

Contamination Prevention in the Manufacture of Crop Protection Products

Guidelines and Best Practices



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 to another selective herbicide requires extremely thorough cleaning coupled with a very low cleaning level (see Chapter 6).

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Dr. Marten Snel (Consultant CPF), Dr. Christian Müller (Syngenta Crop Protection AG), Simon Lee (Dow AgroSciences LLC), Dipl.-Ing. Heiko Wolf (BASF SE), Dr. Wolfgang Schäfer (BASF SE), Dr. Jürgen Henneböle (Bayer CropScience AG), John Olsen (DuPont Crop Protection), Ir. Gunther Baert (Monsanto Company), Ir. Eric Rochedix (SUMITOMO CHEMICAL AGRO EUROPE S.A.S.), Linda Bagley (Dow AgroSciences LLC), Dr. Lennart Weltje (BASF SE) and Dr. Urs Stutz (Syngenta Crop Protection AG).

Foreword

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Dear Reader,

The commitment of the entire Crop Protection industry to Responsible Care® is very well known. Therefore it will come as no surprise that we saw the need to update the information on Contamination Prevention and share the latest best practices on Contamination Prevention.

We hope you are already familiar with our booklet “Implementing Contamination Prevention”. This booklet, first published in 2004 was followed by an updated 2nd edition in 2008, and helped to raise the standard of Contamination Prevention throughout the industry. The booklet became a widely used source of information for the development of improved and more effective implementation of Contamination Prevention procedures for the CropLife International member companies, but also for their External Manufacturers (contractors). The global importance of this booklet is best illustrated by the fact that it has been translated in seven different languages: French, Spanish, Portuguese, German, Russian, Korean and Chinese.

A team of experts from the CropLife International member companies have written this 3rd edition. We decided to change the title of the booklet to **“Contamination Prevention in the Manufacture of Crop Protection Products - Guidelines and Best Practices”** because this emphasizes even more our commitment to provide our industry with guidelines to help implementation of optimal Contamination Prevention.

A contamination incident may have far reaching consequences: increased manufacturing costs, product recalls, product disposal with a possible environmental burden and even a loss of reputation. This dent in credibility may not be limited to the company where the incident occurred in the first place, but could impact our entire industry.

I see it as our obligation to provide agriculture with quality products that live up to the promises made on the label without any undesirable side effects (e.g. on non-target organisms or crop damage) and meet

all regulatory criteria. In other words, we deliver products that can be trusted. This can only be achieved if our industry has appropriate Contamination Prevention management in place.

Are there any golden rules to ensure the prevention of contamination incidents? Please allow me to make some suggestions (there are many more, which you will find in the booklet).

- In any organization, on any production site, everybody needs to believe in the Contamination Prevention philosophy starting at the top management
- Through regular training we must be constantly reminded of the significance of Contamination Prevention. We must avoid becoming complacent!
- Irrespective of the urgency to fill an order, never make short cuts in the procedures, like having a “one-off” reduced cleaning program
- Have clear check lists
- If you are in the fortunate position to build a new installation or update an existing one, think “Contamination Prevention” all the time otherwise you miss a great opportunity

Our experts have been asked to ensure that all aspects of Contamination Prevention are highlighted and give proper guidance for all areas of our processes: production, quality assurance, planning (production scheduling), determining cleaning levels and procurement.

I am certain you will find this booklet very informative and trust you will study it carefully, and urge you to use these “Guidelines” on a frequent basis as reference. This group also sponsored another publication on the closely linked topic: “Prevention and Control of Microbial Growth in Water-based Crop Protection Formulations”. In case you manufacture aqueous formulations, we suggest you consider adopting the best practices described to optimize prevention of microbial growth.

George L. Poe

Chairman CropLife International Operations
Committee

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1. Introduction

The Crop Protection industry utilises 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.

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, formulation as well as in (re-)packaging of agricultural chemical products.

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

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

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 at specific to farm operations (e.g. tank cleaning).
- Issues related to Contamination Prevention in biotechnology and seeds, e.g. GMO / non-GMO contamination during seed production.
- Bulk deliveries and storage of final product at distributors and dealers. Guidelines for implementation of Contamination Prevention measures for handling final product in bulk are considered the responsibility of the individual member companies and the regional Crop Protection Organizations.
- Contamination Prevention in:
 - 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, which are manufactured under pharmaceutical standards (GMP), where animals might be exposed to a contaminant.

3. 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.

3.1 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 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 cleaning level.
- 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 rework campaign.

What can be learnt 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.

3.2 Case History 2: Incorrect cleaning level

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 cleaning level 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 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 reworked (blended) to 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 learnt 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 than before.
- Even if a cleaning level of 2000 ppm would have been safe, never use a cleaning level 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 cleaning level 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.

3.3 Case History 3: Incorrect cleaning procedure

In a formulation plant, a 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 (20000 l) had to be discarded in its entirety.

What can be learnt 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.

3.4 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 cleaning level 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 cleaning level for a change-over from an insecticide in a fungicide.
- A carefully managed, well documented cleaning procedure had been carried out.

What can be learnt from this case history?

- Although the manufacturer followed the legal requirements for cleaning levels, in some cases remaining insecticide residues can cause adverse effects, like a massive kill of predatory 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).
- A cleaning level based on biological properties of the insecticide should be calculated rather than relying only on the values given in PRN 96-8.

3.5 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 intact containers with the same batch number as product used from the inventory of 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 cross contamination had already been carried out. The material was released and ready for packaging before the contamination occurred).
- 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 yields 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 learnt 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.

3.6 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 external manufacturer 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 learnt 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”.

3.7 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.
- The residual amount of the herbicide contaminated the fungicide and the flower bulb crop failed completely.

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

What can be learnt 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?

3.8 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 20000 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 15000 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 learnt 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.).

3.9 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 herbicide. Customers complained of crop damage when using the insecticide. Subsequent analytical testing showed low-level contamination of the product with the herbicide.

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 learnt 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 separate buildings. Whilst an insecticide and a normal rate herbicide would require at least separate rooms with a solid, air-tight wall and separate air handling systems, an insecticide and a highly active herbicide would require separate buildings.

3.10 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 ARIL (acceptable residual impurity level) 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 learnt 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”.

3.11 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 learnt 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).

3.12 Case History 12: Missing labels on the AI drums

A contract manufacturer had to formulate simultaneously an insecticide and a herbicide EC. On the site there was a nearly 100% segregation of herbicides and non-herbicides. 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. This 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 formulating 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.

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

What can be learnt 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.

3.13 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/I product from the warehouse 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/I 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/I) 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 relabeled properly. Incidents of this nature always tend to cause undesirable unrest in the market.

What can be learnt 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.

3.14 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; an insecticide was identified that was not registered on the crop in question in a residue analysis.

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 showing 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 learnt 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.

3.15 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 External Manufacturer 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 rework 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 learnt 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.

4. Contamination Prevention Requirements

Simultaneous manufacturing of crop protection products in multi-product facilities is a common practice, yet introduces the risk of cross-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 their External Manufacturers will commit to the Policy and Requirements in this chapter.

4.1 Contamination Prevention Policy

- They will 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 External Manufacturer will provide available information to their best knowledge to enable the succeeding client of the External Manufacturer to carry out appropriate risk assessments and to set limits for residual impurities. The External Manufacturer will ensure the information exchange by providing data or as a minimum, the other clients contact information.

4.2 General Requirements

- Documented contamination prevention risk assessments must be in place.
- Cleaning levels must be defined.
- Non-herbicides must not be produced in the same equipment as herbicides, i.e. separation 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 history 3.7).

- 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 rework must be managed to minimize any risk of cross contamination.
- All materials must be clearly and properly labeled, this includes but is not limited to: raw materials, intermediates, bulk formulations, finished products, rework, recycle, and waste (see case history 3.12).
- Effective cleaning procedures and validated analytical methods must be available to analyze residues in wash liquids (rinsates), and/or analyze 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 3.1 and 3.3). This applies to all synthesis, formulation, filling and packaging equipment.

4.3 Management Responsibilities

The management of all CropLife International member companies and their External Manufacturers will 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.

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

4.4 External Manufacturing of active ingredients and formulations

4.4.1 Information Exchange

The External Manufacturer 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 cleaning levels (see case history 3.3).
- The physical lay-out of the facility that could impact Contamination Prevention (see case history 3.9).
- 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.

The preceding client must supply to the External Manufacturer the following if requested and available for the previous products:

- Analytical standards.
- Analytical methods to allow determination of the cleaning levels required by the succeeding client. In case it is possible to provide these methods, the External Manufacturer is required to verify that these methods work in his laboratory.
- Cleaning methods. In case it is possible to provide these methods, the External Manufacturer is required to verify that these cleaning methods are effective in his plant, equipment and configuration.

