Contamination Prevention in the Manufacture of Crop Protection Products

Guidelines and Best Practices

Edition 2, October 2019
This Presentation is Made on Behalf of CropLife International and its Corporate Members

Edition 2, October 2019
Contamination Prevention
The goals of CropLife International and its member companies

• Contamination of crop protection products with extraneous active ingredients could have serious consequences.

• Active ingredients of the previous product(s) manufactured in the same unit are typically the source of these contaminants.

• Product Integrity experts of the CropLife International member companies have developed a booklet on the “Contamination Prevention in the Manufacture of Crop Protection Products” with:
  – Guidelines, and
  – Best Practices in all manufacturing steps

• This booklet defines the industry standard which should be implemented industry wide: in all facilities of the member companies and their partners in external manufacturing.
Why is **Contamination Prevention** so important?

Extraneous active ingredients (residual impurities) might:

- Cause crop damage,
- Endanger beneficial non-crop species, like pollinators,
- Present health or environmental hazards,
- Infringe legal requirements and other legislation.
New in 4th edition of the CPMCPP booklet

New key topics include expanded or completely new chapters on:

- warehousing,
- recommendations on how to run a Risk Assessment process,
- improved labeling guidelines,
- addressing calculation of Acceptable Contamination Limits (ACLs) that ensure the residue level of non-listed active ingredients will be below the required MRL.
Contamination Prevention
Example of an Actual Incident

The situation....
✓ Rush order for a bulb treatment fungicide
✓ Product formulated
✓ Unlabeled flex hose used for transfer, previously contained a herbicide
✓ Crop treatment failed
✓ Claim filed, **expensive** court case and loss of a customer

*It is Preventable*
Contamination Prevention
Example of an Actual Incident

The situation....

✓ Soil herbicide was preceded by a ‘highly active’ broad leaf herbicide
✓ Cleaning procedure not followed
✓ Cleaning conducted over two different shifts
✓ Production started without draining rinsate
✓ Herbicide used on potted roses, severe chlorosis (leaf bleaching), seven expensive claims and exhaustive rework

It is Preventable
Contamination Prevention
Example of an Actual Incident

The situation….

✓ Residue content could not be determined due to analytical equipment breakdown
✓ Decision made to continue production with change management approval
✓ Subsequent analysis determined residue above cleaning limit
✓ Soybeans treated did not germinate causing multiple expensive claims

\[2000 \text{ ppm} \quad \text{vs} \quad 1000 \text{ ppm}\]
Contamination Prevention
Example of an Actual Incident

The situation….

- A high melting point active ingredient required the use of a heat exchanger during the formulation.
- Cleaning did not include the heat exchanger as it was not needed for the next formulation.
- Five weeks later, the next formulation requiring the heat exchanger became contaminated because the heat exchanger had not been cleaned.
- The batch had to be discarded

Don’t bypass equipment during cleaning steps

It is Preventable

CropLife International
Contamination Prevention
Example of an Actual Incident

The situation….
✓ Fungicide was packaged following a potent insecticide
✓ EPA default limit for change over (<1000 ppm) was used
✓ No consideration was given to the ecotoxicological risks
✓ Massive kill of predatory insects occurred

Is the default limit always low enough?

It is Preventable
Contamination Prevention

Example of an Actual Incident

The situation….

✓ An operator wrongly connected and transferred a formulation (vessel should be locked if not in use)
✓ The operator did not tell anyone of the error
✓ Thousands of liters of product had to be recalled and destroyed
✓ The wrong formulation transferred was extremely toxic to beneficial insects

It is Preventable
Contamination Prevention
Example of an Actual Incident

The situation….

✓ During the packaging of a corn herbicide, an operator noticed an unusual color and packing was stopped
✓ Material resampled and an unexpected active ingredient detected
✓ The packaging line shared a nitrogen purge with another production line
✓ The purge was open when a transfer occurred at the other line resulting in material being siphoned into the corn herbicide

If it doesn’t look normal stop…

It is Preventable
Contamination Prevention
What is Needed?

Applying the following requirements in multi-product facilities will mitigate the risks

- Separation of herbicides and non-herbicides
- Avoid recycling or reprocessing
- Clear labelling
- Documented Risk Assessments
- Cleaning procedures and analytical methods
Contamination Prevention

What is Needed?

**Promptness in Clean out**

**Refillable container maintenance**

**Define Residual Cleaning Limits**

Additional Requirements

Portable equipment must be dedicated

Assess common raw material vessels
Contamination Prevention
What should Management do?

