PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE
Building responsible supply chains

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暴露监测和分析案例分享

Exposure Control and Monitoring – Case Study

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嘉宾介绍 Speaker Bio

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- 背景：
- 7年CDMO行业EHS&工业卫生管理经验。7 years' experience of EHS&IH management in CDMO.
- 美国注册工业卫生师，中国注册安全工程师。CIH in ABIH/BGC and CSE in China.
- 化学工程与工艺，学士。Chemical engineering and technology, bachelor degree.

议程 Agenda

Hazards of API and intermediate in pharmaceutical industry

制药工业中原料药和中间体的危害

Exposure risk assessment 暴露风险评估

Hierarchy of exposure controls 暴露控制层级

Case study 案例分享

Q&A 问答

制药工业中原料药和中间体的危害
Hazards of API and intermediate in pharmaceutical industry

- 制药行业在药物生产过程中会使用各类化学品，包括中间体、活性药物成分、原料、副产物和杂质。
- The pharmaceutical industry may uses various chemicals in the drug production process, including intermediates, APIs, raw materials, by-products, and impurities.
- 有的物质可能导致严重的健康影响，例如：
- Some compounds may cause significant health effect, such as:

➢ 导致严重靶器官毒性，严重不良反应 Produce serious target organ toxicity or significant adverse effects

➢ 高药理活性，潜在高致敏性 High pharmacological potency, high sensitizing potential

➢ 基因毒性物质 Genotoxic compounds

➢ 低剂量下可能导致生殖毒性和/或发育毒性的物质 Compounds that can produce reproductive and/or developmental effects at low dose

➢ ……

制药工业中原料药和中间体的危害
Hazards of API and intermediate in pharmaceutical industry

- 使用OEL/OEB描述原料和中间体的健康危害，基于现有的化学品健康危害数据建立OEL/OEB

OEL/OEBs are used to describe health hazards of API and intermediate. OELs/OEBs are established based on data available form health hazards of chemicals

- 对于原料药和中间体，通常没有法规规定职业接触限值

No regulatory OELs established for API and intermediate

- 中国国标的粉尘OELs 对比制药行业OEL/OEB

Chinese OELs VS OEB for pharmaceutical industry

序号	中文名	英文名	化学文摘号 CAS 号	PC-TWA mg/m³	
				总尘	呼尘
49	其他粉尘[a]	Particles not otherwise regulated	—	8	—
表中列出的各种粉尘（石棉纤维尘除外），凡游离 SiO_2 等于或高于 10%者，均按矽尘职业接触限值对待。					
[a] 指游离 SiO_2 低于 10%，不含石棉和有毒物质，而未制定职业接触限值的粉尘。					

Ref: Chinese OEL standard GBZ2.1

OEB1	>1000 µg/m3 dust >500 PPM vapor	Almost non-toxic, no irritation, little activity
OEB2	100-1000 µg/m3 dust 50-500 PPM vapor	Maybe a little toxic, irritation, moderate activity
OEB3	10-100 µg/m3 dust 5-50 PPM vapor	Moderate toxic, high activity
OEB4	1-10 µg/m3 dust 0.5-5 PPM vapor	High toxic, corrosive, allergic, high activity
OEB5	<1 µg/m3 dust <0.5 PPM vapor	Very toxic, corrosive, allergic, high activity

Porton OEB

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暴露风险评估 Exposure risk assessment

