



An Overview of Regulation and Control of Pesticide Residues in Food

Richard J. Fussell, Thermo Fisher Scientific, Hemel Hempstead, UK

Key Words

Global Pesticide Regulations,
Pesticide Monitoring Controls,
Pesticide MRLs

Executive Summary

The purpose of this white paper is to provide an overview on the regulation and control of pesticides in the European Union, United States, Japan, China and across the globe. The aim is help analysts gain an understanding of how the ever-changing regulatory landscape can drive the need for the further development of analytical techniques. These methodologies are needed to enable various stakeholders to demonstrate that food in the supply chain is in compliance with prevailing regulations and there is no health risk to consumers, farm workers, bystanders, animals, wildlife, or the environment.



Introduction

The definition of a pesticide given by the [Food and Agriculture Organization \(FAO\) of the United Nations](#) is any substance or mixture of substances intended for preventing, destroying or controlling any pest. This includes vectors of human or animal disease; unwanted species of plants or animals causing harm during or otherwise interfering with the production, processing, storage, transport or marketing of food; agricultural commodities; wood and wood products; or animal feedstuffs. It also includes substances which may be administered to animals for the control of insects, arachnids or other pests in or on their bodies. The term includes substances intended for use as a plant growth regulator, defoliant, desiccant or agent for thinning fruit or preventing the premature fall of fruit, and substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport.¹

One of the earliest recorded uses of pesticides was by Sumerians who used sulphur compounds to control insects and mites in Southern Mesopotamia about 4500 years ago

The earliest recorded uses of pesticides to protect crops from pests and damage were by Sumerians who used sulphur compounds to control insects and mites in Southern Mesopotamia about 4500 years ago, and by the Chinese who used mercury and arsenical compounds for controlling body lice about 3200 years ago.¹ The use of 'inorganic chemicals as pesticides has continued with the use of arsenic, mercury and copper compounds to control pests in 'kitchen gardens' as recent as 100 years ago, while Bordeaux mixture, based on copper sulphate and lime, is still used today to control various fungal diseases.

Pyrethrum, which is derived from the dried flowers of *Chrysanthemum cinerariaefolium* has been used as a natural insecticide for over 2000 years. Although pyrethrum is still used today, pyrethroids (chemically modified synthetic versions of pyrethrum) are more cost effective. The growth in synthetic pesticides occurred in the 1940's with the discovery of the insecticidal effects of organochlorine pesticides such as dichlorodiphenyltrichloroethane (DDT), aldrin and dieldrin. These were effective and inexpensive with DDT being the most popular because of its broad-spectrum activity.² Although these organochlorine compounds were relatively safe to mammals, their indiscriminate use impacted ecosystems, notably bioaccumulation in the food chain highlighted as the cause of the thinning of eggshells of birds of prey (top predators) and a subsequent decline in their numbers.

In 1962 the wider environmental concerns were highlighted by Rachel Carson in her book *Silent Spring* (1962)³, an inspired publication which resulted directly in the introduction of regulations and the development of safer and more environmentally-friendly pesticide products.

In 1962 environmental concerns about the liberal use of pesticides were highlighted by Rachel Carson in her book *Silent Spring*. This inspired publication resulted directly in the introduction of regulations and development of safer, more environmentally-friendly pesticide products



Agrochemical research has since led to the development of modern day insecticide and fungicide chemistries which are more selective, safer and more effective at lower application rates. New active substances (including chemical, bacterium or virus) are still being developed and registered as pesticides, but the actual number of pesticides authorized for use in food production is decreasing as older pesticides are withdrawn. The current 17th edition of the British Crop Production Council's Pesticide Manual⁴ provides information on more than 1600 compounds. Many of these compounds are no longer authorized for use in most parts of the world due to environmental persistence or toxicological concerns and thus are classed as obsolete. However, persistent chemicals continue to be used in some parts of the world (e.g., for control of mosquitoes where malaria is prevalent), and residues of obsolete chemicals are occasionally detected in food. In Europe the number of active substances approved for use on crops has decreased from 1000 in 1993 to around 250 in 2015.

Regulation and Controls

The application of pesticides can result in residues at detectable concentrations in food. Nowadays pesticides can only be authorized for use if it has been scientifically established that the active substances used are effective and can be used safely without harmful effects on people (consumers, growers and bystanders), animals or the environment.

One of the requirements for authorization of a plant protection product (PPP) is establishment of a maximum residue level (MRL) or tolerance. This is the pesticide residue level not likely to be exceeded in a specific food/feed commodity when the PPP is used in accordance with the label instructions. It is important to recognize that MRLs are primarily trading standards and not safety levels as they are usually set much lower than the levels that would pose a risk to consumers: usually 100 times below the no observable effect level (NOEL). Food produce found to contain a pesticide residue above the respective MRL is removed from trade channels.

A large number of different regulatory authorities are involved in regulation and/or control of pesticides around the world. Consequently systems for registration or authorization of PPPs and post registration monitoring controls vary in different countries and regions of the world, although the underlying objectives to develop safe and effective pesticide products that do not cause harm to consumers or the environment are the same.

Consequently, MRLs for the same pesticide-commodity combination are sometimes different in different countries, which can create barriers to trade. Global organizations such as the [Organisation for Economic Co-operation and Development \(OECD\)](http://www.oecd.org/) and the [Codex Alimentarius Commission \(Codex\)](http://www.codexalimentarius.org/) are concerned with the global harmonization of regulation and control of pesticides to facilitate global trade.⁵ Codex international food standards, guidelines and codes of practice have become global reference points for consumers, food producers and processors, national food control agencies and the international food trade. Information on Codex pesticide residue limits is located on the FAO website at <http://www.fao.org/fao-who-codexalimentarius/standards/pestres/en/>

When a specific country or region has not set an MRL for a specific pesticide-commodity combination, and a Codex MRL exists, there is an option for the importing country to use the Codex MRL to facilitate trade.

The food supply is monitored to check compliance with MRLs and ensure consumers are not being exposed to concentrations of pesticides that are harmful to their health.



Laboratories have to be able to analyze as many as possible of the 1600 substances at low concentrations (typically at 10 µg/kg) in many different types of food and feed samples (fruit, vegetables, cereals, products of animal origin, total diet samples and animal feed) because:

- Food and feed are traded in a global market, but the pesticide regulations are not harmonized globally so different pesticides are authorized for use on different crops in different parts of the world
- For regulatory purposes the pesticide residue definitions include the parent compound and toxicologically relevant metabolites, impurities and transformation products
- Unexpected residues can occur through deliberate misuse; the illegal use of obsolete or banned pesticides; the use of sub-standard or counterfeit pesticide formulations; or contamination from various sources including uses to protect public health, spray drift from adjacent fields and transfer during storage and/or packing

To provide comprehensive analysis of the large number of possible pesticide-commodity combinations, laboratories have to use a portfolio of multi-residue methods and single residue methods typically based on mass spectrometry techniques coupled to gas chromatography and liquid chromatography.

With the rapid developments in instrumental methods of chemical analysis, especially mass spectrometry techniques, laboratories have the capability to analyze several hundred pesticides in a single sample. The analytical techniques used to detect, identify and quantify pesticide residues in food are discussed in other associated white papers.

