

# Industry White Paper

## *Challenges to Establishing Harmonized Maximum Residue Levels (MRLs) for Facilitating Global Trade*

This white paper reviews the challenges faced by the agrochemical industry and its stakeholders in the food value chain in establishing harmonized MRLs to support the global trade of agricultural commodities. Addressing these challenges is critical to continue feeding our growing global population in the future.

CropLife America recognizes the efforts of its Residue Experts Work Group, along with input from colleagues around the world in preparing this white paper. For further information, contact Ray McAllister, [rmcallister@croplifeamerica.org](mailto:rmcallister@croplifeamerica.org).



## 1.0 ISSUES

*What are the issues? Why do they exist? Who is affected by them? What will happen if solutions are not found?*

One of the many steps in the registration of a crop protection product on a food or feed crop is the establishment of a Maximum Residue Level (MRL) – the pesticide residue level not likely to be exceeded in a specific food/feed commodity when the product is used in accordance with its approved label.

For many reasons, there is a lack of standardization in establishing MRLs around the world. A few examples are:

- A pesticide may have different registered use patterns in different parts of the world due to differences in geographic location, climate, and dietary and cultural preferences that determine the crops grown and eaten in different regions.
- The numerous regulatory authorities tend to have their own strictly defined criteria for setting MRLs based on their own regional and/or national policies and legal standards.
- Crop groupings vary among countries and influence the setting of crop-group MRLs.
- Definition of residue for a given pesticide may differ among countries.
- There are different methodologies for calculating MRLs.

As a result, MRLs for the same pesticide-commodity combination may differ among countries and regions. This can create barriers to trade.

If a commodity is shipped to a country with a lower MRL or if no MRL is established for a pesticide other than that of the country of origin, the following problems can occur:

- The commodity shipment may be seized, rejected, delayed, or sanctioned by government authorities at the port of arrival.
- The handler/shipper may not get paid, as brokers carry the liability.
- Increased sampling for residue analysis may be required, at increased cost to all involved.
- Supply contracts may be cancelled.
- There may be negative publicity.
- Regulatory enforcement actions are possible.

### Maximum Residue Level (MRL)

- low/trace level of pesticide residue not likely to be exceeded in specific food/feed commodity when pesticide product is used in accordance with its approved label (*i.e.*, strictly defined parameters)
- measured in ppm or mg/kg
- enforcement tool to ensure compliance with registered use of the pesticide product
- standard used to facilitate international trade
- not a health standard
- may also be called 'Maximum Residue Limit' or 'Tolerance'

## 2.0 BACKGROUND AND PROGRESS

*How did the issues arise? What are the factors driving them? What is being done to address them?*

## 2.1 Globalization and Trade

Since the mid-1980s, there has been a growing interdependence among countries as a result of the integration of trade, finance, people, and ideas into one global marketplace. Technological advances, lowered transportation costs, and fast global communication have been some of the drivers. There has also been increasing liberalization of trade and capital markets, with the World Trade Organization (WTO) playing a role in promoting fair trade to overcome protectionism.

The world population is estimated to increase to approximately 9 billion by 2050, which translates into a huge demand for food/feed. In order for the production and trade of agricultural commodities to meet this demand, global harmonization of MRLs is critical. However, global MRL harmonization is a highly complex issue, with multiple stakeholders and many contributing factors (Figure 1). The reasons that MRLs may not be harmonized are presented below, along with some of the key successes and initiatives to address existing discrepancies and prevent further discord.

**Figure 1: Key Stakeholders in Global Food/Feed Production and Trade**



## 2.2 Misconceptions

### 2.2.1 Use Standard, Trade Standard, or Safety Standard?

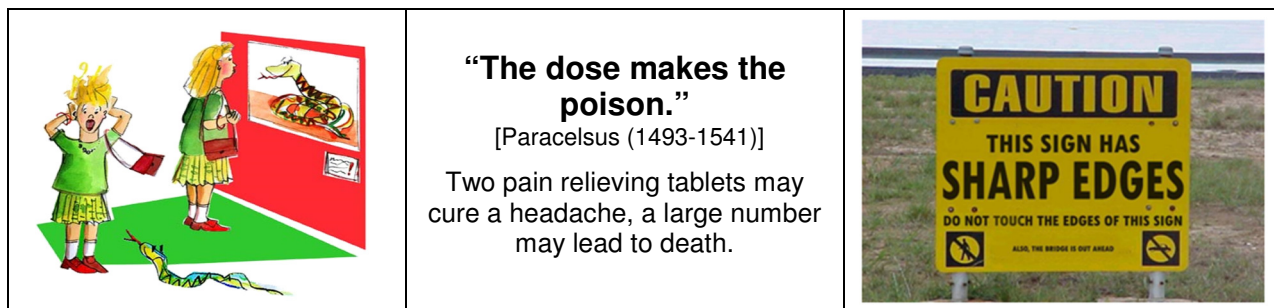
Due to the complexity of the issue and the lack of information in the public domain, there is often the misconception that an MRL is a human safety standard. MRLs are compliance standards to enforce proper use of a pesticide product and enable trade in agricultural commodities. The dietary risk assessment confirms that the level of allowable pesticide residue poses no human health concerns to any segment of the population, including children, pregnant women, seniors, etc. (see Appendices 5.1 and 5.2). MRLs may differ among countries because of differing needs of growers for crop protection. However, the MRLs are always established within the objective of consumer protection.

#### **Dietary Risk Assessment = Exposure x Hazard**

- Exposure = Consumption x Residue
- Hazard = Toxicity (chronic or long-term, and acute or short-term)

(see Figure 2)

**Figure 2: General Examples to Demonstrate Risk (Exposure and Hazard)**



## 2.2.2 Secondary Standards

Secondary residue standards, also referred to as private standards, are additional requirements from the private sector regarding pesticide residue levels in foods. They tend to be more prevalent in the European Union (EU) than in North America. Some EU food retailers, for example, insist on residue standards lower than the EU MRLs in an attempt to meet consumers' desire for "safer food", but by so doing they are undermining the rigorous processes that are used by governmental authorities to regulate residues in the food supply. The secondary residue standards are arbitrary in nature, confusing and burdensome for the growers, and are unnecessarily more restrictive than MRLs. Regulatory MRLs are science-based and can only be established after a full dietary risk assessment has shown that there is no unacceptable risk for consumers. Furthermore, the secondary residue standards set by retailers can limit the market life and sustainability of pest control solutions by encouraging the onset of pest resistance. This is because growers often use lower pesticide application rates or skip applications in an effort to meet such secondary residue requirements. These circumstances should be addressed through educating all parties that such private standards do not improve health or safety.

## 2.3 Crop Field Trials and MRL Determination

### 2.3.1 Purpose of Crop Field Trials

MRLs are based on findings from crop field trials (also referred to as supervised residue field trials), conducted to determine the magnitude of pesticide residues in or on raw agricultural commodities, including animal feed items. The MRLs must reflect the critical Good Agricultural Practice (cGAP). This is the pesticide use pattern or set of instructions (on the pesticide product label) that results in the highest possible residues in the harvested food/feed items. The residue data from these national/regional trials serve as the basis for the MRL calculation (see Figure 3).

#### Crop Field Trial or Supervised Residue Field Trial

- Field trial, or study, conducted according to specific requirements in a written protocol.
- The trials must be "supervised" according to Good Laboratory Practice Standards (GLPS), in order to ensure the reliability and reproducibility of the data.

More crop field trials result in a larger residue data set. More data included in the MRL calculation give greater confidence in the result. However, the number of trials conducted for

minor crops compared to major crops is understandably small due to high cost of field trials, as well as the limited capacity to comply with GLPS in certain developing countries where a lot of minor crops are grown.

