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PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

PSCI Webinar

Managing active pharmaceutical ingredients (API) in manufacturing effluent, Part 2

June 2016

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Our speakers

Dan Caldwell, J&J

Toxicology Fellow in Environment, Health, Safety & Sustainability at Johnson & Johnson. His focus is science advocacy for regulatory assessment of environmental exposure to chemical ingredients. He chairs the Inter Association Initiative PiE Task Force Environmental Control Work Group.

Frank Mastrocco, Pfizer

Pfizer's Director of Environmental Toxicology for the Global Environment, Health & Safety – Product Stewardship Group. His responsibilities include environmental risk assessment support to manufacturing and product operations. He is a lead representative in the area of Pharmaceuticals in the Environment.

Tim Swenson, Pfizer

Environmental Engineer and Associate Director is Pfizer's Global Environmental, Health & Safety organisation. He provides environmental support to Pfizer's manufacturing sites across the network, and has conducted numerous evaluations of API losses in manufacturing effluents.

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Agenda

1. **Context**: Stakeholder Interest in Manufacturing Effluent
2. **Module 1**: Introduction
3. **Module 2**: Conducting An Impact Assessment
4. **Module 3**: Taking Appropriate Action
5. Summary & Next Steps

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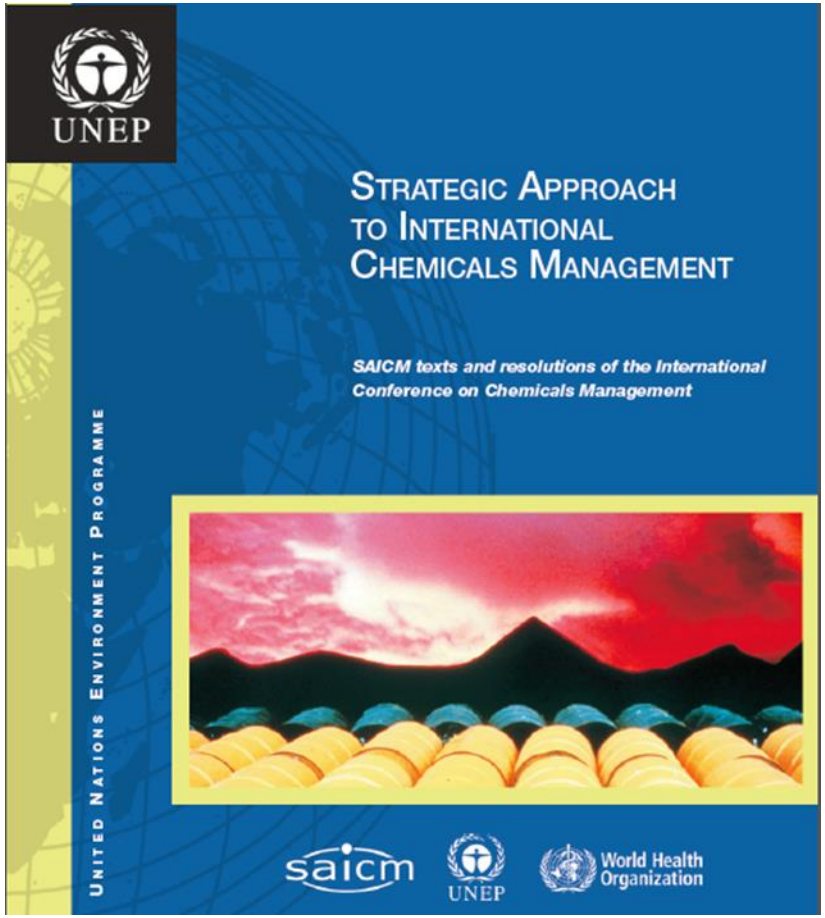
Stakeholder pressures

PRESSURE	MISTRA – The Swedish Foundation for Strategic Environmental Research	Study on the environmental risks of medicinal products – Final Report	Bad Medicine	saicm – UNEP – Strategic Approach to International Chemicals Management
Denial of marketing authorisation / market restiction	✓	✓		
Re-authorisation of LOE products / retroactive enforcement of ERA testing	✓	✓		✓
Environmental parameters added to GMP requirements	[Manufacturing included in ERA]	✓	✓	✓

SAICM

Pharmaceuticals declared 'Top 6' global chemical threat - The fourth session of the International Conference on Chemicals Management (ICCM4), Geneva, 28 September to 2 October, 2015.



