Contamination Prevention in the Manufacture of Crop Protection Products

Guidelines and Best Practices

Addenda 1 and 2
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Dear Reader,

An important commitment of CropLife International, the Crop Protection Operations Committee and its Product Integrity Team, is to ensure that the Crop Protection industry has up-to-date tools to prevent Product Integrity incidents. Based on recent information related to new legislation and new trends in agriculture and manufacturing, it has been decided to supplement the existing guidelines and best practices in the CropLife International publication “Contamination Prevention in the Manufacture of Crop Protection Products” – CPMCPP (published in the spring of 2014).

This supplement consists of two separate addenda written by experts of the CropLife International Product Integrity Team. Addendum 1 gives a method for the calculation of cleaning levels to meet EU legislation, when the contaminating Active Ingredient (AI) is not registered on the treated crop. In the EU, it is required that the MRL (= maximum residue level in the treated crop) of this AI is \( \leq 10 \mu g / kg \) (\( \leq 10 \) ppb). Different requirements may exist in other geographies. This addendum also gives recommendations for the best practices to employ in facilities handling bait formulations, biologicals or products being manufactured to meet an organic certification.

The second addendum addresses best risk mitigation practices when relabeling or overlabeling of end-user packs at distributors/dealers.

I am sure you will agree that both additions to the CPMCPP booklet help the continuous effort in the entire industry to deliver high quality products without undesirable side effects and meet all regulatory criteria.

Susan Lewis

Chair CropLife International Operations Committee
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ADDENDUM 1

Cleaning levels for active ingredients not registered on target crops - Consideration of Maximum Residual Levels (MRLs).

Cleaning levels for products with special applications.
1. Cleaning levels for active ingredients not registered on target crops - Consideration of Maximum Residue Levels (MRLs)

1.1 Introduction
The CropLife International publication (2014) “Contamination Prevention in the Manufacture of Crop Protection Products” provides requirements and best practices for the manufacture of crop protection products in multipurpose production units, and cleaning procedures between production runs. However, these requirements do not explicitly refer to active ingredients which are not registered on target crops. If the contaminating AI is not registered on a target crop additional factors need to be taken into consideration. When determining the cleaning level it needs to be assured that the legally required MRLs for non-registered AIs are met in the produce of the target crops. Known cleaning level models may be insufficient to achieve this requirement.

1.2 Purpose
This document is to provide guidance to all manufacturers of Crop Protection Products on the calculation of cleaning levels for active ingredients which could occur as contaminants in products that will be applied on crops on which the contaminating AIs are not registered.

1.3 Scope
This document addresses cleaning levels for non-registered AIs in formulated products with the following applications:

- Foliar sprays
- Pre-harvest sprays
- Post-harvest treatments

Pre-fruit set applications like soil and seed treatment are outside of scope of this document because a significant uptake of a contaminant from soil to harvested produce is unlikely.

1.4 Risk Analysis
Further to the requirements given in the CropLife booklet below criteria must be taken into account to determine the correct cleaning levels for non-registered AIs:
• The maximum allowed limit of < 1000 ppm for non-listed extraneous ingredients in the following product must never be exceeded.

• Residues of the non-registered AI(s) in the produce treated with a product in which these AIs occur as contaminant must be ≤ the default MRL for non-registered AIs of 0.01 ppm (10 ppb)\(^2\). The legal limit may be different in other geographic regions\(^3\). Since MRLs are typically not established for AIs in crops which are not to be treated with products based on these AIs, a default MRL is deemed necessary by authorities.

• The EU regulation applies to all currently registered AIs when present in crops for which they are not registered. However, it applies also to extraneous materials that have had a registration at some stage in the past, but are no longer on the market. A typical example is biphenyl that can be present in certain solvents used in formulations.

The only way to ensure the residue level of non-registered AIs in a crop will be ≤ 10 ppb, is by “adjusting” the cleaning level (CL) of the contaminating AI in the product applied on that crop during the manufacture of this product. This requires a calculation specific for each crop and country. In these cases the CL of the non-registered AI may be lower than the CLs required to avoid phytotoxicity or other adverse effects on the crop (see the CropLife booklet, Chapter 6, Determination of Cleaning Levels).