### 2.3.2 MRL Calculation Methodology

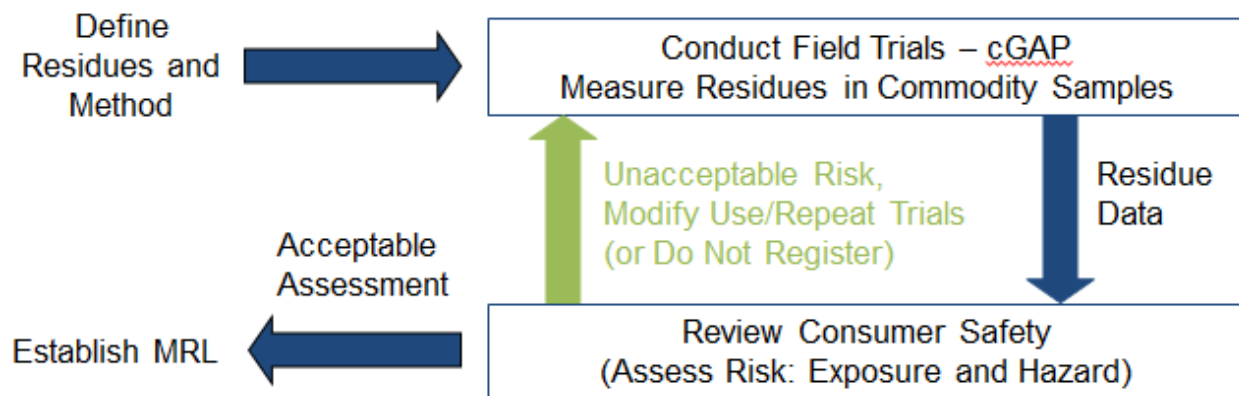
Different methodologies have been used by different regulators over the past several years to calculate MRLs. Some examples are listed below.

- Rounding-up case-by-case based on Highest Residue value, at the discretion of regulator
- EU Methods I and II<sup>1</sup>
- NAFTA MRL Calculator<sup>2</sup>
- OECD MRL Calculator<sup>3</sup>

The two EU methods and the NAFTA method were based on different algorithms, sometimes resulting in quantitatively different MRLs based on the same data sets.

To reconcile different calculation methodologies, the Organization for Economic Cooperation and Development rolled out its OECD MRL Calculator in the spring of 2011. This automated spreadsheet uses statistically-based logic to account for the variability and/or small data sets that may often be encountered. It is the best tool available today for estimating MRLs. Its use has greatly reduced MRL disharmony due to different calculation methods, and it is being promoted for use by all regulatory authorities around the world, regardless of OECD member status.

**Figure 3. Overview of General MRL Setting Process**



### 2.3.3 National/Regional vs. Global Crop Residue Trials

National and regional regulatory authorities often require that crop field trials be conducted within their own geographic boundaries to represent the distribution and production of the particular crop within their country or region. There is a wide range in the number of residue trials required across the different countries and regions. In general, major crops (e.g., soybeans, corn, wheat, rice) require more residue trials than minor or specialty crops (e.g., strawberries, squash, ginseng, dragon fruit, herbs, etc.).

Weed, insect pest, and crop disease problems differ from country to country, resulting in the need for different use patterns and different cGAPs to achieve control. Hence, the use patterns that are required to achieve local crop protection may result in different residue levels and different MRLs in different parts of the world. Nonetheless, it is in the best interests of global MRL harmonization and free trade to strive to harmonize cGAPs globally for crops, as much as possible.

Harmonization of crop field trial requirements, global zoning, proportionality and global joint reviews are examples of initiatives to help harmonize MRLs globally, while addressing the specific needs of the various countries/regions.

#### **Critical Good Agricultural Practice (cGAP)**

- Maximum number of allowed pesticide applications at maximum allowed application rate.
- Minimum re-treatment interval and period between last pesticide treatment and harvest of crop samples (defined by pre-harvest interval - PHI or growth stage at application).

### **2.3.3.1 Harmonization of Crop Field Trial Requirements**

In an attempt to address national differences in residue chemistry requirements, residue experts from industry and from various governments worked together several years ago to develop OECD Test No. 509 ("[Crop Field Trial](#)")<sup>4</sup> and the associated OECD [Guidance Document on Crop Field Trials](#)<sup>5</sup>. These comprehensive documents describe the different number of local trials needed by the major regulatory authorities. They also describe a reduced number of local trials (up to 40%) for situations where the registrant is performing a broader global program using a globally harmonized cGAP. In addition, OECD Test No. 509 is the foundation for presenting up to 50% of the required field trial data from foreign countries. The guideline has already been implemented to a limited degree by a few countries, but it is yet to be widely accepted by the global regulatory community.

### **2.3.3.2 Global Zoning**

Work done over the past decade has compared residue levels across a wide variety of geographical, environmental and climatic zones (temperate, arid, tropical, and Mediterranean) for several active ingredients. The concept known as "Global Zoning" has been developed since 2000 based on analysis of data by the Joint Meeting on Pesticide Residues (JMPR), and published by the OECD/FAO Zoning Project<sup>6</sup>.

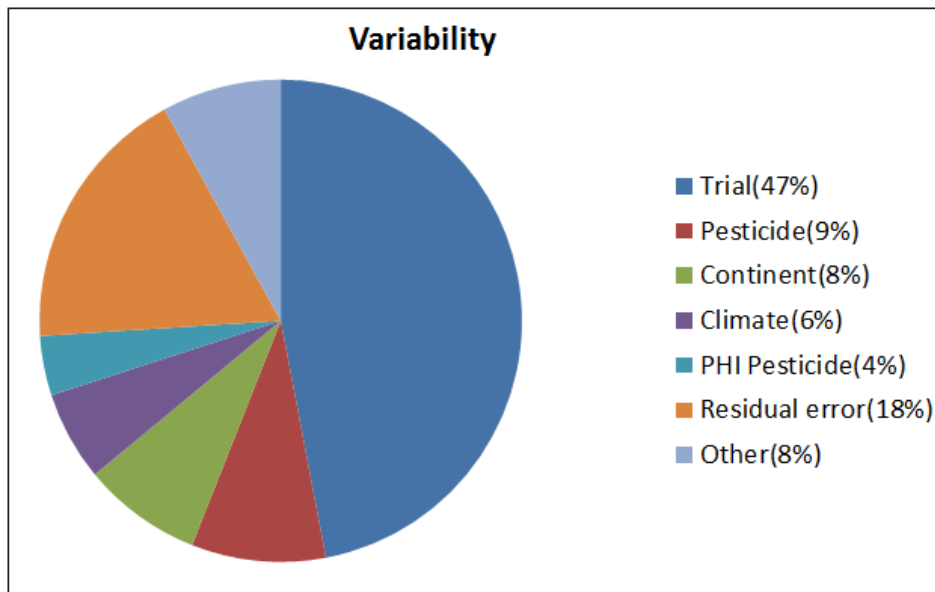
Recently a global residue program was performed with one active ingredient on 17 crops generating 23 raw agricultural commodities representing the four principal analytical matrices (high moisture, low moisture, acidic, and oily). The cGAP for each crop was maintained uniform across geographical regions/zones. Residue variability among trials within a region was consistently greater than the variability of residue trial data across regions (for 21 of 23 commodities). Where greater variability occurred across regions it could be attributed to datasets being too small or to application methods differing among regions.

In another global study organized by IR-4 on tomatoes, a single cGAP, uniform pesticide application equipment, pre-measured test substance, and standardized plot parameters were all used to minimize trial-to-trial variability. Across 27 trials conducted in 22 countries, application accuracy ranged from 95.1 to 112.0% of the target rate. Again, the results showed that residue



variability for trials within a region was greater than variability across continents, climates, or even pesticides (see Fig. 4).

