Contamination Prevention in the Manufacture of Crop Protection Products



Guidelines and Best Practices

This Presentation is Made on Behalf of

and its Corporate Members

Why Contamination Prevention is important

Extraneous active ingredients might

- ✓ Cause crop damage,
- ✓ Endanger beneficial non-crop species, like pollinators,
- ✓ Present health or environmental hazards,
- ✓ Infringe legal requirements and other legislation.

New in 4th ed. of the CPMCPP booklet

New key topics include expanded or completely new chapters on:

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

The situation....

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

It is Preventable

The situation....

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

It is Preventable

The situation....

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

2000 ppm vs 1000 ppm

It is Preventable

The situation....

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

The situation....

- ✓ Fungicide was packaged following a potent insecticide
- ✓ EPA default limit for change over (<1000 ppm) was used</p>
- \checkmark No consideration was given to the ecotoxicological risks
- ✓ Massive kill of predatory insects occurred

The situation....

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

The situation....

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

If it doesn't look normal stop...

Contamination Prevention What is Needed?

Separation of herbicides and non-herbicides

Documented Risk Assessments August 7th, 2019

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

> Avoid cross contamination with rework

Clear labelling

Cleaning procedures and analytical methods

Contamination Prevention What is Needed?

Additional Requirements

Promptness in Clean out

Refillable container maintenance

Define Residual Cleaning Limits

100

100

NA

NA NA

NA NA

33

100

250

250

50

Portable equipment must be dedicated

Assess common raw material vessels

Contamination Prevention What should Management do?

The requirements apply to CropLife member companies and external manufacturers.

The Details...

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

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

Risk assessment process

- Initial Risk assessment
 - Assessment of potential failures
 - Severity
 - Occurrence
 - Detection
 - Risk Priority Number (RPN- ranking of the individual risk)
- Agreed actions
- Re-assessment of the risks

RPN- ranking of the individual risk

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 an acceptable 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 timeframe.					
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) to a tolerable, acceptable 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.					

Risk assessment process

Process evaluated in risk assessment	Possible Failure	Potential impact of failure	Severity	Potential likelyhood failure	Occurrence	Current Process Controls	Detection	PRN						
In-process sampling	Sample size too small	Not possible to run all required tests	3	Wrong sampling instructions	3	Correct sample size published in the lab manual	2	18						
Documentation HPLC data	Harddisc issues	Loss analytical data	7	Harddisc failure of the IT systems	2	Data backed up daily	3	42			7			
Cleaning dry filter of the dust collector	Filter remains uncleaned	Contamination of products due to overload filter	7	Missing instructions on when and how to change the dry filter	3	Written procedures, Training and stickers with cleaning regime and	4	84	Planned Results after completion ac		tion steps			
Rinsate samples used for determination ACL	Following product not sampled for residual	Contamination risk	8	Wrong procedures & missing instructions	4	date None	5	160	Date	Completion Date	Severity	Occurrence	Detection	PRN, after complet-ion action steps
Highly active herbicide stored in common warehouse	Impurities No segregation	Contamination other products in warehouse, mix-ups in manufacture	10	No clear storage guidelines on segregation	4	No dual verification at the staging point	5	200	01-Sep-17	01-Sep-17	3	1	2	6
*Disclaimer: All values in these risk assessments are fictitious and have been chosen to demonstrate the use of this risk assessment tool.														
				Cleaning dry filter of the dust collector	Dedicated filters for specific products, adequately labeled		licated filters for cific products, Joe Doe quately labeled		15-Sep-17	31-Oct-17	7	3	2	42
				Rinsate samples used for determination ACL	Inter prev man proc forev	nsive frequent cont. . training, improved agement of change ess, analytical warned	John Smith		01-Sep-17	12-Sep-17	8	3	2	48
August 7 th . 2019			Highly active herbicide stored in common warehouse	Construct fully segregated (floor to ceiling) room for HAHs.		Peter Jones		15-Dec-17	30-Nov-17	10	5	1	50 18	

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

Re-assessment of the remaining risks

	,	Initia Asses	al Ris ssme	k nt	Risk Assessmen after Actions Completed				
Description Risk / Potential Failure	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	