The requirements apply to CropLife International member companies and their external manufacturers.

Ensure …

- Company Expert Appointed
- Confidentially of Exchanged Information
- Resource Availability
- Application of Requirements and Best Practices
- Training and Awareness
- Good Housekeeping

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The Details…

The following slides outline the specific ‘how’ with each element of contamination prevention.

- Risk Assessment Elements
- Cleaning level determination
- Manufacturing Practices
- Production Unit Cleaning
- Analysis of Residual Impurities
Risk assessment process

• Initial Risk assessment
  – Assessment of potential failures
    • Severity
    • Occurrence
    • Detection
  – Risk Priority Number (RPN- ranking of the individual risk)

• Agreed actions

• Re-assessment of the risks
RPN- ranking of the individual risk

<table>
<thead>
<tr>
<th>Risk Priority Number (RPN)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 to 30</strong></td>
</tr>
<tr>
<td>A risk evaluation with a RPN in the range of 1 to 30 results in a green field. No additional controls are required, unless they can be implemented requiring limited resources (in terms of time, funds and/or efforts). Actions to further reduce the impact are assigned a low priority. Arrangements should be made to ensure the controls are maintained. However, periodic assessment of any process deviations is advisable.</td>
</tr>
<tr>
<td><strong>31 to 99</strong></td>
</tr>
<tr>
<td>A risk evaluation resulting in a RPN in the range of 31 to 99 results in a yellow field. Lowering the risk to a green level should be the first consideration. However, the costs of the additional risk reduction measures should be taken into account. Arrangements should be made to ensure the controls are maintained, in particular if the risk is associated with e.g. quality consequences, complaints or legal requirements. The improvements need to be documented in a strict, documented time frame.</td>
</tr>
<tr>
<td><strong>100 to 200</strong></td>
</tr>
<tr>
<td>A risk evaluation with a RPN ranging from 100 to 200 results in a red field, i.e. these risks must be considered unacceptable. Substantial improvements are required to reduce the risk(s) at a minimum to a yellow level. The work activity should be stopped until appropriate risk controls have been implemented. If the required risk reduction cannot be achieved, the work should not be resumed and remain prohibited and requires consultation with your supervisor and/or senior management.</td>
</tr>
</tbody>
</table>
# Risk assessment process

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>In-process sampling</td>
<td>Sample size too small</td>
<td>Not possible to run all required tests</td>
<td>3</td>
<td>Wrong sampling instructions</td>
<td>3</td>
<td>Correct sample size published in the lab manual</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Documentation HPLC data</td>
<td>Harddisc issues</td>
<td>Loss analytical data</td>
<td>7</td>
<td>Harddisc failure of the IT systems</td>
<td>2</td>
<td>Data backed up daily</td>
<td>3</td>
<td>42</td>
</tr>
<tr>
<td>Cleaning dry filter of the dust collector</td>
<td>Filter remains uncleaned</td>
<td>Contamination of products due to overload filter</td>
<td>7</td>
<td>Missing instructions on when and how to change the dry filter</td>
<td>3</td>
<td>Written procedures, Training and stickers with cleaning regime and date</td>
<td>4</td>
<td>84</td>
</tr>
<tr>
<td>Rinseate samples used for determination ACL</td>
<td>Following product not sampled for residual impurities</td>
<td>Contamination risk</td>
<td>8</td>
<td>Wrong procedures &amp; missing instructions</td>
<td>4</td>
<td>None</td>
<td>5</td>
<td>160</td>
</tr>
<tr>
<td>Highly active herbicide stored in common warehouse</td>
<td>No segregation</td>
<td>Contamination other products in warehouse, mix-ups in manufacture</td>
<td>10</td>
<td>No clear storage guidelines on segregation</td>
<td>4</td>
<td>No dual verification at the staging point</td>
<td>5</td>
<td>200</td>
</tr>
</tbody>
</table>

*Disclaimer: All values in these risk assessments are fictitious and have been chosen to demonstrate the use of this risk assessment tool.

