
Johnson & Johnson

Working safely with active, pharmaceutical ingredients

Roadmap on Carcinogens event: “STOP”

Brussels, October 10, 2023

Michel Vangeel
Sr. Principal Industrial Hygiene & Process Safety Management
Workplace Health & Safety Excellence

Johnson & Johnson

BSOH BELGIAN SOCIETY FOR OCCUPATIONAL HYGIENE

Content

- Hazard identification & communication
- Qualitative & Quantitative Risk Assessments
- Controlling exposures by respecting Hierarchy of Controls

Content

- **Hazard identification & communication**
- Qualitative & Quantitative Risk Assessments
- Controlling exposures by respecting Hierarchy of Controls

Hazard Characterization API

Approach OEL setting API

- **No regulatory** occupational exposure **limits** established for active, pharmaceutical ingredients
- **Identify hazards** of APIs & isolated process intermediates (IPIs) and **safe exposure levels**;
- **Integrated** in R&D **process** steps: Drug Safety Sciences
- Identified during different moments / timelines in the development of an API
- Initial assessments: identification of **Health Hazard Classes**
- During later stage of the development of the product: scientific and databased calculation of exposure limits and related notations
  = **Occupational Exposure Limit**

Basic Hazard Characterization API

Health Hazard Classification (HHC)

- Health Hazard categories:
  a classification system used to assign materials into ***categories*** of increasing severity based upon their inherent pharmacological and toxicological properties (non-clinical and clinical data).

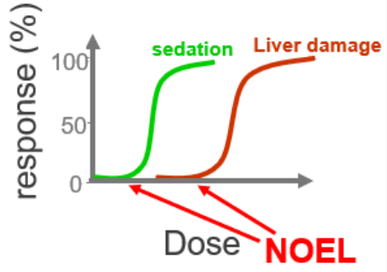
- General criteria:
  - Potency (mg/day)
  - Therapeutic class / Mode of action
  - Acute toxicity
  - Severity of acute effects (i.e. life threatening)
  - Acute warning symptoms
  - Onset of warning symptoms
  - Medically treatable
  - Dermal sensitization
  - Need for medical intervention
  - Likelihood of chronic effects (i.e. cancer)
  - Severity of chronic effects (i.e. life-shortening)
  - Reversibility
  - Alteration of the quality of life (i.e. debilitating)
  - Carcinogenicity
  - Respiratory sensitization
  - Corrosivity

  Professional Judgment

- Occupational Toxicology testing:
  - Skin and eye irritation
  - Skin sensitization

Basic Hazard Characterization API

Occupational Exposure Limit (OEL)



$$\text{OEL (8 hr-TWA)}\ (mg/m^3) = \frac{\text{Point of departure (mg/day) x BW}}{V\ \ (UFs)(MF)(S)(\alpha)}$$

Point of departure: NOEL/NOAEL, LOEL/LOAEL: Identify critical end point considering all available data: including human & animal data; pharmacology, adverse/side effects, carcinogenicity, target organs, Repro/developmental effects, etc Lowest clinical effect dose

BW: Average human body weight (50 kg)

UF: Uncertainty Factors:

- account for differences between people (susceptibilities)
- account for difference between species
- extrapolate from a lowest-observed-effect level (LOEL) to a NOEL
- account for animal study design (subchronic to chronic)

MF: Modifying Factors

- account for database incompleteness, severity of effects, etc.

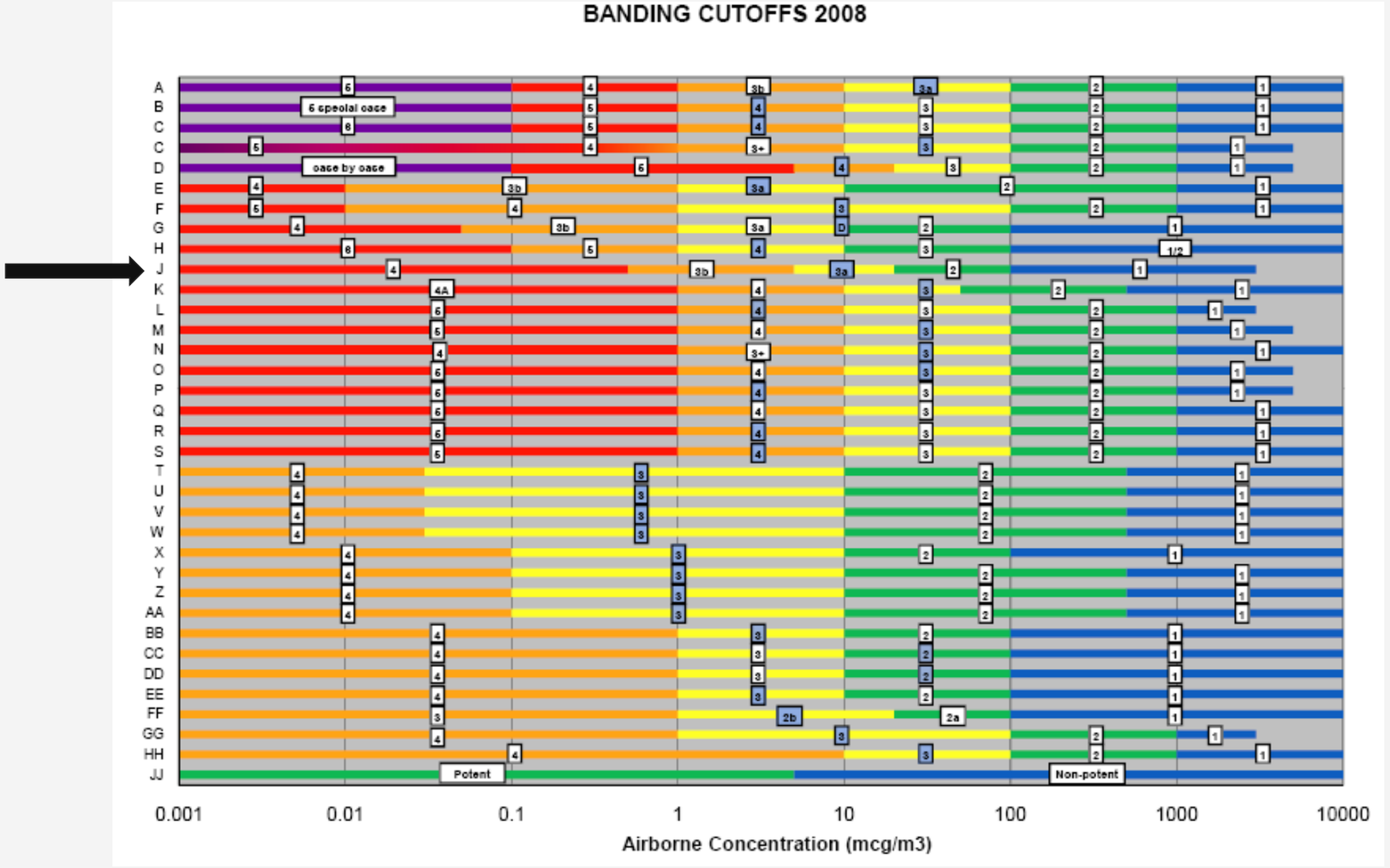
S: Pharmacokinetics (half-life and accumulation)