Risks are lowered to an acceptable level

External Manufacturing Information Exchange

The External Manufacturer <u>must</u> supply the succeeding client the following:

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

List of Actives

Metosulam Mesotrione S-Metolachlor Haloxyfop-p-methyl

Layout of Unit

Location of Facility

External Manufacturing

Information Exchange

$\begin{array}{c} \text{Requestor} \longrightarrow \\ \text{Provider} \downarrow \end{array}$	External Manufacturing	Succeeding Client
Preceding Client	 Analytical standards* Analytical methods* Cleaning methods* 	 Active present in products NOEL**, ED₅ or ED₁₀ of succeeding products Classification data Sample of products to develop NOEL data
Succeeding Client	 Cleaning limits 	

*If requested and available for the previous product **NOEL – No Observable Effect Level

Minimum Requirements for External Manufacturers

Client is responsible for	External Manufacturer is responsible for
Specify the method to achieve cleaning level (succeeding product or flushes)	Cooperate in a full audit for Contamination Prevention
Conduct site audits and due diligence	Trace materials and records for traceability purposes

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

Minimum Requirements for External Manufacturers

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

Client is responsible for	External Manufacturer is responsible for
Specify the method to achieve cleaning level (succeeding product or flushes)	Cooperate in a full audit for Contamination Prevention
Conduct site audits and due diligence	Trace materials and records for traceability purposes
Only use preceding client information for purposes of Contamination Prevention	Appoint a person responsible for Contamination Prevention
Inform External Manufacturers of special risks (highly active Herbicides)	Separation of operations based on the client's risk assessment
Review/update contracts or agreements with best practices in Contamination Prevention	Ensure adequate analytical capabilities
	Ensure written changeover procedures
	Ensure Contamination Prevention training and records of said records
	Ensure labeling of equipment, materials and containers
	Obtain approval of changes that impact contamination prevention
	Not recycling or returning samples to the process
	Rework is approved by the client
	Maintain good housekeeping
	Retention and storage of retained specified by client

Procurement/Purchasing of Active Ingredients

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

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

EITHER

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

OR

- Information exchange for other active ingredients manufactured on the same production and packaging line, and a cleaning matrix in place (provided by customer) and cleaning limits will be achieved (by supplier).
- ✓ Detailed sales specification
- ✓ Chemical analysis and agreement on items on certificate of analysis
- ✓ Notification of process changes

Recommended to complete a self-assessment followed by an audit

Separation of Production Units

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

Equipment separation is key to contamination prevention.

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

Separation of Production Units

A key to contamination prevention is to have dedicated units...

- ✓ Reduce contamination risk
- ✓ Reduce cleaning costs
- ✓ Reduce downtime

Herbicides

e.g. herbicides, defoliants, and desiccants

Non-herbicides

e.g. fungicides, insecticides, acaricides, molluscicides, nematicides, pheromones, plant activators, herbicide safeners, rodenticides, crop oils and adjuvants

Separation vs Segregation in Warehousing and Storage

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

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

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

- Storage in the same building under the same roof:
 - > in different rooms divided by a wall going up to the ceiling,
 - dedicated entrance,
 - no contact / openings to other rooms,
 - no shared ventilation ducts and vent headers.
- Storage in different, not interconnected buildings.

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

Herbicides (NRH, LARH, HAH) <u>must be segregated</u> from all Non-herbicides

- Segregation is also required for all those raw materials, intermediates, formulants, partials and packaging materials which could be potentially contaminated during any of the herbicide manufacturing steps and can be used for nonherbicides.
 - Separation between Herbicides (Als, Intermediates, Raw materials, Partials etc.) is a requirement.
- It is strongly recommended to implement segregation between High Active Herbicides - HAH (application rate < 50 g AI/Ha and herbicides with an ACL in the low ppm range, from all other herbicides (NRH, and LARH, i.e. herbicides with an application rate ≥ 50 g AI/ha.

