Contamination Prevention in the Manufacture of Crop Protection Products

Guidelines and Best Practices

This Presentation is Made on Behalf of

and its Corporate Members

Contamination Prevention
What are the CropLife Requirements?

Ensure that…

- ✓ No extraneous active ingredients are present in products
- ✓ In compliance with legal requirements and local legislation
- ✓ External Manufacturers are provided adequate information to adhere to the requirements

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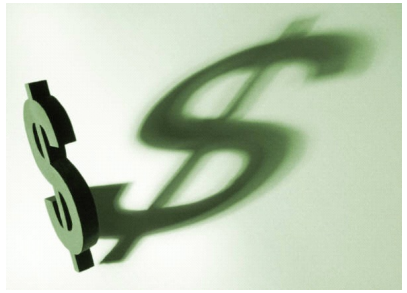
Example Of An Actual Incident

The situation….

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



It is Preventable

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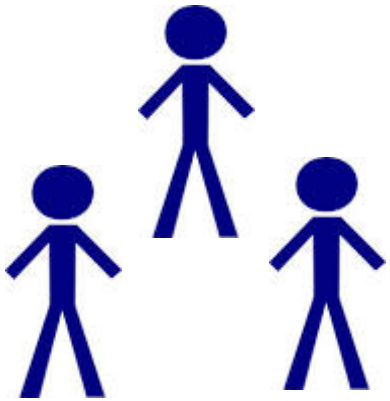
Contamination Prevention

Example Of An Actual Incident

The situation….

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



It is Preventable

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Example Of An Actual Incident

The situation….

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

2000 ppm
vs
1000 ppm

It is Preventable

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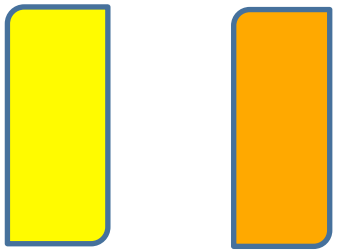
Example Of An Actual Incident

The situation….

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

Don't bypass equipment during cleaning steps



It is Preventable

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Example Of An Actual Incident

The situation….

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

Is the default limit always low enough?

It is Preventable

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Example Of An Actual Incident

The situation….

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

It is Preventable

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Example Of An Actual Incident

The situation….

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

If it doesn't look normal stop…

It is Preventable

Contamination Prevention What is Needed?

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

Separation of herbicides and non-herbicides

Clear labelling

Avoid cross contamination with rework or recycle

Documented Risk Assessments

Cleaning procedures and analytical methods

Contamination Prevention What is Needed?

