

Contamination Prevention in the Manufacture of Crop Protection Products

Guidelines and Best Practices

Fourth Edition



Picture Front Cover

A dose response study with a “highly active” cereal herbicide shows that this compound causes serious crop damage in oilseed rape (Canola™) at one-thousandth of the safe application rate in cereals. A change-over from manufacturing this herbicide with its very low ACL to another selective herbicide requires extremely thorough cleaning (see Chapter 5).

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Guidelines and Best Practices

Fourth Edition

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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.

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Foreword

January, 2019

Dear Reader,

Among the challenges facing us today, as well as in the future, is feeding our growing world population. This requires sustainable agriculture which in turn depends on the modern tools and technologies provided by Plant Science. Crop Protection Products (CPPs) are essential tools to enable those who produce to deliver the desired results. However, CPPs are only effective if high quality of the CPPs is ensured.

The commitment of the CropLife International Operations Committee is to ensure that our member companies, along with our trusted External Manufacturers, implement appropriate contamination prevention systems at all phases of the manufacturing and supply chain process to prevent contamination incidents.

All of us must make sure that a prominent focus on Contamination Prevention is maintained at all stages in the Crop Protection supply chain.

The completely revised fourth edition of “Contamination Prevention in the Manufacture of Crop Protection Products” provides guidelines and best practices to further improve the level of Contamination Prevention. New key topics include expanded or completely new chapters on warehousing, recommendations on how to run a Risk Assessment process, improved labeling guidelines, and a section addressing calculation of Acceptable Contamination Limits (ACLs) that ensure the residue level of non-listed active ingredients will be below the MRL.

On behalf of the CropLife International Operations Committee, I hope you will find that this revised edition assists your ongoing commitment to prevent contamination incidents and to further improve the quality of Crop Protection Products.

Susan Lewis

Chair, CropLife International Operations Committee

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1. Introduction

The Crop Protection industry utilizes multi-purpose equipment for synthesis, formulation and packaging of products. Without careful control, contamination with residual impurities, e.g. active ingredients previously present in the equipment, may occur and possibly trigger adverse effects on sensitive, treated crops or non-target species and may create regulatory issues, i.e. non-conformity.

Customers expect manufacturers to supply products that will protect crops from pests and weeds, while any contamination incident may not only cause undesirable biological effects (e.g. phytotoxicity), it could also tarnish the reputation and image of the entire industry.

This booklet is written for all companies manufacturing crop protection products in order to manage Contamination Prevention risk, providing examples of best practices for Contamination Prevention operating standards and tools.

In the current booklet the convention adopted throughout follows the International Standards Organization definitions:

- **Requirements:** shall, shall not, must, have to, must not.
- **Recommendations:** should, should not.
- **Permission:** may, need not.
- **Possibility and capability:** can, cannot.

2. Purpose and Scope

The purpose of this booklet is to provide guidance to all manufacturers of Crop Protection products in managing and minimizing the risk of contamination. It is applicable to all Contamination Prevention aspects in the synthesis of intermediates and the active ingredients, formulation and (re)-packaging of agricultural chemical products as well as in warehousing and storage of finished products, raw materials, and packaging materials. The contamination prevention guidelines are also applicable in the case of storing and handling of finished product in bulk facilities at distributors/dealers.

These guidelines are globally applicable to all CropLife member companies, and to their current and potential future EMs (External Manufacturers). Suggestions will be made regarding which minimum Contamination Prevention standards should form part of contract manufacturing / distribution agreements/contracts with EMs and Dealers supplying product from bulk facilities to ensure the highest possible product quality.

The following crop protection chemical products fall under the scope of this booklet, either as active ingredients, as formulated products, or as process intermediates used in the synthesis of these products:

- Herbicides (for crop and non-crop uses, irrespective of the application method)
- Safeners.
- Fungicides, Plant Growth Regulators (PGRs), Plant Activators, Insecticides, Acaricides, Pheromones, Molluscicides, Nematicides, Fumigants and Nitrification Inhibitors, (These products can be applied as foliar spray, granular formulation, seed treatments or as any form of soil treatment).
- Rodenticides (applied as baits).
- Adjuvants for agricultural spray tank cleaners, crop oils, and foliar fertilizers.

Excluded from the scope of this document are:

- Contamination Prevention specific to farm operations (e.g., tank cleaning).
- Issues related to Prevention and Control of Microbial Contamination in Crop Protection Products¹.

¹ Prevention and control of microbial contamination in Crop Protection Products are discussed in a separate CropLife International publication: "**Prevention and Control of Microbiological Contamination in Crop Protection Products**", https://croplife-r9qnrx13qxcjra4.netdna-ssl.com/wp-content/uploads/2018/02/Prev_Control_Micr_Cont_official_e-copy_Jan18_-HR.pdf

- Issues related to Contamination Prevention in biotechnology and seeds, e.g. GMO / non-GMO contamination during seed production.
- Biologicals.
- All logistic aspects of bulk deliveries of final product to and by distributors and dealers. Contamination Prevention measures for handling final product in bulk on the distributor level have to conform to the Guidelines presented in this booklet.
- When stricter Contamination Prevention standards are in place than required for crop protection products (e.g. GMP) then these more stringent standards apply:
 - a. Public Health products for non-crop insect control (e.g. treatment of mosquito nets), where humans might be exposed to a contaminant.
 - b. Animal Health products specific for control of ectoparasites.

3. Contamination Prevention Requirements

Simultaneous manufacturing of crop protection products in multi-product facilities is a common practice, yet introduces the risk of contamination. The intent of this chapter is to provide the requirements, applicable across the industry that will mitigate the risks associated with manufacturing products in multi-product facilities.

All CropLife International member companies and the stakeholders mentioned in the scope shall commit to the Policy and Requirements in this chapter.

3.1 Contamination Prevention Policy

- They shall ensure that their products on the market do not contain residual impurities in the form of active ingredients not defined in the product specification, at levels which will prejudice safety and efficacy, or which do not meet regulatory requirements. The individual member companies will set the limits for their products, following an appropriate written risk assessment.
- Legal requirements such as US EPA Pesticide Regulation (PR) Notice 96-8 (see Appendix C) as well as any local legislation must be followed.
- A company which uses an EM shall provide available information to their best knowledge to enable the succeeding client of the EM to carry out appropriate risk assessments and to set limits for residual impurities. The EM shall ensure the information exchange by providing data or as a minimum, the other client's contact information.

3.2 General Requirements

- Documented contamination prevention risk assessments must be in place.
- Acceptable Contamination Levels (ACLs) must be defined.
- Non-herbicides must not be produced in the same equipment as herbicides, i.e. segregation between manufacturing units must be guaranteed. This applies to all synthesis, formulation, filling and packaging operations. An exception from this rule may only be permitted, when stringent verification of cleanliness is confirmed and there is documented approval from senior management.
- Raw material handling must be assessed to minimize the risk of using common raw materials for herbicides and non-herbicides.
- Mobile, portable equipment (vacuum cleaners, flexi hoses, pumps, tools, etc.) must be dedicated for herbicide or non-herbicide areas (see case 10.7).
- Refillable containers (IBCs, ISOs, Big Bags, Rail trucks, etc.) must be treated in the same way as chemical equipment that comes into contact with product.
- Recycle and reconditioning must be managed to minimize any risk of contamination.

- All materials must be clearly and properly labeled, this includes but is not limited to: raw materials, intermediates, bulk formulations, finished products, reprocessing, recycle, and waste (see case history 10.12).
- Effective cleaning procedures and validated analytical methods must be available to analyze residues in wash liquids (rinsates), as well as in the following product.
- A cleaning operation must take place as soon as possible after the production has stopped not only when changing from one product to the next, but also if the equipment will be left idle (see case histories 10.1 and 10.3). This applies to all synthesis, formulation, filling and packaging equipment.

3.3 Management Responsibilities

The management of all CropLife International member companies and their EMs must ensure the following responsibilities and requirements are covered and implemented:

- Nominate a Company contact who is able to speak authoritatively on behalf of the company on all aspects of Contamination Prevention.
- Protect the confidentiality of exchanged information.
- Provide sufficient resources for all aspects of Contamination Prevention.
- Apply requirements and best practices as demonstrated in this booklet.
- Continuous training and awareness.
- Good housekeeping to ensure consistent care, hygiene, cleanliness, orderliness and maintenance of the facilities and processes (Good housekeeping practices).

Exceptions to any of the general requirements must have documented approval from senior management.

3.4 External Manufacturing of active ingredients and formulations

3.4.1 Information Exchange

The External manufacturer (EM) must supply, in a timely manner, the following information to the succeeding client:

- All active ingredients handled in any part of the production and warehouse facilities. If this information is restricted by secrecy agreements, the name of the person to contact at the client for those products.
- Configuration of the production unit in which the product will be synthesized, formulated and/or filled. Ensure that the configuration to be used is cleaned to the required ACLs (see case history 10.3).
- The physical lay-out of the facility that could impact Contamination Prevention (see case history 10.9).

- Parallel operations with emphasis on the degree of segregation, common equipment (including ancillary equipment like tools, vacuum cleaners) and personnel.
- The precise location of the production facility (e.g. GPS coordinates).

The preceding client* must supply to the succeeding client the following information if requested and available for the previous products:

- Confirm the active ingredients present in its product(s).
- Provide, at least, the NOELs, ED₅ and/or ED₁₀ on the registered crops of the succeeding product.
- In the case of lack of NOEL information on the relevant crop(s), similar information on related crops.
- Classification of the product according to the EPA Pesticide Regulation Notice 96-8, based on the worst case scenario, i.e. if the product (irrespective of the formulation) is applied both as low and normal application rate herbicide, then it should be indicated that this is a low application rate herbicide.
- Samples of the product for tests to develop missing NOELs.

* Preceding and succeeding client indicates production sequence at EM.

3.4.2 Minimum Requirements for External Manufacturers

In addition to the guidelines detailed above, it is expected that the items below are incorporated in the agreement / contract between the client and the EM. There may be additional specific requirements agreed between client and EM.

The client is responsible:

- To specify whether the ACL must be achieved in the succeeding product or Cleaning Level (CL) in the wash liquids (rinsates). In all cases, the finished product must meet the agreed ACL.
- To undertake detailed site audits and other due diligence activities (including the cleaning process and results) and support the EM where appropriate.
- To use the information obtained from the preceding client exclusively for the purposes of Contamination Prevention.
- To inform the EM of any special risks associated with the product being brought onto the EM's site (e.g. this product is a highly active herbicide).
- To review and if necessary update existing contracts and/or agreements with EMs to include the best practices as outlined in this document.
- To provide the succeeding client whose product will be manufactured in the same equipment with any available information as requested.

The EM is responsible:

- To co-operate in a full technical audit for Contamination Prevention.
- To trace materials and retain all relevant records as defined by the client to enable traceability.

- To appoint a person responsible for implementation of the Contamination Prevention Guidelines at the EM's site.
- For separation of simultaneous operations based on the outcome of the client's risk assessment.
- To ensure adequate analytical capability is available to meet the client's requirements regarding the ACLs. The analytical facilities are either in-house or at an agreed and client approved location (contract laboratory or at the client's analytical laboratory). In the case of involving a contract laboratory, a validated record of the analytical data should at least be retained at the facilities of the EM.
- There are written changeover procedures, including the clean-out procedures and a check-list to be followed.
- To ensure regular Contamination Prevention training of existing personnel and newly recruited personnel (before being allowed to participate in the manufacturing process), and permanent records of the training are retained.
- To ensure permanent labeling of all equipment (including ancillary equipment), raw material, 'in-process' and 'finished' product containers and waste containers.
- To obtain approval from the client prior to any change that impacts the risk of contamination
- To ensure that samples are not recycled, i.e. samples cannot be returned in the process without the approval of the client.
- To ensure that any reconditioning (blending, recycling) is approved by the client (see case history 10.15).
- To maintain good housekeeping practices.
- To ensure the retention time and storage conditions of retained samples specified by the client are followed.

3.5 Procurement / Purchasing of active ingredients

Suppliers of active ingredients also require regulatory compliance and contamination prevention management.

If an AI is purchased from a supplier, who is the registration owner of the AI, a Letter of Access (LoA) must be in place to allow the formulator" met "client/formulator to submit their registration. However, a LoA in itself does not supply sufficient information to assess compliance with legal requirements, nor does it give the guarantee the product meets the Contamination Prevention criteria of the client (see case history 10.14).

For AIs manufactured by a supplier all principles mentioned in the "Guidelines for Contamination Prevention" apply, e.g. information exchange about the previous product in the equipment etc. It is mandatory to agree on the

information required on a detailed certificate of analysis providing adequate information allowing quality control at the customer's facility.

Protection of a supplier's intellectual property remains important. Therefore it is recommended to implement a secrecy agreement. The business partners should agree in the contract to implement all requirements listed in the booklet.

As a minimum the following aspects must be covered in the supply contract:

- Definition of "contamination" and "contamination prevention" (see Glossary).
- The product(s) must meet all regulatory requirements.
- Agreement reached that:

EITHER

Any non-listed compound(s) in the supplied product(s) must be < 1000 ppm or below, in case of biological activity at lower levels if there are adverse effects on crops, users and environment or if local regulations demand this.

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 including legal standards.
- Chemical analysis (including analytical methods) and an agreed list of the chemicals, which need to be disclosed on the certificate of analysis.
- Notification of process changes as required.

It is recommended to complete the Contamination Prevention self-assessment checklist ideally followed by an audit.

4. Contamination Risk Assessment

A contamination risk assessment must be conducted for the production site, all production units used in the manufacture of crop protection products, as well as for all products manufactured in it before the manufacturing process can be started. Such a risk assessment includes as a minimum a review of all products, the design of the manufacturing site and its production units, separation, the cleaning requirements and capabilities, manufacturing practices and analytical practices. A change in any one of these must always lead to a reassessment of the contamination risk.

4.1 Key factors in contamination risk assessments

The following topics need to be evaluated in contamination risk assessments of production units:

- Design of the production unit (easy to clean and to dismantle, adequate separation etc.).
- Which other active ingredients or products are handled on the manufacturing site and in which production unit.
- Production schedule planning to avoid low cleaning levels (see sub-chapters 5.2.8 and 5.5).
- ACLs in place and up to date (see case history 10.2).
- Verified cleaning method available.
- Reprocessing/recycle and blending practices (see case history 10.15).
- Regional and national legislation impacting manufacturing procedures, waste management etc.
- Demonstrated ability to clean down to low levels of residual impurities in products planned to follow each other in the production schedule.
- Appropriate equipment and facilities for chemical and physical analysis of trace levels of residual impurities preferably in-house, or at well recognized contract laboratories.
- Skilled and trained personnel throughout any operation, training records.
- Contamination risk from airborne particles coming from adjacent buildings on the same manufacturing site or in the same vicinity. This is especially critical when highly active herbicides are being manufactured in neighboring units. Aspects like predominant wind direction, air intake location, ventilation, placement of windows and dust filters must be taken into consideration. Special attention must be paid when the separated production units are compartmentalized in the same building to ensure that the separating wall is completely sealed, and the production areas cannot be accessed during production runs (see case history 10.9).

- Systems to prevent movement of residues from one production unit to the next on shoes, clothing and portable, mobile equipment. This is especially critical on sites handling highly active herbicides.
- Well understood and consistently implemented, written procedures for Management of Change processes, cleaning methods and product release.
- Globally consistent risk assessment in place for evaluation of any production site.

4.2 Design and lay-out of the production unit (see Appendix A)

Successful contamination prevention is directly linked to the design and lay-out of production units which determines the ease with which these unit can be cleaned. All cleaning aspects should be included in the risk assessment.

4.2.1 Assessment of cleaning capability

To assess the suitability of a production unit for handling a particular production sequence two criteria need to be evaluated:

- Design of production unit.
- One of the highest contamination risks in production units is from dead spaces. This applies especially for solids but also for liquid products (both active ingredients and formulations). Dead spaces can allow a build-up of material that could lead to contamination. The “trapped” material sometimes does not only come from the preceding production campaign but even from earlier ones. This material can be released suddenly and contaminate one or even more batches of the subsequent product. Therefore, it is important to critically look at the design of a production unit for potential dead spaces when assessing the contamination risk.
- Successful procedures.
 - o Their four key elements are:
 - Correct cleaning levels (see chapter 5).
 - Cleaning methodology (see chapter 8).
 - Analytical capability (see chapter 9)
 - Documentation (record keeping, retained samples) (see chapters 3 and 7.2)

A helpful guide to determine whether a product changeover can be successfully achieved in a production unit is to review historical data on cleaning ability.

Consistently demonstrated results similar to the following cleaning levels should be available:

- Synthesis of active ingredients: < 50 ppm typically achieved after the equipment has been rinsed with solvent, partial dismantling of pipes and pumps (see table 6, page 71);

- Formulation and packaging of liquid products: < 100 ppm typically achieved after the equipment has been rinsed with a cleaning medium at a maximum of three times (see table 6);
- Formulation and packaging of solid products: < 200 ppm typically achieved after dry cleaning followed either by wet cleaning or “flush cleaning” (see table 7).

4.3 Separation / segregation of production units

Depending on the risk of potential contamination, either separation or in some cases segregation of production units will have to be a key element in Contamination Prevention (see also page 54; 6.6 Warehousing and Storage).

A “production unit” is a combination of equipment used for the manufacture of products. It may be used for multiple products in sequence. A manufacturing site may consist of multiple production units.

Based on the outcome of a risk assessment the decision can be made that a “Separation” of product units can be accepted and a number of common functions like ventilation ducts can be shared.

In the case “Segregation” is required, there must be no shared common equipment (e.g. ventilation ducts and vent headers), which could cause an unplanned transfer of product from one production unit to another. Also valves between reaction vessels may not be a safe form of segregation, because even if it is indicated that the valve is closed, a small leakage could occur. An effective way to achieve segregation is through having different buildings, relocation of critical products into other production units or dedicated manufacturing lines in the same building.

Some site services may have to be shared, e.g. vacuum lines, steam, compressed air and nitrogen. Especially in the case of vacuum lines it is necessary that one-way (no-return) valves have been installed as a safeguard against back flow (see case history 10.8).

The CropLife International member companies require – as key first steps in Contamination Prevention – implementation of the following separation / segregation rules in shared manufacturing facilities to minimize the contamination risk (and at the same time also to reduce both cleaning costs and down-time):

- Segregate “Herbicides” from “Non-herbicides”
- This segregation is achieved by having production units, which are completely dedicated to either “herbicides” or “non-herbicides” (see chapter 3.2).
- The definition of “Non-Herbicides” used by the CropLife International member companies follows the one used in US EPA PRN 96-8 with the exception of Plant Growth Regulators (PGRs).
- “Herbicides” include: All herbicides (crop and non-crop, irrespective of the method of application), defoliants, desiccants.
- “Non-herbicides” include: All fungicides and insecticides, acaricides, molluscicides, nematocides, pheromones, plant activators, herbicide safeners, rodenticides, crop oils and adjuvants, spray tank cleaners, fertilizers and fumigants, plant growth regulators (PGRs) and nitrification inhibitors.
- Besides Responsible Care considerations, additional requirements for separation have to be implemented if any of the following product groups is manufactured on the same site as crop protection products:
 - o Human and Veterinary pharmaceutical products applied orally, topically or as an injection.
 - o Personal Care and other health care products.
 - o Food and feed stuffs (including vitamins).

Various requirements are based on Good Manufacturing Practices (GMP) and legislation specific for each product group. Those individual requirements must be studied in detail before starting any production to determine the degree of separation required.

The following points are recommendations to further mitigate contamination risks:

- Separate all low application rate herbicides (LARH) from normal rate herbicides (NRH). Pesticide Regulation Notice PRN-96-8 (see Appendix C), US EPA divides herbicides in two classes based on their application rate: the dividing line is \leq or $>$ than 560 g AI/ha (0.5 pounds AI/acre).
- CropLife International deemed it necessary to have a sub-class of the LAHRs, namely the Highly Active Herbicides (HAHs). Two reasons: the typically very low application rates of the HAHs ($<$ 50 g AI/ha) and very often NOELs on non-target crops of $<$ 10 mg/ha. More details on the classification of herbicides can be found in table 1 on page 30.
- Consequently, the AIs of HAHs have an even higher potential to cause very serious damage when present as contaminant(s) in a herbicide applied on a non-target crop.
- Combining herbicides registered on the same crops in the same production unit, e.g. all rice herbicides or all cereal herbicides could reduce the contamination risk, however, it is always recommended to calculate the cleaning limits (see chapter 5).

- Manufacturing Plant Growth Regulators (PGRs) on “insecticide” lines. US EPA PRN 96-8 classifies PGRs as normal rate herbicides (see Appendix C). However, it is recommended to manufacture / formulate PGRs in the dedicated non-herbicides equipment, rather than share production in herbicide units. This approach is already practiced by a number of CropLife International member companies and has shown that the contamination risk of PGRs in insecticide units is very much reduced.
- None of the currently known PGRs show herbicidal activity at the registered application rates. This means if PGRs are present as residual impurity at a content of < 1000 ppm, they will not cause crop damage in the succeeding product. Due to this inherently low phytotoxicity, Effective Dose (ED) assessments for PGRs are practically impossible. NOELs for PGRs are, at present, not available.

4.4 Risk assessment process

The purpose of the following paragraphs is to provide guidance on the design and execution of the risk assessment process. Establishing a standardized process for Risk Assessment is key to successful prevention of contamination incidents. Functions and organizations involved in processes and tasks that impact contamination prevention and all other product quality aspects in the manufacturing of Crop Protection Products must have a risk assessment process defined.

The outlined process serves as an example. The design of the process is up to the individual company.

4.4.1 Design of the contamination risk assessment process

To design the Risk assessment process, the inputs, the tools used and the expected outputs as well as the roles and responsibilities must be defined.

Each individual company, based on their Quality Management Systems procedures, should define roles and responsibilities.

The process typically includes stakeholders from Production, Quality, Management and the Process Owner.

An example of a matrix defining Roles and Responsibilities can be found in Appendix D.

Inputs of the risk assessment process are at least those mentioned in paragraph 4.1 and any subsequent changes made to them, such as, but not limited to:

- New or updated procedures.
- New facilities.
- Equipment update in existing facility(ies).
- Changes in product portfolio, or action from a Management of Change.

The output of a completed risk assessment includes:

- Action items and timelines.
- Go / No-Go Decisions, whether to accept or reject the risk.

4.4.2 Process

An initial contamination risk assessment is necessary for all production units and needs to cover all products manufactured in it. This assessment follows the Failure Mode and Effect Analysis (FMEA) methodology.

A change to one of the input sources must be evaluated to determine the need for a revised risk assessment. A decision should be made whether a revision is necessary or not. Decisions must be documented.

Examples of the different process steps can be found in appendix D:

- **Appoint a Risk Assessment Team**

A team must be appointed to identify and evaluate the potential risks in a process. It should include relevant stakeholders of the process.

- **Identification of Potential Failures**

Identifying potential failure modes is a systematic, proactive way to evaluate the source and impact of failures. The potential failure modes must be documented, e.g., in a Quality Risk Assessment Template (QRAT).

- **Analyze and Rate potential failures**

The potential failures must be assessed and rated. E.g., Severity, Occurrence and Detection (SOD) values provide guidance for ranking potential failures based on the impact under the view of severity, likelihood of occurrence and detection of a defined scenario.

- **Calculate and Evaluate Risk**

The rating of the risk needs to be translated into a tangible scale and acceptance levels defined. E.g., the Risk Priority Number (RPN) estimates the risk by multiplying the SOD values. This RPN indicates whether additional measures are necessary or a risk is acceptable, based on the previously defined acceptance levels.

- **Identify Risk Reduction Measures**

For risks not meeting the threshold of the defined acceptance level, adequate measures need to be defined to reduce the risk to an acceptable level, or eliminated completely.

- **Evaluation of the effectiveness of proposed measures**

Before implementation of the risk mitigation measures, it must be ensured that they will lead to the intended result. The risk is re-evaluated considering the proposed measures and if the defined threshold will be achieved. If this re-evaluation indicates success, the defined measures can be implemented. If not, other measures need to be identified.

- **Documentation**

The risk assessment, all measures and approvals must be documented and controlled.

5. Determination of Acceptable Contamination Levels

The ACL required for a product-changeover is the primary indication of the risk involved in the changeover, i.e. the lower the ACL, the higher is the risk and impact of a contamination incident if the cleaning process fails. In addition, more labor, down-time, cost intensive cleaning and increased waste disposal will be needed to achieve the required lower ACLs.

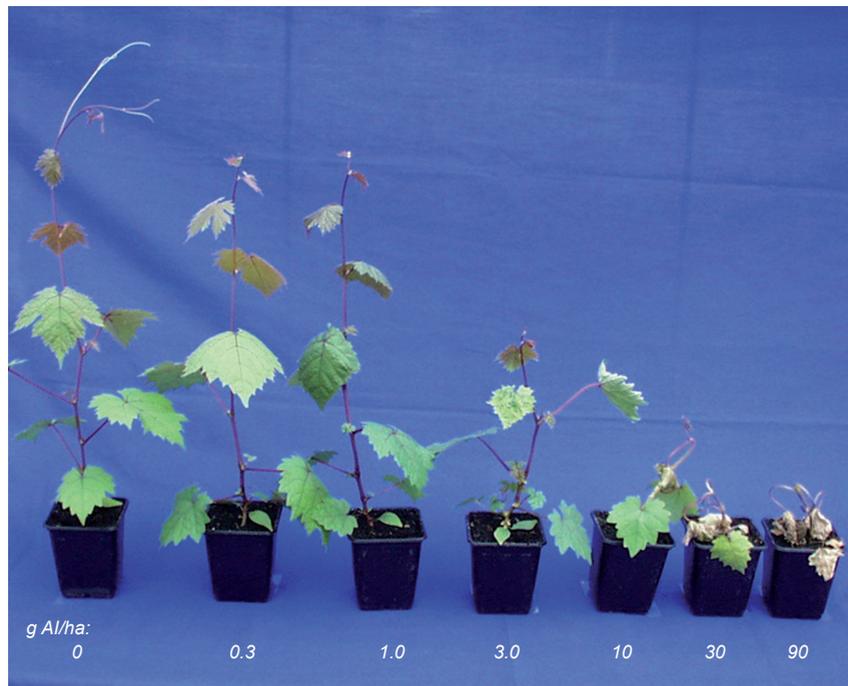


Figure 1: Dose response study of a cereal herbicide as contaminant of a grape fungicide illustrating the damage some active ingredients cause, even at low application rates, when applied on non-target crops. The grape vines were treated with the registered amount of the fungicide with increasing concentrations of the herbicide (numbers in white). The NOEL of the herbicide on grapes is 0.3 g AI/ha, which corresponds with 1.7% of its registered application rate in cereals. This picture illustrates why a strict segregation between “herbicides” and “non-herbicides” is a key requirement in contamination prevention

To optimize production sequencing, it is advisable to develop a cleaning matrix, which must be based on residual impurity levels. An example will be shown for an herbicide packaging unit in sub-chapter 5.2. ACL requirements for insecticidal and fungicidal active ingredients (AIs), as a contaminant in succeeding foliar spray and seed treatment products, will be highlighted in sub-chapters 5.3 and 5.4.

