency × Usage × Residue Occurrence. Applying this risk-ranking system, the following substances are ranked very highly: antimicrobials such as amoxicillin (for all species except pigs), oxytetracycline (for all species except poultry), sulfadiazine with trimethoprim (for pigs and poultry) and tilmicosin (for poultry); antiparasitic drugs, such as the benzimidazoles triclabendazole (for beef and dairy cattle), fenbendazole/ oxfendazole (for sheep/goats and dairy cattle) and albendazole (for dairy cattle), the avermectin ivermectin (for beef cattle), and anti-fluke drugs closantel and rafoxanide (for sheep/goats); anticoccidials, such as narasin, nicarbazin and toltrazuril (for poultry).

The risk-ranking system described is a relatively simple system, designed to provide a basis for selecting the veterinary medicinal products and medicated feed additives that might be prioritised for residue testing in Ireland. It represents one component of a total risk-based approach to designing the residue testing programme for the annual National Residue Monitoring Plan. Other factors which should be taken into account are issues of regulatory concern, such as evidence of misuse of particular veterinary medicinal products and medicated feed additives, animals constituting an increased risk for residues such as cull cows and emergency slaughter animals, and experience/intelligence from other countries with similar agricultural practices.

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At an EU level, EFSA published a series of Scientific Opinions on the public health hazards to be covered by inspection of meat, covering swine (EFSA, 2011), poultry (EFSA, 2012), domestic solipeds (horses) (EFSA, 2013a), farmed game (EFSA, 2013b), sheep and goats (EFSA, 2013c) and bovines (EFSA, 2013d). These opinions cover both biological hazards and chemical hazards that need to be addressed in meat inspection and, also, animal health and welfare issues. Risk ranking of chemical hazards was based on the outcomes of the National Residue Monitoring Plans across the EU Member States for the period 2005 to 2010, together with data from other testing programmes, as well as substance-specific criteria such as the toxicological profile for the substance.

Substances that were ranked in most species as being of high or medium potential concern were the prohibited substances chloramphenicol and nitrofurans and the contaminants dioxins, PCBs and heavy metals (cadmium, mercury and lead). Additional substances that were ranked as of high or medium concern in particular species were growth-promoting agents in cattle, sheep and goats, the prohibited substances nitroimidazoles in pigs and poultry, the mycotoxin ochratoxin A in pigs, and the prohibited substance phenylbutazone in horses. Substances such as licensed veterinary medicines, pesticides, mycotoxins (other than ochratoxin A) and plant toxins were ranked as being of low potential concern in all species. EFSA categorised licensed veterinary medicines as being of low potential concern because they have been subjected to pre-marketing approval which specifies ADIs and appropriate MRLs; therefore, occasional non-compliance with these MRLs is not likely to constitute a concern for public health.

9. References

Animal Remedies Act, 1993 (S.I. No. 23/1993)

Commission Decision 97/747/EC fixing the levels and frequencies of sampling provided for by Council Directive 96/23/EC for the monitoring of certain substances and residues thereof in certain animal products

Commission Decision 98/179/EC laying down detailed rules on official sampling for the monitoring of certain substances and residues thereof in live animals and animal products

Commission Decision 2002/657/EC implementing Council Directive 96/23/EC concerning the performance of analytical methods and the interpretation of results

Commission Regulation 1881/2006/EC setting maximum levels for certain contaminants in foodstuffs

Commission Regulation 37/2010/EU on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin

Council Directive 96/22/EC concerning the prohibition on the use in stock farming of certain substances having a hormonal or thyrostatic action and of beta-agonists

Council Directive 96/23/EC laying down measures to monitor certain substances and residues thereof in live animals and animal products

Council Regulation 315/93/EC laying down Community procedures for contaminants in food

European Communities (Control of Animal Remedies and their Residues) Regulations, 2007 (S.I. No. 143/2007)

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European Communities (Animal Remedies) (No 2) Regulations, 2007 (S.I. No. 786/2007)

EFSA, 2011, Scientific Opinion on the public health hazards to be covered by inspection of meat (swine)

EFSA, 2012, Scientific Opinion on the public health hazards to be covered by inspection of meat (poultry)

EFSA, 2013a, Scientific Opinion on the public health hazards to be covered by inspection of meat (solipeds)

EFSA, 2013b, Scientific Opinion on the public health hazards to be covered by inspection of meat from farmed game

EFSA, 2013c, Scientific Opinion on the public health hazards to be covered by inspection of meat from sheep and goats