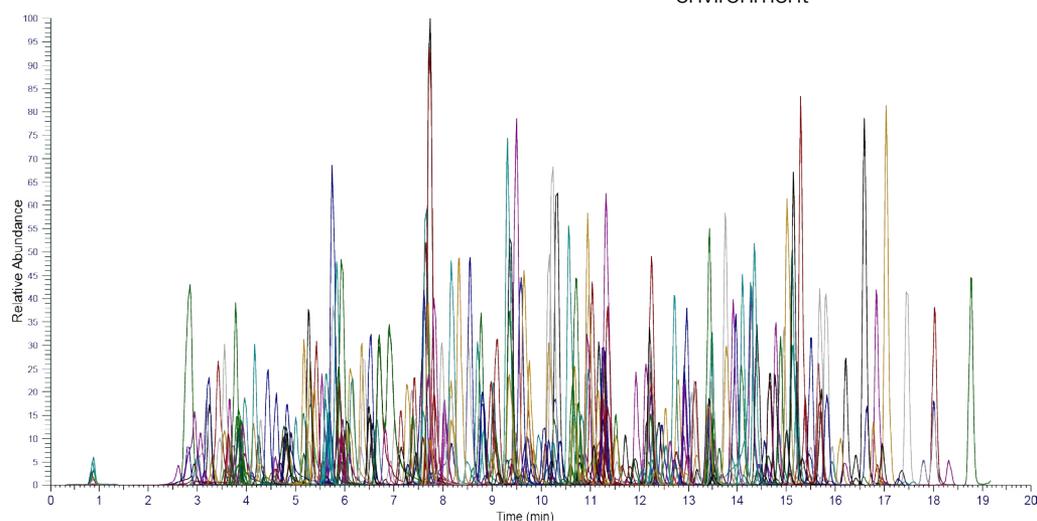


Figure 1. Separation and detection of 450 pesticides by liquid chromatography-triple quadrupole mass spectrometry.



Regulation and Control of Pesticides in the European Union

Regulation of pesticides in food in the European Union is complex because the system is updated frequently, so there are a large number of regulations, directives and transitional arrangements.

All of [these documents are listed](#) or can be searched from the Eurlex website homepage at <http://eur-lex.europa.eu/homepage.html>. A brief high-level overview of the regulations is given below.

In the European Union, the registration and safe use of pesticides can be divided into three main activities:

1. Approval of the active substance
2. Authorization of the uses of the PPP containing the active substance
3. Post registration controls to check compliance with MRLs to protect consumers, animals and the environment

This is an oversimplification as each activity involves several EU Regulations and Directives, inputs from various official and commercial organizations, extensive field trials supervised according to Good Agricultural Practice (GAP), assessment of substantial volumes of scientific data, post registration inspection and monitoring controls, etc. The whole process from discovery of a candidate active substance to the development and marketing of a PPP can take several years and can cost in excess of 200 million Euros.

In the European Union, the registration and placement on the market of PPPs is harmonized under [Regulation \(EC\) No 1107/2009](#) which entered into force on June 14, 2011, replacing Council [Directive 91/414/EEC](#). The EU system is based on a two-tier registration system.

1. New active substances, safeners and synergists are approved at the EU level following assessment against a set of agreed upon criteria outlined in Commission Regulation (EU) No. 283/2013. Approved active substances are contained in the Commission implementing Regulation 540/2011. This is the 'positive' list of active substances that are approved for use in PPPs in the European Union.
2. Existing active substances that have already undergone a review under Council Directive 91/414/EEC are deemed to be approved under Regulation no 1107/2009

Authorizations of PPPs are granted on a national basis because local conditions, environmental conditions and the occurrence of pests (and therefore pesticides) may differ from country to country. For example, in the southern EU member states where it is warmer, there are more insect pests and thus more insecticides are needed. In other parts of the European Union, more humid conditions may result in more fungal infestations and thus more fungicides are needed.

Under [Regulation \(EC\) No 1107/2009](#) there are two basic approaches to product authorization:

1. Zonal authorization (Articles 33–39)
2. Mutual recognition (Articles 40–42)

The concept of zonal evaluation is that when an evaluation is completed by a member state in one of three zones (Northern, Southern and Central EU Zones), other member states located in the same zone can use the same evaluation to grant an approval. This is subject to completion of any national specific data requirements and risk.

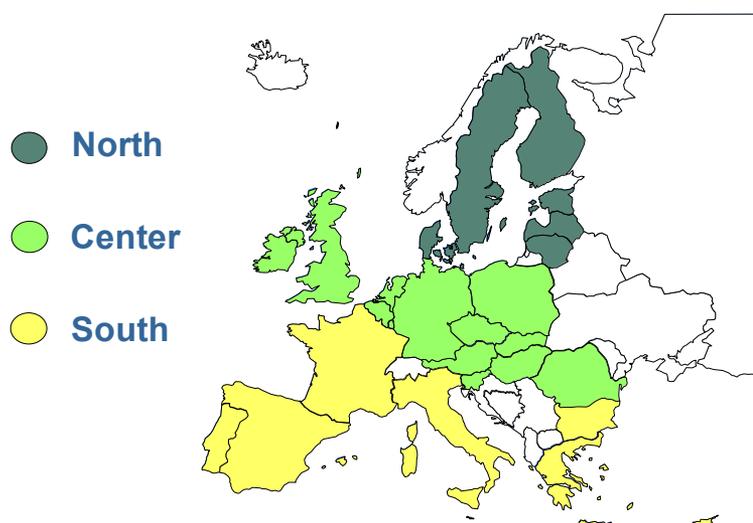


Figure 2. Map of zonal system for authorization of PPPs. Image courtesy of Amadeo Fernandez-Alba, EURL, University of Almeria, Spain.

The main objective is to avoid unnecessary duplication and thus provide a more efficient and cost-effective system. Mutual recognition of the same product for the same use under comparable agricultural practices may be permitted from one authorizing member state to another in the same zone. In specific circumstances (e.g., cultivation under glass) mutual recognition can be across different zones. These approaches are subject to the requirements outlined in the [EC SANCO/13169/2010 guidance document](#).

[Regulation \(EC\) No 1107/2009](#) also includes rules for mutual recognition of trade in parallel products (an imported product identical to one that is already authorized for placement on the market and used in the member state) to ensure the free movement and availability of approved PPPs throughout all EU member states.

The process for approval of an active substance, safener or synergist involves a number of steps. The producer (applicant) submits a dossier of supporting data (field trial data, metabolism data, etc.) for evaluation. The designated Rapporteur Member State (RMS) submits a draft assessment report to the [European Food Safety Authority \(EFSA\)](#) for risk assessment and expert consultation after which EFSA issues an opinion/conclusion. This opinion is then considered by the European Commission in the final decision process and before granting an MRL approval. At an early stage hazard-based cut-off criteria are applied. The active substance is eliminated from the evaluation if it exhibits any of the properties included in the hazard classification (Table 1).

The exclusion criterion for approval, included in Regulation 1107/2009, explicitly indicates that any active substance, safener and synergist with endocrine-disrupting properties that may cause adverse effects in humans cannot be approved for marketing and use unless the exposure to humans under realistic proposed conditions of use is negligible. A similar approval exclusion criterion has been introduced in the new EU Biocidal Products Regulation ([Reg EU 528/2012](#)).