**Figure 4. Global Residue Study – Sources of Observed Residue Variability as Percent of Overall Observed Residue Variability. IR-4 Tomato Trials.**



Conducting a sufficient number of trials to reflect trial-to-trial variability is seemingly a more important determinant of residue values and the subsequent MRLs, than is the geography of where the trials are conducted. Consequently, there is clear scientific justification for using global residue data to grant national registrations.

#### **2.3.3.3 Proportionality**

A considerable body of evidence now exists to show that quantifiable residues are proportional to field application rate of the pesticide within the range of 0.3x – 4x the nominal application rate<sup>7</sup>. This concept is especially important for the calculation and establishment of MRLs, in that it allows for combination of small data sets from different countries at different cGAPs to produce a larger, more robust global data set. Due to insufficient data, proportionality is not currently applicable to certain use scenarios, such as post-harvest, desiccant, and hydroponic uses. The gradual adoption by industry, regulatory agencies, and the Codex Committee on Pesticide Residues (CCPR) of proportionality needs to continue.

#### **2.3.3.4 International Joint Review**

An international joint review (IJR) involves two or more national pesticide regulatory authorities who evaluate a pesticide registration application submission simultaneously and cooperatively. Over the past few years, IJR has become the norm for new pesticide applications. Under the IJR process, each participating national authority simultaneously receives the same dossier in OECD format (single application package including all data for all countries). The authorities develop a schedule and divide the work associated with the review process (*i.e.*, participants determine who will review which portions of the dossier). The completed assessments are

shared, and each national authority makes its own independent regulatory decision, with consultation among participants to develop a common definition of the pesticide residue, harmonized toxicological endpoint selection, and harmonized MRLs. In general, the goal is to achieve the same scientific conclusions from the same data. Each individual country involved in the IJR should issue a regulatory decision within approximately the same time frame.

The overall process for an IJR should result in concurrent registration in the countries involved. This allows earlier access to new products by growers in those countries. Simultaneous adoption of harmonized MRLs by each national authority minimizes trade barriers. IJR has been, in general, successful for harmonizing MRLs among the participating regulatory authorities. A logical extension is to use the IJR process for expansion of uses for registered compounds, something which is currently being heavily encouraged between the United States (US) Environmental Protection Agency (EPA) and the Canadian Pest Management Regulatory Agency (PMRA).

## **2.4 Domestic vs. Import MRLs**

An MRL serves as a reference value for trade, because imported agricultural commodities may be monitored (analyzed) for pesticide residues at a port of entry. The pesticide residue must not exceed the specified MRL of the importing country; otherwise the arriving shipments of the commodity may be rejected. (see Figure 5).

An MRL for a particular pesticide-commodity combination may be established based on:

- a registered domestic use;
- adoption of a Codex MRL (also known as a CXL); or
- an import tolerance petition.

MRLs in destination countries must be regularly reviewed by parties shipping commodities, because new MRLs are continually being established and existing MRLs may be modified by regulatory authorities around the world.

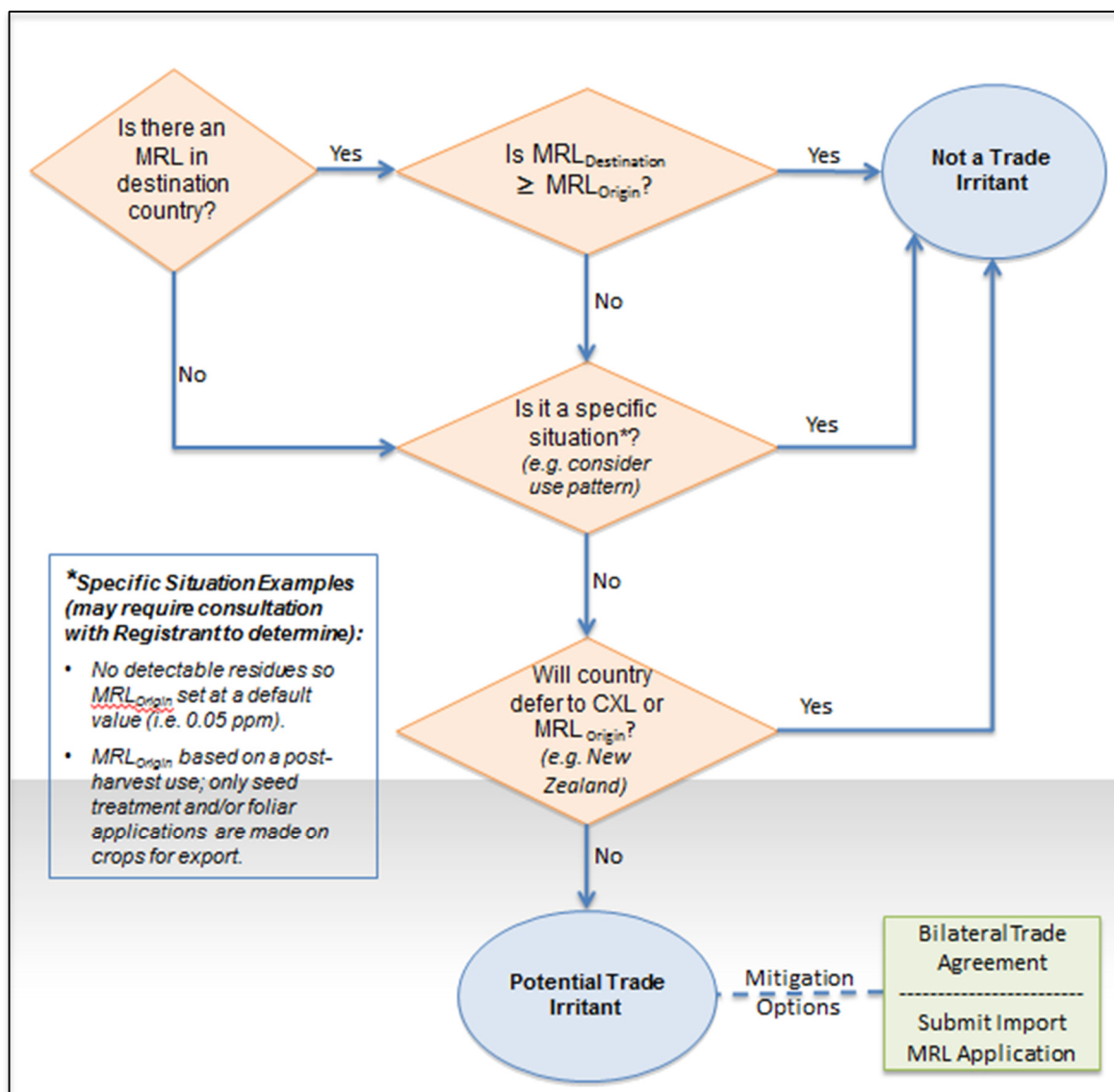
A country may not have a domestic registration for a particular pesticide because the crop on which that pesticide is used is not grown on a production scale in that country. Or it may not be economically viable for a registrant to develop, register and commercialize the pesticide in a given country. In either case, such a country may not have established an MRL associated with the crop commodity. A country may also lack an MRL for a particular pesticide due to differing regulatory processes and timelines for pesticide registration among countries. If there is no domestic MRL, the country may adopt an established CXL. In some cases, a country might defer to the MRL established in the country where the crop was grown. Or an interested party may apply for and be granted an import MRL, applicable solely for produce imported into the country.

If no MRL (domestic, Codex, or import) exists in the national register of the importing country, or if the MRL is too low to cover the potential residues in or on the imported agricultural commodity, the situation needs to be considered more closely. Perhaps the use of the pesticide is such that there will be no significant residues to impact trade (see Figure 5). If none of these options apply, then the appropriate regulatory agencies of the trading partners agree to coordinate/share data to address trade distorting MRLs. This arrangement can take the form of a memorandum of understanding (MOU) or a less formal structure between two cooperating



regulatory agencies. Alternatively, the registrant may wish to submit an import tolerance application.