α: Used to adjust the absorption of a compound such that it equals 100 % via inhalation.

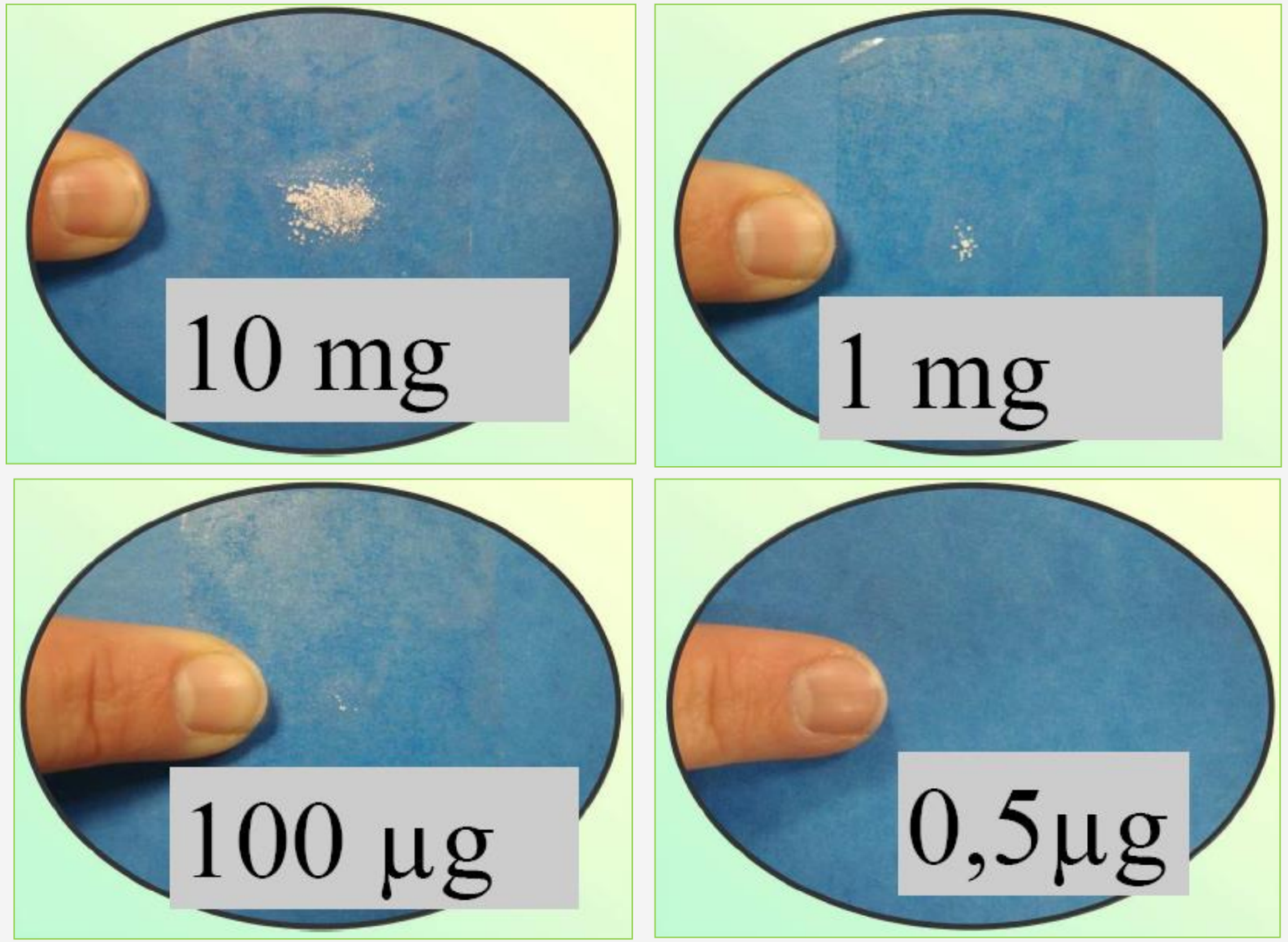
V: Volume of air breathed in an 8-hour workday (10 m^3)