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

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

Separation between **all Non-Herbicides** (Als, Raw Materials, Intermediates, Packaging Materials, etc) <u>must be implemented.</u>

- Exceptions :
 - High bee toxicity: <u>Segregation</u> from <u>all Non-</u> <u>Herbicides</u>, including all raw materials is required .
 - Baits: Repellency must be evaluated.
 <u>Segregation may be necessary</u>, also of finished bait formulations.

Storage of Finished Products in their final sales pack, with temporary labels, or in bulk containers.

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

- Segregation is not required.
- However, Adequate Separation between the finished products must be ensured.
- Care must be taken that all liquid products are stored on the lowest tiers to limit damage caused by leaking containers.

Cleaning Capability

Two critical elements which must always be evaluated...

1. Design of the production unit

(look for 'dead spaces')

2. Cleaning procedures

Cleaning Level Determination

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

- ✓ The No Observable Effect Level (NOEL)
- The application rates of the succeeding product on all crops
- ✓ US EPA Pesticide Regulation Notice 96-8 classification
- \checkmark For insecticides, the LD₅₀ honeybee

NOEL data for Herbicides

NOELs are typically determined from greenhouse studies

Recommended to appoint a specialist to calculate cleaning levels

Greenhouse studies determine the dose and adverse effect levels that will be used as a basis for cleaning levels

Safety Factors and Application Rates

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

Reasons for a factor...

- ✓ Studies are typically conducted in greenhouses
- ✓ Different crop varieties
- ✓ Overlapping in fields
- ✓ Spray volume fluctuation
- ✓ Weather conditions

Highest single or seasonal application rates are used in the calculation of cleaning limits

Cleaning Level (ACL) Calculation

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

3 elements in the equation...

- AR
- NOEL
- Safety factor (SF)

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

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

What is a ppm?

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

- ppm stands for <u>parts per million (one millionth)</u>
 - in solid products a contaminant with a value of 1 ppm is equivalent to:

1 mg / kg of product (= 1 millionth of a kg).

 if the contaminant in a liquid product is a solid, 1 ppm is equivalent to :

1 mg / liter of product (= 1 millions of a liter).

if the contaminant is also liquid, 1 ppm is equivalent to:
 1 μl / liter (1 μl = one millionth of a liter).



How big is a ppm?



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

The contaminant: a HAH was present at 0.4 ppm (0.4 mg / I FP. Even at the very low application rate of 0.4 mg AI / ha, caused irreversible crop damage.

1% of a droplet in 1L has made the difference



What do ppm/ppb mean?

PPM parts per million (ppm)

- 4 drops in a 250L barrel
- one inch in 16 miles,
- one second in 11.5 days,
- one minute in two years.

PPB parts per billion (ppb)

- 1 drop in an Olympic swimming pool
- one sheet in a roll of toilet paper stretching from New York to London,
- one second in nearly 32 years,
- one pinch of salt in 10 tons of potato chips.



ACLs for Als not registered on target crops

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

When determining those ACLs, it needs to be assured that the legally required MRLs for non-registered Als are met in the produce.



ACLs for Als not registered on target crops

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

Definitions:

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

ACL: Acceptable Concentration Level; ppm [mg AI / kg or L formulated product].

DR: Dissipation Rate (default value is 1 – no dissipation, e.g. post-harvest applications). The amount of the applied product is present at harvest after the last application, e.g. if diminished to 20 %, the DR equals 0.2. The assumption is made that the DR of the product and the residual impurity is identical.

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

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

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

SF: Safety Factor (default is 1).

Yield: Average Yield/ha (worst case, average of yield in countries of application): kg produce/ha.

Yield data can be obtained from country specific agricultural statistics on crops, FAOSTAT13 and Factfish14.

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

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

August 7th, 2019



Classification of Herbicides

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

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.