Prior to calculation of the desired CL, a risk analysis is necessary. At a minimum the risk analysis should consider the following application scenarios:

• The application rate and relevant number of applications during the growing season. As worst case scenario all of the multiple applications during a season would be considered relevant.

• A short withdrawal period – the interval between the last application and harvest.

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1 The upper limit for non-listed extraneous ingredients (like residual impurities) is mentioned in “the Manual on the development and use of FAO and WHO specifications for pesticides”, FAO Plant Protection Paper No. 173, ed. 1 (2002): the regulatory limits for non-listed extraneous ingredients will be less than 1.0 g/kg (< 0.10 [%: w/w] or < 1000 ppm.


• The entire crop will be consumed without any further processing, e.g. lettuce, spinach.
• Post-harvest application, e.g. on apples, citrus fruits.
• The crop is grown in greenhouses or under plastic tunnels. This prevents dissipation of the applied product and possible residual impurities through photodecomposition, volatilization and limited wash-off.
• The AI(s) of applied product and as a consequence any residual impurities cannot be metabolized due to the method of application, e.g. fruit dips, or late pre-harvest sprays.

1.5 Consequences of exceeding the MRL
When a government agency finds that produce samples contain residues of unregistered AIs exceeding the MRL, the manufacturer will be asked to give a plausible explanation while during the investigation, sales of the crop are blocked and, ultimately, the crop may need to be destroyed.

The manufacturer will have to demonstrate that measures are in place to consistently achieve residue levels below the MRL in the future. A repeat incident may result in withdrawal of the registration as well as fines, especially if the residual impurity is toxicologically or environmentally relevant.

1.6 Calculation of cleaning levels for non-registered AIs
If the risk analysis indicates a distinct possibility that the MRLs could be exceeded, it is recommended to calculate a separate cleaning level (CL) for the non-registered AI in the following product to ensure the required MRL is not exceeded. This number will differ from the CL used to prevent phytotoxicity etc. on the following crop.

The calculation of the cleaning level of non-registered AIs is as follows:

$$ CL \ [\text{ppm}]= \frac{\text{LL} \times \text{Yield} \times 10^{-3}}{\text{SF} \times \text{AR} \times \text{NRA} \times \text{LF} \times \text{DR}} $$
Definitions:

AR: maximum single application rate of the succeeding product [g FP/ha] or [ml FP/ha].

CL: cleaning level; ppm [mg AI / kg or L formulated product].

DR: Dissipation Rate (default value is 1 – no dissipation, e.g. post-harvest applications).

The amount of the applied product present at harvest after the last application, e.g. if diminished to 20%, the DR equals 0.2. The assumption is made that the DR of the product and the residual impurity is identical.

LF: Loading Factor, this is the portion of the applied product which is effectively captured on the produce. Range: 0.1 - 1.

Examples:
Post-harvest application: LF = 1 (100% of contaminant can be found on the produce)
Pre-fruit set (application before any fruits formed): LF = 0 (0%) (Out of scope, see chapter 1.3)

LL: Legal Limit (expressed as ppb), e.g. European Union: 10 ppb (0.01 mg/kg).

NRA: Number of Relevant Applications (default value is 1).
The NRA is specific for the product, treated crop and geography. It depends on the contaminant and physical-chemical behaviour. As worst case scenario all applications are relevant.

SF: Safety Factor (default is 1).

Yield: Average Yield/ha (worst case, average of yield in countries of application): kg produce/ha.
Yield data can be obtained from country specific agricultural statistics on crops, FAOSTAT⁴ and Factfish⁵.

10⁻³: Conversion Factor (used to convert from ppb to ppm).

⁴http://faostat3.fao.org/home/E
⁵http://www.factfish.com/catalog
Each product owner defines the DR, LF, NRA and SF values based on the risk management policy of that company.

Three examples of this calculation for apples, grapes and spinach using data from Germany are below. The average yield is based on 2013 FAO statistics for that country while using the recommended maximum number of applications for a common fungicide.