Regulation 1107/2009 also requires member states to perform a comparative assessment when evaluating a new application for the authorization of a PPP containing an active substance that is already approved, but has properties that meet one or more of the seven criteria. In such a case the active substance is classified as a candidate for substitution. The purpose of the comparative assessment is to determine if the PPP in question can be replaced (substituted) by another PPP (chemical and non-chemical) that is already available on the market. Where possible alternatives do exist, evaluators should conduct a comparative assessment of the two products to determine their relative safety for human and environmental health and the possible agronomic (e.g., development of resistance), economic and the practical consequences of a substitution. If 'significantly safer' alternatives exist and the substitution is not expected to present unacceptable consequences, uses of the product will be 'substituted', and effectively denied or revoked.

Table 1. Exclusion criteria for the non-approval of active substances.

Human Health	Environmental Health
Carcinogen C1A & C1B	PBT (Persistent, Bioaccumulative & Toxic)
Mutagen M1A & M1B	POP (Persistent Organic Pollutant)
Toxic for Reproduction R1A & R1B	vPvB (very Persistent, very Bioaccumulative)
Endocrine Disruptor	Endocrine Disruptor



The comparative assessment process is described in detail in the Guidance Document on Comparative Assessment and Substitution of Plant Protection Products in accordance with Regulation (EC) No 1107/2009 ([SANCO 11507/2013 rev. 12, October 2014](#)). The aim of comparative assessment and substitution is to reduce risks by gradually replacing products containing candidates for substitution by methods and products of lesser concern. The objective is to improve the protection of human or animal health and the environment while minimizing the economic and practical disadvantages for agriculture. It has been suggested that comparative assessment and substitution may provide an incentive for the pesticides industry to further innovate and develop active substances and PPPs with less hazardous properties.

The likely consequences of these new rules will be that some existing active substances currently in use may have to be replaced in the future, and a lower number of new active substances will be available in the EU zone compared to other non-EU countries.

It is anticipated that the comparative assessment and substitution by member states will result in the use of PPPs that require less risk mitigation and the increased use of non-chemical control or prevention methods. These actions will also contribute to a more sustainable use of pesticides as foreseen by the Sustainable Use Directive 2009/128/EC.

The ARfD refers to the maximum quantity of a substance that can be ingested in a single day without harm to the consumer

The ADI refers to the maximum quantity of a substance which can be consumed every day for a lifetime without harm to the consumer

Before an approved active ingredient can be authorized for use, a dietary risk assessment is also carried out to ensure the potential chronic and acute exposure of consumers to residues remains below the acceptable daily intake (ADI) and the acute reference dose (ARfD) thresholds, respectively.

Candidate active substances that pass the toxicological assessment are then incorporated into formulated PPPs. These are then assessed by large-scale field trials and further studies on resultant residue levels, plant and animal metabolism, environmental fate (air, soil and water), and short-term and long-term fish and wildlife exposure.

Once a substance is approved for use in the European Union, it is included in the positive list of authorized active substances, and member states may authorize the use of PPPs containing it.

The use of products is controlled under Regulation (EC) 396/2005. This involves a rigorous and independent risk assessment to check that any residues remaining on the food crop following the correct use of the pesticide product in field trials will not give rise to any health concerns to the consumer. The results from field trials conducted using GAP (use of the formulated product according to the instructions on the label) is used to set MRLs.



The application rates may vary from one country to another depending on the pest pressure, but MRLs must be set according to the principle 'as low as reasonably achievable' (ALARA). The MRL is based on the sum concentration of the parent form of the active substance and any toxicologically relevant metabolites or other transformation products. MRLs are set to ensure compliance with the label instructions (including any post-harvest usage for transport and storage purposes) and to facilitate trade. The MRLs are set based on the whole fruit, including the peel in the case of oranges and skin in the case of bananas.

An MRL is not a toxicological safety limit, and exceedance of the MRL, for whatever reason, does not necessarily imply an adverse affect on human health. However, any commodities that do not comply with an MRL, which is a legal limit, must not be placed on the market.

Since September 2008 all statutory MRLs have been harmonized and set on an EU-wide basis under [Regulation \(EC\) 396/2005](#), which is divided into seven annexes (see Table 2).

A default Limit of Determination (LOD) value (0.01 mg/kg) applies to all active substances not mentioned in Annexes II, III or IV. This has particular relevance to crops grown outside the European Union.

Specific rules apply in the case of baby foods. [Directive 1999/39/EC](#) requires that baby food not contain any pesticide residue at a level exceeding 0.01 mg/kg. In addition, the directive sets lower levels of 0.003–0.008 mg/kg for a small number of the most toxic pesticides.

The MRLs are based on the sum concentration of the parent form of the active substance and any toxicologically relevant metabolites or other transformation products

To date, more than 150,000 EU MRLs have been set in Annex 2 of Regulation (EC) 396/2005. Proposals to set, modify or delete MRLs in Regulation (EC) 396/2005 are under regular consideration based on EFSA opinions. Any proposed lowering of MRLs requires notification to countries outside the European Union via the [World Trade Organization \(WTO\)](#) to allow those countries to raise any points of difficulty. MRLs are harmonized throughout the European Union but not globally, a situation that can create barriers to trade. This issue is discussed in more detail later in this paper.

In theory, countries outside the European Union can request an import tolerance – an MRL that is set based on uses registered in foreign countries to allow the import of treated commodities from abroad and facilitate trade. In practice import tolerances can be difficult to obtain because the regulation requires an appropriate MRL to be established before an authorization can be given, or treated commodities can be imported. Therefore, if an appropriate MRL is not already set in the regulation, an application for a new or amended MRL must be made, and this can take several months.



Table 2. Summary of annexes to regulation (EC) 396/2005.

Annex	Content
Annex I	Lists 315 commodities
Annex II	Lists substantive MRLs for 245 pesticides
Annex III	Temporary MRLs (compounds previously regulated by national MRLs)
Annex IV	Pesticides not requiring MRLs (the residues arising from PPP use cannot be distinguished from levels arising naturally in the environment) – List of 52 active substances not requiring MRLs
Annex V	Pesticides for which a default MRL (other than 0.01 mg/kg) applies
Annex VI	A list of concentration or dilution factors (processing factors) to calculate whether commodities that have been processed or mixed are in compliance with MRLs set on the primary products
Annex VII	Fumigants

It is the responsibility of the competent authorities in the member states to enforce the safe use of PPPs by checking compliance with MRLs. Exceedances can and do occur for a number of different reasons, including:

- The incorrect use of a pesticide (spray concentrations and/or number of applications were exceeded, or the correct harvest interval was not observed)
- The use of authorized pesticides on unauthorized crops
- Illegal use of a pesticide
- Use of counterfeit products (often unintentional)
- Spray drift from treatment of neighboring crops
- Contamination during storage and transport

Hence, the post-harvest monitoring of food products on the market requires laboratories to have the capability to analyze tens of thousands of pesticide-crop combinations.

Each year throughout the European Union, around 100,000 official samples of food are analyzed for pesticide residues in national monitoring programs and the EU Mandatory Co-ordinated Control Programme (EU MACCP). The number of MACCP samples analyzed each year by each of the 28 member states is proportional to their populations.

