Controlling exposures to API in Chemical Production

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Scope Presentation

• Risk based thinking: tool & guideline

• Implement risk based solutions

• Share solutions
Controlling exposures to API in Chemical Production

• Risk based thinking: tool & guideline
  • Implement risk based solutions
  • Share solutions
Risk Based thinking

- Risk drives the decision, hazard is considered
- Prioritize activities, use of resources and future investments based on risk
- Risk Based thinking assumes that
  - Consider realistic scenarios
  - Integrates approach with QA, engineering and manufacturing
  - Relies on facts and data in the decision making process
- Without Risk Based Thinking
  - Infinite resources will be required to achieve objectives.

Where we were yesterday?
- Former J&J guidelines recommended containment specifications and controls based on OEL and Toxicity levels API.

Where we are Today?
- Recommends containment specifications and controls based on risk. Introduction of Risk Based Exposure Assessment Process (RBEAP) and Risk Based Exposure Assessment Control Guideline (RBEAC)
Risk Based Thinking

Risk Based Exposure Assessment Process (RBEAP)

- Tool created by cross functional team, **IH Steering Team** Janssen Supply Chain
- Process to systematically **assess** inhalation exposure **risks** of activities with Active, Pharmaceutical Ingredients and solvent vapors
- Tool introduced in Fill & Finish, API manufacturing and R&D
- **Team Approach:** Use of stakeholders, involvement operations.
- Provides a **lean**, systematic and pragmatic **methodology** to;
  - **Identify** the chemical **hazards** for each unit operation
  - Identify **priorities** for air **sampling** based on those products that have the potential to generate the highest airborne particulate concentration.
  - Organize the data so that **Similar Exposure Groups** can be established.
  - **Communicate** results to employees, medical and management using a transparent format.
  - Understand future IH air sampling needs and managing changes, ie impact of introducing new products.
  - RBEAP is used to **understand exposure risks** to be able to make **data driven decisions** to prioritize **containment projects**
Risk Based Thinking
Risk Based Exposure Assessment Process (RBEAP)
Six Steps

1. Create a UO Inventory
2. Identify Risk Factors Compounds
3. Prioritize compounds UO sampling
4. Personal Sampling if required
5. Analyze & Communicate Data
6. Periodic Re-Sample

Batch Size, API % or quantity, etc
Solvents – VP, temperature

Assign High, Medium or Low risk to prioritize activities

Periodic re-sampling according to specified criteria

Based on the qualitative risk assessment and respiratory protection requirement.

Analyze using Bayesian Statistics
## Risk Based Thinking

### Risk Based Exposure Assessment Process (RBEAP)

Create inventory of Unit Operations

<table>
<thead>
<tr>
<th>Location</th>
<th>Unit Operations</th>
<th>SEG</th>
<th>Risk</th>
<th>Sampling complete reference last IH report</th>
<th>RBEAP date</th>
<th>APF1</th>
<th>APF2</th>
<th>APF3A</th>
<th>APF3B</th>
<th>APF4</th>
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<td>API1 toevoegen uit container/müllerdrum zeefinstallatie PZE2</td>
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Document all information for each Unit Operations

- General Information
- Active compounds involved
- Selection compound greatest potential airborne exposure
- Respiratory protection required (based on analysis below)
- Document results personal sampling
- Analysis of the IH sample data for ‘worst case’ compound
Risk Based Thinking

Risk Based Exposure Assessment Process (RBEAP)

**Former Approach**

*Not Risk Based.*

Beyond Compliance
More resources and IH Costs.
(Need to sample for each API and process)
IH method required for every chemical
Sampling criteria was hazard based

**Current Approach**

*Risk Based*

Full regulatory compliance
Sampling criteria based on worst case scenario
Cost avoidance with resources and air sampling
Streamlining medical surveillance
Generates statistical data to drive risk based decisions investments
One format to share and communicate results (Internal + Ext)
All IH information in one document
Risk Based Thinking
Risk Based Exposure Assessment Control Guideline (RBEAC)

- Created by cross functional team, IH Council Johnson & Johnson

- The guideline defines the hazards and provides guidance for selecting controls based on exposure risk

- **Team Approach**: engineering, maintenance, operations, quality and EHS

- Provides a step by step process:
  - Assess exposure risks of all activities related to operations, maintenance and cleaning of new or existing installation;
  - Understand and implement appropriate exposure controls strategies.
  - Select controls that manage the risks (not the hazards)
  - Prioritize projects where greatest exposure risk is given the highest priority
  - Stimulate communication between the different stakeholders
  - Allows flexibility for each site to make selections based on internal possibilities
  - Documentation of assessments and decisions so these can be understood now and in the future
Risk Based Thinking

Risk Based Exposure Assessment Control Guideline (RBEAC)

- A navigation map
- 3 sections:
  - overview for first time reader
  - risk based exposure assessment
  - list of exposure control options
Risk Based Thinking
Risk Based Exposure Assessment Control Guideline (RBEAC)
Qualitative Risk Assessment
Risk Based Thinking
Risk Based Exposure Assessment Control Guideline (RBEAC)
Quantitative Risk Assessment