At its first session, held in Dubai, UAE, 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 2015

EU: Revisions to Veterinary Medicines Regulations targets external manufacturing

Text passed Parliament, going to 'tripartite' negotiation

AM N°	Rec/Art	New number	Amendment
377, 378	A 25.1	114, adopted	The competent authority shall ascertain that the manufacturers of veterinary medicinal products from third countries comply with EU legislation applicable, are able to manufacture the veterinary medicinal product concerned and/or carry out control tests in accordance with the methods described in the documentation submitted in support of the application in accordance with Article 7(1) and that they minimize environmental pollution..
plenary	A 92.2	302, adopted	(c) details about the manufacturing site where the veterinary medicinal products are to be manufactured or tested, including data about emissions, discharges and losses of the active substance and its precursors to the environment;
681	A 93.5	213, adopted	5. A manufacturing authorisation may be granted conditionally, subject to a requirement for the applicant to undertake actions or introduce specific procedures within a given time period. The manufacturing authorisation may be suspended if these requirements are not complied with. The manufacturing authorisation shall be refused if manufacturing causes unacceptable risks to the environment.
937	Annex 2 1.3.1 para 1.e	286, adopted	(e) the potential risks relating to the development of antimicrobial resistance during production and use.

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Eco-Pharmaco-Stewardship 'Pillars'

The **Industry Proposal**: the Eco-Pharmaco-Stewardship (EPS)

Pillar 1

Cooperation in R&D: Intelligence-led Assessment of pharmaceuticals in the Environment (iPiE)

- As part of the iPiE project, industry, academia and regulators will develop together models to predict pharmaceutical substance properties and the associated environmental risk potential

Pillar 2

Managing discharges from manufacturing

- Share best practices
- Benchmark operations
- Establish standards
- Define control measures

Pillar 3

Extended Environmental Risk Assessment (eERA)

- Evaluate and limit the potential adverse environmental effects from new drugs as well as "legacy" APIs
- Establishing an ongoing monitoring system throughout the product's life-cycle

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Purpose and Objectives

To provide a framework for
Evaluating & Minimizing API Releases to Water

- Describe how to conduct a PIE Impact Assessment
- Explain how to calculate Predicted Environmental Concentration (PEC) and Predicted No Effect Concentration (PNEC)
- Understand and calculate the Risk Quotient (RQ)
- Describe how to apply the API Release Reduction Hierarchy
- List actions that can reduce API releases to water
- Identify available resources for assistance

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Approach

- Based on “desktop” analysis
- **Not** an indication of actual harm
- Approach and guidance provided is based on industry standard methodology
- Conclusions
  - Not likely to be of concern
  - Potential concern for further evaluation