For the MACCP, each member state analyzes the same 30-40 food types (over a 3-year period) for the same target list of around 190 mandatory and voluntary pesticides in fruits, vegetables and cereals and 65 pesticides in products of animal origin. The list of pesticides is revised annually, and in 2015 a total of 157 mandatory pesticides was sought in fruits, vegetables and cereals. In addition to the analysis of official samples, it is estimated that a further 900,000 samples are analyzed by commercial laboratories each year for the food industry as part of their 'due diligence' programs.

The residue data from official controls are collated, consumer risk assessments are undertaken by EFSA, and priorities for future testing are identified. The most recent [EFSA annual report on pesticide residues in food \(2013\)](#) included results for almost 81,000 food samples from 27 EU member states plus Iceland and Norway. For more than 97% of these food samples pesticide residue levels were within legal limits, with just under 55% of samples free of detectable traces of these chemicals (<0.01 mg/kg). The overall results combine data from the national programs designed by each country, and those from the EU MACCP (11,582 samples of food products) which required all food control authorities to monitor the same "basket" of 12 different food products.

In addition to the analysis of official samples, it is estimated that a further 900,000 samples are analyzed by commercial laboratories each year

The majority of samples (68.2%) were taken from food originating in Europe, 27.7% were taken from food imported from other countries, and the remainder were of unknown origin. The percentage of samples from countries outside the European Union exceeding legal limits was higher (5.7%) than for EU countries (1.4%). However, EFSA concluded that the presence of pesticide residues from the EU MACCP in food was unlikely to have a long-term adverse effect on consumer health. For short-term exposure, the risk of European citizens being exposed to harmful levels of residues via their diet was rated as low.

If a pesticide residue is found at a level of concern for consumers, the information is circulated via the [EU Rapid Alert System for Food and Feed \(RASFF\)](#) so that measures may be taken to protect the consumer. The RASFF is an online portal that was created in 1979 to enable information from monitoring and enforcement programs to be shared quickly and efficiently 24/7 between RASFF members which include the national food safety authorities of the individual member states, the European Commission - Health and Consumer Protection Directorate-General, European Food Safety Authority and affiliated organizations. When a pesticide residue is found in a food or feed that may be a potential risk to consumer health, the rapid exchange of information helps competent authorities act more rapidly to avert a food safety risk in their own member state. The latest published RASFF summary report (2014), together with more recent notifications, and a description of the system, are available online. In 2014 there were a total of 435 notifications including some for the more toxic substances of triazophos, fipronil, methomyl, monocrotophos and dichlorvos mostly in a range of imported commodities. Only 41 notifications concerned pesticides in produce of EU origin. Further details are available in the [RASFF 2014 annual report](#).



Each year throughout the European Union, around 100,000 official samples of food are tested for pesticide residues in national monitoring programs and the EU MACCP combined

Many of these notifications would have resulted in border rejections due to reinforced checks under [Regulation \(EC\) No. 669/2009](#) and subsequent amendments. This regulation places emphasis on an increased level of official controls at border inspection posts, specifically for imported pesticide-commodity combinations from specific countries that are deemed to be of high risk. Starting in 2015 high risk commodities are being analyzed for the same 157 pesticides listed in the EU MACCP.

The [DG Health and Food Safety](#) carries out audits (formerly the FVO), inspections and related non-audit activities to ensure that EU legislation on food safety is properly implemented and enforced by the competent authorities of the member states. These audits and inspections were previously carried out by the Food and Veterinary Office (FVO).

The DG Health and Food Safety also carries out regular audits/inspections in other countries that export commodities to the EU to check that the regulatory process is being properly implemented and enforced. The audit findings, including any corrective actions deemed necessary along with recommendations for improvements to the control systems, are contained in published reports. The actions are followed up by repeat visits. If non-compliances are sufficiently serious, stronger actions may be taken by the European Commission in agreement with member states. Such actions can include legal action, restrictions or even bans on the movement of goods or animals.

In 2006 the European Commission established four Community Reference Laboratories (CRLs, now known as EURLs) for the analysis of food and feed for pesticide residues under [Regulation \(EC\) No 882/2004](#). Nominated EURLs for the analysis of pesticide residues are:

Cereals and feeding stuffs: National Food Institute Department of Food Chemistry, Danish Technical University (DTU), DK-2860 Soeborg, Denmark

Food of animal origin and commodities with high fat content: Chemisches und Veterinäruntersuchungsamt (CVUA) Freiburg, Postfach 100462 D-79123 Freiburg, Germany

Fruits and vegetables: Laboratorio Agrario de la Generalitat Valenciana (LAGV), Burjassot-Valencia, Spain and Grupo de Residuos de Plaguicidas de la Universidad de Almería, Spain

Single residue methods: Chemisches und Veterinäruntersuchungsamt (CVUA) Stuttgart Postfach 1206, D-70702 Fellbach, Germany

These laboratories have a number of responsibilities including coordination with the network of EU National Reference Laboratories, development and provision of new methods, training, organizing EU-wide proficiency testing and responsibility for updating the [EU guidance document SANTE/11945/2015 on analytical quality control and validation procedures for pesticide residues analysis in food and feed](#). The main benefits of sharing information are reduced duplication of effort in the development of new methods and overall improvement in the quality, accuracy and comparability of results at the official control laboratories in the European Union.

Regulation and Controls in the United States

There are three government agencies that share the responsibility for the regulation and monitoring of pesticides on the federal level in the United States.

[The U.S. Environmental Protection Agency \(EPA\)](#) registers (i.e., approves) the use of pesticides and establishes tolerances (the maximum amounts of residues that are permitted in or on a food).

[The U.S. Department of Agriculture \(USDA\)](#) is responsible for enforcement of pesticide tolerances primarily in meat, poultry and certain egg products.

[The U.S. Food and Drug Administration \(FDA\)](#) is responsible for enforcement of pesticide tolerances in other food categories for both domestic and imported produce shipped in interstate commerce.

The EPA regulates the use of pesticides under the authority of two federal statutes: the [Federal Insecticide, Fungicide, and Rodenticide Act \(FIFRA\)](#) and the [Federal Food, Drug, and Cosmetic Act \(FD&C\)](#). FIFRA covers the registration, distribution and use of pesticides. As in other countries the assessments include toxicology, environmental fate and eco-toxicology, and residue chemistry.

The data requirements in support of applications for registration of a pesticide product are specified in 40 CFR Part 158 and for antimicrobial active ingredients and products in 40 CFR Part 161.

In addition to its mandate under FIFRA, the EPA has authority to regulate pesticide products under the [FD&C Act \(formerly FFDCA\)](#). This act authorizes the EPA to establish tolerances or safe levels of pesticide residues in raw agricultural commodities (section 408). The Food Quality Protection Act of 1996 (FQPA) amended the FFDCA by consolidating the EPA's authority for establishing, modifying and revoking pesticide tolerances under FFDCA section 408. Processed food studies are required and many processed food tolerances are established if residues concentrate in the processed food.

All tolerances for raw agricultural commodities (RACs) and processed food/feed commodities (if required) are established under FFDCA section 408. Subsequently, the Antimicrobial Regulation Technical Corrections Act (ARTCA) of 1998 amended the FFDCA by excluding certain antimicrobial pesticides from FFDCA section 408. Tolerances for residues of those pesticides are set by FDA under FFDCA section 409. Maximum contaminant limits (MCLs) for drinking water are established by the EPA under the [Safe Water Drinking Act \(SWDA\)](#).