**Figure 5. Depiction of MRL Considerations for Export of Agricultural Commodities**



## 2.4.1 Codex MRLs (or CXLs)

CXLs are recognized and accepted under the WTO Sanitary and Phytosanitary (WTO-SPS) agreement as trading standards by WTO members. In the absence of domestic MRLs, some importing countries will adopt or defer to CXLs. Three bodies are formally involved in establishing a CXL.

- **Codex Alimentarius Commission (CAC)**

“...established by FAO and WHO in 1963 develops harmonised international food standards, guidelines and codes of practice to protect the health of the consumers and ensure fair practices in the food trade. The Commission also promotes coordination of all food standards work undertaken by international governmental and non-governmental organizations.”

[<http://www.codexalimentarius.org/codex-home/en/>]

- **Codex Committee on Pesticide Residues (CCPR)**

The CCPR is a risk management body made up of governmental officials - usually regulators or food monitoring agents - from the UN's member countries. Its purposes are:

- (a) to establish maximum limits for pesticide residues in specific food items or in groups of food;
- (b) to establish maximum limits for pesticide residues in certain animal feeding stuffs moving in international trade where this is justified for reasons of protection of human health;
- (c) to prepare priority lists of pesticides for evaluation by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR);
- (d) to consider methods of sampling and analysis for the determination of pesticide residues in food and feed;
- (e) to consider other matters in relation to the safety of food and feed containing pesticide residues; and,
- (f) to establish maximum limits for environmental and industrial contaminants showing chemical or other similarity to pesticides, in specific food items or groups of food.

[<http://www.codexalimentarius.org/committees-and-task-forces/en/?provide=committeeDetail&idList=4>]

- **Joint FAO/WHO Meeting on Pesticide Residues (JMPR)**

“...is an expert ad hoc body administered jointly by FAO and WHO in the purpose of harmonizing the requirement and the risk assessment on the pesticide residues. ... comprises the WHO Core Assessment Group and the FAO Panel of Experts on Pesticide Residues in Food and the Environment. ... responsible for reviewing pesticide toxicological data and ... pesticide data residue and for estimating maximum residue levels ... The output of JMPR ... constitutes the essential basis for Codex MRLs for food and agricultural commodities circulating in international trade ...” JMPR draws much of its expertise from national pesticide regulatory authorities, though they function in this capacity independent of their responsibilities in those authorities.

[<http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmpr/en/>]

### **CODEX ALIMENTARIUS International Food Standards**

“The CODEX ALIMENTARIUS international food standards, guidelines and codes of practice contribute to the safety, quality and fairness of international food trade. Consumers can trust the safety and quality of the food products they buy and importers can trust that the food they ordered will be in accordance with their specifications.”

[<http://www.codexalimentarius.org/about-codex/en/>]



While not officially part of the Codex Alimentarius Commission structure, the JMPR provides independent scientific evaluations to CCPR on toxicology and residue studies. The experts are organized by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO).

There are three categories of JMPR review:

- Promulgation of CXLs for new pesticides, as well as for older pesticides that have not been previously nominated;
- Periodic re-evaluation of the existing CXLs for pesticides that have been in the system for 15 years or more; and
- Follow-up evaluations (*e.g.*, use of pesticides on additional crops).

A dossier submitted to JMPR will include residue data from a sufficient number of crop field trials on the crops of interest using the same cGAP, as described on the pesticide product label. JMPR may calculate exposure differently from some countries and establishes its own toxicological endpoints. Residues resulting from registered national uses must fit into the JMPR Acceptable Daily Intake (ADI) in order for CXLs to be proposed. The CCPR, applying risk management principles and relying on the independent scientific advice of the JMPR, discusses and considers advancement of the JMPR-proposed MRLs for adoption by the CAC (see Figure 6).

Certain countries and regions will consider adopting newly established CXLs into their national MRL legislations, providing such CXLs are in compliance with their national/regional requirements. Each year as new CXLs are promulgated or existing CXLs are revised, the EU automatically considers them for adoption into EC regulation 396/2005 as European MRLs. Due to differences in risk assessment policies, data requirements, and crop groupings between the EU and Codex, there are some cases in which the EU will not adopt the CXLs. Japan will consider CXLs as the basis for establishing Japanese MRLs in its MRL positive list when the MRLs of the relevant active ingredient are under review.

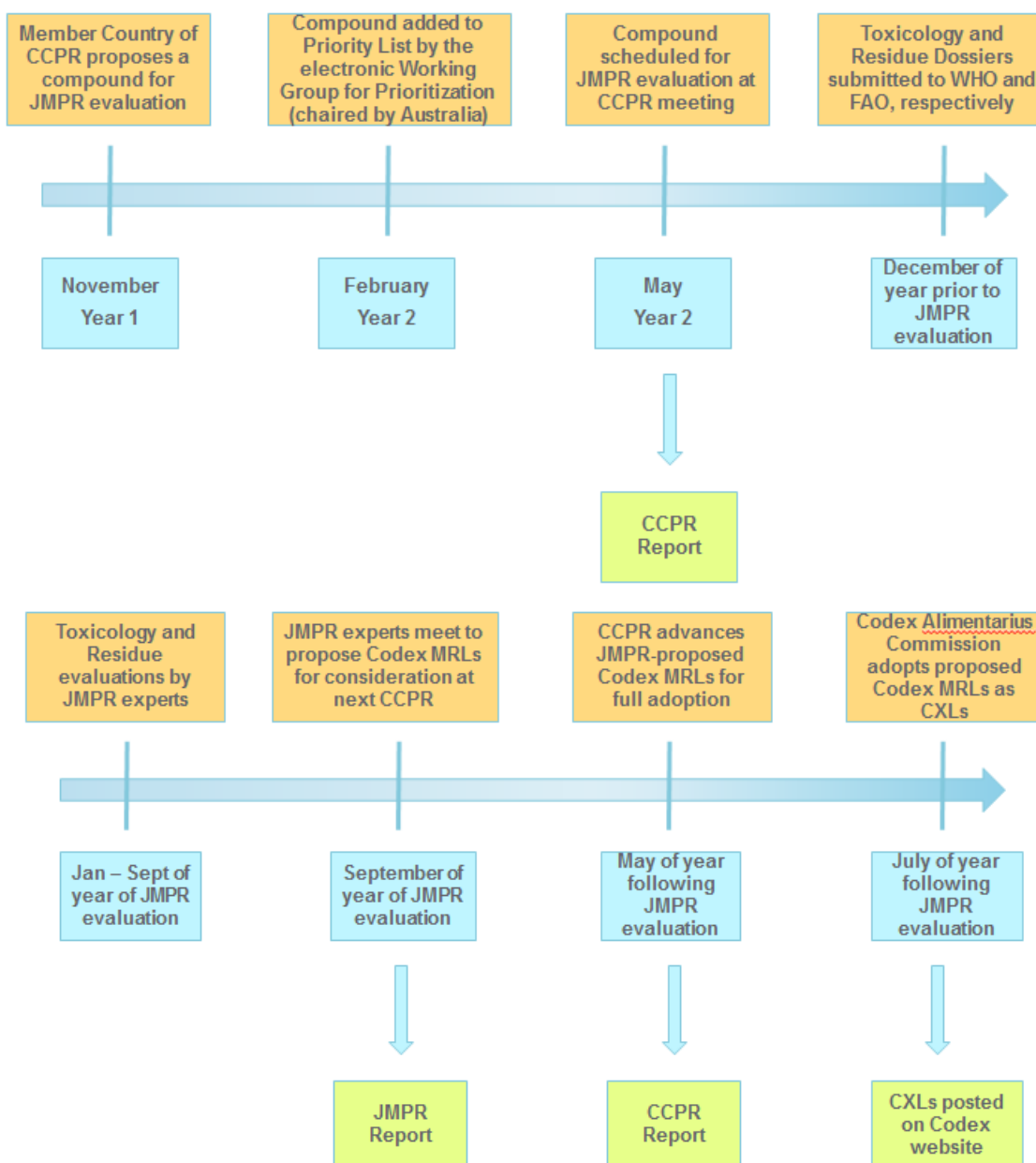
US law requires that EPA align US tolerances with Codex MRLs. When establishing a pesticide tolerance, EPA must "... determine whether a maximum residue level for the pesticide chemical has been established by the Codex Alimentarius Commission. If a Codex maximum residue level has been established for the pesticide chemical and the Administrator does not propose to adopt the Codex level, the Administrator shall publish for public comment a notice explaining the reasons for departing from the Codex level." FFDCA §408(b)(4). Furthermore, registrants have an emerging role and responsibility to define the major trade routes for US crops and inform EPA of any negative impact of harmonizing with Codex. Where alignment is not possible, EPA provides the reason in its notification of proposed regulatory action.