4.4.2 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 External Manufacturer. There may be additional specific requirements agreed between client and External Manufacturer.

* *Preceding and succeeding client indicates production sequence at EM*

The client is responsible:

- To specify whether the cleaning level must be achieved in the succeeding product or in the wash liquids (rinsates). In all cases, the finished product must meet the agreed cleaning level.
- To undertake detailed site audits and other due diligence activities (including the cleaning process and results) and support the External Manufacturer where appropriate.
- To use the information obtained from the preceding client exclusively for the purposes of Contamination Prevention.
- To inform the External Manufacturer of any special risks (e.g. highly active herbicide) associated with the product being brought onto the External Manufacturer's site.
- To review and if necessary update existing contracts and/or agreements with External Manufacturers 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 External Manufacturer 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 External Manufacturer'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 cleaning levels. 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, the analytical data should at least be retained at the facilities of the External Manufacturer.
- There are written changeover procedures, including the clean-out procedures and a check-list to be followed.
- To ensure periodic 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 rework (blending, recycling) is approved by the client (see case history 3.15).
- To maintain good housekeeping practices.
- To ensure the retention time and storage conditions of retained samples specified by the client are followed.

4.5 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 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 3.14).

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 “cross contamination” and “contamination prevention” (see Glossary)
- The product(s) must meet all regulatory requirements

- Agreement reached that

EITHER

- a. 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

- b. 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.

5. Contamination Risk Assessment Elements

A contamination risk assessment is conducted for the production unit and all products manufactured in it. Such a risk assessment includes 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.

There are five main categories contributing to the calculation of cleaning levels which need to be considered for the risk assessment (for details see chapter 6):

1. Product category (low rate herbicide, herbicide, insecticide, other) and separation.
2. Region (legal requirements, e.g. US EPA PRN 96-8).
3. Toxicity on non-target organisms.
4. Application rates.
5. Safety factors.

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

Design and lay-out of production units greatly impact the ease with which such a unit can be cleaned. All cleaning aspects should be included in the risk assessment.

5.1 Separation of production units

Separation of production units is a key element in Contamination Prevention. A “production unit” is a combination of equipment used for the manufacture of product. It may be used for multiple products in sequence. A manufacturing site may consist of multiple production units. “*Separation*” means that there is no shared common equipment (e.g. ventilation ducts and vent headers) that 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 separation because even if it is indicated that the valve is closed a small leakage could occur. An effective way to achieve separation is through having separate 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 3.8).

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

- ***Separate “Herbicides” from “Non-herbicides”***

This separation is achieved by having production units, which are completely dedicated to either “herbicides” or “non-herbicides” (see chapter 4.2).

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:
 - a. Human and Veterinary pharmaceutical products applied orally, topically or as an injection.
 - b. Personal Care and other health care products.
 - c. Food and feed stuffs (including vitamins).

Various requirements are based on Good Manufacturing (GM) guidelines 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 “highly active herbicides” from “normal and low rate herbicides” if the herbicides are registered on different crops.** Considering the difference in the application rates of normal rate herbicides and highly active herbicides, a potential contamination of the normal rate herbicide could result in adverse effects on non-target crops. 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 6).
- **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 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 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. Effective Dose (ED) assessments for PGRs are virtually impossible due to low phytotoxicity and NOEL's are not available at present.

Whenever a production is planned that presents an increased contamination risk, it is recommended that an additional risk assessment is completed and approval from senior operations and marketing management is obtained. These cases should be considered as exceptions with a clear time limit.

5.2 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 chapter 6.2.8).
- Cleaning levels in place and up to date (see case history 3.2).
- Verified cleaning method available.

- Rework/recycle and blending practices (see case history 3.15).
- 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 3.9).
- 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.

5.3 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 the 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 cleaning procedures. Their four key elements are:
 - a. Correct cleaning levels (see chapter 6).
 - b. Cleaning methodology (see chapter 8).
 - c. Analytical capability (see chapter 9).
 - d. Documentation (record keeping, retained samples) (see chapters 4 and 7).

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 5);
- 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 5);
- Formulation and packaging of solid products: < 200 ppm typically achieved after dry cleaning followed either by wet cleaning or “flush cleaning” (see table 6).

6. Determination of Cleaning Levels

The cleaning level required for a product-changeover is the primary indication of the risk involved in the changeover, i.e. the lower the cleaning level, the higher is the risk 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 cleaning levels. 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 a herbicide packaging unit in chapter 6.2. Cleaning level requirements for insecticidal and fungicidal active ingredients as a contaminant in succeeding foliar spray and seed treatment products will be highlighted in chapters 6.3 and 6.4.

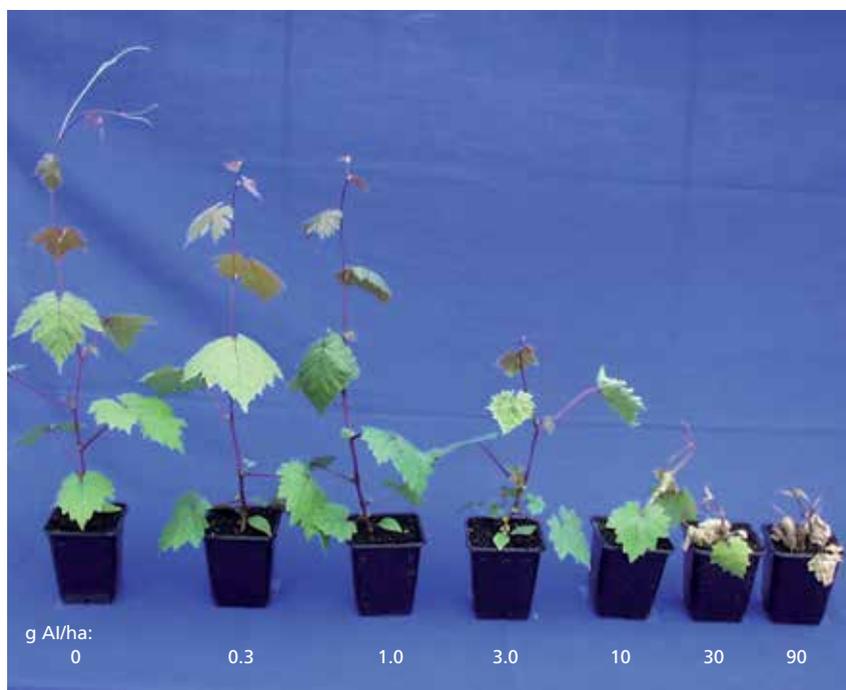


Figure 1: Dose response study of a cereal herbicide as contaminant of a grape fungicide illustrating the damage some active ingredients cause, even at low application rates, when applied on non-target crops. The grape vines were treated with the registered amount of the fungicide with increasing concentrations 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.

6.1 Principles

The objective of setting cleaning levels 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 cleaning levels must be documented and retained for the life-time of the product. Cleaning levels may change over time; the newest version must always be used in operations (version control).

To calculate the cleaning levels, it is necessary to know:

- For low rate herbicides: the No Observable Effect Levels (NOELs) of the active ingredient.
- The 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)¹;
- For insecticides: the LD₅₀ (Honeybee) and the region where the product is used to cover legal requirements.

The lowest NOEL (of the previous AI on the following crop most sensitive to this AI) must always be used, irrespective whether the succeeding product is also applied on [less sensitive] crops with a higher acreage.

The Guidelines on the Toxicologically Significant Levels of Contamination (TSLCs) 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 cleaning levels. The full text of this document is available in Appendix A. The Pesticide Regulation (PR) Notice 96-8 is applicable to products manufactured, imported, and / or used in the US. This means that the cleaning levels

¹ 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 products with the US 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 cleaning level based on biology is lower than the regulatory limits, the biology based level must be used.

In most countries outside the US, the government agencies generally have not defined specific cleaning levels for the crop protection industry, **provided the limits used for the cleaning levels 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.