Health Hazard Categories

Occupational Toxicology Roundtable



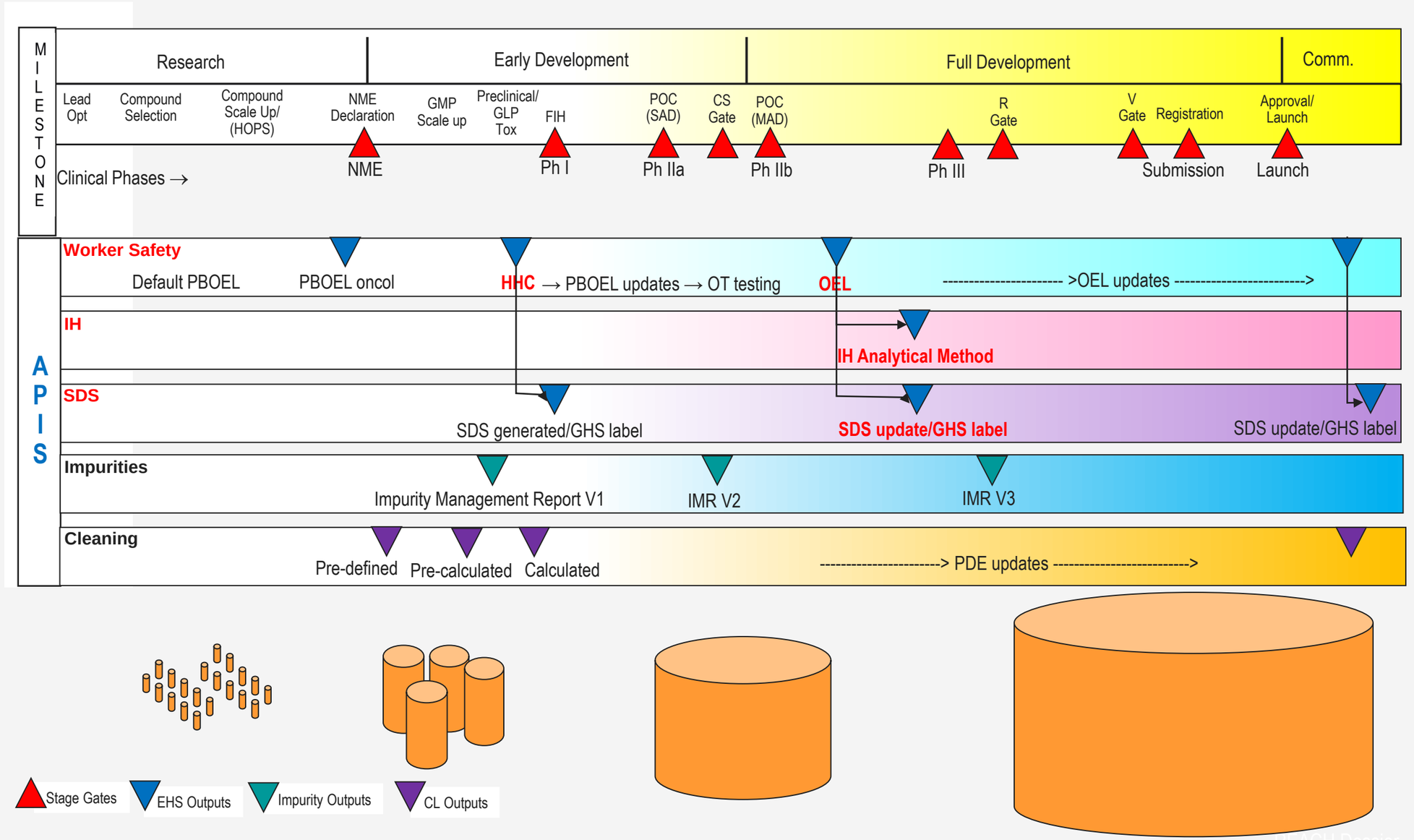
Occupational Exposure Limits



Notations

- **SKIN**: highlights the potential for significant absorption through the skin.
- **DSEN** - Dermal Sensitizer: highlights the potential for a compound to cause delayed allergic skin reactions (sensitization), such as wheals and rashes.
- **RSEN** - Respiratory Sensitizer: highlights the potential for a compound to cause delayed allergic reactions (sensitization), such as shortness of breath, asthma and anaphylaxis.
- **REPRO**-Reproductive Effector: highlights the potential for a compound to have adverse effects on reproduction and fetal development.
- **CORROSIVE** - highlights the potential for a compound to cause destruction of skin and/or eye tissue after a limited period of exposure
- **OTOTOXIC** - highlights the potential for a compound to cause hearing impairment or balance problems, regardless of noise exposure.
- **CYTOTOXIC** - highlights the potential for a compound to interact directly with DNA or DNA-associated macromolecules, resulting in cell death, affecting both healthy and abnormal (i.e., tumor) cells.