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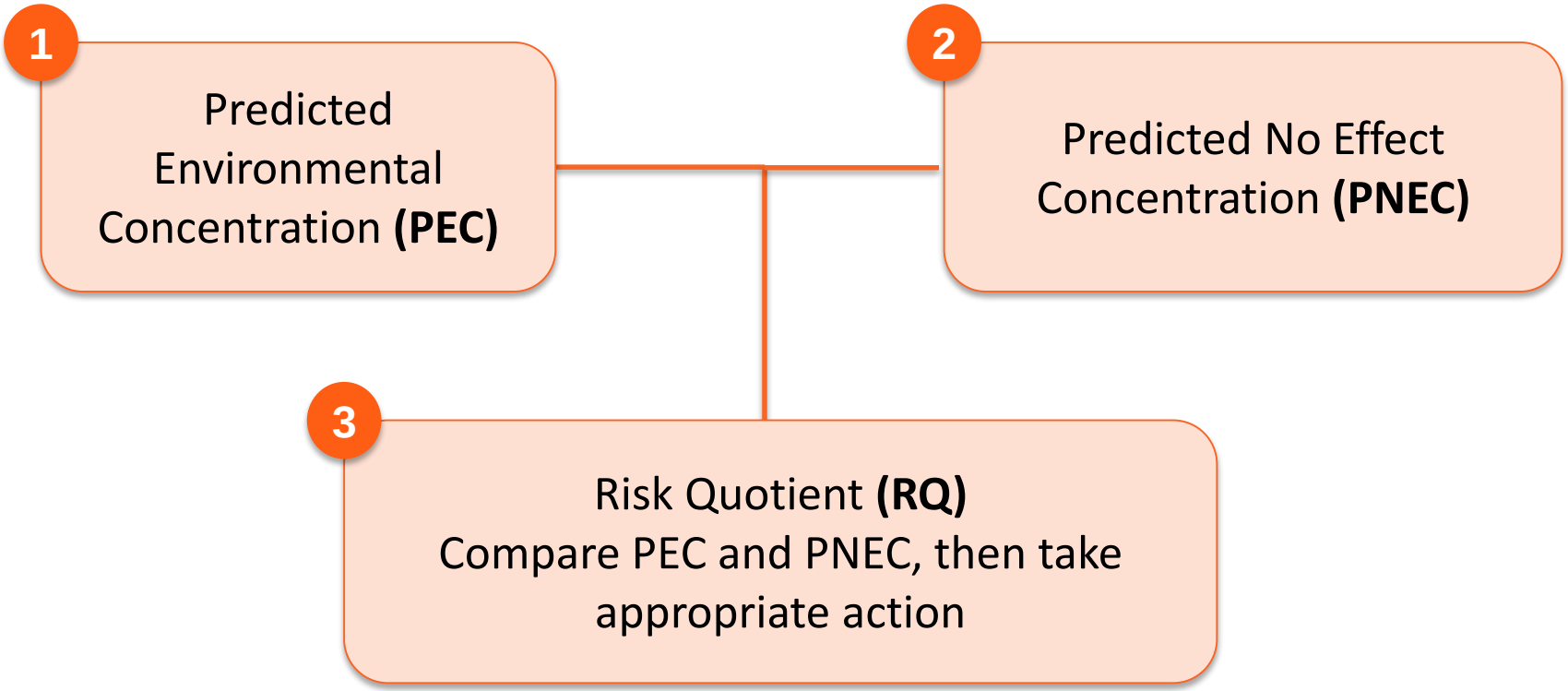
What Is An Impact Assessment?

- Good management practices may not eliminate all API released to water
- ***Your responsibility is to know if the amount released could have a potential impact on the environment and to take appropriate action***
- Requires data and professional judgment



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Impact Assessment Priorities

High environmental interest level
- Sufficient evidence of environmental hazard; and/or high solubility or Log D
- Endocrine active, antibiotic or other mechanism of action with activity in aquatic species
- Location in region/country with regulated discharges
- Sensitive release environment or near drinking water treatment plant

Low product yield, high unaccountable losses

High degree of wet cleaning (vs. dry cleaning)

Product discharge directly to sewer

No or limited wastewater treatment

Treated wastewater discharge to ground

Discharge to sensitive aquatic system

Knowledge Check 1

Question 1

You must conduct Impact Assessments for APIs that have the following characteristics:

(Select all that apply)

a. Endocrine active in local aquatic species
b. High solubility
c. Located in sensitive release environment
d. Treated wastewater discharged to ground
e. Limited wastewater treatment

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Knowledge Check 1

Question 1

You must conduct Impact Assessments for APIs that have the following characteristics:

(Select all that apply)

- ✓ Endocrine active in local aquatic species
- ✓ High solubility
- ✓ Located in sensitive release environment
- ✓ Treated wastewater discharged to ground
- ✓ Limited wastewater treatment