August 7th, 2019



Active Ingredients NOELs

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

ent		Herbicide A Herbicide		cide B	Herbicide C		
ingredien		Metosulam	Mesotrione	S-Metolachlor	Haloxyfop-p-methyl		
Active !!		Classification based on US EPA PRN 96-8					
PC.		low application rate herbicide	low application rate herbicide	normal application rate herbicide	low application rate herbicide		
	Сгор		NOEL [g	Al / ha]			
Crop	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)		
ELLE AL / hal	Tomatoca	0.2	0.40	5	> 200 (registered crop)		
NOC	Turf (golf courses)	25 (registered crop)	280	1500	0.01		



Cleaning Matrix

Example of a table created to show required cleaning levels of

Succeeding Herbicide

previous active ingredients

previous active ingredients			(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 ARILs (ppm)				
	Herbicide A	Metosulam	N/A	5000 < 1000	5.0		
	Herbicide B	Mesotrione	700000		400		
			< 1000	N/A			
		S-Metolachlor	1500000	,	5000		
			< 1000		< 1000		
Herbicide C		Haloxyfop-p-methyl	25		N/A		
ning			US EPA PRN 96-8-based ARILs (ppm)				
clean, -	Herbicide A	Metosulam	N/A	20	100		
V vever			,		5		
(npm)	Herbicide B	Mesotrione	100	Ν/Δ	100		
		S-Metolachlor	250		250		
(6,	Herbicide C	Haloxyfon-n-methyl	100	20	N/A		
		παιοχομοροφοιτιστηγι	25	1	17/7		

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



August 7th, 2019

Production Sequencing

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

orly seque	waste and disposal costs.							
property clea	Production Sequences – Biology based ARILs							
3/01-	Sequence 1	Herbicide A Metosulam	< 1000	Herbicide B Mesotrione + S- Metolachlor	400 < 1000	Herbicide C Haloxyfop-p- methyl	25	Herbicide A Metosulam
	Sequence 2	Nerbicide A Metosulam	5	Herbicide C Haloxyfop-p- methyl	1	Herbicide B Mesotrione + S- Metolachlor	< 1000 < 1000	Herbicide A Metosulam
	Sequence 3	Herbicide C Haloxyfop-p- methyl	25	Herbicide A <i>Metosulam</i>	< 1000	Herbicide B Mesotrione + S- Metolachlor	< 1000 < 1000	Herbicide A Metosulam
	Production Sequences – US EPA PRN 96-8 based ARILs							
	Sequence 1	Herbicide A Metosulam	20	Herbicide B Mesotrione + S- Metolachlor	100 250	Herbicide C Haloxyfop-p- methyl	25	Herbicide A Metosulam
	Sequence 2	Herbicide A <i>Metosulam</i>	5	Herbicide C Haloxyfop-p- methyl		Herbicide B Mesotrione + S- Metolachlor	100 250	Herbicide A Metosulam
	Sequence 3	Herbicide C Haloxyfop-p- methyl	25	Herbicide A <i>Metosulam</i>	20	Herbicide B Mesotrione + S- Metolachlor	100 250	Herbicide A Metosulam



Insecticide Cleaning Levels

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



Honey bee LD₅₀ values are typically available for all active ingredients.

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



Fungicide Cleaning Levels

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





Manufacturing Practices Identification of Incoming Goods

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



- 1. Bill of lading against a purchase order
- 2. Certificate received with specification

3. Identity or perform Quality Control tests prior to release in manufacturing



Changeover and Release of Equipment

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

Written records to be maintained and include...

- ✓ Dates of previous production and cleaning
- ✓ Confirmation of each cleaning step
- \checkmark Analytical evidence verifying content of AI is below the RIL
- Verification that cleaning procedure has been followed, visual inspection, second person sign off, etc.
- ✓ Formal 'release' of equipment







Staging Material(s)



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



- At the warehouse, verify the name and batch number of material when picking
- Use FIFO
- Production to verify the material received is the same as indicated on the batch record



Personnel performing tasks should sign documentation



Shared Equipment

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



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



Shared Equipment

Direct contact



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



If permeable,
 porous, or difficult
 to clean –
 <u>dedicate</u> to a
 specific active.

No Direct Contact



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



Tools

 ✓ Sharing tools is permitted but check to be sure they are clean (no residue present)





 ✓ In a solids plant, vacuum cleaners for equipment must be dedicated when the solids are returned to the process.