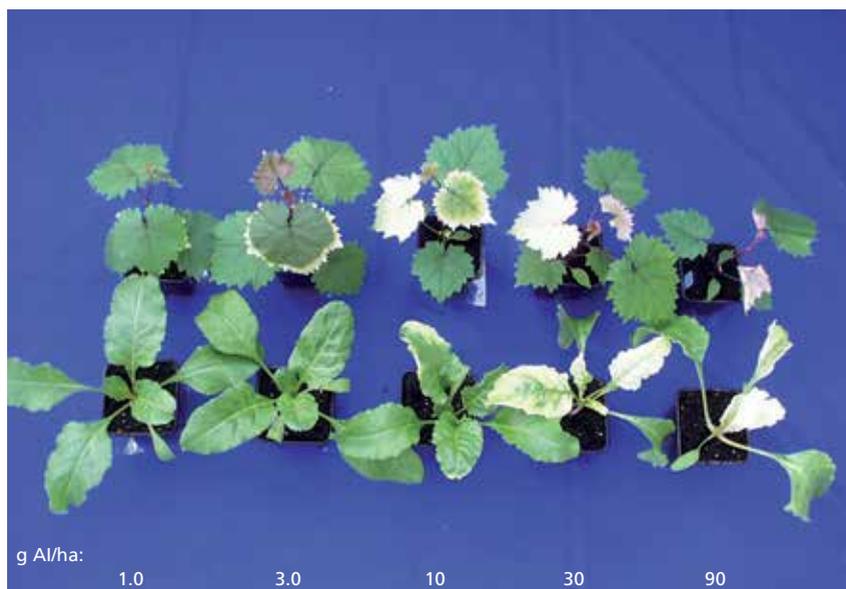


Figure 2: Dose response study of clomazone on grape seedling (top) and sugar beet (bottom). For cleaning level calculations, the NOEL of the residual impurity on the most sensitive crop that the succeeding product is applied on must be used. Grape seedlings are clearly more sensitive than sugar beet.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

6.2 Herbicide cleaning levels

To calculate biology based cleaning levels, it is necessary to have a database with NOEL data. The biology based cleaning levels 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 cleaning levels in liaison with manufacturing and regulatory colleagues.

6.2.1 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 cleaning level. ED_5 or ED_{10} values are often used as starting point for the cleaning level 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.

Extra attention is required when calculating cleaning levels for “highly active herbicides”. “**Highly active herbicides**” 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.

6.2.2 Safety Factors

Safety factors (SFs) are implemented in the calculations of cleaning level 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.

6.2.3 Application rates

Application rates are needed as part of the cleaning limit calculation. It is mandatory 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 cleaning limit the highest single application rate or highest seasonal application rate on the registered crops of the succeeding product will be used, based on the company specific risk assessment.

6.2.4 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 CL² and provide this to the External Manufacturer prior to the production of his product. The External Manufacturer is not expected to calculate the cleaning level for the succeeding client; this is best done by the "RI-specialist" in the succeeding client's organization. The ultimate responsibility for the integrity of the products lies with the succeeding client; while the External Manufacturer has to adhere exactly to the manufacturing guidelines received to assure the quality criteria of the client will be met.

² The various CropLife International member companies may use synonyms for CL: ACL, ARIL, RIL, or TCAL, however, they will all be calculated by using the process described in this chapter.

6.2.5 Equations for calculating herbicide cleaning levels

Biology based cleaning levels are calculated using the following equation:

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

Definitions:

- AR: Application Rate of the succeeding product in gram or ml of formulated product / ha. For the calculation the assumption 1 g = 1 ml can be used.
- 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.
- 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.

See also the Appendix C for information on EPA based cleaning levels.

6.2.6 Calculation of herbicide cleaning levels when the preceding product contains two or more active ingredients

If the preceding herbicide formulation contains two or more active ingredients, cleaning levels for all residual AIs should be calculated.

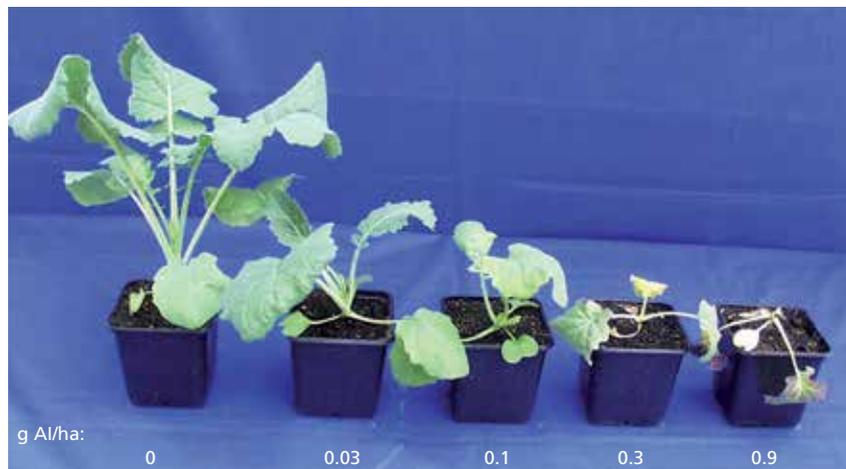


Figure 3: Dose response study of an experimental highly active cereal herbicide (for control of broad-leaved weed species) on the non-target crop oilseed rape. The NOEL on oilseed rape is < 0.03 g AI/ha. The cleaning levels necessary when the succeeding product after this type of herbicide is used on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

Analytical Confirmation will be required to ascertain that the CLs have been achieved for all residual impurities at the change-over. If the cleaning level of one of the AIs has been achieved it cannot be assumed that the cleaning level 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 < CL, that some of the other RIs are only partially removed at that stage.

In case there is more than one potential contaminant, the cleaning level 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 cleaning levels for those AIs should not be higher than the cleaning level of the herbicide with the lowest one.

6.2.7 Example of a cleaning matrix for a herbicide unit

This example shows how to develop a cleaning matrix for a dedicated herbicide unit. The three herbicides are handled interchangeably. The methodology for developing cleaning matrices for synthesis, formulation and repackaging units is identical.

	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 1: 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 RIL.

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	All Preceding Herbicide			
Biology Based ARILs (ppm) ⁴				
Herbicide A	Metosulam	N/A	5000	5.0
			< 1000	
Herbicide B	Mesotrione	700000	N/A	400
		< 1000		
	S-Metolachlor	15000000		5000
		< 1000	< 1000	
Herbicide C	Haloxypop-p-methyl	25	1	N/A
US EPA PRN 96-8 based ARILs (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	20	N/A
		25	1	

Table 2: Example of a Cleaning Matrix for a herbicide manufacturing unit. The NOELs used for these ARIL calculations are listed in Table 1, SF used in this example is 2.

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

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

6.2.8 Effect of the cleaning matrix on product scheduling / sequencing

Analysis of the production sequences as in table 3 shows that there are clearly preferred options. Therefore a careful selection of the production sequence can reduce the contamination risk, save [cleaning] time (< downtime) and reduce waste (< environmental burden and < disposal costs).

<i>Production Sequences - Biologysed ARILs</i>							
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>
<i>Production Sequences - US EPA PRN 96-8 based ARILs</i>							
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 3: 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, sequence 1 (A → B → C → A) avoids the very low cleaning level C → B. In countries implementing US EPA PRN 96-8, the lower EPA based CLs are required for all three changeovers in sequence 1 and 3.

Sequence 2 (A → C → B → A) requires the significantly lower cleaning levels 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 ARILs, see footnote 4 above).

6.2.9 Factors that require extra attention when scheduling the production sequence

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 cleaning level 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 cleaning levels considerable below the values listed in US EPA PRN 96-8 (see case history 3.2).

6.3 Insecticide cleaning levels

In this section on the calculation of cleaning levels, 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 cleaning levels 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.

A cleaning level 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 cleaning level 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 3.4).

6.3.1 Calculation of cleaning levels 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 cleaning level. This ensures that both exposure routes (through contact and feeding) are covered.

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

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

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 cleaning level. 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).

Examples of typical cleaning levels are presented in Table 4:

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 4: Examples of cleaning levels (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.

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

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

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

⁹Candolfi 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.

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 honeybee LD₅₀ > 0.1 µg AI/bee, the suitability of using the bee toxicity data for calculating the cleaning level 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 OECD TG 213/214, 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 cleaning level should be set at a level that will not impact these species.

6.3.2 Calculation of cleaning levels for insecticides in seed treatment applications

In some cases, it may be preferable to calculate a cleaning level for insecticides when the following product is used as seed treatment product rather than use the US ECA 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 logK_{ow} can be used with a trigger value of 3, below which a cleaning level 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 cleaning levels in seed treatment products looks as follows:

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

In the equation for cleaning levels 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 cleaning levels.

6.4 Fungicide Cleaning Levels

This section deals with the calculation of cleaning levels for fungicides as potential contaminants of seed treatment products.

6.4.1 Cleaning levels 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 cleaning level. There may be other fungicidal AIs which also display growth regulator activities on non-target crops.

6.4.2 Cleaning levels for fungicides in seed treatment applications

Also when applied as a seed treatment (FS), azole fungicides are known to display plant growth regulator activities (see case history 3.2). Therefore, it will be a prudent approach to define cleaning levels for these fungicides when preceding seed treatment products. For the above mentioned fungicides preceding a seed treatment product, a cleaning level of 50 ppm is recommended.