The EPA uses the OECD MRL Calculator for establishing legal limits for pesticide residues. If residues of a pesticide exceed the established tolerance, or no tolerance has been established, the crop is considered adulterated and may be seized by the FDA, USDA or a state enforcement agency.

Some pesticides are exempted from the requirement to have a tolerance. This applies in cases where the EPA has found the pesticide use to be safe after review of toxicity and exposure data, the same as for tolerance setting. In addition, there must be a practical method for detecting and measuring levels of the pesticide residues so regulatory officials can ensure that any residues are below the level found to be safe.

MCLs for drinking water are established by the EPA under the SWDA

Under FFDCA section 408(r), the EPA may establish a temporary tolerance or exemption from the requirement of a tolerance on its own initiative or at the request of any person who holds an experimental use permit (EUP). A temporary tolerance allows participants in the EUP program to market or use commodities harvested from EUP test plots.

In certain circumstances an exemption may also be issued for residues of a pesticide not registered for use in the United States. This applies to residues that may be present in imported RACs and processed foods produced abroad, providing the residue is within the tolerance established by the EPA. Although the use of a pesticide in a foreign country is not subject to EPA registration requirements under FIFRA, a pesticide residue in imported food or feed must conform with a tolerance or tolerance exemption established by the EPA. Otherwise the product is considered adulterated.

Shipments of imported food/feed items found to have pesticide residues for which a tolerance or exemption from the requirement of a tolerance has not been issued will be held. The the importer will be required to do one of the following:

- File for a tolerance or exemption from a tolerance
- Return the shipment to the country of origin
- Destroy the shipment

The U.S. FD&C Act authorizes the EPA to establish tolerances or safe levels of pesticide residues in raw agricultural commodities



The EPA has divided the approximately 1200 intentionally-added inert ingredients currently contained in pesticide products into four categories

Tolerances are under review for any intentionally added inert ingredient in a pesticide product which is not pesticidally active. This definition does not include impurities. The EPA has divided the approximately 1200 intentionally-added inert ingredients currently contained in pesticide products into four toxicity categories:

- Category I is danger
- Category II is warning
- Category III is caution
- Category 4 is caution or no signal word at all

The Code of Federal Regulations (CFR) is the official record of all U.S. regulations. The Electronic CFR can be found at <http://www.ecfr.gov/cgi-bin/ECFR?page=browse>.

The regulations are monitored and enforced by a combination of inspections and analysis of food and feed samples for the presence of pesticide residues.

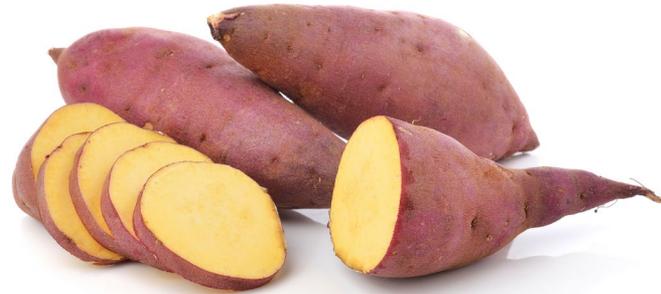
The FDA conducts Compliance Monitoring Programs, Total Diet Studies, Field Assignments and inspections.

In 2015 FDA Pesticide Program began to include both domestic and import samples with a focus on:

- Raw agricultural foods of dietary importance (i.e., foods that comprise the greater part of the U.S. diet that can contribute most to pesticide exposure)
- Foods consumed in large amounts by infants and children
- Foods with high violation rates (i.e., foods with residue levels above tolerance or with no tolerance)

Samples are analyzed for over 800 pesticide residues (parent and metabolites) including: carbamates, synthetic pyrethroids, neonicotinoids, chlorophenoxy acids, substituted urea pesticides and many more. Not all pesticides are analyzed on a regular basis.

Import samples are collected at the point of entry into U.S. commerce. Emphasis is placed on the raw agricultural product which is typically analyzed as the unwashed, whole (unpeeled) raw commodity, but some processed foods are also included. In 2012 a total of 5523 samples were analyzed (1158 domestic and 4365 imported).



The domestic violation rate was 2.8%, comparable with the previous year, while the import violation rate of 11.1% increased from 2.6-7.6% in previous years. This increased violation rate was attributed to the expanded analytical scope (detection of additional pesticide residues) of the pesticide program as a result of the implementation of new analytical technologies in 2010 and 2011. Further details are available at <http://www.fda.gov/downloads/Food/FoodborneIllnessContaminants/Pesticides/UCM432758.pdf>.

If illegal residues are present in the food lot, the lot is removed from commerce. Detention Without Physical Examination (DWPE) may be invoked for future imported lots of the commodity based on the finding of a single violative shipment. DWPE can be applied to product from specific growers, manufacturers or shippers, or to a geographic area or country. The FDA's Import Alerts are available at <http://www.fda.gov/ForIndustry/ImportProgram/ActionsEnforcement/ImportAlerts/default.htm#list>.

The FDA is responsible for enforcement of the Food Safety Modernization Act (FSMA) to ensure the U.S. food supply is safe by focusing on the prevention of contamination rather than responding to it. The FDA will hold food companies accountable for preventing contamination and requires importers to perform supplier verification activities to ensure imported food is safe.

In 2012 a total of 5523 samples were analyzed by the FDA (1158 domestic and 4365 imported)

The Total Diet Study (TDS), sometimes called the market basket study, is an ongoing FDA program that determines levels of various contaminants (including pesticides) and nutrients in foods prepared for consumption. A market basket consists of about 280 food items that represent the typical American diet and that basket is updated periodically to reflect changes. Each food sample is prepared table ready and analyzed to provide realistic estimates of dietary exposure. The TDS is designed as a broad, time-trend survey not to enforce regulations, but to monitor the impact of regulatory actions and to identify potential health hazards. The results are used to focus resources for FDA compliance programs. Regional market baskets are collected four times each year and typically generate around 20,000 results on pesticides and other contaminants.

The USDA Food Safety and Inspection Service (FSIS) is responsible for carrying out the U.S. National Residue Program for Meat, Poultry, and Egg Products. In 2012 samples were screened for 57 different pesticides across multiple classes, and no violations of were detected. More information on this program focused on pesticides and veterinary drugs can be found at <http://www.fsis.usda.gov/wps/wcm/connect/04c818ed-9bb1-44b2-9e3f-896461f1ffb9/2015-Blue-Book.pdf?MOD=AJPERES>.

In May 1991 the USDA along with six states implemented the Pesticide Data Program (PDP), a federally-funded grant program designed to gather statistically-based consumption data for pesticide residues in fresh fruits and vegetables.

The USDA's Agricultural Marketing Service (AMS) collects and analyzes randomly selected samples of raw agricultural products and various processed foods taken near the point of consumption through contracts with the state laboratories. The PDP is not designed for enforcement of EPA pesticide residue tolerances, but provides monitoring data used for risk assessment. The EPA uses PDP data when looking at dietary pesticide exposure. The PDP provides the FDA and EPA with monthly reports of pesticide residue testing and informs the FDA if residues detected exceed the EPA tolerance or have no EPA tolerance established. In instances where a PDP finding is extraordinary and may pose a safety risk, the FDA and EPA are notified immediately.