Dedicated Refillable Containers

As a minimum, the following must be in place:

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







Non-dedicated Refillable Containers

As a minimum, the following must be in place:

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









Labeling Refillable Containers

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

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



When the container is empty, the label should indicate...

- $\checkmark~$ Cleaning status and previous product
- ✓ Date of last cleaning
- ✓ For aqueous products, empty containers should be dry and closed, to avoid microbial growth



Relabeling and Overlabeling

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

- Legal requirements
- Risk assessment
- Risk mitigation measures



Storage of Materials

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



- ✓ The outside of the package is clean
- Herbicide and non-herbicide active ingredients are physically separated
- Non-herbicide inert raw materials are physically separated from herbicide active ingredients
- ✓ Separations clearly marked
- ✓ Clear labeling in place
- Partially used materials must be returned to appropriate storage areas and wrapped



Storage Tanks

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



2 layers of protection should be part of the design:

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

Operating procedures should confirm that processes cannot be fed simultaneously.



Reworking, Blending, and Recycling

Applying these practices will minimize risks...



If collected from external surfaces, discard.



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



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



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

Product release samples must not be recycled.





Reworking, Blending and Recycling

Continued practices...



If not contained within production equipment, discard the dust.



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



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



Off spec material must be labeled.

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

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



August 7th, 2019

Final Product Labeling

Product Label 'X"				
Material Name:	Good Stuff			
Product Code:	XYM985			
Batch Number:	AC151406			
Production Date:	03-14-14			
Quantity:	50.2 kg			

If temporary labels are needed, the product name, batch and quantity should be included...



To avoid mix-ups, label control needs to be in place



Traceability



Traceability must be in place for production, filling and packaging operations. Items to consider:

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



Modifications

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



A Management of Change procedure is in place.



The design change includes the cleaning process.



Yes or No...

- Verify cleaning procedures after change
- ✓ Before first use, ensure cleanliness



Self-Assessment



Completing the '**Contamination Prevention**' self-assessment provides a good baseline for measuring improvement in quality practices.

Documents for Chemical Contamination Prevention and Biological Contamination Prevention are available on the CropLife International website



Production Scheduling



Items to consider when scheduling production:

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

Low rate refers to herbicides with an application rate of \leq to 560 g Al/ha. 'Highly active' refers to herbicides with an application rate of < 50 g Al/ha (See also slide 39)



Cleaning Procedures

Written procedures for cleaning must detail:

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







There are specific guidelines for cleaning <u>liquid</u> versus <u>solid</u> production units.



Visual Inspection

CropL



Visual inspection is a key step in cleaning

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



Wet Cleaning

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





Dry Cleaning

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

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





Cleanout Capability

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

Capability is demonstrated through:

- ✓ Definition of critical parameters (design, process conditions)
- $\checkmark\,$ Selection of low level or difficult cleanouts
- \checkmark Adherence to procedures
- \checkmark Analyses of multiple cycles of residue material
- ✓ Analysis of the succeeding product for RI of previous product

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



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



August 7th, 2019

Cleaning Medium

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

Re-use savings

Ecological



Labeling errors

Storage stability



Residual Impurity Analysis

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



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



Flush results are not a guarantee.


Sampling

Determine sampling locations...

Formulation vessels



Packaging line



Last rinsate



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



Analytical Methods

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

Validation of methods should include:

- ✓ Specificity
- ✓ Recovery
- ✓ Repeatability
- ✓ Linearity

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



Understand the cleaning levels and choose the appropriate analytical approach.



Contamination Prevention Making it Sustainable

Keep all the Pieces Together

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





Disclaimer

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

CropLife International, its employees, its committee members, and its member associations and companies assume no responsibility for consequences resulting from the use of the information herein, or in any respect for the content of this information, including but not limited to errors or omissions, the accuracy or reasonableness of factual or scientific assumptions, studies or conclusions. CropLife International is not responsible for, and expressly disclaims all liability for, damages of any kind arising out of use, reference to, or reliance on information provided in the guidelines. No guarantees or warranties, including but not limited to any express or implied warranties of merchantability or fitness for a particular use or purpose, are made by CropLife International with respect to the information provided in

August 7th, 2019