6.5 Cleaning levels 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 CLs, 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 ARIL should not exceed one-tenth of the content of the AI. This recommendation is implemented by a number of the CropLife International member companies.

7. 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.

7.1 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 3.6).

7.2 Documentation of changeover and release of cleaned equipment

- Ensure the production unit is clean 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:
 - a. The date of the previous production as well as the date of the cleaning operation;
 - b. Confirmation of completion for each step of the cleaning procedure (for details see 9.1.1) (date and operator initials);
 - c. Analytical evidence that the concentration of the residual impurity is below the agreed cleaning level (see chapter 6);
 - d. Completeness check of the cleaning record including cleaning status, visual inspection and sign-off by an independent person, e.g. the supervisor;
 - e. The formal written “release” allowing the use of the entire cleaned equipment for the manufacture of the next product.

7.3 Controls ensuring correct material delivery to the staging point and manufacture

- Separation of staging areas, e.g. herbicide actives and raw materials stored separately from fungicide active ingredients and raw materials.
- Warehouse personnel to verify the name and batch number of the material when picking (see case history 3.12).

- 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).

7.4 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.

Use of portable equipment in a non-herbicide area once it has been in contact with a herbicide should not be permitted unless stringent verification of cleanliness is confirmed (see case history 3.7).

7.4.1 Direct contact with active ingredients

Before any portable equipment comes into contact with a material containing active 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.

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).

7.4.2 No direct contact with active ingredient

Portable equipment, which in normal use does not come into contact with active ingredients (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.

7.4.3 Tools

Sharing tools (e.g. brushes, wrenches, drills, knives, 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.

7.5 Mobile Refillable Containers

There is a potential risk that cross 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.

7.5.1 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:
 - a. Unique identifier (e.g. serial number);
 - b. 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 cross contamination does not occur during offloading operations.

7.5.2 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:
 - a. Unique identifier (e.g. serial number);
 - b. Correct labeling;
 - c. Name of the previous product;
 - d. 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:
 - a. Cleaning status (cleaned/uncleaned);
 - b. Date of last cleaning;
 - c. First date the refillable container was used and the number of refills.

7.5.3 Labeling of Refillable Containers

All refillable containers must always be labeled properly. In addition to the legal requirements the label should include as a minimum:

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

7.6 Storage

Whilst storage of materials may not be considered as an area of risk, precautions need to be taken to ensure a mix-up does not result in contamination. Provided normal industry standards are applied for finished goods, no specific requirements need be considered for storage of different products. However for raw materials some additional steps need to be taken.

7.6.1 Storage Tanks

Feeding from a common inert raw material source presents a potential risk of cross contamination due to backflow. Different equipment can potentially be directly connected to each other through the raw material feed lines. Where this type of piping exists, it should be designed to prevent both the backflow of material from a process vessel to the common raw material vessel and the cross-flow of material from one process vessel to another.

The piping should be designed to provide at least two layers of segregation between multiple processes. Acceptable piping 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.

7.6.2 Chemical Raw Material Storage

Chemical raw materials used in both herbicide and non-herbicide operations may be stored in common warehouse facilities with the following requirements:

- Ensure cleanliness of the outside of the packaged material.
- Herbicide and non-herbicide active ingredients should be physically separated within the storage area.
- Non-herbicide inert raw materials should be physically separated from herbicide active ingredients within the storage area.
- The separations within the storage area are clearly marked.
- All materials must be clearly labeled.
- Partially used materials must be returned to appropriate storage areas in closed dust proof containers or shrink wrapped.

Where a fully electronically controlled warehouse system is in-place, the requirements (2) and (3) do not necessarily apply.

7.7 Reworking, Blending and Recycling

The following practices will assist in minimizing contamination risks:

- Material collected from the external surfaces of equipment or processing areas must be discarded and not reworked into the system, e.g. spilt material, contents of vacuum cleaners.
- Returned product must be checked to ensure the original seal is intact prior to rework/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.
- Materials containing active ingredients being stored for rework 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. Rework 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 Microbial Growth in Water-based Crop Protection Formulations".
- No rework (including blending) of off-spec. or over-aged batches from previous production runs is allowed without a written procedure. At external manufacturers rework can only take place with written approval from the client (see case history 3.15).
- Any kind of off-spec. material should be clearly marked as such.
- For recycling of used cleaning medium see 8.8.

7.8 Labeling

Minimum requirements are described in 7.5.3 and are applicable for all packaged goods. Temporary labels (in case the final label cannot be applied) are allowed if they contain at least the product name and / or product code,

the batch number and the quantity per packaging unit. 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 3.13).

7.9 Traceability of materials

Traceability of materials (excluding packaging materials) should 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.

7.10 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:

- 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.
- Before the equipment is used for the first time, ensure that it has been properly cleaned.

7.11 Self-Assessment

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

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 cleaning level. 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 chapter 6.2.8.

The following manufacturing solutions should be considered:

- Moving a “highly active” product to a production unit with a more favorable product mix.
- Use of a dedicated line.
- Concentrate “high activity” products 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 cleaning procedure must always be verified and documented (7.2).

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.
- 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 (see 7.2).

- 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

Visual inspection is an essential, cheap, quick and effective 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 5:

		Recommended best practices for cleaning after changeovers in <i>synthesis and formulation and packaging of liquid products</i>		
		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 6:

		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 proven that by applying the written cleaning procedure the required cleaning level is consistently achieved. This is even more important in those cases where the residual impurity (RI) analysis are carried out in the used cleaning agent (rinsate / flush material) and not directly in the subsequent product (see 9.1). To demonstrate the cleanout capability the following should be considered:

- Define critical parameters that impact the cleaning, e.g.
 - a. Equipment design, dead spots;
 - b. Physical chemical behavior (e.g. solubility of products in the cleaning medium);
 - c. 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.
- Analyze several cleaning cycles for the residual impurity. This allows determination of the optimum number of cleaning cycles to achieve the requested cleaning level with maximum efficiency.
- Analyze the actual succeeding product for the RI of the previous product and compare the result with the RI concentration found in the used cleaning medium. 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.
- 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 or omitting a manual cleaning step may cause the cleaning operation to fail.

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 level at which undesirable biological, toxicological, ecological effects or regulatory issues could occur. This requires besides specific cleaning levels for each product changeover 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 cleaning level, analytical methods and suggestions which analytical equipment is most suitable. The EM and the succeeding client 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 (solid or liquid)

A cleaning level is defined as the concentration of the residues of the active ingredient(s) of the previous product in the succeeding product, 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 always guarantee that the level of the residual impurity in the following product is automatically below the agreed cleaning level, even if this level is found 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 Residual Impurity Level (RIL). Examples of sample points 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 RI level in the succeeding product.
- The last rinsate after having flushed cleaning medium through the equipment.

It is recommended that sampling bottles are not re-used (see case history 3.11).

Establish which samples need to be retained as well as the required retention time and storage conditions. Storage of cleaning medium samples is not a requirement.

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 3.10).

Some examples of analytical principles for RI analysis are:

- To analyze water based flush 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).
- RILs 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. Glossary

AI	Active Ingredient.
ACL	Acceptable Concentration Level, synonym of cleaning level.
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 cleaning level.
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 need operator identification.
Beads	Beads of glass or zirconium oxide used in bead mills (ball mills).
Changeover	Process of converting a line or machine from running one product to another.
Certificate of Analysis	Report of the analytical results of a 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 by e.g. built-in spray nozzles.
Cleaning capability	A combination of procedures, know-how and appropriate analytical instrumentation to achieve reliably a given cleaning level.
Cleaning level (CL)	The concentration (in ppm) of the previous active ingredient(s), or any other extraneous substance(s), below which it will not cause any adverse biological, toxicological, or ecological effects or regulatory issues in the succeeding product. Various abbreviations with the same meaning are used (see "Guidelines").

Cleaning matrix	A table showing the required cleaning levels (in ppm) for changeovers; the headers of its rows and columns show all potential products of a production unit as preceding (e.g. in rows) and succeeding (e.g. in columns) product and the cells give the cleaning levels.
Cleaning methodology	A combination of methods to clean a production unit including the sequence of the single cleaning steps, e.g. rinsing top down all parts with water + detergent, dismantling and manual cleaning, exchange of dedicated parts like pumps and milling beads, and visual inspection.
Cleaning procedure	Cleaning methodology adjusted to the required cleaning level plus analytical control of success, organization of the release of the unit and documentation of all steps.
Client	Company contracting the production of a product with an external manufacturer.
Configuration of a production unit	The configuration specifies which parts of a production unit are used for a defined production process.
Contamination in a product	The undesired introduction of a component, not defined in the product specification, at levels which will compromise safety and/or efficacy or does not meet regulatory requirements (see "Guidelines").
Contamination Prevention	Any measure, be it organizational or technical, to prevent the occurrence of a contamination incident.
Contamination risk assessment	Assessment of any factor with the potential to contribute to contamination risks.
CropLife International	Global Association of Crop Protection Companies and their regional trade organisations.
Cross Contamination	See "Contamination in a product".
Dead space	Space inside a production unit, which may hold up product that is not subject to the normal flow of material (product and/or cleaning medium) through the unit; should be avoided through design / construction.