<table>
<thead>
<tr>
<th>Action</th>
<th>Severity</th>
<th>Occurrence</th>
<th>Detection</th>
<th>RPN, after completion action steps</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17 3 1 2 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17 7 1 3 21</td>
</tr>
</tbody>
</table>

*Risk assessment process continued |

<table>
<thead>
<tr>
<th>Action</th>
<th>Specific product, adequately labeled</th>
<th>Joe Doe</th>
<th>15-Sep-17</th>
<th>31-Oct-17</th>
<th>7 3 2</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rinseate samples used for determination ACL</td>
<td>Intensive frequent cont. prev. training, improved management of change process, analytical forewarned</td>
<td>John Smith</td>
<td>01-Sep-17</td>
<td>12-Sep-17</td>
<td>8 3 2</td>
<td>48</td>
</tr>
<tr>
<td>Highly active herbicide stored in common warehouse</td>
<td>Construct fully segregated (floor to ceiling) room for HAHs.</td>
<td>Peter Jones</td>
<td>15-Dec-17</td>
<td>30-Nov-17</td>
<td>10 5 1</td>
<td>50</td>
</tr>
</tbody>
</table>

*Disclaimer: All values in these risk assessments are fictitious and have been chosen to demonstrate the use of this risk assessment tool.
### Re-assessment of the remaining risks

<table>
<thead>
<tr>
<th>Description Risk / Potential Failure</th>
<th>Initial Risk Assessment</th>
<th>Risk Assessment after Actions Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Impact</td>
<td>Occurrence</td>
</tr>
<tr>
<td>No segregation in the warehouse, no segregation in the packaging hall, mix-ups.</td>
<td>10 3 4</td>
<td>120</td>
</tr>
<tr>
<td>Staging in the wrong filling line, non-segregated staging areas</td>
<td>10 2 5</td>
<td>100</td>
</tr>
<tr>
<td>Puncture of big bags with forklift truck, covering outside of big bags and other materials in the warehouse with dust containing formulated product. Transfer contaminated dust via the staging areas when charging products.</td>
<td>7 3 2</td>
<td>42</td>
</tr>
<tr>
<td>Spills/dust transferred from warehouse to packaging hall on clothing, shoes, tires of fork lift, tools etc.</td>
<td>4 4 2</td>
<td>32</td>
</tr>
<tr>
<td>Contamination prevention awareness low at the operators' level - training 1X annum, seasonal hires not trained.</td>
<td>6 3 3</td>
<td>54</td>
</tr>
</tbody>
</table>

Risks are lowered to an acceptable level
External Manufacturing Information Exchange

The External Manufacturer must supply the succeeding client the following:

- All crop protection active ingredients handled at the site (contact person if secrecy agreements in place)
- Production unit configuration, confirmed cleaning out documentation
- The physical layout that impacts Contamination Prevention
- Parallel operations (focusing on the separation elements)
- Location of the facility (GPS coordinates)

List of Actives

Metosulam
Mesotrione
S-Metolachlor
Haloxyfop-p-methyl

Layout of Unit

Location of Facility
# External Manufacturing Information Exchange

<table>
<thead>
<tr>
<th>Requestor</th>
<th>External Manufacturing</th>
<th>Succeeding Client</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provider</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Preceding Client | • Analytical standards* | • Active present in products |
|                 | • Analytical methods*   | • NOEL**, ED$_5$ or ED$_{10}$ of succeeding products |
|                 | • Cleaning methods*     | • Classification data |
|                 |                        | • Sample of products to develop NOEL data |

<table>
<thead>
<tr>
<th>Succeeding Client</th>
<th>• Cleaning limits</th>
</tr>
</thead>
</table>

*If requested and available for the previous product

**NOEL – No Observable Effect Level
## Minimum Requirements for External Manufacturers

<table>
<thead>
<tr>
<th>Client is responsible for...</th>
<th>External Manufacturer is responsible for...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specify the method to achieve cleaning level (succeeding product or flushes)</td>
<td>Cooperate in a full audit for Contamination Prevention</td>
</tr>
<tr>
<td>Conduct site audits and due diligence .....</td>
<td>Trace materials and records for traceability purposes.....</td>
</tr>
</tbody>
</table>

- Ensure that there is a clear agreement that includes contamination prevention expectations
- Appoint a person responsible for Contamination Prevention
- Understand contamination risk in your facility
- See Contamination Prevention booklet for details
## Minimum Requirements for External Manufacturers

The following should be incorporated into the agreement/contract between the client and external manufacturer.