Worker Safety in SM New Product & Process Introduction - API

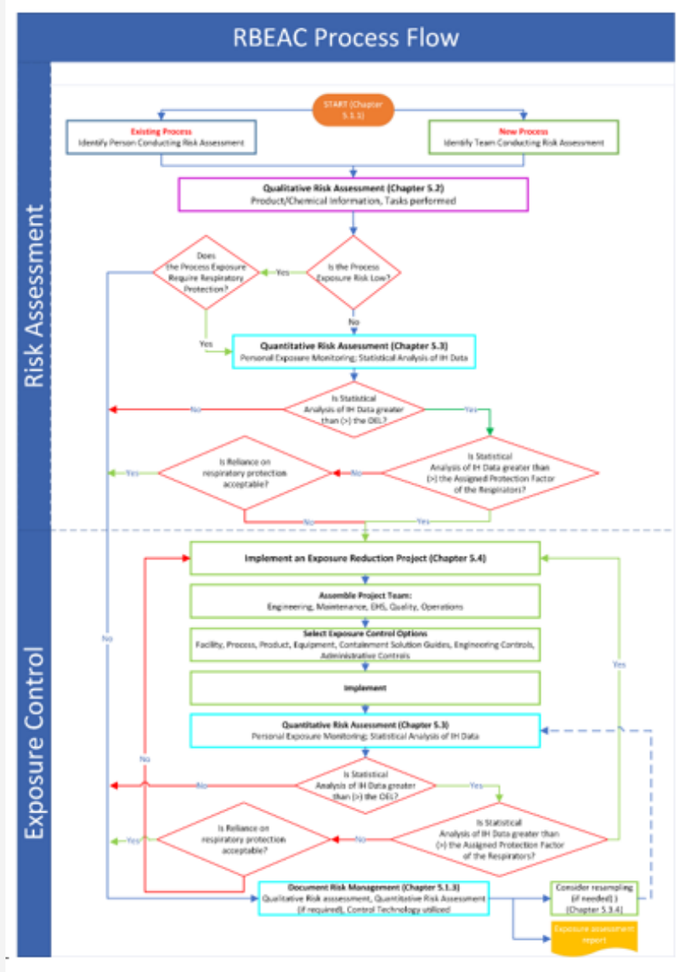


Content

- Hazard identification & communication
- **Qualitative & Quantitative Risk Assessments**
- Controlling exposures by respecting Hierarchy of Controls

Qualitative & Quantitative Risk Assessment

Risk Based Exposure Assessment & Control Process



1. Basic Hazard Characterization
2. Qualitative Risk Assessments
3. Quantitative Risk Assessments
4. Exposure Control Solutions
5. Forms:
   - ✓ CEAT: Chemical Exposure Assessment Tool
   - ✓ CSG: Containment Solution Guides
6. Attachments
   - ✓ Basic information characterization & assessments Unit Operations

Qualitative & Quantitative Risk Assessment

Quantitative Risk Assessment

- **Validated analytical methods** developed for each Active Pharmaceutical Ingredient
- 2 J&J Approved Laboratories: LOEH Belgium, BV USA
- **8-point validation** includes;
  - Sensitivity
  - Standard Curves (linearity)
  - Media Selection
  - Desorption Efficiency
  - Storage Stability
  - Sampling Stability (collection efficiency)
  - Analytical Precision
  - Accuracy
- Level of detection 15 minutes sample: **10% OEL**
- **Disposable Inhalable Samper**, different type of filters (glass fiber, nylon, Teflon, acid coated)

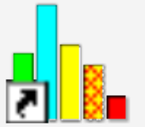
Professor Sleeth University Utah, US

Qualitative & Quantitative Risk Assessment

Quantitative Risk Assessment: monitoring & assessment

- **Perform** industrial hygiene exposure **monitoring** when **qualitative risk results** indicate the **exposure** profile is **uncertain** or exposures may **exceed** occupational exposure limits
- Collect task based **personal breathing zone** air samples
- **Randomly select employees** within each similar exposure group (SEG) to be sampled
- Add blank samples based on number of samples (1 blank / 10 samples).
- Ensure that **Chain of Custody** is followed during sampling and shipping of samples (as per Laboratory Analytical Request Form).

- Use Bayesian **statistics tool** to determine the 95th percentile
- Conduct statistical analysis of sampling results to **determine respirator** specification (e.g. assigned protection factor) if required



IHDataAnalyst.lnk

Qualitative & Quantitative Risk Assessment

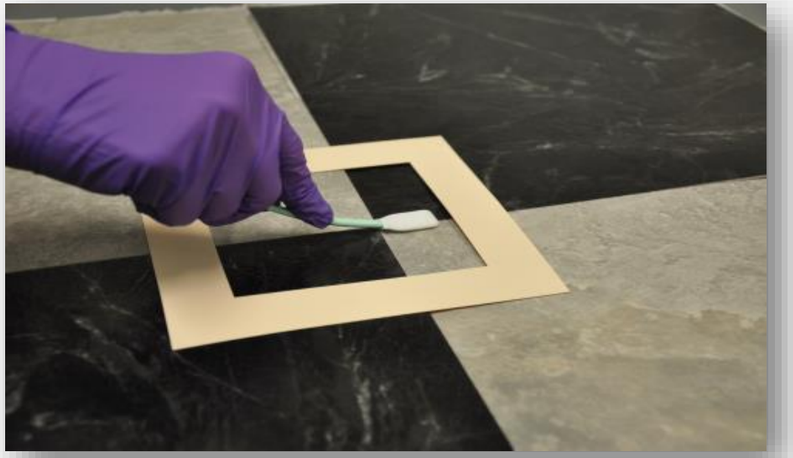
Quantitative Risk Assessment: Containment testing new installations