Defoliant	Any product used to cause the leaves of plants 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 the harvest of potatoes.
Design	Arrangement of the various parts, equipment and inter-linkages of a production unit.
Documentation	Written information of procedures, cleaning records, batch cards, analytical results, and of retained samples etc. There are guidelines on the length of time documentation needs to be archived.
Dry formulation	Synonym for solid formulation.
EC	Emulsifiable Concentrate (a solvent based formulation type).
ED₁₀ (effective dose, 10%)	The dose of an AI required to cause a biological effect of 10% after a specified test duration, e.g. 10% shortening of the stem of a treated plant three weeks after application.
EPA	Environmental Protection Agency (USA).
External Manufacturer	A company manufacturing products for crop protection companies on a contractual basis. The clients are the registration holders. Synonymous with: contract manufacturer, contractor, toll manufacturer and "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.
Flexi hose	Flexible hose, used for transfer of materials when no fixed piping is installed; requires special care in Contamination Prevention.
Flowable	Formulation type, synonym of SC.
Fluidized bed	A method for the formulation and/or drying of granules.
Formulation	A preparation of active ingredient(s) and "inert" chemicals (additives) which are necessary for the application of the active ingredient(s).

Formulation unit	Production unit for formulations.
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. Various techniques are being used, e.g. extrusion granulation, fluidized bed granulation.
HEPA	High Efficiency Particulate Air filter. Generic term for highly efficient filters for airborne particles $\geq 0.3 \mu\text{m}$ (micron, micrometer). Based on particle count the efficiency of HEPA filters is 99.97%.
Herbicide	Any product used to destroy plants (esp. weeds), or to control their growth
Highly active herbicide	Application rate typically below 50 g AI/ha, e.g. sulfonylureas, imidazolinones, triazolopyrimidine sulphonanilides. This is by no means an exhaustive list and there are other herbicides that could fall in this category.
IBC	Intermediate Bulk Container: movable container for liquids or solids between 200 and 5000 liters.
Information Exchange	Exchange of contamination-relevant information (e.g. phytotoxicity, NOELs, analytical methods ...) between CropLife International member companies and/or their external manufacturers and/or their suppliers.
Insecticide	Any product used to kill potentially damaging or harmful insects.
Integrated Pest Management (IPM)	A pest control management system integrating the use of pesticides 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.

Isotainer, ISO tank	ISO standardized container for liquids between 5 and 25 m ³ Volume, which can be transported by road, rail or ship.
Letter of Access (LoA)	Document provided by supplier to third parties co-marketing products with supplier's AI. Required for registration submission by third party.
LD₅₀/LC₅₀ (Lethal dose, 50%; lethal concentration, 50%)	The dose/concentration of an AI or a formulation of a crop protection chemical) required to kill 50% of a test population after a specified test duration defined in the test guideline.
Limit of detection	Lowest residual impurity concentration that can be analytically detected with the assurance, that the signal being detected is due to the residual impurity and not from other causes such as instrument noise.
Limit of quantification	Lowest residual impurity concentration that can be determined repeatable with acceptable precision.
Low application rate herbicide	EPA classification: application rate ≤ 0,5 lb. AI/acre equivalent to ≤ 560 g AI/ha.
Manufacturing	All steps in the operation of manufacturing, including synthesis, and/or formulation, and/or packaging (filling, labeling etc.) and/or repackaging.
Manufacturing site	May consist of multiple production units in the same or in separate buildings.
MSCSG	Manufacturing & Supply Chain Steering Group, previous name of the CropLife International Operations Committee.
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 active ingredient / ha at which the active ingredient has no observable effects on a given, tested species.

Non-crop pest control	Non-agricultural control of insects, other invertebrates, weeds and fungi in industrial areas, rail ways, households, sport- and recreational areas, and in construction materials (wood treatment), etc.
Operations Committee	Committee in CropLife International involved with manufacturing and supply chain policy issues affecting the industry.
Packaging / repackaging	In this booklet, the terms “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 31st, 1996, specifying statutory cleaning levels for products sold or manufactured in the US when changing from different families of products, e.g. from insecticides to plant growth regulators.
Pheromone	A biochemical substance secreted externally by certain animals, e.g. insects, affecting the behavior of other animals of the same species. These substances 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 the 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 active ingredients, formulated products (either in bulk or in temporary or final sales pack).
Product scheduling	Planning the production sequence of different products; different sequences may result in significantly different cleaning levels.
Production record	Production data (e.g. batch card) of individual batches.

Raw materials	Any chemical substance used in the synthesis of intermediates and active ingredients, and in the formulation process of AIs. Note that Intermediates are not classified as raw materials.
Release limit	Synonym for cleaning level.
Release procedure	Organizational procedure to be followed before a production unit can formally be allowed to produce the next product after a product or configuration change.
Residual impurity (RI)	Traces [especially of active ingredient(s)] of the preceding product present in the succeeding product manufactured in the same production unit.
Retain sample	Sample of a produced batch stored to allow later verification of its quality.
Rework	Chemical or physical treatment of a product until it meets the required specification.
RI	Abbreviation for residual impurity – typically residues of the active ingredient of the preceding product.
RIL	Residual impurity level, synonym for Cleaning Level.
Rinsate	Used liquid cleaning medium (water + detergent) or solvent having been 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 pesticide formulation to eliminate or reduce the phytotoxic effects of that pesticide to certain 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	Material Safety Data Sheet (MSDS): Data required by the Government(s) to assure worker protection and treatment for exposure.

Safety factor	This factor is used to enhance the safety margin in the calculation of the cleaning level. Each company is responsible for setting its own safety factors. Safety factors for herbicides usually range from 2 to 10.
Sampling	Sampling should follow an agreed plan describing: how to sample, what to sample, when to sample, from which sample point to take samples, which quantity [sample size], how and where to store them, as well as the period during which the samples have to be retained.
SC (Suspension Concentrate)	An agricultural formulation in which the AI(s) are dispersed as solid particles in a continuous aqueous phase. Often referred to as "Flowable".
SE (Suspo-emulsion)	A liquid, heterogeneous preparation consisting of a stable dispersion of active substance(s) in the form of solid particles and of fine globules in a continuous water phase.
Seed Treatment	Process of coating seeds with fungicides and/or insecticides to protect them against insects or diseases. Germinating seeds may be significantly more sensitive to agrichemicals than more developed plants.
Separation of materials	Separate storage of raw materials and products, e.g. herbicide / non-herbicide usage.
Solid formulation	The collective name for dry formulations. Typically the AI(s) present in solid formulations are high melting point solids milled to a specified particle size. Examples: wettable 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.
Sulfonylureas	Class of highly active herbicides.

Supplier of AIs or A formulated products	company selling AIs and/or formulated products registered in the supplier's name to companies who co-market those products, either as straight products or in formulations that may contain one or more AIs from their own portfolio.
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 pesticides that is absorbed into the tissues of plants and transported within the treated plants also protecting the plant parts that developed after treatment took place (i.e. new growth).
TCAL	Trace Component Action Level - synonym for Cleaning Level.
TSLC	Toxicologically Significant Levels of Contaminants - levels of contaminants that US EPA generally considers to be toxicologically significant, see US EPA PRN 98-8 (Appendix C).
Temporary label	A label to identify a packed product before the final product label can be applied.
Toller, toll manufacturer	See External Manufacturer.
Used cleaning medium	Generic term for "rinsate" and used "solid flush material".
Vacuum cleaner	Portable equipment for removal of dust from equipment, floors and walls. Some vacuum cleaners are especially designed to collect liquid spillage.
WP (Wettable powder)	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 cross 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.
- Provide the production unit with a “washing room / workstation” (see Fig. 7) for the cleaning of dismantled smaller pieces of equipment.
- Grating as floor in manufacturing areas is not recommended. Spills can be much better contained with solid floors.
- Construct walls that are washable and leak-proof or sealed at the edges with no 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 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 final 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:



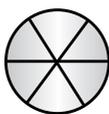
Motor



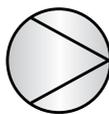
Fan



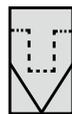
*Solid/
Liquid
Filter*



*Rotary Valve
Feeder*



Pump



*Dust Collector/
Air Filter*

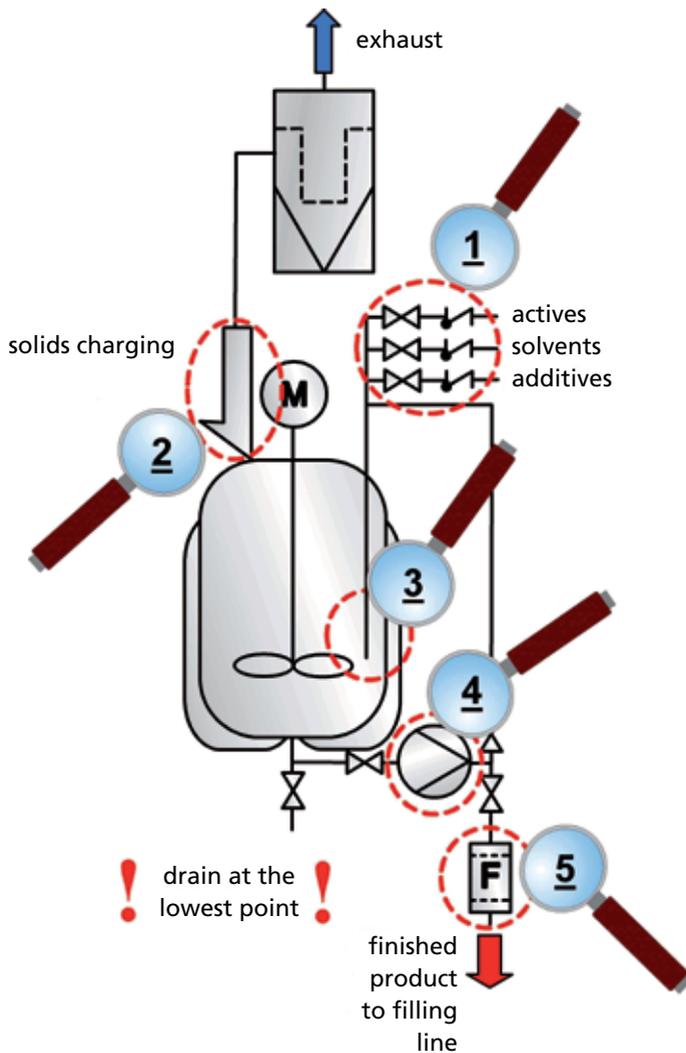


*Sifter
Sieve
Screener*

A.2.1 Liquid formulations

A.2.1.1 SL and EC Formulations

(Explanation of this equipment see next page)

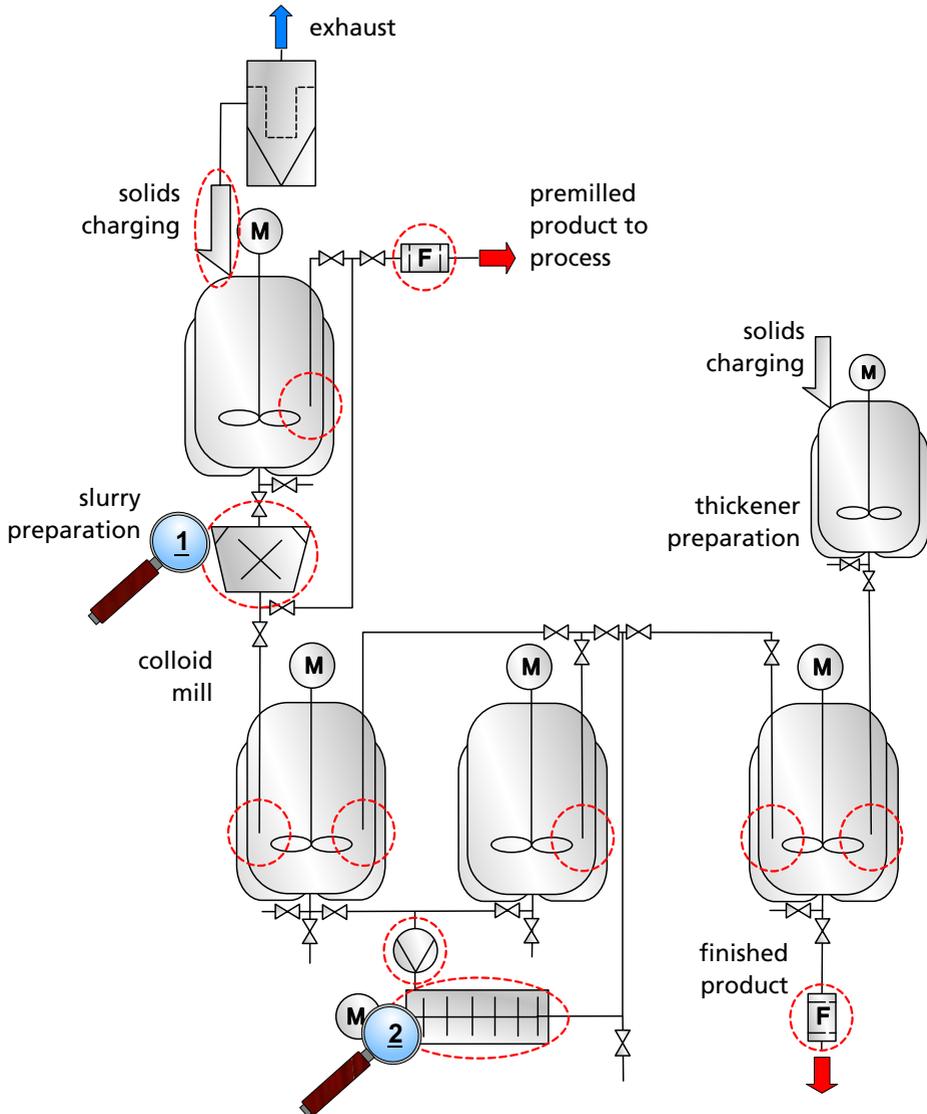


Comments:

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)



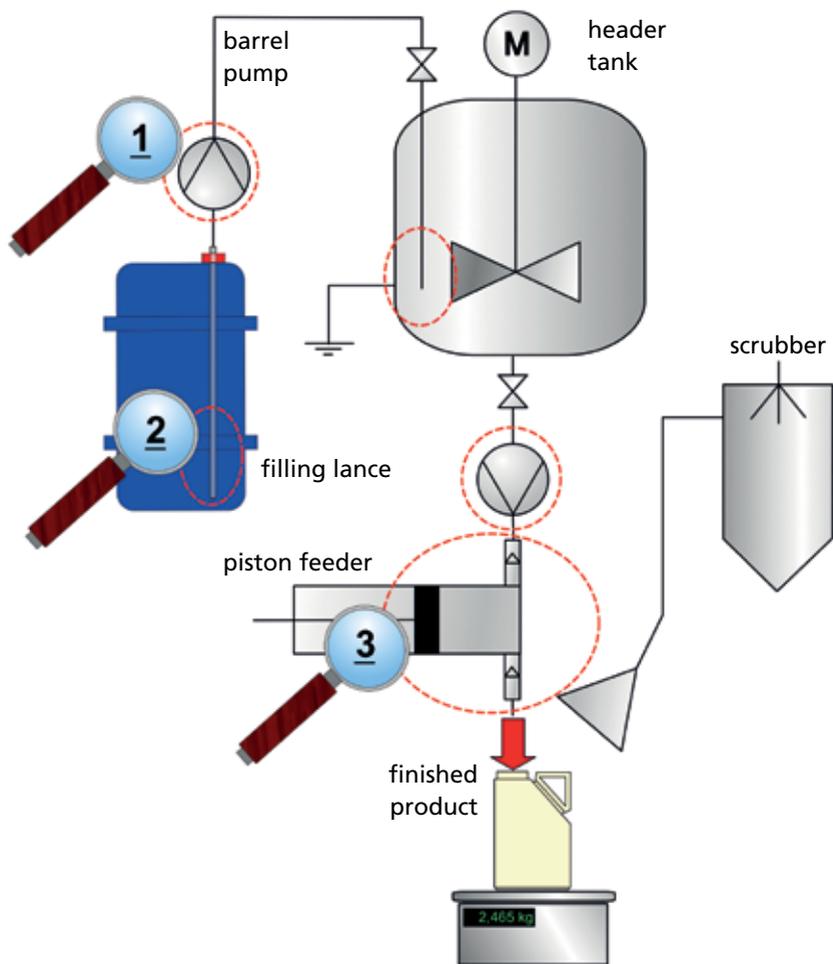
Comments:

Cleaning immediately after the campaign is completed is strongly recommended, even if it is not decided which product will follow in the production sequence. 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 3.3).

