

暴露监测和分析案例分享

Exposure Control and Monitoring – Case Study

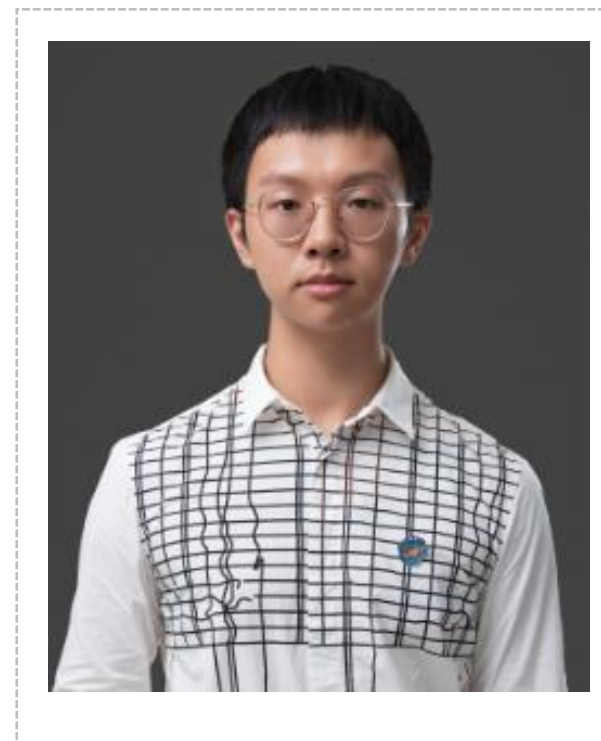
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嘉宾介绍 Speaker Bio

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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 use 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

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

序号	中文名	英文名	化学文摘号 CAS 号	PC-TWA mg/m ³	
				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

Porton OEB

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暴露风险评估 Exposure risk assessment

