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PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Pharmaceuticals in the Environment (PIE)

Presented by

Rachel Rae

Global HSE Associate

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Agenda

1. Global Perspective
2. PSCI Principles-PIE
3. Technical Requirements
4. PEC/PNEC

**DISCLAIMER-Photographs used in tis presentation are not associated with Lilly internal manufacturing facilities*

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Bio

PSCI Role:	Audit Committee Co Chair
Current Role:	Global HSE Consultant-Eli Lilly and Company Ltd
Tasks:	HSE assessments at third party manufacturing and critical suppliers for the human pharmaceutical network. Management of the PIE program for Europe.

Career History:

2013-2015	Six Sigma Black Belt, Production Associate and Environmental Capability program owner-Eli Lilly
2008-2013	Environmental Advisor-Eli Lilly
2006-2008	Senior Environmental Consultant-Jacobs Engineering
2000-2006	Process Industry Inspector-Environment Agency (UK)

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Why are we interested in Pharmaceuticals in the Environment

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- Global focus
- Local regulatory response
- Pollution prevention-APIs are highly toxic
- Protection of human health
- Antimicrobial resistance
- Negative media interest
- Brand image

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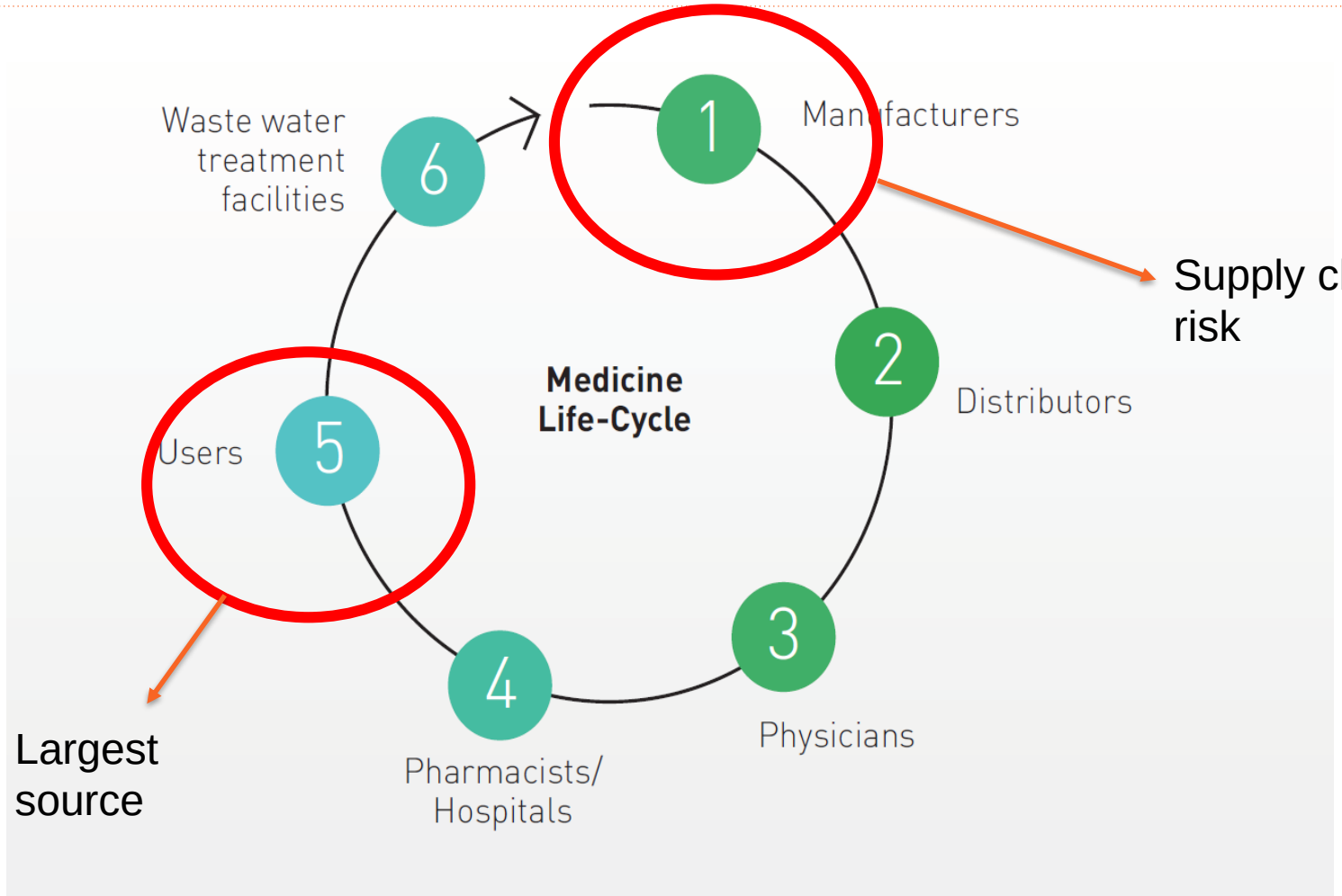
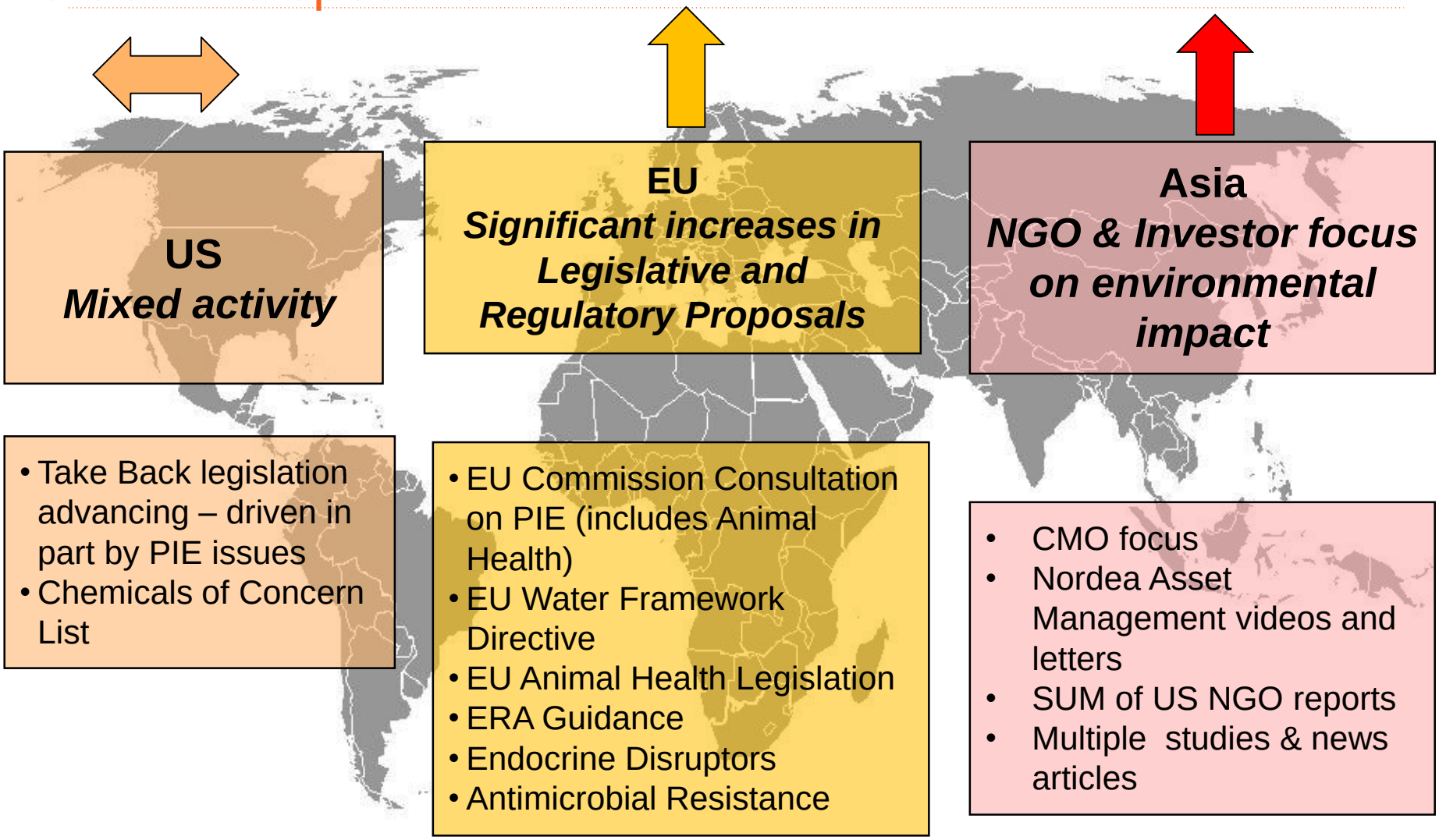
Sources of Pharmaceuticals in Surface Waters



Global Perspective



US
Mixed activity

- Take Back legislation advancing – driven in part by PIE issues
- Chemicals of Concern List

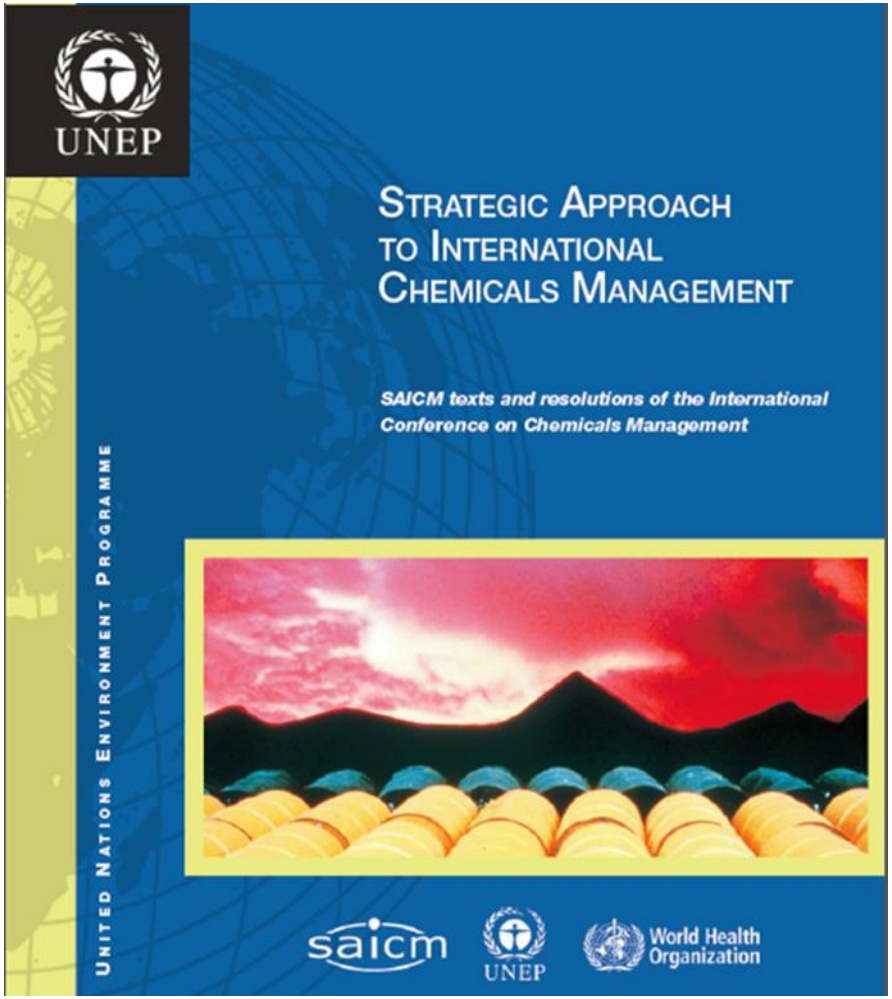
EU
Significant increases in Legislative and Regulatory Proposals

- EU Commission Consultation on PIE (includes Animal Health)
- EU Water Framework Directive
- EU Animal Health Legislation
- ERA Guidance
- Endocrine Disruptors
- Antimicrobial Resistance

Asia
NGO & Investor focus on environmental impact

- CMO focus
- Nordea Asset Management videos and letters
- SUM of US NGO reports
- Multiple studies & news articles

Stakeholders voicing their concerns



At its first session, held in Dubai, United Arab Emirates, from 4 to 6 February 2006, the International Conference on Chemicals Management adopted the Dubai Declaration on International Chemicals Management and the Overarching Policy Strategy. The Conference also recommended the use and further development of the Global Plan of Action as a working tool and guidance document. Together these three documents constitute the Strategic Approach to International Chemicals Management.

Emerging Policy Issues:

- Lead in Paint
- Chemicals in Products
- Endocrine Disrupting Chemicals
- Hazardous substances in electrical and electronic products
- Nanotechnology and manufactured nanomaterials
- Environmentally Persistent Pharmaceutical Products*

*Added October, 2015

The News on China….

New Scientist-2017

Scientific America-2017

Sum of Us-Bad Medicine Report-2015

Asian Scientist- Aug 2017

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Drug Resistance Research

- Harvard Medical School and Technion Institute of Technology demonstrate how bacteria move as they become immune to antibiotics, supported by grants from the NIH and European Health Council*

A cinematic approach to drug resistance

Scientists film bacteria's maneuvers as they become impervious to drugs

September 8, 2016 |

Courtesy of Harvard Medical School and Technion

- Cinematic Approach to Drug Resistance
- **https://www.youtube.com/watch?feature=player_embedded&v=plVk4NVIUh8**

*A Cinematic Approach to Drug Resistance", Harvard Gazette, September 8, 2016

Drug Resistance Research

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Global Response on AMR

- **WHO Health Assembly 2015**
- **UK-One Health Report**
- **UK- O'Neil Report 2016**
- **UN General Assembly 2016**
- **International Federation of Pharmaceutical Manufacturer's and Associations 2016-Davos Declaration**

World Health Organization

GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE

Reduce Environmental pollution

ESTABLISH MINIMUM STANDARDS TARGETING THE EMISSION OF MANUFACTURING WASTE CONTAINING APIs

ENCOURAGE THE PHARMACEUTICAL INDUSTRY TO DRIVE HIGHER STANDARDS THROUGHOUT THEIR SUPPLY CHAINS

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

O'Neill Final Report - 2016

SIGNATORY COMPANIES

Allergan (NYSE: AGN)
AstraZeneca (NYSE: AZN)
Cipla (NSE: CIPLA)
DSM Sinochem Pharmaceuticals (Euronext: DSM)
F. Hoffman-La Roche Ltd., Switzerland (VTX: ROG)
GSK (NYSE: GSK)
Johnson & Johnson (NYSE: JNJ)
Merck & Co., Inc., Kenilworth, New Jersey, U.S.A. (NYSE: MRK)
Novartis (NYSE: NVS)
Pfizer (NYSE: PFE)
Sanofi (EURONEXT:SAN, NYSE: SNY)
Shionogi & Co., Ltd. (TYO: 4507)
Wockhardt (NSE: WOCKPHARMA)

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China Response to AMR

- From 2011 to 2013, national campaign in health-care institutions to promote the rational use of antibiotics
- In 2015, Chinese President Jinping Xi and UK Prime Minister David Cameron signed an agreement to establish a bilateral fund to combat antimicrobial resistance.

- AMR National Action Plan- Announced Nov 2016:
  - National Coordination by NHFPC
  - One Health Concept
  - Investment for research and technology
  - 5 Year Goals
  - International Collaborations

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How we are using PSCI to Address the Issues

55	**Has the facility developed and implemented waste and wastewater manage practice**	**Yes No** **Do the practices cover:** **Characterization of all wastes generated at the facility, including returned products, with regard to regulatory classification (e.g. hazardous waste, special waste, infectious waste, non-regulated solid waste, low-level radioactive waste) and** **n such a** **lisposal** **No** **site** **utical** **(Evaluation may include: treatability, bioaccumulation potential, bio-toxicity potential, and the capacity of on-site treatment works, off-site treatment works, or Publicly Owned Treatment Works (POTWs) receiving the wastewater discharges to effectively perform treatment)** **Are APIs in wastewater subject to treatment, capture, and containment practices to reduce API concentrations to predicted no effect concentration (PNEC) levels?** **Yes No Comments:**

- Have the facility made an evaluation of API discharge
- Is the evaluation above PNEC levels

Gather information to help determine the level of risk

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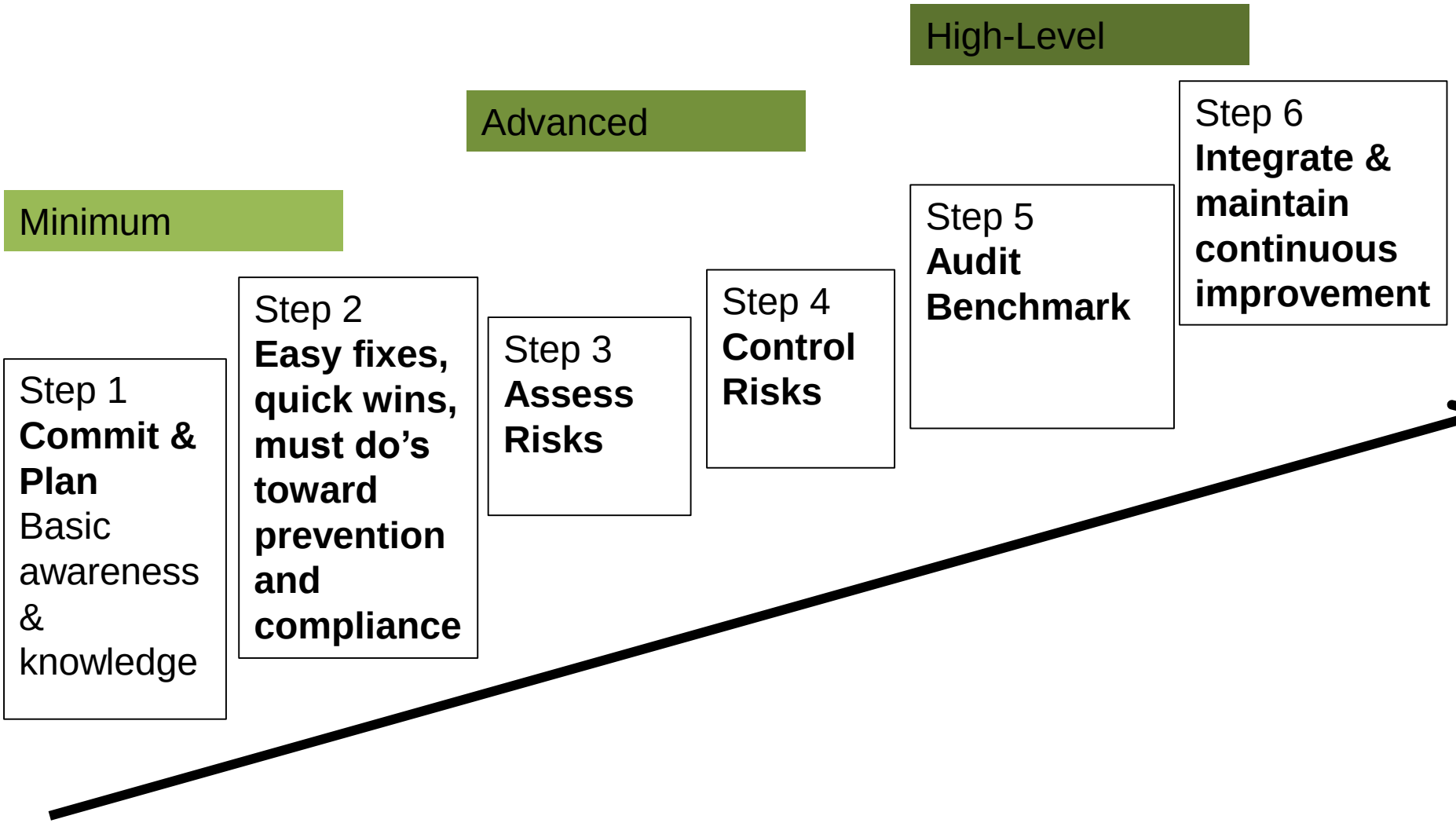
Wastewater Maturity Ladder



Pre Assessment Information

- What information can you gather in advance:
  - What APIs do they handle
  - Safety Data Sheets (SDS)-Example
  - Is there any guidance available for the limit to water (PNEC)
  - Where is the nearest water body-receiving water
  - Flow rates of receiving water bodies

Permits

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- Most discharge permits will address established parameters, e.g., control of pH, biological oxygen demand, chemical oxygen demand, etc.
- Some discharge permits include periodic general toxicity testing, i.e., whole effluent toxicity
- Most discharge permits will NOT directly address active pharmaceutical ingredients (APIs) but DO include a ‘general duty’ clause, i.e., “No toxics in toxic amounts”.

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Technical Assessment-Treatment Technologies

Category of API	Manufacturing	Fill/Form/Finish	Secondary Packaging
Hormone Substances i.e Estradiol, Testosterone	**Process wastewater collected and incinerated**	**Process wastewater collected and incinerated**	Building floor drains should be plugged when packaging is running unless a spill diversion tank/pit is provided. Management practices, such as collecting/removing unused tablets, capsules or liquids from the work area should be in place to **ensure that residual active ingredient is not flushed to sewers.**

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Technical Assessment-Treatment Technologies

Category of API	Manufacturing	Fill/Form/Finish	Secondary Packaging
Oncolytic and Mutagenic	**Process wastewater collected and incinerated**	Collection of concentrated wastewater from milling, granulation, dryer and filling etc. **Secondary treatment for further wash ie activated sludge, bioreatctor**	Building floor drains should be plugged when packaging is running unless a spill diversion tank/pit is provided. Management practices, such as collecting/removing unused tablets, capsules or liquids from the work area should be in place to ensure that residual active ingredient is not flushed to sewers.

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Technical Assessment-Treatment Technologies

Category of API	Manufacturing	Fill/Form/Finish	Secondary Packaging
Non-Hormone/Non-Synthetic Opioid Small Molecule Active Ingredients	At the source collection of concentrated wastewaters (mother liquors, first washes of process equipment, etc.) for incineration. Other process wastewaters are typically managed in **wastewater treatment systems that provide at least secondary treatment (activated sludge, membrane bioreactor).**	Collection of concentrated wastewater from milling, granulation, dryer and filling etc. **Secondary treatment for further wash ie activated sludge, bioreatctor etc**	Building floor drains should be plugged when packaging is running unless a spill diversion tank/pit is provided. Management practices, such as collecting/removing unused tablets, capsules or liquids from the work area should be in place to insure that residual active ingredient is not flushed to sewers

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Technical Assessment-Treatment Technologies

Category of API	Manufacturing	Fill/Form/Finish	Secondary Packaging
Pesticide, Fungicide and Insecticide Products and Synthetic Opioids	Process wastewater collected and incinerated Aqueous cleaning of empty equipment should be incinerated or treated using **pollutant removal technologies, such as hydrolysis, chemical oxidation, or activated carbon adsorption.** These treatment technologies must be demonstrated effective for each specific application and may need to be used in conjunction with one another to provide treatment for all active ingredients used at a facility over a period of time. Active ingredient specific treatment residuals must be incinerated.		Building floor drains should be plugged when packaging is running unless a spill diversion tank/pit is provided. Management practices, such as collecting/removing unused tablets, capsules or liquids from the work area should be in place to insure that residual active ingredient is not flushed to sewers.

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Technical Assessment-Treatment Technologies

Category of API	Manufacturing	Fill/Form/Finish	Secondary Packaging
Large Molecule/Protein Examples: Insulin, Monoclonal Antibodies	**Procedures/Processes should be in place for inactivation of protein before discharge (heat or acid/alkaline denaturing).** Process wastewaters after inactivation are typically managed in wastewater treatment systems that provide at least secondary treatment (activated sludge, membrane bioreactor). Process wastewater collected and incinerated		Building floor drains should be plugged when packaging is running unless a spill diversion tank/pit is provided. Management practices, such as collecting/removing unused tablets, capsules or liquids from the work area should be in place to insure that residual active ingredient is not flushed to sewers.

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Technical Assessment-Treatment Technologies

Category of API	Manufacturing	Fill/Form/Finish	Secondary Packaging
Large Molecule/Antibiotics	**Procedures/Processes should be in place for destruction/inactivation of antibiotics before discharge. High temperature, acid/alkaline hydrolysis and ozonation have been demonstrated as in-plant pre-treatment technologies.** However, these technologies are active ingredient specific and may need to be used in conjunction with one another to provide treatment for all active ingredients used at a facility over a period of time.After control of high strength waste streams, process wastewaters are typically managed in wastewater treatment systems that provide at least secondary treatment plant performance (activated sludge, membrane bioreactor).		Building floor drains should be plugged when packaging is running unless a spill diversion tank/pit is provided. Management practices, such as collecting/removing unused tablets, capsules or liquids from the work area should be in place to insure that residual active ingredient is not flushed to sewers.

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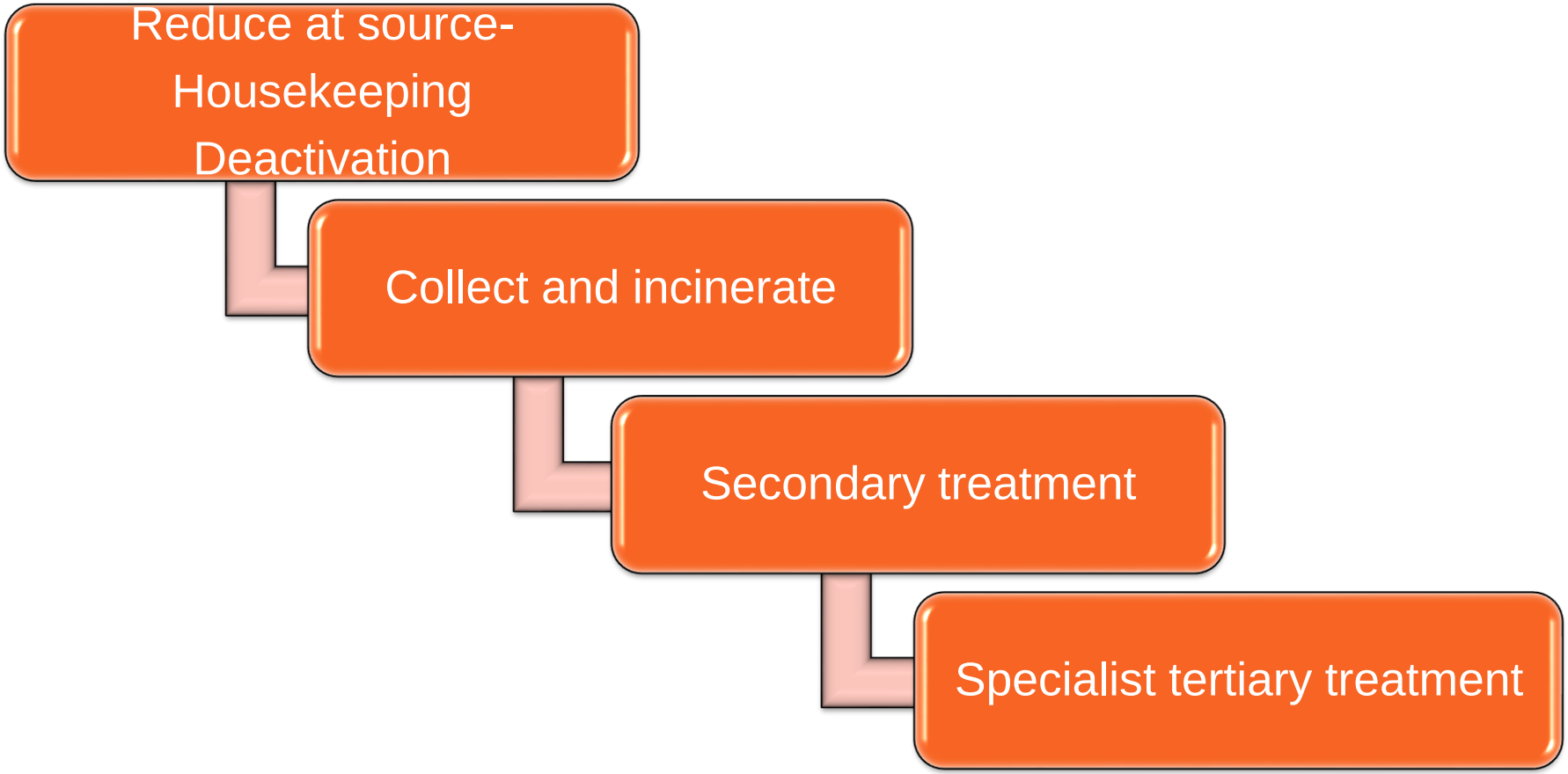
Review Options



Reduce at Source

- Volume-Sources of effluent
  - Process effluent
  - CIP
  - General area cleaning

High volume/high concentration

Low volume/low or high concentration

- Deactivation
  - High temp
  - Chemical treatment-Ph

Spill Containment Options

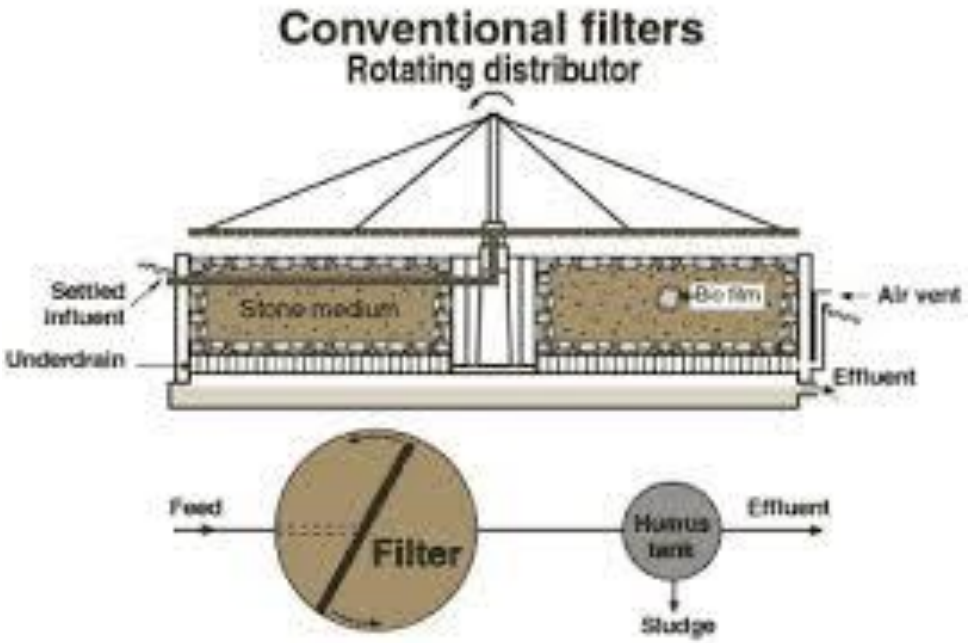
- Catchment drains

- Spill Kits

Secondary Treatment Technologies

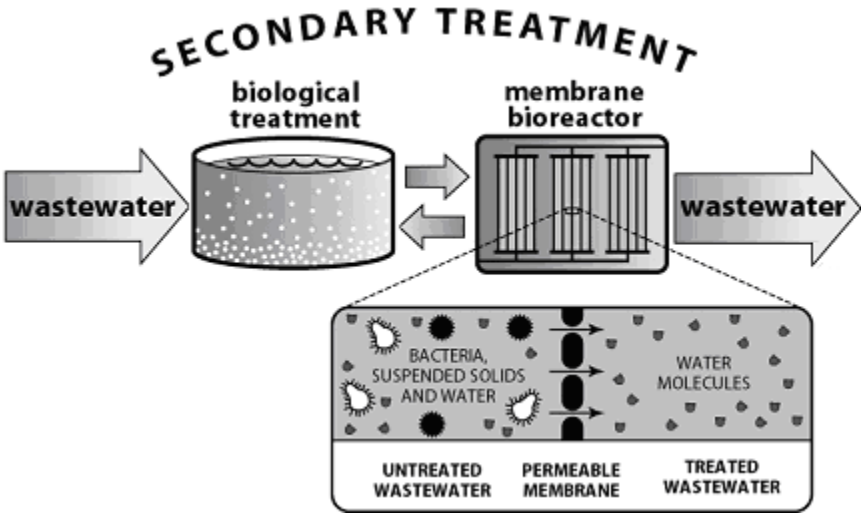
Activated Sludge

Biological Filter Bed



Specialist Tertiary Treatment

Membrane Bioreactor



UV Disinfection

Sand Filtration

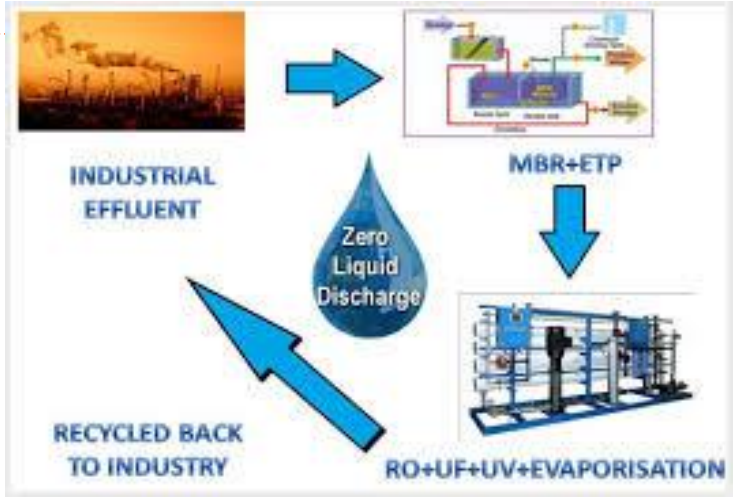
Chlorination

Clarification

Technical Assessment-Onsite Treatment

- Treatment volume-Evidence of overspill
- Inspect Final Discharge Point
  - Where does it discharge too-standing waterbody, sewer, river, sea
  - Can you go to see the discharge point
  - What does the effluent look/smell like
    - Strong solvent odour
    - Visible contamination

Technical Assessment-Onsite Treatment



- Zero Discharge-Reuse of treated effluent

- Check the mass balance volumes-

e.g. is the daily amount of effluent the same as the input to the cooling towers
is the volume far greater then irrigation use

- Doesn't always equal 'zero risk'
  - Ground dispersion may result in:
    - Dermal/inhalation exposure to applicator and/or recreational users
    - Edible vegetation and/or groundwater users
    - Terrestrial organisms
    - Mist inhalation from opened cooling uses.