- 暴露评估的策略

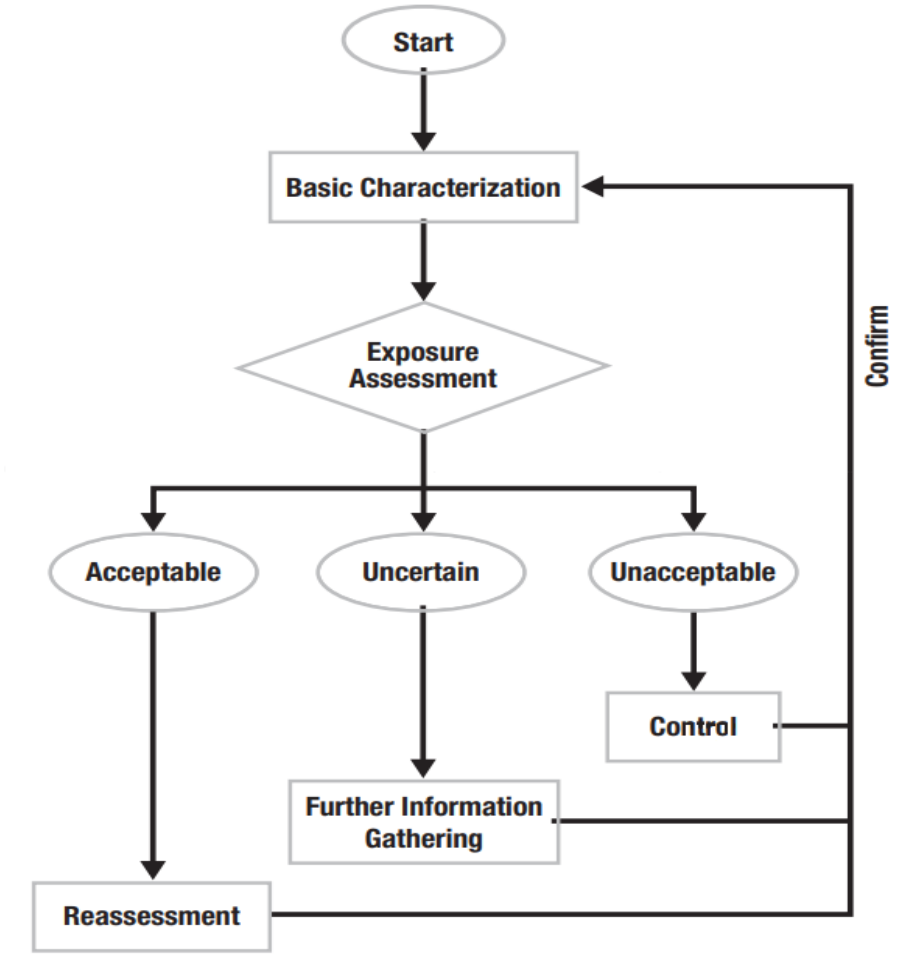
Exposure assessment strategy

➢风险=危害×暴露

Risk=Hazard × Exposure

➢暴露评估是工业卫生项目的核心

Exposure assessment is the core of industrial hygiene programs

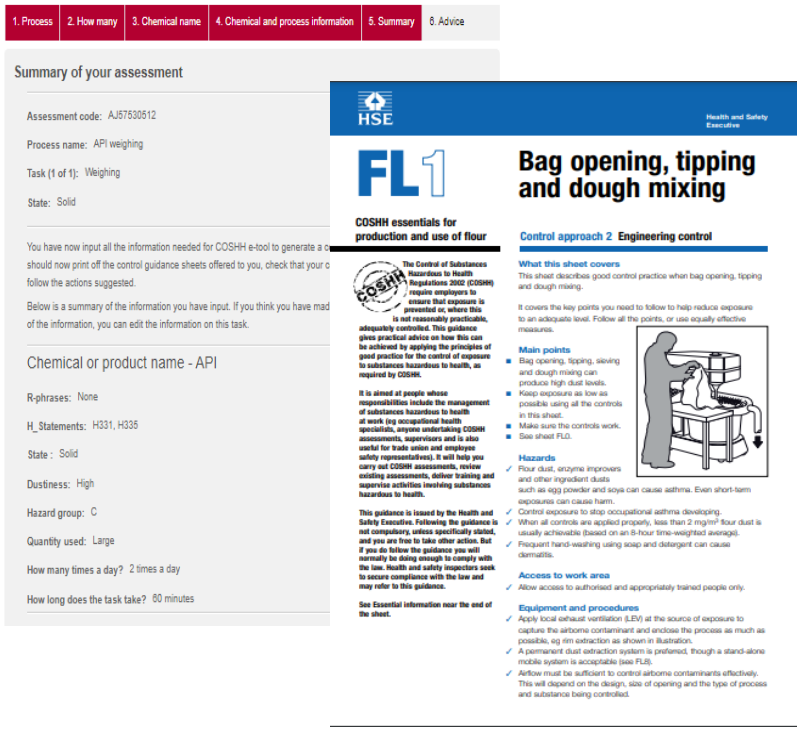


Ref: AIHA

暴露风险评估 Exposure risk assessment

- **定性风险评估 Qualitative assessment**

➢多种工具和指南，例如 Various tools or guides, such as