Promptness in Clean out

Additional Requirements

Portable equipment must be dedicated

Define Residual Cleaning Limits

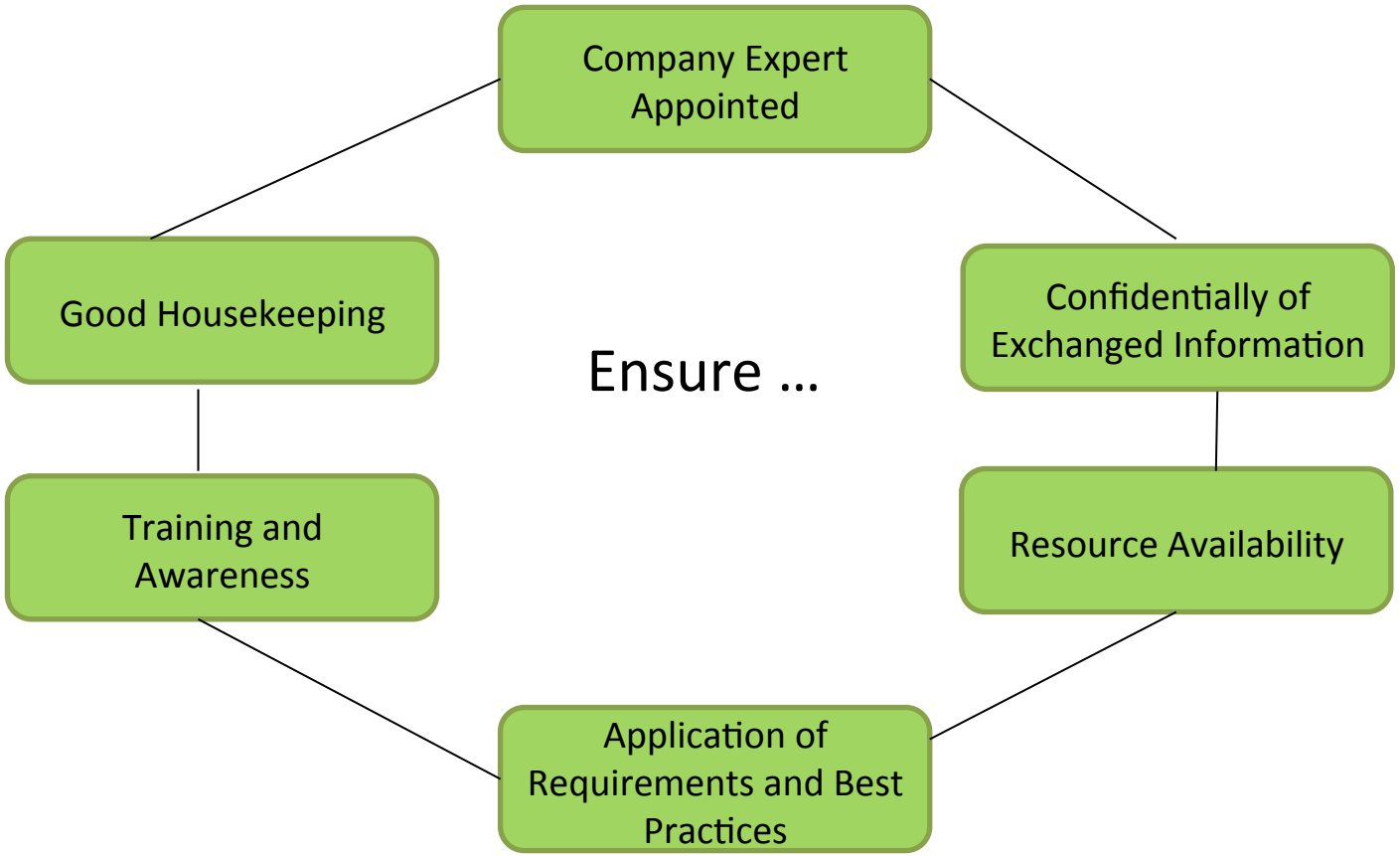
1,000	1,000	1,000	67	100	1,000	1,000	1.0	1,000	1,000
1,000	1,000	1,000	100	100	1,000	NA	1.0	1,000	1,000
1,000	1,000	1,000	67	100	500	NA	1.0	1,000	1,000
1,000	1,000	1,000	33	100	1,000	NA	1.0	1,000	1,000
NA	1,000	1,000	100	100	1,000	1,000	1.0	1,000	1,000
NA									
NA	1,000	1,000	100	100	500	1,000	1.0	1,000	1,000
NA	1,000	1,000	100	100	1,000	1,000	1.0	1,000	1,000
NA	1,000	1,000	100	100	1,000	1,000	1.0	1,000	1,000
1,000	1,000	1,000	119	NA	417	833	20	1,000	1,000
1,000	1,000	1,000	167	NA	833	1,000	20	1,000	1,000
				NA					
1,000	1,000	1,000	250	NA	1,000	1,000	20	1,000	1,000
				NA					
1,000	1,000	1,000	250	NA	1,000	1,000	20	1,000	1,000
				NA					
1,000	1,000	1,000	250	NA	1,000	1,000	20	1,000	1,000
				NA					
1,000	1,000	1,000	50	100	1,000	1,000	1.0	1,000	1,000
1,000	1,000	1,000	50	100	1,000	1,000	1.0	1,000	1,000
1,000	1,000	1,000	100	100	1,000	1,000	1.0	1,000	1,000

Refillable container maintenance

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

External Manufacturing

Information Exchange

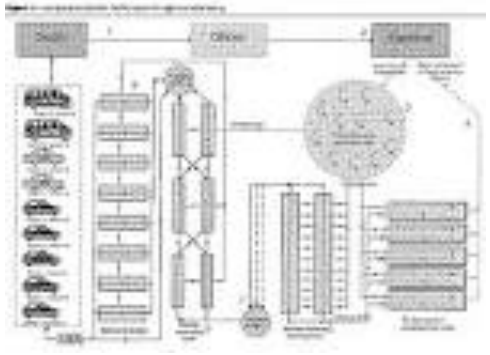
The External Manufacturer must supply the succeeding client the following:

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

List of Actives

Metosulam
Mesotrione
S-Metolachlor
Haloxyfop-p-methyl

Layout of Unit



Location of Facility

External Manufacturing

Information Exchange

Requestor → **Provider ↓**	**External Manufacturing**	**Succeeding Client**
Preceding Client	• Analytical standards* • Analytical methods* • Cleaning methods*	• Active present in products • NOEL**, ED_5 or ED_{10} 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

