

# Get out from Behind your Computer to Conduct Comprehensive EM Investigations

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**2024 Pharmaceutical Manufacturing and Quality Conference**

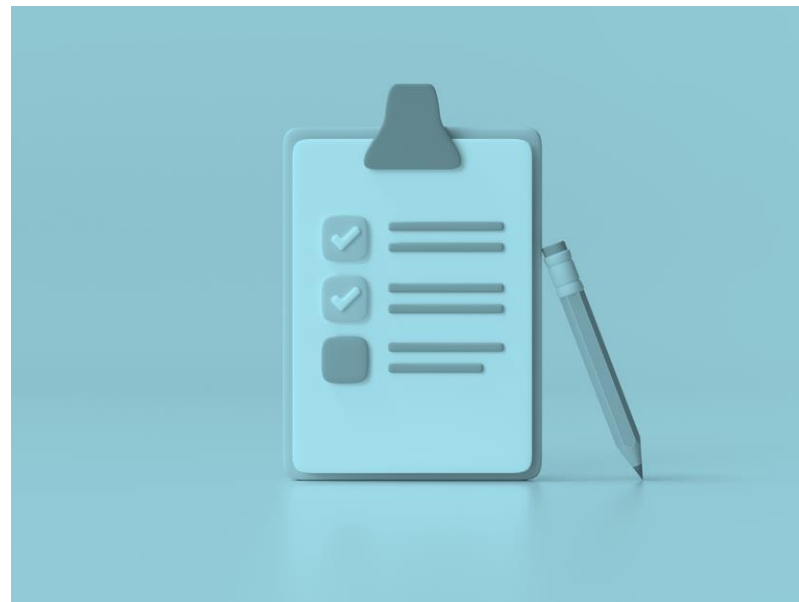
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PEOPLE  
SCIENCE AND  
REGULATION®

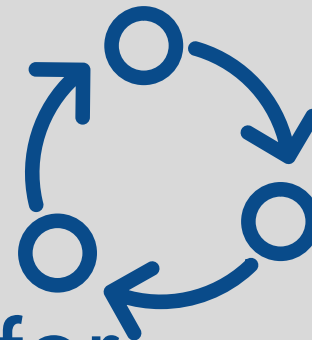
# Overview

- High-Level Process Flow for Action Limit EM Investigations
- Importance of EM Investigations
- Keys to a Robust EM Investigation



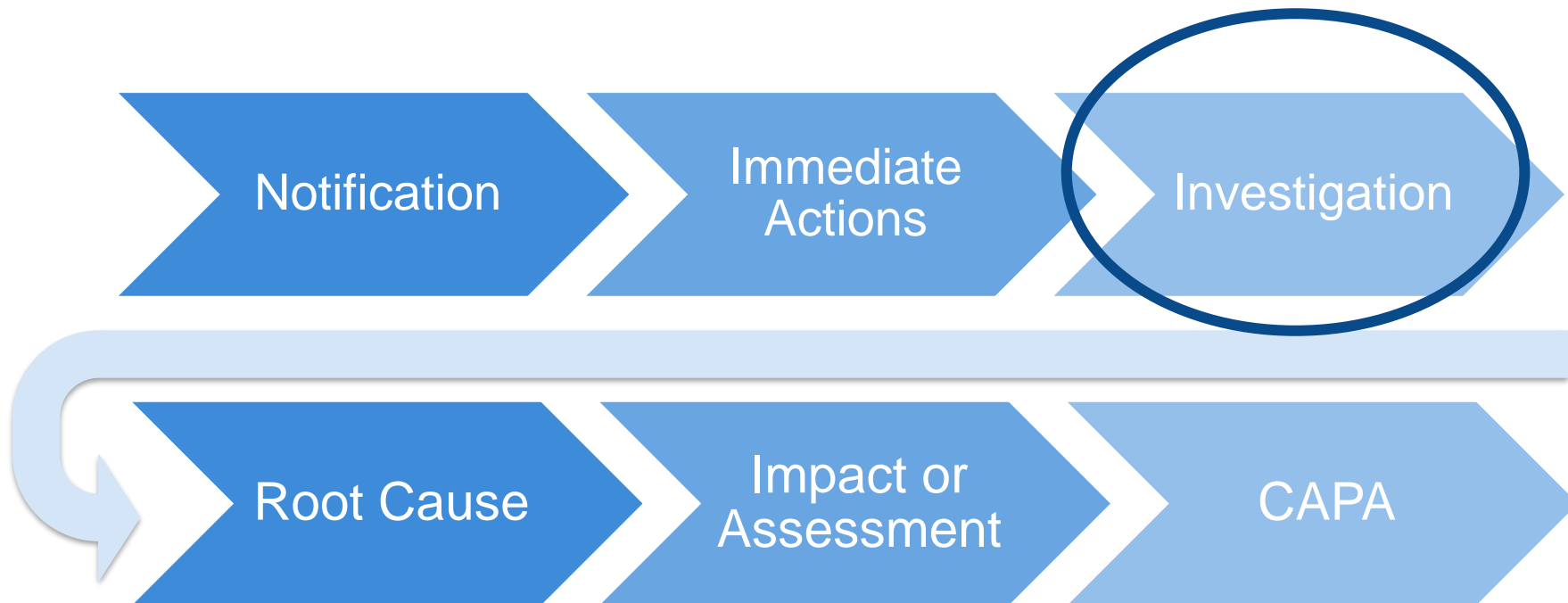
Examples of inadequate investigations and 483s throughout the presentation