Special attention will be paid to ACLs required for AIs that are known to be toxic to non-target organisms (see sub-chapter 5.3.1).

Methodology for the calculation of ACLs for AIs not registered on target crops when Maximum Residue Levels (MRLs) of this residual impurity could be critical are detailed in sub-chapter 5.6.

5.1 Principles

The objective of setting ACLs in multi-purpose manufacturing facilities is to ensure that after the cleaning operations for a product change-over, the succeeding product can be used safely on all crops on which it is registered without the risk of showing adverse effects caused by residual impurities from the previous products. This will only apply to labeled uses of the succeeding products; off-label uses are outside the scope of these guidelines. All calculations of ACLs must be documented and retained for the life-time of the product. ACLs may change over time; the newest version must always be used in operations (version control).

The five key components that contribute to the calculation of ACLs are:

- 1. Product category**
- 2. Region (legal requirements, e.g., US EPA PRN 96-8)**
- 3. Toxicity on non-target crops and non-target organisms (e.g. beneficial insects)**
- 4. Application rates and the number of applications**
- 5. Safety factors**

To calculate the ACLs, the following information is required:

- The No Observable Effect Levels (NOELs) of the active ingredient of any herbicide (see table 1). This is generally not required for fungicides and insecticides.
- The maximum application rates of the succeeding product on all crops on which it is registered plus the number of applications per growing season.
- Classification according to the categories listed in Pesticide Regulation (PR) Notice 96-8, October 31st, 1996 (US EPA PRN 96-8)².

² The value of 1000 ppm for the highest TSLCs referred to in the Pesticide Regulation (PR) Notice 96-8, has been superseded by EPA, 40 CFR – Chapter I, Part 159; published in August 2004. The limit for non-listed extraneous ingredients (like residual impurities) has been set at < 1000 ppm, which aligns this value to the one mentioned in the “Manual on the development and use of FAO and WHO specifications for pesticides”, FAO Plant Production and 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).

- For insecticides: the LD₅₀ (Honey bee).
- The geographical region where the product is registered to cover the legal requirements.

The lowest NOEL(s) (of the previous AI(s) on the following crop most sensitive to this (these) AI(s) must always be used, irrespective whether the succeeding product is also applied on less sensitive crops.

The Guidelines on the Toxicologically Significant Levels of Contamination (TSL-Cs) of the previous product in the succeeding one in the Pesticide Regulation Notice (PRN) 96-8, October 31st, 1996 (issued by the US Environmental Protection Agency (EPA)) should always be consulted when calculating ACLs. The full text of this document is available in Appendix C. The Pesticide Regulation (PR) Notice 96-8 is applicable to products manufactured, imported, and / or used in the US. This means that the ACLs for products with the US and any other countries that implement PRN 96-8 as final destination may never exceed the values for the TSLCs listed in the various categories.

However, it is very important to note that implementation of the EPA guidelines without proper consideration of the biological effects could still lead to serious contamination incidents, because the TSLC may be too high to cover the “biological safety margin” necessary to prevent these incidents. If the ACL based on biology is lower than the regulatory limits, the biology based level must be used.

Extra attention is required when calculating ACLs for “highly active herbicides”. “Highly Active Herbicides (HAHs)” have application rates of less than 50 g AI/ha, while NOELs of less than 10 mg AI/ha on non-target crops are common (see table 1 on the following page).

In most countries outside the US, the government agencies generally have not defined specific ACLs for the crop protection industry, **provided the limits used for the ACLs do not infringe the crop protection legislation**. However, it is understood that US EPA PRN 96-8 is also implemented in Canada, and currently in Mexico as well.

Definition	Highest allowed application rate		Issued by:	Comments
	lbs./acre	g AI / Ha		
Normal Rate Herbicides (NRH)	> 0.5 lbs./acre	> 560 g AI/ha	EPA, PRN 96 - 8. ACL legally binding.	See examples given in Table 3 (5.2.7)
Low Application Rate herbicides (LARH)	≤ 0.5 lbs./acre	≤ 560 g AI/ha	EPA, PRN 96 - 8. ACL legally binding.	See examples given in Table 3 (5.2.7)
Highly Active Herbicides (HAH)	< 0.04 lbs./acre	< 50 g AI/ha	CropLife International	See examples given in Table 3 (5.2.7)

Table 1: 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.



Figure 2: Dose response study of clomazone on grape seedling (top) and sugar beet (bottom). For ACL calculations, the NOEL of the residual impurity on the most sensitive crop that the succeeding product is applied on must be used. Grape seedlings are clearly more sensitive than sugar beet. NOEL of clomazone on sugar beet is 3.0 g AI/ha, on grapes less than 1.0 g AI/ha.

5.2 Herbicide ACLs

To calculate biology based ACLs, it is necessary to have a database with NOEL data. The biology based ACLs allow determining whether those will be above or below the EPA default values. This needs to be done after establishing in which category the contaminant belongs. In the majority of the cases, the previous product contains one or a number of proprietary active ingredients of which NOEL data are available in the company's own data base. It is recommended that each company appoints a specialist (e.g. a biologist or agronomist) responsible for the calculation of all ACLs in liaison with manufacturing and regulatory colleagues.

5.2.1 NOEL data for herbicides

NOEL data for herbicides are not readily available in the scientific literature and are typically generated in the green houses of the company who originally discovered this active ingredient. This means that these NOEL data only apply to the proprietary AI, not necessarily to generic forms of this molecule.

NOELs are developed using dose/response studies generated in greenhouses where visual injuries on crops are measured. A threshold is set between ED_0 (Effective Dose giving a 0 % adverse effect) and ED_{10} (10 % adverse effect) depending on the individual company risk assessment policy.

This ED value is then used as NOEL for the calculation of the ACL. ED_5 or ED_{10} values are often used as starting point for the ACL calculations. Some companies prefer to only use ED_0 in their calculations. In those cases where the AI causes striking visual symptoms (like chlorotic spots) at very low application rates ($< ED_{10}$), it is prudent to always revert to the NOEL based on lower ED values.

5.2.2 Safety Factors

Safety factors (SFs) are implemented in the calculations of ACL to further mitigate potential contamination incidents. Each member company determines the level of the safety factor(s) that align best to the risk management strategy of its company. The typical range is 2 – 10.

The reasons for applying a SF:

- The dose response studies are carried out in greenhouses with constant day and night temperatures, humidity and light regimes.
- When applying crop protection chemicals under field conditions overlapping is often unavoidable; this doubles the application rate in certain areas of the treated field.
- The test plants are kept under optimal conditions without possible periods of moisture, temperature and light stress encountered in the field.
- The test plants are often smaller than those treated in the field, i.e. they will intercept less spray solution/plant.
- The spray volumes used in modern farming are often considerably lower than the spray volume used in greenhouses, resulting in a spray solution with a higher concentration of potential contaminants.

5.2.3 Application rates

Application rates are needed as part of the cleaning limit calculation. It is essential to know the application rates of the formulation on each crop and it needs to be considered that many products have more than one application per season. For the calculation of the ACL the highest single application rate or highest seasonal application rate on the registered crops of the succeeding product must be used, based on the company specific risk assessment.

5.2.4 Manufacture at an External Manufacturer

It is customary for the succeeding client to contact the preceding client requesting the NOEL data on as many crop species as possible. The succeeding client will use these data to calculate the ACL³ and provide this to the EM prior to the production of his product. The EM is not expected to calculate the ACL for the succeeding client; this is best done by the “ACL-specialist” in the succeeding client’s organization. The ultimate responsibility for the integrity of the products lies with the succeeding client; while the EM has to adhere exactly to the manufacturing guidelines received to assure the quality criteria of the client will be met.

5.2.5 Equations for calculating herbicide ACLs

Biology based ACLs are calculated using the following equation:

$$\text{ACL [ppm]} = \frac{10^6 \times \text{NOEL}}{\text{SF} \times \text{AR}}$$

Definitions:

NOEL: No Observable Effect Level in gram AI/ha of the preceding active ingredient on the most sensitive crop on which the succeeding product is registered.

AR: Highest registered Application Rate of the succeeding product in gram or ml of formulated product / ha on the most sensitive crop. For the calculation the assumption 1 g = 1 ml can be used.

SF: Safety Factor, typically ranging from 2 to 10. Each product owner defines the SF value based on the risk management policy of that company.

10⁶: Conversion factor (used to convert to ppm).

³ The various CropLife International member companies may use synonyms for ACL: ARIL, RIL, TCL or TCAL, however, they are all calculated using the process described in this chapter.

5.2.6 Calculation of herbicide ACLs when the preceding product contains two or more active ingredients

If the preceding herbicide formulation contains two or more active ingredients, ACLs for all residual AIs must be calculated.

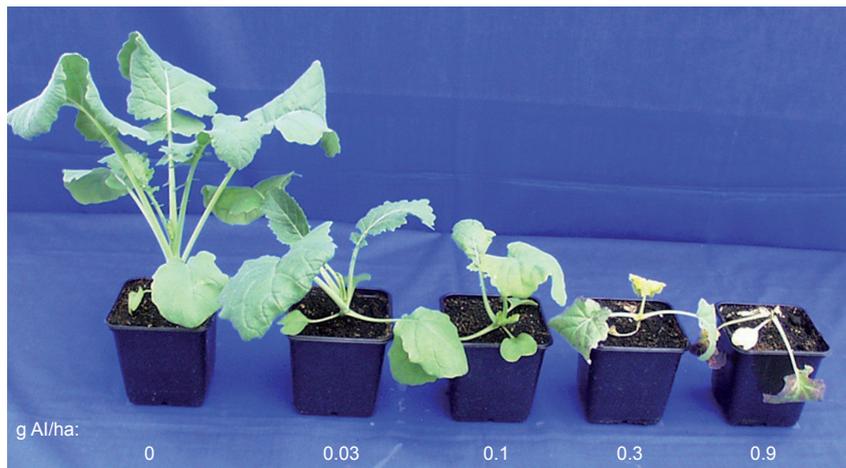


Figure 3: Dose response study of an experimental highly active cereal herbicide (for control of broad-leaved weed species) on the non-target crop oilseed rape. The NOEL on oilseed rape is < 0.03 g AI/ha. The ACLs necessary when the succeeding product after this type of herbicide is used on oilseed rape are very low, often < 2 ppm or even in the ppb range.

Analytical Confirmation will be required to ascertain that the cleaning levels have been achieved for all residual impurities at the change-over. If the ACL of one of the AIs has been achieved it cannot be assumed that the ACL for all RIs has been reached. Chemicals have different solubility characteristics, i.e. they may not be removed by the cleaning medium at the same rate. This means that while one chemical may already have been removed to < ACL, that some of the other RIs are only partially removed at that stage.

In case there is more than one potential contaminant, the ACL has to be calculated and analyzed separately for each one. It should be considered that contaminants may have synergistic effects on non-target crops as well. The combined ACLs for those AIs should not be higher than the ACL of the herbicide with the lowest one.

5.2.7 Example of a cleaning matrix for a herbicide unit

	Herbicide A	Herbicide B		Herbicide C
	Metosulam	Mesotrione	S-Metolachlor	Haloxypop-p-methyl
	Classification based on US EPA PRN 96-8			
	low application rate herbicide	low application rate herbicide	normal application rate herbicide	low application rate herbicide
Crop	NOEL [g AI / ha]			
Corn (Maize)	50 (registered crop)	500 (registered crop)	2500 (registered crop)	0.015
Oilseed Rape	0.005	1.70	800	> 200 (registered crop)
Sugar beet	0.005	1.70	500	> 200 (registered crop)
Tomatoes	0.2	0.40	5	> 200 (registered crop)
Turf (golf courses)	25 (registered crop)	280	1500	0.01

Table 2: Biological information as well as the classification based on US EPA PRN 96-8 of the four herbicidal AIs used in the example of the development of a herbicide cleaning matrix.

The NOELs of these AIs on the different crops are shown in the columns of the appropriate AIs. The numbers of the NOELs in red indicate are the values used to calculate the Acceptable Concentration Level (ACL).

Disclaimer: All values of NOELs and application rates are fictitious and have been chosen to demonstrate the principles behind the development of a cleaning matrix only and should not be used for any other purposes. CropLife International and its member companies cannot accept any liability for incorrect use of these data.

		Succeeding Herbicide (Potentially Contaminated Herbicide)		
		Herbicide A	Herbicide B	Herbicide C
		Treated Crop		
		Maize (Corn), Turf	Maize (Corn)	OSR, S-beet, tomato
		Max. Application Rate [g Formulated Product/ha]		
		200	5000	500
Preceding Herbicide	AI Preceding Herbicide			
Biology Based ACLs (ppm) ⁴				
Herbicide A	Metosulam	N/A	5000 < 1000	5.0
Herbicide B	Mesotrione	700000 < 1000	N/A	400
	S-Metolachlor	15000000 < 1000		5000 < 1000
Herbicide C	Haloxypop-p-methyl	25	1	N/A
US EPA PRN 96-8 based ACLs (ppm) ⁵				
Herbicide A	Metosulam	N/A	20	100 5
Herbicide B	Mesotrione	100	N/A	100
	S-Metolachlor	250		250
Herbicide C	Haloxypop-p-methyl	100 25	20 1	N/A

Table 3: Example of a Cleaning Matrix for an herbicide manufacturing unit. The NOELs used for these ACL (Acceptable Concentration Level) calculations are listed in Table 2, the SF used in this example is 2. The ACLs in the orange cells are biology based and are the ones that have to be implemented although they are considerably lower than those based on PRN 96-8.

⁴ If the value of the ACL is higher than the legally accepted one, this value has to default to < 1000 ppm.

⁵ Biological considerations must override ACLs based on the ACLs listed in EPA PRN 98-8, however, only when the biologically determined ACLs are lower than the EPA values these must be used to ensure prevention of contamination incidents.

5.2.8 Effect of the cleaning matrix on product scheduling / sequencing

Analysis of the production sequences as in table 4 shows that there are clearly preferred options. Therefore a careful selection of the production sequence can reduce the contamination risk, save [cleaning] time (less down- time) and reduce waste (less environmental burden and lower disposal costs).

Production Sequences - Biology based ACLs							
Sequence 1	Herbicide A <i>Metosulam</i>	<1000	Herbicide B <i>Mesotrione + S-Metolachlor</i>	400 <1000	Herbicide C <i>Haloxypop-p-methyl</i>	25	Herbicide A <i>Metosulam</i>
Sequence 2	Herbicide A <i>Metosulam</i>	5	Herbicide C <i>Haloxypop-p-methyl</i>	1	Herbicide B <i>Mesotrione + S-Metolachlor</i>	<1000 <1000	Herbicide A <i>Metosulam</i>
Sequence 3	Herbicide C <i>Haloxypop-p-methyl</i>	25	Herbicide A <i>Metosulam</i>	<1000	Herbicide B <i>Mesotrione + S-Metolachlor</i>	<1000 <1000	Herbicide A <i>Metosulam</i>
Production Sequences - US EPA PRN 96-8 based ACLs							
Sequence 1	Herbicide A <i>Metosulam</i>	20	Herbicide B <i>Mesotrione + S-Metolachlor</i>	100 250	Herbicide C <i>Haloxypop-p-methyl</i>	25	Herbicide A <i>Metosulam</i>
Sequence 2	Herbicide A <i>Metosulam</i>	5	Herbicide C <i>Haloxypop-p-methyl</i>	1	Herbicide B <i>Mesotrione + S-Metolachlor</i>	100 250	Herbicide A <i>Metosulam</i>
Sequence 3	Herbicide C <i>Haloxypop-p-methyl</i>	25	Herbicide A <i>Metosulam</i>	20	Herbicide B <i>Mesotrione + S-Metolachlor</i>	100 250	Herbicide A <i>Metosulam</i>

Table 4: Based on this cleaning matrix, examples of possible production sequences (not all possible sequences are listed in this example)

For a full cycle of all three products significantly different cleaning levels can be required:

- Sequence 1 (A → B → C → A) and sequence 3 (C → A → B → A) both avoid the very low ACL for C → B. In countries implementing US EPA PRN 96-8, the lower EPA based ACLs are required for all three changeovers in sequence 1 and 3.
- Sequence 2 (A → C → B → A) requires the two significantly lower ACLs of 5 ppm for A → C and 1 ppm for C → B (both these low cleaning levels apply also when relying on EPA PRN 96-8 for ACLs, see footnote 4 above).

5.3 Insecticide ACLs

In this section on the calculation of ACLs, special attention will be paid to the ecotoxicological risk of insecticides when contaminating other products. Rather than safety to the next crop, i.e. no risk of phytotoxic damage, the purpose of ACLs for insecticides, is to ensure optimal safety to non-target organisms like bees visiting the treated crops.

US EPA established < 1000 ppm as the threshold level when the residue of an active ingredient of an insecticide remaining in manufacturing equipment would appear in a following product (US EPA Pesticide Regulation (PR) Notice 96-8, see Appendix C). The same threshold level has been proposed for unidentified impurities in the plant protection products regulation 1107/2009/EC.

An ACL for an insecticide AI of < 1000 ppm for insecticides for the control of arthropods in non-crop situations, molluscicides, nematocides, soil fumigants, defoliant or desiccants, is acceptable as no adverse effects are expected to occur due to the type of application.

However, < 1000 ppm as a default ACL for insecticide active ingredients when the following products are fungicides, acaricides (miticides), other insecticides, and plant growth regulators which are applied as foliar sprays, may result in unintended side-effects on non-target organisms (see case history 10.4).

5.3.1 Calculation of ACLs for insecticides in foliar spray applications

For insecticides the calculation is based on the LD₅₀ value for honey bees. Honey bee LD₅₀ values (both oral and contact) are typically available for all active ingredients. The advantage of using these data is that honey bees are sensitive to insecticides in most cases, and data are readily available, generated under Good Laboratory Practice, and highly standardized (i.e. generated according to OECD TG 213/214). If both acute oral and contact LD₅₀ values are available, it is recommended to use the lowest value to calculate the ACL. This ensures that both exposure routes (through contact and feeding) are covered.

Therefore, the calculation for insecticides in foliar spray applications looks as follows:

$$\text{ACL [ppm]} = \frac{10^6 \times LD_{50} \times HQ}{SF \times AR \times MAF}$$

Definitions:

LD₅₀ = The dose of the insecticide that leads to 50% mortality of honey bee expressed in µg AI/bee.

HQ = HQ trigger value derived from Hazard Quotient approach (Sanco, 2002), it is recommended to use 50, which is a validated value used in prevention of incidents with honey bees (EPPO 2010⁶, 2003⁷), (Thompson et al, 2009⁸)

10⁶ = Conversion factor.

SF = Safety factor (default value is 1). Additional safety factors, e.g. in case of IPM (Integrated Pest Management) uses, are the individual decision of the company responsible for calculating the ACL. For instance, the value of the SF could be based on available non-target arthropod (NTA) data on solo-formulations.

AR = maximum single application rate of the succeeding product in

$$\left[\frac{g \text{ FP}}{ha} \right] \text{ or } \left[\frac{ml \text{ FP}}{ha} \right]$$

MAF = Multiple application factor (default value is 1). Depending on the foliar half-life, number of applications and spray interval its value may be increased (according to Candolfi *et al.*, 2001⁹).

⁶ EPPO (2010) *Environmental risk assessment scheme for plant protection products. Chapter 11: Honey bees.* EPPO Bulletin 40, 323–331.

⁷ OEPP/EPPO (2003) *EPPO Standards - Environmental risk assessment scheme for plant protection products - PP 3/10(2) Chapter 10: Honey bees.* Bulletin OEPP/EPPO Bulletin 33(1): 141-145.

⁸ Thompson HM and Thorbahn D (2009) *Review of honey bee poisoning incidents in Europe – evaluation of the hazard quotient approach for risk assessment.* Julius-Kühn-Archiv 423, 160 p.

⁹ Candolfi MR, Barrett KL, Cambell P, Forster R, Grandy N, Huet MC, Lewis G, Oomen PA, Schmuck R and Vogt H (2001) *Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods. Report of the SETAC/ESCORT2 Workshop.* Wageningen, the Netherlands, SETAC Europe, Brussels, Belgium.

Examples of typical ACLs are presented in Table 5:

Application rate of succeeding product [kg FP/ha]	Contaminant LD ₅₀ (µg AI/bee)					
	0.001	0.003	0.01	0.03	0.10	1.0
0.10	500	<1000	<1000	<1000	<1000	<1000
0.25	200	600	<1000	<1000	<1000	<1000
0.50	100	300	<1000	<1000	<1000	<1000
1	50	150	500	<1000	<1000	<1000
2	25	75	250	750	<1000	<1000
4	13	37,5	125	375	<1000	<1000

Table 5: Examples of ACLs (in ppm) calculated according to the above equation using default values for MAF and SF. If the calculation yields a value of greater or equal to 1000 ppm, the legally required default of < 1000 ppm is inserted.

Special attention should be paid when the product following the insecticide is applied in Integrated Pest Management (IPM), where growers may use parasitic or predatory arthropods for pest control.

Data on the toxicity of insecticides on parasitic or predatory arthropods are not as readily available as for honey bees, not available for active ingredients and less standardized. Therefore it is more practical to use the toxicity data for honey bees.

If an insecticide has a honey bee LD₅₀ > 0.1 µg AI/bee, the suitability of using the bee toxicity data for calculating the ACL should be checked, for instance by inspecting available NTA data on solo-formulations. Similarly, for insect growth regulators (IGRs) that do not express their toxicity in an acute bee test according to the OECD Test Guidelines TG 213 and 214, the NTA data should be checked. Another example would be acaricides, which often have low toxicity on honey bees, but are toxic to mites. If predatory mites are used as IPM species in the following crop, the ACL should be set at a level that will not impact these species.

5.3.2 Calculation of ACLs for insecticides in seed treatment applications

In some cases, it may be preferable to calculate an ACL for insecticides when the following product is used as seed treatment product rather than use the US EPA PRN 96-8 default value of < 1000 ppm (Category 1).

This is especially the case when the insecticidal AI is systemic. As an indication for potential **systemic** effect, the $\log K_{ow}$ can be used with a trigger value of 3, below which an ACL calculation should be conducted.

The **AR** is based on the seeding rate of the treated seed and the amount of formulated product (FP) used to coat 100 kg of seeds (seed loading application rate):

$$AR = SWR \left[\frac{kg \text{ seeds}}{ha} \right] \times SLAR \left[\frac{g \text{ FP}}{100 \text{ kg seeds}} \right]$$

$$SWR = \text{Seeding rate} \left[\frac{kg \text{ seeds}}{ha} \right]$$

$$SLAR = \text{Seed loading application rate} \left[\frac{g \text{ FP}}{100 \text{ kg seeds}} \right]$$

So the equation to calculate insecticide ACLs in seed treatment products looks as follows:

$$ACL \text{ [ppm]} = \frac{10^8 \times LD \times HQ}{SF \times SWR \times SLAR}$$

In the equation for ACLs in seed treatment formulations, the conversion factor is **10⁸**.

The **MAF** is omitted from this equation because seed treatments are typically applied one single time.

The value of the Safety Factor has to be decided by the owner of the succeeding product based on detailed information provided by the owner of the preceding insecticide. The order of magnitude of the SF may be considerably higher than the ones used in calculation of herbicide ACLs.

5.4 Fungicide ACLs

This section deals with the calculation of ACLs for fungicides as potential contaminants of foliar sprays and seed treatment products.

5.4.1 Calculation of ACLs for fungicides in foliar spray applications

Foliar fungicides are typically registered on a great number of crops, across a wide spectrum of species often belonging to different botanical families. This also applies to systemic foliar fungicides and is a clear indication that foliar fungicides are highly selective when applied at the registered rates. In the majority of the cases, it is considered safe to use the default value of < 1000 ppm listed for Category 1 of the US EPA PRN 96-8. Because, repeated applications of residual impurities of [foliar] fungicidal active ingredients do not normally cause phytotoxicity in succeeding products provided those are applied as a foliar spray as per the guidelines on the product label of the following product. However, a number of fungicides (esp. the azole fungicides) are known to display plant growth regulator activities. Therefore, if the previous fungicide belongs to this chemical family, it is advisable to check its selectivity on a number of crops, which typically get treated with fungicides and insecticides before deciding on the ACL. There may be other fungicidal AIs which also display growth regulator activities on non-target crops.

5.4.2 Calculation of ACLs for fungicides in seed treatment applications

The following additional critical production sequences need to be taken into account when production scheduling:

- Highly colored active ingredients, e.g. dinitro compounds, or colored formulations (usually seed treatment formulations) often require cleaning to well below the biologically determined ACL in order to meet the color standards specified for the succeeding product.
- Switching from an aqueous formulation to an organic solvent formulation or vice versa requires complete removal of the solvent used to formulate the preceding product. Additional rinsing of the equipment with a solvent that is both miscible in water and organic solvents is one option to solve this problem. To avoid this issue, scheduling EC formulations after EC formulations can reduce cleaning time and consumption of solvents.
- Some azole-fungicides can cause phytotoxicity to seedlings or failure to germinate when they contaminate Seed Treatment fungicides and insecticides at ACLs considerable below the values listed in US EPA PRN 96-8 (see case history 10.2).

5.5 ACLs in succeeding products with an AI concentration below 1 g AI/kg

The AI content of a number of bait products and products for the amateur market (e.g. home- and garden products) is in a number of cases < 1 g. In US EA PRN 96-8 these products are not covered separately. Therefore, theoretically the EPA PRN 96-8 TSLC values can be used to calculate ACLs, however, this would mean that the content of the residual impurity may be higher than of the AI. For this reason it is recommended that the ACL should not exceed one-tenth of the content of the AI. This recommendation is implemented by a number of the Crop-Life International member companies.

5.6 ACLs for active ingredients not registered on target crops: Consideration of Maximum Residue Levels (MRLs)

If the contaminating AI is not registered on the target crop on which the succeeding product is registered, additional factors need to be taken into consideration. When determining those ACLs, it needs to be assured that the legally required MRLs for non-registered AIs are met in the produce of the target crops. Known ACL calculation models may be insufficient to achieve this requirement.

This subchapter addresses the methodology for calculation of ACLs for non-registered AIs in formulated products with the following applications:

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

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

5.6.1 Criteria for determination ACLs for non-registered AIs

The following criteria must be taken into account to determine the correct ACLs for non-registered AIs:

- The maximum allowed limit of < 1000 ppm¹⁰ for non-listed extraneous ingredients in the following product must never be exceeded.
- The maximum residue level 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)¹¹.

¹⁰ 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).

¹¹ Regulation (EC) No. 396/2005 of the European Parliament and of the Council (23rd February, 2005), Chapter III, Article 18.

- The legal limit may be different in other geographic regions¹². 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 ACL 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 ACL of the non-registered AI may be lower than the ACLs required to avoid phytotoxicity or other adverse effects on the crop.

Prior to calculation of the desired ACL, a risk analysis is necessary. The minimum requirements for 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.
- 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 consequently any residual impurities cannot be metabolized due to the method of application, e.g. fruit dips, or late pre-harvest sprays.

¹² New Zealand Food Safety Authority - Pesticide MRL Database. <https://pxmrl.maf.govt.nz/Default.aspx>

5.6.2 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 must 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.

5.6.3 Calculation of ACLs 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 ACL for the non-registered AI in the following product to ensure the required MRL is not exceeded. This number will differ from the ACL used to prevent phytotoxicity etc. on the following crop.