<table>
<thead>
<tr>
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<th>External Manufacturer is responsible for…</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Cooperate in a full audit for Contamination Prevention</td>
</tr>
<tr>
<td>Conduct site audits and due diligence</td>
<td>Trace materials and records for traceability purposes</td>
</tr>
<tr>
<td>Only use preceding client information for purposes of Contamination Prevention</td>
<td>Appoint a person responsible for Contamination Prevention</td>
</tr>
<tr>
<td>Inform External Manufacturers of special risks (highly active Herbicides)</td>
<td>Separation of operations based on the client’s risk assessment</td>
</tr>
<tr>
<td>Review/update contracts or agreements with best practices in Contamination Prevention</td>
<td>Ensure adequate analytical capabilities</td>
</tr>
<tr>
<td></td>
<td>Ensure written changeover procedures</td>
</tr>
<tr>
<td></td>
<td>Ensure Contamination Prevention training and records of said records</td>
</tr>
<tr>
<td></td>
<td>Ensure labeling of equipment, materials and containers</td>
</tr>
<tr>
<td></td>
<td>Obtain approval of changes that impact contamination prevention</td>
</tr>
<tr>
<td></td>
<td>Not recycling or returning samples to the process</td>
</tr>
<tr>
<td></td>
<td>Rework is approved by the client</td>
</tr>
<tr>
<td></td>
<td>Maintain good housekeeping</td>
</tr>
<tr>
<td></td>
<td>Retention and storage of retained specified by client</td>
</tr>
</tbody>
</table>
Procurement/Purchasing of Active Ingredients

If Active Ingredients are purchased, the following are minimum items to be included in a supply contract:

- The definition of ‘cross contamination’ and ‘contamination prevention’ (as defined in the booklet)
- Product supplied must meet all regulatory requirements
- Agreement reached that …

**EITHER**
- Any non-listed compound in the supplied product must be < 1000 ppm or below, in case of biological activity at lower levels if there are adverse effects on crops, users and/or environment.

**OR**
- Information exchange for other active ingredients manufactured on the same production and packaging line, and a cleaning matrix in place (provided by customer) and cleaning limits will be achieved (by supplier).

- Detailed sales specification
- Chemical analysis and agreement on items on certificate of analysis
- Notification of process changes

*Recommended to complete a self-assessment followed by an audit*
Separation of Production Units

Production Unit – combination of equipment to manufacture a product
Separation – no shared common equipment that could cause contamination

Equipment separation is key to contamination prevention.

When sharing services such as nitrogen or air, measures to prevent backflow need to be part of the design.
Separation of Production Units

A key to contamination prevention is to have dedicated units for: **Herbicides and Non-Herbicides.**

This:
- **✓** Greatly reduces contamination risk,
- **✓** Reduces cleaning costs,
- **✓** Reduces downtime, and
- **✓** Reduces the volume of contaminated waste

**Herbicides**
- e.g. herbicides (normal rate, low application rate, highly active), defoliants, and desiccants

**Non-herbicides**
- e.g. fungicides, insecticides, acaricides, molluscsides nematicides, pheromones, plant activators, PGRs, herbicide safeners, rodenticides, crop oils, adjuvants, fumigants, foliar fertilizers
Separation vs Segregation in Warehousing and Storage

**Separation** – storage of compatible materials and products which with regards to Contamination present no or a low risk can be stored in a common area in the same building.

**Segregation** – segregated storage of incompatible materials and products where contact of different materials is not permitted. There must be no shared equipment.

Several levels of segregation exist based on the risk management policies of the individual member companies:

- **Storage in the same building under the same roof:**
  - in different rooms divided by a wall going up to the ceiling,
  - dedicated entrance and loading / unloadings bays,
  - no contact / no connection doors to other rooms,
  - no shared ventilation ducts and vent headers
  - dedicated vacuum cleaners, forklifts, etc….

- **Storage in different, not interconnected buildings.**
Separation / Segregation of Raw Materials, Intermediates, AIs, Partialis, and Packaging Materials in any of the Manufacturing steps of CPPs.

_Herbicides_ (NRH, LARH, HAH) **must be segregated** from all Non-herbicides

_Segregation_ is also required for all those raw materials, intermediates, formulants, partials and packaging materials which could be potentially contaminated during any of the herbicide manufacturing steps and can be used for non-herbicides.

_Separation_ between Herbicides (AIs, Intermediates, Raw materials, Partialis etc.) **is a requirement**.

- It is **strongly recommended** to implement _segregation_ between **High Active Herbicides** - HAH (application rate < 50 g AI/Ha and herbicides with an ACL in the low ppm range, from all other herbicides (NRH, and LARH, i.e. herbicides with an application rate ≥ 50 g AI/ha."

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Separation / Segregation of Raw Materials, Intermediates, AIs, Partials, and Packaging Materials in any of the Manufacturing steps of CPPs.

**Non-Herbicides** (AIs, Raw materials, Intermediates, Partials, Packaging materials):

Separation between *all Non-Herbicides* (AIs, Raw Materials, Intermediates, Packaging Materials, etc) must be implemented.