- 暴露评估的策略

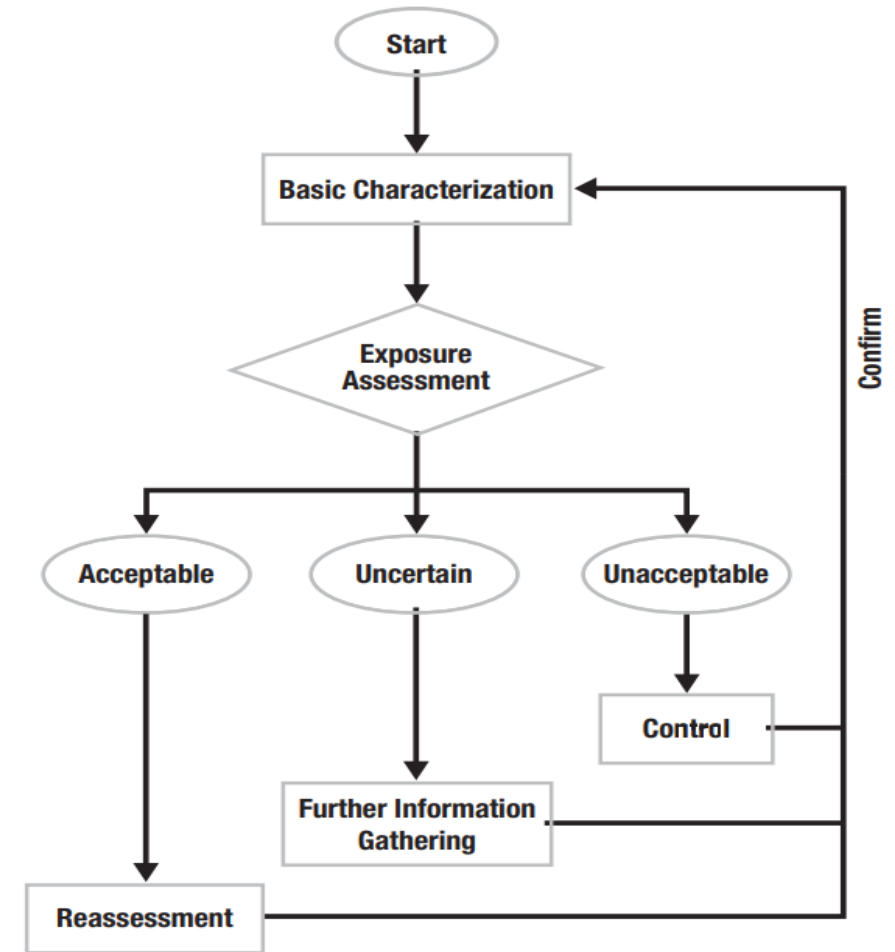
Exposure assessment strategy

➤ 风险=危害×暴露

$\text{Risk} = \text{Hazard} \times \text{Exposure}$

➤ 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

- **定性风险评估 Qualitative assessment**

1. Process	2. How many	3. Chemical name	4. Chemical and process information	5. Summary	6. Advice
Summary of your assessment					
Assessment code: AJ57530512 Process name: API weighing Task (1 of 1): Weighing State: Solid				  COSHH essentials for production and use of flour	
You have now input all the information needed for COSHH e-tool to generate a COSHH assessment. You will now follow the print off the control guidance sheets offered to you. If you check that you follow the actions suggested. Below is a summary of the information you have input. If you think you have made any of the information, you can edit the information on this task.					
Chemical or product name - API					
R-phrases: None H_Statements: H331, H335 State : Solid Dustiness: High Hazard group: C Quantity used: Large How many times a day? 2 times a day How long does the task take? 00 minutes					



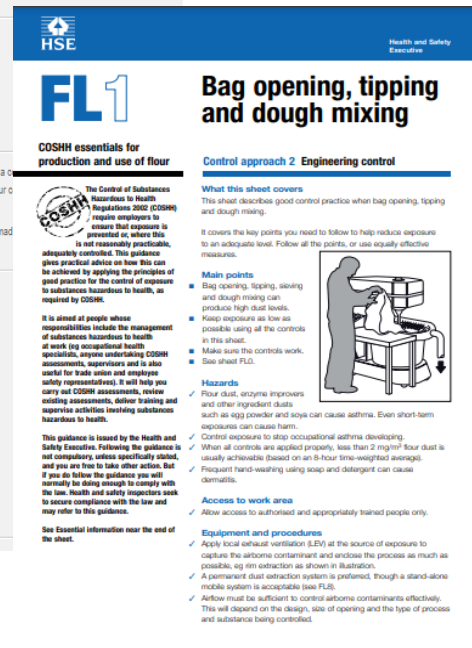
The Control of Substances Hazardous to Health Regulations 2002 (COSHH) require employers to ensure that exposure is controlled as far as is reasonably practicable, adequately controlled.

This guidance gives practical advice on how this can be achieved by applying the principles of good practice for the control of exposure to substances hazardous to health, as required by COSHH.

It is aimed at people whose responsibilities include the management of substances hazardous to health at work (eg occupational health specialists, anyone undertaking COSHH assessments, supervisors and is also useful for trade union and employee safety representatives). It will help you carry out COSHH assessments, review existing assessments, develop training and supervise activities involving substances hazardous to health.

This guidance is issued by the Health and Safety Executive. Following the guidance is not compulsory, unless specifically stated, and you are free to take other action, but if you do follow the guidance you will normally be doing things in compliance with the law. Health and safety inspectors may seek to secure compliance with the law and may issue this guidance.

See [COSHH Essentials for the user of the sheet.](#)



JCS 13.100
G 52

GBZ

中华人民共和国国家职业卫生标准

GBZ/T 298—2017

工作场所化学有害因素职业健康风险评估技术导则

Guidelines for occupational health risk assessment of chemicals in the workplace

2017 - 09 - 30 发布

2018 - 04 - 15 实施

中华人民共和国国家卫生和计划生育委员会 发布

附录B 综合指数法接触指数分级

接触指数 (E2)			
	3	4	5
P _a	133 Pa ~ 1330 Pa	1330 Pa ~ 13300 Pa	>13300 Pa
颗粒物	干燥的 < 小颗粒 > 100 μm 的材料	干燥的和 10 到 100 μm 的材料	干燥的和小于 10 μm 的材料
E ₁	0.5~	1.0~	≥2.0
E ₂	防护设施充分但无维护	防护措施不充分	完全无防护措施
E ₃	设施充分但无维护	设施不充分	完全无设施
E ₄	4分	3分	≤2分
E ₅	2分	1分	0分
E ₆	4分~6分	1分~3分	0分
E ₇	中等用量 (2~20 kg 或 L), 使用者接受过培训	大量量 (20~200 kg 或 L), 使用者接受过培训	大量量 (≥200 kg 或 L), 使用者未接受过培训
E ₈	≥2 h, <4 h	≥4 h, <6 h	≥6 h
E ₉	中等用量 (10~100 kg 或 L), 使用者接受过培训	大量量 (100~1000 kg 或 L), 使用者接受过培训	大量量 (≥1000 kg 或 L), 使用者未接受过培训
E ₁₀	≥10 h, <24 h	≥24 h, <72 h	≥72 h