Some countries will defer to CXLs when monitoring imported foods. However, deferring to a CXL at the time of a trade violation is very different from the adoption of a CXL into the national/regional legislation. For example, in the absence of a Japanese MRL, Japan will not defer to a CXL for an MRL violation; Japan must first adopt the CXL into its national MRL registry before accepting it as a reference MRL for monitoring residues in imported foods. New Zealand has its own MRLs supporting domestic pesticide registrations, but the corresponding CXL may be referenced for imported produce, if it is higher than the New Zealand domestic MRL. This is a very pragmatic system, which could be considered by other countries.

Adoption of CXLs or another country's MRLs, upon confirmation of similarity of cGAPs (with up to 25% variation), is certainly a helpful measure towards increasing global MRL harmonization.

Disappointingly though, certain countries are moving away from using CXLs in favor of introducing their own national MRL registries (*e.g.*, Korea and Hong Kong). With national/regional MRL lists seeming to be the future, it would be in the interests of global MRL harmonization and the facilitation of international trade if these national lists were augmented each year by the automatic adoption of the new CXLs.

**Figure 6. Process for setting Codex MRLs**



Minimum of 18 months from time of submitting dossiers for JMPR evaluation to CXLs being established

Codex website:

<http://www.codexalimentarius.net/pestres/data/index.html?jsessionid=984374F80240BEB6BA7FF8B977948039>

Growers and agricultural exporters today expect CXLs to be in place for new pesticides entering the market. However, it takes 18 months or more from the submission of the dossiers to JMPR until the CXLs can be established. Under the framework of the CCPR process, the JMPR will not review an active ingredient until at least one national registration has been granted for the pesticide use.

A pilot project, conducted with the compound sulfoxaflor, was initiated in 2010 to handle the submission and evaluation of JMPR dossiers within the CCPR process simultaneously with an IJR. The intent was to give national pesticide regulatory authorities the benefit of the independent, parallel recommendations of JMPR. Therefore, the CXLs and national MRLs could be established and harmonized at more or less the same time. For comparative purposes, within this pilot project JMPR proposed CXLs based on both regional and global datasets. CXLs were eventually advanced for adoption at the 2013 CCPR, but based on the regional datasets rather than the global datasets. CXLs were not proposed for certain commodities because of an insufficient number of trials at the regional level. There was a great deal of debate among CCPR members over the use of global data sets, and whether registrations/labels had to be available in all countries/regions where the residue trials were conducted. The use of global datasets for setting CXLs must still be resolved at the international level, because pooling of residue data from different countries is the foundation for harmonizing MRLs, particularly for many minor and specialty crops. We recommend that the process for parallel submissions for IJR and JMPR be implemented for all new active ingredients and that the data package should consist of global residue data.

### **Resource Limitations in Establishing Codex MRLs**

Financial constraints and high workload dictate that the CCPR process must become more efficient to keep up with the increasing demand for Codex MRLs. Various ideas have been proposed, including:

- the crop protection industry and other interested parties providing financial support or fee-for-service to help increase JMPR's capacity; and
- improving JMPR efficiency by directly sharing study reviews from countries involved in OECD work share projects. (see Appendix 5.3).

However, these ideas were dismissed; the first on the basis of potential bias being introduced due to private funding to FAO, and the second on the importance of WHO and FAO maintaining independence for their evaluations.

## **2.4.2 Minimizing Agricultural Trade Disruption**

To minimize the negative impact of MRL differences, some countries may negotiate specific memoranda of understanding (MOUs), which in turn facilitate agricultural trade among partner countries. Though such MOUs are workable solutions for enabling trade among a few countries, they represent a grossly inefficient process for supporting trade on the global level. A more practical solution would be a more efficient Codex system that would allow for the quick promulgation of CXLs that are recognized and accepted by all countries.

## **2.4.3 Import Tolerance (IT)**

In cases where no MRL exists in the importing country (perhaps because there is no domestic registration), or where the domestic MRL is too low to cover potential residues in an imported agricultural commodity, a registrant or other interested party may wish to apply for an import

tolerance (IT). An IT submission (as for a domestic registration) will include all relevant consumer safety data (including crop field trial data from the exporting country(ies)); relevant

### **Taiwan – Additional Requirements for Import Tolerance Petitions**

Taiwan's authority, TFDA, recently started requesting biological efficacy data to be included in import tolerance petitions, even for crops not grown in Taiwan. By having access to the bio-efficacy data, TFDA claims it is able to consider granting a domestic use registration instead an import tolerance in order to support its own growers.

Registrants strongly believe that inclusion of biological efficacy data is a burdensome, unnecessary requirement for import tolerance applications. TFDA's justification for this requirement may have merit if a manufacturer decides there is economic value in marketing the pertinent A.I.-crop uses in Taiwan, but for crops not grown in Taiwan the requirement is certainly unnecessary. Import tolerance petitions need to be made simple rather than more complex.

metabolism studies; appropriate analytical method(s) for MRL enforcement purposes; processing studies for raw commodities typically processed into other exportable food items; storage stability studies; etc. Basic physical-chemistry data on the active ingredient are also typically required.

Only a limited number of countries have a formal regulatory procedure for establishing ITs. These countries/regions include the EU, US, Canada, Hong Kong, South Korea, Taiwan, Japan, and the Russian Federation. In Australia, a written request to Food Standards Australia New Zealand (FSANZ), supported by current trade data, is sufficient for securing an IT. The Australian approach is simple, practical, and cost-effective. Of particular concern is the lack of an IT process in major emerging markets, such as India and China. Without an IT application process, obtaining MRLs is not possible in countries where no domestic registration is pursued, or that do not defer to CXLs. Thus, MRL harmonization and the facilitation of global trade would be much improved if countries like China and India introduced a simple IT regulatory procedure.

In the countries with IT regulatory processes in place, timing often becomes an issue. Most of these countries require that the exporting country have a registered use along with an approved label for the pesticide-crop combination, before an IT application can be submitted to the importing country. This condition alone delays obtaining foreign MRLs by up to two years for new pesticides being registered in US, Canada, or EU. This requirement was recently eliminated by Japan. It would be extremely helpful if other countries followed Japan's lead in this regard.