# High-Level Process Flow for Action Limit EM Investigations

# Action Limit Excursions





# Importance of EM Investigations

# 2022 Baby Formula Shortage

Voluntary recall of contaminated baby formula by a firm, which led to a US nation-wide shortage of baby formula in 2022. This firm also received a 483 from FDA with 4 observations.



Photo credit: Samuel Corum | AFP – Getty Images



## Case Study

# Closer Look at 483 Observations

A. FDA environmental samples collected on 2/1/22-2/2/22 during this inspection confirmed the presence of *Cronobacter sakazakii* on zone two and zone three surfaces in medium and high care areas of powdered infant formula production”.

B. Between 9/25/19 and 2/20/2023, your firm’s environmental samples and finished product testing confirmed the presence of *Cronobacter spp.*

2. Finished Product: Review of your firm’s Non-Conformance Reports (NCRs) indicated that two finished products tested positive for *Cronobacter spp.* as follows:

- Similac Alimentum
- Similac for Spit-Up



Case Study

# *Cronobacter sakazakii*

Per Journal of Applied Microbiology:

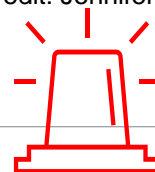
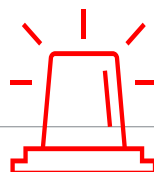
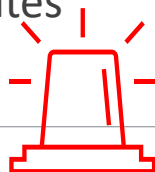
- *Cronobacter sakazakii* (Formerly known as *Enterobacter sakazakii*):
- Gram negative rod
- Most often found linked to the consumption of contaminated powdered infant formula
- Causes necrotizing enterocolitis, bacteremia and meningitis, predominantly in neonates



Photo Credit: Jennifer Hulseley, CDC



## Case Study





# Why is there a problem?

Per CDC, infections are rare, but they can be life-threatening in newborns.

- Who is at risk?
  - Infants < 2 months
  - Premature infants
  - Infants with weakened immune systems