**Example 1:**
Crop: Apples  
Country: Germany  
Crop yield: 25,984 kg/ha  
Application rate: 5 kg/ha  
LL: 10 ppb  
NRA: 10  
LF: 0.25 (25%)  
DR: 0.2 (20%)  
SF: 1

\[
CL = \frac{10 \text{ ppb} \times \frac{25984 \text{ kg}}{\text{ha}} \times 10^{-3}}{1 \times 5 \times \frac{\text{kg}}{\text{ha}} \times 10 \times \text{LF} \times \text{DR}} \quad \text{[ppm]}
\]

\[
CL = \frac{259.840}{1 \times 5 \times 10 \times 0.25 \times 0.2} \quad \text{ppm} = 104 \text{ ppm}
\]
Example 2:
Crop: Grapes  
Country: Germany  
Crop yield: 6,454 kg/ha  
Application rate: 2 kg/ha  
LL: 10 ppb  
NRA: 3  
LF: 0.15 (15%)  
DR: 0.2 (20%)  
SF: 1

\[
CL = \frac{10\text{ppb} \times \frac{6454\text{ kg}}{\text{ha}} \times 10^{-3}}{1 \times 2 \times \frac{\text{kg}}{\text{ha}} \times 3 \times \text{LF} \times \text{DR}} \text{ [ppm]}
\]

\[
CL = \frac{6454}{1 \times 2 \times 3 \times 0.15 \times 0.2} \text{ ppm} = 359 \text{ ppm}
\]

Example 3:
Crop: Spinach  
Country: Germany  
Crop yield: 16,620 kg/ha  
Application rate: 3 kg/ha  
LL: 10 ppb  
NRA: 2  
LF: 0.80 (80%)  
DR: 0.2 (20%)  
SF: 1

\[
CL = \frac{10\text{ppb} \times \frac{16620\text{ kg}}{\text{ha}} \times 10^{-3}}{1 \times 3 \times \frac{\text{kg}}{\text{ha}} \times 2 \times \text{LF} \times \text{DR}} \text{ [ppm]}
\]

\[
CL = \frac{16620}{1 \times 3 \times 2 \times 0.80 \times 0.2} \text{ ppm} = 173 \text{ ppm}
\]
2. Cleaning levels for products with special applications

2.1 Manufacture of products for use in ‘Organic Farming’
Produce from crops grown using ‘Organic Farming’ methods must not show residues of crop protection chemicals not listed for use in ‘organic’ crops. Organic produce containing residual impurities must be taken off the shelf and may not be sold as ‘organic’ even if the residues are below the MRL (set for ‘non-organic’ produce). This will require a segregation of products for Organic Farming; this includes formulation, filling, re-filling and packaging activities. Recycled material must not contain compounds not listed for use in ‘organic’ crops.

2.2 Biopesticides
Different definitions exist for ‘microbial and biochemical pesticides’. A comprehensive summary of ‘microbial and biochemical pesticides’ is given below:

‘Biopesticides’ are pesticides derived from natural materials. They can be ‘microbials’ based on living organisms such as bacteria, fungi, viruses and viroids or ‘macrobials’ based on macroorganisms, or ‘botanicals’ based on plant extracts, or ‘biochemicals’ which may contain pheromones and other semiochemicals, as well as other natural products such as hormones, minerals and enzymes. Biopesticides can be used as insecticides, fungicides, herbicides, nematicides, plant or animal growth regulators, plant strengtheners, biostimulants, biofertilizers and more’.

For chemical substances defined as ‘biopesticides’, e.g. fatty acids, sulphur, pyrethrum, the cleaning levels described in the CropLife booklet should be applied as a minimum standard.