## 2.5 Crop Groupings/Representative Crops

### Crop Group Example

In the US, crop field trials conducted for the representative crops:

- Orange or tangerine/mandarin
- Lemon or lime
- Grapefruit

may enable the setting of a single US Tolerance for the entire **Citrus Fruit Crop Group 10-10**, which includes:

#### Sub-group 10-10A

Calamondin; citron; citrus hybrids; Mediterranean mandarin; orange, sour; orange, sweet; satsuma mandarin; tachibana orange; tangerine (mandarin); tangelo, tangor; trifoliate orange; cultivars, varieties, and/or hybrids of these

#### Sub-group 10-10B

Australian desert lime; Australian finger-lime; Australian round lime; brown river finger lime; kumquat; lemon; lime; mount white lime; New Guinea wild lime; Russell River lime; sweet lime; Tahiti lime; cultivars, varieties, and/or hybrids of these

#### Sub-group 10-10C

Grapefruit; Japanese summer grapefruit; pummelo; tangelo; unqi fruit; cultivars, varieties, and/or hybrids of these

Grouping of crops based on taxonomic and/or agronomic similarity is a practical solution for the establishment of MRLs for similar crops. Because of the numerous commodities that comprise some crop groups, it is impractical to conduct crop residue and product efficacy trials for all of the crops in the group.

Therefore, MRLs can be based on residue data for crops (using similar cGAPs) that are considered representative of the group. Representative crops for the group are generally the most important with respect to production and consumption, and/or those expected to have the highest residues. Data from representative crops can then be extrapolated to the entire group of related crops, including minor crops that might not be supported otherwise.

Regulatory authorities exercise scientific judgment when establishing a single MRL to cover an entire crop group, considering carefully the differences in the residue levels observed among representative crops of that group. For example, in the US, the maximum observed residues for each of the representative crops must typically be within 5X of one another in order for a crop group MRL to be set. A crop group may be subdivided into smaller, more closely related or similar sub-

groups with their own representative crops. A sub-group MRL may be more appropriate than a parent-crop-group MRL because of large differences in residue levels among the representative crops.

Unfortunately, crop groups defined by various regulatory authorities around the world are not harmonized. Geographic location, climate, and dietary and cultural preferences determine the crops grown in different regions. And, because national or regional crop groups are obviously influenced by the economically important crops in the country/region, different crop grouping systems inevitably occur. Likewise, the representative crops in one country or geographic region may not be important or may not be grown at all in another country or region.

The IR-4 Project has led efforts of EPA, PMRA, and the International Crop Grouping Consulting Committee (ICGCC) over the past several years to revise and harmonize crop groups at the international level. The foundation of the work is the updating and revision of the commodities comprising the crop groups currently used by EPA and PMRA. During the revision process, comments and input from the 40+ countries represented on the ICGCC are gathered and considered. This facilitates creation of crop groups that include economically important commodities grown outside of the US and Canada. Revisions to crop groups proposed by ICGCC are simultaneously considered in updating the [Codex Classification of Foods and Animal Feeds](#),<sup>8</sup> as well as corresponding regulations in the US and Canada. Representative

crops are also designated, as new Codex crop groups are adopted.

All countries are encouraged to adopt the new Codex crop groups, rather than creating their own. Additionally, acceptance of representative crop residue data for any of the commodities of a crop group or sub group should be considered when an import tolerance is being requested. The crop grouping project for Codex is expected to be completed by 2016, though we recognize the keeping it up to date will be a perennial process. (See IR-4 website for Crop Grouping status; <http://www.ir4.rutgers.edu/Other/CropGroup.htm>.)

### Codex Classification of Foods and Animal Feeds

- Complete listing of food/feed commodities in international trade, classified into groups.
- Reference for JMPR/CCPR in establishing MRLs.
- Promotes cross-reference names to describe commodities (*i.e.*, aubergine / eggplant, corn / maize, etc.)
- Facilitates establishment of crop group MRLs.

## 2.6 Definition of Residue (DoR)

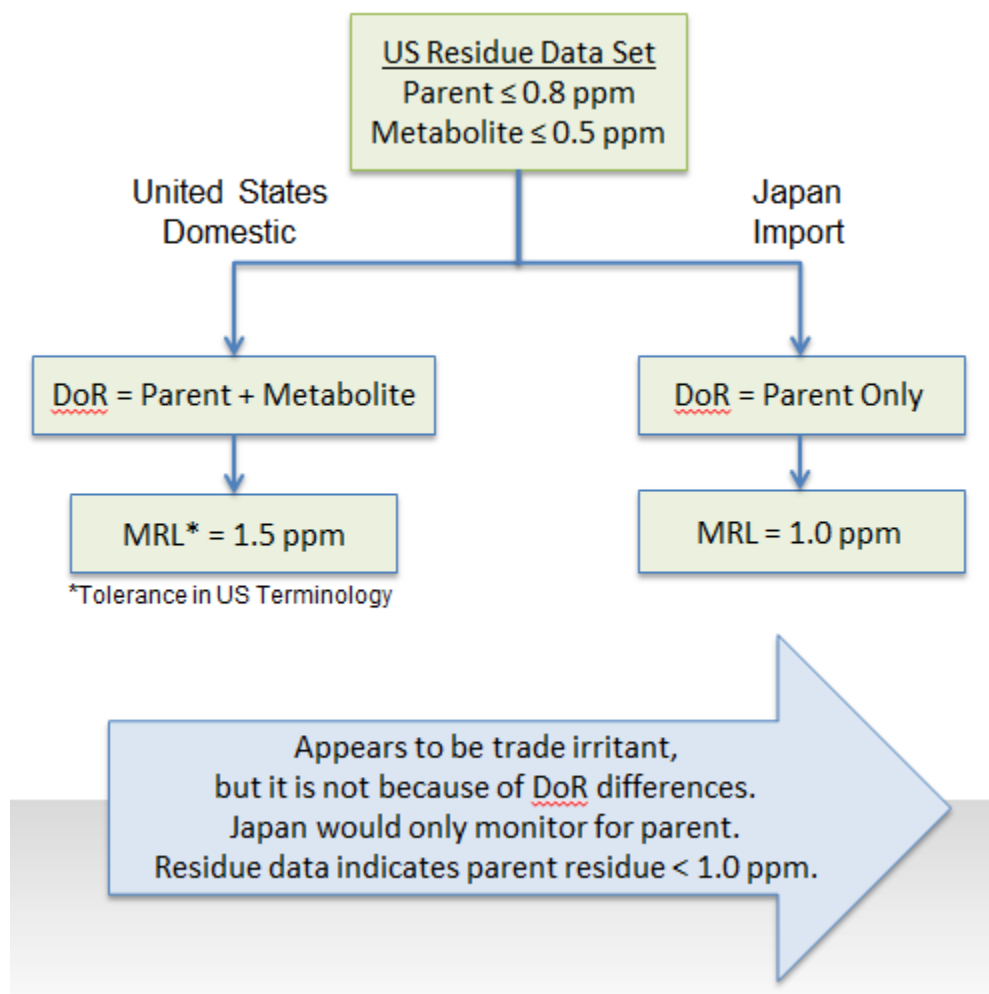
The combination of the pesticide, its metabolites, and other transformation products of toxicological relevance, that can occur in/on a food or animal feed item after application of a pesticide to a crop, is considered the residue. The Definition of Residue (DoR) is used for two regulatory purposes:

- **Setting and Enforcing MRLs**  
Emphasis is on the analyte(s) – parent compound and/or its metabolites – which may indicate a possible misuse of the pesticide and which also can be detected and measured readily by a broad base of national laboratories using standardized analytical methods. The analytical method(s) should be simple (*i.e.*, use of an indicator molecule); suitable for practical routine monitoring and enforcement of the MRL; reasonable from a cost perspective; and capable of measuring multiple pesticides (multiresidue method).
- **Dietary Risk Assessment** (Section 2.2.1; Appendices 5.1 and 5.2)  
Emphasis is on the analysis of the parent compound and its toxicologically significant metabolites, taking into consideration both exposure and relative toxicities. It will include metabolites and degradation products of toxicological concern.