The Pesticides Data Program run by the USDA informs the FDA and EPA on pesticides findings if residues detected exceed tolerances set or if residues are detected for which no tolerances have been set

The number of samples collected by the individual states is apportioned according to each state's population. Samples are randomly chosen from specifically selected sites (i.e., at distribution centers rather than the farm gate) close to the time and point of consumption and are selected without regard to country of origin, variety or organic labeling. In 2013 a total of 10,104 samples (87% fruit and vegetables) were analyzed for around 450 pesticides at parts per billion concentrations, much lower than the EPA tolerances. No residues were detected in 40% of the samples. Excluding water, residues exceeding the tolerance were detected in 0.23% of the samples, and residues with no established tolerance were found in 3.0% of the samples. Further details can be found at <http://www.ams.usda.gov/AMSV1.0/pdp>.

The PDP is now a critical component of the Food Quality Protection Act (FQPA) of 1996. The pesticide residue data generated by this program are used to better inform the public of the safety of the nation's food supply. As of May 2012, thirteen states are participating in the PDP. For more information about USDA food safety programs, visit www.ams.usda.gov.

For more information about pesticides and food, visit the EPA's website at <http://www.epa.gov/pesticides/food>.

In addition to the PDP program, individual states do play an important role in regulation and enforcement. For example, California, Florida and Texas are three big U.S. agricultural states, and each has a different approach to how they regulate pesticides at state and at local levels. A detailed description of the programs in the different states is outside the scope of this paper, but an overview of the system in the state of Florida is given in the following text to provide an insight.

The TDS is an ongoing FDA program that determines levels of various contaminants in nutrients and food

The Bureau of Chemical Residue Laboratories in the Division of Food Safety, Florida Department of Agriculture and Consumer Services (FDACS), is responsible for the chemical analysis of poisonous or deleterious chemical residues remaining in or on human food produced or marketed in Florida. It is also responsible as for the regulatory enforcement of federal pesticide residue tolerances and guidelines adopted by the state for raw agricultural produce and some processed commodities such as honey.

The State of Florida conducts a Pesticide Residue Regulatory Enforcement Program. Samples are collected from fields, packing houses, central warehouses, wholesalers, retailers and importing facilities. Samples are grouped into four categories:

1. Core commodities which account for approximately 80% of samples. This category contains products that are consumed more frequently, are grown in Florida or have been found to contain violative residues in past years.
2. Auxiliary commodities which account for approximately 10% of samples. This category contains all other products which are not specifically listed as core commodities.
3. Discretionary samples. Approximately 7% of samples are collected by chemical residue field inspectors at their discretion based on knowledge of current pesticide use practices and anticipated problems.
4. Investigatory samples. Approximately 3% of samples collected are in response to a known residue violation found either in a regulatory sample analyzed in Florida, by another state, or by the FDA.



The Florida State laboratory equipped with state-of-the-art analytical instrumentation for chemical residue and contaminant analyses is headquartered in Tallahassee. Each year the Chemical Residue Laboratory performs more than 400,000 analyses on 3000 samples (approximately 1500 for each USDA PDP and regulatory requirement combined).

Approximately 50% of the food samples analyzed do not typically contain any detectable pesticide residues. The majority of residues that are detected are below established tolerances and guidelines. The average violation rate during the past decade has been approximately 2%. Approximately 70% of these violations occurred because no tolerances were established for the pesticide-crop combination. The decrease in pesticide residue violations, compared to violations in the 1960's, has been achieved through the department's rigorous regulatory and extensive pesticide application education programs.

Residue confirmation procedure(s) are performed on all positive pesticide residue findings. When a sample is found to contain a pesticide residue exceeding the established tolerance, or a residue that has no tolerance for that commodity, the lot is placed under a stop-sale/ stop-harvest order. A confirmation sample from the same lot is collected and analyzed. If a violation is confirmed, the contaminated lots are subject to voluntary destruction.

Regulation and Controls in Japan

There are four major laws in Japan relevant to food safety and standards in general:

1. Food Safety Basic Law
2. Food Sanitation Law
3. Japan Agricultural Standards Law
4. Health Promotion Law

The Food Safety Basic Law sets the principles for developing a food safety regime and also sets up the role of the Food Safety Commission, a food-related risk assessment body.

The Food Sanitation Law ensures the safety and sanitation of foods through the Ministry of Health, Labour and Welfare (MHLW), a food risk management agency. This law also prohibits the sale of foods containing harmful substances. It is available in English on the Japan External Trade Organization (JETRO) website at <http://www.jetro.go.jp/en/reports/regulations/>.

In Japan pesticides are regulated under the Food Safety Basic Law (enacted in May 2003). This is an over-arching law with many subsidiary related laws to provide comprehensive legislation to ensure food safety for the purpose of protecting public health. Pesticide tolerances are set by the MHLW through the Drug and Food Safety Committee. More information can be found at <http://www.mhlw.go.jp/english/topics/foodsafety/>.

The Japanese MHLW introduced a new system for the regulation of pesticides, feed additives and veterinary drugs in 2006.

This included publication of a 'positive list' with tolerances (MRLs) set for 758 chemicals (more than 800 in 2015) which included approximately 600 pesticides. A list contains 15 substances that pose a high risk to humans and should not be detected in food. By contrast 65 substances are exempt because they pose no threat to human health. A uniform limit set at 0.01 mg/kg applies to compounds for which MRLs have not been established which is equivalent to the EU default MRL of 0.01 mg/kg.

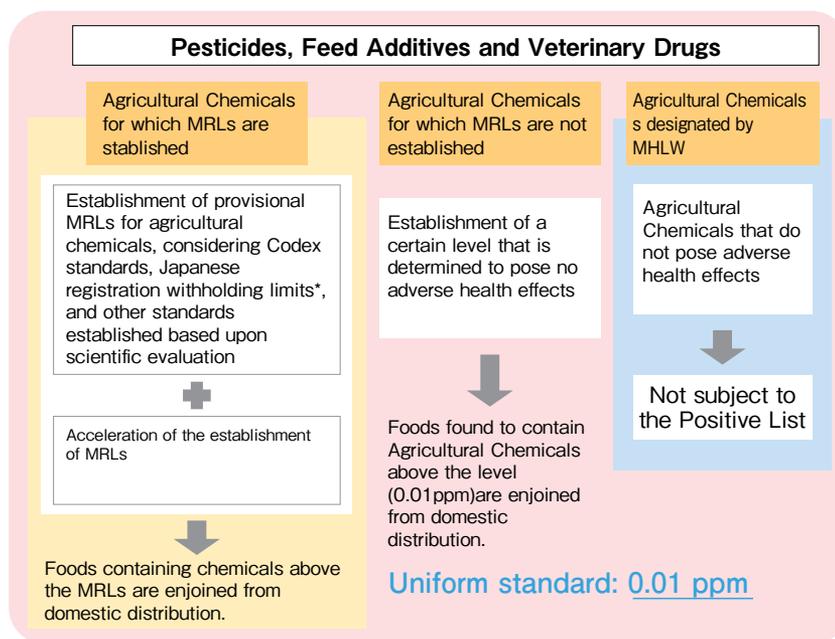


Figure 3. Summary of the 'positive list' system enacted in 2006.⁶

***Registration withholding limits:**

In terms of agricultural chemical residues in crops under the Agricultural Chemicals Regulation Act, the highest acceptable concentration limits of agricultural chemical residues had been established for commodity groups for some agricultural chemicals based on the result of exposure assessment until the introduction of the Positive List System in Japan. These limits have been used as one of the basis for establishing "Provisional MRLs" under the Positive List System.