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

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

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.

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 sub-chapter 5.6).

- 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.

¹³ <http://faostat3.fao.org/home/E>

¹⁴ <http://www.factfish.com/catalog>

Three examples of this calculation are given for apples, grapes and spinach respectively, 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

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

$$ACL = \frac{259.840}{1 \times 5 \times 10 \times 0.25 \times 0.2} \text{ [ppm]} = 104 \text{ ppm}$$

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

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

$$ACL = \frac{64.540}{1 \times 2 \times 3 \times 0.15 \times 0.2} \text{ [ppm]} = 359 \text{ ppm}$$

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

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

$$ACL = \frac{166.200}{1 \times 3 \times 2 \times 0.80 \times 0.2} \text{ [ppm]} = 173 \text{ ppm}$$

5.7 ACLs for products with special applications

5.7.1 Manufacture of products for use in 'Organic Farming'

Produce from crops grown using 'Organic Farming' methods must not show residues of crop protection chemicals that are 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.

5.7.2 Biopesticides

Different definitions exist for 'microbial and biochemical pesticides'^{15 16 17}. A comprehensive summary¹⁸ 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 'macrobiols' 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, nematocides, plant or animal growth regulators, plant strengtheners, biostimulants, biofertilizers and more.

For chemical substances defined as 'biopesticides', e.g. fatty acids, sulphur, pyrethrum, the ACLs described in this booklet should be applied as a minimum standard.

For biologicals (biological organisms) used as e.g. 'biopesticides', (these can be bacteria, fungi, viruses, spores, nematodes), different rules apply. Biological organisms can multiply exponentially and therefore a residual impurity limit in the formulation is not in the scope of this booklet and will not be defined here. 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.

¹⁵ EPA definition, see <https://www.epa.gov/ingredients-used-pesticide-products/what-are-biopesticides>

¹⁶ EU definition, *Encouraging innovation in biopesticide development. European Commission (2008). Accessed on 20 April 2012*

¹⁷ OECD, see <http://www.oecd.org/chemicalsafety/pesticides-biocides/biologicalpesticideregistration.htm> *Biological Pesticides (or BioPesticides including microbials - bacteria, algae, protozoa, viruses, fungi, pheromones and semiochemicals, macrobiols/invertebrates such as insects and nematodes, and plant extracts/botanicals)*

¹⁸ Knoell Consult GmbH, <http://www.knoellconsult.com/en/agrochemicals/biopesticides>

5.7.3 Bait formulations, contaminants with repellent effect

Certain substances (e.g. methaldehyde, permethrin, cyhalothrin) may have an unintended repellent side effect. This means that the target organisms (insects or other pests) are not attracted to such a contaminated product and avoid contact, therefore the product would be ineffective. 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.

6. Manufacturing Practices

The purpose of this chapter is to summarize all essential components of Manufacturing Practices that should be considered for successful Contamination Prevention management.

For information on sampling see chapter 9.2.

6.1 Identification of incoming goods on site

- Check the bill of lading against the purchase order.
- Check the Certificate of Analysis against the specification.
- Verify the identity or perform quality control (e.g. chemical and physical analysis, visual inspection) of the incoming materials prior to release for production (see case history 10.6).

6.2 Documentation of changeover and release of cleaned equipment

- Ensure the production unit has been cleaned, the concentration of residual impurities is below the relevant ACL and corresponding records are available prior to production start.
- A written record of each specific changeover of the production unit must be retained for a time period defined by the manufacturer, client and / or local legislation. The written record may include, but is not limited to the following:
 - o The date of the previous production as well as the date of the cleaning operation;
 - o Confirmation of completion for each step of the cleaning procedure (for details see 9.1.1) (date and operator initials);
 - o Analytical evidence that the concentration of the residual impurity is below the agreed ACL (see chapter 5);
 - o Completeness check of the cleaning record including cleaning status, visual inspection and sign-off by an independent person, e.g. the supervisor;
 - o The formal written “release” allowing the use of the entire cleaned equipment for the manufacture of the next product.

6.3 Controls ensuring correct delivery of materials from the warehouse to the staging points and other manufacturing areas

- Warehouse personnel to verify the name and batch number of the material when picking (see case history 10.12).
- Production personnel to compare the product name of the material received from the warehouse at the manufacturing point with the one on the batch card for the final product.

- Signatures of the personnel performing these tasks may be required.
- Apply bar coding (if implemented).

6.4 Shared portable / interchangeable equipment

Facilities handling multiple active ingredients may wish to use portable equipment such as pumps, motors, flexible hoses, filters, tools etc., in all areas. Careful management of these pieces of portable equipment is necessary to ensure no contamination can occur when transferring from one area of a plant to another. Define written procedures for the use of shared equipment.

To approve the use of this equipment for the next product the following information needs to be checked and available:

- The last product made in the equipment,
- Manufacturing Date,
- Cleaning history / date,
- Official release date (verification of cleanliness required).

It is recommended to have the cleaning status shown on the equipment.

Use of portable equipment in a non-herbicide area once it has been in contact with an herbicide should not be permitted unless stringent verification of cleanliness is confirmed (see case history 10.7).

6.4.1 Direct contact with active ingredients (AIs)

Before any portable equipment comes into contact with a material containing AIs ingredient(s), proof is necessary that this equipment has been appropriately cleaned. Verification of cleanliness must be carried out before use.

Any portable equipment, which has been in direct contact with an active ingredient, must be treated as any other piece of contaminated chemical equipment and cleaned in accordance with the facilities cleaning procedures.

It is recommended to clean the equipment immediately after production and label appropriately. Special attention needs to be paid when the portable item becomes part of a common tool, e.g. a pump.

Portable equipment that is permeable, porous or difficult to clean must be dedicated to the specific active ingredient (e.g. filter cloths, rubber hoses, seals).

6.4.2 No direct contact with active ingredient

Portable equipment, which in normal use does not come into contact with AIs (e.g., mechanical guards, electrical motors), may be transferred between plants where different active ingredients are used / produced. Such equipment must be clean and visually inspected to ensure there is no chemical residue or dust present.

If such equipment is to be moved from a herbicide to a non-herbicide facility, the risks of sharing the equipment must be assessed and procedures in place to ensure there has been no contact with an active ingredient.

6.4.3 Tools

Sharing tools (e.g., brushes, wrenches, drills, knives, and sampling equipment) between facilities producing multiple active ingredients is permitted, but they must be clean and visually inspected to ensure there is no residue or material present. Tools must be thoroughly cleaned as soon as possible after use. In a solids plant, vacuum cleaners must be dedicated for each individual production unit.

6.5 Mobile Refillable Containers

There is a potential risk that contamination could occur when refillable containers (e.g. rail cars, iso-containers, tank trucks, IBCs) are used, re-used or when they are used for multiple products. In principle these types of container should be considered in the same manner as chemical vessels in direct contact with product.

To avoid microbial contamination of water-based products in refillable container please follow the recommendations outlined in “Prevention and Control of Microbiological Contamination in Crop Protection Products” (2018).

6.5.1 Dedicated Refillable Containers

A documented container management system should be in place including as a minimum:

- A process for tracking containers, their status, their contents, location and
- history which includes:
 - Unique identifier (e.g. serial number);
 - Correct labeling.
- An inspection procedure at the manufacturing facility is in place to check the returned refillable containers prior to use. As a minimum, this should include opening and inspecting the containers to ensure that there is no ‘residual material, in the returned container.
- Dedicated containers not subjected to cleaning between refills need to have their contents transferred in a manner that prevents backflow (i.e. one way valves, anti-back siphoning mechanism, top loading etc.) to ensure contamination does not occur during offloading operations.

6.5.2 Non-dedicated Refillable Containers

A documented container management system should be in place including as a minimum:

- A process for tracking containers, their status, their contents, location and history which includes:
 - Unique identifier (e.g. serial number);
 - Correct labeling;
 - Name of the previous product;
 - Cleaning date.
- A refillable container used previously for other crop protection products should never be used without adequate, validated cleaning. A written cleaning procedure must be available for the cleaning of refillable containers that are cleaned within a manufacturing facility.
- If the cleaning is outsourced to another company (e.g. at an isotainers cleaning station), checks to verify the cleanliness of the container must be described and confirmed by the cleaning company e.g. by issuing a cleaning certificate. These facilities must have passed an industry standard audit program (e.g. NTTC, SQAS etc.) or an equivalent program.
- An inspection procedure at the manufacturing facility is in place to check all returned cleaned refillable containers prior to use. This must include as a minimum opening up and inspecting the containers to ensure that there is no residual material in the returned container.
- Containers previously used for herbicides should not be used for non-herbicides, unless stringent verification of cleanliness is confirmed.
- The best practice to identify an empty refillable container and its history is to check the following information:
 - Cleaning status (cleaned/uncleaned);
 - Date of last cleaning;
 - First date the refillable container was used and the number of refills.

6.6 Warehousing and Storage

This section outlines best practices, recommendations and requirements for safe warehousing and storage of raw materials, intermediates, partials, active ingredients, formulations, formulation concentrates, and finished CPPs.

These storage facilities are typically on the manufacturing site, but can also include external warehouses directly managed by the company or contractors. Refer for best practices on storage of labels and packaging materials to 7.2.1.5. Storage of seeds, fertilizers etc. are outside of the area of control by the CropLife International members and therefore out of scope.

When repackaging / recombination / relabelling / copacking operations of finished CPPs are performed in the warehouse, they have to be managed according to the appropriate chapters in this guideline.

Based on assessments of the potential contamination risk, separation and segregation requirements, recommendations will be presented.

The rules on storage of these products are governed by three considerations:

- **Contamination prevention.**
- **EHS criteria based on flammability:** It is a legal requirement to segregate flammable from non-flammable products. The separation / segregation requirements based on contamination prevention are equally applicable in the allocated areas for flammable materials.
- **Regulatory requirements.**

Potentially serious contamination incidents could occur and are traceable to the warehouse when material is escaping from leaking containers, punctured big bags, packaging soiled on the outside or after use in the staging area. This is especially critical when stored on top of others. If thorough cleaning is not carried out immediately, further contamination will occur by spreading material around with dirt adhering to tires of fork lifts, foot wear etc.

Based on the contamination risk, several “levels” of separation or even segregation must be considered:

- **Separation** – storage of compatible¹⁹ 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.
 - o To avoid mix-ups, these materials and products must be stored in specifically allocated bays (i.e. dedicated areas) and minimally divided with e.g. a chain link fence. The distance between the materials must be considered safe from a contamination prevention point of view. As a minimum, a hand width distance is recommended (> 10 cm).

¹⁹ *Compatible materials do not present an unacceptable risk from a contamination prevention point of view (e.g. normal rate herbicides for cereals).*

Incompatible materials present an unacceptable risk from a contamination prevention point of view (e.g. an insecticide with high bee toxicity and a mildew fungicide).

- **Segregation** – storage of incompatible materials and products where contact of different materials is not permitted. There must be no shared equipment (e.g. ventilation ducts and vent headers).

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, however, in different rooms divided by a wall going up to the ceiling with dedicated entrance, and no contact and openings to other rooms (i.e., no holes in the wall like gaps for piping, etc.). This requires also dedicated equipment like exhaust lines, forklifts, vacuum cleaners, etc. As a best practice, incoming materials (as well as materials going out) are handed over in a transfer area and then moved with dedicated equipment inside the segregated area.
- Storage in different, not interconnected buildings. The required distance between these buildings depends on the potential impact of a contamination incident. Requirements for dedicated equipment etc. are the same as mentioned above.

Where an electronically controlled warehouse system is in-place, a risk assessment must demonstrate if other crop protection products including raw materials, intermediates etc. could be stored alongside finished goods in their commercial package.

6.6.1 Storage of Raw materials and active ingredients in the warehouses of syntheses and formulation plants

Chemical raw materials, including formulants, used in both herbicide and non-herbicide operations may be stored in common warehouse facilities.

However, the following storage requirements must be implemented in the warehouses of the synthesis and formulation plants:

1. Active ingredients (AIs) of low application rate herbicides (LARHs) as well as those of normal rate (NRHs) must be segregated from AIs of any non-herbicide (fungicides, insecticides etc.).
2. The same segregation requirement applies to active ingredients of insecticides with high bee toxicity (see 5.3 Insecticide ACLs) and any other non-herbicide.
3. Active ingredients of LAHRs, especially when the NOELs are low like in the case of highly active herbicides (HAHs), should be segregated from normal rate herbicides (NRHs).
4. It is recommended not to store any AI, raw material, formulant, etc., in the close proximity of colored substances like pigments, dyes (irrespective of the packaging used for these colored materials).
5. The physical and/or biological properties of raw materials (and the finished products in which these are used) may necessitate segregation. This applies

in particular to biologicals, baits and seeds (see 5.7.2 “Biopesticides” and 5.7.3 “Bait formulations, contaminants with repellent effect”). E.g., raw materials for baits and finished bait formulations could pick up odors from other materials stored in the warehouse which make the final product unusable

6.6.2 Storage and handling of active ingredients, raw materials and formulants in the staging area of synthesis and formulation plants

For all the materials in the staging area, specific precautions should be taken to limit the contamination risk. Similar to the suggestions made for the storage of materials in the warehouse, it is recommended not to store any AI, raw material, formulant etc., in the close proximity of colored substances like dyes, pigments (irrespective of the packaging used for the colored materials).

1. Ensure cleanliness of the outside of any packages.
2. AIs of insecticides with high bee toxicity must be segregated from any other non-herbicide.
3. The raw materials and formulants left-over after the production run (often referred to as partials) must be packaged and labeled appropriately, and removed from the staging area. The partials have to be treated the same way as the active ingredients it has been used for. The best practice is to mark them clearly with an additional label, e.g., “for use in herbicides only”, “for use in insecticides only”, etc., before returning these partials to the designated area in the warehouse.

6.6.3 Storage of Finished Products

The risk of accidentally damaged / leaking containers and thus contamination between different end-user products when in their final sales pack is relatively low. Typically, a small number of packs would be affected in that case.

- Finished product in bulk which will be processed further should be stored in the same area of the warehouse as the product of that formulation in the end-user packs. This also applies to the same products with a temporary label.
- To minimize the risk of an incident, finished products of low application rate herbicides should not have other finished products with different indications, like fungicides or insecticides, underneath.
- Liquid finished products should not be stored above solid finished products to minimize the risk of contamination by leaking containers.

6.6.4 Storage Tanks

This paragraph deals with storage tanks of raw materials, active ingredients, intermediates, and formulated products.

Feeding from a common tank presents a potential risk of contamination due

to backflow. Different installations can potentially be connected to each other through feed lines. The piping must be designed to prevent the backflow and cross-flow of materials (see case history 10.8).

Acceptable designs may include the following piping elements:

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

In addition, operating procedures and / or mechanical/software interlock systems should be in place to confirm that the processes are not fed at the same time.

Acceptable confirmation methods may include:

- Lock out / tag out procedures for multiple isolation valves in series.
- Second level sign-off for correct position of multiple isolation valves in series.
- Software interlocks of multiple isolation valves.

6.6.5 Transport aspects

End use products (formulations of herbicides, fungicides, insecticides or any other indication) in their final commercial packages are allowed for combined transport in e.g. trucks or sea containers. However, the restrictions for separation and segregation as described in the sections 6.6.1 to 6.6.3 must also be followed for combined transport of raw materials, formulants, AIs etc.

6.7 Reprocessing, Blending and Recycling

The following practices will give guidance on optimization of reprocessing, blending and recycling with emphasis on reduction of contamination risks:

- Besides the necessary analytical proof of the reprocessed, blended and recycled products being in spec., in the case of blended products it must be ascertained that in some countries blended products have fulfilled certain legal criteria, e.g. notification of the relevant authorities and approval of planned procedures.
- Any material collected from the external surfaces of equipment or processing areas must be discarded and not re-introduced into the system, e.g. spill material, contents of vacuum cleaners.
- Returned product must be checked to ensure the original seal is intact prior to reprocess / recycle. Where the seal is not intact the product should be discarded. Otherwise a detailed risk assessment must be undertaken.
- Product release samples must not be added back to the process but must be discarded (see case history 10.11).
- Materials containing active ingredients being stored for reprocessing need to be quarantined or segregated from other packaged materials containing different active ingredients. These different materials must not be stored on

the same pallet. Reprocessing should be managed with the same controls as for any other raw materials containing active ingredients.

- Dust and/or oversize or undersize particles collected from solids processing (milling, sieving etc.) may be returned to the process provided normal precautions to avoid mix-ups and contamination are taken.
- Dusts not contained within production or extraction equipment must be disposed of and not recycled.
- Rinsates may be recycled provided they are treated as any other active ingredient or raw material and the appropriate controls are in place to avoid any mix-ups. For aqueous rinsates the possibility of microbial contamination should be evaluated. For more details see the separate booklet **“Prevention and Control of Microbiological Contamination in Crop Protection Products” (January 2018)**²⁰.
- No reprocessing (including blending) of off-spec. or over-aged batches from previous production runs is allowed without a written procedure. At EMs reprocessing can only take place with written approval from the client (see case history 10.15).
- In a number of countries, regulatory authorities insist that the proposed blending procedures are in line with the registered manufacturing process. This information must be submitted with approval in writing by the product owner confirming the proposed process. Analytical proof may be required to confirm the reconditioned material now meets spec.
- Any kind of off-spec. material must be clearly marked as such.
- For recycling of used cleaning medium see 8.8.

6.8 Traceability of materials

Traceability of materials shall be in place for any kind of production, filling and packaging operation. Production records (batch cards) for each manufactured batch need to consider:

- Ingredients used including their batch/lot numbers and the quantities.
- Manufacturing conditions.
- Batch / lot number of the manufactured batch/lot and its quantity; date, names and initials of the operators responsible for charging and verification of the materials.

6.9 Modification of the production unit / equipment and plant design

A modification of a production unit could impact the contamination risk due to the changed equipment design. When there is a need to modify / update the production unit, ensure that:

²⁰ Electronic copy: https://croplife-r9qnrxt3qxxjira4.netdna-ssl.com/wp-content/uploads/2018/02/Prev_Control_Micr_Cont_official_e-copy_Jan18_-HR.pdf

- A Management of Change procedure is in place which includes Contamination Prevention aspects.
- The design changes improve the cleanability of the production unit (e.g. avoid small radius pipe bends, consider the right choice of material with smooth surfaces for piping, vessels and tanks, easy dismantling). See also Appendix A.
- The cleaning procedures are verified after the changes have been completed.
- The effectiveness of the cleaning procedures must be checked in the first production batches of the first product manufactured after the changes.
- Before the equipment is used for the first time, ensure that it has been properly cleaned.
- When the destination of a production unit will be changed to another category of CPPs (e.g. from an herbicide unit to a fungicide or insecticide unit or vice versa), a detailed risk assessment and change-over must be executed.

6.10 Housekeeping and site maintenance

6.10.1 Housekeeping

The role of housekeeping in the prevention of contamination is often underrated. Housekeeping is not only responsible for consistently maintaining high levels of cleanliness inside the various buildings, but also for the regular maintenance of the areas outside the buildings, the tank farm, all roads on the site, the perimeter fence, and the overall appearance of the site.

6.10.2 Site maintenance

6.10.2.1 Weeds and Pests

Prevention of weed development and control of pests, e.g. insects, may be necessary. The choice of products, time of application and application method should be defined by the site.

Herbicides and insecticides used in these programs could cause contamination of products handled at the site even a long period after application.

- Products used to treat weeds and insects on sites should be selected together with site management.
- Applicators must follow label information as well as spray distances to e.g. formulation units as agreed with site management.
- As a best practice close all outside doors and windows during the application and shut down the air intake (dryers, air jet mill etc.) during application.

6.10.2.2 Movement of personnel

Rules must be implemented for movement of personnel between workshops, production units or even laboratories when this is a critical topic as a result of the risk assessment.

To prevent the transfer of e.g. contaminated dust into the various plant areas by foot wear or clothing, several approaches are available:

- Personnel must go through a sluice (e.g. including an air shower) when entering a unit and to change clothes. Only then entrance into (and exit from) defined areas will be allowed.
- It is only possible to enter manufacturing areas from outside by walking through a tray filled with a detergent (and a disinfectant if microbial contamination is an issue) or using an adhesive mat. Both equipment's must be replaced routinely.
- Use entrance control or records for the affected areas.

6.11 Self-Assessment

A “self-assessment” should be carried out using the attached questionnaire “Contamination Prevention Audit Checklist for Self-Assessment” (see Appendix B).

The completed checklist presents an up-to-date picture of the level of Contamination Prevention management practices in place for any given production unit at the manufacturing site. It could be used as initial step for a risk assessment and continuous improvement.

7. Labeling

In every single step in the manufacturing process of Crop Protection Products correct labeling is essential (from the reception of incoming goods to warehousing the end-user products).

The main reasons are:

- Labeling errors could lead to the wrong raw materials used in the synthesis of active ingredients and/or in formulations that could result in contamination incidents, products not meeting specification and/or being out of regulatory compliance.
- For end-users, labeling errors could result in incorrect applications leading to: safety issues, crop damage and / or environmental issues e.g. killing beneficial organisms like pollinators, etc.

It is important to be aware that regulatory authorities consider the product labels of end-user products binding legal documents, and supplying faulty labeled products is a significant non-compliance. The label must reflect accurately the information given in the registration documents and has to list all relevant local regulations local regulations.

For these reasons labeling, including relabeling and overlabeling form an essential part of Product Integrity management procedures and are subject to a set of guidelines.

7.1 Labeling during the manufacturing process

In Chapter 7, Manufacturing Practices, labeling is mentioned specifically in a number of the procedures listed. That section does not replace the information in Chapter 6, but will highlight some labeling requirements in more detail.

Depending on the equipment or packaging the following requirements apply.

7.1.1 Receipt of incoming goods

All incoming goods need to be properly identified to allow traceability during the manufacturing process.

Packaged goods (e.g. raw materials in drums, IBCs, boxes; packaging material; label rolls) need to be labeled accordingly. See chapter 6.1 for the necessary controls.

7.1.2 Production preparation

Ensure that all materials prepared for the production are in line with the recipe (Bill of Materials (BOM)), released and labeled accordingly.

Unlabeled material must never be used for manufacturing and must, without exceptions, be quarantined immediately. Additional electronic identification systems

(e.g. Barcode, RFID) could be applied. Label control needs to be in place to avoid mix ups (see case history 10.13).

7.1.3 Labeling of refillable containers

Irrespective whether the refillable [mobile] container is dedicated or non-dedicated, the labels should, besides the legal requirements, include as a minimum:

- Name of the material, and product code.
- Batch number.
- Production date.
- Quantity.

For rinsates the contaminant must always be identified.

For further information, and guidelines pertaining to mobile refillable containers please refer to Chapter 6.5.

7.1.4 Temporary labels

Temporary labels on containers (in case the final label cannot be applied) are allowable provided they contain, besides the legal requirements, at least:

- The product name and / or product code.
- The batch number.
- The quantity per packaging unit.

Temporary labels should always be attached to all the individual containers.

7.2 Relabeling, overlabeling

This section 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.

7.2.1 Relabeling and overlabeling at facilities not under direct management of the manufacturer

The scope of this section is the relabeling and overlabeling of end-user packs at distributors/dealers, i.e., at facilities not under direct management of the manufacturer. This process must not be carried out without approval of the Crop Protection Product manufacturer.

Out of scope of this section are:

- Relabeling of returnable packs which are to be refilled at the distributor / dealer site / sales outlet and it is required to obtain instructions from the manufacturer.
- Adding stickers with additional information. The owner of the product should define requirements for the use of stickers.

7.2.1.1 Definitions

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

- **Relabeling:**

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

- **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.

7.2.1.2 Legislation

The registration owner/manufacturer and the distributor/dealer need to ensure that all legal requirements pertaining to relabeling / overlabeling are implemented. The registration owner of the product will have to instruct the manufacturer/distributor/dealer on the legal requirements and verify that all criteria have been fulfilled.

Depending on the geography these legal requirements can vary. In some countries overlabeling is prohibited.

7.2.1.3 Justification

Reasons for the relabelling / overlabeling of Crop Protection Products include, but are not limited to:

- Regulatory reasons:
 - o Change of the registration number.
 - o Withdrawal of use in certain crops or indications.
 - o Reduced number of applications or longer re-entry and/or pre-harvest intervals.
 - o Widening of the application spectrum – registration for new crops/broader pest spectrum.
 - o Changes in hazard warning and caution statements.
 - o Changes to transport regulations.
- Commercial and Supply Chain reasons:
 - o Additional commercial opportunities not covered by the current label.
 - o Inventory near the end of shelf life.
 - o Need to shift stock due to demand into a region with a different language and a different registration with its specific registration number and label.
 - o Damaged, stained or faded labels.

7.2.1.4 Risks to be considered

Generally relabeling is the preferred option, rather than overlabeling.

The following risk factors need to be considered prior to a relabeling / overlabeling operation:

- *Traceability*. Besides adherence to the legal requirements, it must be ensured that the lot number on the replacement label is traceable to that on the original label e.g.:
 - o If the lot number is printed (e.g. ink jet) on the container that is to be over-labeled / 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.
 - o 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* on the container (e.g. UN-number) 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 relabeling / overlabeling area and secured while awaiting disposal, before introducing the replacement labels.
 - o To establish how many updated labels have been consumed for the relabeling / overlabeling campaign inventory control is a must.
 - o If the relabeling / overlabeling takes place at a facility not under direct control of the manufacturer, the label inventory needs to be controlled by the manufacturer.
 - o Counterfeiting. Strict label inventory control is essential to minimize the possibility of counterfeiting.

7.2.1.5 Risk Mitigation

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 relabeling / overlabeling e.g. enclosed with a chain linked fence. Only the product that is to be over-labeled or relabeled, together with the required replacement labels, should be stored in this area. Storage of other products and/or labels within the dedicated relabeling / overlabeling area should be prohibited.

- Only replacement labels supplied by the registration owner of the product can be used.
- A properly trained employee of the registration owner or designated representative should, whenever possible, be present during the entire relabeling / overlabeling 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 relabeling / overlabeling 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 secondary packaging, e.g. labels on outer cartons. This should be documented by the designated representative, 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 the area and secured.
- Surplus labels should be returned to the registration owner or, if agreed, destroyed.
- Damaged containers must never be relabeled / overlabeled.
- At the completion of the relabeling / overlabeling operation an inventory reconciliation of the labels should be made and documented.
- The batch numbers of all materials need to be recorded for traceability.

8. Cleaning of the production unit

Cleaning of the production unit is essential for effective contamination prevention. An optimized production sequence will mitigate the contamination risk and reduces waste.

A cleaning procedure must take into account the type of operation (synthesis, formulation or packaging of liquids or solids), the configuration of the production unit as well as the specific production sequence to ensure the content of the residual impurity is below the ACL. In this chapter, a number of recommended best practices will be discussed.

8.1 Production scheduling

An example of a production sequence planning can be found in sub-chapter 5.2.8: “Effect of the cleaning matrix on product scheduling / sequencing”.

The following manufacturing solutions should be considered:

- Moving a product with a low ACL e.g. highly active herbicides or bee-tox relevant insecticides, to a production unit with a more favorable product mix.
- Use of a dedicated line.
- Concentrate products with an acceptable ACL for uses in compatible crops in one production unit.