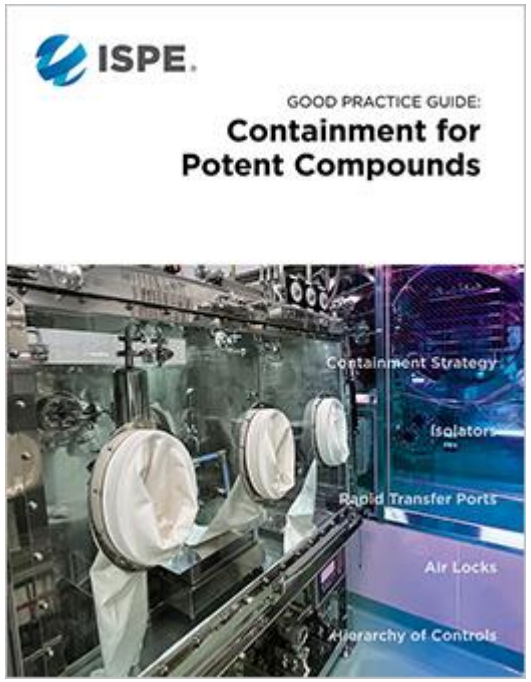


Ref: COSHH UKHSE

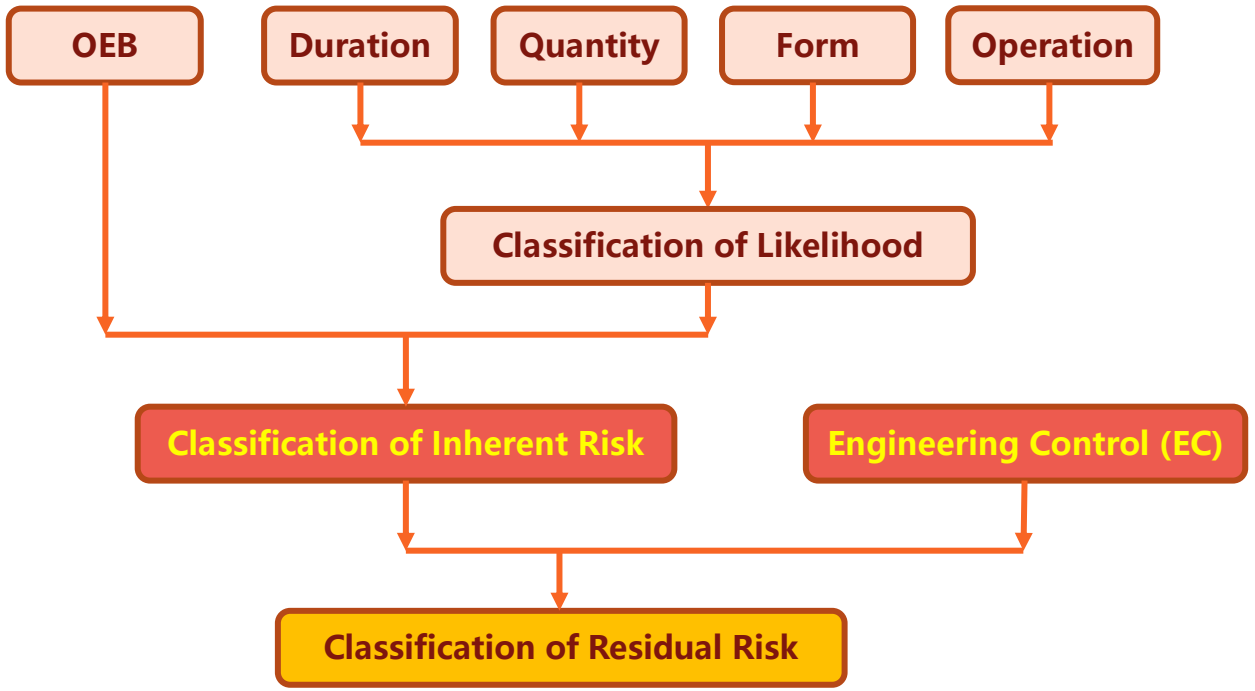
Ref: Chinese guideline GBZ/T 298

暴露风险评估 Exposure risk assessment

- 定性风险评估 Qualitative assessment



Ref: ISPE Good Practice Guide



Porton internal IHA tool

暴露风险评估 Exposure risk assessment

- **定量风险评估 Quantitative assessment**

①针对特定原料药/中间体的暴露检测 IH exposure monitoring for specific API/intermediate