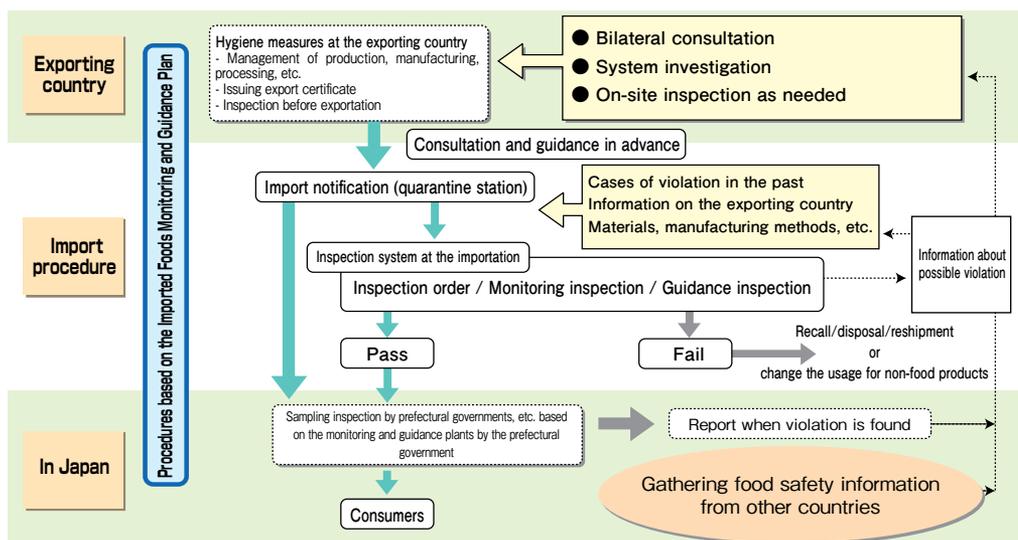


Figure 4. Monitoring system in Japan schematic.⁶

Since this introduction all Japanese agricultural products and all imports to Japan must comply with MRLs established for pesticides on the 'positive list'. Violative samples are removed from the domestic market, destroyed or re-shipped, or used in a non-food system.

The systems implemented in Japan for the control of pesticides in foods are complex. A large number of consignments are tested, but still it is a small percentage of the total number of food consignments. However, a large percentage of consignments are tested by exporter businesses before shipment to Japan. The extremely low violation rate indicates that the system is effective.

Regulation and Controls in China

In China the Ministry of Agriculture (MoA) is the main authority responsible for enforcement of the Law on the Quality and Safety of Agricultural Products (LQSAP) and the Regulation on the Control of Agrochemicals (RCA).

The authorization procedure for pesticides is set out in the RCA and carried out by the Institute for the Control of Agrochemicals, Ministry of Agriculture (ICAMA) under the control of the MoA. Authorization is a three-stage process starting with efficacy and residue trials. After completion of the field trials, applicants submit field trial data together with an application for a temporary authorization. ICAMA reviews the data pack within three months and on the basis of the review may grant a temporary MRL for one year. The temporary MRL permits the PPP to be placed on the market. During the period when the temporary authorization is valid, applicants are required to submit an application for an official authorization together with detailed data on the efficacy, toxicology, residues and environmental impacts. If the data review is successful then an official authorization is granted for five years and is subject to renewal.

The authorization procedure for pesticides is set out in the RCA and carried out by ICAMA under the control of the MoA. Authorization is a three-stage process

The FVO reported that 25,000 PPPs containing over 600 active substances were authorized for use in 2012. The number of PPPs and active substances were substantially higher than in the European Union.



MRL setting in China is also performed under the authorization procedure; it is the joint responsibility of the MoA and the National Health and Family Planning Commission (NHFPC). On March 20, 2014 the Chinese NHFPC released the National Food Safety Standard – Maximum Residue Limits for Pesticides in Foods (GB 2763-2014) which was implemented on August 1, 2014, replacing GB 2763-2012. The new standard covers almost all food categories and all pesticides used in China. Compared to GB 2763-2012, 65 pesticides and more than one thousand (1357) MRLs for pesticides in food have been added. A total of 473 new MRLs have been set for fruits and 431 MRLs for vegetables. In addition, MRLs have been set for fruit juices, preserved fruits and dried fruit for the first time in China. Further details are at <http://www.fas.usda.gov/data/china-maximum-residue-limits-pesticides-food>.

The General Administration of Quality Supervision, Inspection and Quarantine (AQSIQ) is a government body at the ministerial level and is the main competent authority (CA) in charge of food safety controls at import and export. Under the control of AQSIQ there is a network of 35 Entry-Exit Inspection and Quarantine Bureaus (CIQs) at the provincial level with more than 300 branches at the local level. These bureaus are responsible for implementing official controls at primary production locations on the use of PPPs and the application of pesticides. They also provide advice and training to growers on the safe use of PPPs and promote GAPs. The China National Accreditation Service for Conformity Assessments (CNAS), under the approval of the Certification and Accreditation Administration of the People's Republic of China (CNCA) and under control of AQSIQ, is responsible for the registration of food business operators, including packing-houses for different types of products (excluding fruit). This organization is also in charge of accreditation of CIQ official laboratories and organizes proficiency tests (PTs) for pesticide residues.



AQSIQ has established a quick response system to take preventive, safeguarding and recuperative measures against the possible risk or potential harm caused by imported and exported food of animal or non-animal origin. AQSIQ also participates in the formulation and implementation of the Chinese Program on Residue Monitoring and Control for food of animal-origin. This annual monitoring program covers a wide range of microbiological and chemical contaminants and residues including pesticides in a diverse range of commodities. The program is divided into sub-programs for different commodities falling under the responsibility of different CAs. A more detailed description of the program was given in an FVO report⁷ on a pesticides inspection visit to China in 2012.

On March 20, 2014, the Chinese NHFPC released the National Food Safety Standard – Maximum Residue Limits for Pesticides in Foods. More than one thousand (1357) maximum residue limits for pesticide in food have been added to GB 2763-2014

Global Harmonization of Regulations and Controls

As mentioned earlier, the OECD and Codex organizations are promoting the need for globalized harmonization of regulations for pesticides and harmonized MRLs (both level and residue definition) to facilitate global trade in agricultural commodities.

The OECD is an international economic organization of 34 countries founded in 1961 to stimulate economic progress and world trade. The OECD's first strategic objectives for 2024 include protection of human health and the environment facilitated through harmonized science-based requirements and methodologies for risk assessment (toxicity and exposure). The OECD has published a report on a global approach to the regulation of agricultural pesticides and sustainable pest management at <http://oecd.org/chemicalsafety/pesticides-biocides/OECD-Pest-Vision-Final.pdf>.

Proposals include:

- The mutual recognition of pesticide reviews and work sharing among regulatory authorities in OECD countries.
- Further development of integrated crop management approaches with a greater role for non-chemical and biological control measures
- Greater cooperation in the fight against illegal trade in pesticides
- The minimization of non-tariff barriers created by having different MRLs in different countries

Codex is responsible for implementing the Joint FAO/WHO Food Standards Program. Codex international food standards, guidelines and codes of practice have become the global reference points for consumers, food producers and processors, national food control agencies and the international food trade.