8.2 Generic cleaning procedures

Generic cleaning procedures for synthesis and formulation and packaging of liquid products are listed in table 5 and for formulation and packaging of solid products in table 6 respectively. The effectiveness of the cleaning process must always be ensured and documented (sub-chapter 6.2).

Written cleaning procedures must detail:

- The cleaning medium used (e.g. organic solvent, water, detergent, bleach, caustic soda, bentonite, kaolin, sand, silica, sugar, talc).
- The sequence in which the individual parts of the manufacturing line are cleaned (see case history 10.1).
- The addition of the cleaning medium into the equipment, e.g. by use of a rotating spray head or high pressure cleaner.
- The number of flushes (liquid or solid) applied and the minimum quantity of the cleaning medium per flush.
- The (partial) dismantling of the equipment and the manual cleaning of the individual parts with the cleaning medium (if needed).
- The description of sampling locations for flush samples and their cleaning requirements.

- The process of drying inner surfaces (if necessary) by either heating or purging the equipment with nitrogen or compressed air.
- The disposal / recycling procedure for the used cleaning medium.

8.3 Visual inspection

As one of the first steps of the cleaning process, a visual inspection is an essential, cost efficient and quick way to assess the effectiveness of a cleaning step. The cleaning step must be repeated if traces of residual material are visible in the equipment.

Mirrors and fiber-optic cameras are valuable tools for the inspection of dead spaces, e.g. interior of flanges, pipes etc. in the equipment.

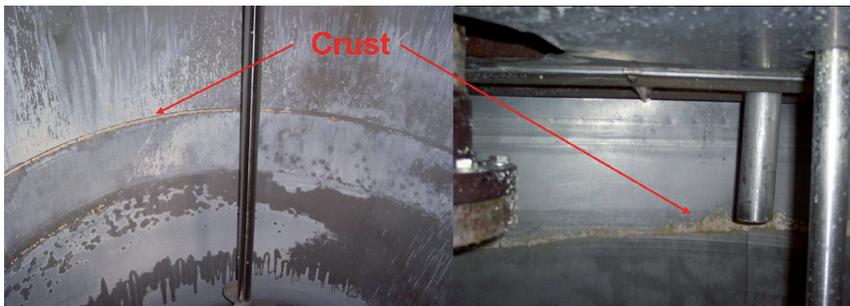


Figure 4: Visual inspection of the interior of a reactor revealing unwanted material is still present, and therefore, further cleaning is required.

Table 6:

		Recommended best practices for cleaning after changeovers in synthesis and formulation and packaging of liquid products		
		Blue = "must have" cleaning steps / Green = optional cleaning steps		
			Preceding and succeeding product contain the same AIs	Cleaning Level ≥ 100 ppm ^{1) 2)}
Cleaning steps		Synthesis	Formulation and packaging of liquids	
Complete drainage of installation				
Wet cleaning incl. dismantling of equipment for manual cleaning of critical parts (see 8.4)	←----- Cleaning Sequence -----→	Wet cleaning with the solvent of the preceding product or any other suitable solvent. Used cleaning medium to be disposed of or recycled		Used cleaning medium to be disposed of or recycled
Cleaning with detergent for chemical destruction of the residual impurity (if available)				
Wet cleaning with the solvent of the succeeding product or any other suitable solvent		Remove solvent incompatible with the subsequent product. Used cleaning medium to be disposed of or recycled	Remove solvent incompatible with the succeeding product. Used cleaning medium to be disposed of or recycled	Remove solvent incompatible with the succeeding product. Used cleaning medium to be disposed of or recycled
Visual inspection (see 8.3)				
RI Analysis (see 9.1)				
Release of cleaned equipment (see 7.2)				
Cleaning Costs (downtime, man hours)				
High				
Medium				
Low				
Waste Generation (Used cleaning agent)				
High				
Medium				
Low				

1) Listed cleaning levels given for guidance only. Cleaning procedures have to be verified to assess achievable cleaning level (see 8.7)

2) For cleaning level < 100 ppm apply multiple wet cleaning cycles. N/A: Not Applicable

Table 7:

Recommended best practices for cleaning after changeovers in formulation and packaging of solid products

Blue = "must have" cleaning steps

		Preceding and succeeding product contain the same AIs	Cleaning Level > 200 ppm and 1000ppm ¹⁾	Cleaning Level <200 ppm ¹⁾²⁾	Cleaning Level < 200 ppm ^{1) 2)}	Cleaning Level < 20 ppm ¹⁾
Cleaning Steps						
Complete drainage of installation	←----- Cleaning Sequence ----->					
Dry cleaning incl. dismantling of equipment for manual cleaning of critical parts		Recovered material to be recycled into preceding product	Recovered material to be recycled into preceding product	Recovered material to be recycled into preceding product	Recovered material to be recycled into preceding product	Recovered material to be recycled into preceding product
Wet cleaning (see 8.4)				Used cleaning medium to be disposed of		Used cleaning medium to be disposed of
Flush cleaning (see 8.5)					Flush partially disposed of and partially recycled	Flush partially disposed of and partially recycled
Dry cleaning incl. dismantling of equipment for manual cleaning of critical parts					Recovered material to be added to flush	Recovered material to be added to flush
Visual inspection (see 8.3)						
Residual Impurity analysis (see 9.1)		N/A				
Release of cleaned equipment (see 7.2)						
Cleaning Costs (downtime, man hours)						
High						
Medium						
Low						
Waste Generation						
High					Used cleaning agent & flush	
Medium			Used cleaning agent	Used flush		
Low						

1) Listed cleaning levels given for guidance only. Cleaning procedures have to be validated to assess achievable cleaning levels (see 8.7).

2) Either cleaning sequence can be applied. Choice of sequence depends on equipment design, drying possibility, waste disposal considerations.

N/A: Not Applicable

8.4 Wet Cleaning

Wet cleaning is typically applied to manufacturing lines for liquid products, but in many cases also forms one of the cleaning steps for manufacturing lines of solid products. Wet cleaning is not suitable for equipment where rinsate collection is difficult or even impossible (e.g. tableting machine, fluid bed dryer).



Figure 5: Interior of a mixer before and after wet cleaning using a rotating spray head, followed by drying

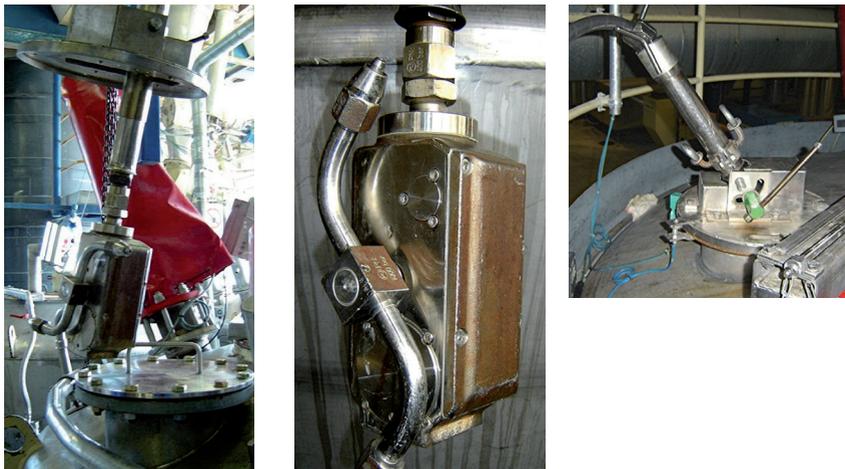


Figure 6: Mobile spray head for reactor and tank cleaning. To be installed on a free flange and connected to a high pressure water supply. The spray head is rotating vertically and horizontally around the pipe axis.



Figure 7: Workstation for the mechanical, manual cleaning (“brushing”) of small, dismantled equipment parts.



Figure 8: Cleaning of a reactor with a hot water, high pressure cleaner. Pipe cleaning nozzle spraying forward (1 jet) and backward (3 jets), pulling a flexible hose through a pipe, even vertically upwards. Note the personal protection equipment of the operator to protect him from splashes of the hot, high pressure water.

8.5 Dry Cleaning with solid, inert material

The solid flush material consists of inert material without active ingredient, either the pure carrier or a combination of carrier and surfactants. The solid flush needs to be suitable for the purpose considering the composition of the preceding and succeeding products.

Deposits of solids (powder, granules) are removed from the manufacturing line by opening or (partially) dismantling the equipment followed by brushing and/or vacuum cleaning the interior.



Figure 9: Vacuum cleaning granules from partially dismantled packaging equipment using a special industrial vacuum cleaner with HEPA filter to control dust.

8.6 Demonstrated cleanout capability

The demonstrated cleanout capability is ensured when the required cleaning level is consistently achieved after applying the written cleaning procedures. This is very important, especially in those cases where the release of the final product is based on the residual impurity (RI) content in the used cleaning agent (rinsate / flush material) and not directly in the succeeding product (see 9.1). To demonstrate the cleanout capability the following should be considered:

- Define critical parameters that impact the cleaning, e.g.
 - o Equipment design, dead spots;
 - o Physical chemical behavior (e.g. solubility of products in the cleaning medium);
 - o Process conditions (e.g. residence time, temperature, agitation, mass/volume flow).

- Select product changeovers (with different product combinations) requiring a low cleaning level and/or a product that is difficult to clean (e.g. a sticky active ingredient, a sticky formulation, a product containing a strongly colored AI or a dyestuff etc.).
- Adhere strictly to the cleaning procedure to ensure reproducibility of the process.
- Define the optimum number of cleaning cycles to achieve the requested cleaning level with maximum efficiency.
- Analyze the actual succeeding products for the RI of the previous product and compare the result with the RI concentration found in the used cleaning medium to confirm the effectiveness of the cleaning process. Repeat the same cleaning procedure on different change overs an appropriate number of times to demonstrate reproducibility.
- If any of the critical parameters change (see above) the cleaning capability needs to be re-evaluated. This has to go through the MOC process.
- Use of statistical techniques with an appropriate number of samples to review cleaning performance and adverse trends.

To ensure that each time the cleaning results are as expected it is necessary to follow exactly all the steps and conditions listed. This also means that the configuration of the equipment must remain the same as described in the cleaning procedure.

Train the operators to adhere strictly to the cleaning procedure. For example, changing the cleaning medium or its concentration, decreasing / increasing the cleaning medium quantity, shortening / increasing the time of the rinsing cycle, changing the temperature of the wet cleaning or omitting a manual cleaning step may cause the cleaning operation to fail (see case history 10.1).

8.7 Recycling of used cleaning medium

Recycling of used cleaning medium must be a balanced decision, based on a risk / benefit assessment considering the following items:

- Contamination risks due to mix up or improper labeling of stored used cleaning medium.
- Quality risks due to deterioration of the stored used cleaning medium (chemical or bacterial / fungal).
- Savings achievable by re-use of the used cleaning medium. Ecological benefit from waste reduction.

9. Analysis of Residual Impurities

Products manufactured must not be released before it is demonstrated that the concentration of residual impurities is below the ACL, the level at which undesirable biological, toxicological, ecological effects or regulatory issues could occur. This requires proven sampling procedures, analytical methods and analysis.

Implementing the sampling and the analytical procedures discussed in this chapter are of equal importance irrespective whether the product is manufactured in-house or at an External Manufacturer (EM).

In the case of outsourcing, it is the responsibility of the product owner to provide the ACL, analytical methods, or a SOP describing correct measurements of possible contaminants, and suggestions which analytical equipment is most suitable.

The EM and the succeeding client have to work together to design the trace analysis and sampling regime appropriate for the particular facility.

9.1 Residual Impurity analysis in the product vs. in the flushes or rinsates (solid or liquid)

An Acceptable Concentration Level (ACL), also referred to as Residual Impurity Level (RIL) is defined as the content of the residues of the active ingredient(s) of the previous product in the succeeding product which does not cause adverse effects, thus not in the flush material. Therefore, the RI is preferably analyzed in the succeeding product, but may be analyzed in the flush material.

It must be stressed that the determination of the residual impurity in the flush material does not automatically guarantee that the level of the residual impurity in the following product will always be below the agreed ACL, even if the cleaning level is achieved in the flush material.

9.2 Sampling

Each facility must have a documented sampling procedure that ensures representative sample or samples are taken from appropriate points in the process to ensure all the equipment has been cleaned to below the cleaning level and appropriate labeled. Examples of samples are:

- Product from the actual formulation or synthesis vessel before the start of packaging.
- The first bottle or bottles packaged on the line when analyzing the ACL in the succeeding product.
- The last rinsate after having flushed cleaning medium through the equipment.

Sampling bottles must not be re-used (see case history 10.11). Samples from the laboratory must not be returned to the process (including retain samples).

Analytical records including raw data must be retained for finished product and cleaning medium.

9.3 Development of analytical methods for residual impurities

An analytical method will need to be developed for the determination of the RI in the succeeding product and/or in the last flush material. It should also be taken into consideration that contamination can happen in the analytical lab itself. Therefore, appropriate systems need to be in place; such as always use clean glassware and where possible use disposable vials, test tubes, pipette tips, etc. Correct cleaning of analytical instruments is essential. Failure to do so could result in false positives (see case history 10.10).

Some examples of analytical principles for RI analysis are:

- To analyze water-based rinsing materials one of the methods available is to determine TOC (Total Organic carbon). Cleaning levels above 50 ppm can usually be analyzed with standard analytical technology (GC-FID, HPLC and UPLC).
- Cleaning levels below 50 ppm usually ask for more specific and sensitive analytical principles like HPLC-MS, GC-MS or GC-ECD technology.

Any analytical method must be validated; the validation should adequately address the following points at the relevant content:

- Specificity of the method - ability to separate the signal of the AI from other components.
- Recovery - ability to accurately quantify the amount of the AI (e.g. by spiking).
- Repeatability - ability to get the same result when analyzing the same sample a few times, different weights and different analysts.
- Linearity - ability to reliably quantify a component over a range of contents.

10 Incident Case Histories and Learning Experiences

The basis for successful Contamination Prevention is effective risk management. The “Guidelines”, which form the basis for this risk management, are primarily based on knowledge gained from actual incidents, rather than being developed only from theory. We would like to invite you to study these case histories and learning experiences of real incidents, because this will make it easier to understand the reasons for these “Guidelines”. Also, when you get involved in training staff on Contamination Prevention, presenting the case histories described in this booklet will help you to engage with your audience because we can all relate to real life experiences more easily than with dry theoretical issues.

10.1 Case History 1: Improper cleaning process

Several growers complained that their potted roses showed severe chlorotic (= very striking, white) spotting of the leaves after treatment with a soil herbicide for control of weeds. This greatly reduced the market value of the container plants and required extra labor for pruning the plants to improve their appearance.

The suspension concentrate (SC) soil herbicide was made in a flowables plant after a cereal herbicide containing a highly active broad leaf herbicide component, which caused as first symptom chlorosis of broad-leaved weeds.

Analysis of the soil herbicide for the active ingredient from the cereal herbicide showed that this was present at a level of 87 ppm. This is considerably above the No Observable Effect Level (NOEL) of the residual impurity on roses.

The root cause investigation showed:

- The equipment was cleaned by two different shifts. Normally only one single shift would clean the installation. The written cleaning procedure was ignored, and the equipment was cleaned in the wrong order.
- Rather than cleaning the hopper first as prescribed, the first shift decided to clean the formulation vessels and the bead mills. A sample of the last rinsate (representative for the cleaning level of the vessels and bead mills) was collected and the analysis showed that the concentration of the residual impurity was below the required ACL.
- The second shift had to clean the hopper. After dry cleaning, the hopper was hosed down with water and left to dry till next morning. The rinsate was collected in the first formulation vessel in which the slurry of the next product (SC) would be prepared. The cleaning guidelines were ignored and the slurry vessel was not drained.
- The next shift was not told that the slurry vessel contained contaminated rinsate and the formulation process of the next product was started.

This incident resulted in seven expensive claims from rose growers plus a drawn-out reconditioning campaign.

What can be learned from this case history?

- Have a written cleaning procedure with a check list for equipment cleaning outlining every single step of the cleaning procedure and the order in which these have to be carried out. The written procedure must be tested to confirm the cleaning effectiveness.
- Assure that each and every step has been entered on the batch card with the initials of the operator carrying out each particular step and the time it was carried out. Missed steps must be investigated.
- Take and analyze a sufficient number of samples of the rinsate(s) and/or of the next product to confirm the cleaning has been effective.

10.2 Case History 2: Incorrect ACL

On thousands of hectares, soybeans failed to germinate. All the soybeans had been coated with a fungicide seed dressing to protect against soil borne diseases. A fungicide formulation plant received rush orders for two soybean fungicides: a foliar fungicide belonging to the azole family and a seed treatment fungicide.

The seed treatment fungicide contains a strong dye, making the cleaning process difficult and very time consuming (the dye tends to stick to the walls of the equipment). Traces of the dye, when not fully removed from the equipment, will color the almost white formulation of the foliar fungicide, thus creating a quality issue. Therefore the formulation of the foliar fungicide was scheduled before the formulation of the seed treatment product.

The assumption was made that - since a fungicide was following another fungicide on the line - the EPA approved ACL of < 1000 ppm would be applicable.

The root cause investigation showed:

- After cleaning, following the production run of the foliar fungicide, the concentration of the residual impurity (i.e. the concentration of the active ingredient of the foliar fungicide) could not be determined due to a breakdown of the analytical equipment. However, the production of the seed treatment fungicide was started immediately without waiting for the analytical instruments to be repaired.
- Since these were rush orders, it had been decided, without prior management approval, to minimize the number of cleaning cycles, because the products were both applied on soybeans.
- The entire inventory of seed treatment fungicide was quarantined when analysis revealed that the level of the azole contaminant (from the previous product) in the actual seed treatment fungicide was more than 6000 ppm.

- A quick trial at a local field station showed that the safe level of the azole as seed treatment on soybean was 2000 ppm.
- Based on market pressure, the product was reconditioned to achieve an azole level of 2000 ppm and delivered to the farmers.
- Subsequent research in a greenhouse showed that the actual safe level of this azole fungicide in soybean seed treatment fungicides to be a factor 10 lower (200 ppm).

Failure of the treated soybeans to germinate resulted in a series of expensive claims.

What can be learned from this case history?

- Never try to make shortcuts in the cleaning procedures, no matter how much business pressure. You risk a contamination incident, which can easily create more business disruption.
- Even if an ACL of 2000 ppm would have been safe, never use an ACL above 1000 ppm. This will not only infringes the levels allowed by EPA (<1000 ppm, EPA Pesticide Regulation Notice 96-8, Appendix C), but also the regulatory, legally binding limit for a non-listed extraneous ingredient of < 0.1 % w/w or <1000 ppm.
- The default EPA ACL of < 1000 ppm when switching from one fungicide to another fungicide is not (always) applicable for changeovers from foliar fungicides to seed treatment fungicides or insecticides (Chapter 6). This can be especially dangerous when the preceding fungicide in the equipment belongs to the azole family, which often displays a growth regulator effect (e.g. inhibition of germination) at certain concentrations.

10.3 Case History 3: Incorrect cleaning procedure

In a formulation plant, an herbicide emulsion concentrate (EC) had a pronounced yellow color, while typically the product had a golden light brown color. For this reason the product was out-of-specification.

Chemical analysis showed contamination with an active ingredient (AI) that was formulated five weeks earlier and has an intense yellow color.

The root cause investigation showed:

- Both AIs are solids at room temperature and need to be melted before they can be formulated in ECs.
- The molten AIs are formulated in a formulation vessel heated to 70-80°C. This vessel is also used for formulating other liquid herbicide formulations.
- Only heated formulated products have to pass through a heat exchanger before going to the header tank of the filling line. However, all other products will go straight to the header tank and do not pass through the loop with the heat exchanger.
- After formulating the yellow product the valves to the loop were closed and only the direct piping was cleaned.
- When the next product with a high melting point was formulated five weeks later the heat exchanger loop was opened.
- Since the heat exchanger had not been cleaned a residual film had built up forming a yellow deposit on the walls, which was dissolved slowly when the next product passed through the loop.

The first batch (20 000 l) had to be discarded in its entirety.

What can be learned from this case history?

- Cleaning of the lines should be carried out as soon as possible after finishing the production run using the exact configuration used in the process. This process needs to be described very clearly in the cleaning procedure.
- Never allow the film adhering to the inner walls to dry up and form a deposit that could contaminate the next product.

10.4 Case History 4: Insufficient awareness of ecotoxicological risks

In greenhouses parasitic wasps were successfully used to control aphids in cucumbers. However, after applications of a new fungicide for control of mildew, a widespread mass kill of these biological control agents was observed. This was totally unexpected because the fungicide was known to be virtually free of side-effects on non-target arthropods.

Samples were collected at a number of growers. All samples showed the same contents of residual amounts of a very potent insecticide. The growers were requested to return all packages of the fungicide and use alternative products till the cause of the incident had been discovered and replacement material was available.

The root cause investigation showed:

- The product packaged before the fungicide was the insecticide in question, which was detected in this fungicide at a content of 600 ppm.
- For determination of the ACL the US EPA Pesticide Regulation (PR) Notice 96-8 served as the guideline and the following value was used: PRN 96-8 allows < 1000 ppm as ACL for a change-over from an insecticide in a fungicide.
- A carefully managed, well documented cleaning procedure had been carried out.

What can be learned from this case history?

- Although the manufacturer followed the legal requirements for ACLs, in some cases remaining insecticide residues can cause adverse effects, like a massive kill of parasitic wasps.
- The values given in US EPA Pesticide Regulation (PR) Notice 96-8 give the legal maximum content that may not be exceeded; however, lower concentrations are allowed and can be determined by the manufacturers.
- When switching from any insecticide to other fungicides, acaricides, nematicides, but also to other insecticides, a cautious approach is necessary. (See Chapter 6.3).
- An ACL based on biological properties of the insecticide should be calculated rather than relying only on the values given in PRN 96-8.

10.5 Case History 5: Failure to report error in product transfer

Nowadays, to ensure that complete pollination takes place in greenhouse grown paprikas, aubergines (= eggplant), tomatoes and peppers, growers introduce bumblebees and other beneficial insects in their greenhouses (Integrated Pest Management). After applications of an insecticide with very low bee toxicity to control caterpillars, a very high mortality of the bumblebees and other beneficial arthropods was observed in greenhouses. In view of very favorable experiences with this insecticide and the simultaneous introduction of the pollinators in the past, this situation took the growers by surprise. The government advisory service was asked to determine the reason behind this incident.

Samples were collected from original unopened containers with the same batch number as product applied by the affected growers. All samples were contaminated with an insecticidal AI with a known very high toxicity to bees; as a consequence the beneficial insects were killed. This insecticide is not registered on any of the treated crops.

This observation was reported to authorities dealing with food safety in the country where the incidents happened and also in the surrounding countries. This triggered the question from the authorities which systems the industry has in place to prevent contamination incidents.

The root cause investigation showed:

- During the production process, an operator wrongly connected and transferred a small quantity of material from the formulation vessel containing a formulation of the contaminating AI into the vessel already filled with the insecticide specific for control of caterpillars. (Quality control including analysis for potential contamination had already been carried out before the incident occurred and the material had been released ready to be packed).
- The operator did not report this error expecting that nobody would notice this.

The costs associated with this incident were very high. Thousands of liters of formulated product had to be written off, while disposal was costly. The product already delivered had to be recalled and incinerated.

Compensation for decreases in yield and quality was paid, while the indemnification of the growers was 20 times higher than the costs of the product replacement and its disposal.

What can be learned from this case history?

- Valves of formulation vessels must be kept lock closed. When a connection needs to be established between vessels, it must be double checked and authorized prior to any product transfer.
- It is very important to have only material pertinent to the current production present in the production area. This greatly reduces the chance of having mix-ups.

- Even if it may be embarrassing to report errors they must be reported immediately. Establish a work environment in which operators feel comfortable to report (human) errors. This will allow that the contaminated material can be quarantined and stay within the perimeters of the manufacturing site, greatly reducing the economic impact of such a contamination.
- Incidents can attract a lot of unwanted attention from authorities and the press which can be very damaging to the reputation not only of the product owner but the industry as a whole.

10.6 Case History 6: Failure to determine identity of one of the raw materials

A herbicide active ingredient was synthesized by esterification of its acid with n-hexanol to form the n-hexyl ester. Prior to releasing the AI for formulation, the active ingredient batch was sampled and sent to the QC laboratory. The gas chromatogram revealed besides the n-hexyl ester an unknown peak that was identified as the corresponding n-propyl ester of the herbicide active ingredient.

The root cause investigation showed:

- The alcohol n-hexanol was supplied by an EM and delivered in a road tanker.
- Quality Control (QC) for incoming goods released the alcohol shipment and it was pumped into a 40000 liters dedicated bulk tank still containing approximately 20000 liters of n-hexanol.
- The alcohol was pumped from the bulk tank through dedicated piping to the synthesis plant.
- Samples from the dedicated n-hexanol bulk tank showed that the tank contained a blend of n-hexanol and n-propanol.
- In this facility, the standard quality check for bulk products in the raw materials acceptance procedure is a check of the Certificate of Analysis (CoA) submitted by the alcohol producer with each shipment. Since the CoA gave the expected information the material was released.

Since globally, only the n-hexyl ester of this herbicide has been registered, the active ingredient was not in regulatory compliance and had to be disposed of (incinerated).

What can be learned from this case history?

- Although checking the CoA of incoming raw materials without additional analysis is cost-effective, it creates a far bigger dependence on the reliability of the quality systems of the supplier, while an error made during loading of the shipment at the supplier cannot be detected before the raw material has been processed. Therefore, an assessment of the facility of the supplier with a strong emphasis on the correct Contamination Prevention and loading procedures is highly recommended.
- Consider simple lab checks such as refractive index, color, pH, viscosity or other rapid identity tests as QC check for incoming goods.
- In synthesis where a mix-up of raw materials is not only a contamination, but also a safety hazard, proper identification of the incoming goods is a “must”.

10.7 Case History 7: Improper use and labeling of interchangeable parts

A large grower gained an unexpected contract to grow 10 ha of a special, high value flower bulb. He placed a rush order for a special “bulb treatment” fungicide giving the manufacturer less than a week before the planting date to deliver the product. The treated crop failed completely.

The root cause investigation showed:

- The product was formulated in a dedicated fungicide formulation vessel. A flexi hose was used to transfer material to the header tank of the fungicide filling line, using a dedicated [fungicide] pump. The operator could not find the flexi hose for fungicides in its usual place, so he used a flexi hose he discovered in the next room (the dedicated herbicide filling area).
- This flexi hose had last been used to transfer a herbicide EC formulation and would be used again for the same purpose the next morning. It had not been cleaned and contained a residual amount of the herbicide. The flexi hose had no label with information on its cleaning status nor was there a label giving the name of the herbicide.
- The residual amount of the herbicide contaminated the fungicide and the flower bulb crop failed completely.

The claim was settled after a long and expensive court case, while the grower switched to a different supplier for all his crop protection products.

What can be learned from this case history?