➢优势 Advantage

➢药物生产的同时开展采样 Monitoring during API/drug production

➢暴露水平的真实反馈 Reflect real exposure

Sample pump

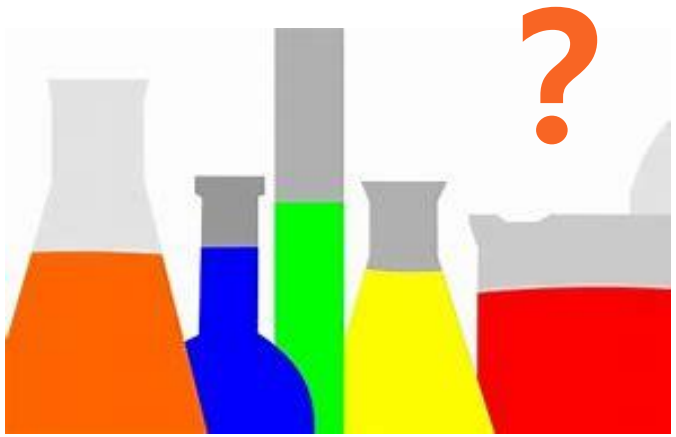
Calibrator

Sampler

Swab

暴露风险评估 Exposure risk assessment

- 劣势： Disadvantage
- 需要经过验证的采样和分析方法 Validated sampling & analytical method
- 成本高昂 High cost
- 时间受限 Time limit
- 有限的资源 Limited resources