- 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)

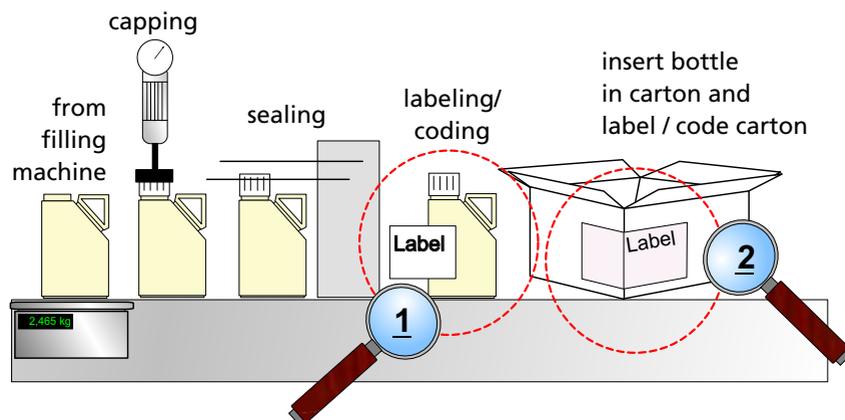


Comments:

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.
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

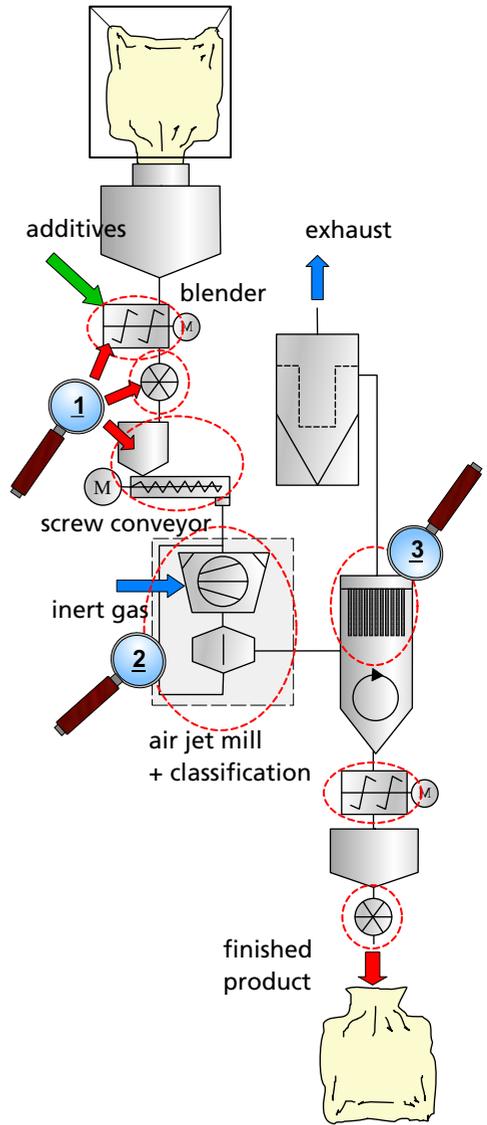
A.2.2.1 Dry milling – WP formulations granular formulations

(Explanation of this equipment see next page)

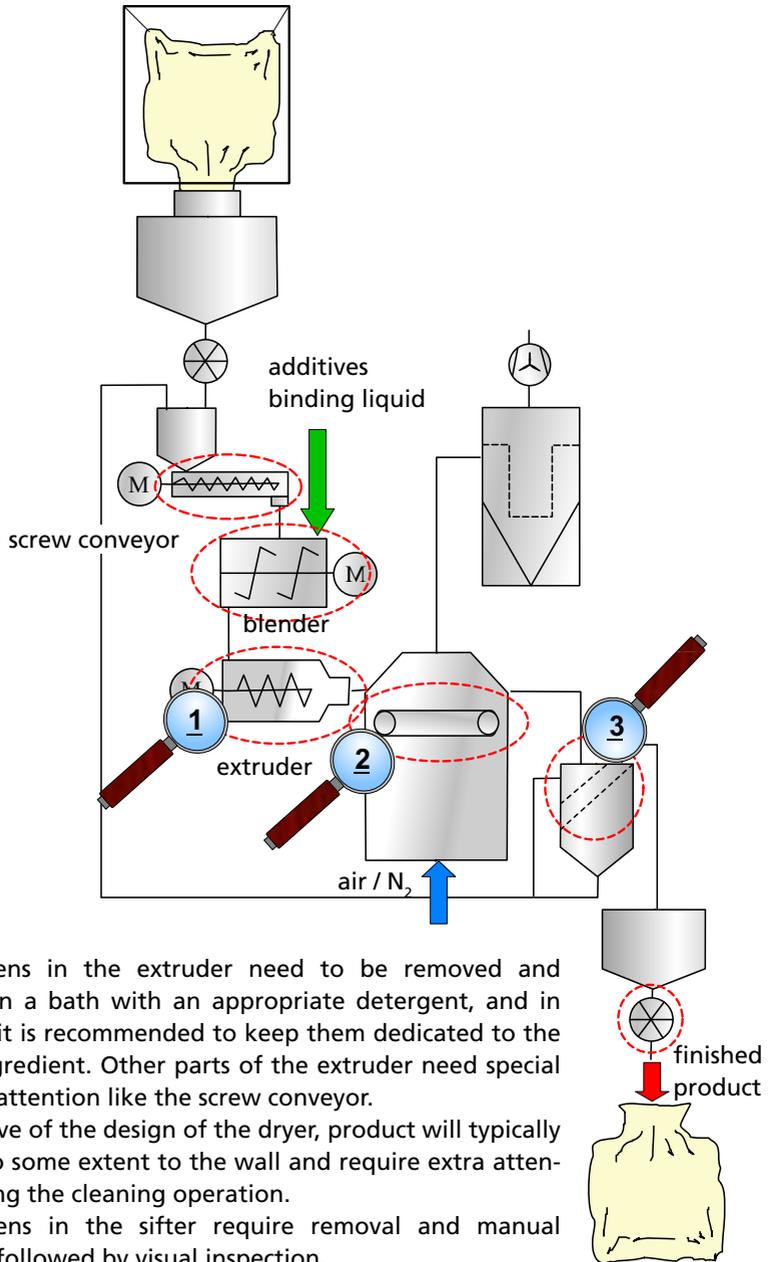
One of the general concerns in the manufacture of solid formulations is dust that can escape from the equipment at a number of places. Good house-keeping is always of the greatest importance in any type of manufacturing of Crop Protection products, but it is even more critical when manufacturing solid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



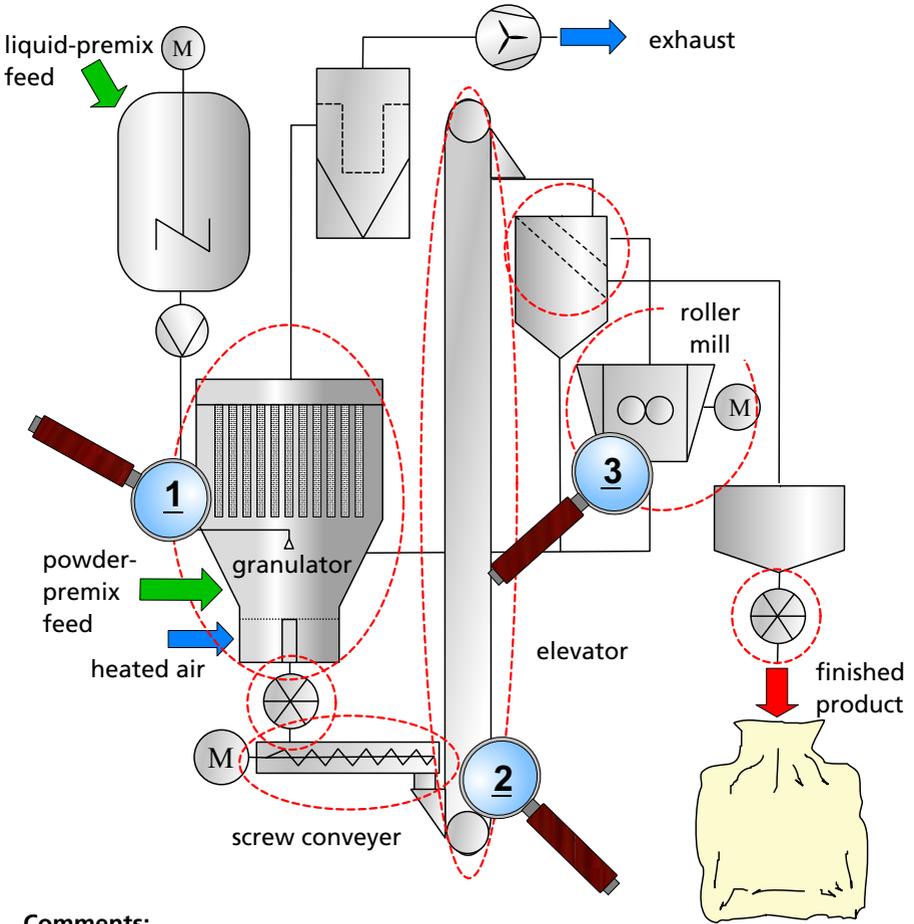
A.2.2.2 Extrusion Granulation



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.