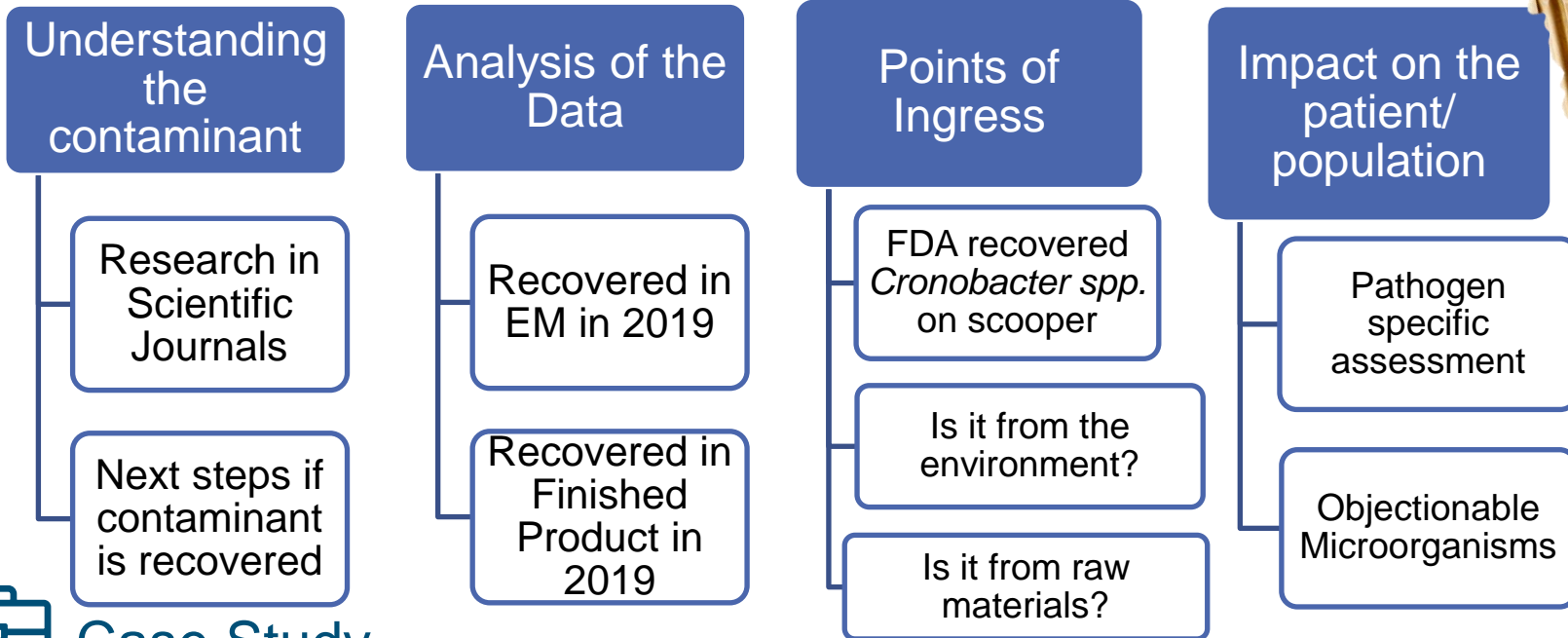
Per FDA, there was a negative outcome from these contaminated baby formulas.



## Case Study



# Possible Missed Key Components



## Case Study



# Keys to a Robust EM Investigation

# Keys to a Robust EM Investigation



Correct Identification of the Microorganism



Understand the Contaminant



Analysis of Data



Identify Contamination Sources



Find Points of Ingress



Map Contamination Transport



Identify Sources of Proliferation



Impact of the Product on the Patient

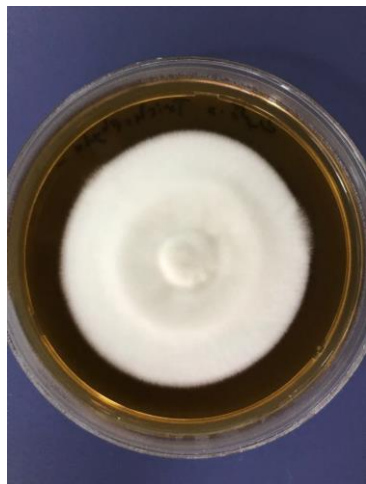
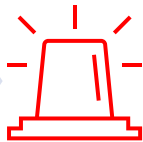