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Diagram:

1. Does the process exposure risk require respiratory protection?
   - Yes → Is the process exposure risk low?
     - Yes → Quantitative Risk Assessment: Personal Exposure Monitoring; Statistical Analysis of IH Data;
     - No → Is reliance on respiratory protection acceptable?
       - Yes → Is Statistical Analysis of IH Data greater than (>) the OEL?
         - No → Is Statistical Analysis of IH Data greater than (>) the Assigned Protection Factor of the Respirators?
           - Yes → No
           - No → Yes
       - No → No
   - No → No

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Risk Based Thinking
Risk Based Exposure Assessment Control Guideline (RBEAC)
Exposure Control Project

Diagram:
1. Define Project Scope
2. Assemble Project Team: Engineering, Maintenance, EHS, Quality, Operations
4. Implement
5. Quantitative Risk Assessment: Personal Exposure Monitoring; Statistical Analysis of IH Data;
Risk Based Thinking

Risk Based Exposure Assessment Control Guideline (RBEAC)

Post control Quantitative RA

Quantitative Risk Assessment
- Personal Exposure Monitoring; Statistical Analysis of IH Data;

- Is Statistical Analysis of IH Data greater than (>\) the OEL?
  - Yes
  - Is Statistical Analysis of IH Data greater than (>\) the Assigned Protection Factor of the Respirators?
    - Yes
    - Document Risk Management:
      - Qualitative Risk Assessment; Quantitative Risk Assessment (if required);
      - Control Technology Utilized
    - No
  - No
  - Is reliance on respiratory protection acceptable?
    - Yes
    - Document Risk Management:
      - Qualitative Risk Assessment; Quantitative Risk Assessment (if required);
      - Control Technology Utilized
    - No
Risk Based Thinking
Risk Based Exposure Assessment Control guideline

**Former Approach**
*Not Risk Based.*
Containment recommended based on OEL
More focus on high potent compounds
Expensive investments not aligned with risk
No flexibility

**Current Approach**
*Risk Based*
Better understanding of hazards and risks (SHOW ME THE DATA)
Communication encouraged between stakeholders
Guidance for selecting controls (more flexibility)
Prioritize execution projects related to highest risks
Controlling exposures to API in Chemical Production

- Risk based thinking tool & guideline
- Implement risk based solutions
- Share solutions
Implement risk based solutions

- High potent compounds
- Potent compounds
- General upgrade
- Administrative controls
Product flow high potent compounds

Previous situation

- Raw Materials
- Intermediates
- API’s HR
- API’s ZR

Suppliers

PP Beerse

Warehouse

Central washing facility

Customers

Plant 1
Plant 2
Plant 3
Plant 4

Plant 1
Plant 3
Plant 4

PHU

QA
Product flow high potent compounds

Current situation

Suppliers

PP Beerse

Warehouse

Suppliers

PP Beerse

Raw Materials

Intermediates

API’s HR

API’s ZR

Customers

2 Weighing Down flow Booths

1 MEuro

Weighing Isolator

0.8 MEuro

Bulk Isolator

0.8 MEuro

RTP containers

0.2 MEuro

RTP containers

0.2 MEuro

Plant 1

Plant 2

Plant 3

Plant 4

Final Crystal Area

8.9 MEuro

Small Volume Area

5.7 MEuro

JJPAC

PTS

HCLT-Bay

23 MEuro

Weighing Isolator

0.8 MEuro

Final Crystal Area

8.9 MEuro

HCLT-Bay

Weighing Cabinet

0.02 MEuro

1 Isolator

0.07 MEuro

Central washing facility

1 Isolator

0.07 MEuro

RTP-wash isolator

0.9 MEuro

PHU

Central washing facility

QA

Connecting a World of Pharmaceutical Knowledge
Containment solutions Potent Compounds
Flexible containment
Containment solutions Potent Compounds

Drum charging system / powder transfer system
Containment solutions Potent Compounds

Adaptor sleeve – FIBC long neck – delumper/powder transfer
Containment solutions Potent Compounds

Contained dump station bags
General upgrade

Upgrade Equipment

- e.g. Upgrading of centrifuges
  - Inflatable seals
  - Welded parts
  - Finishing
  - CIP
General upgrade
Upgrade Production Areas

Design for cleanability

Construction materials
- monolith floors
- trespa walls

Sprinkler piping

Window ledge

Concrete junction tiles
General upgrade
Construction of Compartments

Enclosure of ‘exposed’ areas
(centrifuges, dryer discharge, …)

- Protection of the employees
- Reduction of the risk for cross contamination
Administrative controls

- Focus on understanding hazards, risks and controls
- RPE aligned with statistical analysis
  RBEAP – full RPE program
- Standard process:
  - Preparation
  - Communication
  - (De) Gowning
  - Waste
- Tools:
  - warning signs / belt
  - communication sets
  - demisting
Implement Risk Based solutions