暴露风险评估 Exposure risk assessment

- **定量风险评估 Quantitative assessment**

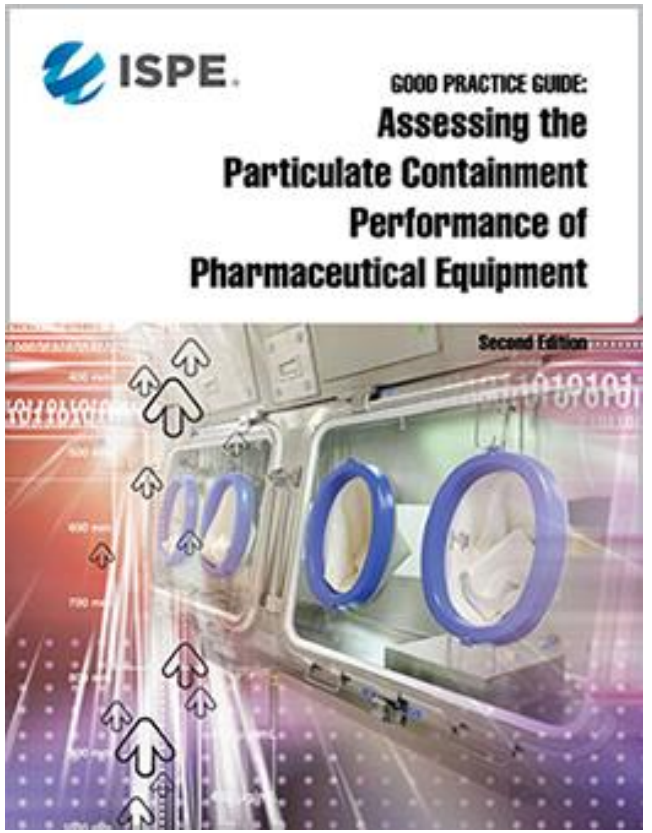
②替代物测试 Surrogate test

➢遵循 ISPE指南 Follow ISPE guide

➢密闭性能目标 CPT

➢测试环境 Test environment: FAT? SAT?

➢测试物料 Test material: Lactose? Naproxen sodium?