Technical Assessment-Administration Controls

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Technical Assessment-Offsite Treatment

- Permitted Volumes vs Daily Flows
  - What are they limited to
  - Compliance history
  - Specific parameters
- Treatment Capability
  - Do the know what the treatment type is
- Where is the final discharge point

What is an Environmental Risk Assessment?

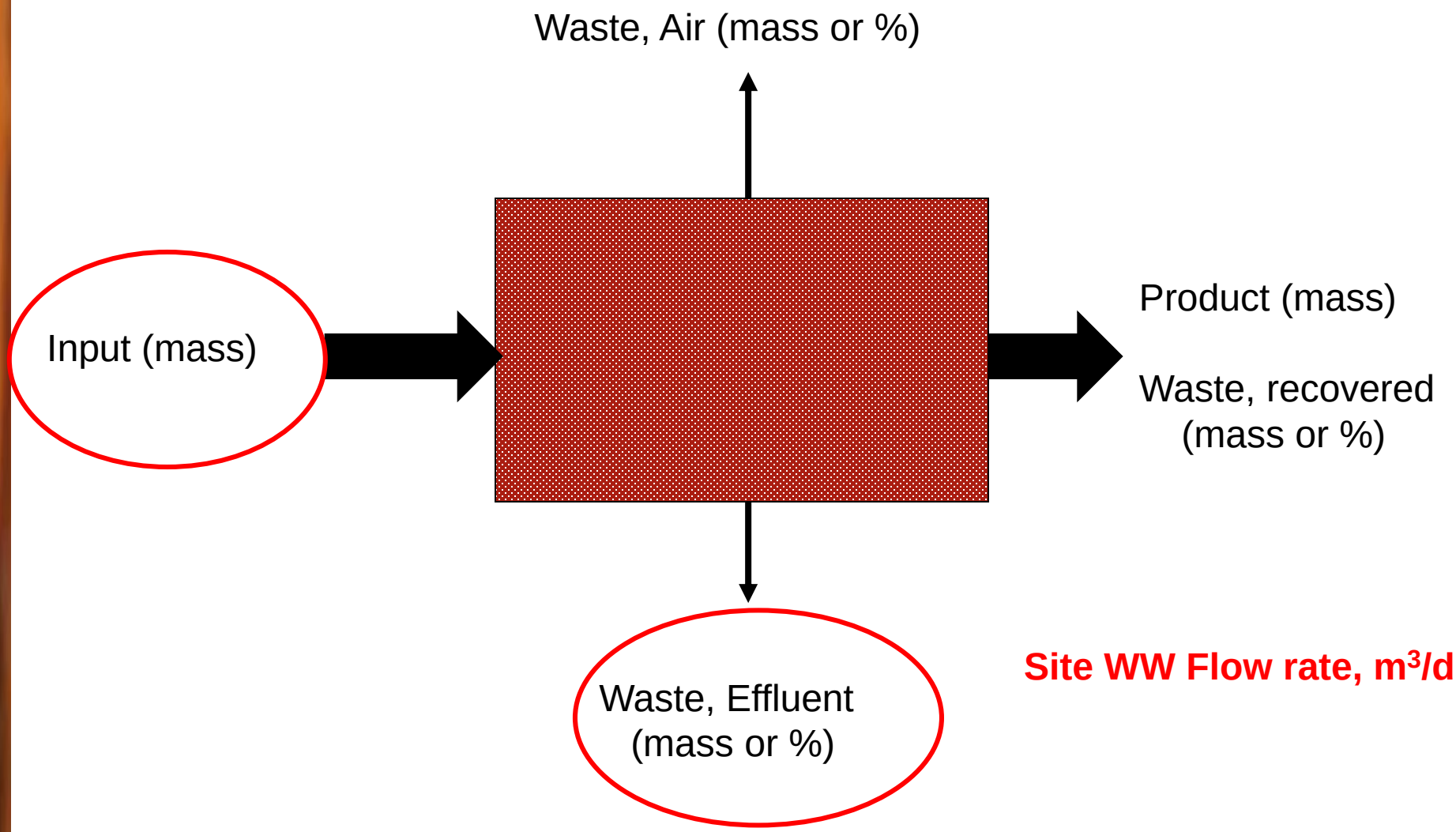
- Good management practices may not eliminate all API released to water
- Site responsibility is to know whether the amount released could have a potential impact on the environment
- Environmental Risk Assessment requires data and professional judgment

Predicted Environmental Concentration **(PEC) (Concentration in Effluent)**

Predicted No Effect Concentration **(PNEC) (Concentration Limit)**

Risk Quotient (RQ)
PEC /PNEC <1, Low risk
PEC /PNEC >1, Potential risk:
Reassess/take appropriate action

Mass Balance Approach



PEC Data Collection & Analysis

- Review batch records to determine API losses
- Estimate API losses (account for batch and cleaning cycles)
- Estimate treatment plant removal efficiency using the API chemical and physical properties, literature, or assume 0%
- Get wastewater and receiving water flows

Examples

On-Site

batch records	wastewater POG[1]
product yield	wastewater flows
batch/year	WWTP unit ops
cleaning cycles	API analyses[2]

Off-Site

POTW flow
POTW unit ops
receiving water flow

1 POG = Point of Generation
2 API analysis of wastewater, solvent waste, solid waste, etc.

Mass Balance Loss -Example

Using mass balance values

1. Must be representative of the process
2. Consider control chart for calculated losses

Date of Manufacture	Item Code	# of vials filled	Amount of API in vials (kg), (calculated)	Amount of API not in vials (kg), (calculated)	Daily sum of amount not in vials
04-JAN-2011 14:13:03	000000000000	15767	18.037448	0.095552	0.216272
04-JAN-2011 14:18:08	000000000000	15745	18.01228	0.12072	
11-JAN-2011 14:12:12	000000000000	15740	18.00656	0.12644	0.332416
11-JAN-2011 14:09:54	000000000000	15765	18.03516	0.09784	
11-JAN-2011 14:24:55	000000000000	15756	18.024864	0.108136	
18-JAN-2011 10:52:49	000000000000	15723	17.987112	0.145888	0.283768
18-JAN-2011 10:46:36	000000000000	15730	17.99512	0.13788	
25-JAN-2011 16:24:28	000000000000	15534	17.770896	0.362104	0.491976
25-JAN-2011 16:22:15	000000000000	15737	18.003128	0.129872	
	Avg Number of vials filled	Avg Amount of API in vials (kg)	Avg Amount of API not in vials (kg)	Worst Case API in Wastewater (kg)	Limit API in Wastewater (kg/day)
	15721.89	17.99	0.15	0.29	0.65
				Cumulative Daily Worst Case (kg)	
				0.49	

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Sources of PNEC Information

Published data – Journals such as: Environmental Toxicology and Chemistry, Environmental Science and Technology, Aquatic Toxicology, others

- Vestel, J. et al. Use of acute and chronic ecotoxicity data in environmental risk assessment of pharmaceuticals, Environmental Toxicology and Chemistry, Accepted Article DOI: 10.1002/etc.3260

- Company specific values

Calculating the Risk Quotient

$$\text{Risk Quotient (RQ)} = \frac{\text{PEC}}{\text{PNEC}} = \text{<1 or >1?}$$

Risk Quotient		
Less than (<) 1	Indicates that the expected concentration is lower than the concentration indicating low/no potential environmental risk	
Greater than (>) 1	Indicates that the expected concentration exceeds the no-effect concentration indicating the potential for risk	

Guidance

Environmental Toxicology and Chemistry, Vol. 9999, No. 9999, pp. 1–10, 2015
Published 2015 SETAC
Printed in the USA

Hazard/Risk Assessment

A RISK-BASED APPROACH TO MANAGING ACTIVE PHARMACEUTICAL INGREDIENTS IN MANUFACTURING EFFLUENT

DANIEL J. CALDWELL,*† BIRGIT MERTENS,‡ KELLY KAPPLER,§ THOMAS SENA
PETER WILSON,# ROGER D. MEYERHOFF,†† NEIL J. PARKE,†† FRANK MASTROCC
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§Johnson & Johnson Consumer Group of Companies, Skillman, New Jersey
||Sanofi, Paris, France
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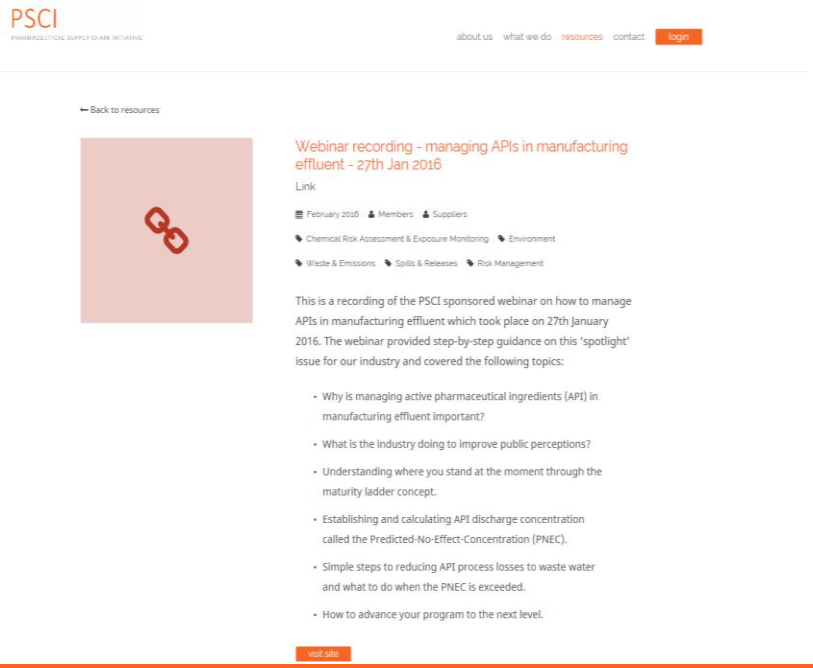
‡‡Pfizer, New York, New York, USA
§§LIF, Swedish Association of the Pharmaceutical Industry, Stockholm, Sw



https://pscinitiative.org/resource?resource=292

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Stormwater: Issues and best practice

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Agenda

1. Issues
2. Potential pollution sources
3. Stormwater pollution prevention

Rain in China

The annual total of certain areas along the southeastern coast amounts to more than **80 inches** (**2,000 mm**).

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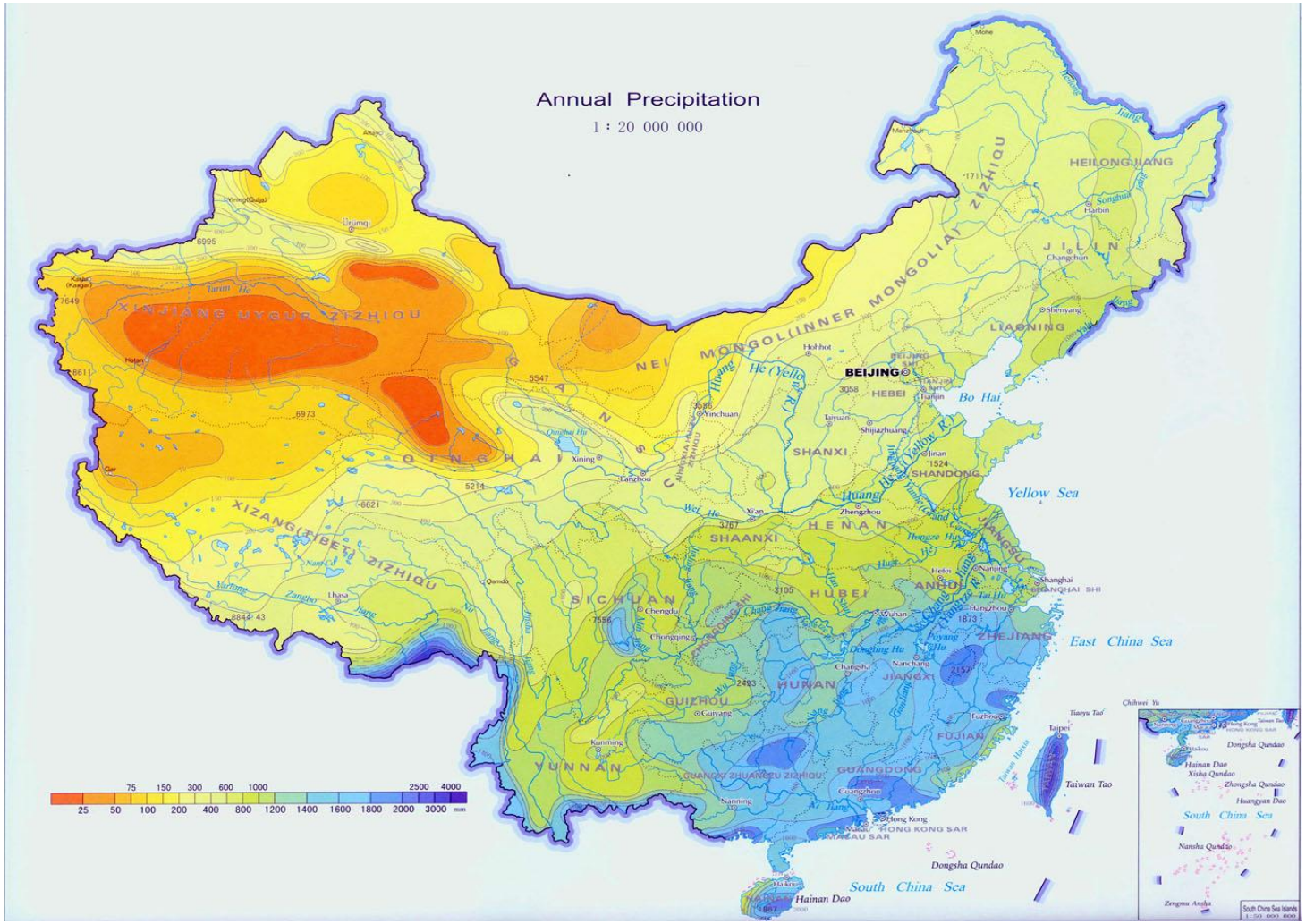

Source: Chinamaps.org

What Is Stormwater Runoff?

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Stormwater runoff is water from rain or snowmelt that does not immediately infiltrate into the ground and flows over or through natural or man-made storage or conveyance systems.

What Are Its Impacts?

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Runoff from areas where industrial activities occur can **contain toxic pollutants** (e.g., heavy metals and organic chemicals) and other pollutants such as trash, debris, and oil and grease, when facility practices allow exposure of industrial materials to stormwater. This increased flow and pollutant load can impair waterbodies**, degrade biological habitats, pollute drinking water sources, and cause flooding and hydrologic changes to the receiving water, such as channel erosion.**

Types of activities at industrial facilities with potential of pollution in stormwater

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- Loading/unloading operations
- Outdoor storage
- Outdoor process activities
- Dust or particulate generating processes
- Illicit connections and non-stormwater discharges
- Waste management

Examples

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Stormwater pollution
Loading/unloading operations

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- Incomplete bunding
- No spill retention capacity

Stormwater pollution
Outdoor storage

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- No secondary containment for outdoor storage of hazardous material

Stormwater pollution
Outdoor process activities

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- Open structure building without sufficient retention capabilities

Stormwater pollution
Dust or particulate generating processes

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- Insufficient capacity or no dust filters
- Ashes from coal fed boilers and/or stacks

Stormwater pollution
Illicit connections and non-stormwater discharges

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- Overflow of waste water tanks
- Leakage from cooling towers with contaminated water (recycled from waste water treatment plant

Stormwater pollution
Waste management

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- Storage of hazardous waste without bunding or secondary containment

Stormwater pollution prevention
4 steps

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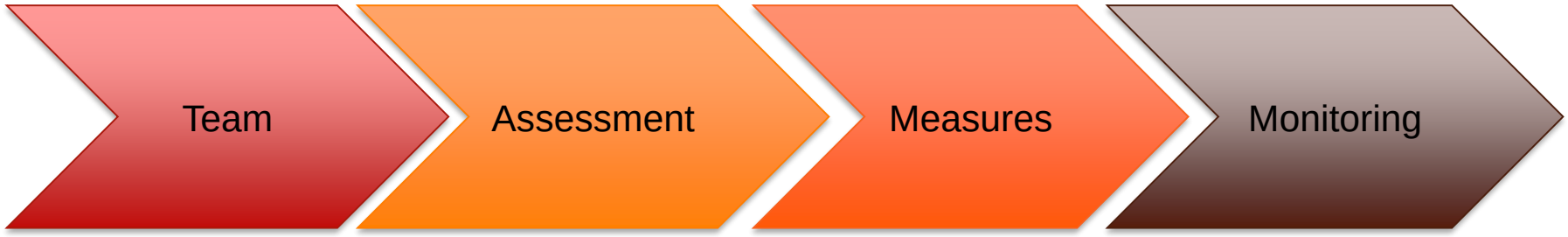
- Step 1: Form a team of qualified personnel
- Step 2: Assess potential stormwater pollution sources
- Step 3: Select appropriate control measures
- Step 4: Inspection and monitoring of controls



Form a team of qualified personnel

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- The team should consist of those people on-site who are most familiar with the facility and its operations
- Team should consists ideally of members from the following departments:
  - HSE
  - Engineering
  - Effluent treatment operators

Assess potential stormwater pollution sources

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- Assess the different pathways how storm water can be contaminated
  - Mass balance of API process
  - Fate of water from equipment washing
- Site tours to identify gaps

Select appropriate control measures

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- Hierarchy of control measures
  - Eliminate
  - Reduce
  - Mitigate
- Engineering controls preferable over administrative controls
- Analysis of all stormwater before release

Inspection and monitoring of controls

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- Regular site tours to control controls and identify new issues
- Regular training of personnel about stormwater control
- Continuous improvement mind set needed to guarantee future success

The Pharmaceutical Supply Chain Initiative

Need more information?

Visit: www.pscinitiative.org

Email: the PSCI Secretariat at info@pscinitiative.org

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Environmental Protection Programs, Authorisations, Air, Material Storage and Waste Management

Presented by

Caroline O'Brien

Director, Global Compliance - Operations

AstraZeneca

Bio

- Caroline is Director, Global Compliance for Operations for AstraZeneca and is located in Macclesfield, UK
- Bachelors Degree in Microbiology from the University of Liverpool. PhD from the University of Newcastle-upon-Tyne.
- 20 years experience with AstraZeneca in Pharmaceutical Production, EHS, Quality and Compliance

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Agenda

1. **Management Systems**
2. Authorisations and Permits
3. Auditor Insights
4. Air Emissions
5. Material Storage
6. Waste Management

Management Systems
Organization and Staffing

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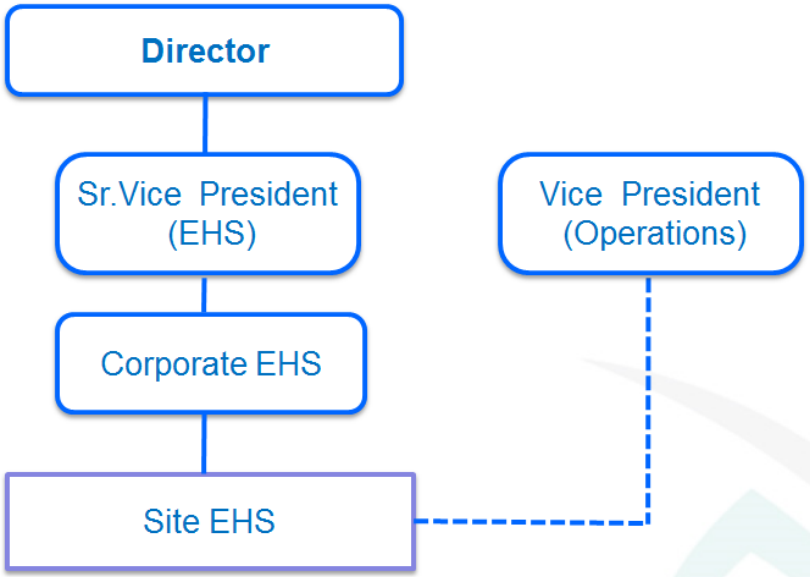
- Review the site organization chart with a focus on EHS
- Where does the EHS lead report to?
- Does the EHS staff and environmental staffing level appear adequate?
- Is there a Corporate EHS organization?
- What is the reporting relationship of site EHS to Corporate EHS ?
- What support does the Corporate EHS organization provide?



Total Employees : 1452
Working days : 24 x 7
Schedule : 4 Shifts
EHS Staff: : 10
Environmental : 7

Management Systems
Policies and Procedures

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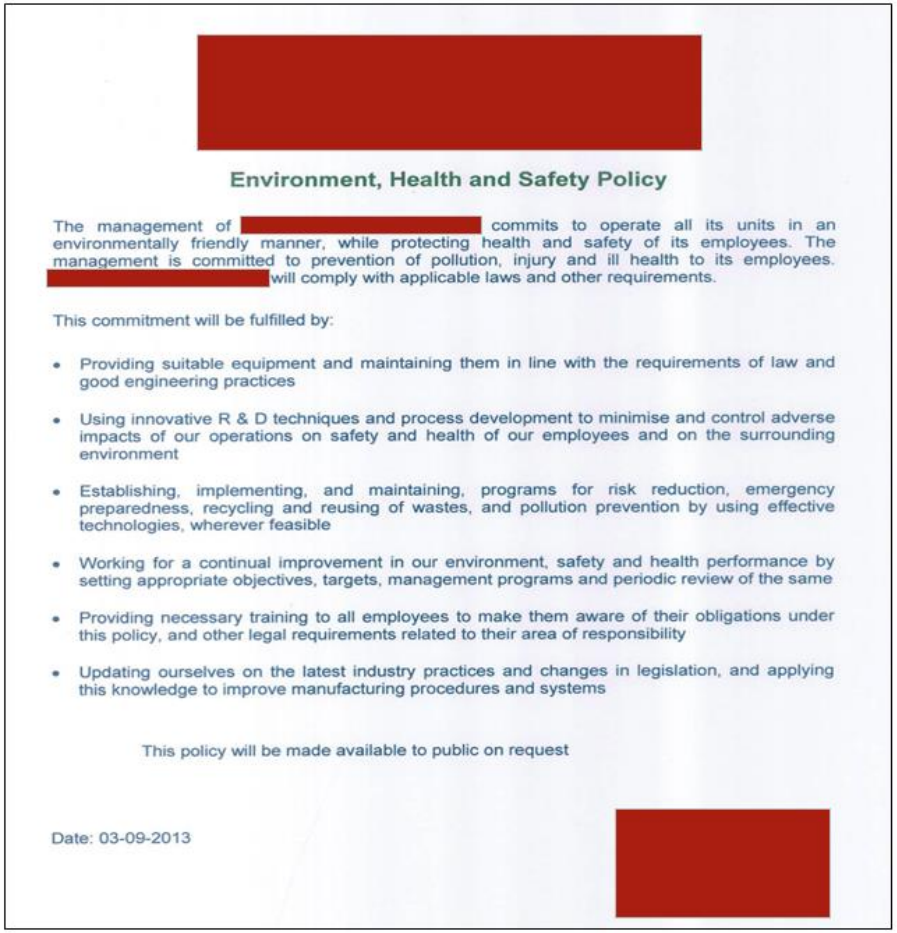
SUPPLY CHAIN
INITIATIVE



[redacted]

Environment, Health and Safety Policy

The management of [redacted] commits to operate all its units in an environmentally friendly manner, while protecting health and safety of its employees. The management is committed to prevention of pollution, injury and ill health to its employees. [redacted] will comply with applicable laws and other requirements.

This commitment will be fulfilled by:

- Providing suitable equipment and maintaining them in line with the requirements of law and good engineering practices
- Using innovative R & D techniques and process development to minimise and control adverse impacts of our operations on safety and health of our employees and on the surrounding environment
- Establishing, implementing, and maintaining, programs for risk reduction, emergency preparedness, recycling and reusing of wastes, and pollution prevention by using effective technologies, wherever feasible
- Working for a continual improvement in our environment, safety and health performance by setting appropriate objectives, targets, management programs and periodic review of the same
- Providing necessary training to all employees to make them aware of their obligations under this policy, and other legal requirements related to their area of responsibility
- Updating ourselves on the latest industry practices and changes in legislation, and applying this knowledge to improve manufacturing procedures and systems

This policy will be made available to public on request

Date: 03-09-2013

[redacted]

- Ask for the sites environmental, health and safety policy
- How are people trained in it?
- Are procedures in place for environmental activities?
- Do the operating procedures include environmental aspects?
- Is there clear evidence that the procedures are followed?

Management Systems Certifications

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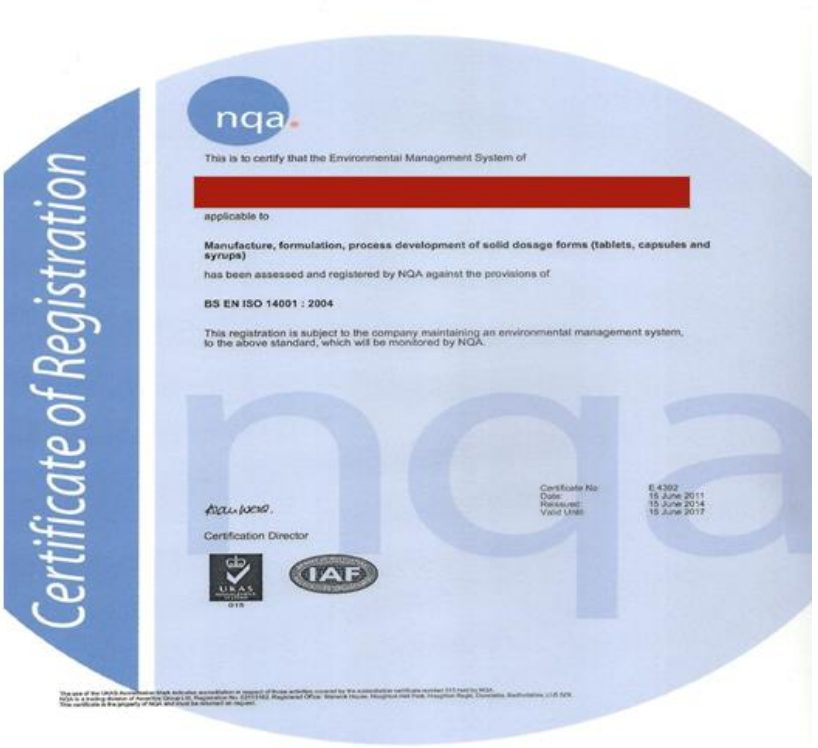
- Is the site ISO 14001 registered?
- If so, when was first registration?
- When is the next re-certification?