性、按时间、假期记录、培训记录等 6 项, 每项 1 分, 总分为 6 分。

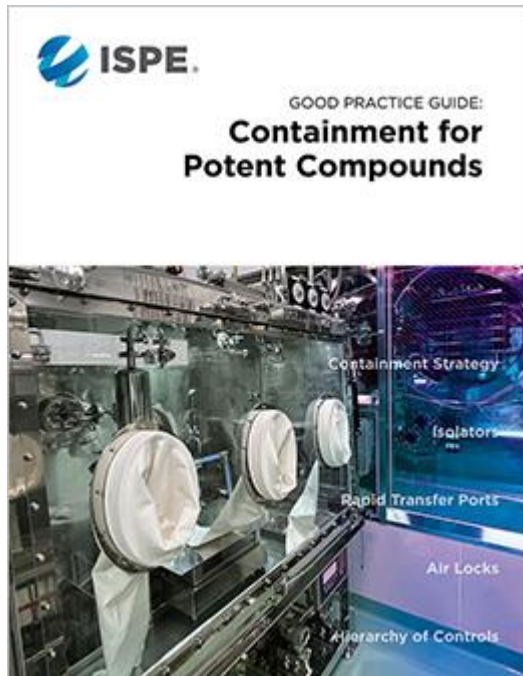
培训、演练、维护保养等 4 项内容, 每项 1 分, 总分为 4 分。

、职业病危害警示与告知制度、职业病危害项目申报制度、职业病危害因素检测与评价制度、职业病危害防护用品管理制度、职业病危害监测及评价管理制度、职业病危害应急救援与管理制度、岗位职业卫生操作规程等 12 项, 每项制度建立 0.5 分, 制度执行良好 0.5 分, 某项制度未建列为 0 分, 总分 12 分。

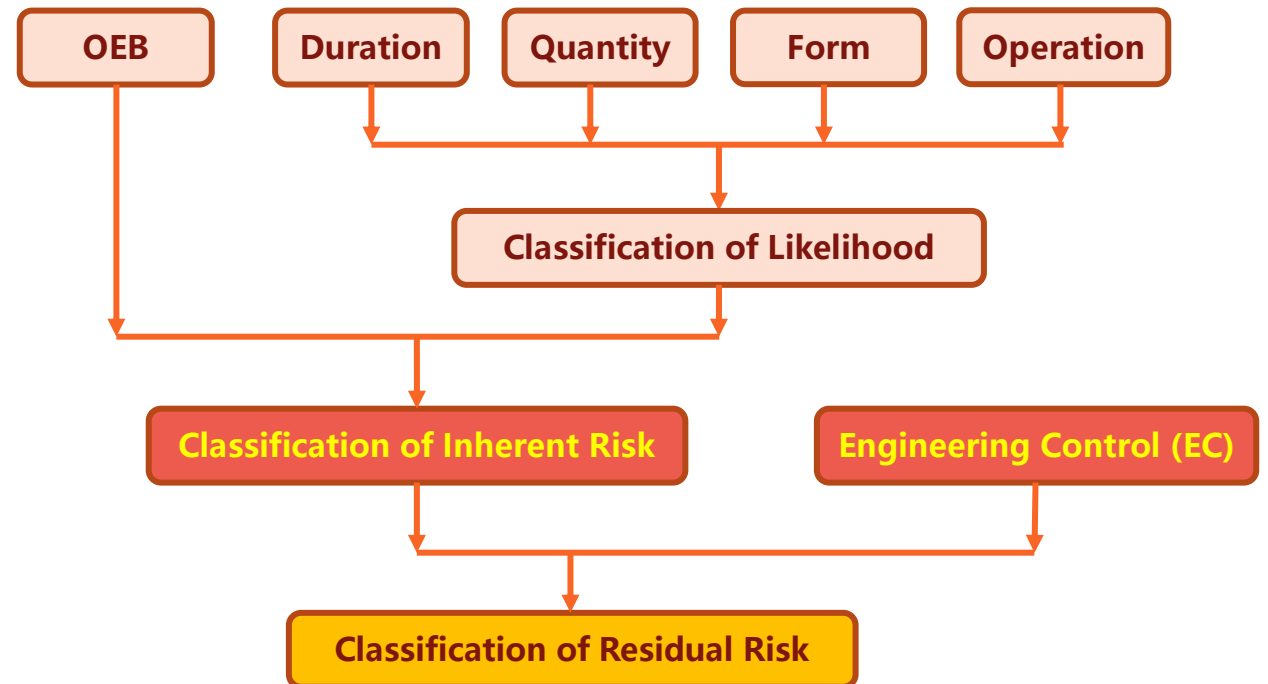
Ref: Chinese guideline GBZ/T 298

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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Hierarchy of exposure controls 暴露控制层级