# The Case of the Misidentification and Misunderstanding



Microbial Identification

- *Trichophyton rubrum*
- *Neisseria gonorrhoea*

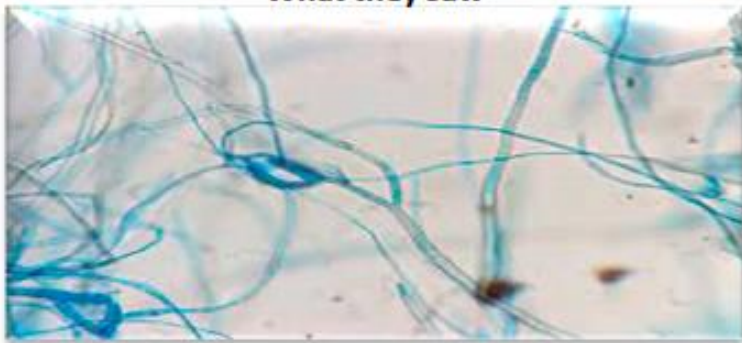


Correct Microorganism Identification

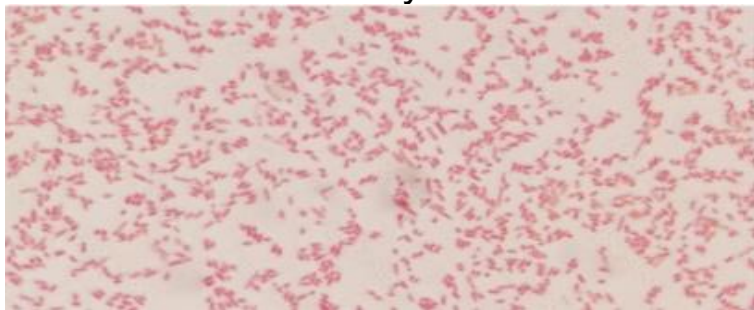
Understanding the Contaminant

# The Case of Misidentification and Misunderstanding

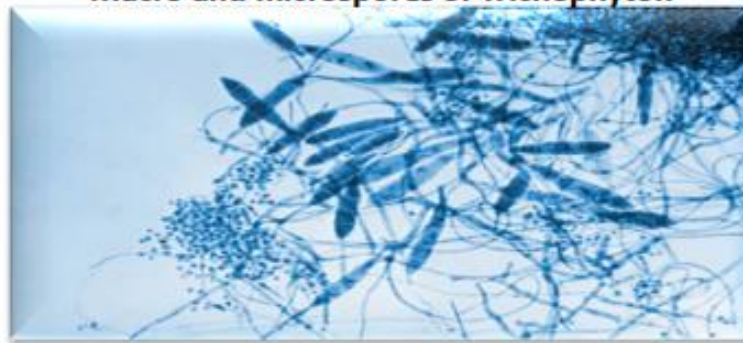
What they saw



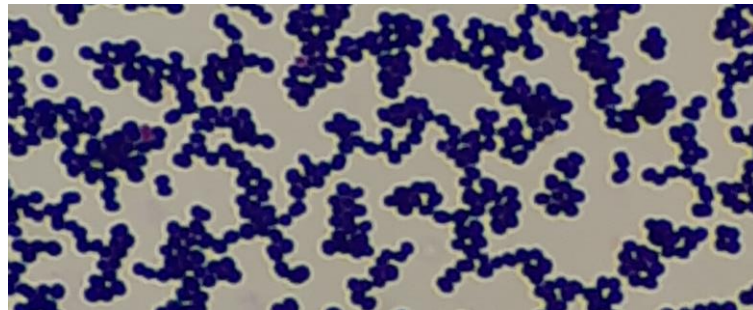
What they saw



Macro and microspores of Trichophyton



What it most likely should have looked like



# The Case of Misidentification and Misunderstanding



## Avoided \$1.5M mistake

# Understand the Contaminant

## Bacteria, Yeast, & Mold

Gram Reaction, Mold, or Yeast

Growth Characteristics

Probable Source

## Mold Only

Reproductive Stage

Phylum / Division



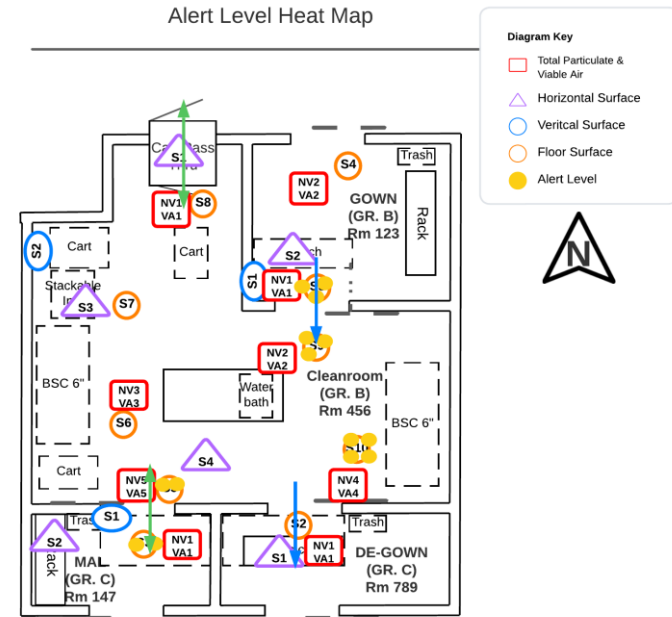
# Types of Trending



# Analysis of Data

## Heat Maps

- Sample type
- Area
- Microorganism
- Specific area or related areas
- Material, Equipment, Personnel Flow