SEPARATE

Herbicides

e.g. herbicides, defoliants, and desiccants

Non-herbicides

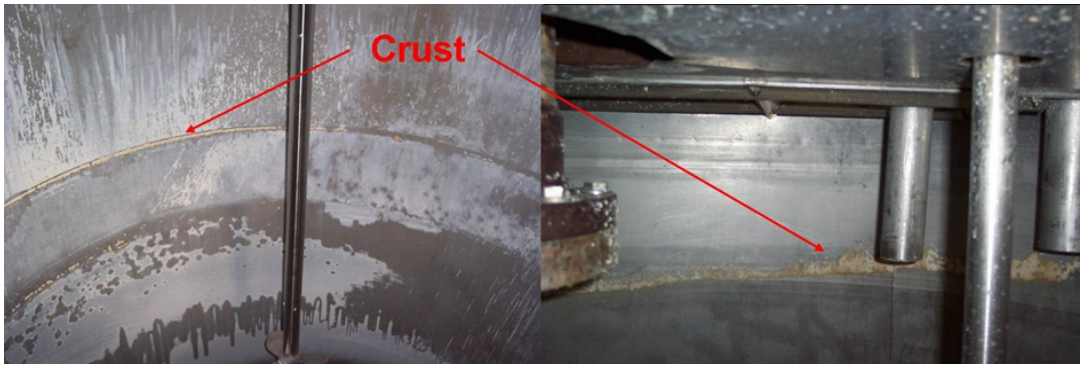
e.g. fungicides, insecticides, acaricides, molluscicides, nematicides, pheromones, plant activators, herbicide safeners, rodenticides, crop oils and adjuvants

Cleaning Capability

Two critical elements which must always be evaluated…

1. Design of the production unit

(look for 'dead spaces')



2. Cleaning procedures

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Cleaning Level Determination

Key items needed to calculate levels

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

NOEL data for Herbicides

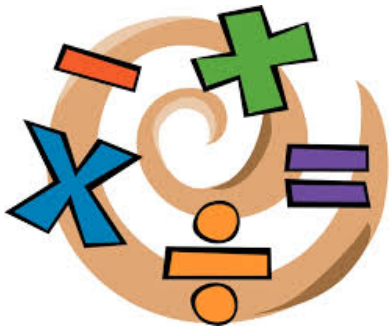
NOELs are typically determined from greenhouse studies

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 Calculation

The Cleaning Level is inversely proportional to the Application Rate (AR)!

3 elements in the equation…

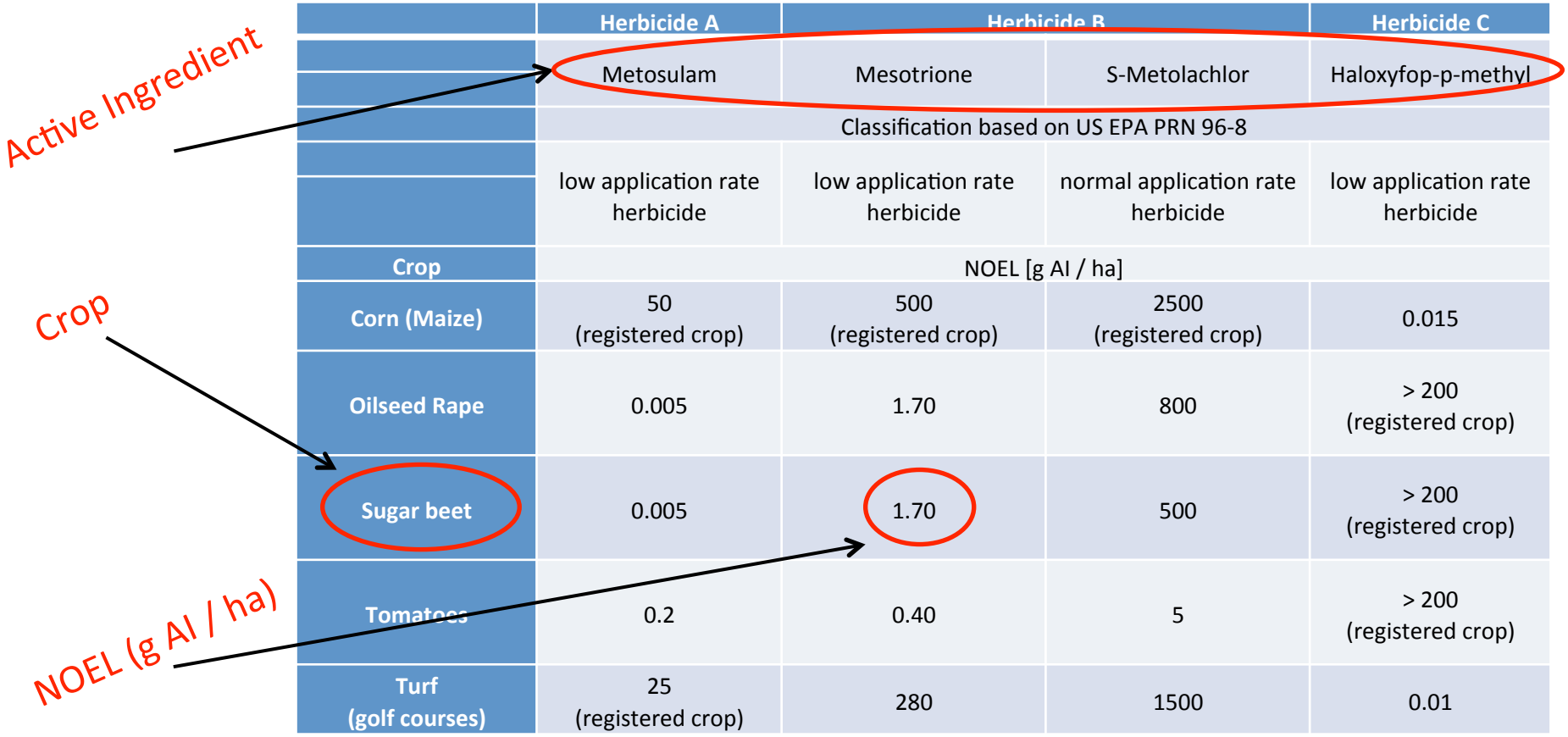
- AR
- NOEL
- Safety factor (SF)