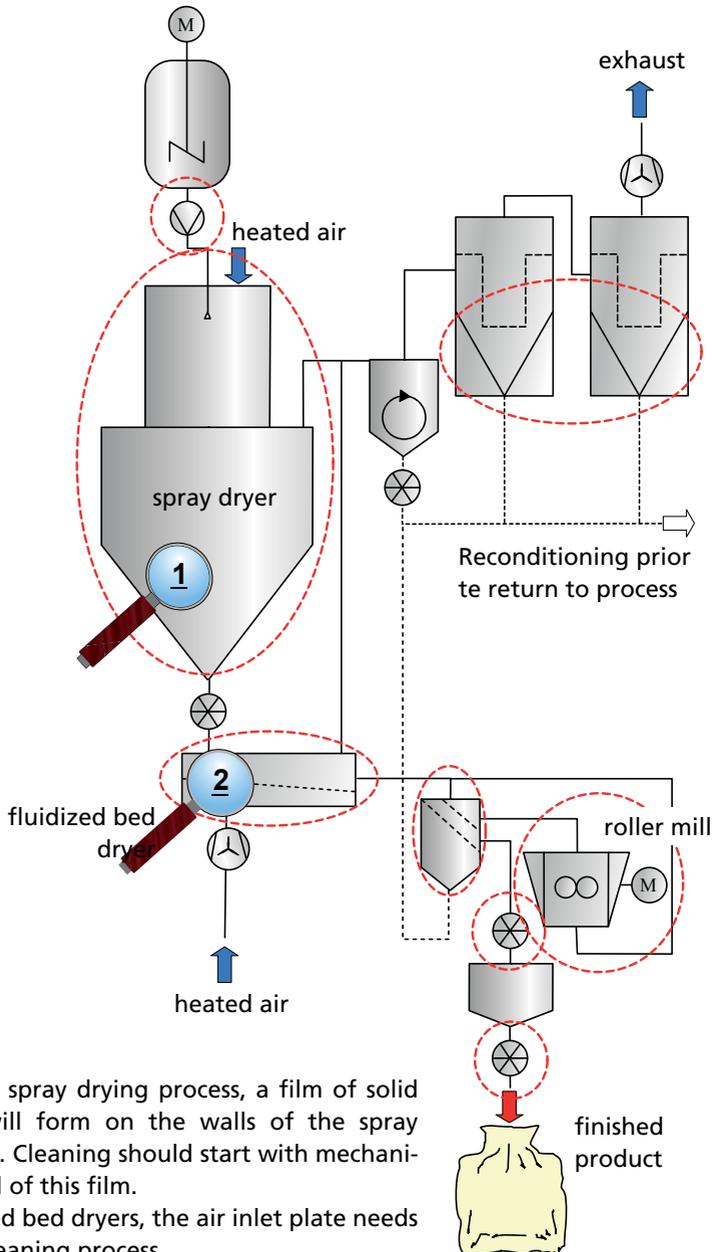
A.2.2.3 Fluidized bed granulation



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

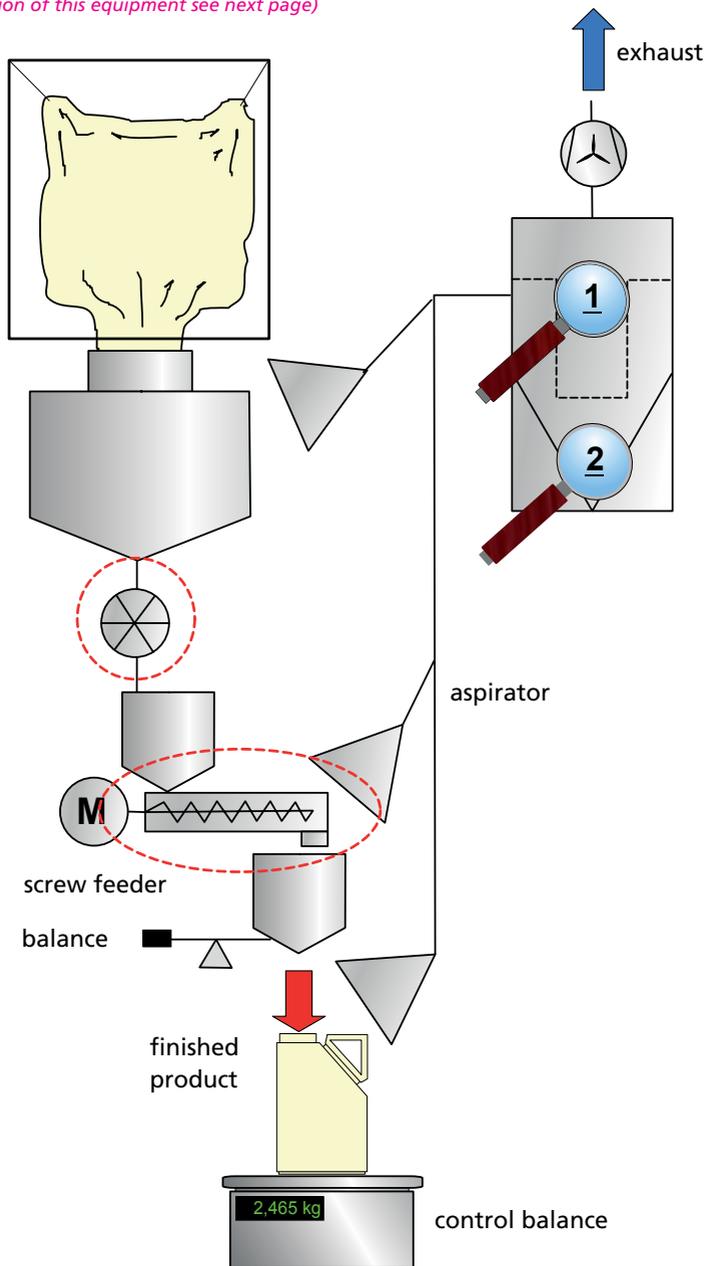


Comments:

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 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 External Manufacturers 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 external manufacturer audit checklist.

The frequency of the Self-Assessment / External Manufacturer audit is determined by each client and the external manufacturer 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 External Manufacturer'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 External Manufacturer's facilities may be audited less frequently.

Both in the case of Contamination Prevention Self-Assessment and External Manufacturer 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 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 of CropLife International “Guidelines for Contamination Prevention” 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	<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? If yes, with which frequency? Do you report changes immediately?			

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 a charging hopper will be used which contained a different active ingredient.</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)? • Normal rate herbicides? • 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	<ul style="list-style-type: none"> • Insecticides belonging to the Neonicotinoids family? • 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 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 separated (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 of Product Groups	Yes	No	Comments/ Proposed Action Plans
4.2	<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 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? • Mobile equipment: <ul style="list-style-type: none"> • Containers for intermediates / products? 			

4.	Separation of Product Groups	Yes	No	Comments/ Proposed Action Plans
4.6	<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 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 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 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 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? 			
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 of Product Groups	Yes	No	Comments/ Proposed Action Plans
4.10.2 Warehousing	<p>Are Herbicide and non-herbicide 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 6.2.7)?</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 cleaning levels? If not, how are the cleaning levels 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	<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 cleaning level 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	<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	<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? 			
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 rework or blending of this material could be an option?			
9.3	Is rework of off-spec material done following a procedure approved by the client and with his/her written authorization for each occurrence?			

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



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 (DACS) 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 DACS 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 contaminating 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.

IV. 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 a 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.

Graphic design:



Keigoed^[e] graphic design, www.keigoede.nl, Almen, The Netherlands

Crop Life International A.I.S.B.L.

326 Avenue Louise, box 35
1050 Brussels, Belgium

Tel. + 32 2 663 15 50
Fax + 32 2 663 15 60
E-mail: croplife@croplife.org