Ref: ISPE Good Practice Guide

暴露风险评估 Exposure risk assessment

➢空气和表面采样

Airborne particulate and surface sampling

➢样品分析

Sample analysis

➢数据解读和报告

Data interpretation & report

Personal sampling

Static sampling

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Case study 案例分享

Q&A 问答

暴露控制层级 Hierarchy of exposure controls

- 遵循控制层级实施暴露风险控制

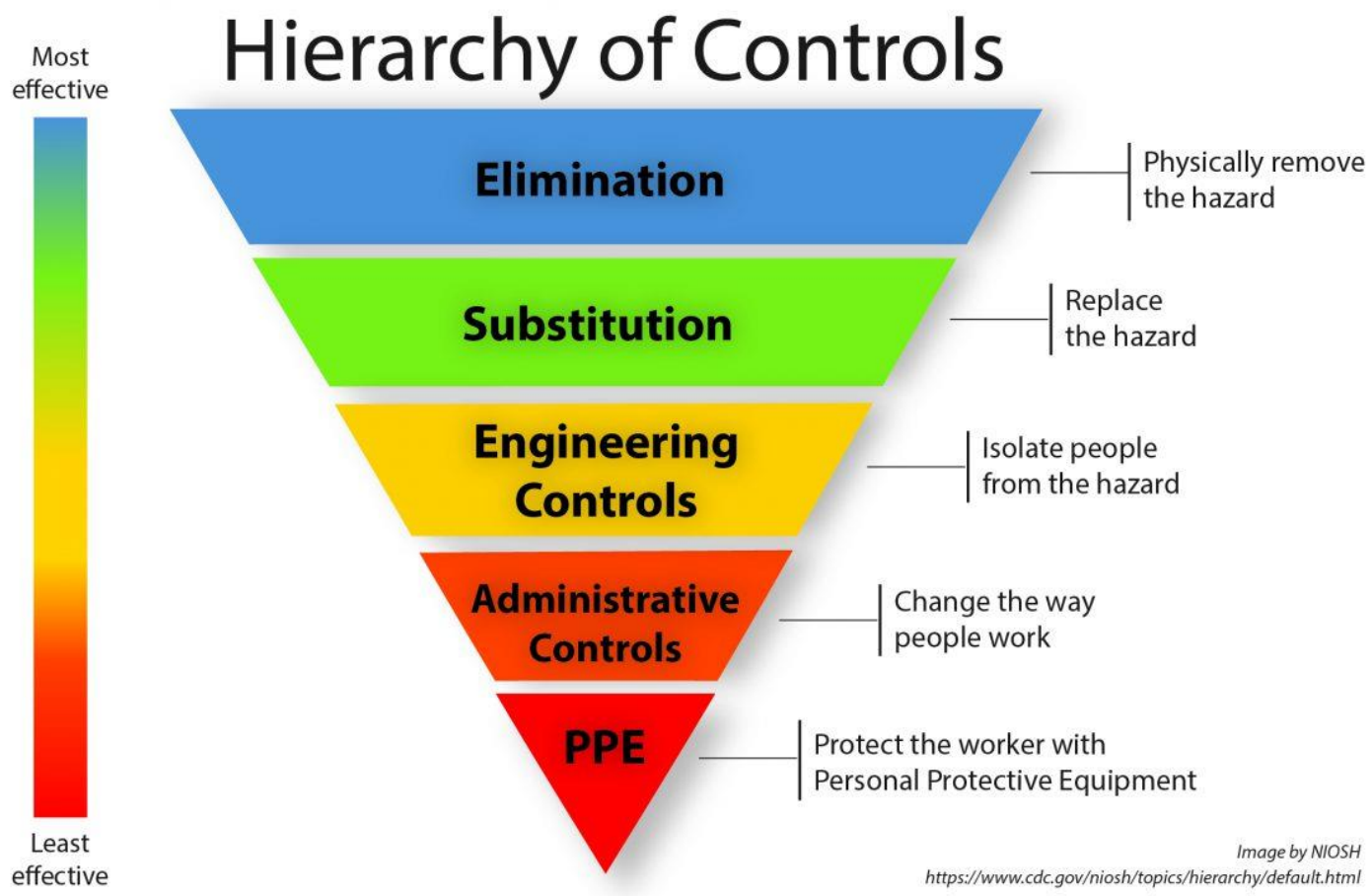
Follow the hierarchy of controls

- 消除&替代更适合早期

Elimination, substitution for early period

- 关注工程控制措施

Focus on Engineering Controls



暴露控制层级 Hierarchy of exposure controls

- 工程控制措施（一级密闭）的关键 The Key of Engineering Controls (Primary containment)

➢密闭性能，维护 Containment Performance, Maintenance

➢人体工程学 Ergonomics

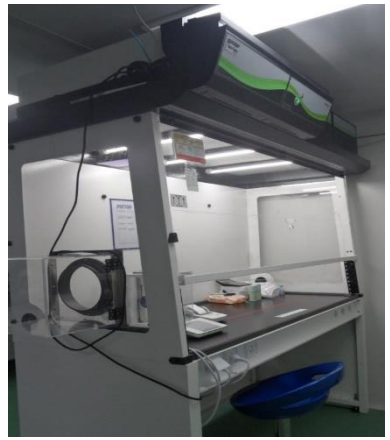
➢兼容性 Compatibility

➢因地制宜 According to process conditions

Automatic packing in rigid isolator

Multi-use device with rigid isolator

Flexible isolator



Weight cabinet

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案例分享 Case study

- 案例：某中间体合成步骤的暴露评估和工程改善

Case: Exposure assessment and EC improvement of an intermediate process

◆化学品基本信息 Basic info, chemicals:

➢ 中间体1，固体粉末，腐蚀性, 皮肤致敏，OEL=5μg/m3

Intermediate1, solid powder, corrosive, dermal sensitizer, OEL=5μg/m3

➢ 原料2，固体粉末，OEL=1000μg/m3

RM2, solid powder, OEL=1000μg/m3

➢ 溶剂，易燃，OEL=30mg/m3

Solvent, flammable, OEL=30mg/m3

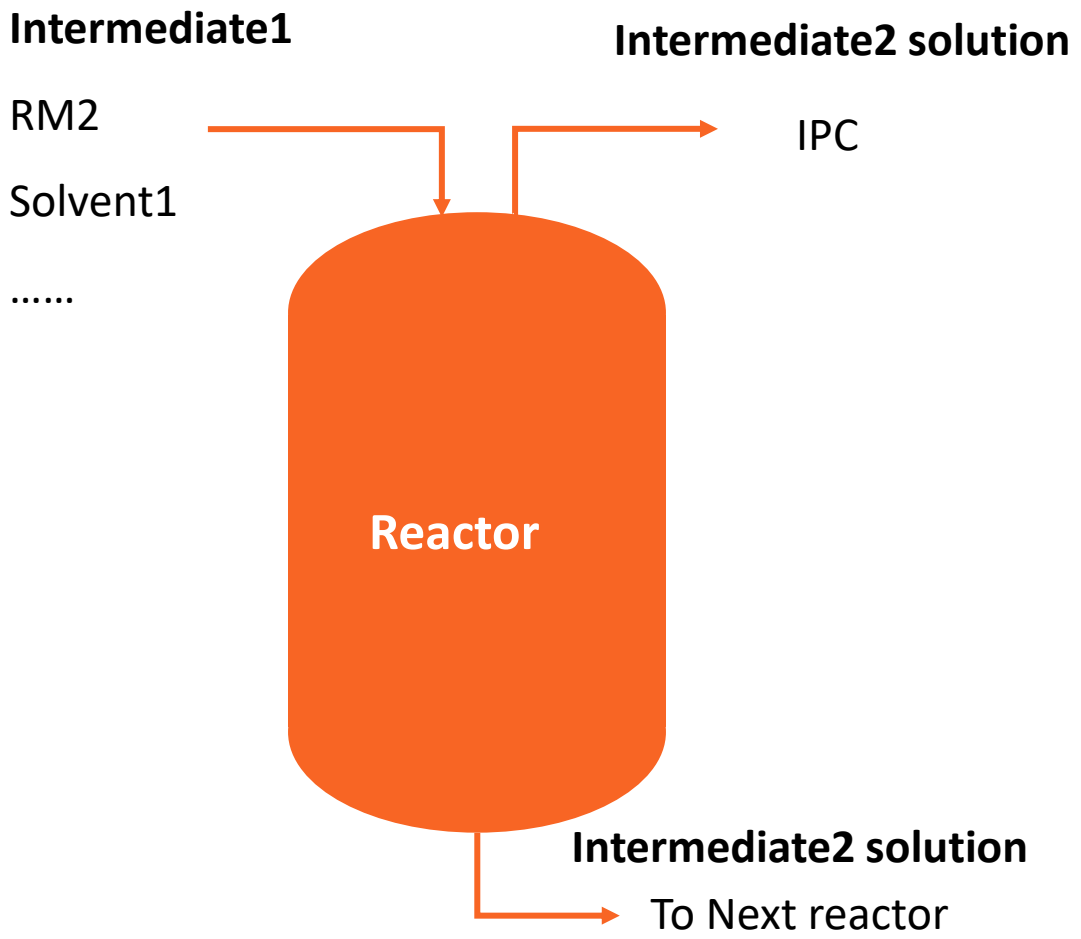
➢ 中间体2，OEL=5μg/m3

Intermediate2, OEL=5μg/m3

*Data comes from client, in vitro and animal study

案例分享 Case study

- 合成步骤 Synthetic step
- 单元操作 Unit operation
  - 分零、称量 Dispensing, weighting
  - 投料 Charging
  - 中控取样 In process sampling
  - 管道转料到下一个反应釜 Transfer to next reactor via pipe



案例分享 Case study

- 定性风险评估 Qualitative assessment

物料名称	OEL (μg/m³)	严重性级别(OEB级别)	物料状态（固体，液体）	单元操作	重量 kg(/L)	接触时间 (h)	可能性分数	可能性级别	固有风险级别	工程控制措施	工程控制级别	剩余风险级别	剩余高风险 ≥4级
中间体1	5	4	固体：粉末状干品，堆密度0.3-0.5(含)g/ml，直径20(含)-100目之间	Solid dispensing固体分料	15.00	0.50	14	3	4	层流罩DFB	4	4	1
中间体1	5	4	固体：粉末状干品，堆密度0.3-0.5(含)g/ml，直径20(含)-100目之间	Reactor charging solid反应釜固体投料	15.00	1.00	14	3	4	PTS	4	4	1
RM2	>1000	1	固体：粉末状干品，堆密度0.3-0.5(含)g/ml，直径20(含)-100目之间	Reactor charging solid反应釜固体投料	0.10	0.10	11	3	1	LEV（万向罩）	5	2	
溶剂1	>1000	1	液体：20℃饱和蒸汽压 1(含)-10KPa	Liquid Charging from Drum从桶中投液体物料	142.00	0.50	10	2	1	LEV（半密闭罩）	4	1	
中间体2	5	4	液体：20℃饱和蒸汽压 1(含)-10KPa	In Process Sampling中控取样	0.05	0.10	7	2	3	长寿工厂自制取样器+LEV（万向罩）	2	2	