- Exceptions:
  - **High bee toxicity:** Segregation between *all Non-Herbicides*, including all raw materials is required.
  - **Baits:** Repellency must be evaluated. Segregation may be necessary, also of finished bait formulation.
Storage of Finished Products in their final sales pack, with temporary labels, or in bulk containers.

*Finished Herbicide* and *finished Non-Herbicides products* can be stored in a common (i.e. the same) warehouse.

- Segregation is not required.

- However, *Adequate Separation* between the finished products must be ensured.

- Care must be taken that all liquid products are stored on the lowest tiers to limit damage caused by leaking containers.
Cleaning Capability

Two critical elements which must always be evaluated...

1. Design of the production unit
   (look for ‘dead spaces’)

2. Cleaning procedures

   ![Image of a crust]

   - Cleaning Levels
   - Cleaning Methods
   - Analytical Documentation
Cleaning Level Determination

Key information required for calculation of ACLs (Cleaning levels):

- The No Observable Effect Level (NOEL)
- The application rates of the succeeding product on all crops
- US EPA Pesticide Regulation Notice 96-8 classification
- For insecticides, the LD$_{50}$ honeybee
NOEL data for Herbicides

NOELs are typically determined in greenhouse studies

Recommended to appoint a specialist to calculate cleaning levels

The dose and adverse effect levels that will be used as a basis for cleaning levels are determined in greenhouse studies
Safety Factors and Application Rates

Safety factors in cleaning level calculations further mitigate potential adverse effects.

Reasons for a factor…
- Studies are typically conducted in greenhouses
- Different crop varieties
- Overlapping in fields
- Spray volume fluctuation
- Weather conditions

Highest single or seasonal application rates are used in the calculation of cleaning limits
Cleaning Level (ACL) Calculation

The ACL is inversely proportional to Application Rate (AR)!

3 elements in the equation...

- AR
- NOEL
- Safety factor (SF)

\[
Cleaning\ Level[ppm] = \frac{10^6 \times NOEL}{SF \times AR}
\]

If the preceding herbicide formulation contains 2 or more actives, cleaning limits for all actives need to be calculated.
What is a ppm?

In contamination prevention, it is customary to express ACLs in ppm.

• **ppm** stands for *parts per million (one-millionth)*
  ➢ in solid products a contaminant with a value of 1 ppm is equivalent to:

  \[
  1 \text{ mg / kg of product} = \text{one-millionth of a kg}.
  \]

  ➢ if the contaminant is a solid in a liquid product (with a density of 1.0), 1 ppm is equivalent to:

  \[
  1 \text{ mg / liter of product} = \text{one-millionth of a liter}.
  \]

  ➢ if the contaminant is also liquid, 1 ppm is equivalent to:

  \[
  1 \mu l / \text{liter or 1 microliter / L of product} (1 \mu l = \text{one-millionth of a liter}).
  \]
How big is a ppm?

The right hand side of this field has been treated with a herbicide (applied at 1.0 L FP/ha). The application caused irreversible crop damage. It could be proven that this herbicide was contaminated.

The contaminant: Residual amounts of a HAH was present at 0.4 ppm - a concentration of 0.4 mg / L of the applied herbicide. Even at this very low application rate of 0.4 mg AI / ha, this contaminant caused irreversible crop damage.

Leaving agriculture for a moment: another way to illustrate how small a millionth part really is: What is 1 ppm of a calendar year?

An one-millionth part of a year is 32 seconds
What is a ppb?

• An other unit used in our industry and also for instance by regulatory authorities:

  ppb

  ➢ ppb stands for parts per billion = 1/1 000 000 000

• In discussions on residues of non-registered AIs in produce this unit is often used.

• To show how small a ppb really is the following examples:

  ➢ 1 drop in an Olympic swimming pool

  ➢ one second in nearly 32 years,
ACLs for Active Ingredients (AIs) not registered on target crops

If the contaminating AI is not registered on the target crop on which the succeeding product is registered, additional factors need to be taken in consideration.

When determining those ACLs, it needs to be assured that the legally required MRLs (= Maximum Residue Levels) for non-registered AIs are not exceeded in the produce.
ACLs for AIs not registered on target crops

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

Definitions:

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

**ACL:** Acceptable Concentration 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 is 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.

**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 behavior. 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, FAOSTAT13 and Factfish14.