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6EPA definition, see https://www.epa.gov/ingredients-used-pesticide-products/what-are-biopesticides
8OECD, see http://www.oecd.org/chemicalsafety/pesticides-biocides/biologicalpesticideregistration.htm Biological Pesticides (or BioPesticides including microbials - bacteria, algae, protozoa, viruses, fungi, pheromones and semiochemicals, macrobials/invertebrates such as insects and nematodes, and plant extracts/botanicals)
For biological organisms used as ‘biopesticides’, e.g. bacteria, fungi, viruses, spores, nematodes, different rules apply. Biological organisms are able to multiply exponentially and therefore a residual impurity limit in the chemical formulation cannot be defined. Vice versa, a contamination of a biological organism with a pesticide could have unintended adverse effects on the organism itself. As best practice a segregation of biological organisms and other crop protection products is recommended. This includes manufacturing, filling and packing operations as well as storage.

2.3 Bait formulations, contaminants with repellent effect
Certain substances (e.g. methaldehyde, chlorine based products, permethrin, cyhalothrin) may have an unintended repellent side effect. This means that the target organisms (insects or other pests) are not attracted by such a contaminated product and avoid contact hence the product does not achieve its intended use. Based on long-term experiences a default value of 50 ppm is considered a reasonable limit. The limit may be lower depending on the substance and target organism and should be defined by the manufacturer.
ADDENDUM 2

Overlabeling and Relabeling Guidelines for Crop Protection Products
at Distributors/Dealers
1. Overlabeling and Relabeling Guidelines for Crop Protection Products at Distributors/Dealers

1.1 Introduction
Labeling procedures designed to prevent Product Integrity issues apply globally to all CropLife International (CLI) member companies, their affiliates as well as present and future external manufacturers (e.g. contractors, toll manufacturers, manufacturing partners etc.). These procedures are briefly outlined in the CropLife International publication (2014) “Contamination Prevention in the Manufacture of Crop Protection Products”.

This document is an addendum to the above booklet and will be incorporated into the next edition.

Correct labeling of Crop Protection Products is essential. Two main reasons are:

- Labeling errors could lead to incorrect use of the product and result in contamination incidents. For end-user products, some possible consequences are: safety issues; crop damage; environmental issues e.g. killing desirable organisms like pollinators; etc.
- In the case of end-user products, the regulatory authorities consider Crop Protection Product labels binding legal documents, and supplying faulty labeled products is a significant non-compliance. The label must reflect verbatim the information given in the registration documents.

For these reasons labeling, overlabeling and relabeling are an essential part of Product Integrity management procedures.

1.2 Purpose and scope
This document focuses on the overlabeling and relabeling of end-user packs at distributors/dealers, i.e. at facilities not under direct management of the manufacturer. These operations are usually carried out on behalf of the Crop Protection product manufacturer.

Relabeling of returnable packs which are to be refilled at the distributor/dealer site / sales outlet will not be considered and it is recommended to obtain instructions from the manufacturer.
This guideline is intended to:

- Ensure that any relabeled or overlabeled product will meet all industry quality assurance standards and contamination prevention criteria during any relabeling and/or overlabeling activity,
- Maintain traceability,
- Ensure the supply of labels is strictly controlled.

Adding stickers with additional information is out of the scope of this document. Requirements for the use of stickers should be defined by the owner of the product.

Crop Protection product companies and distributors/dealers are strongly urged to implement these guidelines to help reduce the chances of product integrity incidents, and avoid liability issues.

The convention adopted throughout these guidelines is that when “must” is used, this indicates a requirement. Other qualifiers, e.g. “should”, “could” relate to recommendations and best practices, based on the experiences of CropLife International member companies.

1.3 Definitions
It is necessary to distinguish between overlabeling and relabeling. These concepts cannot be used interchangeably:

**Overlabeling:**
For the purpose of this document overlabeling means the complete covering of an existing label with a new label, that is permanently fixed to the container.

**Relabeling:**
Removing all labels from package and subsequently applying new labels, i.e. at a given moment in this process the package will be without a label.

1.4 Legislation
The registration owner/manufacturer and the distributor/dealer need to ensure that all legal requirements pertaining to overlabeling/relabeling are implemented. The registration owner/manufacturer of the product will have to instruct the distributor/dealer accordingly and verify that all criteria have been met.
Depending on the geography these legal requirements can vary.