Conduct quantitative assessment for high risk operation

➢传统的操作方式可能导致不可接受的暴露

Traditional operations may lead to unacceptable exposures

案例分享 Case study

传统的操作方式 Traditional operations

- 单元操作：固体分零 Unit operation: Powder dispensing
- ➢一级密闭：层流罩 Primary containment: DFB
- ➢二级密闭：独立的分料间 Secondary containment: independent dispensing room

替代物测试结果
Surrogate test result (unit: μg/m3)

采样批次 Batch	操作者呼吸区 PBZ	层流罩外 Outside of DFB
1	779	1.77
2	389	0.595
3	309	0.195

Unacceptable exposure, how to improve?

案例分享 Case study

改良的操作方式Improved solutions

- 一级密闭：硬质隔离器+连续袋

Primary containment: Rigid isolator + continuous liner

替代物测试结果
Surrogate test result (unit: μg/m3)

采样批次 Batch	个体浓度 PBZ	分料间外 Outside of the room
1	< 0.0501	< 0.0522
2	< 0.0484	< 0.0446
3	< 0.0485	< 0.0498
4	< 0.0464	< 0.0462

案例分享 Case study

传统的操作方式Traditional operations

- 单元操作：固体投料 Unit operation: solid charging
  - 一级密闭：粉料输送系统 Primary containment: Powder Transfer System
  - 二级密闭：独立的投料间 Secondary containment: independent charging room

替代物测试结果
Surrogate test result (unit: μg/m3)

采样批次 Batch	操作者呼吸区 PBZ
1	1090
2	671
3	1500

Unacceptable exposure, how to improve?

案例分享 Case study

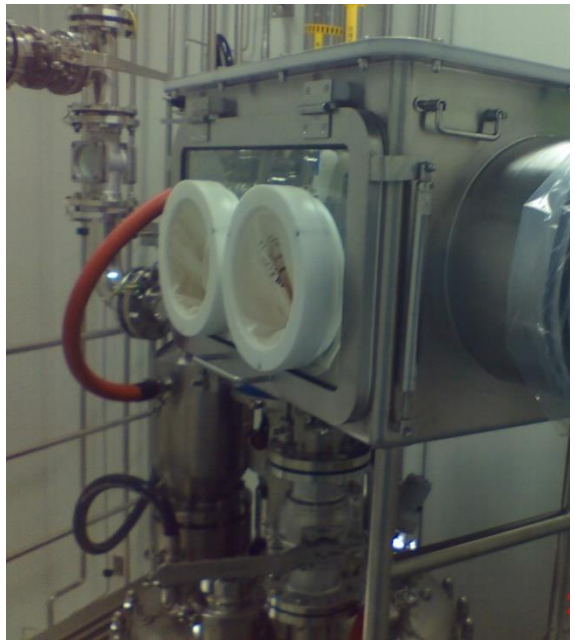
改良的操作方式 Improved solutions

➢一级密闭：硬质隔离器+连续袋

Primary containment: Rigid isolator + continuous liner

替代物测试结果
Surrogate test result (unit: μg/m3)

采样批次 Batch	操作者呼吸区 PBZ
1	0.669
2	0.195
3	0.626



总结 Summary

- API和中间体危害，OEL&OEB Hazards of API and intermediate, OEL&OEB
- 暴露控制策略 Exposure assessment strategy
- 定性、定量评估 Qualitative, Quantitative assessment
- 暴露控制层级，工程控制措施 Hierarchy of exposure controls, Engineering Controls
- 案例：评估，工程控制提升 Case: assessment, Engineering Controls improvement

提问环节 Q&A