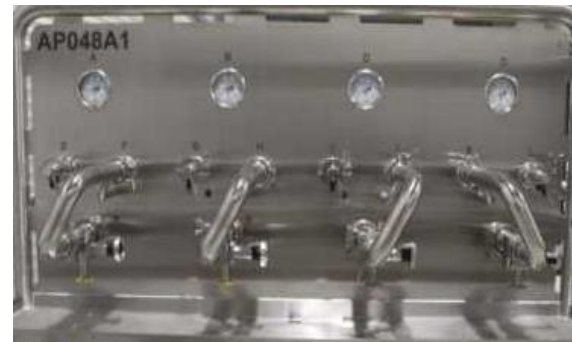
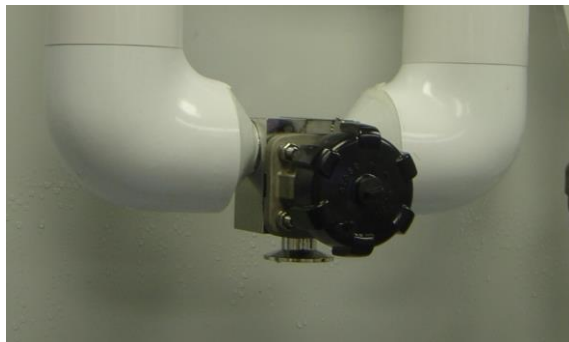


# Types of Trending

## Analysis of Data

Trending related to sampling techniques

- Same utility on same day, on different days, or a defined period (e.g., compressed air, WFI, etc.)



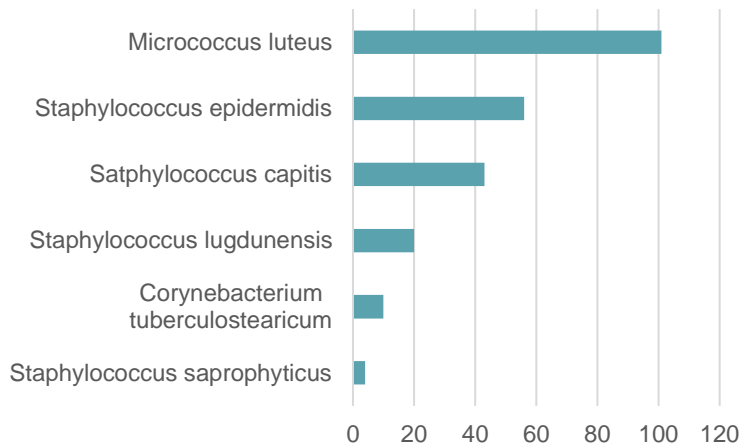
# Types of Trending



# Analysis of Data

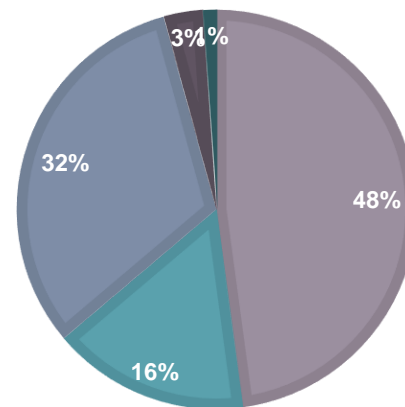
## Graphs Related to Microorganism Identifications