- Whenever possible avoid the use of interchangeable parts, such as flexi hoses. Fixed, dedicated piping is always the safest solution.
- As best practice, interchangeable parts should be dedicated to a product and a production line during the whole manufacturing campaign and their use (the product or the line) clearly labeled. At the moment an interchangeable part is disconnected from the line, it must be drained completely and cleaned immediately irrespective of whether it is used for another product or put into storage.
- Ensure by appropriate labeling that the history of the interchangeable parts can be traced even if they are dedicated to one class of products; what was the last product, how was it cleaned and to which level?

10.8 Case History 8: Shared utilities of common lines for separate installations

A liquid corn herbicide was formulated, analyzed and released by the site quality control laboratory for packaging. The plant started to package the product. After packaging 20 000 liters, one of the operators noticed the product had an unusual color. They stopped packaging and re-sampled the tank.

The root cause investigation showed:

- The subsequent analysis showed that an unexpected active ingredient was present at a concentration above the residual impurity level.
- Checks showed that the first 15 000 liters were within specification.
- This formulation and packaging line shared a nitrogen purge line with another installation. During the packaging, somebody had transferred a batch of a different product to the other installation. The nitrogen purge line was open and siphoned some product into the corn herbicide tank.

The quick reaction of the operator prevented further material from becoming contaminated. Catching this error in time, before any product had left the manufacturing site, helped to limit the costs and prevent any undesirable publicity.

What can be learned from this case history?

- Avoid interconnection of separate installations via purge lines, ventilation lines or utility piping (steam, compressed air, etc.).
- Common lines and installations must have effective backflow prevention.
- Operator training and constant awareness are major factors in preventing incidents.
- Always report anything out of the usual immediately (color, smell, consistency etc.).

10.9 Case History 9: Inadequate separation of two formulation units

Two formulation units were operating simultaneously in different rooms separated by a solid wall. One unit was formulating an insecticide, the other one a solid herbicide. Customers complained of crop damage when using the insecticide. Subsequent analytical testing showed low-level contamination of the insecticide product with the active ingredient of the herbicide formulation.

The root cause investigation showed:

- The wall between the two rooms in the plant was in fact not completely sealed, as there were a few small holes in it, primarily to accommodate piping.
- An oversized exhaust blower was installed in the insecticide unit to improve personal protection from the insecticide dust. This caused the insecticide room to be at a lower atmospheric pressure than the herbicide room, thereby sucking herbicide dust through the holes into the insecticide dust collector. Recycling dust from the collector transferred the herbicide into the insecticide.

This resulted in lots of concern for product quality, quarantined finished product, resampling, and retesting while in the meantime no deliveries of product to customers could take place.

What can be learned from this case history?

- Contamination can happen between two products that are running simultaneously even if separated by a “solid” wall going all the way to the ceiling.
- Do not make design changes, e.g. additional pipe work, increased blowers, additional doors or windows, without understanding all the implications, including contamination risk.
- Do not rely on a wall to be a fool-proof barrier; it is hard to seal all the holes.
- Increased incompatibility of products requires more separation between production areas and may even require different buildings or even segregation by a long distance depending on e.g. the prevailing wind direction. An insecticide (or other non-herbicides) and a normal rate herbicide would require at least separate rooms with a solid, air-tight wall and separate air handling systems. Depending on the outcome of the risk assessment an insecticide and a highly active herbicide could require separate buildings.
- The lower the Residual Impurity Levels the higher are the requirements for separation or even segregation is necessary. For liquids segregation is highly recommended for ACLs below 1 ppm (below 100 ppm for solids).

10.10 Case History 10: Contaminated laboratory equipment

Residual amounts of a highly active herbicide were found in an insecticide formulation. In repeat sampling and analysis, residual amounts of this herbicide showed up in every sample that was analyzed. The values found for this herbicide were all consistently in the low ppm range (< 5 ppm), which in this case meant well above the ACL of 1 ppm. The insecticide could not be released for it was almost certain that with the residual level of the herbicide phytotoxicity would occur on the crops on which the insecticide was registered.

The root cause investigation showed:

- The active ingredients of the insecticide and the highly active herbicide are synthesized in separate buildings more than 3 km apart.
- Formulation of herbicides and non-herbicides always takes place in completely separate units on this site.
- The LC/MS used to analyze herbicide residues in this insecticide was used in the past for analysis of process impurities in the herbicide in question.

This last finding triggered very intensive cleaning of the LC/MS as well as replacement of a number of critical parts in the instrument. The instrument was unavailable for more than a week.

This meant that the release of a number of products was on hold till it could be demonstrated conclusively that the data were reliable. The insecticide initially suspected of being contaminated had been in specification all the time.

What can be learned from this case history?

- When conducting a root cause analysis, do not automatically exclude the analytical laboratory from the investigation.
- The analytical data indicating that contamination occurred may actually be a “false positive”.

10.11 Case History 11: Improper sample recycling

More than 8000 young citrus trees died following application of an insecticide. One single sales package (a drum) of the insecticide was found to contain high levels of a low application rate herbicide. All other drums were also tested analytically, but did not show any traces of the herbicide.

The root cause investigation showed:

- Herbicide production took place in a building separated completely from the insecticide / fungicide production, while contamination of that particular insecticide batch was not detected in the retained sample.
- As standard practice, irrespective from the production line, 2 – 3 kg samples of all products were collected in identical white buckets and brought to the Quality Control (QC) laboratory. After QC analysis, all samples were returned to the production line to be recycled.
- The labeling of the white buckets was not consistent and showed a lot of variation, while after analysis, the laboratory placed both herbicide and insecticide buckets in the same area for collection and return to production lines.
- By mistake a bucket of the low application rate herbicide was returned to the insecticide drum filling and added to the contents of one drum.

The manufacturer had to indemnify the growers of the irreversibly damaged trees, moreover this incident caused a serious dent in the manufacturer's reputation.

What can be learned from this case history?

- Containers holding any product must always be clearly and consistently labeled.
- Site labeling policy must be defined, understood and applied consistently by all.
- Release samples must not be added back to the process.
- Therefore, as a rule of thumb, avoid recycling laboratory or retained samples whenever possible. Take small but representative samples to reduce the quantity to be disposed of.
- Review (risk assess) existing recycle processes to ensure they are appropriate and controlled adequately.
- Encourage plant operators to be vigilant and check labels before emptying contents into vessels, containers, etc. Use different containers/ labels (size, color) for incompatible materials (herbicides, fungicides/ insecticides).

10.12 Case History 12: Missing labels on the AI drums

A contract manufacturer had to formulate simultaneously an insecticide and an herbicide EC. Both AIs were solid at room temperature and had to be melted in a hot water bath, which could hold ten 200 L drums at one time. On the site there was a nearly 100% segregation of herbicides and non-herbicides, however, the hot water bath was the only area on the site that was used for both herbicides and non-herbicides.

The root cause investigation showed:

- Five drums of each AI were placed overnight in the water bath to allow formulation of both the insecticide and herbicide next morning.
- The forklift truck operator noticed that the labels had fallen off, but thought he remembered exactly where he placed the drums with the insecticidal AI and with the herbicidal AI.
- The drums were delivered at the staging stations and emptied immediately into the formulation vessel.
- The QC lab noticed that the insecticide was contaminated with the herbicide and vice versa.

Reprocessing was impossible and both formulations had to be discarded resulting in loss of active ingredient, extra labor and incineration costs.

What can be learned from this case history?

- Melt only the drums of one AI at the time if one water bath (or steam cabinet) is available on the site and make it dedicated to one particular production run.
- Make sure each drum is marked permanently before placing in the water bath.
- If a label has fallen off and the drum becomes “anonymous”, quarantine that drum, sample the drum and do not release till QC has identified its contents.
- Never deliver unlabeled drums to the staging area.
- Never charge a reactor without verification of the label on the drum or big bag.

10.13 Case History 13: Improper labeling

A packaging plant had to fill 1 liter bottles with two different EC formulations of the same herbicidal AI with 90 and 360 g AI/l, respectively. The day shift bottled the 90 g AI/l formulation, while the night shift was responsible for 360 g AI/l product. The bottles were identical in color and shape. One of the dealers noticed that the labels on the boxes and those on the bottles did not match and alerted the local affiliate immediately.

The root cause investigation showed:

- One of operators on the night shift was ill. To help things run faster for the night shift, the day team collected a spool of the 360 g AI/l product from the ware house in advance and placed this next to the labeler.
- This spool was mistakenly put on the labeler and 500 bottles of the 90 g AI/l product ended up with labels for the product with the four-fold higher concentration.
- This error was not spotted: no difference in bottles, the trademark and label color was the same.
- The labeled product was put in pre-printed cardboard boxes with the correct outer-box label (90 g AI/l) and shipped to dealers in a foreign country.

A country-wide recall action was initiated; nearly all the faulty product could be retrieved, shipped back to the manufacturing site, decanted, assayed and re-labeled properly. Incidents of this nature always tend to cause undesirable unrest in the market.

What can be learned from this case history?

- Only labels and cardboard boxes of the product that is currently in production should be allowed on the factory floor.
- A wider residue study was started on the treated crops and all crops with non-allowable residue concentrations had to be destroyed. The formulation manufacturer was fined for selling products that were non-compliant.

10.14 Case History 14: Third party purchased AI

For the production of one of its proprietary insecticidal formulations, an AI was purchased from a third party manufacturer; also the registration holder of this AI. A Letter of Access from the third party supplier was in place to allow registration of its customers' formulations, however no information exchange on the AI specification was agreed.

A government food inspector collected a sample of produce treated with the formulation containing the purchased AI; in a residue analysis a residue of an insecticide AI was identified that was not registered on the crop in question.

The root cause investigation showed:

- The third party supplier manufactured the AI on a production line shared with a chemically closely related insecticidal product, however, without informing the customers.
- In several markets this second insecticidal AI was not registered on the same crops as the product registered by the customer. Random sampling by government agencies of crops showed that in a number of cases the residual content of the non-registered insecticide exceeded allowed levels.
- A wider residue study was started on the treated crops and all crops with non-allowable residue concentrations had to be destroyed. The formulation manufacturer was fined for selling products that were non-compliant.
- Retained samples of the purchased AI have been checked and showed the content of the residual impurity of the non-registered AI was considerably higher than allowed. Several batches of the technical grade AI were out of compliance.

What can be learned from this case history?

- From a legal point of view, any AI has its own registered specification including limits for by-products.
- The supplier must provide a list of all potential impurities to allow the formulator to carry out analytical verification. In case the supplier has only provided a Letter of Access, he is solely accountable for meeting all parameters listed in the specification.
- When setting up a purchasing agreement for technical grade active ingredients, it is essential that the legal parameters regarding residual impurities in the purchased product are clearly defined and consistently meet the legal requirement applicable in the territories in which the products formulated from these AIs will be registered.
- The supplier must agree to meet these requirements.
- To allow a proper risk assessment it is desirable that the supplier can show which contamination prevention systems are in place.

10.15 Case History 15: Incorrect recycling

A crop protection chemicals company outsourced the formulation and packaging of a novel granular fungicide formulation in 250 g water soluble bags. The formulation of the extruded granules was straw colored.

Half-way through the first day of the packaging run, one of the operators at the EM noticed that the formulation also contained strange dark brown granules. The packaging run was stopped immediately.

The root cause investigation showed:

- The fully enclosed packaging unit was from the beginning dedicated to packaging non-herbicidal products. The production records confirmed this.
- The unit in which the granules of the novel formulation were formulated had been cleaned following the guidelines for change-overs prior to production. The cleaning level of the formulation unit achieved for the preceding AI was < 25 ppm.
- The brown granules were isolated and contained the AI of the insecticide formulation that was packaged immediately prior to the novel formulation.
- The content of the contaminating insecticidal AI in the sampled fungicide bags fluctuated from 25 to 1,200 ppm.
- The packaging unit was dust free and was vacuumed as soon as any loose granules were detected, e.g. from a broken water soluble bag.
- The vacuum cleaner was dedicated to this particular packaging cubicle and free from outside dust.
- When the reservoir of the vacuum cleaner was full, the collected material was returned to the hopper, rather than being disposed of as industrial waste.
- The previous customer of the EM had approved this recycling procedure. The previous production run had lasted more than two months. Therefore the operators assumed that this was a routine industry-wide practice.

After obtaining written approval of the client, a time consuming reconditioning campaign was carried out successfully, but the delivery of this product and the following products was delayed. Since the incident was discovered on the manufacturing site before shipping product out, the financial damage could be limited.

What can be learned from this case history?

- There is an inherent risk associated with recycling material.
- In agreements / contracts, the client and the EM need to agree in writing whether recycling is permitted and which procedures should be in place.
- The succeeding client must be informed whether recycling was applied during manufacturing the previous product and which procedure was used.
- In the change-over procedure, it must be stipulated that vacuum cleaners are completely dust free (also internally) before they can be used in the area where the next product is manufactured.

10.16 Case History 16: Faulty management of returned co-packs

A number of apple growers observed that within 24 hours after application of a fungicide, the leaves looked like they had been treated with an herbicide. These symptoms occurred only if the fungicide had been tank mixed with an adjuvant supplied by the same fungicide manufacturer.

Although the symptoms disappeared with time, the initial phytotoxicity was reported to relevant authorities. They conducted extensive residue analysis of the ripe fruits looking for non-listed AIs and blocked their sales awaiting the results. The apples contained < 10 ppb of the phenoxy herbicide (see the root cause investigation below). Sales were now allowed, but there was an unavoidable delay in bringing the perishable produce to the market. This event caused a dent in the confidence in the manufacturer.

The root cause investigation showed:

- The manufacturer markets a co-pack²¹ for broad spectrum weed control in cereals. This co-pack consists of three separate containers (1. a normal rate herbicide, 2. a low application rate herbicide, and 3. an adjuvant) packaged in an outer box with a label (+ registration number) describing how to apply this co-pack.
- After the finish of the application season all unsold co-packs were recalled for one of the herbicide formulations was approaching the end of its shelf-life and would require reconditioning.
- All returned co-packs were opened, the containers were removed and sorted in their separate groups.
- Rather than storing the containers till the next production run of the co-pack, the adjuvant containers were marketed immediately for use in a top fruit fungicide.
- The ACLs of possible residues in the adjuvant sold in the co-pack were based on NOELs on the crops on which the co-pack would be applied.
- NOELs of other crops on which the adjuvant could be applied were not taken into consideration in the ACL calculations.
- The adjuvant was formulated and packaged in a dedicated herbicide unit.
- The previous product on the herbicide line was a phenoxy herbicide. The adjuvant contained < 100 ppm phenoxy residue.

²¹ All components of a co-pack constitute together the final registered product and to achieve the label claim, every container in the co-pack needs to be added to the spray tank. The individual components may sometimes also be registered on their own often for other indications.

Co-packs are presented in many different forms, e.g., the containers may also be packaged as one unit with the containers "fused" together. This makes it difficult to standardize industry guidelines and each manufacturer is advised to develop their own rules on prevention of labeling incidents and stock control of returned co-packs.

What can be learned from this case history?

- When co-packs are returned to the plant and the outer pack is dismantled, it is necessary to quarantine the individual components and store those separately. These should be used the next time the co-pack is manufactured after verification of the shelf life.
- To avoid possible chemical contamination of adjuvants it is recommended to only formulate and package adjuvants and surfactants in a dedicated non-herbicide unit.

Glossary

AI	Active Ingredient
ACL	Acceptable Contamination Level. The content (in ppm) of residues of the previous AI(s) below which it will not cause any adverse biological, toxicological, or ecological effects, or regulatory issues in the succeeding product. Synonyms: ARIL, RIL, TCL, TSLC
Acaricide	Any product used to control mites (Acaricides are also often referred to as miticides).
Analytical capability	A combination of available analytical equipment, methodology and know-how, demonstrated by successful analysis of residual impurities.
ARIL	Acceptable Residual Impurity Level, synonym of ACL.
Batch Record / Batch Card / Log Sheet	Documentation that provides the history of a batch from the raw materials and quantities used, manufacturing steps performed and in-process and final testing. Batch records require operator identification.
Beads	Beads of glass or zirconium oxide used in bead mills (ball mills).
Big Bag	Big bag is the commonly used term for a FIBC (Flexible Intermediate Bulk Container). Also called bulk bag. Used for storing and transporting dry bulk goods like powders, granules, pellets etc.
BOM	Bill of materials. List of all materials and quantities required for to manufacture a defined amount of product.
Changeover	Process of converting a line or machine from running one product to the next product.
Certificate of Analysis (CoA)	Report of analytical results of a production batch.
Chemical Raw Materials	All chemical substances in formulations that are not listed as AIs.

Clean-in-place (CIP)	Technology for cleaning production units without dismantling e.g. by built-in nozzles.
Cleaning capability	A combination of procedures, know-how and appropriate analytical instrumentation to achieve reliably a residual impurity level equal or below a given ACL.
Cleaning matrix	A two dimensional table showing the required ACLs (in ppm) for changeovers; the headers of the rows and columns show all potential products of production unit as preceding (e.g. in the columns) and succeeding product (e.g. in the rows).
Cleaning methodology	A combination of methods to clean a product unit including the sequence of the single cleaning steps, e.g. rinsing all parts top down with water + detergent, dismantling and manual cleaning, exchange of dedicated parts like pumps and milling beads and visual inspection.
Cleaning procedure	Cleaning methodology designed to achieve the required ACL plus analytical control confirming success, organization of the release of the unit and documentation of all steps.
Client	Company contracting the production of a product (e.g. AIs, raw materials, formulations) with an external manufacturer (EM).
Compatible / Incompatible	<p>Terms used in warehousing of Crop Protection Products:</p> <ul style="list-style-type: none"> • Joint storage of Compatible materials does not present an unacceptable risk from a contamination prevention point of view (e.g. normal rate herbicides for cereals). • Joint storage of Incompatible materials presents an unacceptable risk from a contamination prevention point of view (e.g. an insecticide with high bee toxicity and a mildew fungicide).
Configuration of a production unit	The configuration specifies which parts of a production unit are used for a defined process.

Contamination of a product	The undesired introduction of a component, not listed in the product specification, at levels which will compromise the safety and/or efficacy and/or causes the product not to meet regulatory requirements
Contamination Prevention	Any measure, be it organizational or technical, to prevent the occurrence of contamination.
Contamination Risk Assessment	Assessment of any factor with the potential to contribute to contamination risks.
CropLife International	Global Federation of Multinational, Research-based Crop Protection Companies and its regional industry associations.
Dead space	Space inside a production unit which may block product not subject to the normal flow of material (product and/or cleaning medium) through the unit; should be avoided through the design/construction
Defoliant	Any product used to cause the leaves to drop off prior to the harvest, e.g. in cotton.
Desiccant	Any product for artificially accelerating the drying of plant tissues, e.g. prior to harvesting potatoes.
Design	The arrangement of the various parts, equipment and inter-linkages of a production unit.
Documentation	Written and/or electronic information of procedures, cleaning records, batch cards, analytical results and retained samples etc. There are guidelines on the length of time documentation needs to be archived.
Dry formulation	Synonym for a solid formulation.
EC	Emulsifiable Concentrate (a solvent based formulation).
ED₁₀₋ (Effective dose of 10 %)	The dose of an AI required to cause a biological effect of 10 % after a specified test duration, e.g. a 10% stem shortening three weeks after application.
EPA	Environmental Protection Agency (USA).
EPP0 (OEPP)	European and Mediterranean Plant Protection Organisation (OEPP is the French abbreviation).

External Manufacturer (EM)	A company manufacturing products for crop protection companies on a contract basis. The clients are the registration holders. Synonymous with: contract manufacturer, contractor, toll manufacturer, “toller”
Extrusion	A formulation process for granules. These are formed by forcing the wetted formulation through screens with small diameter holes followed by a drying process.
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act (US EPA Federal Regulation Pesticide Statutes.
Flexi hose	Flexible hose. Used for transfer of materials when no fixed piping is installed; requires special care in Contamination Prevention.
Flowable	Liquid formulation type, synonym of SC. See Suspension Concentrate.
Fluidized bed	A method for the formulation and/or drying of granules.
Formulant	Any substance other than active ingredients intentionally incorporated in a formulation.
Formulation	A preparation of AI(s), and the “inert” chemicals (+ formulants) to form a stable product allowing the application of the AI(s) either directly or after dilution.
FS	Flowable formulation used for seed treatments.
Fungicide	Any product used to control pathogenic fungi (Control of plant diseases).
Granulation	A process of forming granules from a liquid preparation. Various techniques can be used, e.g. extrusion granulation, fluidized bed granulation.
HEPA filter	High Efficiency Particulate Air Filter. Generic term for highly efficient filters for airborne particles $\geq 0.3 \mu\text{m}$ (micron, micro meter). Based on particle count, the efficiency of HEPA filters for particles with above mentioned size is 99.7 %.
Herbicide	Any product used to control the growth of plants, esp. used to control weeds.

Highly Active Herbicide (HAH)	A sub-class of the US EPA category “Low Application Rate Herbicides (LARH)”. The difference is that HAHs have application rates of < 50 g AI/ha and typically low NOELs of < 10 mg/ha on non-target crops. Some examples: sulfonylureas, imidazolinones, triazolopyrimidine sulphonanilides, arylpicolinates, however possibly, other herbicides could also fall in this sub-class. HAHs often require low to very low ACLs and very intensive equipment cleaning at change-overs.
Housekeeping	Ensure consistent care, order, hygiene and maintenance of the facilities and processes.
IBC	Intermediate Bulk Container; movable container for liquids and solids.
Information Exchange	Exchange of contamination prevention-relevant information (e.g. phytotoxicity, NOELs, analytical methods) between CropLife International member companies and/or their EMs and/or their suppliers.
Insecticide	Any product used to control insects
Integrated Pest Management (IPM)	A pest control management system integrating the use of crop protection products and biological control systems. It aims to reduce or minimize risks to human health and the environment. IPM emphasizes the growth of a healthy crop with the least possible disruption to agro-ecosystems and encourages natural pest control mechanisms. See also the FAO Code of Conduct. ²²
ISO, Isotainer, ISO tank (container)	International Standards Organization standardized container for liquids which can be transported by road, rail and/or ship. Typical volumes between 17,500 and 32,000 liters.
Letter of Access (LoA)	Document provided by supplier to third parties co-marketing products with the supplier’s AI. Document is required for registration submission by a third party.

²² http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Code/CODE_2014Sep_ENG.pdf

LD₅₀ / LC₅₀ (Lethal dose, 50 %; lethal concentration, 50 %)	The dose/concentration of an AI or formulation required to kill 50 % of a test population after a specified test duration in the test guideline.
Limit of detection	Lowest residual impurity that can be analytically detected with the assurance that the signal being detected is due to the residual impurity and is not caused by other sources such as instrument noise.
Limit of quantification	Lowest residual impurity concentration that can be determined repeatable with acceptable precision.
Low Application Rate Herbicide (LARH)	One of the two classes of herbicides recognised by US EPA in PRN 96-8: herbicides with an application rate ≤ 0.5 lb AI/ acre (equivalent to ≤ 560 g AI / ha).
Manufacturing	All steps in the manufacturing operations, including synthesis, and/or formulation, and/or packaging (filling, labelling etc.) and or repackaging.
Manufacturing site	This may consist of multiple production units in the same or in separated buildings.
Material Safety Data Sheet (MSDS)	Material Safety Data Sheet (MSDS): Data on the chemical, environmental, physical and toxicological characteristics required by the Government(s) to assure worker protection.
Maximum Residue Limit (MRL)	Maximum concentration of a residue that is legally permitted or recognized as acceptable in or on or agricultural commodity or animal feedstuff.
Nematicide	Any product used to control eel worms (= nematodes) parasitizing plants.
Nitrification inhibitor	A chemical inhibitor of the oxidation of ammonium compounds into nitrites and nitrates.
NOEL	No Observable Effect Level: the highest rate in g AI/ ha at which the AI causes no observable effects on a given, tested species.
Non-Crop pest control	Non - agricultural control of insects, other invertebrates, weeds and fungi (molds), e.g. on industrial sites, railways, households, sport-and recreational areas and in construction materials (wood treatment), etc.

Normal Rate Herbicides (NRH)	One of the two classes of herbicides recognised by US EPA in PRN 98-8: herbicides with an application rate > 0.5 lb AI/ acre (equivalent to > 560 g AI / ha).
Operations Committee	Committee in CropLife International addressing manufacturing and supply chain issues affecting the industry.
Packaging / repackaging	In this booklet, “packaging” and “repackaging” can be used interchangeably for the process of enclosing and protecting products for storage, distribution, sale and end-use.
Packaging unit	Production unit for packaging.
Pesticide Regulation (PR) Notice 96–8 (PRN 96-8)	US EPA document issued on October 31, 1996, specifying statutory cleaning levels for products sold or manufactured in the USA when changing from different product families, e.g. from herbicides to insecticides.
Pheromone	A biochemical substance secreted externally by certain animals, e.g. insects, affecting the behavior of other animals of the same species. These compounds are effective at very low doses.
Phytotoxicity	Any unplanned or deliberate damage to plants, e.g. total kill, burned leaves, chlorosis, stunted growth, failure to germinate, delayed germination, etc.
Preceding/succeeding client	Indicates the sequence in which products of these clients are manufactured in the same production unit (applies equally to synthesis, formulation, packaging and repackaging).
Product	Intermediates, active ingredients, technical concentrates, premixes of AIs, formulation concentrates, formulated products (either in bulk or in temporary or final sales packs).
Product scheduling	Planning the production sequence of different products; different sequences may result in significantly different cleaning regimes.
Production record	Production data of individual batches (e.g. batch card).

Raw materials	Any chemical substance used in the synthesis of intermediates and AIs, and in the formulation process of AIs. Note that intermediates are not classified as raw materials.
Reconditioning	Chemical or physical treatment of a product until it meets the required specification.
Release procedure	Organizational procedure that has to be followed before a new production unit can be formally allowed to produce the next product after the previous one, or after a configuration change.
Residual Impurity (RI)	A non-listed impurity from an AI / AIs (and possibly other chemicals) originating in a product previously in the equipment and not sufficiently removed during the cleaning procedure prior to the change-over.
Retain sample	Sample of a production batch stored to allow possible verification of its quality at a later moment in time.
RIL	See ACL.
Rinsate	Liquid cleaning medium: water + detergent and/or detergent used to wash the residual product out of a production unit.
Rodenticide	Product for control of rodents, e.g. rats and mice.
Safener	A chemical added to a crop protection product to eliminate or reduce the phytotoxic effects of that crop protection product on certain target crops. Typical examples are safeners used in formulations of “grass killers” that are applied in cereals and maize to make them safer to the crop.
Safety Data Sheet (SDS)	Data required by the Government(s) to assure worker protection and treatment for exposure. Previously known as MSDS.
Safety factor	Factor used to enhance the safety margin in the calculation of the ACL. Each company is responsible for setting its own safety factors. Safety factors for herbicides usually range from 2 – 10.