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

Each product owner defines the DR, LF, NRA and SF values based on the risk management policy of that company.
## Classification of Herbicides

<table>
<thead>
<tr>
<th>Definition</th>
<th>Highest allowed application rate</th>
<th>Issued by</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal Rate Herbicides (NRH)</strong></td>
<td>lbs./acre ≥ 0.5 lbs./acre</td>
<td>&gt; 560 g AI/ha</td>
<td>EPA, PRN 96 - 8. ACL legally binding.</td>
</tr>
<tr>
<td><strong>Low Application Rate Herbicides (LARH)</strong></td>
<td>≤ 0.5 lbs./acre</td>
<td>≤ 560 g AI/ha</td>
<td>EPA, PRN 96 - 8. ACL legally binding.</td>
</tr>
<tr>
<td><strong>Highly Active Herbicides (HAH)</strong></td>
<td>&lt; 0.04 lbs./acre</td>
<td>&lt; 50 g AI/ha</td>
<td>CropLife International</td>
</tr>
</tbody>
</table>

**Classification of herbicides.** *In geographies in which the US EPA pesticide Regulation Notice PRN 96-8 is implemented, the associated ACLs are legally binding. If biology based ACLs are lower than the legally required values, the biological ACLs must be used. Highly active herbicides are a sub-class of the LARHs. The ACLs for HAHs always require extra attention; these are typically considerably lower than those of LARHs.*
### Active Ingredients NOELs

Example of a table created to show the NOELs of active ingredients on different crops

<table>
<thead>
<tr>
<th>Crop</th>
<th>NOEL [g AI / ha]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corn (Maize)</strong></td>
<td></td>
</tr>
<tr>
<td>Registered Crop</td>
<td>50 (registered crop)</td>
</tr>
<tr>
<td><strong>Oilseed Rape</strong></td>
<td></td>
</tr>
<tr>
<td>Registered Crop</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Sugar beet</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Tomatoes</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Turf</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Herbicide A</th>
<th>Herbicide B</th>
<th>Herbicide C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metosulam</td>
<td>low application rate herbicide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesotrione</td>
<td>low application rate herbicide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-Metolachlor</td>
<td>normal application rate herbicide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloxyfop-p-methyl</td>
<td>low application rate herbicide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Classification based on US EPA PRN 96-8
Cleaning Matrix

Example of a table created to show required cleaning levels of previous active ingredients

<table>
<thead>
<tr>
<th>Preceding Herbicide</th>
<th>AI Preceding Herbicide</th>
<th>Biology Based ARILs (ppm)</th>
<th>US EPA PRN 96-8 based ARILs (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbicide A</td>
<td>Metosulam</td>
<td>N/A 5000 &lt; 1000</td>
<td>100 5</td>
</tr>
<tr>
<td>Herbicide B</td>
<td>Mesotrione</td>
<td>700000 &lt; 1000</td>
<td>100 5</td>
</tr>
<tr>
<td></td>
<td>S-Metolachlor</td>
<td>1500000 &lt; 1000</td>
<td>250 5</td>
</tr>
<tr>
<td>Herbicide C</td>
<td>Haloxyfop-p-methyl</td>
<td>25 1</td>
<td>100 20</td>
</tr>
</tbody>
</table>

[1] If the value of the ARIL is higher than the legally accepted one, this value has to default to < 1000 ppm.
Production Sequencing

The preferred options in sequencing production: avoid low cleaning limits. Optimum sequencing can reduce contamination risk, cleaning time and waste and disposal costs.

<table>
<thead>
<tr>
<th>Production Sequences – Biology based ARILs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence 1</td>
</tr>
<tr>
<td>Sequence 2</td>
</tr>
<tr>
<td>Sequence 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Production Sequences – US EPA PRN 96-8 based ARILs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence 1</td>
</tr>
<tr>
<td>Sequence 2</td>
</tr>
<tr>
<td>Sequence 3</td>
</tr>
</tbody>
</table>
Insecticide Cleaning Levels

The purpose is to ensure optimal safety to non-target organisms such as pollinators visiting the treated crop.

Honey bee $\text{LD}_{50}$ values are typically available for all active ingredients.

An equation for calculating Insecticide Cleaning Levels can be found in the booklet in more detail (see chapter 5.3).
Fungicide Cleaning Levels

If a fungicide has herbicidal and/or growth regulator characteristics (e.g. members of the azole family), additional tests on selectivity are recommended. The regulatory maximum allowed limit is <1000 ppm.
Manufacturing Practices
Identification of Incoming Goods

A few steps need to be completed when receiving goods into a facility...