$$\text{Cleaning Level [ppm]} = 10\uparrow 6 \times NOEL/SF \times AR$$

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

Active Ingredients NOELs

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



	Herbicide A	Herbicide B		Herbicide C
	Metosulam	Mesotrione	S-Metolachlor	Haloxyfop-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

Cleaning Matrix

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

		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 ARILs (ppm)		
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	*Haloxyfop-p-methyl*	25	1	N/A
		US EPA PRN 96-8 based ARILs (ppm)		
Herbicide A	*Metosulam*	N/A	20	100 5
Herbicide B	*Mesotrione*	100	N/A	100
	S-Metolachlor	250		250
Herbicide C	*Haloxyfop-p-methyl*	100 25	20 1	N/A

Cleaning level (ppm)

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

Production Sequencing

There may be preferred options in sequencing production, avoid low cleaning limits. Optimum sequencing can reduce cleaning time and waste.

Properly sequenced to avoid low cleaning levels

Production Sequences – Biology based ARILs							
Sequence 1	**Herbicide A** ***Metosulam***	**< 1000**	**Herbicide B** *Mesotrione + S-Metolachlor*	**400** **< 1000**	**Herbicide C** ***Haloxyfop-p-methyl***	**25**	**Herbicide A** ***Metosulam***
Sequence 2	**Herbicide 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** ***Metosulam***	**< 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** ***Metosulam***	**5**	**Herbicide C** ***Haloxyfop-p-methyl***	**1**	**Herbicide B** *Mesotrione + S-Metolachlor*	**100** **250**	**Herbicide A** ***Metosulam***
Sequence 3	**Herbicide C** ***Haloxyfop-p-methyl***	**25**	**Herbicide A** ***Metosulam***	**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 LD_{50} values are typically available for all active ingredients.

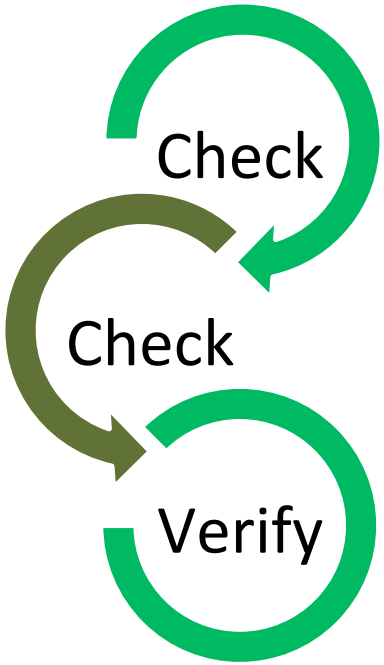
An equation for calculating Insecticide Cleaning Levels can be found in the booklet in more detail (see chapter 6.3).