Sampling procedure	Sampling must follow an agreed plan describing: how to sample, what to samples, frequency, from which sampling point to collect samples, which quantity [sample size], how and where to store them, and the required storage period (minimally the legally prescribed retention period).
Segregation	In the context of Contamination Prevention, storage of incompatible materials and products where contact of different materials is not permitted, i.e. segregation is required. The storage must take place in individual rooms and there must be no shared common equipment (e.g. ventilation ducts and vent headers). People traffic between these rooms is not permitted without a change of clothing, shoes, etc. Additional information can be found on page 56.
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. For additional information see page 55.
Solid formulation	The collective name for dry formulations. Typically the AIs in these formulations are high melting point solids milled to a specified particle size. Examples: wetttable powders, granules, dusts.
Solid flush material	Solid inert material used to remove residual product from a production unit; e.g. bentonite, kaolin, sand, silica, sugar, talc.
Supplier of AIs or formulated products	A company selling AIs and/or formulated products registered in the name of the supplier to co-market those products, either as straight products or in formulations that may contain one or more AIs from their own portfolio. See also: Letter of Access.
Systemic	Any compound that affects the entire organism or bodily system, e.g. a toxin that affects the nervous system of insects.
Systemic Pesticides	Any group of crop protection products of which the AI(s) is absorbed into the tissues of plants and transported (translocated) within the treated plants also protecting the plant parts developed after treatment (i.e. new growth).

Suspension Concentrate (SC) = “Flowable”	A stable suspension of an AI(s) with water as the fluid intended for dilution with water before use.
Suspo-emulsion (SE)	A liquid, heterogeneous preparation consisting of a stable dispersion of AI(s) in the form of solid particles and of fine globules in a continuous water phase.
TCL	Trace component level, see: ACL.
TSCL	Toxicologically Significant Levels of Contaminants – concentration levels of contaminants that US EPA considers to be toxicologically significant, see: ACL and US EPA 96-8 (Appendix C).
Temporary label	A label to identify a packed product before the final product label can be applied.
Toll manufacturer, “Toller”	See External Manufacturer
Wettable powder (WP)	A powder preparation to be applied as a suspension after dispersion in water.

Appendix A - Equipment design

Equipment design plays a significant role in determining the ease of cleaning ability of any production unit. Investment in easy-to-clean equipment and avoidance of potential traps for any kind of contaminant helps to optimize cleaning circles and reduce downtime cost. The knowledge about critical parts in existing production units allows implementing an adequate risk assessment and cleaning procedures.

A.1 Equipment design for improved cleaning efficiency

Contamination Prevention requirements form an important consideration in the design of new or in the modification of existing production units. The following design ideas for improving cleaning efficiency should be considered:

- Include state of the art technology to reduce contamination potential: Clean-in-place (CIP) technology, e.g. rotating spray heads in tanks, in-line analyzers, etc.
- Consider automation of the cleaning procedure on lines equipped with a Process Control System.
- The type of cleaning has to be included in the design. In the case of wet cleaning the technical equipment must be liquid-tight, the internal surfaces of the equipment corrosion resistant and smooth to avoid trapping of product. Certain plastics (used for e.g. pipes) may absorb active ingredient and solvents and cannot be cleaned properly. The use of non-absorbent material is recommended.
- Design a sufficient number of cleaning access panels to allow good visual inspection of the interior of the equipment and easy access with cleaning equipment.
- Provide valves at the lowest point in the piping to allow easy drainage.
- Design the production unit with adequate surrounding space and logical disassembly points to facilitate cleaning. Consider quick fittings on equipment to allow rapid disassembly and inspection.
- Slope piping to maximize drainage. Bends in piping (especially those with small radius that could serve as a hold-up) shall be minimized whenever possible. Avoid U-shaped pipes.
- Select technical equipment (reactors, valves etc.) with “zero dead spaces” (no rectangular corners in containers, and no dead legs) to minimize the risk of trapping material and to allow easy drainage.
- Install sampling devices throughout the process to assist the analytical and troubleshooting needs after cleaning. Design the sampling devices with easy cleaning in mind.

- Consider closed unloading and packaging stations, for powders with dedicated pre-filter.
- Include contamination prevention considerations in the design of the air intake and exhaust. This should include predominant wind direction and a suitable particle size filter.
- Provide the production unit with a “washing room / workstation” (see Fig. 7) for the cleaning of dismantled smaller pieces of equipment.
- For contamination prevention purposes, solid floors should be preferred in manufacturing areas rather than steel or galvanized floor grating, as possible spills could be much better contained.
- Construct walls that are washable and leak-proof or sealed at the edges without crevices.

A.2 Illustrations of the production units with practical suggestions for cleaning critical parts

Cleaning of production units to levels below the agreed cleaning level is one of the key success factors for successful Contamination Prevention. In this chapter, special attention will be paid to critical, hard-to-clean areas, in various types of formulation and packaging units. Although effective cleaning of production units for intermediates or active ingredients is equally important in Contamination Prevention management, no illustrations will be provided because the various synthesis processes often require a much wider range of equipment configuration than formulation and packaging units. Critical areas in synthesis units are centrifuges, filters, dryers and equipment by which the final synthesis product (e.g. intermediates or fi active ingredients) is transferred to bulk containers, drums etc.

The drawings of the various formulation units are schematic and will vary from production unit to production unit. However, in each production unit, similar critical areas will be present. These areas are surrounded by red circles. The first time a particular critical area shows up in an illustration, attention will be drawn to this area with a magnifying glass and relevant comments will be made. If this critical area shows up again in a different production unit, the identical comments will not be repeated, although the critical area is highlighted again in the drawing.

Legend:



Motor



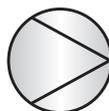
Fan



*Solid/
Liquid
Filter*



*Rotary Valve
Feeder*



Pump



*Dust Collector/
Air Filter*

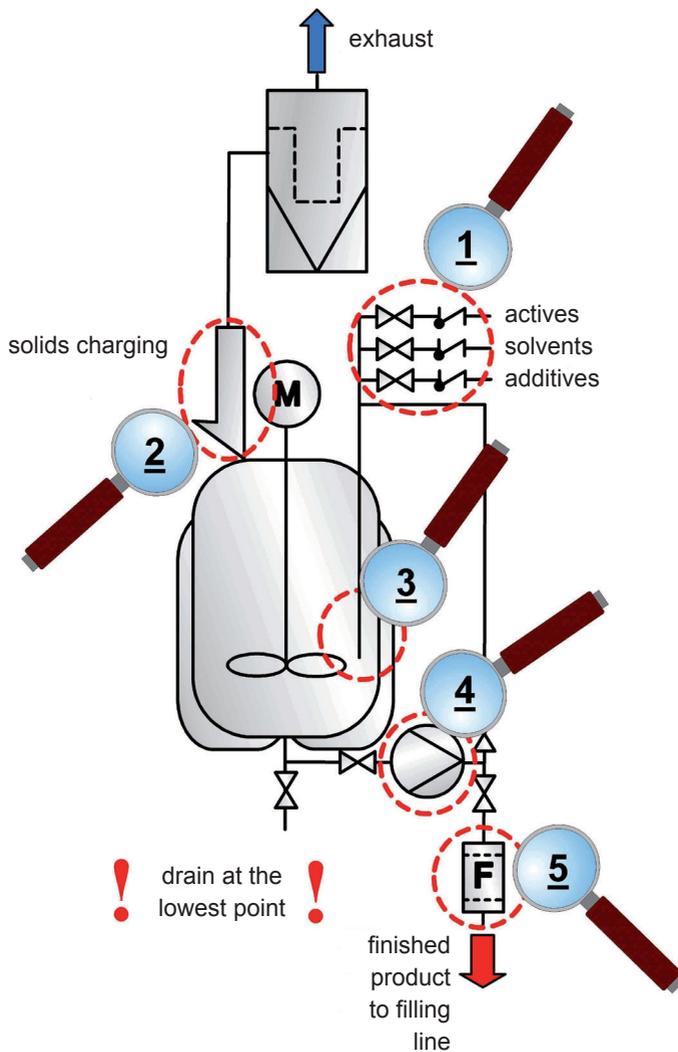


*Sifter
Sieve
Screener*

A.2.1 Liquid formulations

A.2.1.1 SL and EC Formulations

(Explanation of this equipment see next page)

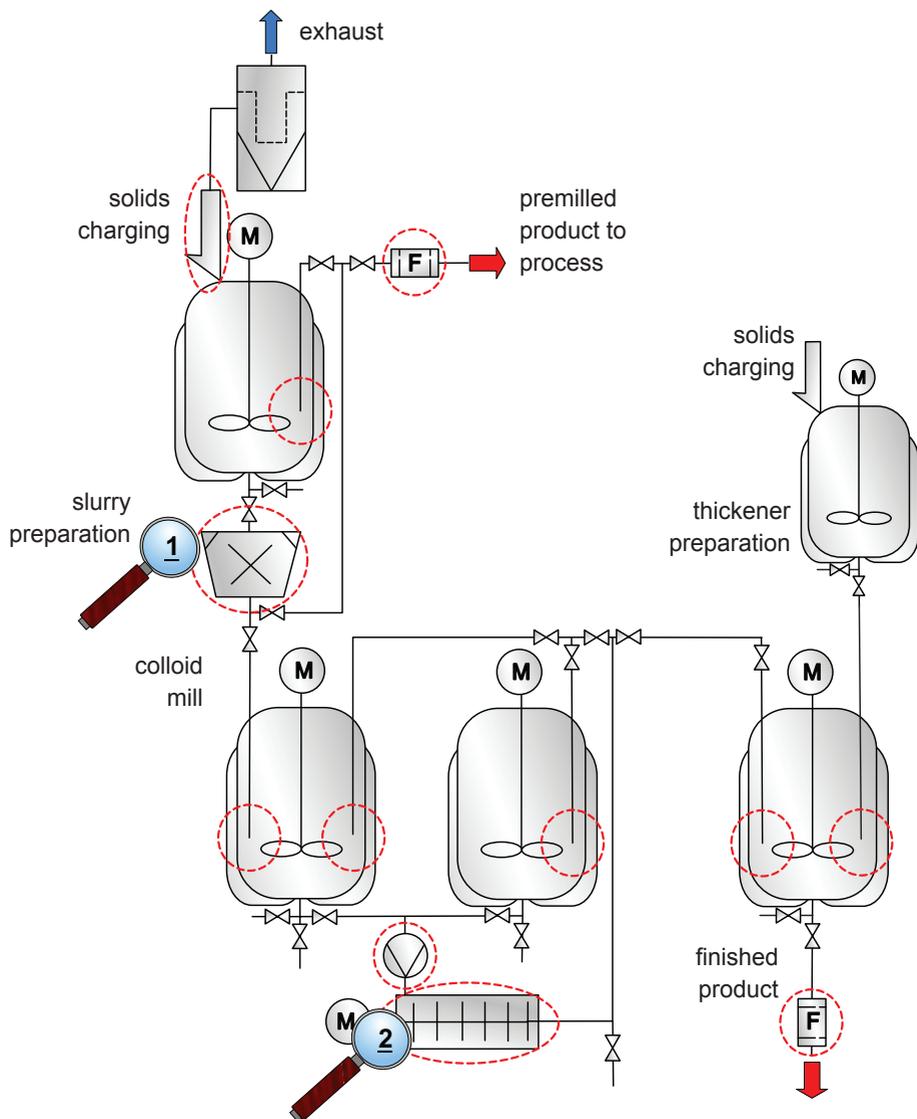


Comments:

1. Lines coming from bulk tanks must have reliable backflow prevention that is checked periodically. This is especially critical if the solvents and additives (e.g. surfactants) are drawn from bulk tanks that also feed other production units. Where vessels or filling lines can be fed from multiple bulk tanks containing different active ingredients, formulations or raw materials, the lines not in use should be blanked off or disconnected to ensure the wrong material is not added by mistake or mechanical failure.
2. In the area of solids charging two points need to be managed very carefully:
 - Adding only the correct solids to the process.
 - Dust generation requires extra attention, not only during the process (Contamination Prevention and industrial hygiene), but also when changing to the succeeding product. This is an area where special attention must be paid to good housekeeping.
 - The dust collected in the filter shall preferentially be disposed of. If a recycling of dust is envisaged, an approved procedure must be strictly followed detailing the measures to avoid mix up of collected dust during storage and recycling into the succeeding product. Never recycle dust collected from floors or walls into the process!
3. Deposits may form at dip pipes and require longer cleaning time than the rest of the formulation vessel. Especially when clean-in-place practices are followed, the cleanliness of the dip pipes needs to be checked, ideally by a visual inspection.
4. Pumps are always difficult to clean and ideally the pump is cleaned separately.
5. Replacing the filter bag before starting the formulation campaign of the succeeding product is a “must”.

A.2.1.2 Wet (liquid) milling, SC formulations

(Explanation of this equipment see next page)



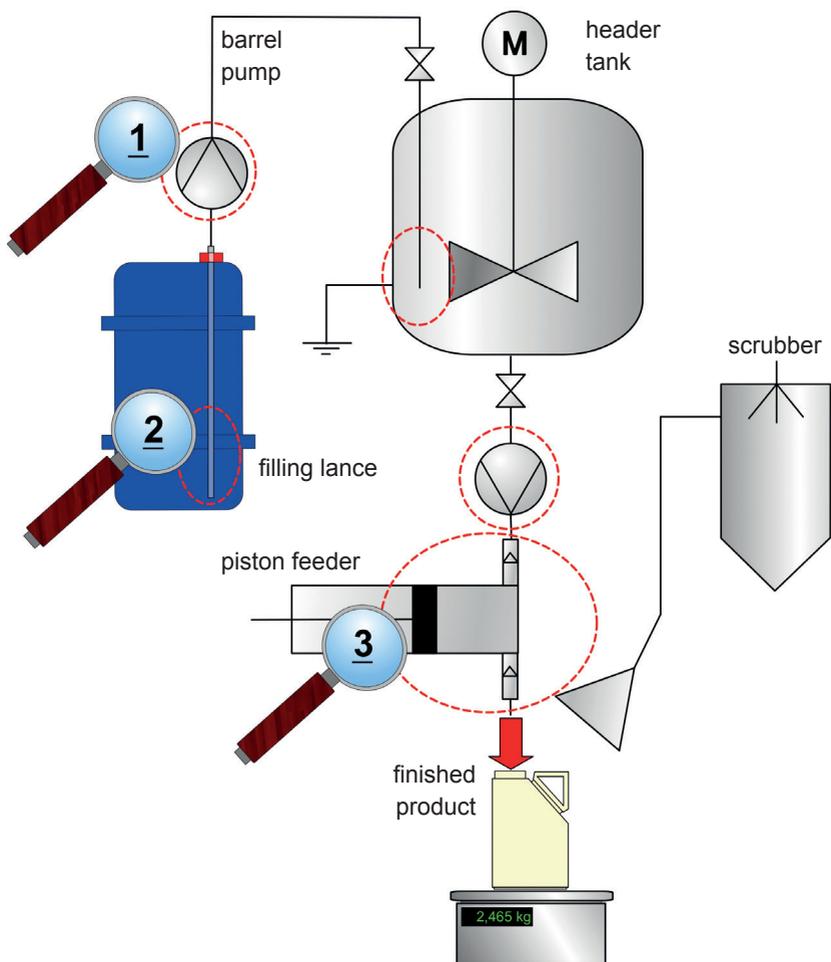
Comments:

Cleaning immediately after the campaign is completed is strongly recommended, even if it is not decided which product will follow in the production sequence, or the installation will be idle for a shorter (e.g. a weekend) or longer period (see case history 10.1). In the case of a production unit for flowable formulations, it is even more important due to the fact that a film of a flowable formulation, which contains solid particles of the active ingredient(s), thickening agents etc. is very hard to remove once dried. If this film has not been completely removed during cleaning, it may dissolve into the succeeding product and cause contamination (see case history 10.3).

1. The colloid mill needs extra attention in the cleaning process, because of the inherent design of the unit and the high shear rates, a solid film is certain to build up in places which are difficult to clean. Opening may be necessary for cleaning and inspection of the cleanliness.
2. It is recommended to use dedicated beads for each active ingredient manufactured in the bead mill. The beads should be cleaned and stored between campaigns - clearly labeled with the name of the active ingredient for which they must be used.

A.2.1.3 Liquid product packaging/ repackaging/ refilling

(Explanation of this equipment see next page)

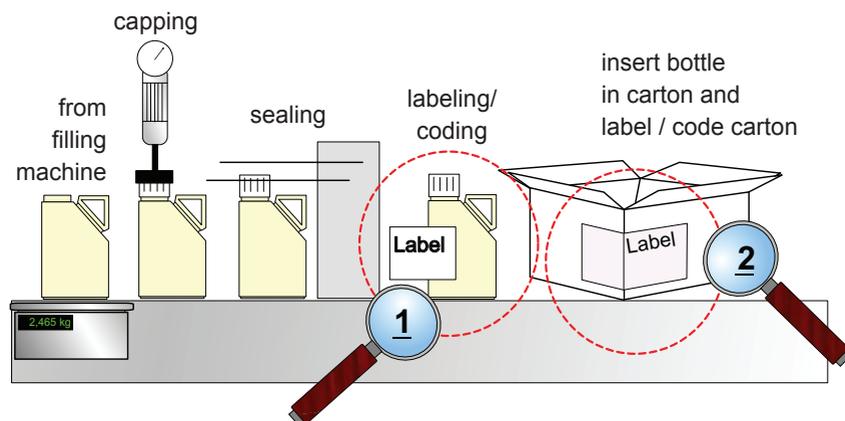


Comments:

This illustration deals with packaging liquid products (this could be liquid active ingredients or formulations) from bulk containers (drums, bulk tanks, isotainers, IBCs) into smaller end-user packs. It is imperative to verify that the material in the bulk container corresponds with the labels on the end-user containers. These comments apply equally to the packing of liquid active ingredients into drums or similar packs.

1. The cleaning history and the attained cleaning levels of the mobile or stationary barrel pump as well as the flexi hoses or solid piping connecting the bulk container to the header tank of the filling unit must be known. Before this equipment is used, a release procedure is required. It is important to have dedicated pumps and flexi hoses for herbicides and non-herbicides. Pumps are always difficult to clean and ideally the pump is cleaned separately.
2. The filling lance needs to be cleaned both inside and outside as soon as possible after the packaging run is finished to avoid drying up of residues of the previous product.
3. Since certain plastics may absorb active ingredients and therefore cannot be cleaned properly, equipment containing such plastics should be dedicated. Non-dedicated parts must be made from non-absorbent material, e.g. stainless steel.

A.2.1.4 Labeling of products



Comments:

1. Incorrect labeling of the containers can cause crop damage and/or safety risks to users. In addition, it also infringes crop protection laws and can result in considerable fines (see case history 10.13).
2. Incorrect labeling of the outer cartons and pallets results in similar issues. Incidents of this nature often result in product recalls to allow relabeling of the cases and/ or containers.

These comments of course apply also in the case of packing solid formulations.

A.2.2 Dry (solid) formulations

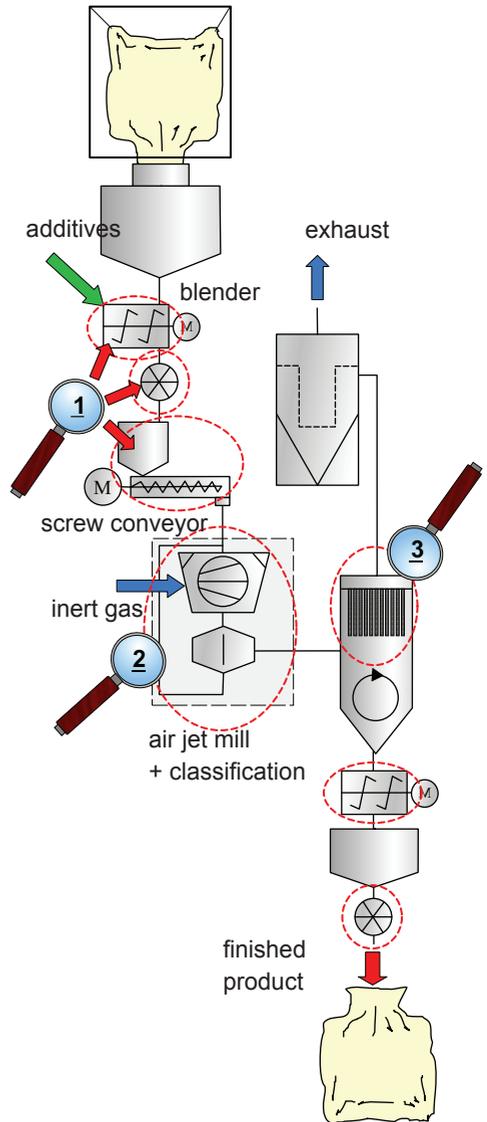
A.2.2.1 Dry milling – WP formulations granular formulations

(Explanation of this equipment see next page)

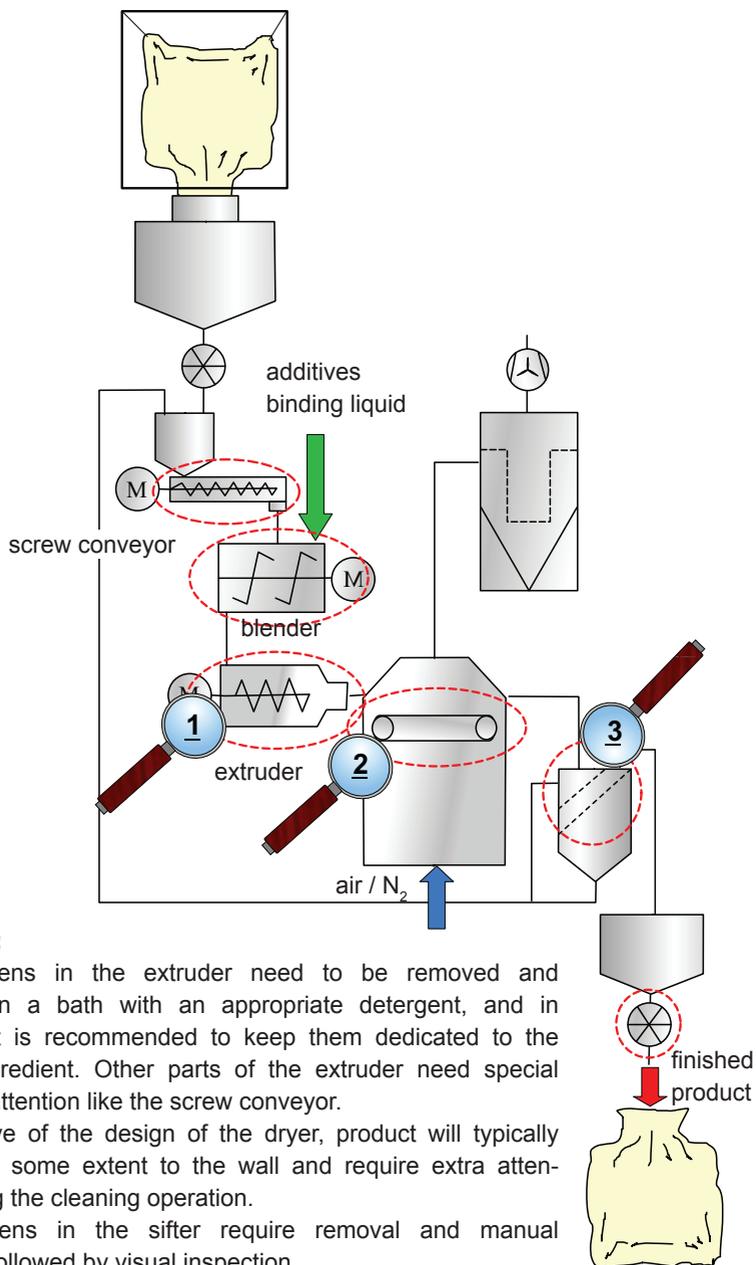
One of the general concerns in the manufacture of solid formulations is dust that can escape from the equipment at a number of places. Good housekeeping is always of the greatest importance in any type of manufacturing of Crop Protection products, but it is even more critical when manufacturing solid products.

Comments

- “Caking” of solid materials to the walls and moving parts of screw conveyors, rotary valves, feeders and blenders is hard to avoid, for it is often linked to the physical properties of the solids used. The most effective way of cleaning is by (partially) dismantling the screw conveyor, rotary valves and blenders followed by mechanical cleaning first to remove any solid deposit. Only then, cleaning with pressurized water should be carried out.
- The air jet mill (or the mechanical mill) should be opened and first cleaned mechanically followed by wet cleaning. Wipe tests (also referred to as swab tests) are a very good method to determine the potential residue of the preceding active ingredient adhering to the wall of the equipment. Sometimes these residues may be invisible, but in the case of highly active products, they could still cause contamination of the succeeding product.
- Since the “dust” collected in the filter and in the cyclone could form “lumps” which could be released into the succeeding product, these parts require extra thorough cleaning. Use of product dedicated filter tubes / bags is recommended. Carefully manage the packaging, labeling and storage of dedicated filter bags to avoid inadvertent reuse with the wrong product in a future manufacturing campaign.



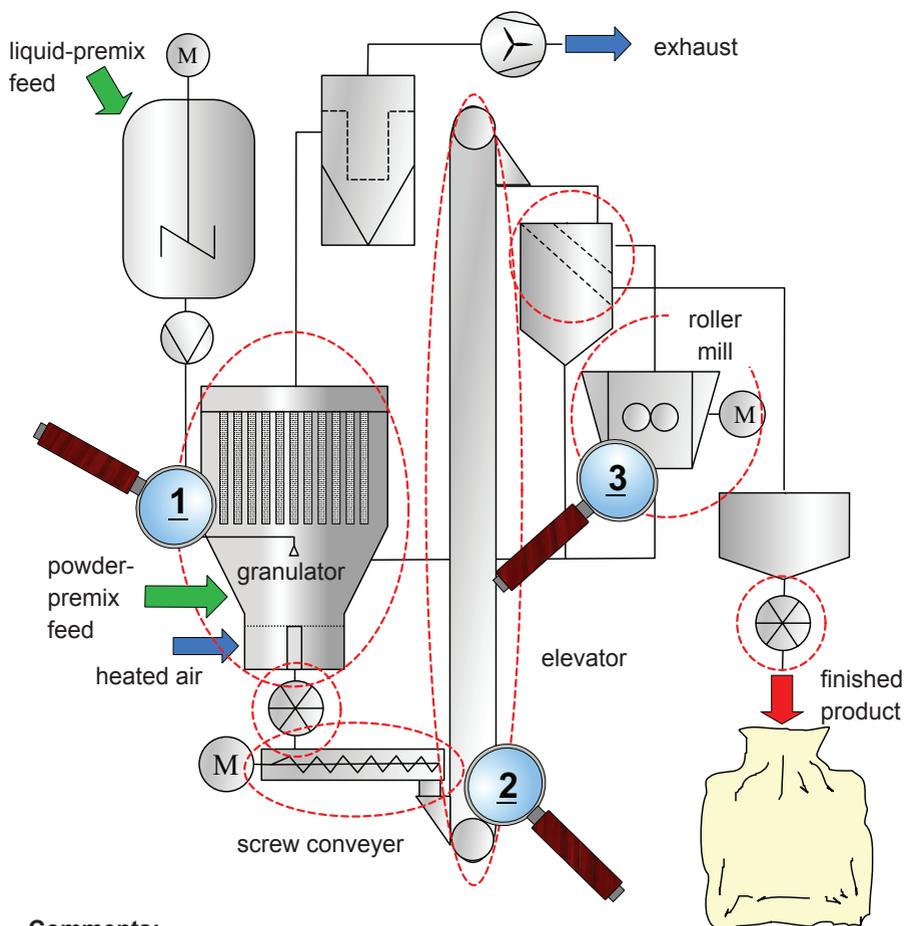
A.2.2.2 Extrusion Granulation



Comments:

1. The screens in the extruder need to be removed and cleaned in a bath with an appropriate detergent, and in addition it is recommended to keep them dedicated to the active ingredient. Other parts of the extruder need special cleaning attention like the screw conveyor.
2. Irrespective of the design of the dryer, product will typically adhere to some extent to the wall and require extra attention during the cleaning operation.
3. The screens in the sifter require removal and manual cleaning followed by visual inspection.