**Most Frequently Occurring Microorganisms**



**Percentage of Microorganisms**

■ GPC ■ GPR ■ GPR with spores ■ Mold ■ GNR

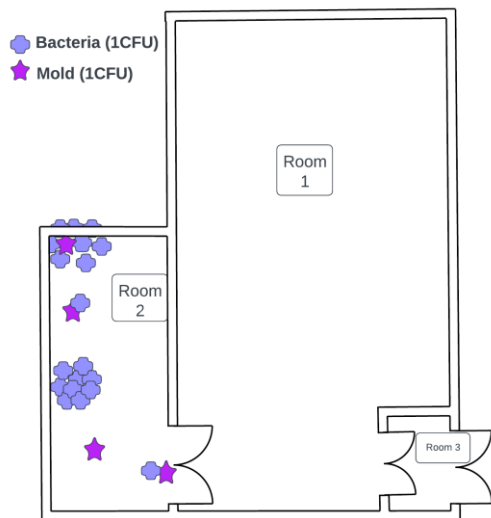




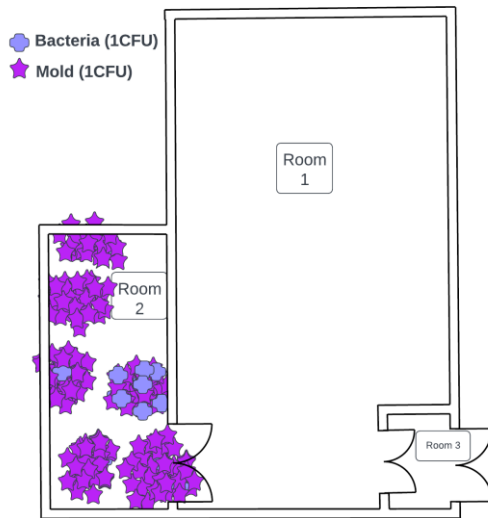
# Case Study

A firm failed to recognize a mold trend after enumeration. The company's SOP clearly identified a mold trend, as "3 or more recoveries of mold in one day".

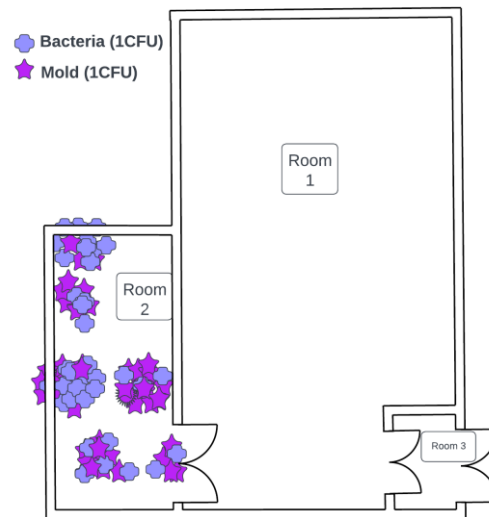
October



November



December





# Case Study



Identify Contamination Sources



Find Points of Ingress



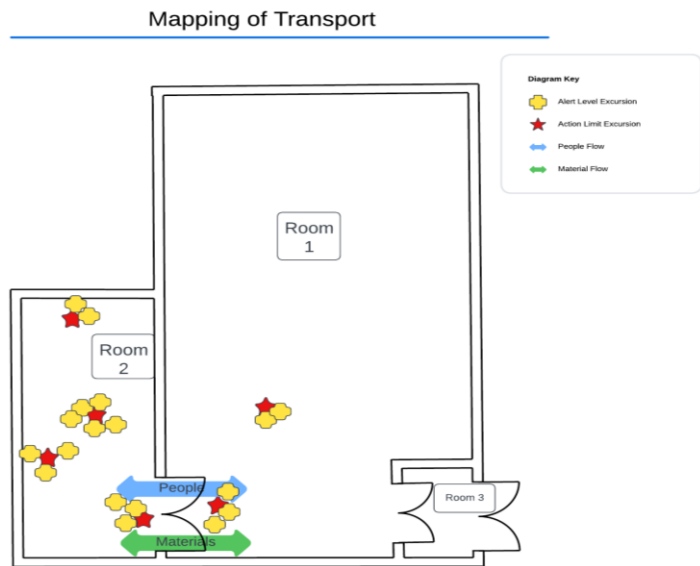
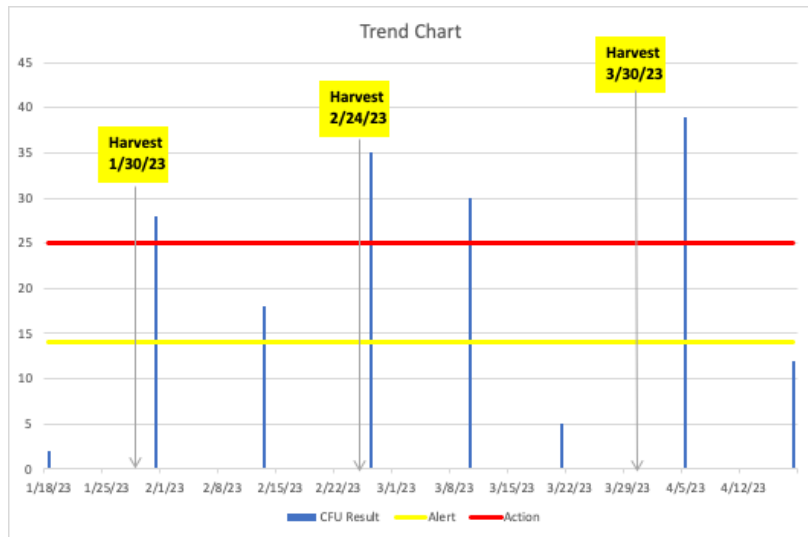
Map Contamination Transport