Fungicide Cleaning Levels

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

Manufacturing Practices
Identification of Incoming Goods

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



1. Bill of lading against a purchase order

2. Certificate received with specification

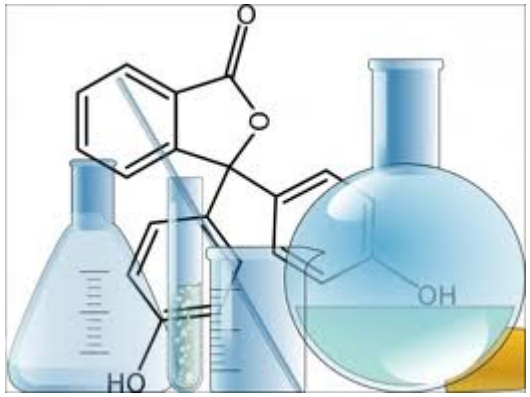
3. Identity or perform Quality Control tests prior to release in manufacturing

Changeover and release of equipment

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

Written records to be maintained and include…

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



Staging Material(s)

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

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

- Personnel performing tasks should sign documentation

Shared Equipment

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

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

Shared Equipment

Direct contact

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

- ✓ If permeable, porous, or difficult to clean – <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 non-herbicide 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
- ✓ Visual inspection upon return to a plant
- ✓ Backflow prevention in place to avoid cross-contamination during offloads

Non-dedicated Refillable Containers

As a minimum, the following must be in place:

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

Labeling Refillable Containers

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

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

When the container is empty, the label should indicate…

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

Storage of Materials

Raw materials for herbicide and non herbicide operations may 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:

- ✓ 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.

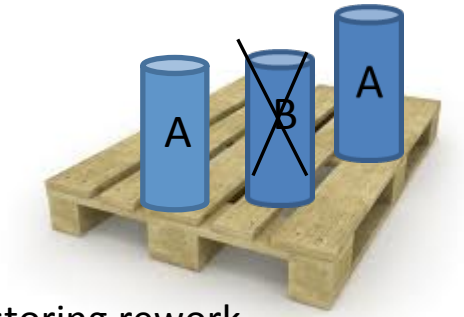
Reworking, Blending, and Recycling

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.

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…

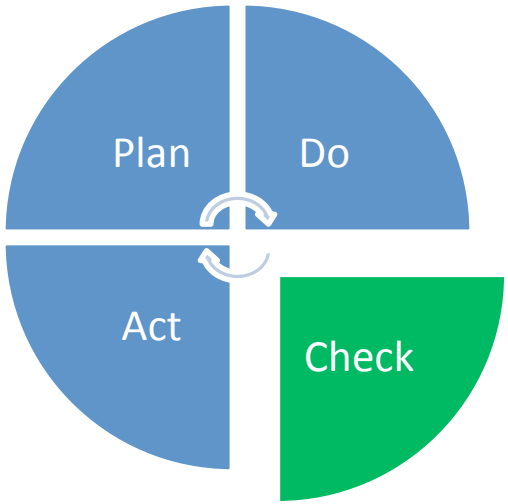
A Management of Change procedure is in place.

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.

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 ≤ to 560 g AI/ha.
'Highly active' refers to herbicides with an application rate of < 50 g AI/ha

Cleaning Procedures

Written procedures for cleaning must <u>detail</u>:

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

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

Visual Inspection

Visual inspection is a key step in cleaning

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

Wet Cleaning

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

Dry Cleaning

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

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

Cleanout Capability

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

Capability is demonstrated through:

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

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

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

Cleaning Medium

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

Re-use savings

Ecological

Labeling errors

Storage stability

Residual Impurity Analysis

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

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

Flush results are not a guarantee.

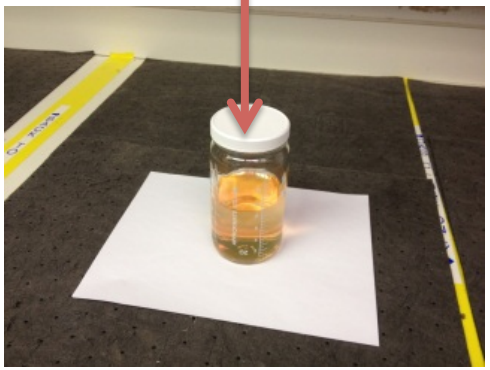
Sampling

Determine sampling locations...

Formulation vessels

Packaging line

Last rinsate



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

Analytical Methods

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

Validation of methods should include:

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

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

Understand the cleaning levels and choose the appropriate analytical approach.

Contamination Prevention Making it Sustainable

Keep all the Pieces Together

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

Disclaimer

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