1. Bill of lading against a purchase order
2. Certificate received with specification
3. Identity or perform Quality Control tests prior to release in manufacturing
Changeover and Release of Equipment

Ensure production equipment is clean and documentation is available *prior* to start up.

Written records to be maintained and include…

- Dates of previous production and cleaning
- Confirmation of each cleaning step
- Analytical evidence verifying content of AI is below the RIL
- Verification that cleaning procedure has been followed, visual inspection, second person sign off, etc.
- Formal ‘release’ of equipment
Staging Material(s)

Store herbicide actives and associated raw materials separately from non-herbicide actives and associated raw materials

- At the warehouse, verify the name and batch number of material when picking
- Use FIFO
- Production to verify the material received is the same as indicated on the batch record
- Personnel performing tasks should sign documentation
Shared Equipment

Create a procedure for using shared equipment, identifying steps to take when transferring from one area to another.

Use of shared equipment in a non-herbicide area, once it has been in contact with a herbicide, should not be permitted.
Shared Equipment

Direct contact

✓ Verify appropriate cleanliness
✓ If in contact with an active, clean similar to other equipment.

✓ If permeable, porous, or difficult to clean – dedicate to a specific active.

No Direct Contact

✓ If transferred, verify clean (no residue or dust).
✓ Assess risk when sharing between herbicide and non-herbicide areas.
Tools

✓ Sharing tools is permitted, but they must be absolutely **clean!** Check is needed before they can be used. *(no product residues, dust, grease, etc. should be present!)*

✓ In a solids plant, vacuum cleaners for equipment **must be dedicated** and thoroughly cleaned before the next process run, especially when the solids are returned to the process.
Dedicated Refillable Containers

As a minimum, the following must be in place:

✓ Process to track containers (status, location, etc.) including serial numbers and labeling
✓ Visual inspection upon return to a plant
✓ Backflow prevention in place to avoid cross-contamination during offloads
Non-dedicated Refillable Containers

As a minimum, the following must be in place:

✓ Date of first use and number of times refilled
✓ A process to track containers including serial numbers, labeling, previous product, and cleaning date
✓ If cleaned within a manufacturing facility, a written cleaning procedure
✓ If cleaning is outsourced, verification checks at manufacturing location
✓ Inspection prior to use
✓ Containers used for herbicides must not to be used for non-herbicides
Labeling Refillable Containers

In addition to the legal requirements, at a minimum the label should include…

- Name of material
- Product code
- Batch number
- Production date
- Quantity

When the container is empty, the label should indicate…

- Cleaning status and previous product
- Date of last cleaning
- For aqueous products, empty containers should be dry and closed, to avoid microbial growth
Relabeling and Overlabeling

Relabeling and overlabeling at facilities not under direct management of the manufacturer cannot be carried out without approval of the Crop Protection Product manufacturer.

– Legal requirements

– Risk assessment

– Risk mitigation measures
Storage of Materials

Raw materials for herbicide and non herbicide operations may only be stored together if:

- The outside of the package is clean
- Herbicide and non-herbicide active ingredients are physically segregated
- Non-herbicide inert raw materials are physically segregated from herbicide active ingredients
- When products can be stored in a common area, the separations clearly marked
- Clear labeling in place
- Partially used materials must be returned to appropriate storage areas and wrapped
Storage Tanks

Feeding from a common inert raw material tank can be a risk...

2 layers of protection should be part of the design:

- Multiple isolation valves in series
- Blanked/blind flanges
- Isolation valve and blanked/blind flange
- Isolation valve with a physical break

Operating procedures should confirm that processes cannot be fed simultaneously.
Reworking, Blending, and Recycling

Applying these practices will minimize risks...

If collected from external surfaces, discard.

Dust and over-size materials collected from solids processing may be returned.

If seal on returned material is not intact, discard. If intact, conduct risk assessment.

If storing rework, quarantine, segregate and only store the same product on the pallet.

Product release samples must not be recycled.
Reworking, Blending and Recycling

Continued practices…

If not contained within production equipment, discard the dust.

Rinsates may be recycled if treated like an active or raw material.

Recycling cleaning medium, first includes a risk/benefit discussion.

Written procedure is needed for reworking off-spec or over-aged product.

At external manufacturers, rework can only occur with written approval from client.