Management Systems
Goals and Environmental Impact Reduction

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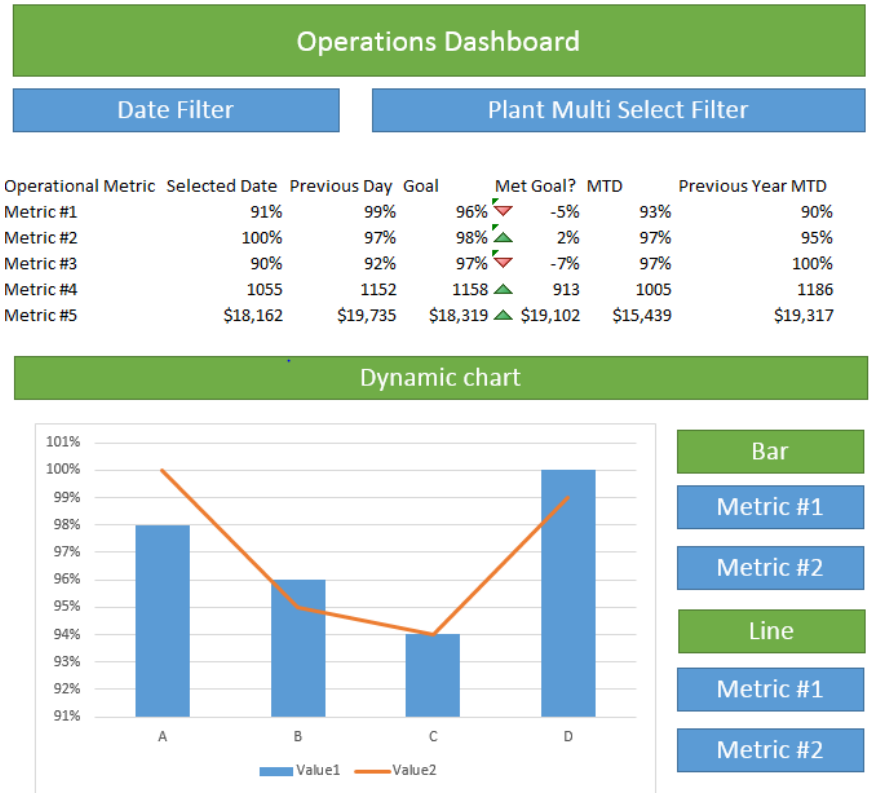

- Does the facility have clear environmental goals?
- Are they set locally or at the corporate level?
- Is there clear support for achieving the goals?
- Review the methods that facility has in place to measure key environmental impacts generation and disposal

Management Systems
Compliance and Event History

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PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

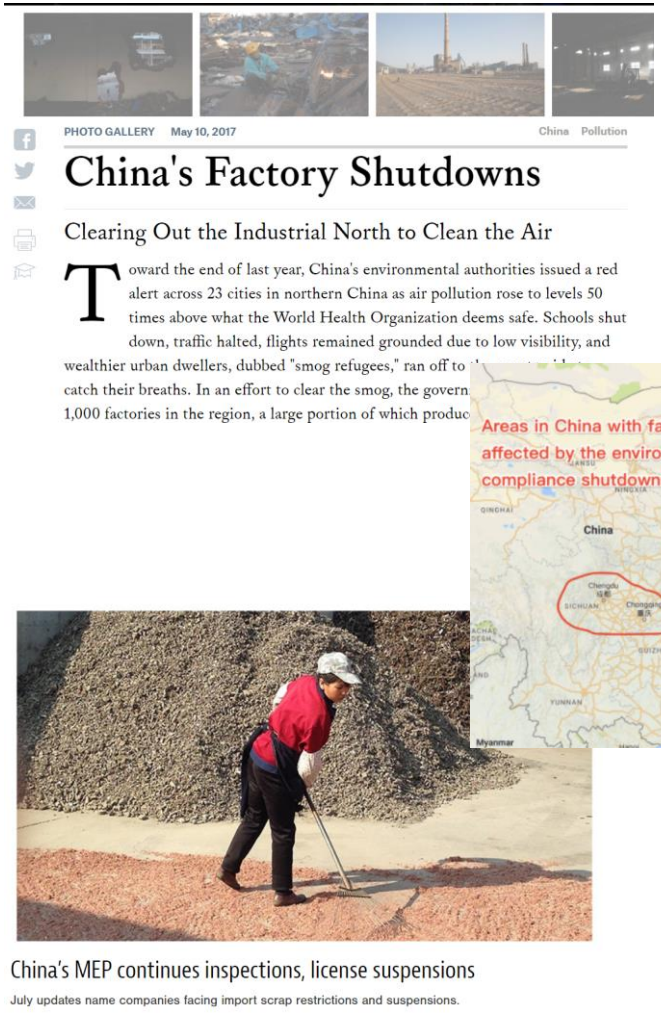

PHOTO GALLERY May 10, 2017 China Pollution

China's Factory Shutdowns

Clearing Out the Industrial North to Clean the Air

Toward the end of last year, China's environmental authorities issued a red alert across 23 cities in northern China as air pollution rose to levels 50 times above what the World Health Organization deems safe. Schools shut down, traffic halted, flights remained grounded due to low visibility, and wealthier urban dwellers, dubbed "smog refugees," ran off to
catch their breaths. In an effort to clear the smog, the govern
1,000 factories in the region, a large portion of which produc

China's MEP continues inspections, license suspensions

July updates name companies facing import scrap restrictions and suspensions.

- Review compliance history via web search
- Review compliance history with the site during the visit including:
  - Status of authorisations
  - Any notices of violation
  - Any fines or penalties for non-compliance
  - Any spills or unplanned releases

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SUPPLY CHAIN
INITIATIVE

Agenda

1. Management Systems
2. **Authorisations and Permits**
3. Auditor Insights
4. Air Emissions
5. Material Storage
6. Waste Management

Authorisations and Permits Document Review

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- Focus should be on permit compliance
- Validity, specificity…..
- Review a sample of performance reports from at least the last year
- If time permits, you can review previous years

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SUPPLY CHAIN
INITIATIVE

Agenda

1. Management Systems
2. Authorisations and Permits
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4. Air Emissions
5. Material Storage
6. Waste Management

Auditor Insights
Preparation for the Site Visit

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Preparation is Key

- Supplier website
- Internet
- Google satellite imagery

Pollution
Guardian Environment Network

Apple wakes up to Chinese pollution concerns

A Chinese-led campaign to clean up Apple's supply chain is finally gaining traction

Xie Xiaoping for ChinaDialogue, part of the Guardian Environment Network

Tuesday 4 October 2011 10.16 EDT

The NRDC and Chinese campaigners wrote Tim Cook, Apple's CEO, asking him to clean-up the company's supply chain for products such as the iPhone. Photograph: Brendan Mcdermid/REUTERS

In the face of sustained pressure from Chinese green groups, Apple has finally broken its silence on pollution problems in its supply chain, for the first time

Auditor Insights
Background Information Review

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Auditor Insights
Background Information Review

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PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Auditor Insights
Background Information Review

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Groundwater collection and runoff

Potentially impacted lake

Auditor Insights
Opening Meeting

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INITIATIVE

- Overview presentation – supplier
- Site tour expectations – be specific
- Documents
- Permission to photograph
- Neighbours

Auditor Insights
Tour of the Facility Exterior

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INITIATIVE

First Impressions Count !!!

Auditor Insights
Tour of the Facility Exterior

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- **Particularly look for the following:**
  - Surface water
  - storm drains
  - General housekeeping
  - Excavations for construction.
  - Storage or placement of waste materials exterior to the facility.
  - Evidence of releases
  - Visible emissions from air emission sources
  - Significant dead vegetation

Auditor Insights
Tour of the Facility Interior

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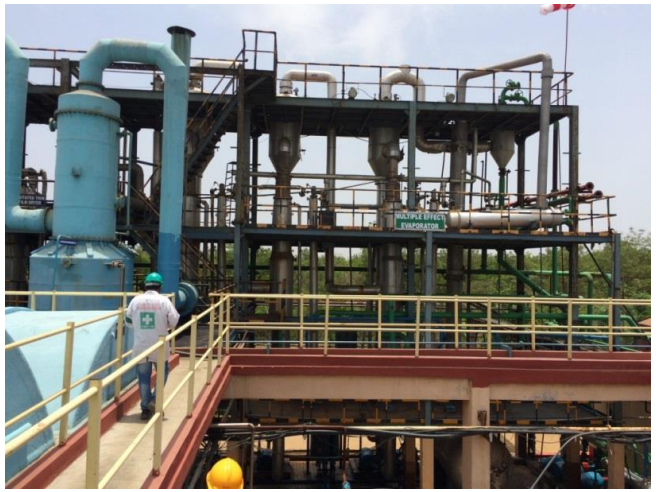
INITIATIVE

Interior Tour should include:

- Boilers and Diesel Generators
- Fuel storage areas
- Wastewater collection and treatment systems
- Stormwater collection and discharge systems
- Waste storage areas



Auditor Insights
Tour of the Facility Interior

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Interior Tour should also include:

- Process areas
- Water extraction wells
- Potable water delivery and storage systems
- Deep wells or borings for waste or wastewater disposal
- Underground storage tanks
- Air pollution control equipment for boilers and process emissions
- Solvent storage and recovery
- Incinerators

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INITIATIVE

Agenda

1. Management Systems
2. Authorisations and Permits
3. Auditor Insights
4. **Air Emissions**
5. Material Storage
6. Waste Management

Air Emissions
Storage Tanks Controls

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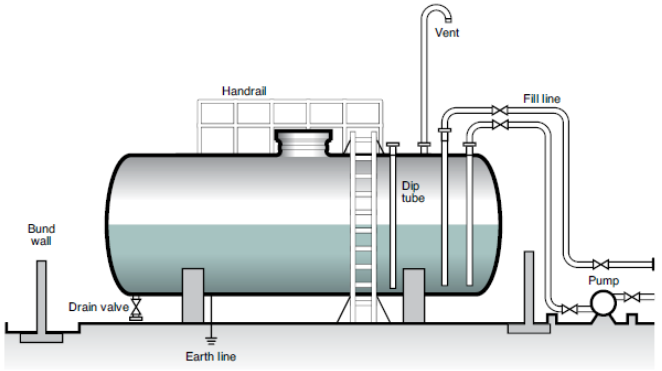
- Management and control of emissions from storage tanks
- Determine what controls are in place
- Look for controls (and emergency plans) in place for storage of bulk quantities of volatile toxic or highly flammable compounds
- Review Authorisations



Air Emissions
Process Emission Controls

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- Determine what controls are in place on process equipment
- Determine if the operating parameters and maintenance of the air pollution control equipment is understood and in place
- Review the Authorisation for any specific requirements for vent controls on process equipment

Air Emissions
Process Emission authorisations

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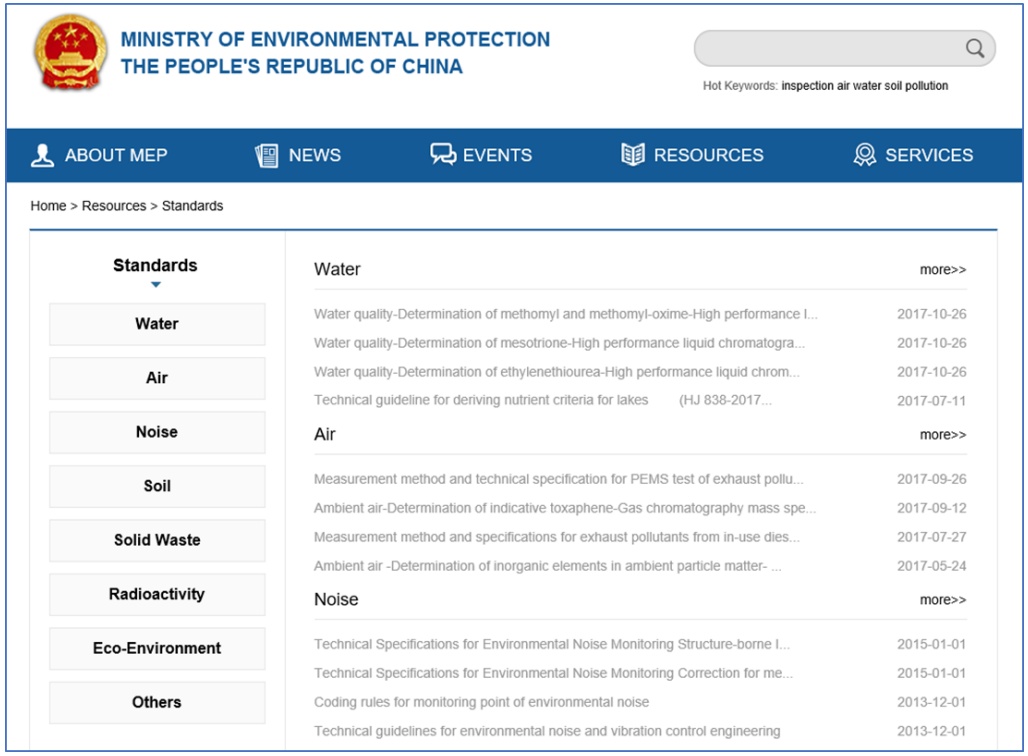
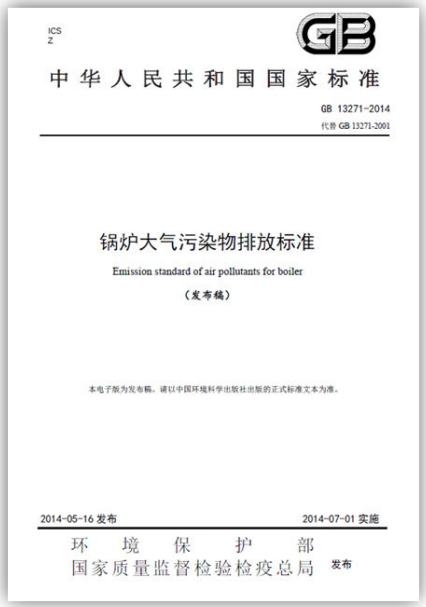


Requirements may include:

- Specific Limits on emissions
- Ambient air quality sampling and limits
- General conditions



Air Emissions
Fuel Burning Equipment Emission Controls

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- Confirm the number of boilers on-site, size and the fuel used
- Identify control equipment in place
- Look for visible opacity at the stack

Air Emissions
Fuel Burning Equipment Particulate and Dust Control

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- Tour the coal handling facilities and boiler ash handling
- Review storage practices to minimize dust and potential runoff to stormwater from coal and ash
- Determine disposal location for boiler ash

Air Emissions
Fuel Burning Equipment Authorisations

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INITIATIVE

- Review authorisation for any specific requirements for emissions, fuel rates, and/or ambient air standards
- Be sure to review any general conditions for requirements as well (e.g., malfunction requirements)

Air Emissions
Odour Controls

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SUPPLY CHAIN
INITIATIVE

- Note any odours on your interior and exterior tour
- Review odour control systems in place with facility staff
- Confirm operation and maintenance are adequate to prevent nuisance odours
- Confirm operation is in compliance with the Authorisation

Air Emissions
Noise

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- Noise limitations fall under ambient air quality requirements
- Be sure to review noise monitoring records when you complete the assessment of other ambient air quality monitoring
- While many of the facilities are located in industrial or commercial zones with higher noise allowances, be sure to compare to the Authorisation limits

Category of Area/Zone	Limits in dB (A) Leq	
	Day Time	Night Time
Industrial Area	75	70
Commercial Area	65	55
Residential Area	55	45
Silent Zone	50	40

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SUPPLY CHAIN
INITIATIVE

Agenda

1. Management Systems
2. Authorisations and Permits
3. Auditor Insights
4. Air Emissions
5. **Material Storage**
6. Waste Management

Material Storage Containers

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- Review storage of drummed and bagged materials
- Assess if warehouses are properly managed and have containment for potential releases
- Look for poor material storage practices
- Review the requirements of the Authorisation

Material Storage Tanks

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- Look for appropriate maintenance on tanks
- Do the tanks have overflow and overfill protection?
- Fire detection and suppression
- Check for appropriate containment
- Review tank truck loading and unloading practices

Material Storage
Underground Storage Tanks

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INITIATIVE

- Where are they?
- Review construction and containment methods
- Review methods used to determine leaks Review tank truck loading and unloading practices

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SUPPLY CHAIN
INITIATIVE

Agenda

1. Management Systems
2. Authorisations and Permits
3. Auditor Insights
4. Air Emissions
5. Material Storage
6. **Waste Management**

Waste Management Regulatory Framework

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中文简体版 | 中文繁体版 | 移动版

MINISTRY OF ENVIRONMENTAL PROTECTION
THE PEOPLE'S REPUBLIC OF CHINA

Hot Keywords: inspection air water soil pollution

ABOUT MEP | NEWS | EVENTS | RESOURCES | SERVICES

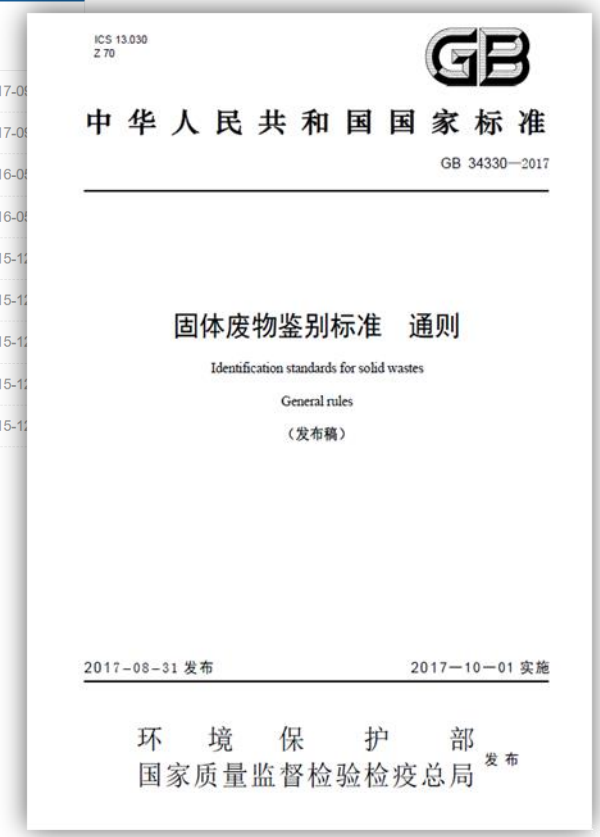
Home > Resources > Standards > Solid Waste

Standards

- Water
- Air
- Noise
- Soil
- **Solid Waste**
- Radioactivity
- Eco-Environment

Solid Waste

Standard for pollution control on Polychlorinated Biphenyls (PCBs)-... -- GB 13015-2017	2017-0
Identification standards for solid wastes-General rules (GB 34330-... -- GB 34330-2017	2017-0
Solid waste-Determination of Lead and Cadmium - Graphite Furnace At... -- HJ 787-2016	2016-0
Solid waste—Determination of Lead，Zinc and Cadmium—Flame Atomic ... -- HJ 786-2016	2016-0
Solid waste — Determination of total barium — Graphite furnace at... -- HJ 767-2015	2015-1
Solid waste—Determination of total barium—Graphite furnace atomic... -- HJ 767-2015	2015-1
Waste solid—Distilling of organic compound — Microwave extraction -- HJ 765-2015	2015-1
Solid Waste — Determination of metals — Inductively coupled plasm... -- HJ 766-2015	2015-1
Solid Waste-Determination of Organic Phosphorous Pesticides-Gas Chr... -- HJ 768-2015	2015-1


ICS 13.030
Z 70

GB

中华人民共和国国家标准

GB 34330—2017

固体废物鉴别标准 通则

Identification standards for solid wastes

General rules

（发布稿）

2017-08-31 发布　　2017-10-01 实施

环境保护部
国家质量监督检验检疫总局 发布

Waste Management
Identification, Characterization, and Inventory

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FORMAT FOR MAINTAINING RECORDS OF HAZARDOUS WASTES BY THE OCCUPIER OR OPERATOR OF A FACILITY

1. Name and address of the occupier or operator of a facility :
2. Date of issuance of authorisation and its reference number :
3. Description of hazardous waste :

Physical form with description	Chemical form	Total volume (m³) and weight (in kg.)

4. Description of storage and treatment of hazardous waste :

Date	Method of storage of hazardous wastes	Date	Method of treatment of hazardous wastes

Schedule I
[See rules 3 (1)]

List of processes generating hazardous wastes

S.No.	Processes	Hazardous Waste *	
26.	Production or industrial use of synthetic dyes, dye-intermediates and pigments	26.1	Process waste sludge/residues containing acid or other toxic metals or organic complexes
		26.2	Dust from air filtration system
27.	Production of organo-silicone Compounds	27.1	process residues
28.	Production/formulation of drugs/pharmaceuticals & health care product	28.1	Process Residues and wastes
		28.2	Spent catalyst/spent carbon
		28.3	Off specification products
		28.4	Date-expired, discarded and off-specification drugs/medicines
		28.5	Spent organic solvents
33.	Disposal of barrels containers used for handling of hazardous wastes chemicals	33.1	Chemical-containing residue arising from decontamination.
		33.2	Sludge from treatment of waste water arising out of cleaning/disposal of barrels/containers
		33.3	Discarded containers/barrels/liners contaminated with hazardous wastes/chemicals
34.	Purification and treatment of exhaust air, water & waste water from the processes in this schedule and common industrial effluent treatment plants (CETP's)	34.1	Flue gas cleaning residue
		34.2	Spent ion exchange resin containing toxic metals
		34.3	Chemical sludge from waste water treatment
		34.4	Oil and grease skimming residues
		34.5	Chromium sludge from cooling water
35.	Purification process for organic compounds/solvents	35.1	Filters and filter material which have organic liquids in them, e.g. mineral oil, synthetic oil and organic chlorine compounds
		35.2	Spent catalyst
		35.3	Spent carbon
36.	Hazardous waste treatment processes, e.g. incineration, distillation, separation and concentration techniques	36.1	Sludge from wet scrubbers
		36.2	Ash from incineration of hazardous waste, flue gas cleaning residues
		36.3	Spent acid from batteries
		36.4	Distillation residues from contaminated organic solvents

- The site should have a documented process to identify and properly characterize all of its waste streams
- An inventory of wastes generated should be available on site
- The inventory should include at a minimum:
  - Point of Generation (process generating the waste)
  - Hazardous characteristics and classification (corrosive, flammable, radioactive, etc.)
  - Annual Generation Rate

Waste Management
Storage and Handling

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INITIATIVE

- Waste storage areas should be secured and managed
- Located indoors or in covered
- Impervious floors with secondary containment
- Storage areas clean and free of debris and accumulated liquids
- Sufficient aisle space

Waste Management
Storage and Handling

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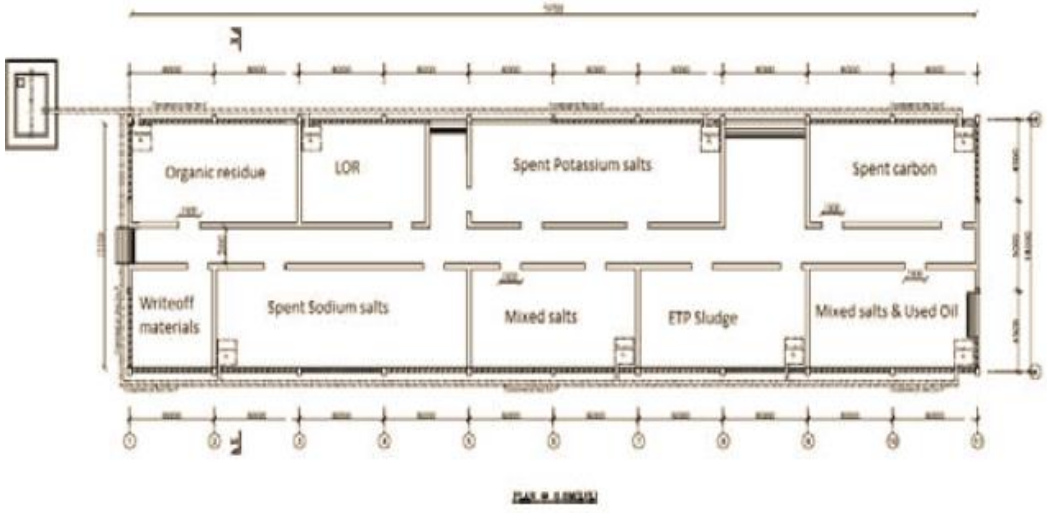
SUPPLY CHAIN
INITIATIVE

Review the following:

- Inspection program
- Separate storage for incompatible wastes
- Suitable emergency response equipment in place
- Suitable PPE available for personnel managing waste
- Proper security and signage



Waste Management
Bio-Medical Waste

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INITIATIVE

- Confirm with the site if they generate biohazardous wastes (e.g., microbiological testing wastes)
- Review storage and handling methods
- Must be managed appropriately while on site
- Segregated from other hazardous wastes
- Confirm disposal method and location
- Incinerated at an approved location

Waste Management
Disposal

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INITIATIVE

- Waste must be disposed at the location specified in the Authorisation
- Confirm locations of disposal
- Tracking system for waste shipments and shipment records retention
- Review hazardous waste manifests

Waste Management
Vendor Considerations

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INITIATIVE

- Does the facility audit their waste vendors?
- Do they have the right authorisations?
- Determine frequency, audit protocols, auditor qualification
- What is described in the contract?

The Pharmaceutical Supply Chain Initiative

Need more information?

Visit: www.pscinitiative.org

Email: the PSCI Secretariat at info@pscinitiative.org

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PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

Fire Safety Audit – A Brief Introduction on Loss Prevention Survey.

Presented by

Tony Wu, Senior Loss Prevention Consultant
XL GAPS

22nd November 2017 Shanghai

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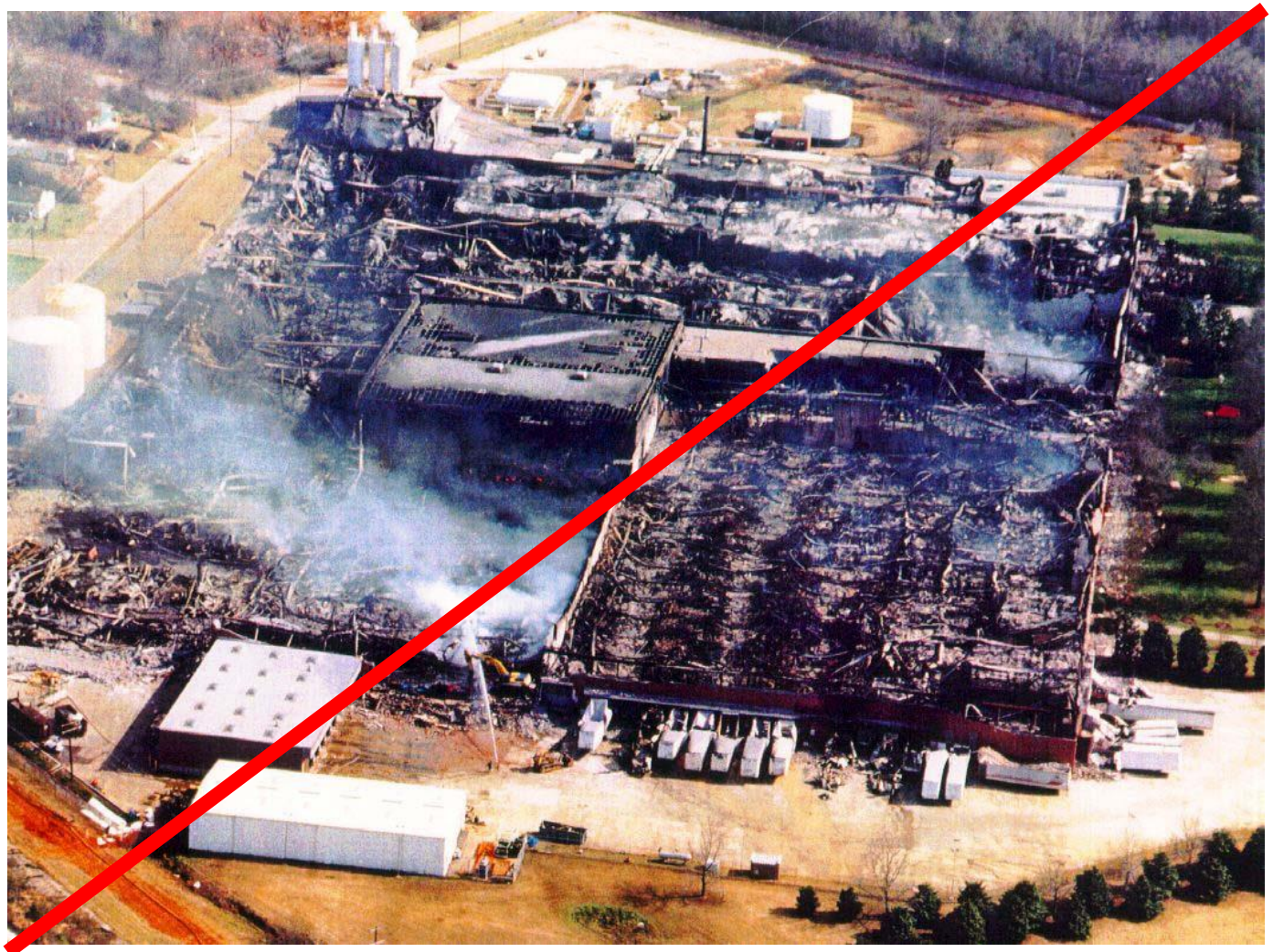
INITIATIVE

Why Are We Here?

We aim to prevent a severe loss at your facility!