Identify of Sources Proliferation

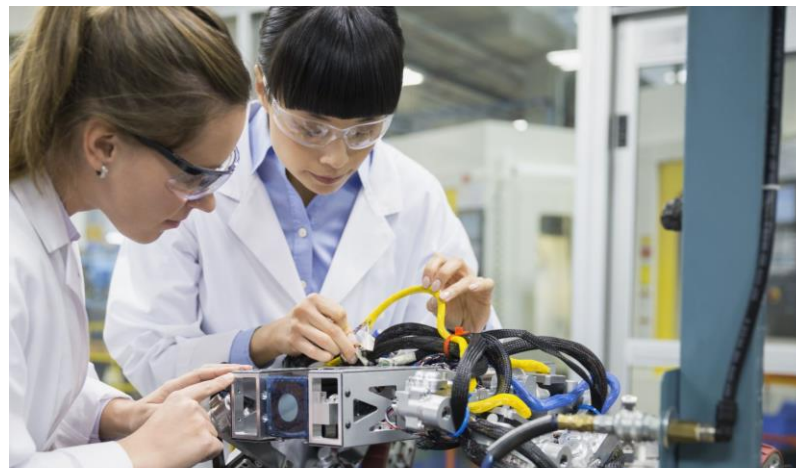
# Case Study

A company had an increase in the action limit excursions in harvest cleanroom and adjacent cleanrooms.



## Gemba Walk (現場) Or Investigative Walkthroughs

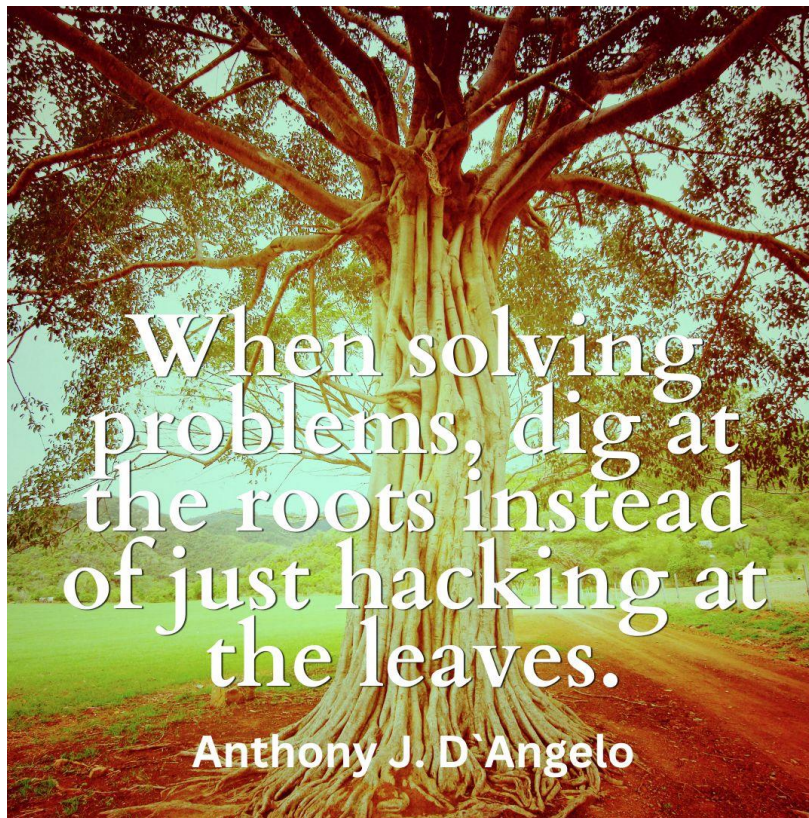
- Develop a checklist
- Cross-functional (QA, Manufacturing, Facilities, Maintenance, Cleaning)
- Review the processes and cleaning that occur in the area
  - Include observation and interviews



Identify sources of contamination

Identify points of ingress

Identify areas for proliferation



When solving  
problems, dig at  
the roots instead  
of just hacking at  
the leaves.

Anthony J. D'Angelo



Thank You!