- SMEPAC protocol: ISPE Good Practice Guide:
  Assessing the particulate containment performance of pharmaceutical equipment
- Evaluate compliance with Design Exposure Limit included in User Requirement Specifications (50% most potent API)
- Select Surrogate: for example paracetamol micronized
  - 25 mm PTFE (teflon) filter (5.0 µm)
  - LOD: < 1 nanogram/filter
- Protocol to validate containment new installations
  - static monitoring: 120° around transfer ports
  - background monitoring
  - personal breathing zone samples during activity
  - worst case approach = challenge the installation
  - monitor during 3 runs

Qualitative & Quantitative Risk Assessment

Quantitative Risk Assessment: dermal assessment

- Wipe sampling protocols and analytical methods validated by J&J-approved labs
- Collect 100 cm^2 wipe samples at identified locations
- Measure surface contamination, eg work surfaces, equipment
- Not a measure of individual exposure
- Confirm effectiveness of cleaning or decontamination, e.g. in case of skin notation, DSEN
- Evaluate cross contamination non processing areas
- Compare values with Surface Target Value



Content

- Hazard identification & communication
- Qualitative & Quantitative Risk Assessments
- **Controlling exposures by respecting Hierarchy of Controls**

Hierarchy of Control process flow

EHS&S - IH

- **Focus on outcome RA**
  - ✓ Chemicals and Noise
  - ✓ Identification unit operations
  - ✓ Identify level of exceeding limits
  - ✓ Evaluate specific hazards (CMR, acute toxic)
  - ✓ Evaluate frequency unit operations
- **Outcome:**
  Overview unit operations with risk rating

Engineering / Facilities

- **Focus on technical solution**
  - ✓ Identify Technical solution
  - ✓ Perform impact assessment on reduction risk
  - ✓ Evaluate engineering challenges and complexity
  - ✓ Evaluate additional areas positive impact
  - ✓ Range total project cost
- **Outcome:**
  Technical solutions with preferability rating

Management

- **Review information**
  - ✓ Review risk rating (high number, high risk)
  - ✓ Review feasibility rating (high number, high preference)
- **Outcome:**
  Management Decision (approved, rejected or put on hold) and timing