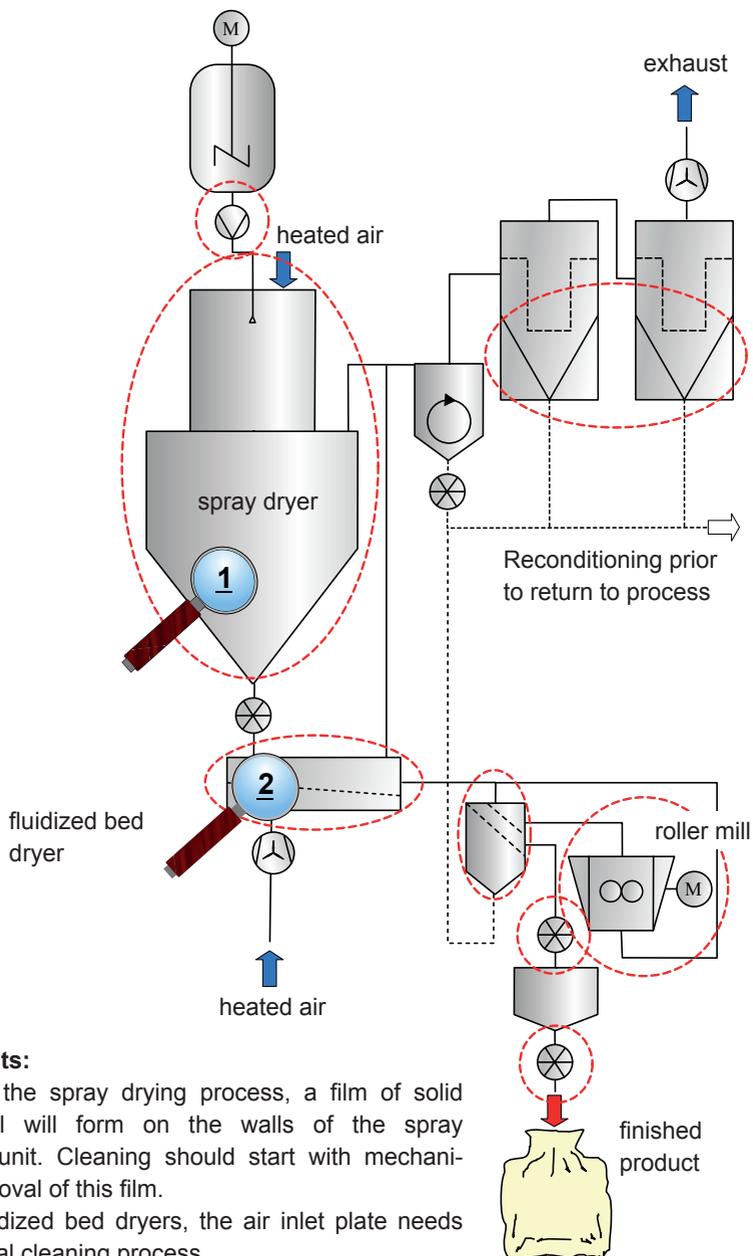
A.2.2.3 Fluidized bed granulation



Comments:

1. The entire granulation unit is prone to build-up of solid material, especially in the filter. During changeovers, dismantling of this unit and use / exchange of dedicated filter tubes is strongly recommended. Again, as in fluidized bed dryers, the air inlet plate needs special care.
2. Bucket elevators are not recommended at all, because they are so hard to clean. Elevators often have dead spaces, which make them extra critical from an ease of cleaning point of view. Before release for the manufacture of the succeeding product, a visual inspection is a must, and wipe tests may help to confirm cleanliness.
3. The roller mill needs to be dismantled and cleaned manually followed by visual inspection.

A.2.2.4 Spray Drying – Granular Formulations

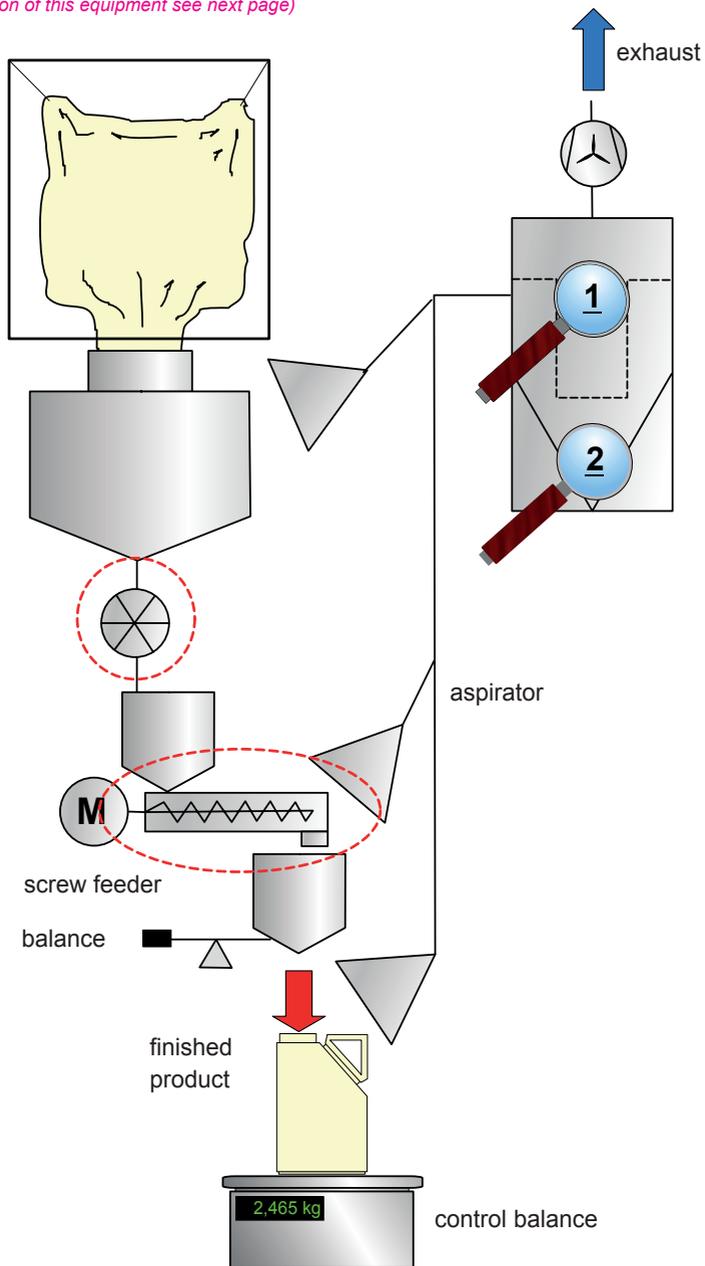


Comments:

1. During the spray drying process, a film of solid material will form on the walls of the spray drying unit. Cleaning should start with mechanical removal of this film.
2. For fluidized bed dryers, the air inlet plate needs a special cleaning process.

A.2.2.5 Solid products refilling / repackaging

(Explanation of this equipment see next page)



Comments:

Although the same principles apply as for refilling and repackaging of liquid products, there are some differences worth mentioning:

1. As best practice, each filling line should have its own individual filter and exhaust system. If the exhaust system is shared with other filling lines or formulation units then any line / unit not in use shall be blanked off (fixed piping) or disconnected (flexible piping) from the shared exhaust system. Pre-filters (also applies to mobile ones) shall be installed in the exhaust system at spots with high dust loads, e.g. powder drum filling, to trap the dust at the source. Pre-filters are essential, in those cases where a low application rate herbicide or a highly active herbicide (see table 1, page 30) is handled in the line / unit and the potential translocation of the dust through the shared exhaust system into another line / unit is a high contamination risk.
2. If the dust is recycled,
 - a. it is necessary to have dedicated filter systems for each packaging line, and
 - b. change filter bags at each product changeover. Labeling requirements are similar to those for interchangeable parts, while proper storage rules for these filter bags apply if they are to be re-used later.

Appendix B - Checklist / Self-Assessment

This Self-Assessment will help EMs to assess compliance of their manufacturing processes and technical equipment with the key Contamination Prevention criteria and the competency of their staff. A negative reply to questions in the checklist, which do not have informative character, should have a corresponding action plan to improve, or an explanation of why an improvement is not needed.

This checklist can also be used as the Contamination Prevention section of a client's EM audit checklist.

The frequency of the Self-Assessment / EM audit is determined by each client and the EM individually based on their own Contamination Prevention risk assessments and must be adjusted to cover events that impact the Contamination Preventions risk.

Frequent audits will be required whenever:

- The product mix in a multi-purpose facility has been changed and a new active ingredient has been added to the EM's portfolio.
- After completion of the action plan to correct any non-conformity with the Contamination Prevention criteria.

When a proven, reliable Contamination Prevention performance has been demonstrated, and no equipment or portfolio changes have taken place, the EM's facilities may be audited less frequently.

Both in the case of Contamination Prevention Self-Assessment and EM audits, the lead auditor should preferably be an outside expert (e.g. the QC manager from a different site of the same company, or an independent Contamination Prevention consultant).

Contents

1. Management Responsibility.
2. Information Exchange.
3. Type of Operation.
4. Separation / Segregation of Product Groups.
5. Product Exchanges.
6. Documentation.
7. Material Identification and Traceability.
8. Equipment Design for Improved Cleaning Efficiency.
9. Further Contamination Prevention Aspects.

1.	Management Responsibility	Yes	No	Comments/ Proposed Action Plans
1.1 Standards	<p>Does your site have a company standard / guideline / policy covering Contamination Prevention?</p> <p>Are the Standards / Guidelines published in the CropLife International booklet: "Contamination Prevention in the Manufacture of Crop Protection Products - Fourth edition (2019)" being implemented??</p> <p>If other, please describe.</p>			
1.2 Responsible Person	<p>Do you have an appointed person in your organization for the implementation & maintenance of the Contamination Prevention program?</p> <p>Name:</p> <p>In the role since (date):</p>			
1.3 Training	<p>Do you provide regular Contamination Prevention awareness training to:</p> <p>Existing personnel?</p> <p>New personnel, including temporary personnel?</p> <p>Functions?</p> <p>How often?</p>			

1.	Management Responsibility	Yes	No	Comments/ Proposed Action Plans
1.3 cont'd	<p>Do you have a formal Contamination Prevention training module?</p> <p>Are training records maintained?</p> <ul style="list-style-type: none"> • For permanent staff only? • Both permanent and temporary staff? <p>Record retention period?</p>			
1.4 Awareness raising	Describe any other awareness raising activities.			

2.	Information Exchange	Yes	No	Comments/ Proposed Action Plans
2.1 Contact person	Who is the focal point in your company for your clients for any discussions on information exchange? Name:			
2.2 Confidentiality of clients' information	Do the contracts with your clients allow you to disclose the name of the preceding products and their active ingredients to the following client? If not, due to existing secrecy agreements: Do your previous clients allow disclosure of their company's name and the name of their Contamination Prevention contact person to your succeeding client?			
2.3 Active ingredients	Do you provide your clients with a list of all active ingredients handled on your site, listed by production units? Do you provide your clients with updates of this list when new active ingredients are added to your portfolio? Do you report changes immediately? If yes, with which frequency?			

2.	Information Exchange	Yes	No	Comments/ Proposed Action Plans
2.4 Plant configu- ration	<p>Do you discuss the configuration of the equipment with the client when you make a product for the first time?</p> <p>If the unit can be combined from different parts, do you inform the client of all active ingredients which were last in all these parts?</p> <p>Example: the formulation vessel was used for the previous product, but the charging hopper that will be used contained a product with a different active ingredient in the previous production run.</p>			

3.	Type of Operation and Product Mix	Yes	No	Comments/ Proposed Action Plans
3.1 Type of Operation	Does the manufacturing site: <ul style="list-style-type: none"> • Synthesize? • Formulate: <ul style="list-style-type: none"> ○ solids? ○ liquids? • Package: <ul style="list-style-type: none"> ○ solids? ○ liquids? 			
3.2 Product mix agricultural chemicals	Does the manufacturing site manufacture, formulate or package: <ul style="list-style-type: none"> • Low application rate herbicides (EPA definition; ≤ 560 g AI/ha)? • Highly active herbicides (< 50 g AI/ha; see table 1)? • Normal rate herbicides (> 560 g AI/ha)? • Plant growth regulators? • Insecticides / fungicides for foliar or soil application? • Insecticides / fungicides for seed treatment? • Insecticides for foliar applications? 			

3.	Type of Operation and Product Mix	Yes	No	Comments/ Proposed Action Plans
3.2 cont'd	<ul style="list-style-type: none"> • Insecticides belonging to the Neonicotinoids family or other insecticide families with high toxicity to non-target arthropods (e.g. honey bees)? • Rodenticides? • Non-crop pest control? 			
3.3 Product mix non-agricultural chemicals	<p>Does the manufacturing site manufacture, formulate or package:</p> <ul style="list-style-type: none"> • Food and feed stuffs (inclusive vitamins)? • Human pharmaceutical products which are applied orally, topically or as an injection? • Veterinary products which are applied orally, topically or as an injection? • Human cosmetics and other health care products? 			
3.4	Please provide a list of all active ingredients handled in each of the production units on this site.			

4.	Separation / Segregation of Product Groups	Yes	No	Comments/ Proposed Action Plans
<p>If the manufacturing site handles more than one of the product groups mentioned in 3.2, please answer all questions in chapter 4</p>				
<p>4.1 Herbicides and insecticides / fungicides</p>	<p>Are the production units completely separated (except steam, nitrogen, and compressed air lines) by:</p> <ul style="list-style-type: none"> • Being in separate buildings? • Being in same building, but fully compartmentalized, with <ul style="list-style-type: none"> • no common ventilation system or other potential cross flows, • ancillary equipment (e. g. vacuum cleaners, air filters, tools, used spare parts) dedicated either to herbicides or to non-herbicides and marked accordingly? • Are operating staff when moving from herbicides to insecticides / fungicides required to change footwear and work clothing? 			
<p>4.2 Highly active herbicides</p>	<p>Are the production units completely segregated (except steam, nitrogen, and compressed air lines) from other product groups (including other herbicides) by:</p> <ul style="list-style-type: none"> • Being in separate buildings? 			

4.	Separation / Segregation of Product Groups	Yes	No	Comments/ Proposed Action Plans
4.2 cont'd	<ul style="list-style-type: none"> • Being in same building, but fully compartmentalized, with <ul style="list-style-type: none"> • no common ventilation system or other potential cross flows, • ancillary equipment (e. g. vacuum cleaners, air filters, tools, used spare parts) dedicated either to highly active herbicides or to other product groups and marked accordingly? • Are the operating staff, maintenance workers and visitors required to change (over)shoes, protective equipment and overalls/ overcoats when moving from highly active herbicide areas to other areas? • Are measures taken that no unfiltered air blows outside, e.g. non opening windows, locked doors, etc.? • Is the room under negative pressure and regularly monitored? 			
4.3 Plant growth regulators (PGR)	<p>Do you manufacture PGRs on shared lines together with:</p> <ul style="list-style-type: none"> • Herbicides? • Insecticides / fungicides? 			

4.	Separation / Segregation of Product Groups	Yes	No	Comments/ Proposed Action Plans
4.4 Rodenticides and non-crop pest control products:	<p>Are the production units completely separated (except steam, nitrogen, and compressed air lines) from other product groups by:</p> <ul style="list-style-type: none"> • Being in separate buildings? • Being in same building but fully compartmentalized? 			
4.5 Agricultural chemicals and non-agricultural chemicals (see 3.3)	<p>Are the production units completely separated (except steam, nitrogen, and compressed air lines) by:</p> <ul style="list-style-type: none"> • Being in separate buildings? 			
4.6 Incomplete separation	<p>Do herbicides and insecticides / fungicides, if not completely separated, share equipment like:</p> <p>Fixed equipment:</p> <ul style="list-style-type: none"> • Bulk storage tanks in a tank farm: <ul style="list-style-type: none"> • For raw materials / intermediates? • Final product? • Container loading / unloading stations? • Transfer lines (“pipelines”) with manifolds? • Common ventilation system? <p>Mobile equipment:</p> <ul style="list-style-type: none"> • Containers for intermediates / products? 			

4.	Separation / Segregation of Product Groups	Yes	No	Comments/ Proposed Action Plans
4.6 cont'd	<ul style="list-style-type: none"> • Pumps? • Flexible hoses? Filters? • Charging devices, e.g. funnels, suction pipes? • Vacuum cleaners? • Tools, e.g. shovels, spoons, sampling devices? • Others? Please list. 			
4.7	Fixed Equipment			
4.7.1 Common bulk storage tanks ("tank farm") for ingredients	<p>Are there one-way valves or other backflow protection installed?</p> <p>Can these common bulk storage tanks feed ingredient to the herbicide and insecticide / fungicide process at the same time?</p>			
4.7.2 Manifold connecting transfer lines, if applicable	<p>How do you identify the correct connectors when you set up the transfer line at set up the transfer line at</p> <p>Do you change the connections at the manifold during a running manufacturing campaign?</p> <p>How do you clean the transfer lines and the connectors at the manifold? Please describe.</p>			

4.	Separation / Segregation of Product Groups	Yes	No	Comments/ Proposed Action Plans
4.8	Mobile equipment			
4.8.1	<p>Is all the mobile equipment mentioned (e.g. pumps, flexible hoses, vacuum cleaners, tool kits, refillable containers etc.):</p> <ul style="list-style-type: none"> • Dedicated to herbicide or insecticide / fungicide production units? <p>Or:</p> <ul style="list-style-type: none"> • Assigned to a specific product, never being removed from the line at least during the whole manufacturing campaign and cleaned as part of the changeover process? 			
4.8.2	Are there written procedures for the cleaning of mobile equipment?			
4.8.3	<p>Is this mobile equipment properly labeled or color coded, showing its dedicated use?</p> <p>Is there a log book or tagging system for each interchangeable piece of equipment?</p> <p>Do these records include:</p> <ul style="list-style-type: none"> • Last product this equipment was used for? 			

4.	Separation / Segregation of Product Groups	Yes	No	Comments/ Proposed Action Plans
4.8.3	<ul style="list-style-type: none"> • Date of last use? • Date when the equipment was cleaned? • Cleaning method applied? • Cleaning status? 			
4.8.4 Mobile bulk containers	<p>Are mobile bulk containers (e.g. IBCs, isotainers, big-bags, road / rail tanks, waste containers) assigned to the manufacture of a single product for the entire manufacturing campaign?</p> <p>Are they used for dedicated, temporary storage of:</p> <ul style="list-style-type: none"> • Inert ingredients? • Active ingredient containing materials (premix, final product, e.g. prior to packaging)? • Waste (e.g. used cleaning medium to be recycled) <p>Do such containers remain dedicated to the same product after the end of its manufacturing campaign?</p>			
4.8.5	<p>Are these bulk containers properly labeled with clear identification of the product?</p> <ul style="list-style-type: none"> • Is the adhesion of the labels adequate? • Is the history of these containers traceable, i.e. the last product? • Is the cleaning status shown? 			

4.	Separation / Segregation of Product Groups	Yes	No	Comments/ Proposed Action Plans
4.8.6	<p>Are all types of bulk containers decontaminated in-house?</p> <ul style="list-style-type: none"> • If not, please list exceptions <p>If yes, is there a written and validated cleaning procedure available?</p> <p>Is the decontamination of bulk containers sub-contracted?</p> <p>If yes:</p> <ul style="list-style-type: none"> • Which cleaning standard must the sub-contractor adhere to? • How do you verify the cleanliness of the bulk containers? 			
4.9 Melting products in drums	<p>If drums have to be placed in a hot water bath or hot air oven, e.g. for melting an active ingredient or lowering the viscosity of certain surfactants:</p> <ul style="list-style-type: none"> • Are measures taken to prevent labels being lost/destroyed and traceability being lost, e.g. by marking the top of the drum with the name of the product with permanent, waterproof paint? 			

4.	Separation / Segregation of Product Groups	Yes	No	Comments/ Proposed Action Plans
4.9	<ul style="list-style-type: none"> • Are the hot water baths or hot air ovens dedicated to the campaign of one single product, i.e. no raw materials or active ingredients for other products will share the hot water bath or hot air oven at the same time? See history 10.12 			
4.10	Handling / warehousing of common raw materials to herbicides and non-herbicides manufacture			
4.10.1 Handling	<p>Are there raw materials that are common to both herbicides and non-herbicides e.g. solvents, surfactants etc.?</p> <p>Is it ensured that a partially consumed container of a common material - after it has been opened in the herbicide area - will never be taken into the non-herbicides area?</p> <p>Are such containers labeled "For Use in Herbicides only" and stored with the herbicide ingredients?</p>			

4.	Separation / Segregation of Product Groups	Yes	No	Comments/ Proposed Action Plans
4.10.2 Warehousing	<p>Are herbicide and non-herbicide active ingredients or materials for further processing stored separately in:</p> <ul style="list-style-type: none"> • Separate buildings? • Different compartments or in dedicated, clearly marked areas in the same building, e.g. clear markings on the floor, walls and /or signs and/or color coding? • Different store room with visual markings? 			

5.	Product Changeover	Yes	No	Comments/ Proposed Action Plans
5.1	Changeover management and cleaning levels			
5.1.1 Change-over management	Has a person been assigned responsibility for the approval of the release of the cleaned equipment for the next manufacturing campaign, including sign-off?			
5.1.2 Cleaning levels	<p>Is there a system in place to make sure the equipment is cleaned immediately after the production run?</p> <p>Are there up-to-date cleaning levels available for each production sequence in each unit (see chapter 5.2.7)?</p> <p>Do the cleaning levels include all active ingredients handled in the production units?</p> <p>Is there a procedure to ensure that the cleaning levels are updated whenever the product mix or production sequences are changed in a shared production unit?</p> <p>Is the client informed immediately?</p> <p>Do the clients provide the required ACLs?</p> <p>If not, how are the ACLs determined?</p>			

5.	Product Changeover	Yes	No	Comments/ Proposed Action Plans
5.2	Analysis of cleaning levels (residual impurity)			
5.2.1	<p>Are there analytical capabilities available to determine residual impurities below the cleaning levels requested by the client?</p> <ul style="list-style-type: none"> • For “contaminant in the rinsate” analysis? • For “contaminant in the succeeding product” analysis? 			
5.2.2	<p>Where are trace analyses of the residual impurities performed?</p> <ul style="list-style-type: none"> • In the analytical laboratory on site? • In an external contract laboratory? • Which company? Please name: • In the client’s analytical laboratory? 			
5.2.3	<p>Is the residual impurity analytical method validated in the target cleaning level range:</p> <ul style="list-style-type: none"> • For linearity? • For recovery? 			
5.2.4	<p>Are the residual impurities determined:</p> <ul style="list-style-type: none"> • In the succeeding product? 			

5.	Product Changeover	Yes	No	Comments/ Proposed Action Plans
5.2.4	<p>If yes:</p> <ul style="list-style-type: none"> • How many batches are typically analyzed? • Is a sample taken from the vessel? • Is a sample taken from the 1st pack? <p>Or:</p> <ul style="list-style-type: none"> • In the last rinsate? <p>Is the cleaning level analyzed at every product changeover?</p> <ul style="list-style-type: none"> • If not, please explain: 			
5.2.5	<p>Are analytical samples, laboratory samples and / or retained samples (at the end of their storage period):</p> <ul style="list-style-type: none"> • Prevented to be recycled back to the process? • Disposed of? 			

5.	Product Changeover	Yes	No	Comments/ Proposed Action Plans
5.3	Cleaning procedures			
5.3.1	<p>Are there written and validated cleaning procedures in place?</p> <p>How was the cleaning validation done? Please describe.</p>			
5.3.2	<p>Does the cleaning procedure specify:</p> <ul style="list-style-type: none"> • The cleaning medium to be used? • The cleaning equipment to be used? • The cleaning conditions to be used (e.g. temperature, time)? • The sequence in which the individual parts of the manufacturing line are to be cleaned? • How to charge the cleaning medium into the equipment? • The number of cleaning cycles, the duration of each cleaning cycle and the minimum quantity of cleaning medium per rinse? • Dismantling and manual cleaning where required? • Sampling locations? 			

5.	Product Changeover	Yes	No	Comments/ Proposed Action Plans
5.4 Recycling of used cleaning medium	<p>Is used cleaning medium recycled back into the process? If yes, please provide more details.</p> <p>Is the client in agreement that the used cleaning medium is recycled into his product?</p> <p>If the used cleaning medium is recycled, are the containers in which the used cleaning medium is collected immediately labeled after the cleaning has been completed?</p> <p>Are containers for used cleaning medium cleaned before use?</p>			
5.5	Release procedure for the cleaned equipment of the production unit			
5.5.1 Release procedure	<p>Is there a release procedure for the cleaned equipment prior to starting the next campaign? Does this procedure include the following:</p> <ul style="list-style-type: none"> • Visual confirmation for adequate cleanliness? • Verification of the cleaning record for completeness to ensure traceability? 			

5.	Product Changeover	Yes	No	Comments/ Proposed Action Plans
5.5.1 cont'd	<ul style="list-style-type: none"> • Verification whether the installations and the shared equipment (pumps, flexi hoses etc.) are properly labeled including the name of the previous active ingredient and the cleaning levels achieved? • Verification that results of the RI analysis meet the specified cleaning limit (as the confirmation for effective cleaning)? 			
5.5.2 Completeness check for cleaned equipment	<p>Do the operators, involved in readying the equipment for the next production run, put their signature on the cleaning record and enter the time at which the individual cleaning steps have been completed?</p> <p>If a step in the cleaning of the equipment is not carried out, will this be marked on the cleaning record with a brief explanation?</p> <p>Is it ensured that the next campaign cannot be started before the person responsible for the equipment release has inspected the cleaned installation and has signed the appropriate documentation?</p>			

5.	Product Changeover	Yes	No	Comments/ Proposed Action Plans
5.6	Release procedure for the product manufactured after changeover			
5.6.1	<p>Does the product release procedure include the following:</p> <ul style="list-style-type: none"> • Who is authorized to release the product? • Steps to be agreed with the client for the release of non-conforming product? • Quarantine of product manufactured after changeover until the first batch(es) is (are) formally released? • Release decision based on the residual impurity analysis to confirm that the agreed ACL has been achieved? 			