Off-spec material must be labeled.
Final Product Labeling

### Product Label ‘X’

<table>
<thead>
<tr>
<th>Material Name:</th>
<th>Good Stuff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Code:</td>
<td>XYM985</td>
</tr>
<tr>
<td>Batch Number:</td>
<td>AC151406</td>
</tr>
<tr>
<td>Production Date:</td>
<td>03-14-14</td>
</tr>
<tr>
<td>Quantity:</td>
<td>50.2 kg</td>
</tr>
</tbody>
</table>

If temporary labels are needed, the minimum label information required is:

- the product name,
- Batch, and
- Quantity.

To avoid any mix-ups, labels need to be checked and approved before they are allowed to be attached to the containers.
Traceability

Traceability must be in place for all production, filling, packaging and warehousing operations.

Items to consider:

- Ingredients used (lot numbers/quantities)
- Manufacturing conditions
- Batch/lot of the product
- Date, names and initials of personnel responsible for charging and verification
Modifications

When a production unit is modified or updated, ensure that...

A Management of Change procedure is in place.

The design change includes the cleaning process.

Yes or No...

✓ Verify cleaning procedures after change
✓ Before first use, ensure cleanliness
Completing the ‘Contamination Prevention’ self-assessment provides a good baseline for measuring improvement in quality practices.

Documents for Chemical Contamination Prevention and Microbiological Contamination Prevention are available on the CropLife International website.
Production Scheduling

Items to consider when scheduling production:

- Using dedicated lines
- Moving low application rate and/or ‘highly active’ herbicides together with comparable products
- Consolidating ‘highly active’ products in one unit

Low application rate refers to herbicides with an application rate of ≤ 560 g AI/ha.
‘Highly active’ refers to herbicides with an application rate of < 50 g AI/ha – a sub-class of the LARHs
(See also slide 39)
Cleaning Procedures

Written procedures for cleaning must detail:

- Cleaning medium used
- The order in which parts/lines are cleaned
- How the cleaning medium is applied
- Flush quantity
- Dismantling and manual cleaning
- Flush sample locations
- Internal equipment drying
  - Instructions for handling cleaning medium (dispose/recycle)

There are specific guidelines for cleaning liquid versus solid production units.
Visual Inspection

Visual inspection is a key step in cleaning

- If residue is present, repeat cleaning step as appropriate.
- Use tools, like mirrors, to inspect for dead spaces.
Wet Cleaning

Depending on the design, wet cleaning is recommended for liquid products and can also be applied in solid products cleanout.
Dry Cleaning

A solid flush uses an inert material.
After solid flushing:

✓ Deposits are removed by opening or dismantling equipment.
✓ Brushing or vacuuming interiors
Cleanout Capability

Cleanout capability is demonstrated when the cleaning level is consistently achieved using the cleaning procedure.

Capability is demonstrated through:
- Definition of critical parameters (design, process conditions)
- Selection of low level or difficult cleanouts
- Adherence to procedures
- Analyses of multiple cycles of residue material
- Analysis of the succeeding product for RI of previous product

If any of the critical parameters change, re-evaluation is required.

Training of all personnel involved is key to ensure effective repeatable cleanouts.
Cleaning Medium

Recycling used cleaning medium should be based on a risk assessment.

- Re-use savings
- Ecological benefits
- Labeling errors
- Storage stability
Residual Impurity Analysis

Can be performed on the flush or in the succeeding product.

Analysis in the succeeding product versus the flush medium is preferred.

Flush results are not a guarantee.
Sampling

Determine sampling locations...

- Formulation vessels
- Packaging line
- Last rinsate

✓ Do not re-use sampling containers
✓ Establish storage and retention of samples
✓ Retain all analytical data
Analytical Methods

Analytical methods need to be developed for the determination of residual impurities.

Validation of methods should include:
✓ Specificity
✓ Recovery
✓ Repeatability
✓ Linearity

Contamination can occur in the lab; systems should be in place to use clean glassware, vials, etc.

Understand the cleaning levels and choose the appropriate analytical approach.
Contamination Prevention

Making it Sustainable

Keep all the Pieces Together

- Believe in the Philosophy of Contamination Prevention
- Do not become complacent
- Do not allow short cuts
- Build contamination prevention into the design
Disclaimer

The “Contamination Prevention in the Manufacture of Crop Protection Products, Guidelines and Best Practices” booklet makes recommendations about best practices to prevent and control Product Integrity incidents. The technical information contained therein is provided to CropLife International members, their External Manufacturers (EMs), non-members, and a broader public audience. While CropLife International makes every effort to present accurate and reliable information in the booklet, CropLife International does not guarantee the accuracy, completeness, efficacy, timeliness, or correct sequencing of the information provided in the booklet or the present training module. This training module is aimed to help understanding the information in the booklet, without replacing it.

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