Conclusions

• Complete upgrade installations
• High investment: IH & Quality & Ergo
• Respect Hierarchy of Controls
• Statistical analysis exposures activities requiring RPE
• Team work
• Strength for Chemical Production Site: identified as Launch Plant API manufacturing J&J
Controlling exposures to API in Chemical Production

- Risk based thinking tool & guideline
- Implement risk based solutions
- Share solutions
Tool developed by cross functional team, **IH Steering Team** Janssen Supply Chain

Why do we need this tool?
- No standard engineering designs for exposure control
- Limited opportunities to get it right!
- Leverage existing capital and intellectual property

Documents proven solutions for common unit operations: weighing, dispensing, compression, reactor charging, glove box

Solutions 3 categories: Pharma, Chemical and Laboratory Operations

Part of the project, inexpensive to generate

Objectives:
- Capture and share current best practices and solutions
- Eliminate reinventing the wheel for engineering control technologies
- Support solutions that maintain exposures below OEL (includes statistical data)
- Designing cost effective solutions and effective use of Capital monies and spends
Share the solution

Containment solution guides - approach

- Submitted by Engineering and Industrial Hygienist
- Quality Review by members of IH steering Team
- Select price winner each quarter
- Posted on E-room
Share the solution

Containment solution guides – example 1
Share the solution

Containment solution guides – example 1
Share the solution

Containment solution guides – example 1
### Share the solution

**Containment solution guides – example 1**

<table>
<thead>
<tr>
<th>Unit Operation</th>
<th>Site</th>
<th>Date</th>
<th>Reference #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changing reactor</td>
<td>Chemical Production</td>
<td>August, 7th 2030</td>
<td>Chemical Manufacturing</td>
</tr>
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</table>

**SECTION 10. LESSONS LEARNED – GENERAL REMARKS**

1. The exhaust of the isolator is connected to an existing VCC-system. Due to a higher pressure drop in the pipe work, a re-circulation velocity > 0.5 m/s could not be achieved compared to the design value. It is advised to reduce the exhaust of the isolator separate to the atmosphere, if the composition of the exhaust gases allows this under local authority legislation.

2. Since other systems (e.g. centrifuge dryer) were also connected to the existing VCC-system, the pressure profile in the isolator was influenced due to fluctuations in the pressure profile within the VCC-system. The isolator is partially covered by installing a buffer box on the VCC-system at the tie-in. A separate exhaust for the isolator (see 1.) could also solve this problem.

3. The intake of nitrogen was located at an entry point at the top of the isolator, resulting in a nitrogen flow straightforward to the aspiration point and 'death spots' in the corners of the isolator measured as oxygen content and/or particles. The installation of a nitrogen diffuser (e.g. inert pipe with several nozzles) assures a nitrogen flow throughout the complete cross-section of the box, avoiding 'death spots'.

4. Since the isolator is installed in a multipurpose environment, Hydron was selected as glove material. Although the good chemical resistance of this compound, field testing showed-out that there is a migration of dimethylformamide (DMF) through the gloves. This must be further investigated.

5. During shake-down testing the isolator flooded when the CIP-sequence was initiated. To solve this problem (partially) the initial drain valve (bromine diaphragm valve) was replaced by a sanitary stainless steel ball valve. For safety reasons (finger trap), this drain valve is opened by the DCS system and must be normally closed by the operator, pushing 2 buttons simultaneously.

6. Based on too high resistance, the check valve in the exhaust of the isolator, was replaced from a spring-loaded type to a hinge plate type.

7. Qualification tests (e.g. particle count and microbiological) should be performed whilst the drum(s) are docked to the isolator. It was noticed that the atmosphere in the drum(s) influences the measurements inside the isolator.

8. Concerning tightness of the isolator, the same problems during the helium leak testing were encountered as noticed in the Small Volume Area (project EM38). At the end the limit was set on 1.10^-7 mbar. If it is advised to do a visual aeronautics test (indicator cloth) prior to the helium leak testing. This aeronautics test allows for specific leak detection. If a leak occurs during the helium leak test, the background value becomes often to high so recovery of the area is needed. Helirant isn’t suitable for specific leak detection.

9. Since oval glove ports are used, a specific leak was detected on the upright sides of the ports (less tension of the glove O-ring). A better performance could be obtained by an extra square O-ring in the first groove of the glove port (see chapter on glove changing).

10. With this custom made and fixed equipment it is extremely important to spend enough time on ergonomics before and during construction and installation. Several ergonomic reviews took place, mock-ups were built for each isolator. During qualification no ergonomic risks were identified.
Share the solution

Containment solution guides – example 2
Share the solution

Communication channels

- **IH Steering Team** Janssen Supply Chain: cross functional team
  - Industrial Hygienists
  - Engineering
  - Toxicology
  - Occupational Health
  - Corporate IH
  - Operations

- Engineering Competence Groups

- IH network meetings

- Sharepoint folders
Conclusions

• Advantages Risk Based Thinking

• Prioritize implementation containment projects

• Document & share solutions

• Stimulate communication stakeholders