Hierarchy of Controls

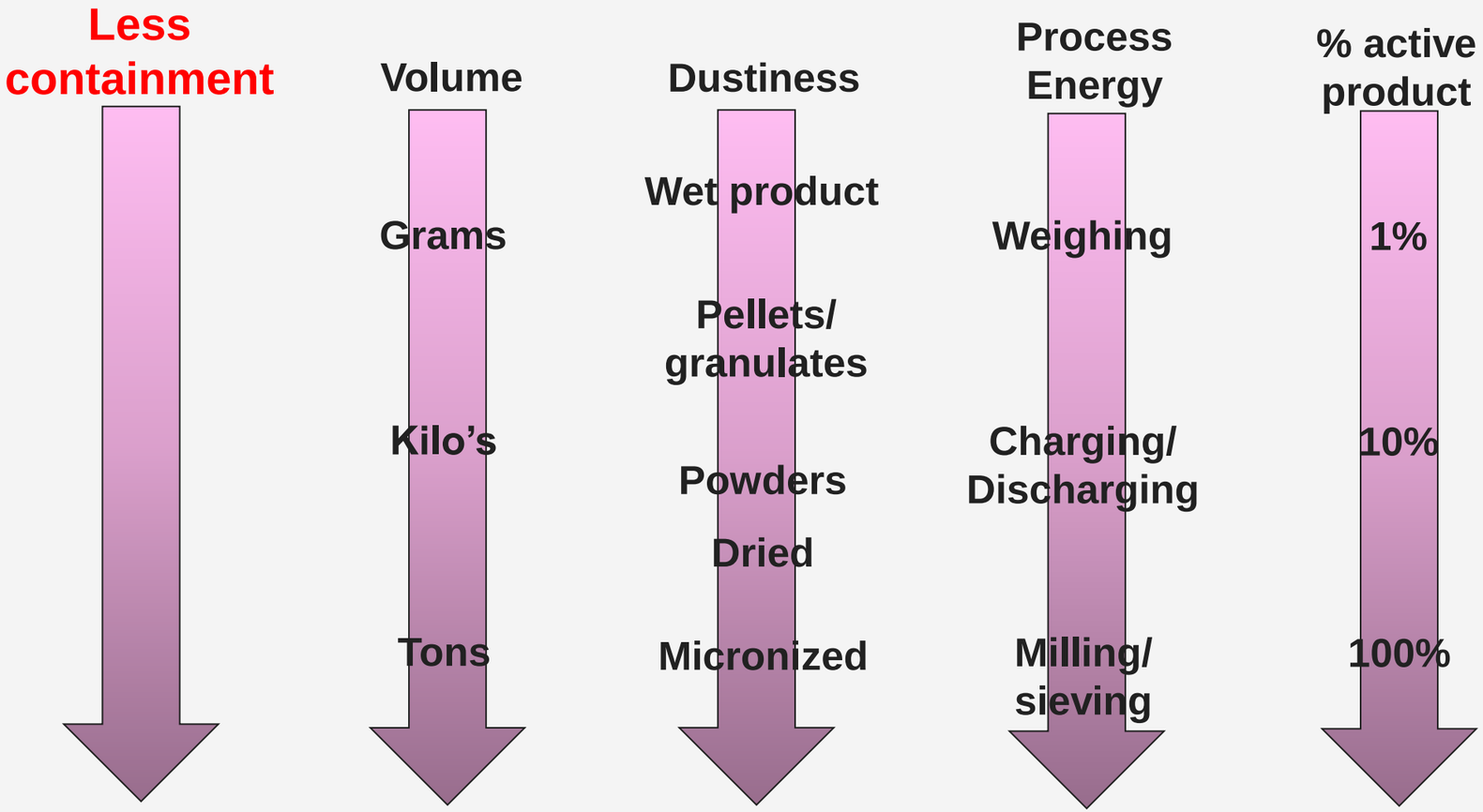
Approach

- Focus on product transfer
- Primary containment:
  - Isolator technology
  - Flexible containment: big bags, endless liner, …
  - Containment devices: PTS/DCS, powder feed unit, split butterfly valves, …
  - Ventilation systems: cabinet, down flow booth, LAF
- Secondary Containment:
  - Separation areas: control flow air pressure difference
- Personal Protective Equipment
- Importance of on-the-job training & maintenance

Hierarchy of Controls

Approach

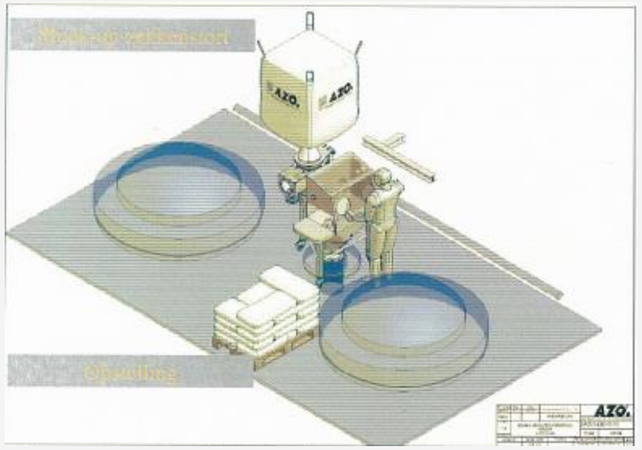
For each Health Hazard Class



Reactor charging

Contained dumping station

- Supplier: AZO Belgium
- Containment level: 20 μg/m^3
- Specifications
  - Custom made
  - Continuous liner back site to collect empty bags
- Considerations:
  - ergonomic review (mock-up)
  - on the job training operators
  - additional charging level

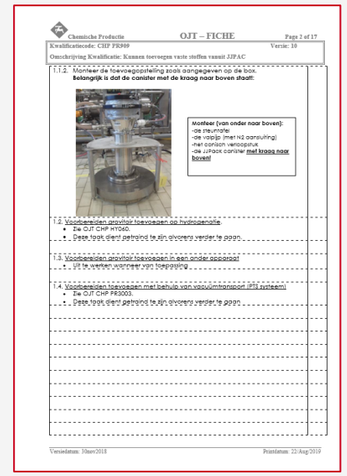


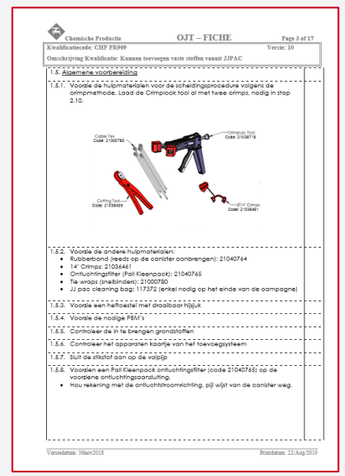
Reactor charging

Flexible containment

- Supplier: ILC Dover
- Containment level: 5 μg/m³
- Specifications
  - Commercially available
  - Double bags
  - Cut & crimp
- Considerations:
  - ergonomic advantage: limit manual handling
  - on the job training operators
  - additional charging level / valve mounted on reactor


Chemische Productie — OJT – FICHE — Page 1 of 17
Kwalificatiecode: CHP FR909 — Versie: 10
Omschrijving Kwalificatie: Kunnen toevoegen vaste stoffen vanuit JJPAC
Taakanalyse / Doelstellingen : KUNNEN — OK
Voorbereiding per plant of specifiek apparaat.
Een JJPac kan toegevoegd worden op verschillende manieren.
- Men kan gravitair werken of met behulp van vacuümtransport (PTS systeem).
- Wanneer men gravitair werkt moet men ook nog een onderscheid maken naar het soort apparaat omdat dan de opbouw en montage van de JJPac canister zal verschillen naargelang het apparaat.
- Het principe van aankoppelen en ledigen van een JJPac is steeds hetzelfde ongeacht of het nu gravitair gebeurt of via vacuümtransport
1. Voorbereiding tt.v. gravitair toevoeg.
1.1. Voorbereiding proviat toevoegen via vaste fys.
1.1.1. Haal de box aan met de toevoegopstelling voor JJpac's
Versiedatum: 30nov2018 — Printdatum: 22-Aug-2019