1.5 Possible Justification
Reasons for the overlabeling/relabeling of the end-user pack of Crop Protection Products include but are not limited to:

- **Regulatory reasons:**
  - Change of the registration number,
  - Withdrawal of use in certain crops or indications,
  - Reduced number of applications or longer withdrawal period,
  - Widening of the application spectrum – registered on new crops/wider indications,
  - Changes in hazard warning and caution statements,
  - Changes to transport regulations.

- **Commercial and Supply Chain reasons:**
  - Widening of the application spectrum could create additional commercial opportunities,
  - Inventory near the end of shelf life,
  - Need to shift stock due to demand in a region with a different language and a different registration with its specific registration number and label.
  - Damaged cartons, stained or faded labels.

1.6 Risk Avoidance
The following risk factors need to be considered prior to an overlabeling/relabeling operation:

- **Traceability.** It must be ensured that the lot number on the replacement label is traceable to that on the original label e.g.
  - If the lot number is printed (e.g. ink jet) on the container that is to be overlabeled/relabeled care must be taken that this number is still visible and not covered by the replacement label. Additional steps will be needed if the operation consists of multiple batch numbers.
  - If the product is relabeled, it is necessary to ensure that the correct lot number appears on either the container or the replacement label.

- **Similar visual appearance of labels.** Each company has its own brand image so at the first glance all labels for a particular container size and different products may look identical.

- **Regulatory required statements** (e.g. non-refillable container) must not be covered by the new label.
• **Identical shape and size of containers.** In the case of relabeling, at some stage the containers will be without a label for a short period of time. Extra precautions are necessary to avoid these containers being incorrectly labeled, especially when more than one relabeling operation is planned.

• **Label Inventory.** To avoid mix-ups outdated labels must be removed from the overlabeling/relabeling area and secured while awaiting disposal, before introducing the replacement labels. To establish how many updated labels have been consumed for the overlabeling/relabeling campaign inventory control is a must.
  - If the overlabeling/relabeling takes place at a facility not under direct control of the manufacturer the label inventory needs to be controlled.
  - **Counterfeiting.** Strict label inventory control is advisable to minimize the possibility of counterfeiting.

### 1.7 Risk Mitigation Guidelines

It is recommended to implement the following procedures to mitigate the risks outlined in the previous section.

• **Set up a dedicated clearly marked area for overlabeling/relabeling e.g. enclosed with a chain linked fence.** Only the product that is to be overlabeled or relabeled, together with the required replacement labels, should be stored in this area. Storage of other products and/or labels within the dedicated overlabeling/relabeling area should be prohibited.

• **Only replacement labels supplied by the registration owner/manufacturer of the product can be used.**

• **A properly trained employee of the manufacturer should whenever possible be present during the entire overlabeling/relabeling process at a distributor/dealer and assume responsibility for the label inventory management.**

• **Before start-up of the operation, it is necessary to verify that the correct replacement labels have been supplied (e.g. Batch number check, label version number).**

• **If an overlabeling operation is to be carried out, the new labels must be wider and higher than the original label in order to cover the original label in its entirety, if legally allowed.** It must be ensured that the original label is not legible through the new label, e.g. by the choice of paper for printing the new label.

• **The release of the overlabeled/relabeled product should only be permitted following verification that the correct label and batch**
number have been put on the container. This applies also to the labels on outer cartons. This should be confirmed by the signature of the manufacturer’s employee, or the responsible person of the distributor/dealer.

• Labels must be securely attached to the container.
• After completion, all replacement labels must be removed from this area before a new overlabeling/relabeling operation can be started.
• Surplus labels should be returned to the manufacturer or, if agreed, destroyed.
• Damaged containers must never be overlabeled/relabeled.
• At the completion of the overlabeling/relabeling operation, a mass balance of the labels must be performed, i.e. number of labels supplied minus number of labels used on the container minus labels damaged/lost during the operation, must equal the number of labels remaining at the end of the operation. This should be confirmed by the signature of the manufacturer’s employee, or the responsible person at the distributor/dealer.
• The batch numbers of all materials need to be recorded for traceability.

It is recommended that the above points are captured in a written Standard Operating Procedure (SOP) and that this SOP is approved by the manufacturer.
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