6.	Documentation	Yes	No	Comments/ Proposed Action Plans
6.1 Records retention	<p>Are records retained? How long do you retain the following documents?</p> <ul style="list-style-type: none"> • Cleaning records: _____ years. • Batch cards: _____ years. • Analytical results of residual impurity levels, including chromatograms: _____ years. 			
6.2 Final product sample retention	<p>Do you keep retained samples?</p> <ul style="list-style-type: none"> • If yes, how long are they retained? <p>Are the storage conditions for retained samples defined? Are these samples kept under lock and key?</p>			

7.	Material Identification and Traceability	Yes	No	Comments/ Proposed Action Plans
7.1 Raw material identification	<p>Are incoming goods identified by:</p> <ul style="list-style-type: none"> • Name, material code (“identity number”) and the batch number(s) mentioned on the bill of lading? • Chemical / physical analysis to confirm identity? • Chemical / physical analysis to confirm quality? 			
7.2 Production preparation / staging point	<p>Are controls in place to ensure that the correct and released material is delivered from the warehouse to the production unit and added to the process? Please specify how:</p>			
7.3 Material traceability	<p>Are production records / batch cards completed and retained for each individual batch manufactured?</p> <p>Do the records itemize the following details:</p> <ul style="list-style-type: none"> • Batch numbers and the exact quantities of raw materials added into the process? • Batch number and quantity of each batch produced? 			

7.	Material Identification and Traceability	Yes	No	Comments/ Proposed Action Plans
7.3 cont'd	<ul style="list-style-type: none"> • The names of the operators and their initials for each step completed? • RI analysis result? • QC result? 			
7.4 Labels	<p>Is there a procedure to ensure that only the correct labels will be applied to the products (This includes temporary labels.)? Please explain methodology.</p> <p>In case temporary labeling is required before the final labels can be attached, do these labels include (as a minimum) the following information:</p> <ul style="list-style-type: none"> • Product name and product code? • Batch number and production date? • Quantity (for bulk containers only)? 			

8.	Equipment Design for Improved Cleaning Efficiency	Yes	No	Comments/ Proposed Action Plans
8.1 Pipe work	<p>Is the technical equipment aligned from top floor down to bottom floor, with no U-shaped pipe work in the manufacturing line where material could get trapped?</p> <p>Is the pipe work sloped to allow easy drainage?</p> <p>Does the pipe work provide valves at the lowest point to allow easy drainage?</p> <p>Does the pipe work avoid bends with small radius (especially in solids and flowables production units) to minimize the risk of trapping material?</p> <p>Does the pipe work offer enough cleaning access panels for easy access with cleaning equipment and easy visual inspection?</p>			
8.2 Technical equipment	<p>Are formulation and packaging lines equipped with “Clean in Place” (CIP) installations?</p> <p>Do you apply an automated cleaning process controlled by a Process Control System?</p>			

8.	Equipment Design for Improved Cleaning Efficiency	Yes	No	Comments/ Proposed Action Plans
8.2 cont'd	<p>Are unloading and packaging stations closed in (i.e. in their own compartment), and in the case of powders equipped with dedicated pre-filters?</p> <p>Does the technical equipment (reactors, mills, driers etc.) have:</p> <ul style="list-style-type: none"> • Enough cleaning access panels to allow easy access with cleaning equipment and thorough visual inspection for cleanliness? • Internal surfaces that are corrosion proof and smooth to avoid trapping of product? • Adequate surrounding space and logical disassembly points equipped with quick fittings to allow rapid dismantling and inspection? • An air handling system (air intake and exhaust) suited to prevent contamination? <p>(please describe)</p>			
8.3 Change of equipment configuration	<p>In case the configuration of the production unit is changed (e.g. new apparatus, different [e.g. larger or smaller] vessels, filling line, changed geometry of pipe work) are the following steps undertaken:</p>			

8.	Equipment Design for Improved Cleaning Efficiency	Yes	No	Comments/ Proposed Action Plans
8.3	<ul style="list-style-type: none"> • Are the clients informed in writing about the change of the configuration? • Are the cleaning procedures revalidated and adjusted if required? 			

9.	Further Contamination Prevention Aspects	Yes	No	Comments/ Proposed Action Plans
9.1	Are spills returned back into the process?			
9.2	Is the client informed when material does not meet final product specification and reconditioning or blending of this material could be an option?			
9.3	Is reconditioning of off-spec material done following a procedure approved by the client following the relevant government regulations and with written authorization of the client for each occurrence?			
9.4	Which rules are implemented for movement of personell?			

Appendix C - Pesticide Regulation (PR) Notice 96-8



Office of Pesticide Programs

Pesticide Regulation (PR) Notice 96-8

October 31, 1996

PESTICIDE REGULATION (PR) NOTICE 96-8

NOTICE TO MANUFACTURERS, FORMULATORS, PRODUCERS AND
REGISTRANTS OF PESTICIDE PRODUCTS

ATTENTION: Persons Responsible for Registration of Pesticide Products

SUBJECT: Toxicologically Significant Levels of Pesticide Active Ingredients

This notice sets out the Environmental Protection Agency's (EPA's) interpretation of the term "toxicologically significant" as it applies to contaminants in pesticide products that are also pesticide active ingredients. This notice provides risk-based concentration levels of such contaminants that will generally be considered toxicologically significant. These concentrations are defined according to the type of pesticide that is contaminated and the pesticide category of the contaminant. As provided by regulation, registrants must report to EPA contamination exceeding toxicologically significant levels. This Notice sets out procedures for reporting such contamination.

The following contamination scenarios are excluded from this notice:

- (1) rodenticides as a contaminant and/or as the contaminated product;
- (2) microbial and biochemical pesticides that are manufactured in fermenters and that are contaminated by active microbial pesticide ingredients; and
- (3) plant-pesticides that are contaminated with other active plant-pesticide ingredients.

EPA would like to clarify that the Agency's previous position on toxicologically significant levels of impurities that are also AIs would apply to pesticides that are exempt from this notice. In other words, any level of a contaminant in these three exempted categories would be considered potentially toxicologically significant and must be reported to EPA.

I. BACKGROUND

EPA requires all impurities of toxicological significance to be reported and accepted as part of product registration (40 CFR 158.167). EPA also requires that registrants propose upper certified limits for toxicologically significant impurities in technical grade active ingredients or products produced by an integrated system (40 CFR 158.175), and may require upper certified limits for other impurities. At the time EPA promulgated these regulations it did not set quantitative criteria for determining whether an impurity is toxicologically significant. Rather, EPA has taken the position that any level of an active ingredient that is an impurity or contaminant in another product is potentially toxicologically significant and must be reported to the Agency. Failure to report such an impurity is a violation of FIFRA section 12(a) (1) (C) (composition of the product differs from that registered with the Agency).

The Agency did make clear at the time it promulgated its current reporting regulations that its interpretation of the term toxicologically significant could be subject to further refinement to the extent new information on impurities was available to the Agency. Based on the analysis conducted during the development of this notice, the Agency has now determined that for certain pesticides (see section IV below) it can establish generally applicable quantitative criteria for determining the toxicological significance of contaminants that are also active ingredients. For this reason, EPA is today further refining its interpretation of the term "toxicologically significant."

In Section IV of this notice, EPA is setting risk-based levels at which active ingredients that are contaminants will generally be considered "toxicologically significant." For the purposes of this notice, a contaminant is defined as an active ingredient that is not accurately listed on the product's confidential statement of formula or listed in the discussion of impurities. This notice addresses only impurities that are also active ingredients; EPA's position on other impurities has not changed.

Additionally, nothing in this notice changes the conditions outlined in the Bulk Pesticides Enforcement Policy (Bulk Policy) dated July 11, 1977 and amended on March 4, 1991. The Bulk Policy is an important part of applying the 40 CFR Part 158 standards to bulk pesticides at repackaging/refilling establishments (often retail dealers). Specifically, EPA's position that both parties (the registrant

and the repackager) are accountable for the integrity of the product as set out in the Bulk Policy remains the same.

II. OBJECTIVES

EPA determined that this interpretation on cross contamination should:

- Recognize that cross contamination is a reality, and that not all cross contamination is problematical;
- Set a clear standard that can be readily applied by EPA/States and the regulated industry alike;
- Ensure that allowable cross contamination does not pose unreasonable adverse effects;
- Minimize the paperwork burden for EPA and registrants;
- Maintain accountability for the product from the registrant to the end user; and
- Not preclude marketplace/private solutions to correct problems that do arise.

III. APPROACH

EPA decided that a risk-based approach would most likely meet these objectives. EPA considered the risks for several endpoints, including human health, adulterated food, contamination of ground water, and ecological effects to determine which endpoints would be most sensitive to cross contamination and what levels of cross contamination could be tolerated and remain generally protective of human health and the environment. For each endpoint, an analysis was done to evaluate a reasonable worst case scenario or a range of potential scenarios to see if an overall, generally protective contaminant concentration could be determined. EPA grouped contaminants and pesticides into different categories (see the table in section IV) to yield a scheme of toxicologically significant concentrations. The following end points were considered. In most cases phytotoxicity to the target plants is the most sensitive endpoint and, therefore, the limiting factor in determining toxicological significance.

Human health effects: Because cross contamination caused by a specific AI is most likely an intermittent event, short-term exposure is most likely. Therefore, EPA focused on the potential risks to individuals who would be handling contaminated products. The analyses of these human health risks show that acute risks to humans at the cross contamination levels allowed by this interpretation are negligible. Although intermittent contamination is the most likely scenario for cross contamination, it is possible that the same AI contaminant would be present in a particular pesticide product over a long period of time. EPA analyses indicate that chronic exposure to cross contamination is unlikely to present an unreasonable

risk to human health. EPA also considered contamination in pesticides applied to the human body (e.g. insect repellents) and concluded that the risks from cross contamination at the level set in this notice for these pesticides are negligible.

Adulterated food: Theoretically, a contaminant could cause residues in food or feed for which no tolerance has been established or that are in excess of an established tolerance. In this case, that food or feed would be adulterated under the Federal Food, Drug, and Cosmetic Act. EPA's analysis indicates that this is a highly unlikely occurrence. Moreover, because cross contamination with a specific AI occurs intermittently and at low levels, EPA believes that potential exposure to and dietary risk from residues of unreported contaminants under this notice would be negligible.

Ground water: The possibility of the contamination of ground water was raised as a potential concern in locations with sandy soils and shallow aquifers. The Florida Department of Agriculture and Consumer Services (DACCS) conducted a preliminary ground water modeling exercise using a number of conservative assumptions regarding leachability, pesticide half-life, and product application rate. EPA accepts the Florida DACCS conclusion that, while contamination of ground water is possible, it is of minimal concern because pesticide AIs as contaminants at the levels allowed by this notice are unlikely to move to ground water in concentrations that would pose significant risk to human health.

Ecological effects/ phytotoxicity: Based on a preliminary review of potential ecological effects from cross contamination (e.g. risks to birds, aquatic organisms, and plants), EPA believes that plant toxicity, or phytotoxicity, is the most sensitive endpoint given the relatively low concentrations of contaminants being considered. EPA believes that phytotoxicity damage poses the greatest potential for ecological harm. EPA's phytotoxicity analyses focus on the direct application of the contaminated product to terrestrial plants because this scenario represents a higher level of exposure than other exposure pathways, such as runoff and off-target drift.

EPA conducted several risk analyses based upon phytotoxicity as the end point of concern to determine the appropriate toxicologically significant levels. These analyses are presented in a technical support document (See section VII on how to obtain more information).

Rationale for not including certain microbial and biochemical pesticides and plant-pesticides: Many microbial and certain biochemical pesticides are manufactured in fermenters. A likely source of contamination of these pesticide products arises when a fermenter is used also for the production of a different microbial pesticide active ingredient. Quantitative criteria are not appropriate for determining whether active microbial pesticide ingredients are contaminants of

“toxicological significance”. This is because microorganisms can multiply in the environment, and especially in association with target pest hosts. The criteria of from 20 ppm to 1000 ppm as “toxicologically significant levels” (Section IV) when applied to a microbial pesticide active ingredient could allow for the presence of thousands to millions of contamination microorganisms per gram or milliliter of pesticide product. It cannot be assumed that such levels of contamination are of insignificant toxicity, especially to non-target organisms.

EPA is in the process of developing policy for regulatory oversight of plant-pesticides, including defining the scope of oversight. Therefore, any determination of whether the quantitative criteria for toxicological significance apply to plant pesticides should be made once the plant-pesticide rule is finalized. Where applicants/registrants voluntarily submit plant-pesticides for EPA regulation, the reporting as discussed in Section V of this Notice will remain applicable unless otherwise changed by regulation.

VI. TOXICOLOGICALLY SIGNIFICANT LEVELS OF CONTAMINATION

The following table defines the levels of contaminants that EPA generally considers to be toxicologically significant. Specifically, the presence of a contaminant at a concentration greater than the concentration specified in the table will generally be considered toxicologically significant. Each contaminant should be considered individually.

The toxicologically significant levels apply to all registered products that are sold or distributed, regardless of whether the container is non-refillable (i.e., “packaged product”) or refillable (i.e., “bulk product.”) The toxicologically significant levels do not apply to products that are not sold or distributed, such as tank mixtures in an end user’s application equipment.

Toxicologically Significant Levels of Contaminants (1,2)

Category	Type of Contaminant	Type of Pesticide that is contaminated	Toxicologically Significant Level (3) (ppm) (4)
1	Insecticide (5), fungicide, molluscicide, or nematocide in ...	Any insecticide, fungicide, molluscicide, nematocide, herbicide, plant growth regulator, defoliant, or desiccant	1000
2	Herbicide, plant growth regulator, defoliant, or desiccant in ...	Any pesticide (6) where the contaminant is accepted for use on all sites for which the product is labeled	1000
3	Any pesticide (6) other than a low application rate herbicide (7) in ...	An antimicrobial pesticide	1000
4	Normal rate herbicide (8), plant growth regulator, defoliant, or desiccant in ...	Any herbicide, plant growth regulator, defoliant, or desiccant	250
5	Any pesticide (6) in ...	A pesticide (6) applied to the human body	100
6	Normal rate herbicide, plant growth regulator, defoliant, or desiccant in ...	Any insecticide, fungicide, molluscicide, or nematocide	100
7	Low application rate herbicide in	A low application rate herbicide	Level of quantification (9) or 100 ppm, whichever is higher
8	Low application rate herbicide in	A normal rate herbicide, plant growth regulator, defoliant, or desiccant	Level of quantification (9) or 20 ppm, whichever is higher
9	Low application rate herbicide in ...	A pesticide (6) other than a herbicide, plant growth regulator, defoliant, or desiccant	Level of quantification (9) or 1 ppm, whichever is higher

Notes:

- (1) For the purposes of this notice, a contaminant is defined as an AI that is not on the product's confidential statement of formula or listed in the discussion of impurities.
- (2) The following contamination scenarios are excluded from this notice:
 - a) rodenticides as a contaminant and/or as the contaminated product;
 - b) microbial and biochemical pesticides that are manufactured in fermentors and that are contaminated by active microbial pesticide ingredients; and
 - c) plant-pesticides that are contaminated with other active plant-pesticide ingredients. EPA would like to clarify that the Agency's previous position on toxicologically significant levels of impurities that are also AIs would apply to pesticides that are exempt from this notice. In other words, any level of a contaminant in these three exempted scenarios would be considered potentially toxicologically significant and would have to be reported to EPA.
- (3) This column presents the toxicologically significant level, i.e., the concentration at or above which EPA would consider the contaminant to be toxicologically significant.
- (4) The concentration is determined in ppm based on the ratio of the weight of the contaminant to the weight of the formulated product.
- (5) The FIFRA definition of insect includes mites and other arthropods that are not classified by scientific nomenclature as "insects." See FIFRA section 2(o).
- (6) The phrases "any pesticide" and "a pesticide" do not include the pesticides that are specifically exempt from this notice as described in note #2 above.
- (7) For the purposes of this notice, a low application rate herbicide is defined as a herbicide with a maximum labeled application rate of AI less than or equal to 0.5 pounds AI/acre. This definition is intended to include products with AIs that are amino acid inhibitors or ALS inhibitors, including but not limited to the sulfonylureas, imidazolinones, and triazolopyrimidines.
- (8) For the purposes of this notice, a normal rate herbicide is defined as an herbicide with a maximum labeled application rate of AI greater than 0.5 pounds AI/acre.
- (9) For purposes of this notice, the level of quantification is the level of quantification achievable by EPA or its designated representative (State Lead Agency) using an analytical method suitable for enforcement purposes at the time the analysis is performed.

For categories 7, 8 and 9, the level of quantification is included in the table because EPA does not currently have analytical methods to detect and quantify these AIs in other products at concentrations as low as 100 ppm for category 7 (or lower for categories 8 and 9). EPA does not want to set a standard it cannot enforce. Conversely, EPA does not want to set a standard that constantly changes over time as analytical methods are continuously refined. Therefore, the standard of category 7 is the level of quantification until the point in time when the quantification limit drops below 100 ppm. The standard would then be 100 ppm, which is the limit based on toxicological significance. For purposes of this notice, the level of quantification is the level of quantification achievable by EPA or its designated representative (State Lead Agency) using an analytical method suitable for enforcement purposes at the time the analysis is performed.

In selecting the levels in the table, EPA attempted to strike a reasonable balance between greater protectiveness and cost/burden considerations. If future experience indicates that these values are not sufficiently protective, the Agency may find it appropriate to modify these levels of toxicological significance.

EPA believes the values in the table are generally protective in most contaminant/ product combinations. Because it is impracticable to consider every potential contaminant/ product permutation, however, adverse effects could occur when contamination is present below the concentrations in the table.

The Agency recognizes that these standards will not prevent all possible adverse effects from occurring; this is not a zero risk standard. For example, EPA is aware of a situation where a normal rate herbicide contaminated an insecticide at levels below 100 ppm (as set out in Category 6) and plant damage occurred. The Agency will continue to deal with such situations using other regulatory tools including section 6(a)(2) of FIFRA.

Accordingly, this notice does not excuse applicants or registrants from the requirement to submit to EPA factual information regarding unreasonable adverse effects of a pesticide under section 6(a)(2) of FIFRA and EPA regulations at 40 CFR 152.50(f)(3). If an applicant or registrant possesses factual information not previously reported to EPA indicating that a contaminant in a product may pose risk to human health or the environment in concentrations lower than those specified in the above table, that information must be submitted to EPA. Failure to submit such information on a timely basis is a violation of sections 12(a)(2)(B)(ii) and 12(a)(2)(N) of FIFRA. In addition, the distribution or sale of any product containing an unreported contaminant that exceeds the levels identified in this notice is a violation of section 12(a)(1)(C) (composition differs) of FIFRA.

V. WHAT REGISTRANTS MUST DO

A. CONTAMINANT LEVEL EQUAL TO OR GREATER THAN THE TOXICOLOGICALLY SIGNIFICANT LEVEL

If an applicant or registrant knows or has reason to believe that a contaminant that EPA would consider toxicologically significant (i.e. an AI at a concentration equal to or greater than the appropriate level in the table) may be present, s/he must then include an expanded discussion of the possible formation of the impurity and the amounts at which it might be present in accordance with 40 CFR 158.167(c). EPA would then make a regulatory decision on whether to approve the registration or amendment to allow the sale and distribution of the product under FIFRA. Sale or distribution of a pesticide, which equals or exceeds the toxicologically significant level prior to EPA approval of the registration amendment, would be a violation. Reporting would be required regardless of where the contamination would be expected to occur in the production and distribution processes. As noted in the preamble to the regulations at 40 CFR 158.167, formulators utilizing registered materials are not required to seek information on the identity or level of impurities in the registered technical products they purchase. The Agency realizes that such information may not be made known to the formulator.

To submit an expanded discussion in accordance with 40 CFR 158.167(c), an applicant or registrant must provide EPA with

- 1) the identity of the contaminant and
- 2) the concentration at which it might be present. The information should be sent to EPA as follows.

For US Postal Service submissions:

Document Processing Desk (PM Team #) Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency 401 M Street, S.W. Washington, D.C.
20460-0001

For courier deliveries:

Document Processing Desk (PM Team #) Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency Room 266A, Crystal Mall 2 1921 Jefferson Davis Highway Arlington, VA 22202-4501.

B. CONTAMINANT LEVEL LESS THAN THE TOXICOLOGICALLY SIGNIFICANT LEVEL

If an applicant or registrant knows or has reason to believe that a contaminant may be present at a concentration that is less than the toxicologically significant level, s/he is not required to report this information to EPA. Please note that if a product is distributed or sold with levels of contamination that are equal to or exceed the toxicologically significant level, the product is in violation of FIFRA, irrespective of the registrant's knowledge.

However, adverse effects could still occur below the “toxicologically significant” concentrations set out in this notice. Registrants are reminded that they are responsible for reporting any adverse effects under FIFRA section 6(a)(2). Specifically, if an applicant or registrant possesses factual information not previously reported to EPA indicating that a contaminant in a product may pose risk to human health or the environment in concentrations lower than those specified in the above table, that information must be submitted to EPA. Failure to submit such information on a timely basis is a violation of sections 12(a)(2)(B)(ii) and 12(a)(2)(N) of FIFRA.

This notice is not intended to relieve registrants from liability that may exist under State law resulting from damage caused by contaminants.

As noted above, this notice is intended to inform registrants of the interpretation of the term “toxicologically significant” that the Agency intends to apply in implementing the provisions of 40 CFR Part 158. It is not intended, nor can it be relied upon, to create any rights enforceable by any party on litigation with the United States. EPA officials may act at variance with the guidance when circumstances indicate that a contaminant is of toxicological significance at levels different from those set forth in this notice.

EPA will take any regulatory action necessary to ensure that the levels of contamination in a product do not cause unreasonable adverse effects to human health or the environment.

VI. EFFECTIVE DATE

This notice is effective immediately.

VII. FURTHER INFORMATION

The public comments received on the proposed interpretation, the comment summary and response document, and the technical support document for this notice are available in the public docket under document number “OPP-00424.” The public docket is located at: Public Docket and Freedom of Information Section, Field Operations Division, Office of Pesticide Programs, U.S. Environmental Protection Agency (7506C), Room 1132, Crystal Mall #2, 1921 Jefferson Davis Highway, Arlington, Virginia, 22202.

Appendix D - Risk assessment based on the Failure Mode and Effect Analysis (FMEA)

Using a hypothetical model, the risk analysis process will be demonstrated. Following the actual risk assessment, each potential failures / risks will be assigned *Severity, Occurrence and Detection value*²³ (SOD-value). These values are used to calculate the *Risk Priority Number (PRN)*. The PRN-number determines in which of the three risk categories each the potential failure will be classified²⁴. All these values and PRNs must be documented in a *Quality Risk Assessment Template (QRAT)*.²⁵

D.1 Situation analysis:

An External Manufacturer is specialized in the packaging of Water Dispersible Granules (WDGs) of insecticides and fungicides in jars or water soluble bags (with a waterproof outer bag).

The clients of this EM formulate these WDGs in their own facilities and ship these in big bags to the EM for packaging. One of the clients is interested in engaging the EM in a long term contract for packaging high volumes of a WDG of a highly active herbicide (HAH) in 50g jars.

Before negotiating an agreement a risk assessment would have to be conducted.

Facilities used by the EM:

There are three packaging lines in a joint packaging hall, each with an individual staging area located in the warehouse. There is a wall from floor to ceiling between the warehouse and the packaging hall with a large sliding door to allow a fork lift truck to service both the warehouse and the packaging hall. There is no separation between the filling lines which may be operated simultaneously.

The big bags are stored in separated bays in a single warehouse with one outside door to the unloading dock. The packaged products are stored in a separate warehouse.

²³ See Appendix D.2, D.3 and sub-chapter 4.4.2, page 20.

²⁴ See Appendix D.3 for Classification of the PRN in three risk categories.

²⁵ The QRAT before and after corrective measures are in place is shown in Appendix D.4.

The key potential failures:

To mitigate the potentially very high contamination risks that would result from the introduction of a HAH on this dedicated non-herbicide site, the following potential failures were observed and required actions were initiated:

- A mix-up resulting in a HAH granule containing big bag being charged in a hopper scheduled for a fungicide could result in a major contamination incident that would very likely be detected only after the alleged fungicide was applied and had caused major phytotoxic damage.
- Since HAHs are active at very low application rates, dust contaminating the non-herbicide products could result in contamination issues. Puncture of big bags can lead to spillage of HAHs and generate dust containing the AI of the HAH.
- Insufficient attention was paid to contamination prevention training leading to unfavourable detection and occurrence scores.

Corrective Action Program:

Total segregation of the HAH-herbicide storage, staging area and packaging areas.

- Dedicated door to loading area and possibly a separate loading dock.
- No connecting doors with the non-herbicide warehouse and packaging hall. A door between the HAH-warehouse and the HAH-filling line was considered acceptable.
- Separate air intake and exhaust system for HAH-areas is considered absolutely necessary.
- Change packaging of the HAH- granule formulation from big bags to more robust, less susceptible to punctures fibre drums.
- Implement strict people movement. Clothing and shoes worn in the dedicated HAH-areas must not be worn in the non-herbicide area.
- Improved contamination prevention training (min. once a month) with training records, also for temporary staff.

D.2 Assessment of potential failures (SOD-values)

Score*	Severity (Impact)**
1	Very low - Non-measurable impact.
2 - 3	Low - Impact is acceptable.
4 - 6	Medium - Impact on internal standard, non-conformities, large administrative and management burden, incident(s) contained within own facilities. No outside impact.
7 - 9	High - Impact results in: contamination incidents, financial losses, reputation damage, product recalls, adverse environmental effects, regulatory issues.
10	Very high - Impact negatively influences the freedom to operate, causing serious financial losses and/or significant reputation damage, infringes regulatory compliance, litigation.
Score*	Occurrence (Likelihood)
1	Very unlikely - could happen theoretically.
2	Unlikely - could happen, but very rarely.
3	Likely - could happen occasionally.
4	Very Likely - could happen any time.
Score*	Detection
1	Can be detected very easily and resolved immediately.
2	Can be detected easily, but not resolved immediately.
3	May be detected by chance (i.e. as a coincidence).
4	May be detected during maintenance, inspections or audits.
5	Very unlikely detected within own facility/production phase.

* The individual scores of Severity, Occurrence and Detection (SOD values) are multiplied with each other to give the Risk Priority Number, see Appendix D.2.

** The SOP scores for possible failures are set by each individual company.

D.3 Classification of Risk based on the Risk Priority Number (PRN) ***

Risk Priority Number (PRN)	
1 to 30	A risk evaluation with a PRN 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.
31 to 99	A risk evaluation resulting in a PRN 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.
100 to 200	A risk evaluation with a PRN 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.

*** Classification of risk based on PRN-numbers is decided by the individual companies.

D.4 Quality Risk Assessment Template (QRAT) *

Description Risk / Potential Failure	Initial Risk Assessment				Risk Assessment after Actions Completed			
	Impact	Occurrence	Detection	PRN	Impact	Occurrence	Detection	PRN
No segregation in the warehouse, no segregation in the packaging hall, mix-ups.	10	3	4	120	10	1	2	20
Staging in the wrong filling line, non-segregated staging areas	10	2	5	100	10	2	2	40
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.	7	3	2	42	7	2	2	28
Spills/dust transferred from warehouse to packaging hall on clothing, shoes, tires of fork lift, tools etc.	4	4	2	32	4	1	2	8
Contamination prevention awareness low at the operators' level - training 1X annum, seasonal hires not trained.	6	3	3	54	6	2	1	12

* Disclaimer: This example is based on a hypothetical situation. The potential failures and numbers have been selected to demonstrate the process and should not be used for other purposes.

Graphic design:



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