For a particular compound, the DoR can differ for dietary risk assessment and for MRL enforcement. For MRL enforcement, a simple DoR, ideally with a single analyte, is required because of the practical consideration of running multi-residue analytical methods in monitoring labs. In contrast, for dietary risk assessment purposes, it is important to include all relevant analytes in the DoR so that the collection of quantitative residue data on critical components of the total residue is not overlooked during analysis of the regulatory residue trials.

A registrant can propose a DoR for MRL enforcement. However, regulatory authorities make the decision on the actual analytes that must be included in the methods used for measuring the trace quantities of pesticide residues in commodities in the food/feed chain. Typically, the parent chemical is included in the method, but metabolites or degradation products, if deemed relevant by an authority, are also included. The difficulty for trade arises when different national authorities propose different DoRs for setting and enforcing MRLs (see Figure 7).

**Figure 7. Hypothetical Example - Perceived Trade Irritant, 1.5 vs. 1.0 ppm MRL**



If authorities agreed to harmonize the DoRs for MRL enforcement, this type of issue would not occur. Alternatively, DoR information could be incorporated into international MRL databases.

## 3.0 CALL TO ACTION

### *How does one help?*

Harmonizing MRLs raises multiple complex issues. Overcoming the associated challenges is critical to supporting the global trade of agricultural commodities so as to continue feeding our growing global population in the future. Global MRL harmonization is possible, but it requires the participation of all stakeholders. Communication, partnerships and cooperation are critical to success.

### 3.1 Growers and Others in the Food Value Chain

Growers and exporters in the food value chain can contribute to MRL harmonization efforts by:

- Communicating their needs to registrants and regulators regarding crop/product, acreage, export market (country & value), and anticipated growth in new export markets;
- Share with registrants and regulatory agencies any residue data that have been generated;
- US growers populating the USDA-FAS MRL Priority Database with their MRL needs;
- Being aware of MRLs in other countries prior to shipping produce and commodities internationally ([www.mrlatabase.com](http://www.mrlatabase.com), or other databases that provide information about MRLs, registration status, labels, pests, use patterns, etc.);
- Lobbying national governments to support modernizing the Codex process;
- Lobbying main importing countries to adopt CXLs or the exporting countries' MRLs.

### 3.2 Industry (Pesticide Manufacturers and Distributors)

Registrants can support MRL harmonization efforts by:

- Harmonizing cGAPs for global supervised residue trials;
- Making OECD Joint Review submissions;
- Considering domestic registrations in key export markets;
- Planning for import tolerances when choosing locations and number of residue trials;
- Working with governmental regulators to nominate pesticides for CXLs;
- Engaging in regional CropLife association work;
- Submitting the same residue data to all national/regional regulatory authorities;
- Partnering with different associations for data generation on minor crops and for ITs;
- Communicating and informing consumers that MRLs are trading standards.

### 3.3 Regulatory Authorities

National and regional regulatory authorities can support MRL harmonization efforts by:

- Participating in International Joint Reviews;
- Considering toxicological endpoints from other national authorities;
- Applying the concept of proportionality to residue data;
- Prioritizing needs for foreign/import MRLs;
- Using refinements for dietary exposure assessments;
- Supporting Codex processes;
- Adopting new CXLs if greater than national MRLs, or when no national MRLs are available;

- Deferring to CXLs or to exporting country's MRLs for imported produce;
- Adopting Codex Crop Groupings;
- Accepting representative crop data to set import tolerances for other crops;
- Establishing MRLs always for the traded Raw Agricultural Commodity rather than a peeled commodity (e.g., peach, kiwi fruit);
- Implementing a regulatory process for establishing ITs;
- Agreeing on a global standard template for IT submissions;
- Eliminate requirement that a registered use for a given pesticide-crop combination be established in the country of origin before an IT application can be submitted to the importing country, as Japan has done;
- Engaging in capacity building and outreach;
- Accepting OECD guideline studies;
- Avoiding instituting new, burdensome regulatory schemes (own requirements, own MRLs).

## 4.0 REFERENCES

<sup>1</sup> Guidelines for residue data under Directive 91/414/EEC and EC 396/2005. Appendix I – Calculation of maximum residue levels and safety intervals. 22/7/1997. Commission of the European Communities, Directorate General for Agriculture. Document 7039/VI/95 EN, 13 pp. Posted at [http://ec.europa.eu/food/plant/pesticides/guidance\\_documents/mrls\\_en.htm](http://ec.europa.eu/food/plant/pesticides/guidance_documents/mrls_en.htm). Direct link: [http://ec.europa.eu/food/plant/plant\\_protection\\_products/guidance\\_documents/docs/app-i.pdf](http://ec.europa.eu/food/plant/plant_protection_products/guidance_documents/docs/app-i.pdf)

<sup>2</sup> Guidance for Setting Pesticide Maximum Residue Limits Based on Field Trial Data. Regulatory Proposal PRO2005-04 and U.S. Docket No. EPA-HQ-OPP-2007-0632-0003. 9/28/2005. U.S. Environmental Protection Agency. Office of Pesticide Programs, & Health Canada, Pest Management Regulatory Agency. Posted at <http://www.epa.gov/opp00001/international/naftatwg/mrl-calculator.html>. Direct link: <http://www.regulations.gov/contentStreamer?objectId=090000648026e8ed&disposition=attachm&contenttype=pdf>. See also the NAFTA MRL Calculator spreadsheet, <http://www.epa.gov/oppfead1/international/naftatwg/mrl-calculator.xls>

<sup>3</sup> OECD MRL Calculator: Statistical White Paper. Series on Pesticides No. 57. ENV/JM/MONO(2011)3. 01-Mar-2011. Organization for Economic Co-operation and Development, Environment Directorate, Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. 53 pp. Posted at: <http://www.oecd.org/env/ehs/pesticides-biocides/oecdmaximumresiduelimitcalculator.htm>. Direct link: [http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2011\)3&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2011)3&doclanguage=en). See also Users Guide and MRL Calculator spreadsheet posted there.

<sup>4</sup> OECD Guideline for the Testing of Chemicals, Crop Field Trial. OCED/OCDE Test No. 509. Adopted 7 September 2009. 44 pp. Posted at: [http://www.oecd-ilibrary.org/environment/test-no-509-crop-field-trial\\_9789264076457-en](http://www.oecd-ilibrary.org/environment/test-no-509-crop-field-trial_9789264076457-en)

<sup>5</sup> Guidance Document on Crop Field Trials. 12-Oct-2011. Series on Pesticides No. 66, Series on Testing and Assessment No. 164. OECD Unclassified Document ENV/JM/MONO(2011)50.

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66 pp. Posted at  
[http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2011\)50&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2011)50&doclanguage=en)

<sup>6</sup> Report of the OECD/FAO Zoning Project. 16-May-2003. OECD SERIES ON PESTICIDES Number 19. ENV/JM/MONO(2003)4. 85 pp. Posted at  
<http://www.oecd.org/chemicalsafety/pesticides-biocides/2955870.pdf>

<sup>7</sup> Discussion Paper on Principles and Guidance for the Use of the Concept of Proportionality to Estimate Maximum Residue Limits for Pesticides. CX/PR 13/45/6. March 2013. Joint FAO/WHO Food Standards Programme. Codex Committee on Pesticide Residues. 7 pp. Posted at:  
[ftp://ftp.fao.org/Codex/Meetings/ccpr/ccpr45/pr45\\_06e.pdf](ftp://ftp.fao.org/Codex/Meetings/ccpr/ccpr45/pr45_06e.pdf). See also, Report of the 45th Session of the Codex Committee on Pesticide Residues (WHO FAO REP13/PR), Appendix VIII, p. 70. [http://www.codexalimentarius.org/input/download/report/799/REP13\\_PRe.pdf](http://www.codexalimentarius.org/input/download/report/799/REP13_PRe.pdf). Additional development of the concept of proportionality is being pursued by the OECD Residue Chemistry Expert Group in the context of revising Crop Field Trial Guidance.