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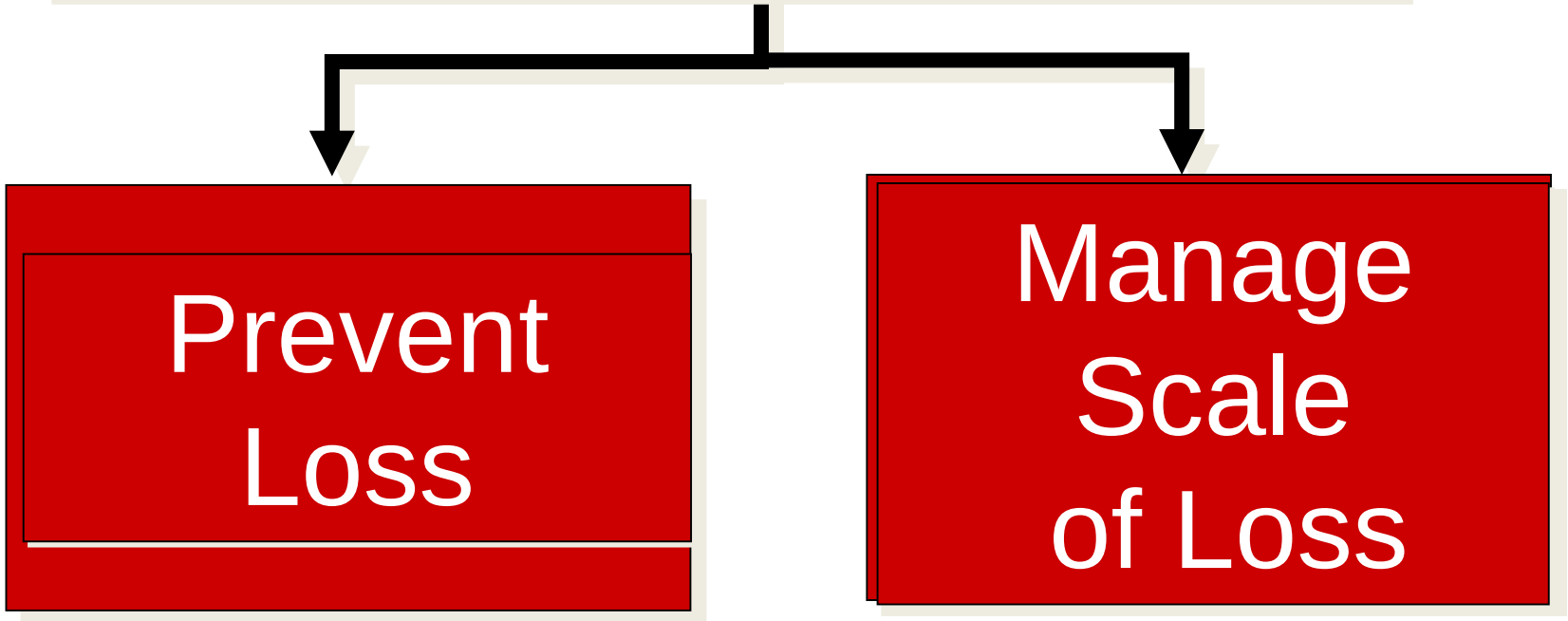
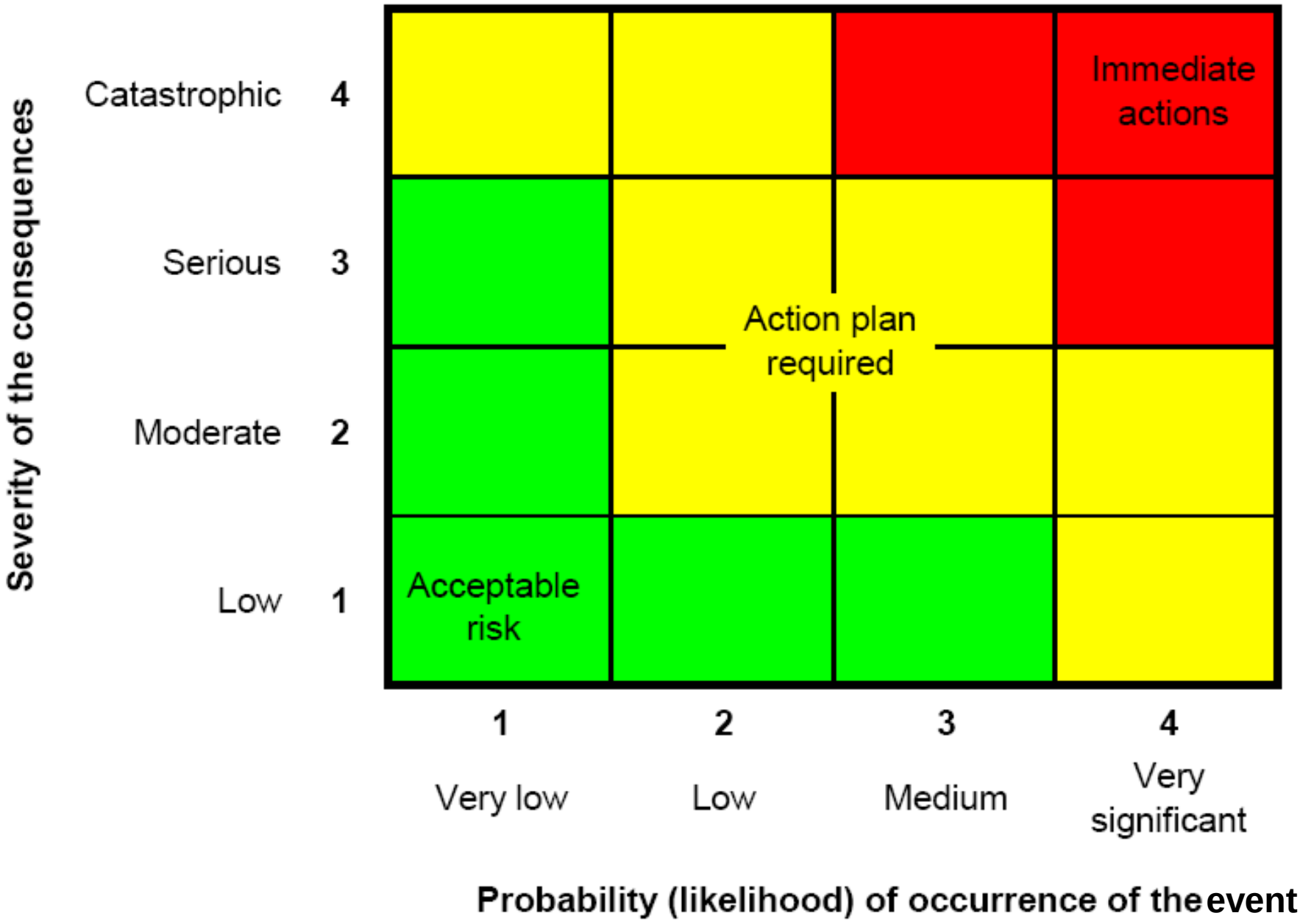
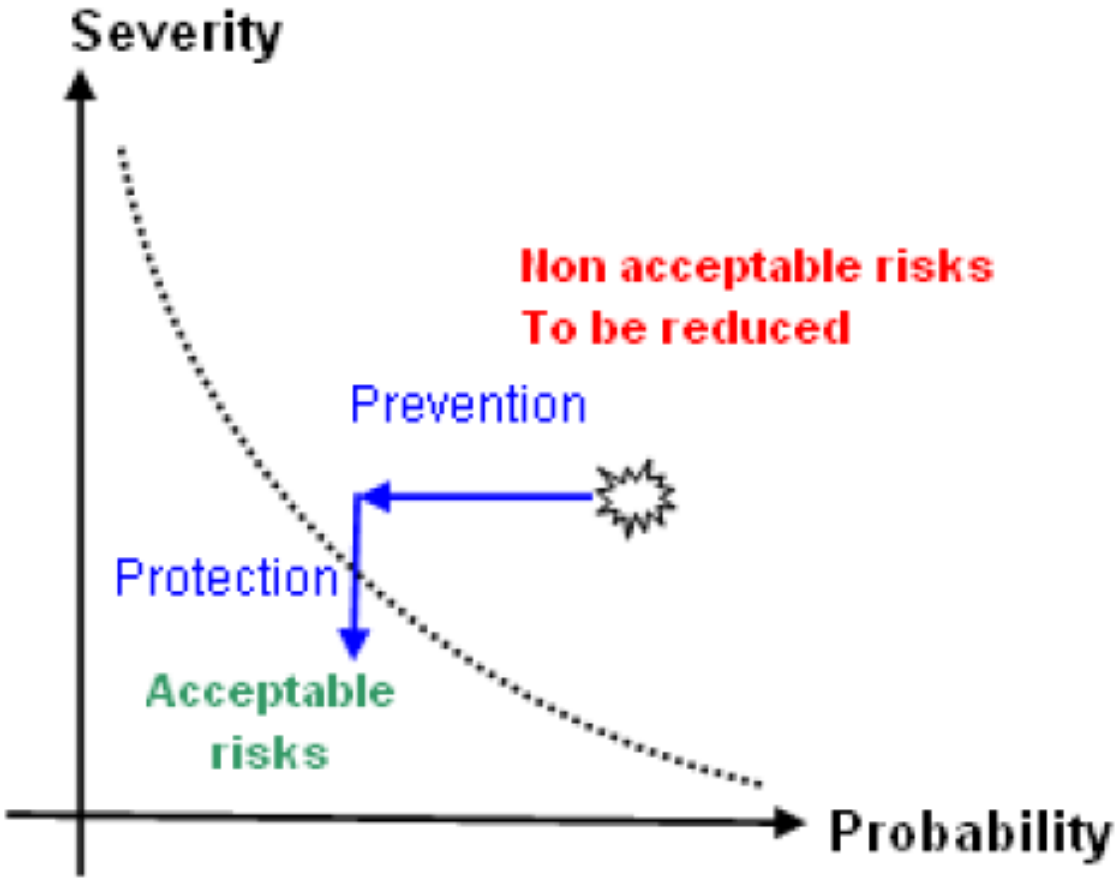
SUPPLY CHAIN
INITIATIVE

Systems Approach to Property Loss Control




Severity of the consequences
Catastrophic 4
Serious 3
Moderate 2
Low 1
Immediate actions
Action plan required
Acceptable risk
1
2
3
4
Very low
Low
Medium
Very significant
Probability (likelihood) of occurrence of the event

The graph here after shows the effect of the risk reduction actions:



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INITIATIVE

Use of Codes and Standards

- Corporate Fire Protection Standard; (Pfizer Corporate Standard)
- NFPA Codes; (National Fire Protection Association)
- International Standards;
- Local Codes (fire and building) – GB Codes;
- GAP Guidelines and FM Data Sheets;
- Performance Based Design;
- Common Sense;

Loss Prevention Survey: Scope of Work

- Management Program; (Policy, Practice and Record)
- Fire Protection System; (Design, Functionality, Sequence of Event)
- Building Construction, Exposures, and Security and Surveillance;
- Process Hazard; (Industrial Safeguards against Occupancy Hazard)
- Natural Hazards; (Site Selection, Design Guideline and Emergency Response Plan)

The Top 5 Qualities of a HPR Risk: Highly Protected Risk

- A desire on the part of the management to reduce the risk of fire and physical damage to a minimum, expressed in terms of visible support for prevention and protection efforts;
- Conscientious application by personnel of the establishment's own operational safety rules;
- Adequate automatic sprinkler protection (wherever combustible loading presented);
- Particular protection for "hot" spots and points at risk of serious interruption;
- Human intervention, internal and/or external, to take charge of an incident, and available at all times;

Management Program:
GAPS "OVERVIEW" - 14 Human Element Programs

Hot Work Permit: Key Points

- Application and Approval (Classification on Hazardous Operation，Designated Area，Outdoor rather than Indoor，Replacement Method，No Impairment Status exists on Fire Protection Equipment)；
- Safety Clearance（11 meter Rule）；
- Fire Watch (Separated from Hot Work Operator);
- Continuous Spot Monitoring；
- The Fire Watch is acquainted with the Fire Alarm Notification Procedure and be equipped with portable fire extinguisher;
- Extended Spot Monitoring for 1.0 hour；
- Intermittent Spot Checking for 3.0 hours; (1.0 hour interval)
- Signature on the Permit and Keeping the record;

Do Hot Work Programs Work?
Gross Losses (Average), 1975-2000

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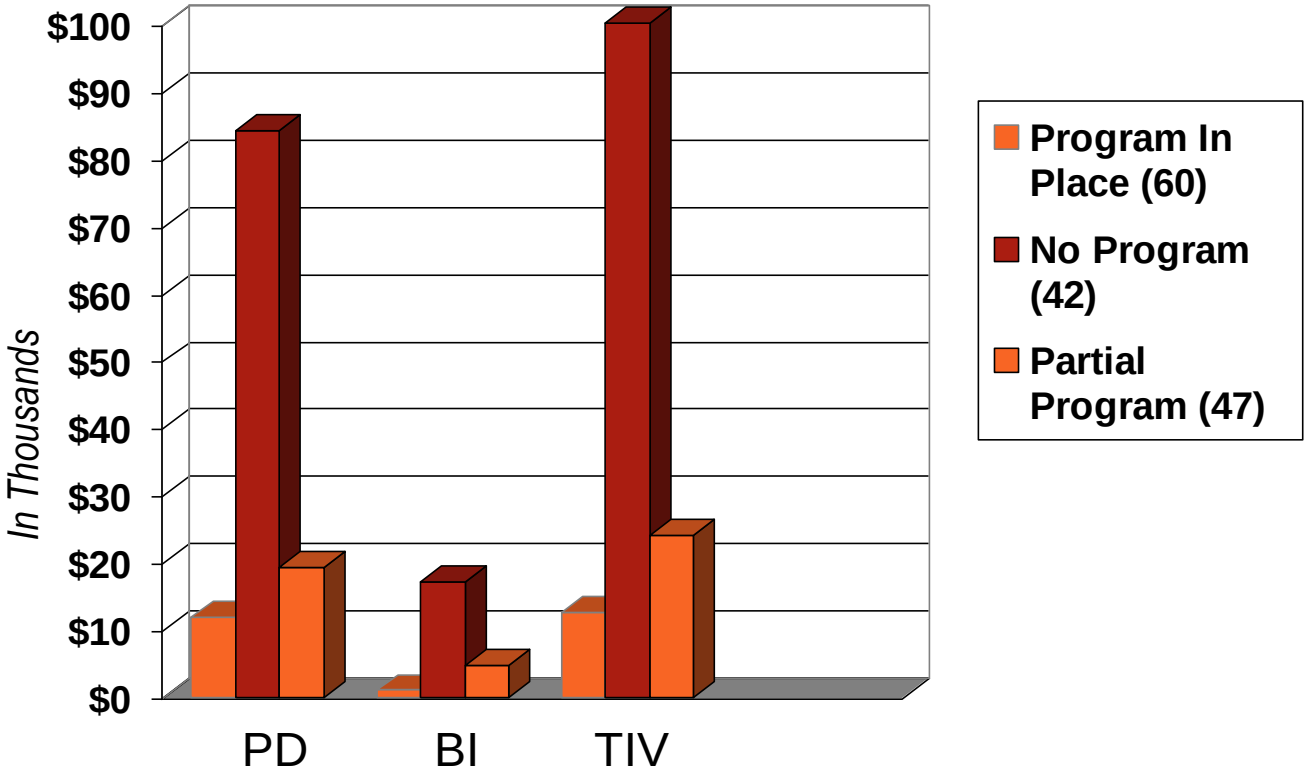
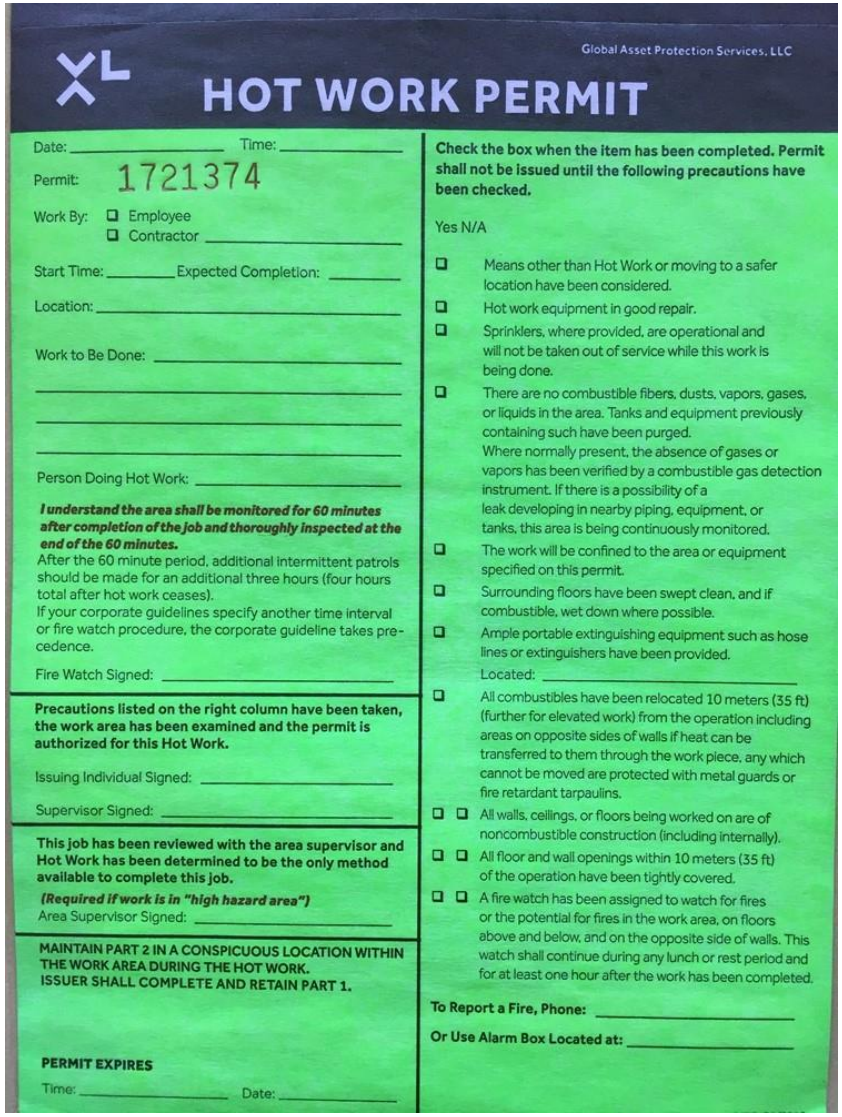


Hot Work Permit Form



Global Asset Protection Services, LLC

HOT WORK PERMIT

Date: _____ Time: _____

Permit: 1721374

Work By: ☐ Employee
☐ Contractor _____

Start Time: _____ Expected Completion: _____

Location: _____

Work to Be Done: _____

_____

_____

_____

Person Doing Hot Work: _____

I understand the area shall be monitored for 60 minutes after completion of the job and thoroughly inspected at the end of the 60 minutes.
After the 60 minute period, additional intermittent patrols should be made for an additional three hours (four hours total after hot work ceases).
If your corporate guidelines specify another time interval or fire watch procedure, the corporate guideline takes precedence.

Fire Watch Signed: _____

Precautions listed on the right column have been taken, the work area has been examined and the permit is authorized for this Hot Work.

Issuing Individual Signed: _____

Supervisor Signed: _____

This job has been reviewed with the area supervisor and Hot Work has been determined to be the only method available to complete this job.

(Required if work is in "high hazard area")
Area Supervisor Signed: _____

MAINTAIN PART 2 IN A CONSPICUOUS LOCATION WITHIN THE WORK AREA DURING THE HOT WORK.
ISSUER SHALL COMPLETE AND RETAIN PART 1.

PERMIT EXPIRES

Time: _____ Date: _____

Check the box when the item has been completed. Permit shall not be issued until the following precautions have been checked.

Yes N/A

- ☐ Means other than Hot Work or moving to a safer location have been considered.
- ☐ Hot work equipment in good repair.
- ☐ Sprinklers, where provided, are operational and will not be taken out of service while this work is being done.
- ☐ There are no combustible fibers, dusts, vapors, gases, or liquids in the area. Tanks and equipment previously containing such have been purged.
  Where normally present, the absence of gases or vapors has been verified by a combustible gas detection instrument. If there is a possibility of a leak developing in nearby piping, equipment, or tanks, this area is being continuously monitored.
- ☐ The work will be confined to the area or equipment specified on this permit.
- ☐ Surrounding floors have been swept clean, and if combustible, wet down where possible.
- ☐ Ample portable extinguishing equipment such as hose lines or extinguishers have been provided.
  Located: _____
- ☐ All combustibles have been relocated 10 meters (35 ft) (further for elevated work) from the operation including areas on opposite sides of walls if heat can be transferred to them through the work piece, any which cannot be moved are protected with metal guards or fire retardant tarpaulins.
- ☐ ☐ All walls, ceilings, or floors being worked on are of noncombustible construction (including internally).
- ☐ ☐ All floor and wall openings within 10 meters (35 ft) of the operation have been tightly covered.
- ☐ ☐ A fire watch has been assigned to watch for fires or the potential for fires in the work area, on floors above and below, and on the opposite side of walls. This watch shall continue during any lunch or rest period and for at least one hour after the work has been completed.

To Report a Fire, Phone: _____

Or Use Alarm Box Located at: _____

RSVP – Restore Shut Valve Promptly

Impairments can be of three types:

Emergency, Planned or **Hidden**.

Managing each type requires special considerations.

An **Emergency** impairment occurs when an unforeseen incident requires you to partially or totally impair a protective system. An example of an emergency impairment is shutting down a sprinkler system to repair a sudden pipe break.

Loss Prevention Survey

You control a **Planned** impairment by determining what work must be done, and by deciding how and when it will be done. Examples of planned impairments include shutdowns for sprinkler system maintenance or for relocating sprinkler heads in an area being remodeled.

Most serious is the **Hidden** impairment. This type of impairment can remain undiscovered for a lengthy time, with no steps being taken to reduce chance of fire in the affected area. Hidden impairments can happen when systems are not restored after work is complete due to improper notification or poor follow-up, or when systems are maliciously shut down. A strong fire protection equipment inspection program will uncover hidden impairments promptly.

Impairments: Fire Protection Equipment Impairment Handling

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- Expect and plan for them!
- Minimize duration and size
- Minimize hazardous operations
- Provide special precautions
- Provide temporary protection

RSVP Tag:

SHUT OFF TAG No. 5301

RSVP*

***RESTORE SHUT VALVES PROMPTLY**

When necessary to shut off fire protection equipment for planned or emergency reasons, changes or repairs, 4 minutes or 4 hours remember ...

... External Contacts

- ☐ 1. Telephone Gap Services.
- ☐ 2. Notify the public fire brigade.
- ☐ 3. Contact your alarm service agency.

... Internal Precautions

Before the Impairment

- ☐ 1. Schedule only *one planned* impairment at a time.
- ☐ 2. Brief department heads in areas where fire protection will be shut off.
- ☐ 3. Alert plant fire brigade.
- ☐ 4. Provide emergency access to impaired area.
- ☐ 5. Make sure all other plant fire protection equipment is in service.
- ☐ 6. Have all materials, tools and manpower ready when protection is shut off so the job can be completed as swiftly as possible.

OFFICE REMINDER No. 5301

RSVP*

***RESTORE SHUT VALVES PROMPTLY**

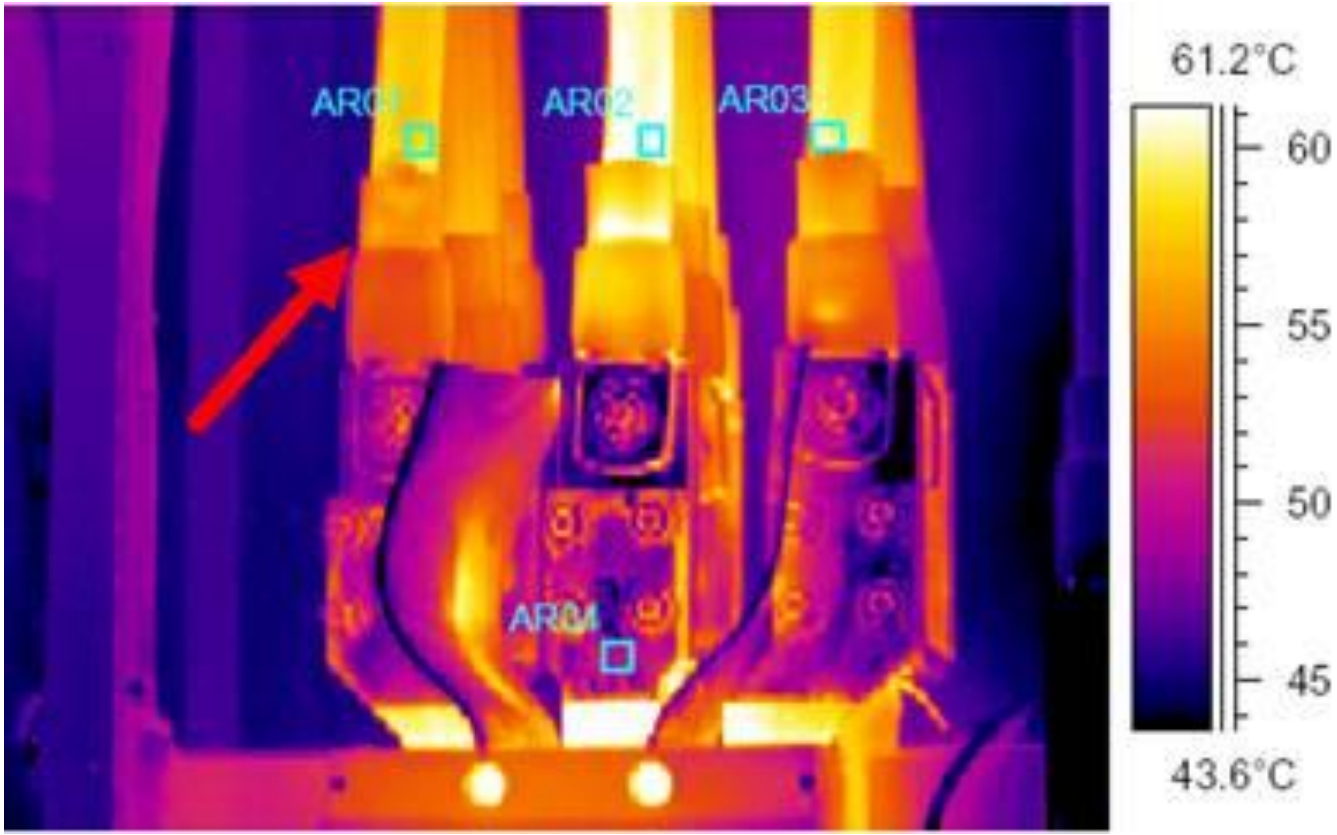
During the Impairment

- ☐ 1. In areas of impairment:
  - Stop hazardous production or maintenance operations.
  - Prohibit the use or processing of flammable combustible liquids.
  - Prohibit cutting, welding or other hot work.
  - Enforce "No smoking" regulations.
  - Maintain continuous fire watch patrols.
  - Keep all fire doors closed where possible.
  - Have trained personnel with extra equipment, such as portable fire extinguishers and charged hose lines, standing by.
- ☐ 2. Attach the Gap Services "RSVP" Shut Off Tag to *each* Shut Valve or other impaired equipment.
- ☐ 3. Keep the "RSVP" Office Reminder in a visible place.
- ☐ 4. Station someone at shut valve when excessive distance from work area.
- ☐ 5. If scope of impairment must be increased, discuss immediately with Gap Services.
- ☐ 6. Work continuously until protection is restored.

After the Impairment

- ☐ 1. Verify that full protection has been restored.
- ☐ 2. Report restoration to Gap Services and others.

Maintenance – Infrared Thermalgraphic Scanning Inspection on Electrical Equipment



Maintenance – Infrared Thermalgraphic Scanning Inspection on Electrical Equipment

Preventive Maintenance

The infrared thermographic scanning inspection is an effective method to diagnose the loose connect, broken insulation, overloading on circuit, dirt on the electrical connection and foresee the potential electrical fire. By providing prompt corrective measure, the potential electrical fire is preventable.