The Codex Committee on Pesticide Residues (CCPR), a risk management body made up of government officials from member countries of the United Nations, establishes MRLs (also known as CXLs) which are recognized as trading standards by WTO members. A dossier of residue's data is first submitted to the Joint FAO/WHO Meeting on Pesticide Residues (JMPR). A panel made up of independent pesticide experts review the dossiers and advise the CCPR on the toxicology and proposals for MRLs, etc. When a specific country or region has not set a specific MRL, and a Codex MRL exists, then there is an option for the importing country to use the Codex MRL to facilitate trade. However, even when CXLs are available, there is no harmonized acceptance of CXLs from different importing countries.

U.S. law requires the EPA to align U.S. tolerances with Codex MRLs. If a CXL exists and an administrator does not propose to adopt the Codex level, then a written explanation must be published. By contrast member states of the European Union will not accept CXLs that are at higher levels than existing EU MRLs, including default MRLs. In fact the importation into the European Union of treated commodities with residues levels above the relevant EU MRL would be illegal. Subject to satisfactory supporting data, it may be possible in some circumstances to change the EU MRL, but it is likely to be a slow process.



Information on the Codex pesticide residue limits is located on the FAO UN site at <http://www.fao.org/fao-who-codexalimentarius/standards/pestres/en/>.

As mentioned above, the problems are not only caused by differences in the level or concentration of the residue, but also in the residue definition for the same pesticide in the same commodity in different parts of the world. This was highlighted in a recent lecture by Monika Bross, entitled 'Importance of Residue Definitions for MRL enforcement and monitoring programs' and presented at the Latin American Pesticide Residues Workshop (LAPRW) 2015 <http://www.laprw2015.com/>. Examples are given in Figure 6 and Figure 7.

Further information on Codex MRLs and trading problems caused by the lack of global harmonization is given in an industry white paper entitled "Challenges to Establishing Harmonized Maximum Residue Levels (MRLs) for Facilitating Global Trade" published by [CropLife America](#).

This publication proposes that specific problems are caused by secondary residue standards implemented by some food retailers, particularly in the European Union. The implementation of "private or secondary" arbitrary residue standards at lower levels than EU MRLs to meet consumers' desire for safer food undermine the regulatory MRLs which are based on rigorous science. These policies encourage growers to use lower application rates or miss applications in an attempt to meet the secondary standards with the associated risk of reducing the market life and sustainability of pest control solutions, since less effective control may allow the onset of pest resistance. A counter argument could be that these policies may encourage integrated crop management using a combination of chemical and non-chemical strategies.

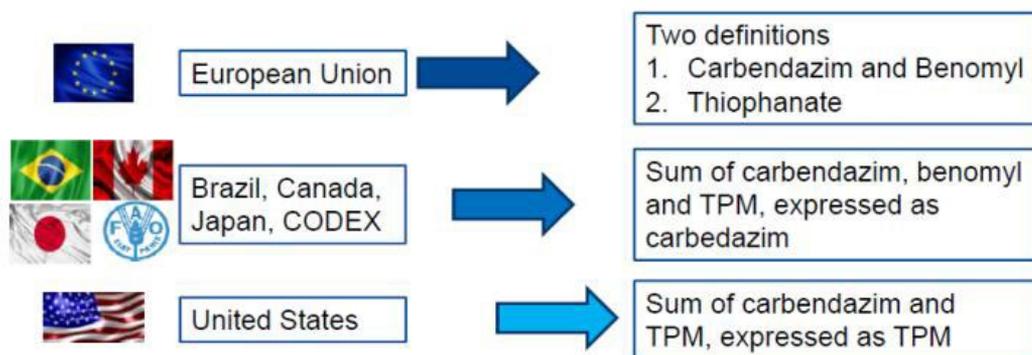


Figure 6. Carbendazim, benomyl and thiophanate methyl from presentation by Monika Bross at LAPRW 2015.

➤ Complex, internationally not aligned residue definitions

Fluxapyroxad in crops



Figure 7. Fluxapyroxad in crops from presentation by Monika Bross at LAPRW 2015.

Conclusion

The pesticides regulatory landscape is complex, and it is not possible to include all aspects of regulations and control of pesticides within the European Union, North America, Japan and China, much less other regions and countries of the world. For example the impact of other legislation such as the EU Water Framework Directive on the use of pesticides is outside of the scope of this paper.

Clearly, global harmonization of MRLs is going to take a long time, if it happens at all. The variations between different levels of MRLs for specific pesticide-commodity combinations and differences in residue definitions for the same pesticide in the same commodity in different parts of the world create difficulties for global trade and potential difficulties for laboratories trying to ensure the correct methods are always employed. The situation is further complicated by constant updates to regulations, the increasing complexity of supply chains, the development and introduction of new pesticides by the agrochemical companies and increasing fraud in the trading of PPPs.

The development of appropriate analytical methods using state-of-the-art instrumentation is required to ensure that the food supply is compliant with pesticide regulations. The development of fast, cost-effective and valid multi-analyte methods that enable the screening, detection, identification and quantification of pesticide residues at low concentrations in food will be the subject of future white papers.

References

1. Unsworth, John. History of Pesticide Use. International Union of Pure and Applied Chemistry website, May 10, 2010. [Online] [IUPAC History of pesticides](http://www.iupac-chemistry.org/History_of_Pesticides/) (accessed June 28th, 2016).
2. Pesticide Usage in the United States: History, Benefits, Risks, and Trends; Bulletin 1121, November 2000, K.S. Delaplane, Cooperative Extension Service, The University of Georgia College of Agricultural and Environmental Sciences.
3. Carson, Rachel. Silent Spring; 40th Anniversary Edition, Houghton Mifflin Harcourt, 2002 ISBN 0618249060, 9780618249060 http://books.google.co.uk/books?hl=en&id=HeR110V0r54C&dq=silent+spring&printsec=frontcover&source=web&ots=1r4bWmIR2G&sig=RFBfJr0UBxYcFAS7Y6YdVWkSwwQ&sa=X&oi=book_result&resnum=6&ct=result#PPP1.M1 (accessed June 28th, 2016).
4. *The Pesticide Manual*, 17th Edition. MacBean, C. (editor). British Crop Production Council, Alton, UK, 2012.
5. *A cooperative global approach to the regulation of agricultural pesticides and sustainable pest management*. OECD, France. [Online] <http://www.oecd.org/chemicalsafety/pesticides-biocides/OECD-Pest-Vision-Final.pdf> (accessed June 28th, 2016).
6. *Measures to Ensure Food Safety* <http://www.mhlw.go.jp/english/policy/health-medical/food/dl/pam-phlet.pdf>, published by the Food Safety Department, Pharmaceutical and Food Safety Bureau, MHLW, Japan, 2013.
7. Final Report of an Audit carried out in China In Order to evaluate Controls of Pesticides in Food of Plant Origin Intended for Export to the European Union-DG(SANCO) 2012-6289-MR Final. http://ec.europa.eu/food/audits-analysis/audit_reports/details.cfm?rep_id=3016

To find a local representative, visit:

www.thermofisher.com/foodandbeverage