Chemische Productie — OJT – FICHE — Page 2 of 17
Kwalificatiecode: CHP FR909 — Versie: 10
Omschrijving Kwalificatie: Kunnen toevoegen vaste stoffen vanuit JJPAC
1.1.2. Monteer de toevoegopstelling zoals aangegeven op de box.
Belangrijk is dat de canister met de kraag naar boven staat!
Monteer (van onder naar boven):
-de reductie
-de vlotjs (met N2 aanvulling)
-het corison verbindstuk
-de JJPack canister met kraag naar boven!
1.2. Voorbereiden proviat toevoegen via hydrogenatie
- Zie OJT CHP HY060
- Deze taak dient gehoord te zijn alvorens verder te gaan
1.3. Voorbereiden gravitair toevoegen in een ander apparaat
- Uit te werken volgorde van toepassing
1.4. Voorbereiden toevoegen met behulp van vacuümtransport (PTS systeem)
- Zie OJT CHP PE3003.
- Deze taak dient gehoord te zijn alvorens verder te gaan
Versiedatum: 30nov2018 — Printdatum: 22-Aug-2019


Chemische Productie — OJT – FICHE — Page 3 of 17
Kwalificatiecode: CHP FR909 — Versie: 10
Omschrijving Kwalificatie: Kunnen toevoegen vaste stoffen vanuit JJPAC
1.5. Algemene voorbereiding
1.5.1. Voorde de hulpmiddelen voor de schellingsprocedure volgens de crimpmethode. Laad de Crimplock tool al met twee crimps, nodig in stap 2.10.
1.5.2. Voorde de andere hulpmiddelen:
- Rubberband (reeds op de canister aanbrengen): 21040764
- 14" Crimps: 21036461
- Ontluchtingsfilter (Pall Kleenpack): 21040765
- Tie wraps (snelbinder): 21000780
- JJ pac cleaning bag: 117372 (enkel nodig op het einde van de campagne)
1.5.3. Voorde een heftoestel met draaibaar hijsuk
1.5.4. Voorde de nodige PBM's
1.5.5. Controleer de te brengen grondstoffen
1.5.6. Controleer het apparaten kaartje van het toevoegsysteem
1.5.7. Sluit de slikstof aan op de vlotjs
1.5.8. Voorsien een Pall Kleenpack ontluchtingsfilter (code 21040765) op de voorziene ontluchtingsaansluiting.
- Hou rekening met de ontluchtstroomrichting, pijl wijst van de canister weg.
Versiedatum: 30nov2018 — Printdatum: 22-Aug-2019

Reactor charging

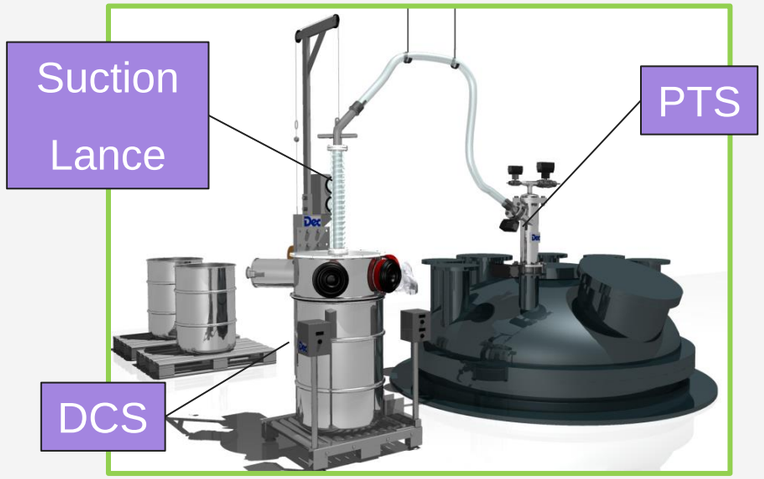
Flexible containment with suction hopper & Powder Transfer System

- Supplier: ILC Dover, DEC
- Containment level: 5 μg/m³
- Specifications
  - Bags & Powder Transfer System commercially available
  - PTS mounted on dedicated valve reactor
  - Suction hopper: custom made design: delumper & nitrogen nozzles
  - Double bags
  - Cut & crimp
- Considerations:
  - ergonomic advantage: limit manual handling
  - on the job training operators
  - FAT testing done with worst case product

Reactor charging

Drum Containment System with Powder Transfer System

- Supplier: DEC, De Dietrich
- Containment level: 1 μg/m³
- Specifications
  - Drums & Powder Transfer System commercially available
  - PTS mounted on dedicated valve reactor
  - Suction lance
- Considerations:
  - ergonomic challenge: posture, weight, repetition
  - on the job training operators



Reactor charging

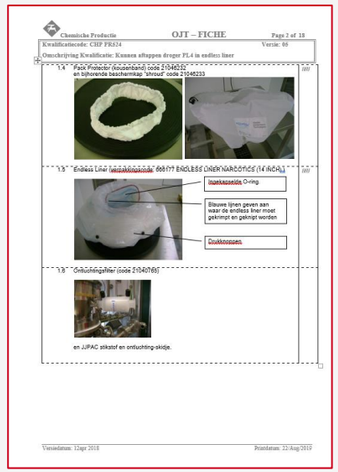
Isolator technology

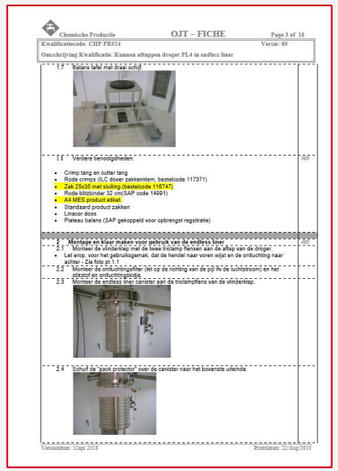
- Supplier: Extract Technology, SKAN
- Containment level: 0.01 μg/m^3
- Specifications
  - Custom made
  - Rapid Transfer Port CRL
- Considerations:
  - importance ergonomic design
  - URS template
  - preventive maintenance