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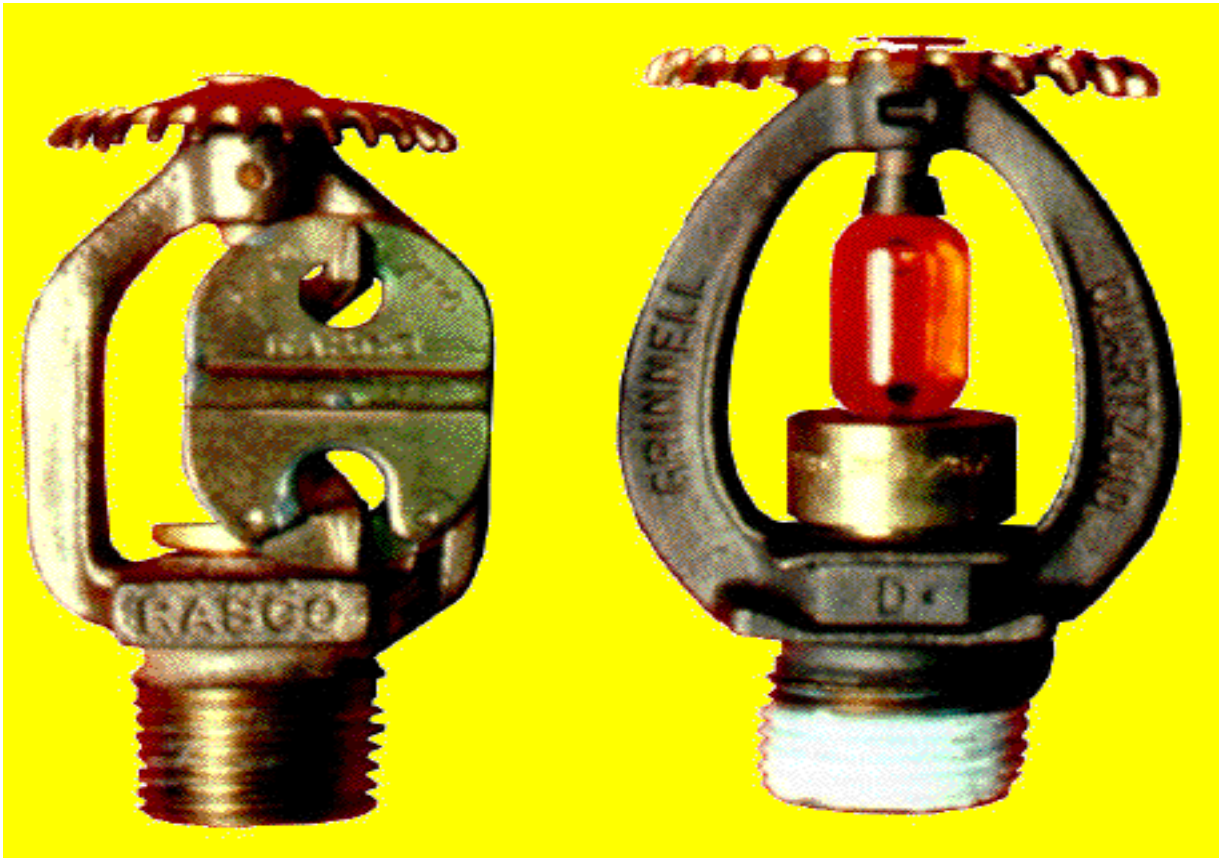
Automatic Sprinkler Protection and Fire Pump System



Roof Temperature Curve in a Fire Scene

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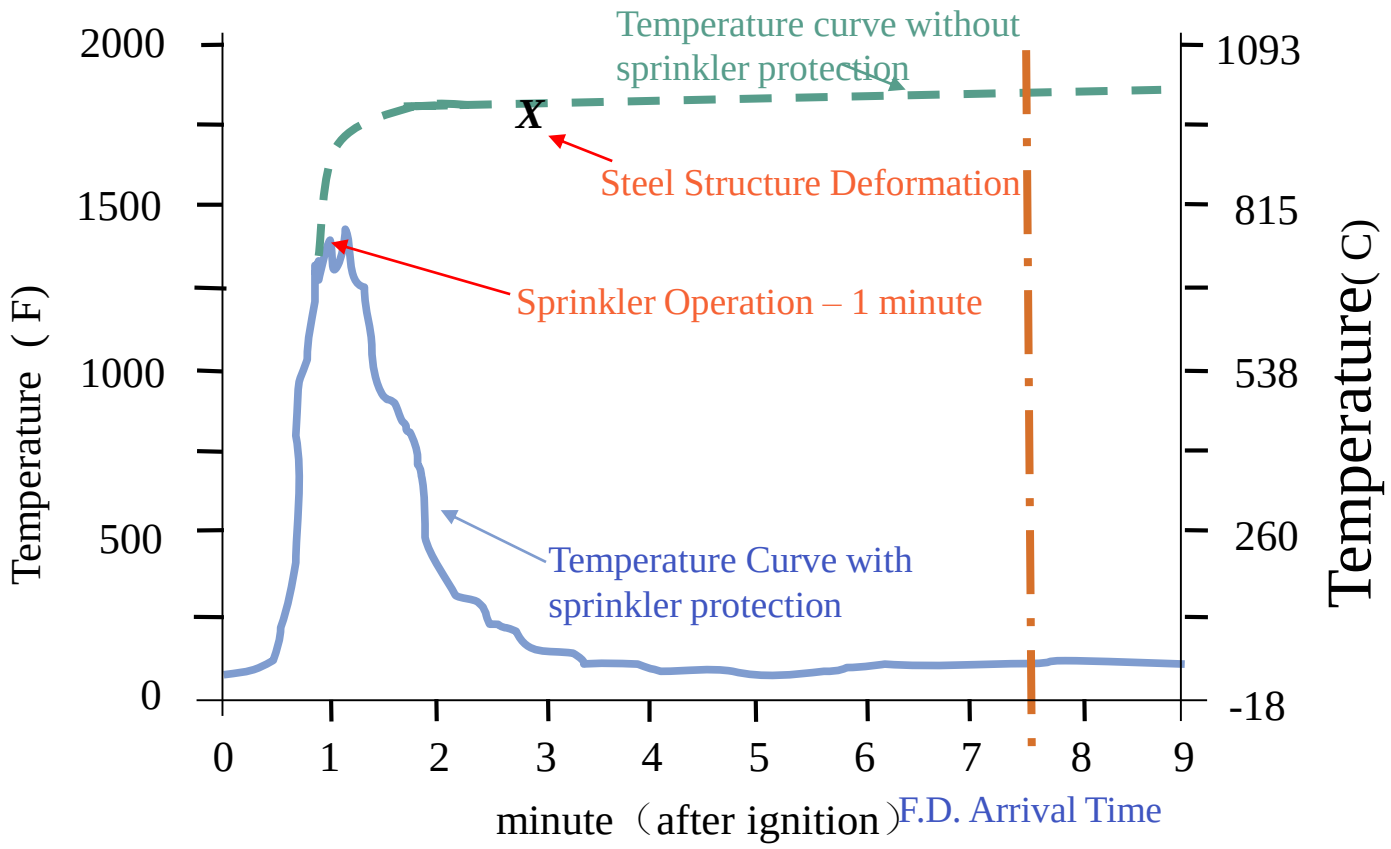

Sprinkler System Design-

Hydraulic Calculation (Design Table NFPA13)

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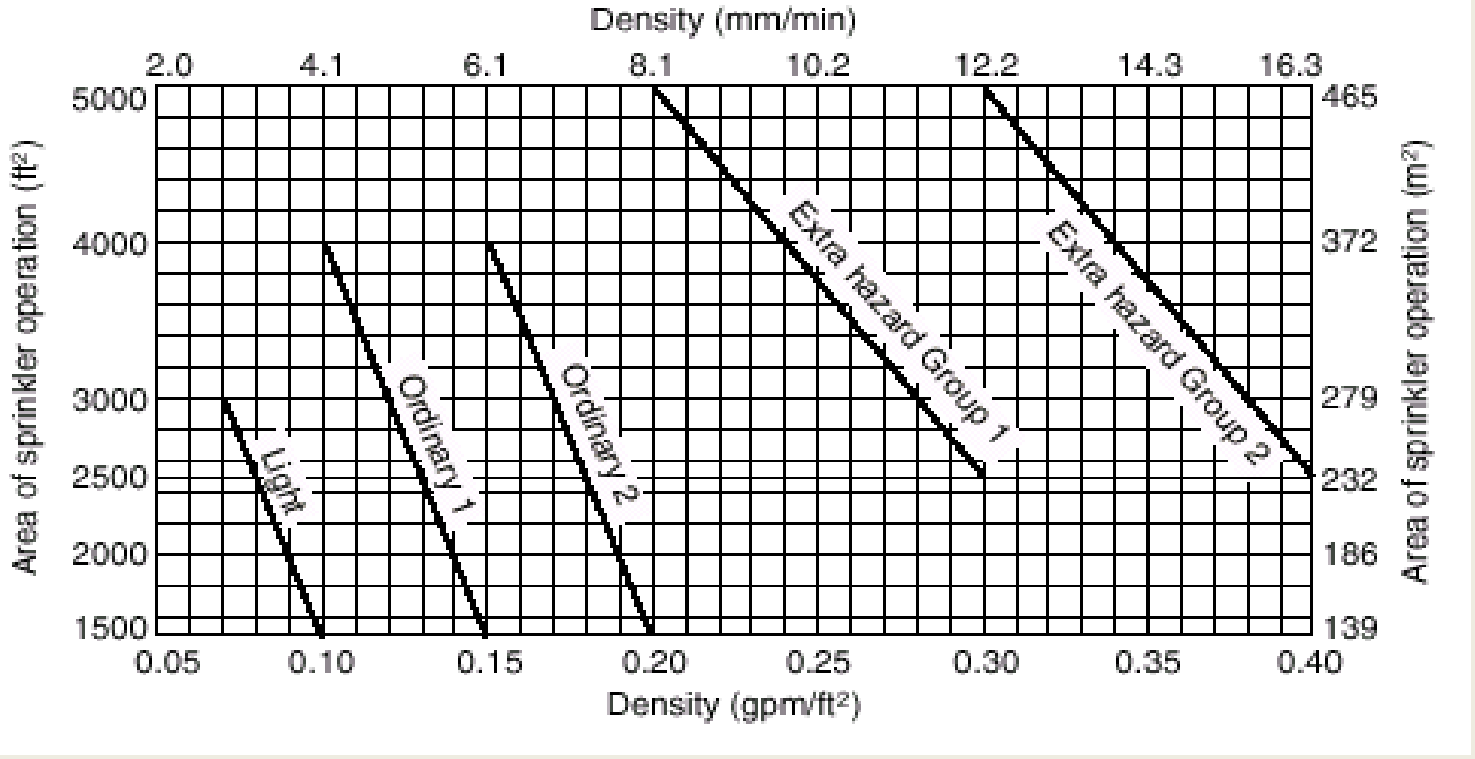

Source, NFPA 13

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Determining Water Supply Needs

$$\left[\text{Sprinkler System Demand} + \text{Hose Stream Demand}\right] \times \text{Required Duration} = \text{Estimated Water Supply Demand}$$

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Water Supply Example

- Sprinklers: 12.2 l/min/m². over 278.8 m²
- Hose stream demand: 2840 l/min
- Required duration: 3 hours

(12.2 l/min/m²) (278.8 m²) (110%) = 3741 l/min

Hose demand = 2840 l/min

3741 l/min + 2840 l/min = 6581 l/min

(6581 l/min) (60 min/hr.) (3 hrs.) = 1185 m³

Fire Pump System：Fire Pump and Water Tank

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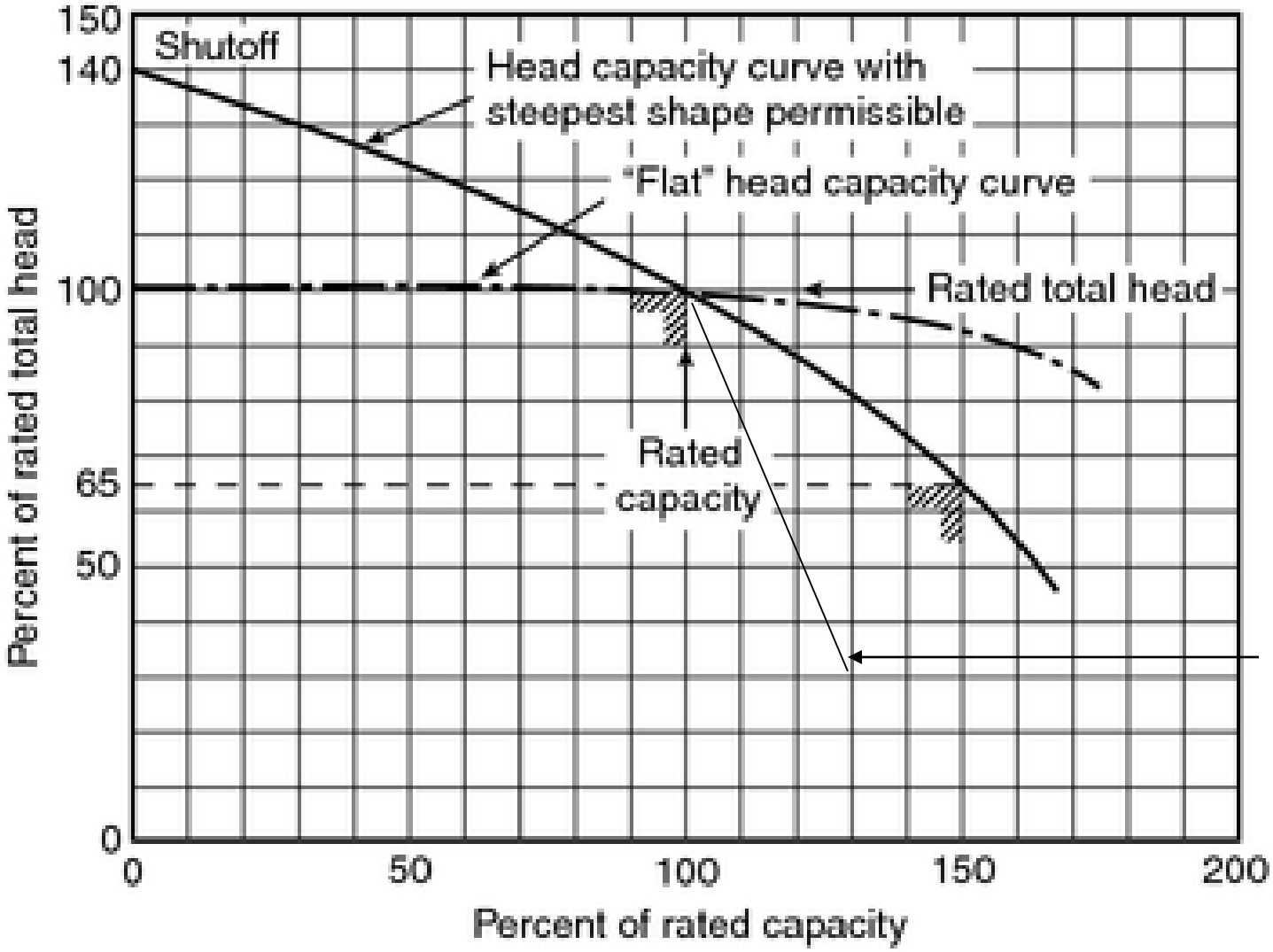
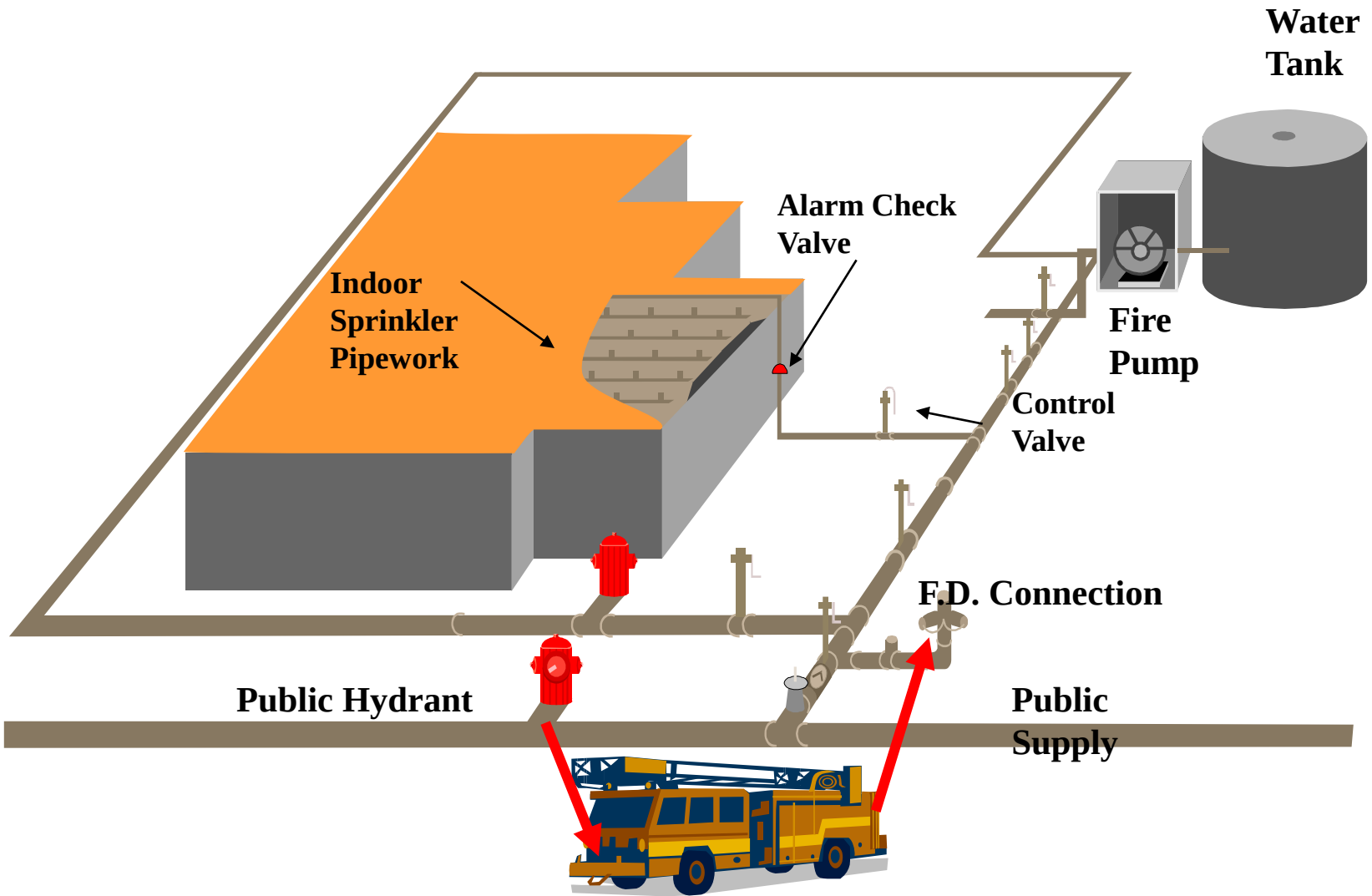
FM Approved Fire Pump Performance Curve:



Non-FM Approved Fire Pump Performance Curve

Fire Protection System Layout:



Construction – Avoid Using Combustible Building Material

Loss Preventive Measures for existing EPS installation:

- DO NOT use cutting or welding equipment on or near the wall.
- DO NOT store combustible material near the wall.
- Where possible, DO NOT have materials penetrate through the wall.
- If possible, remove all electrical equipment (outlets, switches, etc) from the wall. If the equipment has to stay, test the equipment annually.
- Inspect the wall weekly for damage. Repair the damage immediately.

Solutions for existing EPS installation: Replacement with Non-combustible Building Material; Or

- Apply a 12.7 mm thick gypsum board over the existing panel Apply spray-on fire proofing;
- Install a row of automatic sprinklers 304 mm from wall on both sides of the wall;
- Install smoke/heat detectors on both sides of the wall and in attic above ceiling;
- Provide a cut-off area by building a 3-hr fire wall with approved fire doors and fire-stopping at penetrations.

Hydraulic Machine Safeguards: (FM D.S.7-98)

Convert existing hydraulic systems to less flammable hydraulic fluid systems whenever possible; Or

- Provide interlock to limit hydraulic fluid supply to a fire by the detection of excess temperature or “rate-of-temperature-rise” detector above the equipment, or through the use of a sprinkler water flow switch;
- Provide automatic sprinkler water or foam extinguishing systems. Design the systems for 8.0 L/min/m^2 over the 280 sq. m. protected area. Dike, drain and trap oil reservoirs;
- Provide a low fluid level switch to shutoff the hydraulic fluid pump supply; (set the sensitivity less than 95 liter per hydraulic fluid tank);
- Provide an emergency shutoff device at minimum 6.1 meter. away from the hydraulic equipment;

Natural Hazards：

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Munich Re Nathan Natural Hazard Database: Earthquake

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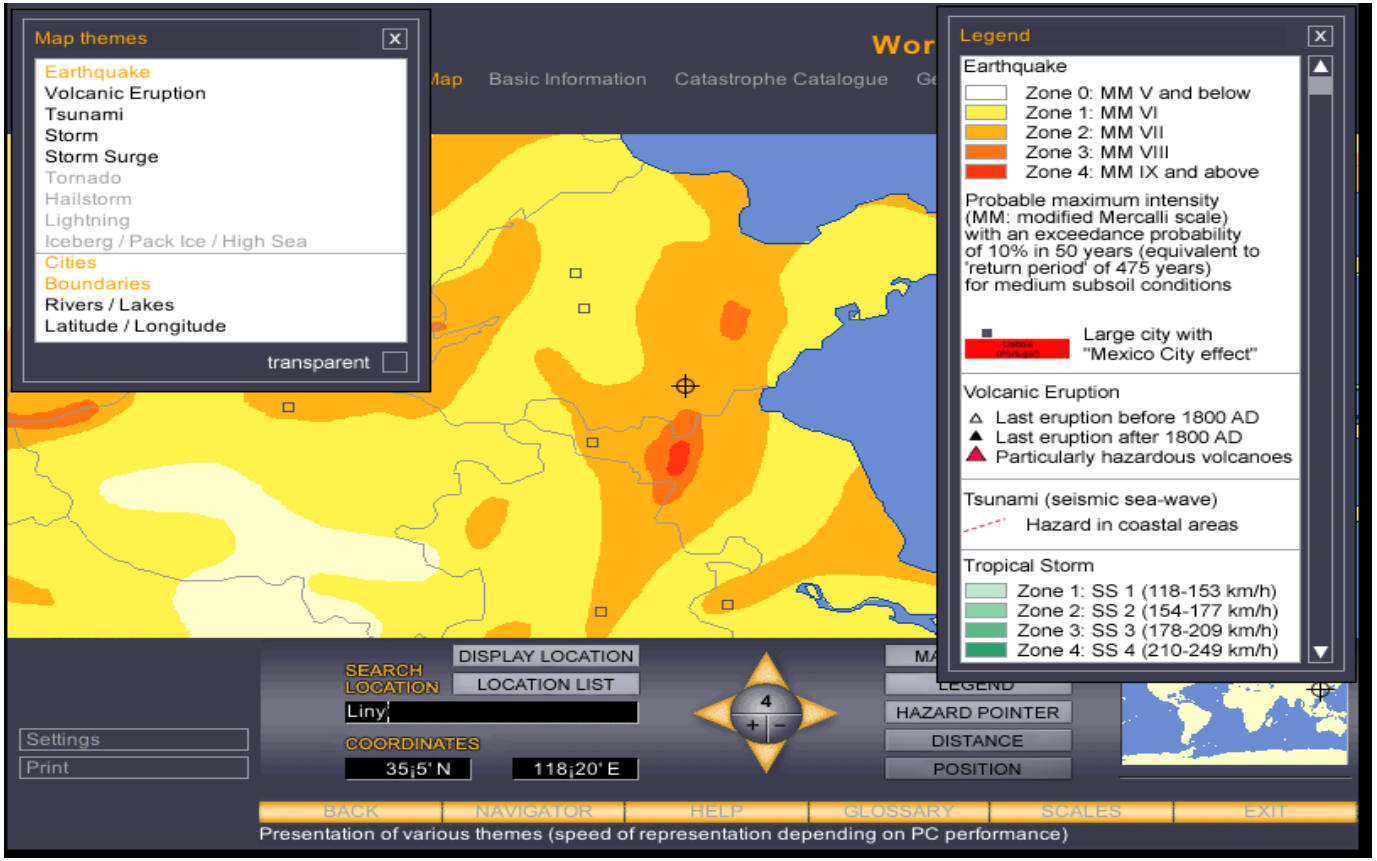

Natural Hazards: Require Site GPS Coordination for evaluation on Flood, Earthquake, Windstorm, etc.

Risk Score Rating

Weighted and summarized Risk value for ordinary commercial and industrial business

Overall Risk Score	Extreme

Hazard Score Rating

Hazard zoning values for significant natural hazards

	low – high	hazard rating
Earthquake		Zone 2
Volcanoes		No hazard
Tsunami		No hazard
Tropical cyclone		No hazard
Extratropical storm		Zone 1
Hail		Zone 4
Tornado		Zone 3
Lightning		Zone 3
Wildfire		Zone 2
River flood		Zone 100
Flash flood		Zone 4
Storm surge		No hazard

Q & A

- Thank you very much!

Contact us:

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PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

The Pharmaceutical Supply Chain Initiative Training for Auditors – IH Topics

Compiled by:
PSCI Audit Committee

Presented by David Lu and Li Liu

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Agenda (180 minutes)

- **END IN MIND** – discovering PSCI critical & PSCI other issues
  - PSCI IH Principles
  - PSCI Critical Finding for IH

- **Key concepts** in the Industrial Hygiene program & **Red Flags**

  - PSCI industrial hygiene (IH) principles & critical findings
  - Start with the SDS – do we align?
  - Fundamentals of control banding
  - IH Monitoring
  - Hierarchy of controls in pharma
  - Medical Surveillance
  - Employee Training
  - Red flags for IH

- **Group exercise on industrial hygiene**

What are the PSCI Health & Safety Principles applicable to IH?

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1. Worker Protection
Suppliers shall protect workers from over exposure to chemical, biological, physical hazards and physically demanding tasks in the work place and in any company provided living quarters.

3. Emergency Preparedness and Response
Suppliers shall identify and assess emergency situations in the workplace and any company provided living quarters, and to minimize their impact by implementing emergency plans and response procedures.

4. Hazard Information
Safety information relating to hazardous materials - including pharmaceutical compounds and pharmaceutical intermediate materials - shall be available to educate, train, and protect workers from hazards.

PSCI Auditor Training | NOV 2017

Managing Potent and Sensitizing API Compounds
What is in a GOOD IH PROGRAM

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- An onsite person who has had training in control of hazardous agents
- Access to expert (e.g. certified industrial hygienist, qualified consultant)
- Inventory of hazardous chemical agents, in particular potent materials, sensitizers, carcinogens and reproductive hazards.
- Information on chemical agents from customers and suppliers and use of a banding system
- Access to MSDS data and communication of risks, procedures and controls to staff using the hazardous agents.

Managing Potent and Sensitizing API Compounds
What is in a GOOD IH PROGRAM

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- Chemical risk assessments – chemicals used, operations performed, assessment of control measures (including non-production tasks such as maintenance of equipment, handling of waste)
- Procedures and training on storage / use and cleaning of PPE.
- Sampling and monitoring data as appropriate
- Risk based health surveillance.
- Incident/exposure records

Using the PSCI Questionnaire for IH

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- Don’t just answer yes/no
- Identify what they do and let the PSCI company understand ANY concerns with the approach you see.
- Ultimately – find the single question to place in your conclusions about acceptable to be CAPABLE and EFFECTIVE at handling the APIs they are under contract to handle. Find one question where you will document whether OEL approach aligned between the companies.
- When it is unknown whether exposure are acceptable – write the finding to have the company secure the data to ensure their control strategy is supported.
- ALWAYS – reference what you SAW in the field, not what you read in a SOP. Be sure to document what you did or did not see on your tour! This is very important for possible sharing of future audit reports between PSCI members.

Using the PSCI Questionnaire for IH

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Safety Questions – for IH

- 62. Have any significant Health & Safety incidents occurred at this facility over the past three years?
- 63. Does the facility provide the following types of HSE (Health, Safety & Environment) training to employees (full-time, temporary, or contractor)?
  - Hazard Communication
  - Personal protective equipment & Respirator use

PSCI Occ Health/IH Questions

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- 81. Has the facility established practices to eliminate hazards of materials using the hierarchy of exposure control:
- 82. Does the facility perform risk assessments for chemicals handled? Mark the technologies in use.
- 83. Has the facility established occupational exposure levels for all Active Pharmaceutical Ingredients (API) and hazardous substances?
- 84. Has the facility established exposure control capabilities for handling pharmaceutical compounds?
- 85. Does the facility perform risk-based medical monitoring or employee health surveillance which includes recording, investigation and follow-up? List Methods used.

PSCI Occ Health/IH Questions

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- 86. Has the facility developed and implemented a plan to protect First Aid Responders and Medical Professionals from exposure to body fluids?
- **87. Does the facility perform exposure monitoring for the following health and safety risks? Mark per category.**
- 88. Is there a site procedure to inform employees of the results of exposure evaluations and monitoring results?
- 89. Does the site provide Personal Protective Equipment (PPE) for face, eye, foot, head, and hand protection?
- **90. Does the facility rely primarily on respiratory protective devices and/or engineering controls to protect employees who handle chemicals to achieve exposure levels below the exposure limit?**

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Occ Health/IH Questions

- 91. Does the facility use any of the following respiratory protection equipment for worker protection against exposure to chemicals or pharmaceutical compounds. Mark those and comment on appropriateness.
- **92. Are there provisions for fit testing, training, use, cleaning, inspecting, storing, and maintenance of respirators?**
- 120. Does the facility maintain Safety Data Sheets (SDSs) for all hazardous substances?
- 121. Does the facility have a training program covering the properties and health effects of the hazardous substances, use of and access to SDSs, container labelling and safe handling procedures?

Occ Health/IH Questions

Process Safety Management Questions

- 94. Does the facility have processes to manage chemical hazards safely in order to prevent catastrophic events involving **highly toxic, flammable, reactive and/or corrosive substances**?
- 117. Are emergency response plans in place and when was the plan updated?
- 118. Does the site have an on-site emergency response team that is trained for fire or other emergencies?
- 119. Does the site use off-site consequence modelling to evaluate to potential off-site impact of chemical releases?

Industrial Hygiene – What are we after?

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PSCI Audit Findings

Critical Findings:

- Are **very** high risk findings that require immediate action to protect human life, the health of employees or the environment;
- May result in loss of license to operate or serious damage to reputation;
- Require immediate corrective action by the supplier;
- Need to be communicated to the audit sponsor prior to audit report finalization.

Examples for critical findings:

- Severe violations of human rights or labor rights (e.g. presence of child labor in a facility or forced labor, over-excessive working hours);
- Health and safety issues that can cause immediate life threatening situation or serious injuries to employees and other individuals on site;
- Environmental or safety issues that could result in serious and immediate harm to the community.

Other findings:

- Are all other major or minor audit findings, which need to be corrected by the supplier in an appropriate period of time?

Q1. Did you discover a known or highly probable situation that could cause immediate harm? If so, describe and help us understand why?

Q2. Is site CAPABLE to EFFECTIVELY manage our pharmaceutical risks in our Contract?

Q3. Is the site handling APIs correctly for themselves and others? (Brand Risk)

IH Red Flags – potential IMMEDIATE CONCERN

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- Site handling their API as NUSIANCE DUST 10 mg/m3 because no regulatory limit. No banding approach exists for products without limits. Site is handling potent pharmaceuticals.
  - Site has never seen the API – OEL from the PSCI member company SDS. When you compare the two with them, you find major differences in classifications and OEL.
- IH monitoring (if collected) has had faulty interpretation – there are clear overexposures and no action.
- Highly potent pharmaceutical being handled (<10 mcg/m3), operation is OPEN , respirator required by SOP is NOT on the site or completely wrong for the hazard class (e.g. not a respirator or respirator protection factor too low). No segregation and unsure if nearby personnel are also overexposed.