<sup>8</sup> Joint FAO/WHO Food Standards Programme, Codex Alimentarius Commission (1993) Codex Classification Of Foods And Animal Feeds. Section 2 *in* Codex Alimentarius, Volume 2, Pesticides Residues in Food, 2<sup>nd</sup> Edition. Food and Agriculture Organization of the United Nations World Health Organization. Rome, 1993. Posted at  
[http://www.codexalimentarius.org/download/standards/41/CXA\\_004\\_1993e.pdf](http://www.codexalimentarius.org/download/standards/41/CXA_004_1993e.pdf). A searchable database of the classification information is kept up to date at  
<http://www.codexalimentarius.net/pestres/data/commodities/index.html?collapse=all>.



## 5.0 APPENDICES

### 5.1 Dietary Risk Assessment

Before an MRL can be granted for a commodity, the impact of residues from the use of the pesticide on that particular crop needs to be evaluated from the standpoint of consumer safety relative to dietary exposure. MRLs can only be granted if the resulting total dietary exposures to consumers are below the regulatory human reference values. These regulatory values are the Acceptable Daily Intake (ADI), or chronic reference dose (cRfD) in USA, which is used as the reference value in chronic (long-term) dietary assessment, and the Acute Reference Dose (ARfD), which is used as the reference value in acute (short-term, < 24 h) dietary assessments. As a first cut (Tier 1), dietary exposures are conservatively estimated assuming residues at the MRL and 100% of the crop treated for all registered crop uses. Such assessments are clearly conservative because actual residues will be lower than the MRL, and it is improbable that all planted area of a given crop would be treated with the particular pesticide of interest. Due to this conservatism in Tier 1 assessments, some countries (*e.g.*, US) have adopted refinement measures which include use of actual residue data from field trials, monitoring studies and programs; use of actual or estimated percent crop treated values; edible portions of produce and commodities; and probabilistic methods to calculate distributions of acute dietary exposures for sub-populations of consumers. The challenge to establishing new MRLs comes when Tier 1 assessment indicates that the exposures exceed the ADI/cRfD or the ARfD. If a country does not have procedures in place to refine the dietary exposure assessment appropriately, then new uses and MRLs may not be permitted, even though actual exposures in the general population would not approach the ADI or ARfD. Further, not all countries accept the refinement techniques, so there may be disharmony in the basic “registerability” of a compound worldwide. Consequently, the lack of appropriate techniques to conduct tiered dietary exposure assessments can serve as an obstacle to obtaining MRLs for new commodities.

### 5.2 Cumulative Risk Assessment in relation to setting MRLs

Cumulative risk assessment for compounds causing the same or similar toxicological effects is a challenging topic, and it complicates the setting of MRLs. Cumulative risk assessment is required under both EU and US pesticide regulations. Pesticides belonging to certain chemical groups (organophosphates, N-methyl carbamates, triazines, chloroacetanilides, and pyrethrins/pyrethroids) have been assessed on a cumulative basis by EPA as required by the 1996 Food Quality Protection Act (<http://www.epa.gov/pesticides/cumulative/>). In the EU, ideas of how to perform the cumulative risk assessments, as required under EC Regulations 396/2005 and 1107/2009, are currently under development. One of the most challenging and controversial aspects to emerge recently is that of compiling compounds into different classes or groups for the purposes of performing dietary exposure assessments. An MRL is not a human safety standard *per se*, but the trace residues (which are the basis for the MRL) resulting from a registered agricultural use of a pesticide must be acceptable from a dietary intake perspective. Understandably, cumulative risk assessments are complex, even for compounds that are structurally related and that have a well-defined, common mechanism of toxicity, *e.g.*, organophosphate pesticides inhibiting acetylcholinesterase. However, cumulative risk assessment takes on an amorphous new dimension of complexity when mechanisms of action are not known or are ill-defined, but yet the compounds are generally lumped together in the same group because they cause similar toxic effects to the same target organ or biological system. The creation of so-called Cumulative Assessment Groups (CAGs) is currently the

focus of attention in the EU<sup>9</sup>. There is much debate among toxicologists whether mixtures of distinctly different compounds assigned to a particular CAG exert their effect(s) in a dose-additive manner or whether they should be considered individually for the purposes of defining toxicological endpoints. Similarly, one can argue whether the trace residues of compounds in mixtures should be additive or not for the purposes of dietary risk assessment and setting MRLs. Discussion of the debate is far beyond the scope of this paper, but it is clear that the development of novel approaches for dealing with cumulative risk from residue mixtures will continue in the EU and globally, because consumer protection is paramount when it comes to regulating pesticide residues in the global food chain. By default, setting MRLs is an integral part of cumulative dietary assessment. Hopefully, sound, pragmatic decisions will prevail in regulatory agencies, such that MRLs can be established in a timely manner to support global trade. One must always keep in mind that high levels of human protection are already incorporated into pesticide regulation, and being overly cautious in the evolving science of cumulative risk assessment serves only to hinder innovation and availability of more efficacious products for today's farmers.

### **5.3 Toxicological Endpoints**

The derivation of the ADI and ARfD values lays the foundation for human safety assessment. National authorities and JMPR experts reviewing the same toxicological database will occasionally draw differing conclusions regarding their choice of the chronic and acute studies to determine the No Observable Adverse Effect Levels (NOAELs). To make matters more complicated, a particular authority may decide to apply an additional safety factor, say 3x to 10x, to the standard 100x uncertainty factor (10x inter-species and 10x intra-species variability) when deriving the ADI and/or ARfD from the NOAELs. Such differences of scientific opinion at the toxicological level have serious consequences when it comes to performing the national dietary risk assessments, which determine that the residues/MRLs are safe for the consumer. For example, when there is an order-of-magnitude difference in the ADI set by two authorities, not only may the Tier 1 dietary assessment using MRLs fail for the lower ADI, but a refined assessment using the actual residue data may fail also. This may limit the number of domestic crop uses that can be registered and the import tolerance MRLs that can be obtained in the country imposing the additional safety factor.

### **5.4 Proposal for Improving Efficiency of JMPR by Using National Evaluations and Reviews**

At the 2013 CCPR, CropLife International proposed that national authorities of member countries involved in an OECD work share/joint review provide their evaluations and reviews directly to CCPR, together with proposals for CXLs and toxicological endpoints. Prior to a CCPR meeting, member-country proposals would be circulated to all CCPR members for comment, the same as JMPR evaluations are, and then they would be discussed in the CCPR plenary session. If no objections were raised, the proposed CXLs would be advanced through the Codex system. If concerns were raised, then the proposals would be referred to JMPR for full evaluation. This novel approach to improve efficiency utilizing national reviews performed by regulatory experts (some of whom also serve as JMPR experts), was summarily dismissed by the JMPR secretariat, because WHO and FAO assertively maintained that independent evaluations are essential.

CropLife America (CLA) believes this proposal has merit for modernizing the CCPR process and improving efficiency. CLA fully supports safety evaluations which are science based and not biased by national policies. However, we see that there is significant duplication of effort among the multiple national assessments by JMPR experts.

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<sup>9</sup> EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), 2013. Scientific Opinion on the identification of pesticides to be included in cumulative assessment groups on the basis of their toxicological profile. EFSA Journal 2013;11(7):3293, 131 pp. doi:10.2903/j.efsa.2013.3293. Posted at <http://www.efsa.europa.eu/en/efsajournal/pub/3293.htm>.