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

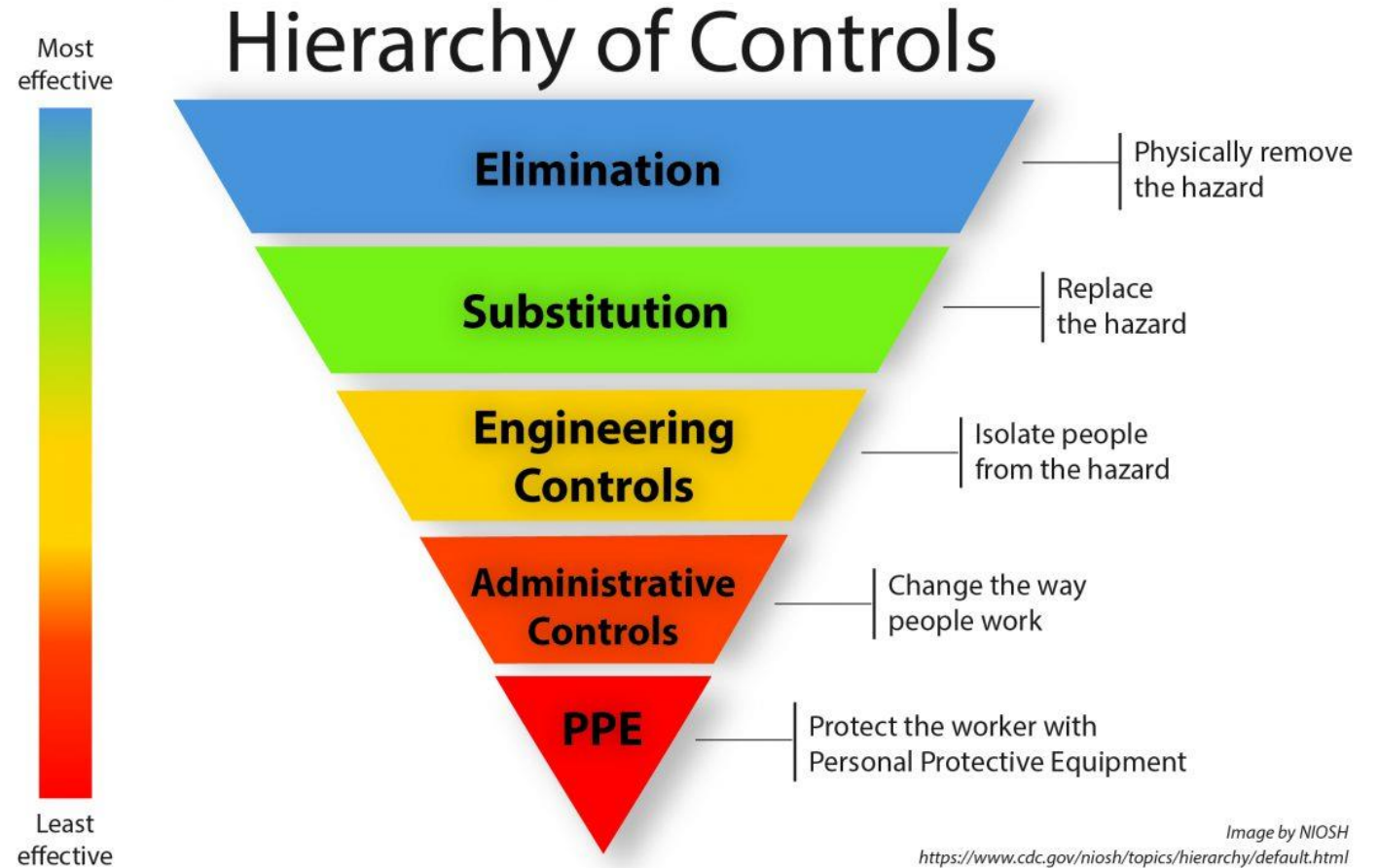
Follow the hierarchy of controls

- 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



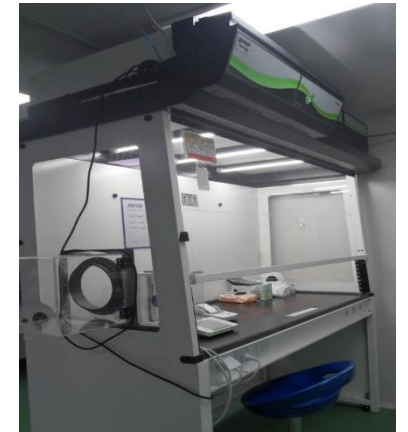
Automatic packing in rigid isolator



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=5 μ g/m³

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

- 原料2，固体粉末，OEL=1000 μ g/m³

RM2, solid powder, OEL=1000 μ g/m³

- 溶剂，易燃，OEL=30mg/m³

Solvent, flammable, OEL=30mg/m³

- 中间体2，OEL=5 μ g/m³

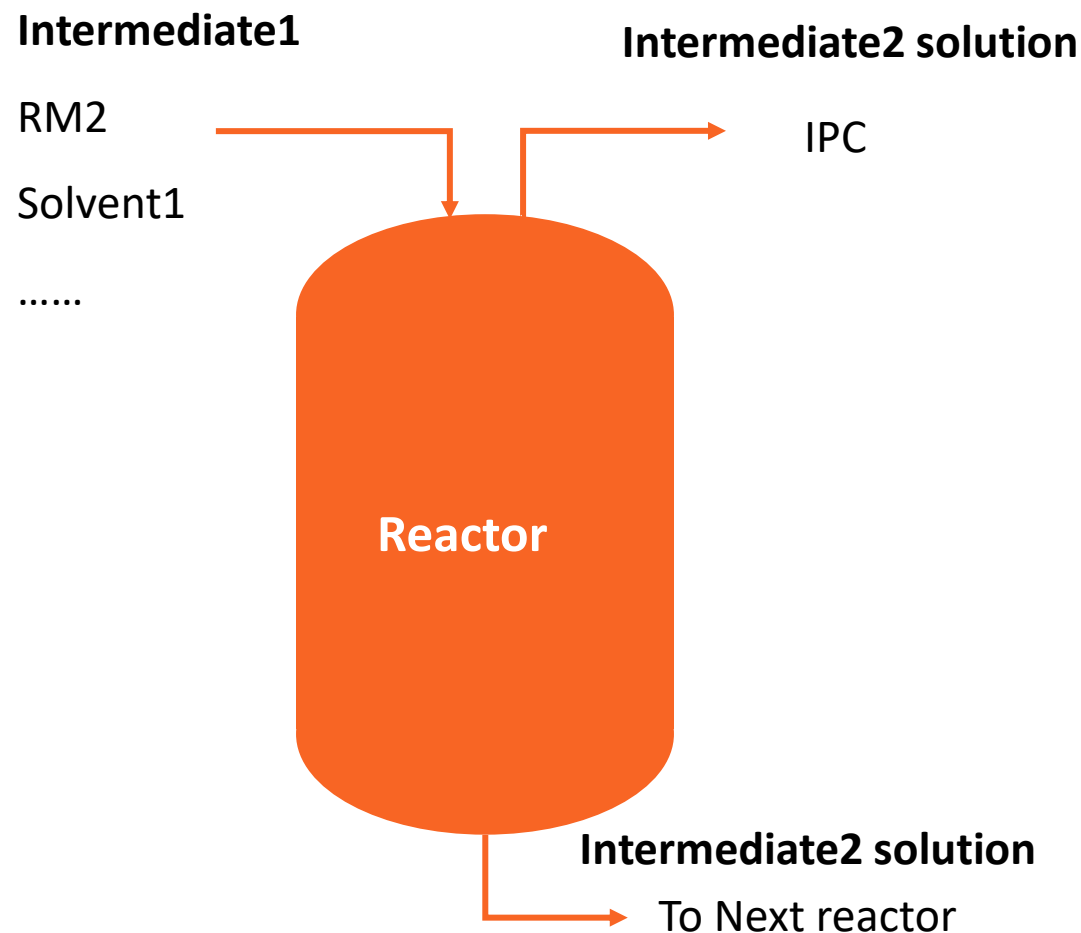
Intermediate2, OEL=5 μ g/m³



*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
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°C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°C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: $\mu\text{g}/\text{m}^3$)

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: $\mu\text{g}/\text{m}^3$)

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: $\mu\text{g}/\text{m}^3$)

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: $\mu\text{g}/\text{m}^3$)

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