IH Red Flags – potential IMMEDIATE CONCERN

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- During tour of area with highly toxic gases and/or solvents – you smell strong odors, experience irritation, see wrong PPE, and no alarm or shut-offs. Dust masks being used on solvents/gases. Process venting is directed into the room where people work.
- The site lacks any data to justify that they know their workers are protected. This combines with poor Hazcom and PPE practices.
- No capable resource being used to manage IH issues/concerns.
- Site performs QC sampling in warehouse on the open floor for ALL chemicals.
- There is no LEV in the centrifuge unloading or dryer loading rooms where wet cakes are being handled. Limited PPE is being worn.
- There is NO IH sampling data for <u>any</u> process or chemical on record.

Immediate Harm…..

Easy

- Concept of Immediately Dangerous to Life and Health (IDLH) can be applied. Typically applies to acutely Toxic materials, gases and solvents. NIOSH – is a USA reference for IDLH values.
- IH monitoring has documented exceedances emission exceeding Respirator Protection Factors
- Protection for spill and emergency responders is insufficient for risk

Experience

- For APIs that are potent compounds – a different model is necessary to understand
  - Carcinogens
  - Sensitizers
  - Highly Potent Pharmaceuticals
  - Hormones
  - Reproductive Hazards

First Question - Do we agree on Hazards of API? and Controls Needed?

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- API Supplier – Generic
- API Supplier – Proprietary Chemistry as Contract Manufacturer
- Drug Product Pharma Company

Differing Data Sets & Handling Expectations

First Question - Do we agree on Hazards of API? and Controls Needed?

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1st question – do we they agree on classification and occupational exposure limit?

Excise: Group Review on SDSs for Telmisartan (10 min)

- *Aldrich SDS*
- *BI SDS*

A few foundational basics….

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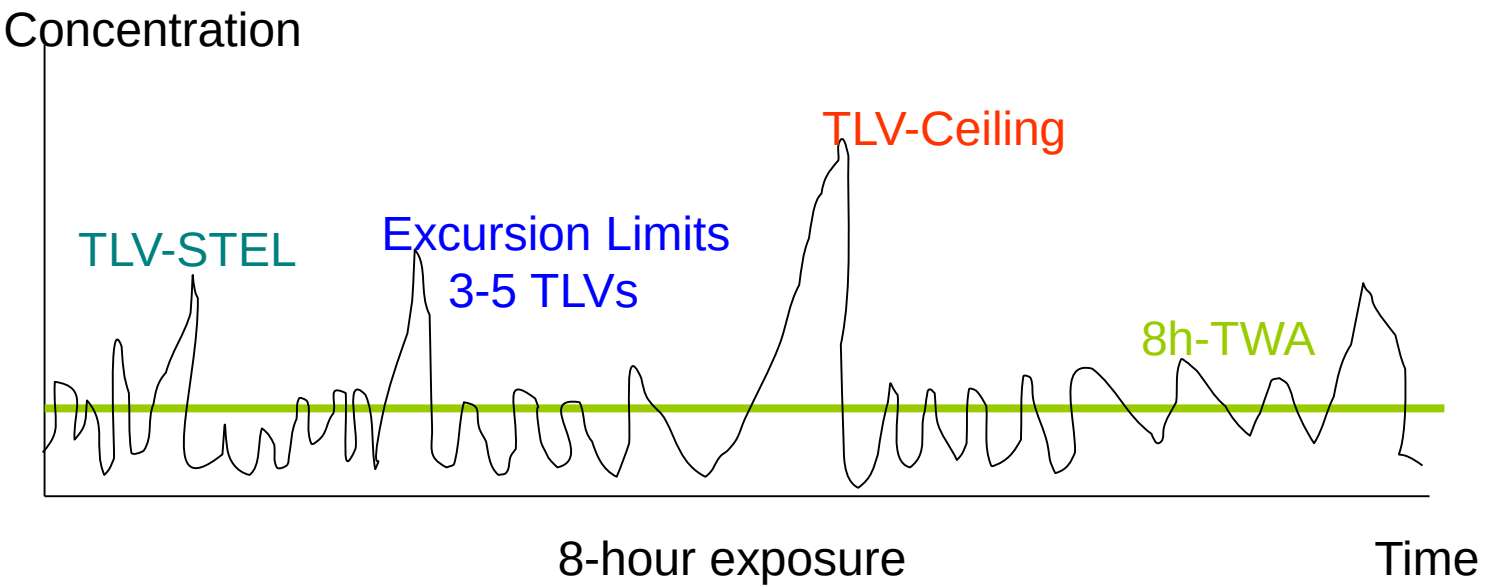
- **Occupational Exposure Limit (OELs)**
  - A numerical air concentration limit expressed as PPM or mg/m3 over a stated time duration (8hr, 12hr, 15 min, Ceiling) which nearly all adult workers may be exposed to during their working lifetime without adverse effects.
  - Interpretation and limitations of OELs



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- **Development:**
  - General Workers Safety
  - OELs for solvents
  - Measuring of exposures: OELs

- **Legal exposure limits exist for many chemical compounds**
  - Threshold Limit Value (TLV) ACGIH
  - Permissible Exposure Level (PEL) OSHA
  - Recommended Exposure Limit (REL) NIOSH
  - Occupational Exposure Limit (OEL) , Germany (AGW / MAK)
  - Exposure Control Limits (ECL)

Exposure Limits for chemicals and APIs

- Compare exposure levels of some well-known toxic solids

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Parathion (E 605) (values defined in many countries)	0.05-0.1 mg/m³
Sodium-fluoride	1-2.5 mg/m³
Potassium-cyanide	5.0 mg/m³

What is important? very well known and
very clear correlation human and animal tests

Exposure Limits for chemicals and APIs
- Exposure Data and where to find them

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https://www.osha.gov/pls/oshaweb/

See standard 1910.1000
(See: Regulations ; Standards - 29 CFR;
-1910 Subpart Z - Toxic and Hazardous Substances)

https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10147

UNITED STATES DEPARTMENT OF LABOR

- Part Number: 1910
- Part Title: Occupational Safety and Health Standards
- Subpart: Z
- **Subpart Title: Toxic and Hazardous Substances**
- **Standard Number: 1910.1000 TABLE Z-1**
- **Title: TABLE Z-1 Limits for Air Contaminants.**

GPO Source: e-CFR

TABLE Z-1 LIMITS FOR AIR CONTAMINANTS

NOTE: Because of the length of the table, explanatory Footnotes applicable to all substances are given below as well as at the end of the table. Footnotes specific only to a limited number of substances are also shown within the table.

TABLE Z-1. - LIMITS FOR AIR CONTAMINANTS

Substance	CAS No.(c)	ppm (a)(1)	mg/m(3)(b)(1)	Skin designation
Acetaldehyde	75-07-0	200	360	
Acetic acid	64-19-7	10	25	
Acetic anhydride	108-24-7	5	20	

Exposure Limits for chemicals and APIs
- Exposure Data and where to find them

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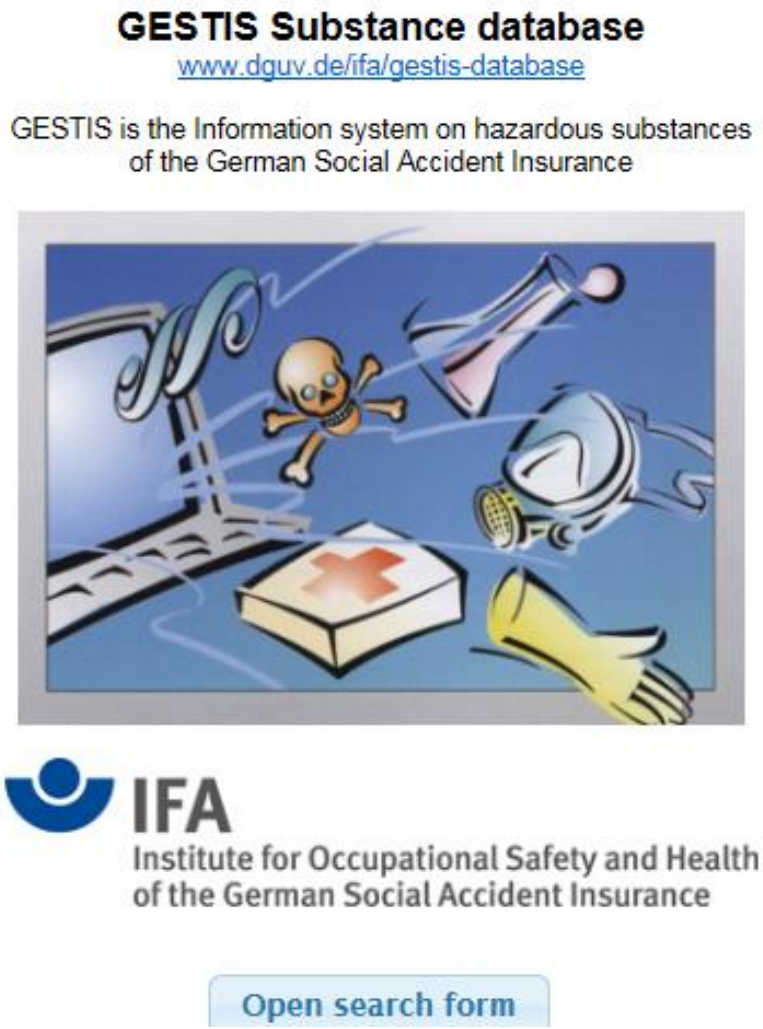

http://gestis-en.itrust.de/nxt/gateway.dll/gestis_en/000000.xml?f=templates$fn=default.htm$vid=gestiseng:sdbeng$3.0

International limit values are also available.

- **General dust limits – are chemical powders inert?**
  - **Legal limits do not exist for most pharmaceutical compounds –**
  - **BUT responsible is the producer of API and Drug product**

- **Big Pharma does see a need to have internal limits based on science**
  - **Minimum Considerations:**
  - Average Daily Exposure (data from human tests) / NOELs (animal)
  - Measurements of Lactose versus specific compounds

Exposure Limits for chemicals and APIs
- Types of exposure limits and introduction of internal banding

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- **Exposure limits**
  - Maximum concentration of a chemical in the air without a health hazard.
  - Time weighted average (TWA), typical for 8 hours (one shift)
  - Short time Limits (STEL), typical 15 min or 60 min

- **Pharma internal exposure limits and exposure bands are established!**
  - Internal exposure limits for active pharmaceutical ingredients (APIs)
  - Describe System is in company specific SOP
  - Align with all involved parties in the company

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Pharmacological data / Mode of action

- Toxicological data:
  - Single and repeat-dose toxicity
  - Local tolerance, sensitization
  - Reproductive and developmental effects
  - Mutagenicity
  - Carcinogenicity
- Human/pharmacological data:
  - Lowest pharmacological active dose
  - Recommended single / daily dose
  - Adverse effects in clinical trials / at therapeutic use
  - Pharmacokinetic and metabolism
  - Reports of occupational accidents or adverse effects

A few foundational basics….

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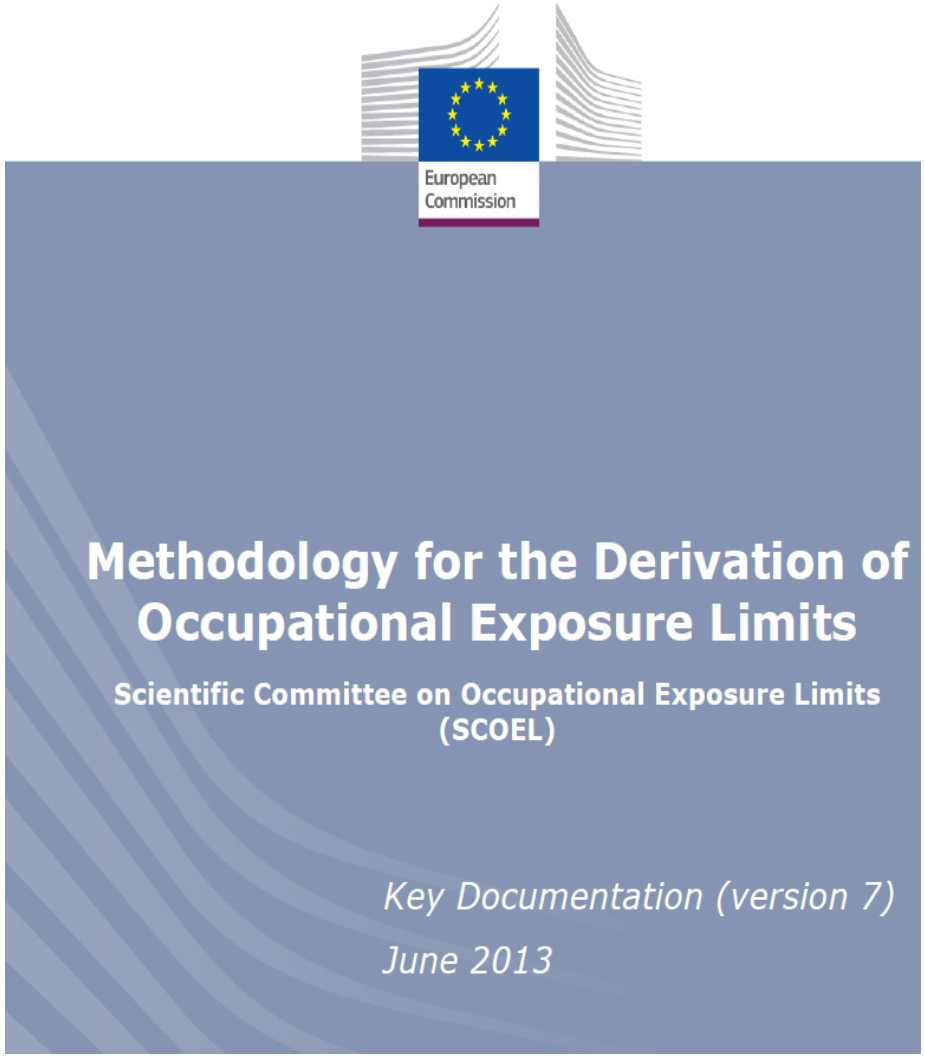
$$OEL\ (mg/m^3) = \frac{NOEL\ (mg/kg/day)\ x\ BW\ (kg)}{V\ (m^3/day)\ x\ S\ x\ UF\ x\ \alpha}$$

- NOEL = the no-observable-effect-level (mg/kg/day)
- BW = average human body weight (50 kg)
- V = volume of air breathed in an 8-hr work day (10 m^3/day)
- S = time, in days, to achieve a plasma steady state
- UF = uncertainty factors
- α (alpha) = % absorbed through inhalation

Reference for OEL Development



A few foundational basics….

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- **Occupational Exposure Banding** – Pharmaceutical Industry Method

  - Classify the Hazard Bands and pick your Default Band: The method a company establishes to setup rules for identifying a control strategy for handling materials with limited toxicology data for safe handling. The bands may be created using rule sets, limited toxicology, and Risk Phrases from the Global Harmonization Standard. Typically found on a MSDS.

  - An established set of recommended ENGINEERING and CONTROL strategies for handling chemicals within a chemical exposure band. Companies who set OELs generally have these. NOT typically found on a MSDS.

OEL Banding Concept

- Criteria e.g. but for reference see also PSCI homepage

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OEL Category	**1** Low toxicity or pharmacological activity	**2** Moderate toxicity or pharmacological activity	**3** Medium toxicity or pharmacological activity	**4** High toxicity or pharmacological activity	**5** High/ Very high toxicity or pharmacological activity
OEL / [µg/m^3]	≥ 1000	100 – <1000	10 - <100	1 - <10	<1
Therapeutic dose (about)* / [mg]	≥ 200	20 - 200	2 - 20	0.2 - 2	<0.2
Repeat-dose toxicity	Low	Moderate	Severe systemic effects	Severe systemic effects	Very severe
Reproductive Hazard	No	No	No or only at high doses	Reproductive effects	Severe reproductive effects
Mutagenicity	No	No	No	Mutagenic	Highly mutagenic
Carcinogenicity	No	No	No or only at high doses (threshold)	Carcinogenic	Potent carcinogen
Sensitisation	Not sensitising	Not sensitising	Sensitizer	Sensitizer	Highly sensitising

* Attention: depending on the mode of action and adverse effects, a higher or lower classification might be adequate

Exposure Limits for chemicals and APIs
- Typical banding concept for reference see also PSCI home page

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Bands	Pharm./Toxic Effects	Exposure Limits	API Example
Band 1	very low	> 1000 µg/m^3	Ibuprofen Paracetamol
Band 2	low	100 – 1000 µg/m^3	
Band 3	moderate	10 – 100 µg/m^3	
Band 4	moderate	1 – 10 µg/m^3	L-Adrenaline
Band 5	High/ very high	< 1 µg/m^3	Genotoxic, cytotoxics APIs…,

Compounds with limited/no data, e.g. intermediates:

- Default value is typically G 3 **unless there is an indication for high toxicity or pharmacological activity.**
- Therefore before using default G 3 consider at least in addition:
  - pharmacological activity for intermediates (compared to final API)
  - “in silico” evaluation (Computer based expert systems taking into account SAR / QSAR–structure activity relationships –qualitative / quantitative)
  - mutagenicity test (Ames test)
- -> if positive: use at least G 4 (<10 µg/m³)

Make sure that any additional information or knowledge about the substance in regard to pharmacological or toxicological effects is timely taken into account and lower limits are set timely if needed

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On Line Control Banding Information and Tools

- COSHH (Control of Substances Hazardous to Health) Essentials (UK HSE, 2006)
  http://www.coshh-essentials.org.uk/
- ILO (International Labour Organization) International Chemical Control Kit (ILO, 2006)
  http://www.ilo.org/public/english/protection/safework/ctrl_banding/index.htm
- AIHA Control Banding Working Group
  http://www.aiha.org/content/insideaiha/volunteer+groups/controlbanding.htm
- NIOSH Control Banding
  http://www.cdc.gov/niosh/topics/ctrlbanding/
- ISPE Volume 7 (2010) “Risk Based Manufacture of Pharmaceutical Products”
- PSCI website – type in “IH, Banding, or Containment” on the resource link

Managing Potent and Sensitizing Compounds Exposure Control Banding

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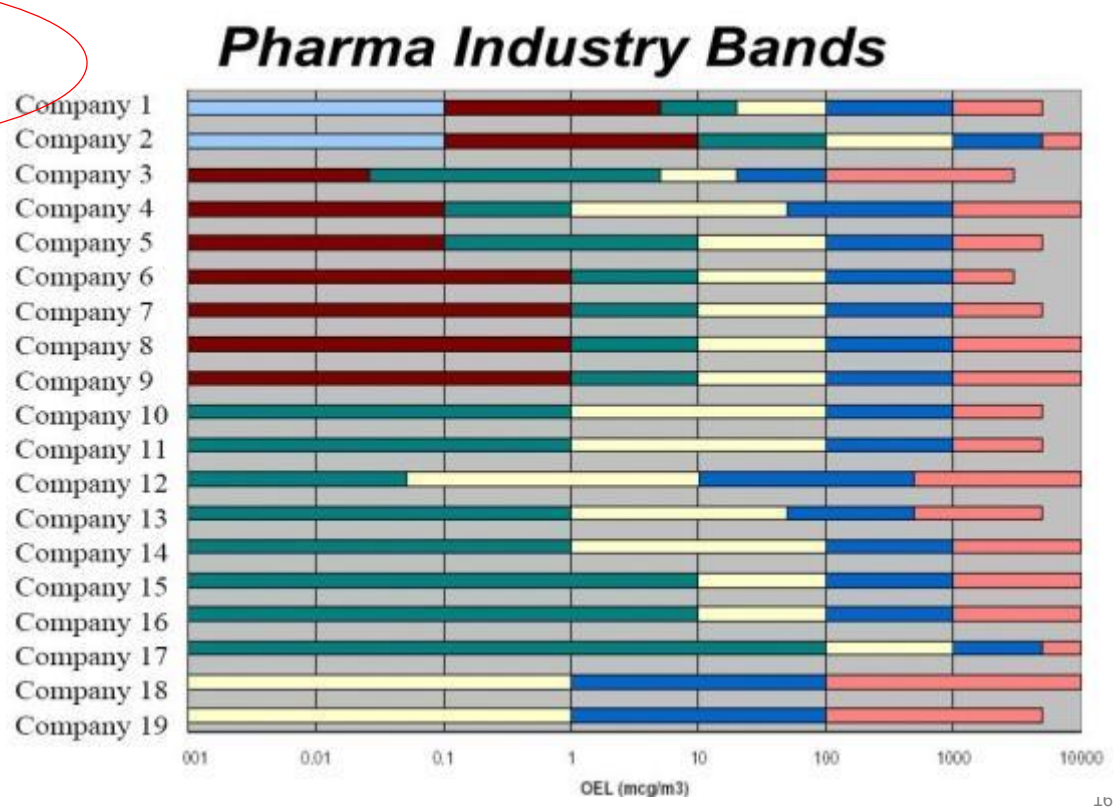
- Example of exposure control banding:
  - OEB 1 (>1000 ug/m3)
  - OEB 2 (100-1000 ug/m3)
  - OEB 3 (10-100 ug/m3)
  - **OEB 4 (1-10 ug/m3)**
  - **OEB 5 (<1 ug/m3)**

Yes – variation does exist



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Variation in Design Criteria in Pharma

Criteria / # of companies	OEL	½ OEL	¼ OEL	0.1 OEL	Dispersion potential
	5	3	2	1	1

Criteria / # of companies	OEB upper end	Arithmetic mean	Geometric mean	OEB Lower end	Anywhere in OEB
	2	2	1	7	1

Source: CONTROL BANDING IN THE PHARMACEUTICAL INDUSTRY, BRUCE D. NAUMANN, Ph.D., DABT Merck & Co., Inc.

Managing Potent and Sensitizing Compounds
Factors Influencing Exposure

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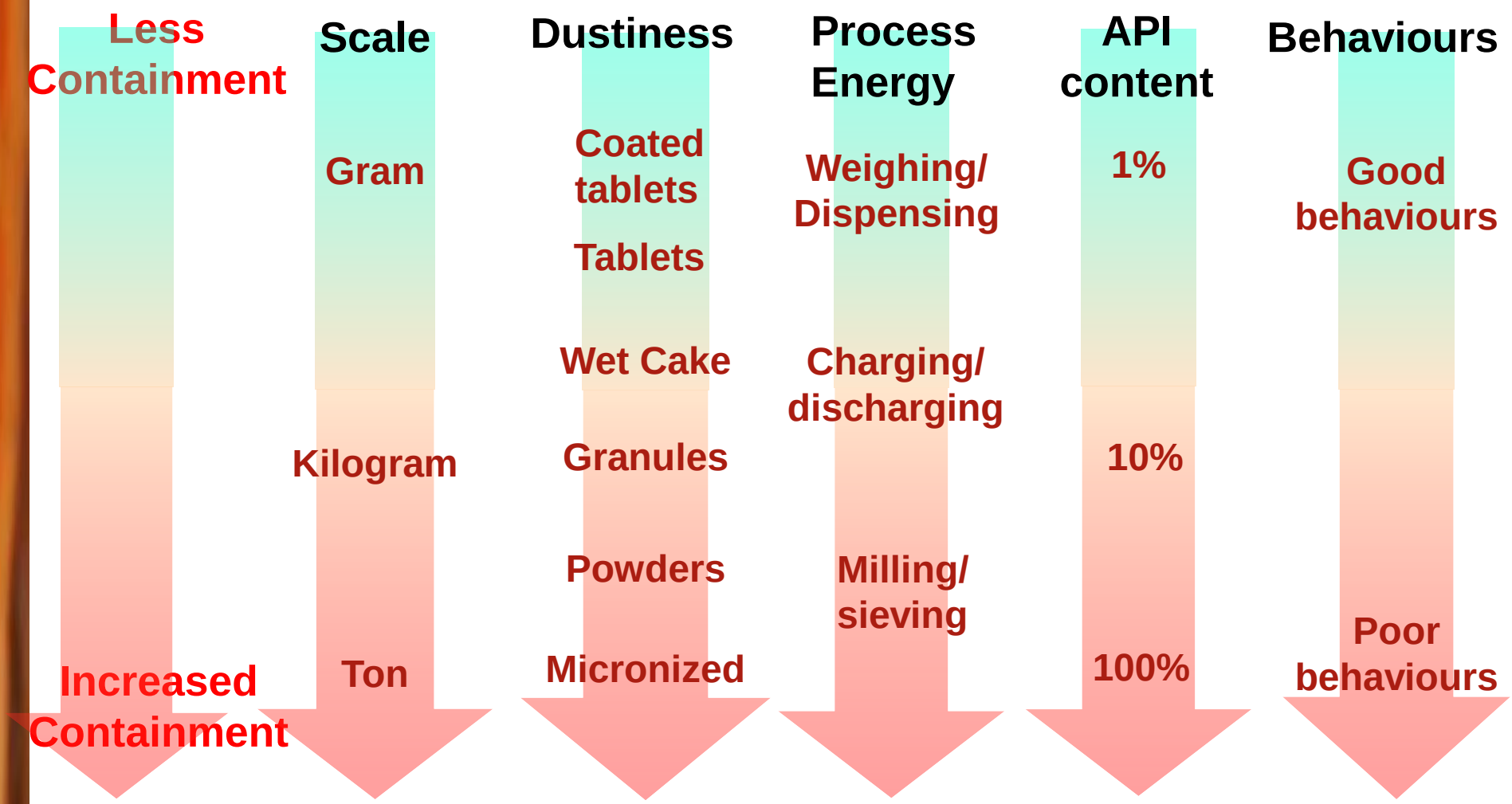

WHY? Because APIs are not Nuisance Dust

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INDUSTRIAL HYGIENE / WORKER EXPOSURE RED FLAGS

- Look at MSDS between companies – do they agree on OEL and classifications? Differences >20X are of concern.
- We know APIs do not have regulatory exposure limits – PSCI companies DO NOT treat APIs as NUSIANCE DUST. Agree on the required exposure limit and control banding. If none exists – Red Flag.
- API /DP companies for Pharma MUST have internal processes for setting final API and intermediate control banding and implementing those practices – especially in development and for intermediates.
- Industrial hygiene workplace monitoring needs to CONFIRM their strategy is working, especially when exposure limits are low and PPE in use is very minimal. No data is a RED FLAG.
- IH Capability in some parts of the world is a challenge. We typically encourage our partners to hire consultants.

Be really careful of UNITS of MEASURE in your reports

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- mg/m3
- mcg/m3
- μg/m3
- ng/m3

API Manufacturer Limit : 0.1 mg/m3

PSCI Member Limit: 0.1 mcg/m3

Banding Exercise – What mass can your eyes no longer see?

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Average worker breathes about 17 M3 in a workday

Photo from web reference “IP Powertools – Understanding the OSHA Silica PEL”

Band Range	Mass Inhaled over 8hr day
10,000 μg/m3	4% sugar pack
1,00 μg/m3	0.4% sugar pack
100 μg/m3	0.04% sugar pack
10 μg/m3	0.004% sugar pack
1 μg/m3	0.0004% sugar pack
0.1 μg/m3	0.00004% sugar pack

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High Potential Exposure Concerns

- Reactor charge/material transfer
- Drying/discharging
- Granulation/mixing
- Milling/de-lumping
- Dispensing/weighing/repackaging
- Maintenance activities
- Cleaning / Heel Removal
- Process upsets/spills

When doing a PSCI audit for a member company – get their banding categories and tools.

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SAMPLE: Control Banding Implementation

Band	PPE	Facility Design	Engineering Controls	Equipment Cleaning and Maintenance
Level 1	•Gloves •uniforms	•General Ventilation •Shared HVAC •General Filtered Exhaust •Recirculate Permitted •Common Gowning & De-gowning	•Passive Ventilation/Dilution •Open Mat'l Conveying and/or Mat'l Transfers •Open Process Equipment	•Open Process Equipment Transport to Cleaning Area •Manual Cleaning
Level 2	•Respirators •Tyvek coveralls	•Pressure Differential To Selected Adjacencies •Open Process Area •Closed Building •Process segregation with doors •Gowning/De-gowning Room	•Standard Equipment Design (Normally Closed) •Local Exhaust Ventilation •Mat'l Conveying Essentially Open with Hardware Remediation •Pressure Convey •Laminar flow	•Open Process Equipment Cleaned In-Situ
Level 3	•Maximum PF respirator	•HEPA Filtration •Room Finishes & Surface MOC's and Utilities Are Designed for Ease of Cleaning •Process segregation with airlocks •Decon Shower	•Standard Equipment Design with Separate Mechanical Space •Glovebox or Glovebag •Closed Material Conveying •Minimize Make/Break Connections •Split butterfly valves (SBV)	•Provide CIP with Rinse Water Capture •Closed equipment maintenance capability
Level 4	•Seek expert assistance •Respirators not adequate for "open" processing •Redundant PPE with engineering controls	•Seek expert assistance •Dedicated HVAC •HEPA Filtration w/Safe Change •No Exhaust Return •Closed Process Area •Closed Building •Separate Gowning & De-gowning •Automation	•Seek expert assistance •Process Equipment iDesigned for Total Containment •Closed Mat'l Transfers with Barrier Add-ons •Vacuum Convey •Minimize Mat'l Conveying Steps •Minimize Material Transfer Connections •Isolator with continuous liner •Enhanced/purgable SBV	•Seek expert assistance •Minimize Waste via Process and Formula Optimization •Protective barriers for laptops, paperwork, documents

IH Monitoring Basics

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- Personal Breathing Zone Samples vs Area Samples
- Total Dust vs API dusts at Drug Product Sites
- Training of sampler and report writer?
- # of samples, # of days sampled
- Verify the Math on protection factors
- Short tasks data versus full shift data
- No data – use company's commissioning data on their web site
- Focus is ONLY on API and not on solvent/gases – BIG issue for wetcakes.

Is it well managed?

Does it seem appropriate?

Most important, is to qualify the scope of the data you did see.