Discharging dryer

Endless liner

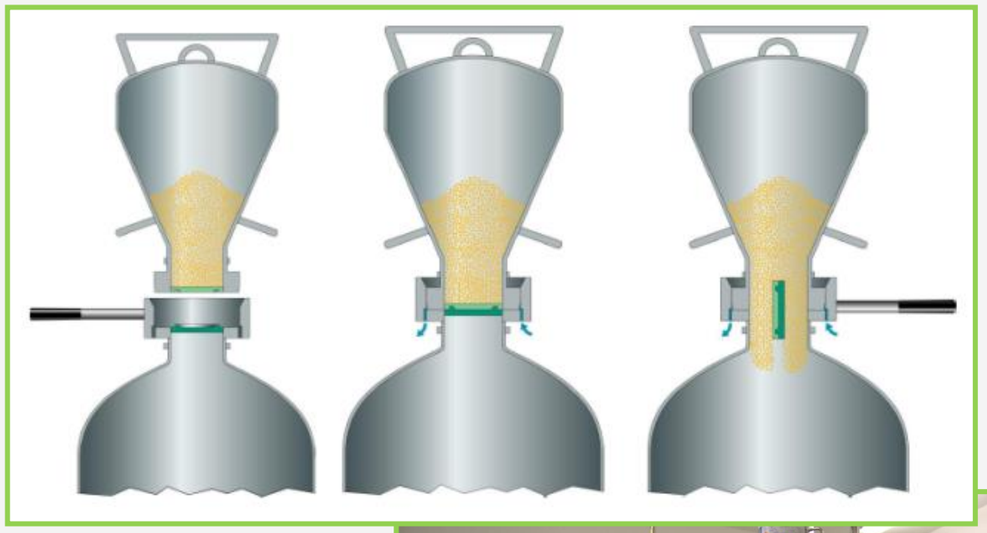
- Supplier: ILC Dover
- Containment level: 1 μg/m³
- Specifications
  - Mounted under valve dryer
  - Cut / crimp
- Considerations:
  - turning platform: ergonomic improvement
  - limited weight, combination with RTP drum





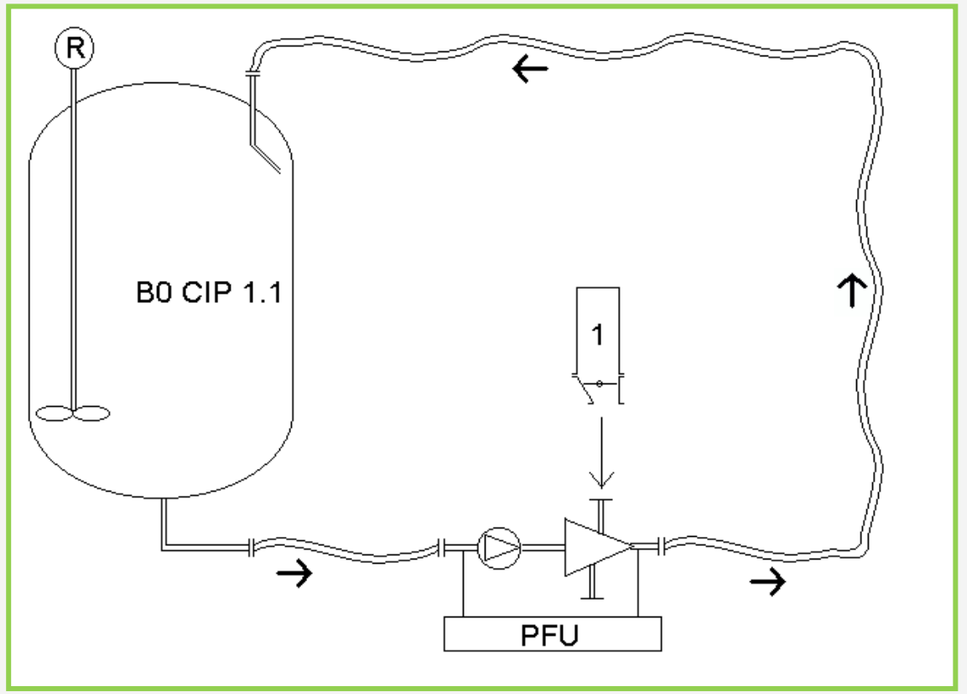
Charging mixer

Split butterfly valve & Cleaning In Place



Charging mixer

Powder feed unit (venturi) & CIP



Weighing Warehouse

Down flow booth (with screen)

- Supplier: Howorth, Hosokawa, Extract Technology,…
- Containment level: 1 - 100 μg/m^3
- Considerations:
  - importance position & training operator
  - concentration depending on amount and product
  - movable screen with gloves

Weighing API Quality Control

Weighing samples & bringing into a solution

- Weighing API before analysis
- Bring API in solution
- Different technologies with different containment
  - Vented weighing balance
  - Biosafety Cabinet
  - Weighing Isolator

Summary

- Process embedded in R&D to develop hazard communication data supported by Occupational Toxicology
- Tools developed and implemented to support the Qualitative Risk assessments
- Validated analytical methods in place for each API to support evaluation of dermal and inhalable exposure at the workplace
- Statistical analyses based on personal monitoring samples during identified activities to verify containment levels installations
- Integrated process controlling exposures by respecting Hierarchy of Controls

Q&A


Johnson & Johnson