EFSA, 2013d, Scientific Opinion on the public health hazards to be covered by inspection of meat (bovine animals)

FSAI, 2014, Risk-Based Approach to Developing the National Residue Sampling Plan (for Veterinary Medicinal Products and Medicated Feed Additives)

ISO/IEC 17025 General requirements for the competence of testing and calibration laboratories

Regulation (EC) No 178/2002 of the European Parliament and of the Council laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety

Regulation (EC) No 882/2004 of the European Parliament and of the Council on official controls performed to ensure the verification of compliance with feed and food law, animal health and animal welfare rules

Regulation (EC) No 396/2005 of the European Parliament and of the Council on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC

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Appendix I

Residue classification according to Annex I of Council Directive 96/23/EC

Group A – Substances having an anabolic effect and unauthorised substances

- (1) Stilbenes, stilbene derivatives, and their salts and esters
- (2) Antithyroid agents
- (3) Steroids
- (4) Resorcylic acid lactones including zeranol
- (5) Beta-Agonists
- (6) Compounds included in Annex IV to Council Regulation (ECC) No 2377/90 (now Table 2 of Commission Regulation 37/2010/EU)

Group B – Veterinary drugs and contaminants

- (1) Antibacterial substances, including sulphonamides and quinolones
- (2) Other veterinary drugs
 - (a) Anthelmintics
 - (b) Anticoccidials, including nitroimidazoles
 - (c) Carbamates and pyrethroids
 - (d) Sedatives
 - (e) Non-steroidal anti-inflammatory drugs (NSAIDs)
 - (f) Other pharmacologically active substances
- (3) Other substances and environmental contaminants
 - (a) Organochlorine compounds including PCBs
 - (b) Organophosphorus compounds
 - (c) Chemical elements
 - (d) Mycotoxins
 - (e) Dyes
 - (f) Others

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Appendix II

National Reference Laboratories, Ireland

Under Council Directive 96/23/EC, each Member State is required to designate National Reference Laboratories (NRLs). The responsibilities of these laboratories are described in Article 14 of Directive 96/23/EC. The following laboratories are designated in Ireland as National Reference Laboratories and their current responsibilities for the specific substance groups listed in Appendix I are shown.

Veterinary Public Health Regulatory Laboratory, Department of Agriculture, Food and the Marine, Backweston Campus, Young's Cross, Celbridge, Co. Kildare

Groups A2, A5 and A6 [Chloramphenicol and Dapsone only]

Groups B1, B2f [Carbadox only] and B3c [except for farmed finfish]

State Laboratory, Young's Cross, Celbridge, Co. Kildare

Groups A1, A3, A4 and A6 [Nitroimidazoles and Chlorpromazine only]

Groups B2b [Nitroimidazoles only], B2d, B2e, B2f [Corticosteroids only] and B3d

Teagasc Food Research Centre, Ashtown, Dublin 15

Group A6 [Nitrofurans only]

Groups B2a [except Emamectin], B2b [Anticoccidials only] and B2c

Marine Institute, Rinville, Oranmore, Co. Galway

Groups B2a [Emamectin only], B2f [Teflubenzuron and Diflubenzuron only], B3c [for farmed finfish only] and B3e [Malachite Green and Leuco Malachite Green only]

Pesticides Control Laboratory, Department of Agriculture, Food and the Marine, Backweston Campus, Young's Cross, Celbridge, Co. Kildare

Groups B3a, B3b and B3f

(NOTE: The current list of the National Reference Laboratories and their areas of responsibility are available on the FSAI website at https://www.fsai.ie/enforcement_audit/monitoring/national_official_labs.html)

European Union Reference Laboratories

There are four European Union Reference Laboratories for residues of prohibited substances, veterinary medicines and contaminants, namely, **Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)**, Berlin, Germany (Beta-agonists, Anthelmintics, Anticoccidials including Nitroimidazoles, Non-steroidal Anti-Inflammatory Drugs), **RIKILT - Instituut voor Voedselveiligheid**, Wageningen, The Netherlands (Stilbenes, Antithyroid agents, Steroids, Resorcylic acid lactones, Sedatives, Mycotoxins), **ANSES - Laboratoire de Fougères**, Fougères, France (Antibacterial substances, Dyes, Carbadox and Olaquinox, Chloramphenicol, Dapsone, Nitrofurans) and **Istituto Superiore di Sanità - ISS**, Rome, Italy (Chemical elements). The responsibilities of these laboratories are detailed in Annex V of Directive 96/23/EC.