Occupational Hygiene Sampling

Particulate

- indirect
  - filters
  - impactors
  - impingers
  - cyclones
- direct
  - aerosol photometry
  - condensation nuclei
  - beta attenuation
  - electric charge

Gases & Vapors

- indirect
  - adsorption
    - tubes (active)
    - badges (passive)
  - absorption
    - impingers
- direct
  - colorimetric
    - detector tubes
  - gas chromatography
  - spectrophotometry

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Flowrate Calibrators

Electronic - Gilibrator

Soapless – the BIOS Defender

Indirect Gas & Vapor Sampling

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- Syringe
- Bag
  - Can fill with a pump – integrated
  - Need chemically inert materials
  - Tedlar, Teflon, Saran, Halar, Mylar
- Vacuum container
  - Summa canister
- Cryogenic
  - Condense the contaminant

Summa Canisters

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Minican

- Size of canisters: 400 ml – 6 L
- Sampling time: 5 min grab sample to 24 hrs
- EPA TO-15 Method: 62 organic compounds
- Non-target compound library search: tentatively identified compounds (TIC)

Indirect Gas & Vapor Sampling

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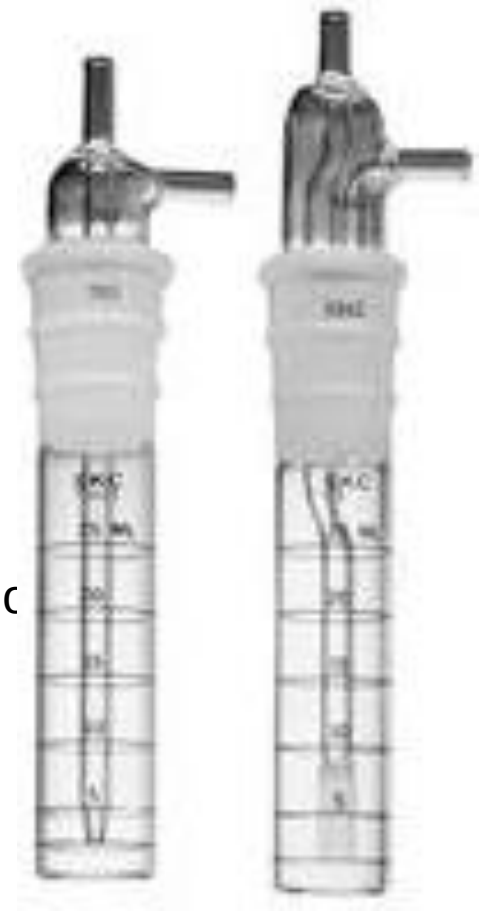
- ABsorption (dissolution in liquid)
  - The *key* is solubility
  - Can get up to 80—90% collection efficiency
    - Put in series to get even higher efficiency
  - Only as a last resort (when nothing else works)
- Typical liquids
  - Water, toluene, ethanol, isopropyl alcohol
  - Can cool liquid for better removal, but also get mo condensed water vapor
- Types of samplers
  - Midget impinger/Bubbler – fritted disk



Indirect Gas & Vapor Sampling

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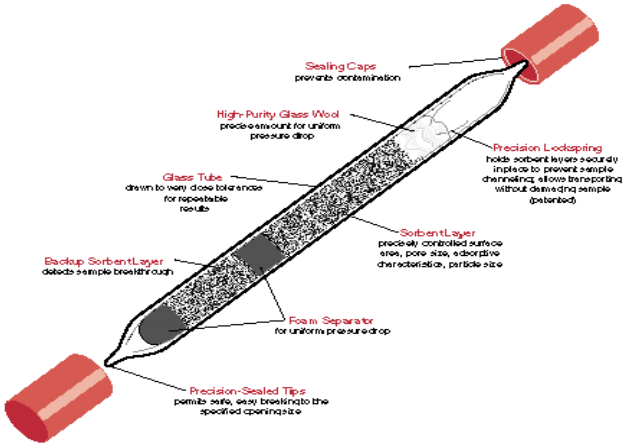
- ADsorption
  - Gases and vapors adhere to surfaces of solids via weak, reversible intermolecular forces – van der Waals



- l
  - Chemically treated filters, trap reactive gases and vapors

Passive Diffusion Samplers

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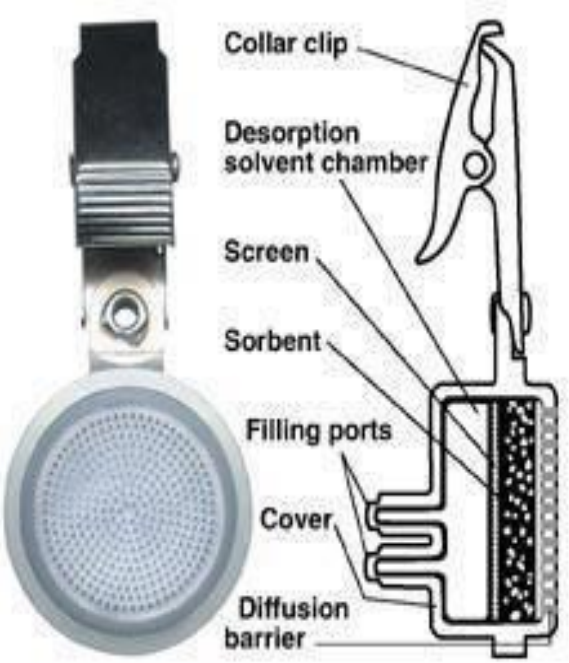

3M 3520 Organic Vapor Monitor

3M 3500 Organic Vapor Monit

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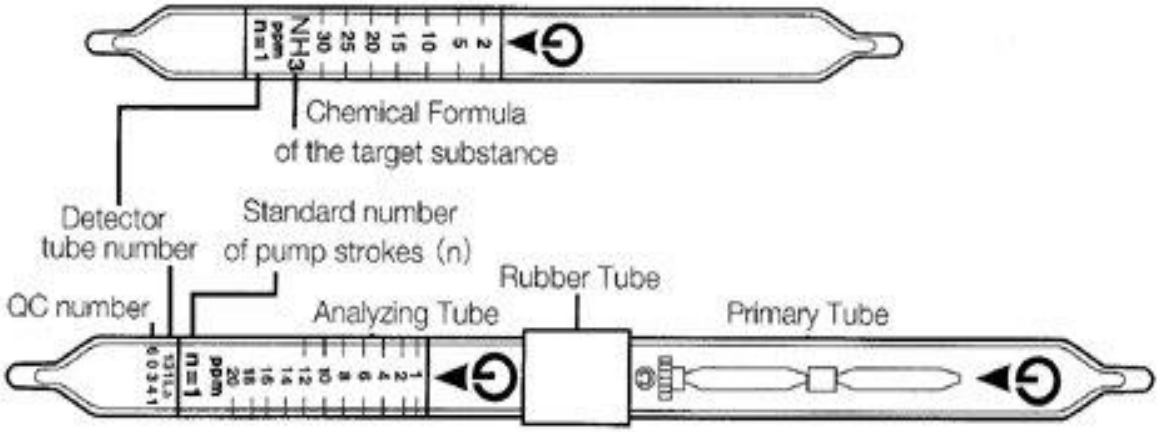
Detector Tubes

- Principle of Operation
  - a colorimetric chemical reaction takes place between a reagent impregnated onto a granular carrier (silica gel, alumina, clay, etc.) in a glass tube and a gas or vapor in the air drawn through the granular bed, resulting
  - color change
  - length of stain



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Detector Tubes - cont'd

- Types of Detector tube systems
  - Sensidyne/Gastec — Piston
  - Matheson/Kitagawa — Piston
  - MSA — Bellows
  - Draeger — Bellows
- "Cardinal Rule" - *don't mix tubes of one type with pump of another*

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Combination Detectors

- PID - Photo-ionization Detector
  - spectrophotometry & electrochemical
  - organic compounds ionized in presence of UV light; amount of ions determines current
  - $RH + hv \text{ ----- } RH^+ + e^-$
  - different UV lamps with different energy (in eV) (9.8 eV, 10.6 eV, and. 11.7 eV) will detect different chemicals

ppbRAE 3000

1 ppb to 10,000 ppm

UltraRAE 3000

0.05 to 10,000 ppm in VOC mode and 50 ppb to 200 ppm in benzene-specific mode

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Sampling for Particulates

- Indirect
  - collection, followed by later analysis
  - delayed results
- Direct
  - collection and analysis combined
  - real-time reading

Classification of Particle Sizes

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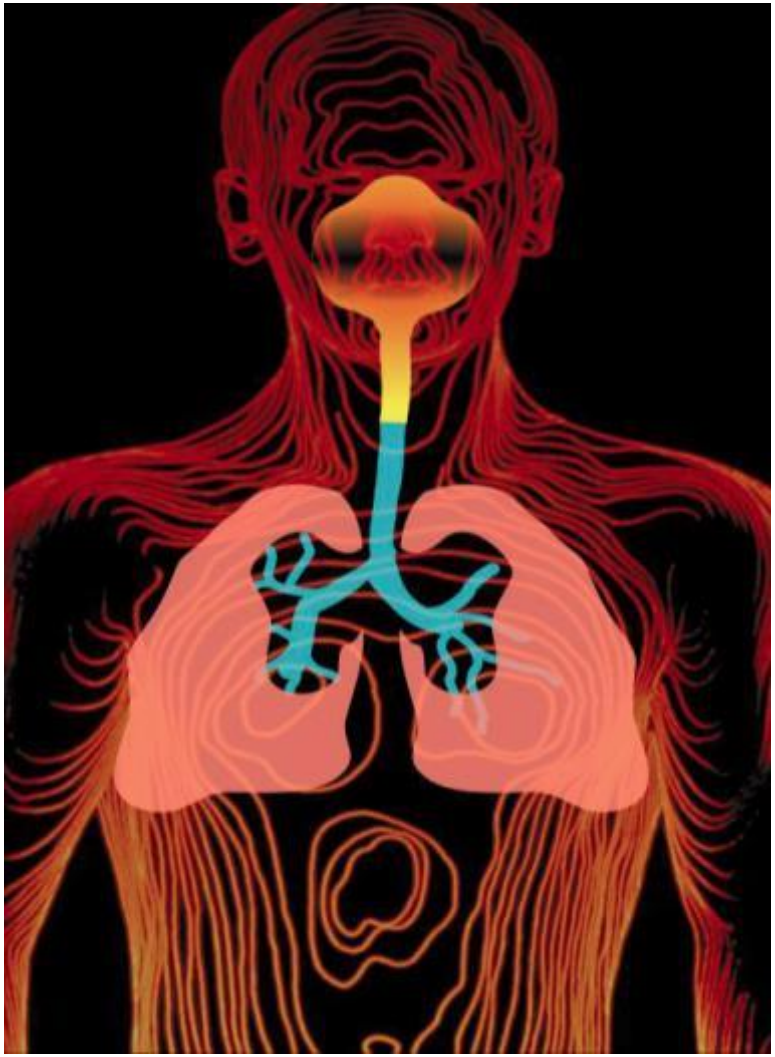
- **Inhalable Particulate Mass (IPM)**
  - 50% collection of 100 μm particles
  - mass fraction entering nose and mouth
- **Thoracic Particulate Mass (TPM)**
  - 50% collection of 10 μm particles
  - subfraction of inhalable penetrating past larynx
- **Respirable Particulate Mass (RPM)**
  - 50% collection of 4 μm particles
  - subfraction of inhalable penetrating to the alveolar



*(See ACGIH Appendix C: Particle Size-Selective TLVs)

Classification of Particle Sizes

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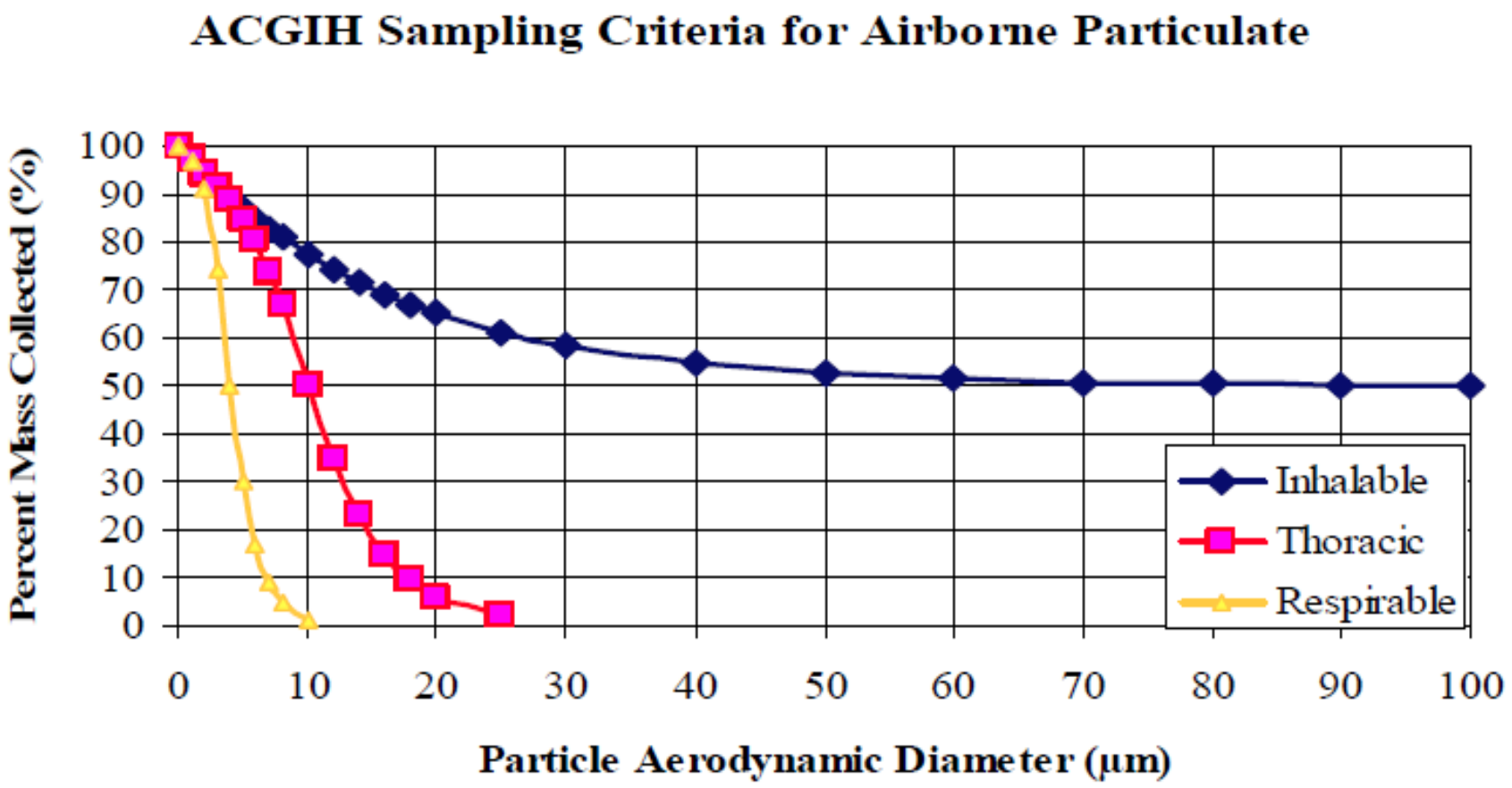

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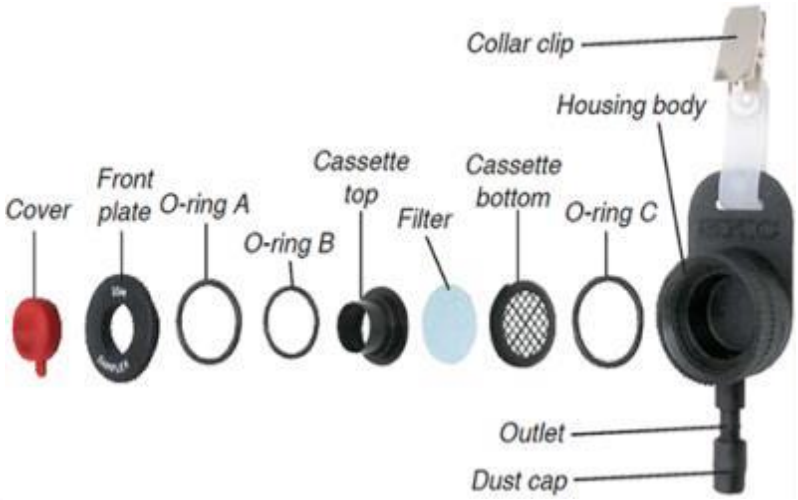
Sampling for Particulates

- Inhalable



- Thoracic

- Respirable

However, What We Do Now

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- Total dust
  - A misnomer
  - Only includes particulates that can be collected by a 37-mm filter cassette.
  - Could underestimate actual airborne particulate concentrations

Sampling for Thoracic Fraction

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Thoracic cyclone (PPIs)

Parallel Particle Impactors

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Respirable Dust Sampling

Aluminum
– 2.5 l/m

Dorr-Oliver
– 1.7 l/m

SKC GS-1
– 2.0 l/m

Real-time Sampling
- Aerosol spectrometer

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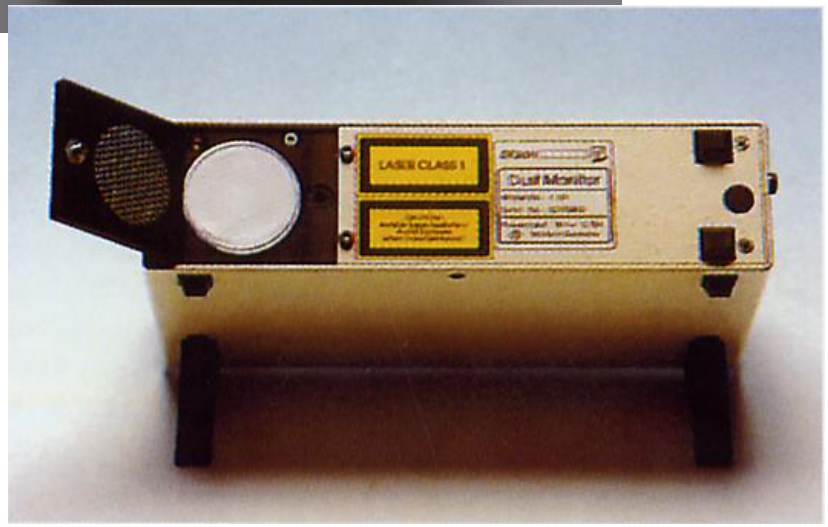

Photos@Grimm Aerosol Technik GmbH&Co KG
*www.**grimm**-aerosol.de*

Aerosol-Spectrometer

- single particle counts and size classification

- additional filter (Teflon)
- collect particles for calibration

Real-time Sampling Example
- Emptying of dryer (working area with a low air exchange)

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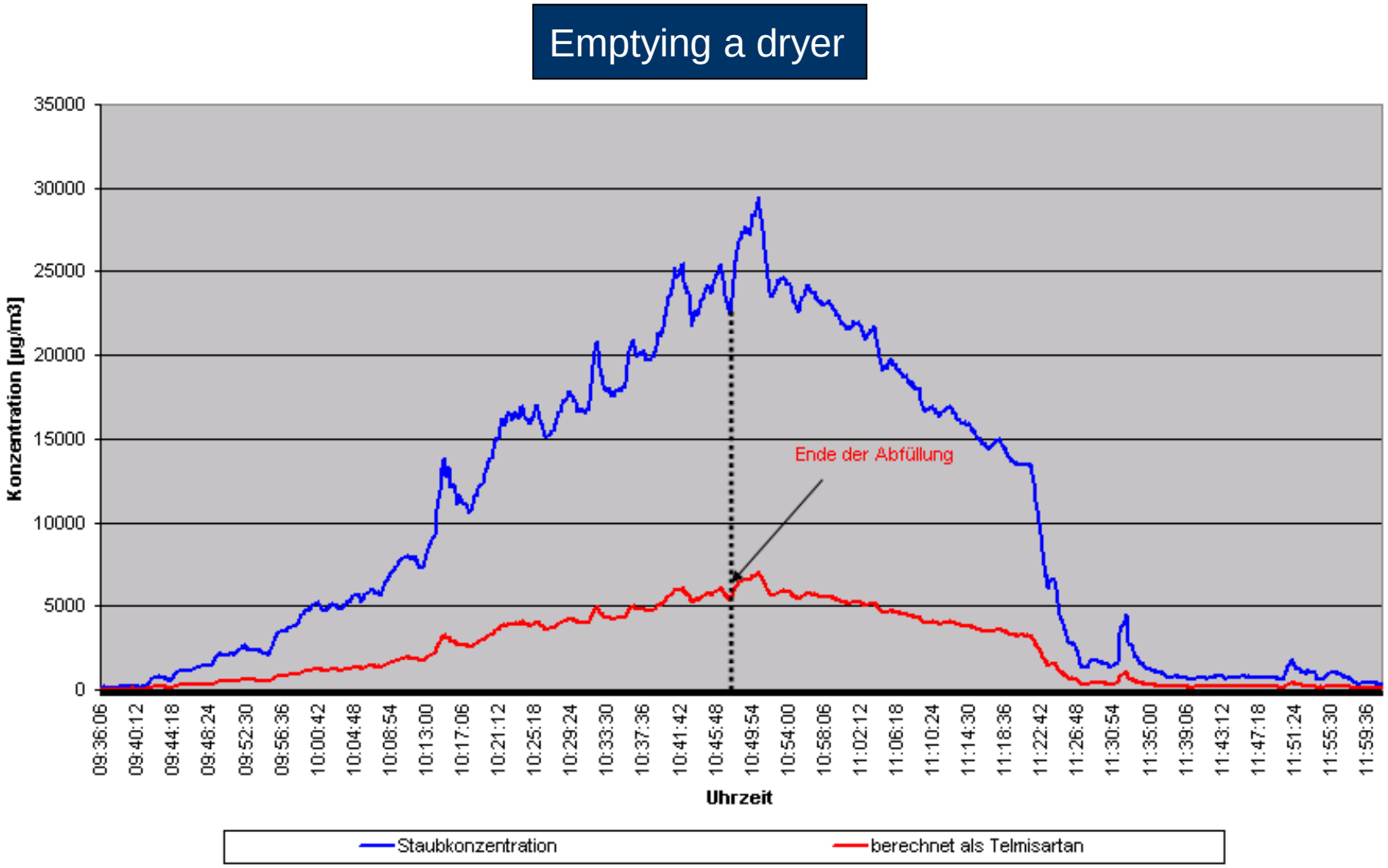

Grapik BI@ M. Lumb

Real-Time Sampling Example
Emptying of dryer (working area with optimized air exchange)

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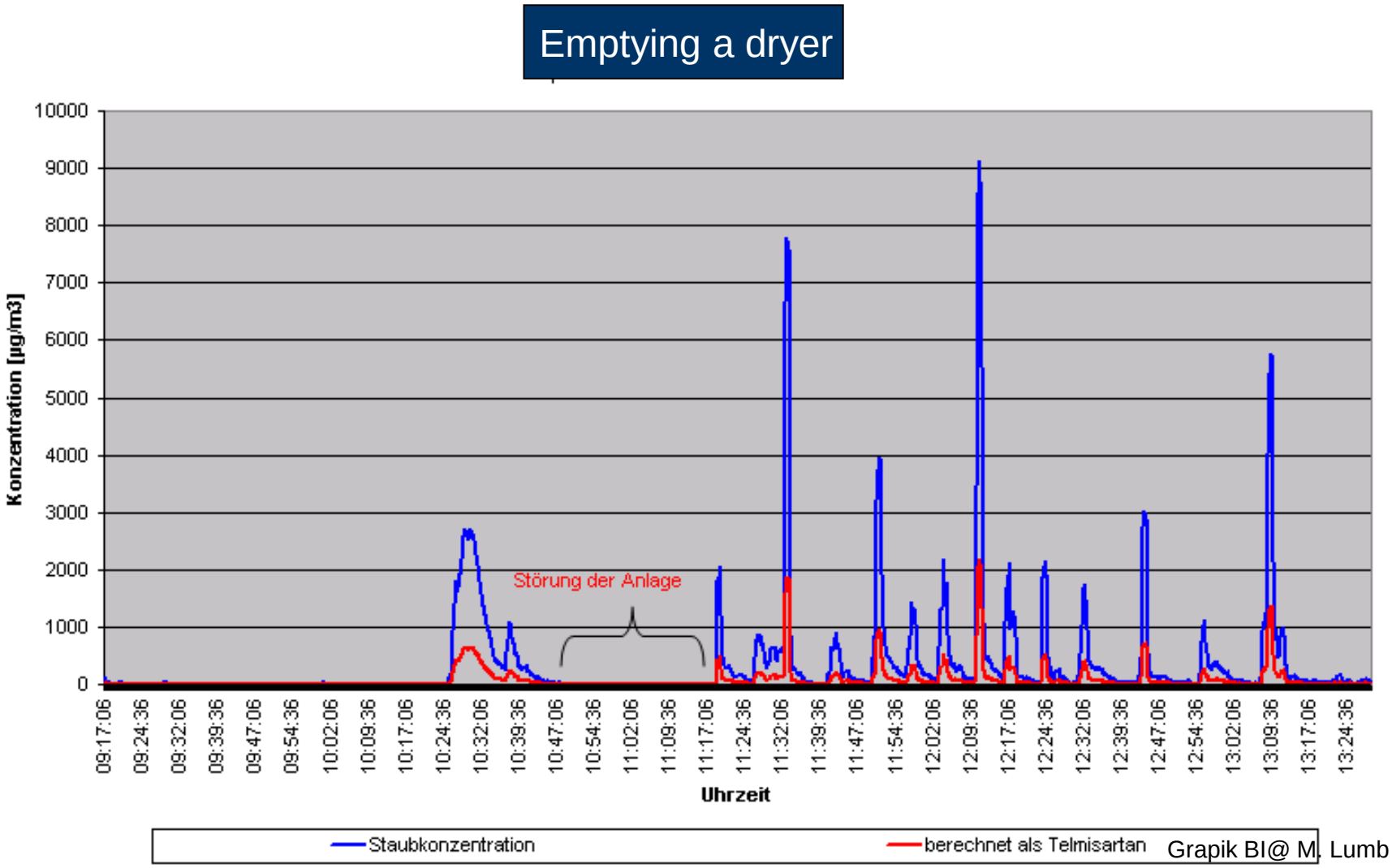

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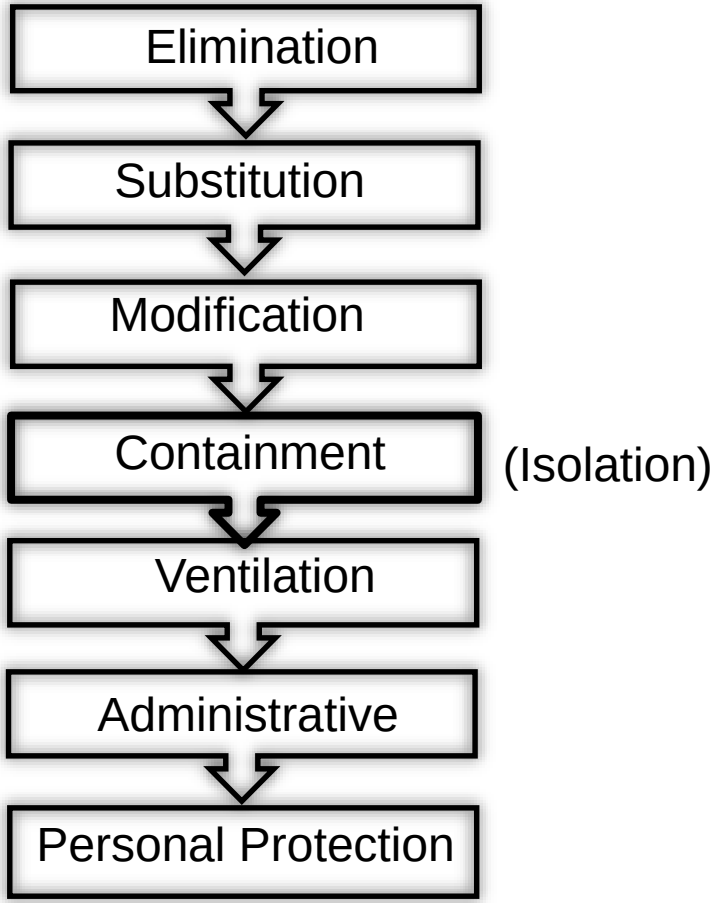
Hierarchy of Exposure Control



PSCI Questionnaire – It now makes you identify the controls you observed.

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SAMPLE: Engineering Control Capabilities from PSCI website

Engineering Control	Capability (μg/m3)*
Walk-in fume hood	< 5000
Laminar flow booth (horiz)	< 500
Laminar flow w/ continuous liner	< 100
Downflow booth	< 100
Downflow booth w/ screen	< 25
Split butterfly valve (SBV)	< 10
Single chamber glovebox (GB)	< 1
SBV w/ purge capability	< 0.5
Glovebox isolator around continuous liner	< 0.1
GB w/ RTP (rapid transfer port)	< 0.05
Multi-chamber GB w/ RTP/ESBV	< 0.01

** operator exposure during unit operation*

Transfer Mechanisms

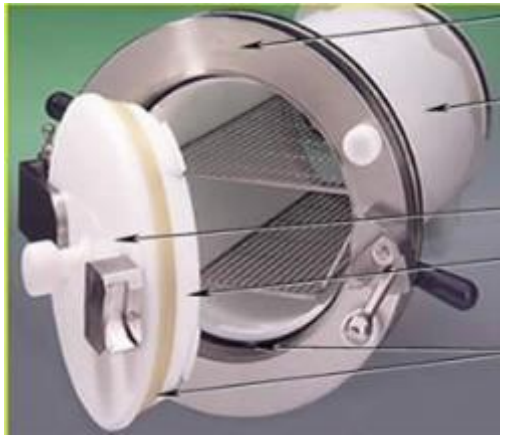
Cut & tape bag

Cone valve

Split Butterfly Valve

Containment flap

Continuous liner



Alpha/beta flange

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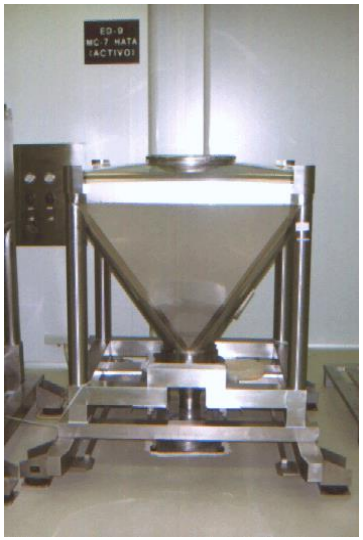
Material Transfers

Active- open

Active- closed



IBC

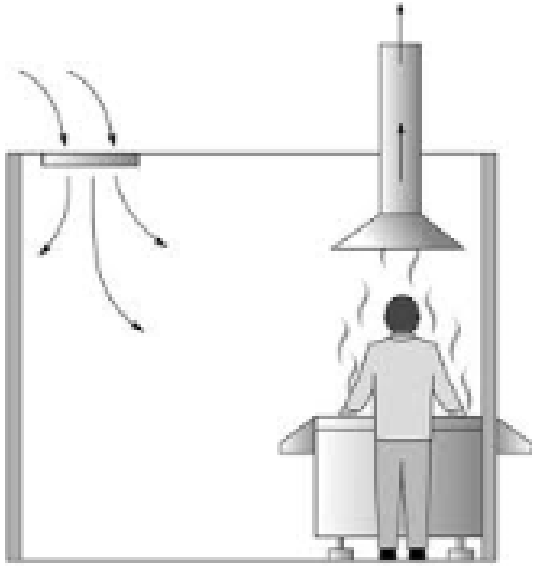
FIBC

Isolators

Flexible- glovebag

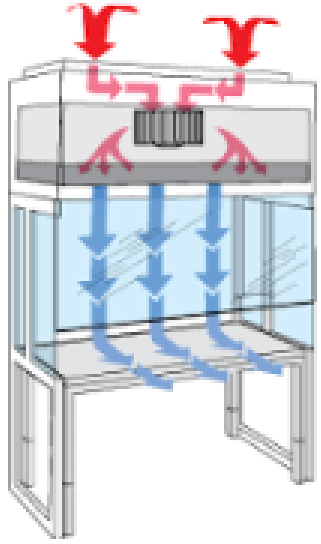
Rigid- glovebox

Local Exhaust – GOOD vs BAD



Dusts aren't hot vapors!

Laboratory Controls



No worker protection

2nd question – based on controls in place, are people protected?

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- If what you saw didn't use the Hierarchy of Engineering Controls, but was more heavily reliant on PPE or work procedures….ARE THEY ADEQUATELY PROTECTIVE?

- Are PPE and Containment requirements documented in the manufacturing ticket or batch record?
- Are personnel wearing the correct/required PPE?
- Does the site's Respirator Program appear to be adequately managed?
- If the site is handling highly potent API powders or drug products, have they implemented containment measures to avoid "open handling"? Is there an actual engineering improvement plan?
- If the site is handling potent API powders or drug products, have they implemented a comprehensive Industrial Hygiene Monitoring Program (i.e. more than just cursory area samples or particle counting)?

3rd Question – do we have adequate Respiratory Protection?

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The values of the APF in EU and other countries [edit]

Studies of respirator's performance was carried out not very often, and almost all of these studies were conducted in USA (and UK). It is possible that the lack of information about the RPD efficiency in the workplaces, was the reason behind developing these assigned PF in several European countries, whose values differ significantly from the evidence-based values of APFs in the US and UK.

The Assigned Protection Factors for some main RPD types, developed in several EU countries[2] [hide]

RPD type	APF in several EU countries			
	Finland	Germany	Italy	Sweden
FFP2 filtering facepices	10	10	10	10
Elastomeric half masks with P2 filters	10	10	10	10
FFP3 filtering facepices	20	30	30	20
Elastomeric half masks with P3 filters	-	30	30	-
Negative pressure air-purifying respirators with full face mask and P2 filters	15	15	15	15
Negative pressure air-purifying respirators with full face mask and P3 filters	500	400	400	500
Powered Air-Purifying Respirators (PAPRs) with loose-fitting hood or helmet, and THP3 filters	200	100	200	200
PAPRs with full face mask, and TMP3 filters	1000	500	400	1000
SARs with full facepiece and negative pressure demand air supply	500	1000	400	500
Supplied Air Respirators (SARs) with full facepiece and positive pressure demand air supply	1000	1000	400	1000
SCBAs with full facepiece and positive pressure demand air supply	-	≥ 1000	1000	-

Source - Wikipedia

Am I a respirator?

PPE Use/Re-use?

Training?

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PPE Program

Storage / Clean

Solvents + Dusts?

Right Gloves?

Shoes?

Fit-testing

CPC Coveralls

Do the controls protect nearby workers and products?

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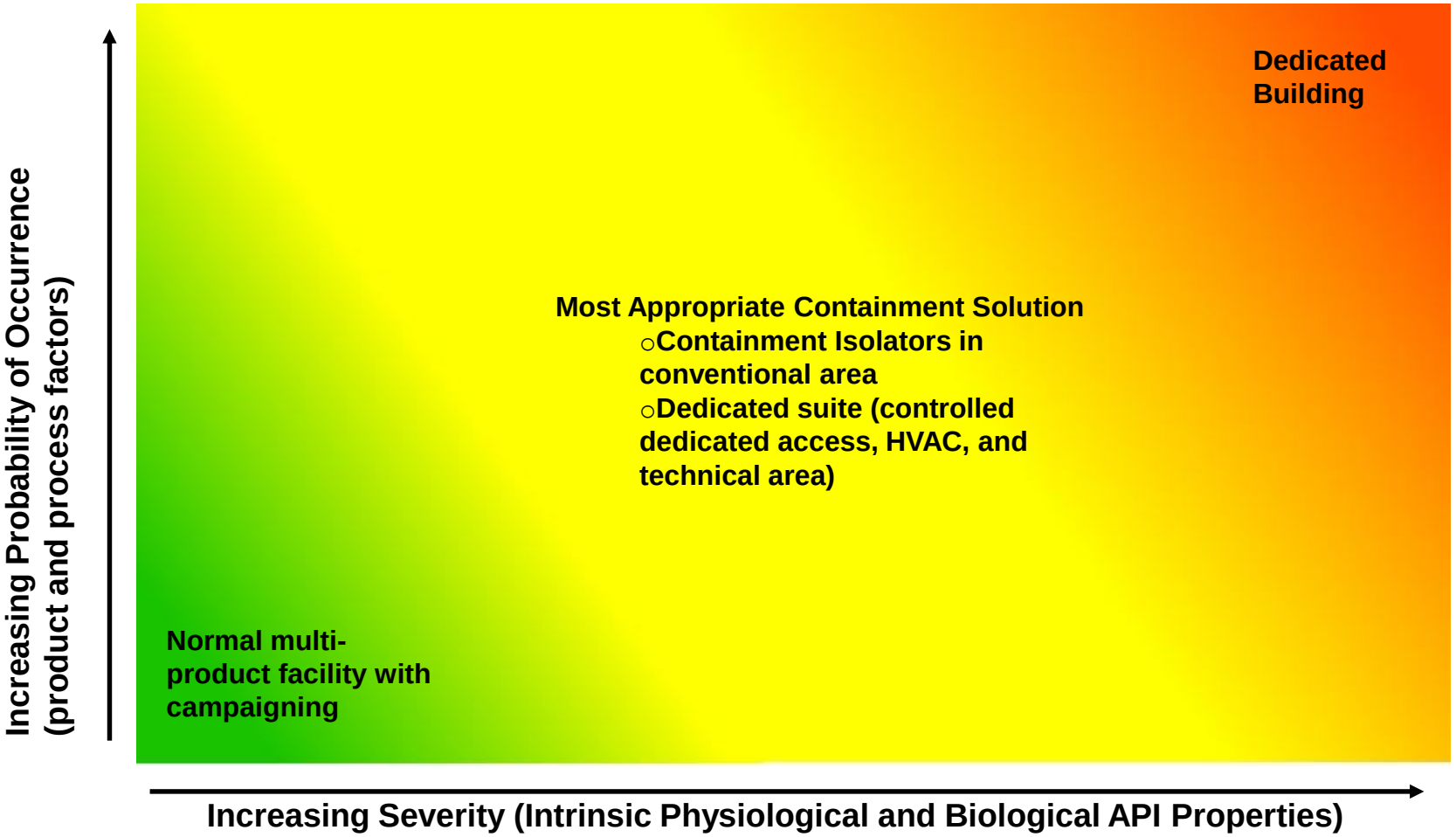

Case Study….potent steroid

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- API manufacturer of Generic material did not set their own limits but found a limit on the web from another company and used it.

- PSCI member limit was 500X times lower. Data exchange revealed similar thought process on setting limits but different toxicology data was being used. PSCI member process allows for updating when new data available. End Result – companies aligned within 5X on OEL accounting for different safety margin practices.

- Company had no workplace monitoring data to verify they were meeting their previous limit or the new limit. They were in a dedicated suite. API company asked to immediately upgrade from dust masks and install better controls. API manufacturer collected IH data to verify that their final PPE/engineering was protective. Engineering controls were implemented in a very focused way reducing costs. Company applying approach to all their chemical manufacturing.

- <u>DATA IS YOUR FRIEND</u>. In absence – default to more protective PPE & SOPs

Do you see why this is the first question?

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- API Supplier – Generic
- API Supplier – Proprietary Chemistry as Contract Manufacturer
- Drug Product Pharma Company

Differing Data Sets & Handling Expectations

1st question – do we they agree on classification and occupational exposure limit?

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Personal Protective Equipment (PPE)

- PPE are a barrier, to protect from chemical or physical exposure

Eye / Face Protection	**Head Protection**	**Foot Protection**	**Hands Protection**
Body Protection	**Hearing Protection**	**Respiratory Protection**	**Anything else?**

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Focus on Respiratory Protection:

A lack of oxygen is the greatest danger for human life:

Humans are able to survive
- **7 days** without food,
- **3 days** without liquid,

but: only **3 minutes** without oxygen.

Also consider gloves, gowning…

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Most important factors to consider when choosing filtering respiratory protection devices.

- The hazards in your environment must be known
- work requirements and the external conditions.
- Check the nominal protection factor NPF
  - protection level required by your respirator
  - protection level of the necessary filter

Rem.: NPF indicates the mathematically calculated maximum protection performance.

@Dräger 2015: This slide is based on the publication “ the Filter Selection Guide” from Dräger

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Checklist prior to use filtering respiratory protection:

- Enough oxygen in the ambient air?
- What contaminants are in the ambient air?
- What are the concentrations of the contaminants?
- Are the contaminants in gas, particle, or vapour form? Or are they a mixture?
- Do the contaminants have adequate warning properties (e.g. smell or taste?)
- What are the applicable Occupational Exposure Limits (OEL)?
- In addition to respiratory protection, is other
- Other personal protection equipment (e.g. eye or ear protection) required?

@Dräger 2015: This slide is based on the publication “ the Filter Selection Guide” from Dräger

IH Work Practices
- selection of filter and makes types

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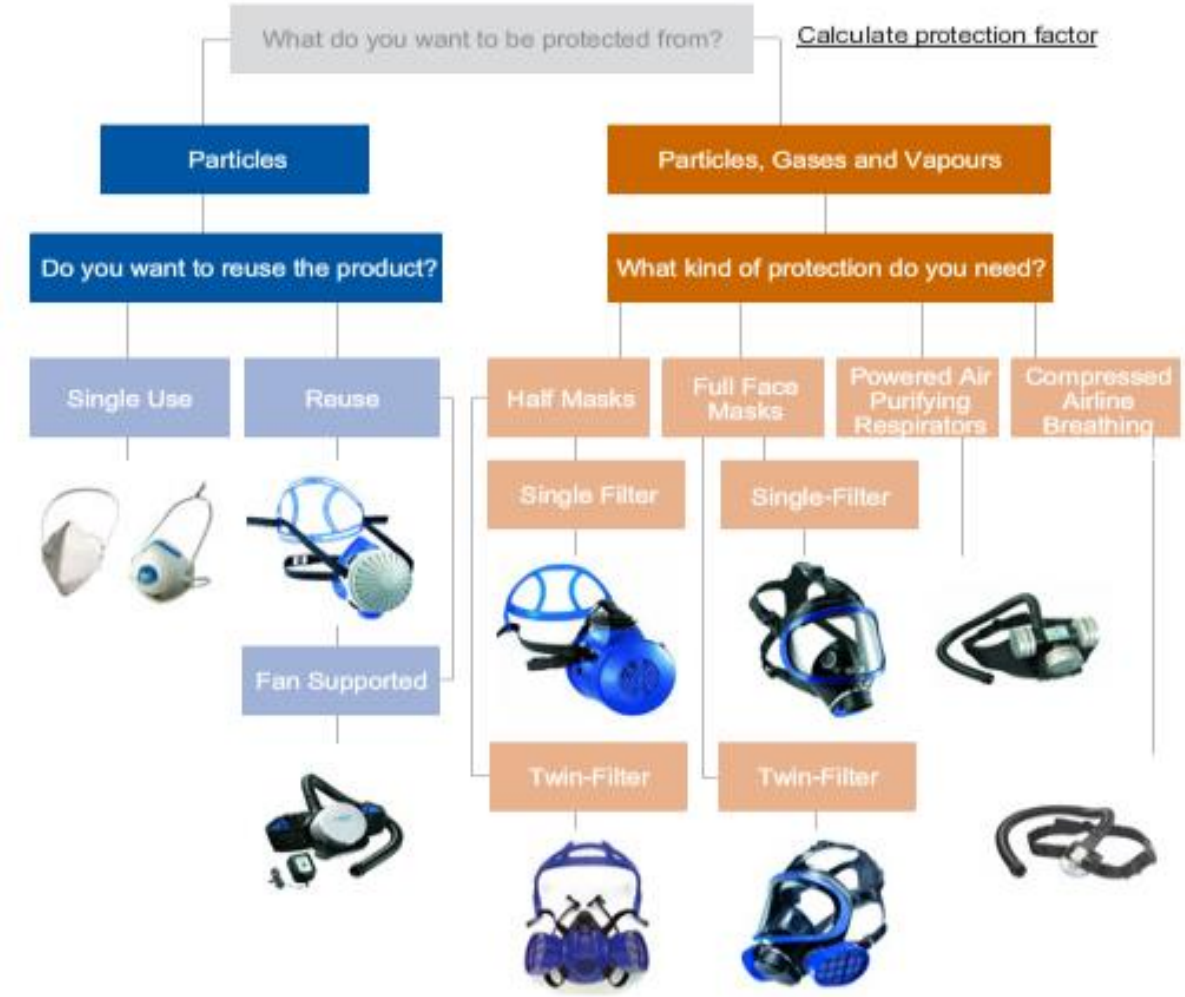

Slide by U. Bertram@Dräger 2015

IH Work Practices
- Protection Factor

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Attention the protection factor depends from company evaluation of the producer of the mask (nominal protection factor) and may be tighter by national legislation

Keep in mind :
performance indicated by the nominal protection factor can only be achieved when :

- respiratory protective device is worn correctly
- properly maintained
- user does have a cleanly shaven face
- the correct size of the mask is assured (each employee one mask based on fit test)

@Dräger 2015: This slide is based on the publication “ the Filter Selection Guide” from Dräger

IH Work Practices
- Protection Factor

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RPF (Respirator Protection factor -as defined on the OSHA homepage) :
"… **workplace level of respiratory protection that a respirator or class of respirators is expected to provide to employees when the employer implements a continuing, effective respiratory protection program as specified by this section…."**

https://www.osha.gov/pls/oshaweb/

In **US Fit Testing** is a key requirement.
Qualitative and quantitative fit testing might be a legal requirement to set protection factors adequately.

IH Work Practices
- Protection Factor by type of mask and country

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Protection Factors of masks:

According to EN

Type of Respirator	Class	Nominal PF	APF Fin	APF D	APF It	APF Sw	APF UK
Filtering Half Mask EN 149	FF P1	4	4	4	4	4	4
	FF P2	12	10	10	10	10	10
	FF P3	50	20	30	30	20	20
Half Mask EN 140	P1	4	4	4	4	4	4
	P2	12	10	10	10	10	10
	P3	48		30	30		20
	GasX	50	20	30	30	20	10
Full Face Mask EN 136	P1	5	4	4	4	4	4
	P2	16	15	15	15	15	10
	P3	1000	500	400	400	500	40
	GasX	2000	500	400	400	500	20

Note: Refer to EN 529 for Details

IH Work Practices
- Protection Factors enforced in US

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According to OSHA

Assigned Protection Factor (APF) of masks:

Type of Respirator[1] [2]	Half Mask	Full Facepiece	Helmet / Hood
Air Purifying Respirator	10[3]	50**	-
Powered Air Purifying Respirator (PAPR)	50	1,000	25 / 1,000*
Supplied Air Respirator (SAR) -Demand Mode -Continuous Flow Mode -Pressure Demand	10 50 50	50 1,000 1,000	- 25 / 1,000* -
Self Contained Breathing Apparatus (SCBA) -Demand Mode -Pressure Demand	10 -	50 10,000	50 10,000

[1] Employers may select respirators with higher protection.
[2] an effective respiratory program must be implemented.
[3] includes filtering facepiece respirators.
* Manufacturer must provide test data to demonstrate an APF of 1,000 is achieved.
** Per (Canada) CSA Z94.4-02, the APF for a full face mask is 100.

IH Work Practices
- Gloves and IH

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	复合膜			丁腈			无衬里氯丁橡胶			有衬里聚乙烯醇			聚氯乙烯（乙烯）			天然乳胶			氯丁橡胶 / 天然乳胶混合物			无衬里丁基			无衬里氟橡胶/丁基		
	BARRIER™			SOL-VEX®			29-系列			PVA™			SNORKEL®			*CANNERS 和 HANDLERS™			*CHEMI-PRO®			CHEMTEK™ BUTYL			CHEMTEK™ VITON/BUTYL		
化学品	降解等级	渗透时间	渗透率	降解等级	渗透时间	渗透率	降解等级	渗透时间	渗透率	降解等级	渗透时间	渗透率	降解等级	渗透时间	渗透率	降解等级	渗透时间	渗透率	降解等级	渗透时间	渗透率	降解等级	渗透时间	渗透率	降解等级	渗透时间	渗透率
140. Pyridine 吡啶	▲	>480	E	NR	-	-	NR	-	-	G	10	F	NR	-	-	F	10	F	P	10	F	▲	465	E	DD	40	-
141. Rubber Solvent 橡胶溶剂	-	-	-	E	>360	E	E	43	G	E	>360	E	NR	-	-	NR	-	-	NR	-	-	-	-	-	-	-	-
142. Silicon Etch 硅腐蚀剂	▲	>480	E	NR	-	-	E	>480	-	NR	-	-	F	150	-	NR	-	-	P	-	-	-	-	-	-	-	-
143. Skydrol® 500B-4	▲	>480	E	NR	-	-	NR	-	-	-	-	-	NR	-	-	NR	-	-	NR	-	-	E	>480	E	DD	>480	E
144. Sodium Hydroxide 氢氧化钠 50%	E	>480	-	E	>360	-	E	>480	-	NR	-	-	G	>480	-	E	>360	-	E	>360	-	E	>480	-	E	>480	-
145. Stoddard Solvent 斯陶大溶剂	▲	>480	E	E	>360	E	E	139	G	E	>360	E	F	57	G	NR	-	-	G	10	G	-	-	-	-	-	-
146. Styrene 苯乙烯	▲	>480	E	NR	-	-	NR	-	-	G	>360	E	NR	-	-	NR	-	-	NR	-	-	G	26	-	E	>480	-
147. Sulfur Dichloride 二氯化硫	-	-	-	P	>480	E	NR	-	-	-	-	-	-	-	-	NR	-	-	NR	-	-	-	-	-	-	-	-
148. Sulfuric Acid 硫酸 47%（蓄电池用酸）	-	-	-	E	>360	-	E	>360	-	NR	-	-	G	>360	-	E	>360	-	E	>360	-	-	-	-	-	-	-
149. Sulfuric Acid 硫酸, 95-98%（浓缩）	E	>480	E	NR	-	-	F	24	-	NR	-	-	G	26	-	NR	-	-	NR	-	-	E	>480	-	E	>480	-
150. Sulfuric Acid 硫酸 120%（发烟硫酸）	▲	>480	E	-	-	-	F	53	G	NR	-	-	▼	25	G	-	-	-	-	-	-	-	-	-	-	-	-
151. Tannic Acid 单宁酸, 65%	-	-	-	E	>360	-	E	>480	E	P	-	-	E	>360	-	E	>360	-	E	>360	-	-	-	-	-	-	-
152. Tetrahydrofuran 四氢呋喃 (THF)	▲	>480	E	NR	-	-	NR	-	-	P	115	F	NR	-	-	NR	-	-	NR	-	-	F	13	F	DD	10	F
153. Toluene (Toluol) 甲苯（甲基苯）	▲	>480	E	F	34	F	NR	-	-	G	>1440	E	NR	-	-	NR	-	-	NR	-	-	P	20	F	E	313	-
154. Toluene Diisocyanate (TDI) 甲苯二异氰酸酯 (TDI)	▲	>480	E	NR	-	-	NR	-	-	G	>360	E	P	-	-	G	7	G	G	65	VG	E	>480	-	E	>480	-

Source: Ansell Product Catalogue 2015

Medical Surveillance




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- Regulations can vary on formality of program and scope – know your local countries requirements
- Medical surveillance challenges for APIs in China
- Generally – programs globally exist for respirator protection, noise, some vaccines.
- Is there an occupational physician for the site who understands and sees the workers IH profiles and establishes the medical surveillance program?
- For highly potent compounds – does the site have any special medical surveillance programs, including biological monitoring?
- Has the site experienced high blood results / occupational health events – what is their response action?
- If the material is a sensitizer, has the site established processes to protect people with known allergies?
- How is the site managing reproductive hazards with men and women?
- What is the frequency of IH Health type events at the site?
- How does the site investigate workplace exposure events?

Is it well managed?

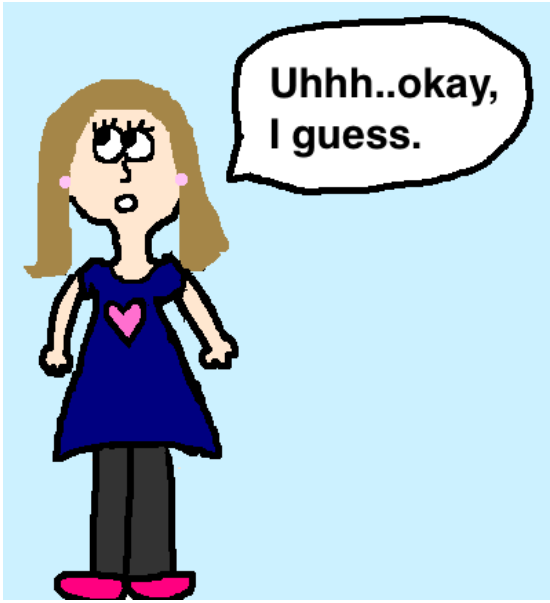
Does it seem appropriate?

Company has limited IH data…what to do?

- Situation: API company hired IH consultant and measured total dust of one unit operation. Data for that one chemical on that one day showed the Respirator being worn was sufficient. Some containment in place and PPE and work practices generally seem to align to what you have seen of control bandings?

- Your PSCI member company has a different API of varying particle size/density and uses different unit operations.

- Your PSCI member company requires data to support the control strategy but does not have an analytical limit to give the company.



Company X lacks IH data to establish the effectiveness of their control strategy. Unit Operations Y should be assessed with priority as a minimal protection factor of 50X is currently in use with a relatively open process.

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Other SDS Classification Issues

- Material is a Dangerous Good for Shipping and API company is not aware of the toxicology data driving this decision
- Packaging, Shipping, and handling practices need awareness
- If shipped to EU, CLP product labeling for some products (e.g. feed) NOV be impacted.
- Combustible Dust Classification
- Process Safety Data NOV not NOV not be on the SDS depending on the company philosophy.
- Labeling for receiving customer country and shipping country

Let's test our rating alignment

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Site is currently handling compounds with the highest hazard category of Containment (<1 ug/m3). As outlined in the IH (Industrial Hygiene) section of this report PSCI member has critical concerns over the open handling of API.

- Exposure Control Program Improvements*
  - Improve Periodic Monitoring for High Potency API & Low OEL Solvents (e.g., Methylene Chloride & API (Drying/Milling) to confirm PPE (Primary control) provides adequate protection.
  - Apply statistical methods for data collected when determining acceptability of sampling results (task based).
  - Respiratory Protection Improvements: Confirm suitability of current respirator(s) for Methylene Chloride (consider airline for this contaminant) and develop cartridge change out schedule for filters and adsorbent cartridges (for other contaminants).
  - Implement improved Lab Safety / Lab Hygiene practices:
    - Fume Cabinet Use: Certify Performance of Hoods,
    - Train employees on proper hood use
    - Improve housekeeping
  - Containment capabilities – Site High potency lab and Facility X are capable for OEL <1 ug/m3.

Let's test our rating alignment

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Report Findings:

Voluntary respirator program in place

Employee exposure monitoring conducted in late 2012 for nuisance dust. However, business was unable to produce air sampling results to quantify exposures.

General dust control was minimal, with dry sweeping of product and dust buildup at many of the work stations.

Random respiratory compliance check made with filling operation for Sulfuric Acid. Exposures had not been quantified and employees were not utilizing respiratory protection during open filling of this product that is severely irritating to the respiratory system.

Report Findings

- Adopted SaNOVridge banding system and refined to align with their business needs.
- Exposure assessment extends upstream into business development to assure exposure control elements are considered during bidding process.
- Visual Management Systems used to highlight level & risk of materials (Potent Compounds), proper PPE and gowning & chemical specific HazCom.
- Commitment to engineering controls was evident in both manufacturing & laboratory (isolators & ventilated balance enclosures rated for nanogram containment).
- Established exposure monitoring program that is growing & adopting AIHA assessment model.

Let's test our rating alignment

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Drug Product site – no potent compound handling

- Fume cupboard used in QC laboratory, but no testing carried out on face velocity (66);
- No exposure monitoring has been carried out at the site (74, 75);
- Site has not provided fit testing, cleaning program or maintenance of cartridge respirators. Cartridges changed every 6 months (79);

Example API Site

Q68	**Not all SDSs of hazardous chemical are available.And there was no OEL data for the API and intermediate. No exposure control hierarchy at facility.** **No LEV was provided to the powder and solvent handling tasks.**	**PSCI principle**	**Site Visit**	**Collect SDSs for all hazardous chemical. Consider the effective engineering control for the chemical and dust exposure.**
Q69	**Very limited engineering control was used for the chemical exposure risk control. Site rely on the PPE for the risk control.**	PSCI principle	Site Visit	**Consider the effective engineering control for the chemical and dust exposure. Establish occupational exposure banding.**
Q72	**On-the-job occupational health medical monitoring for employee were conducted. However, pre hire job employee occupational health surveillance was not conducted. And the QC team members were not in the on job occupational health medical monitoring scope.**	PSCI principle	Document Review	**Develop the pre job occupational health medical check plan**
Q74	**And from the 2017 monitoring record, the total dust in the packaging area of plant X and Y are 21mg/m3 and 32.3mg/m3. But there was no effective remediation plan conducted after the monitoring.**	PSCI principle	Document Review	**Develop effective remediation plan for the dust control.**
Q76	**Gauze respirators were used for the dust and solvent exposure control at some jobs in the site.**	**PSCI principle**	**Site Visit**	**Stop use gauze respirator on facility.And conduct the effectiveness assessment for the current PPE matrix.**

IH Red Flags – PSCI "Other" type of examples

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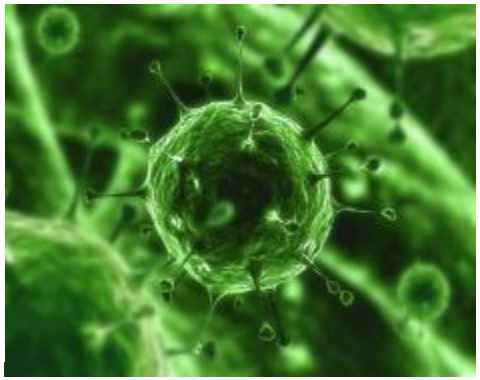
- IH Program in place but some minor differences between OELs and Protection factors between companies.
- PPE and IH Programs written centrally by API company – instructions on posters, SOPs, etc., do not match what is available at the site. Need confirmation of all SOPs and PPE actual requirements so workers can be protected. No evidence of immediate overexposure concerns.
- Site not doing respirator fit testing
- Site has not linked occupational workplace exposure to their health surveillance program fully
- Combination of all controls appear to be protecting workers but process is HIGHLY dependent on PPE and administrative controls. Engineering improvements to improve control are strongly recommended.
- Site has not assessed exposure risk and potential in lab areas.
- IH data collected is very limited, all area samples (no personal results)
- LEV exists, but designs and photos show it is most likely highly ineffective to control risks and no (or very minimal) PPE is being used. The site needs a review of its engineering control strategy and data collected on LEV/exposure performance…no potent compounds.

Biosafety & Radiation Safety

- Just as there are Control Bands for Chemicals, there are Risk Groups for Biosafety Hazards and the establishment of Biosafety Control Bands (1-4) for Biologicals. Do the companies agree?

- If sites have products with ionizing radiation and/or BSL 3 or 4 operations be sure the correct expert is part of the evaluation. Generally special government licenses may be required.



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Agenda (180 minutes)

- **END IN MIND** – discovering PSCI critical & PSCI other issues
  - PSCI IH Principles
  - PSCI Critical Finding for IH
- **Key concepts** in the Industrial Hygiene program & **Red Flags**
  - PSCI industrial hygiene (IH) principles & critical findings
  - Start with the SDS – do we align?
  - Fundamentals of control banding
  - IH Monitoring
  - Hierarchy of controls in pharma
  - Medical Surveillance
  - Employee Training
  - Red flags for IH
- **Group exercise on industrial hygiene**

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Questions & Resources?

- Thank you for the opportunity.

- Part of the slides are based BI…. Ell Lily…