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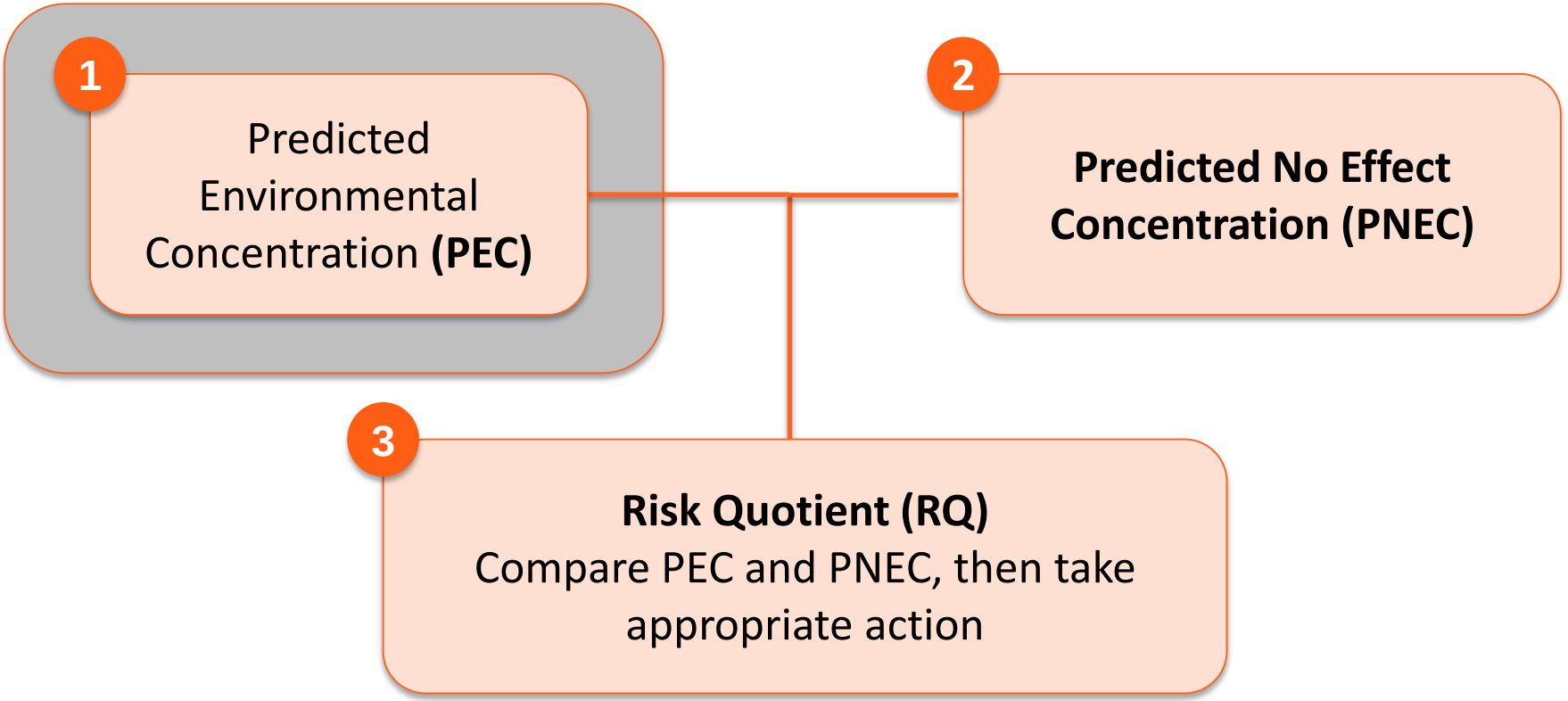
Conducting An Impact Assessment



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Step 1: PEC

1

Predicted Environmental Concentration **(PEC)**

→ ***How much API will end up in the environment?***

API Mass Balance Fundamental

Mass (M) = Flow (Q) x Concentration (C)

$$\textbf{PEC} = \frac{\text{API Loss}}{\text{Reduction and dilution factors}}$$

- Reduction: predicted treatability
- Dilution: high volume drives concentration down

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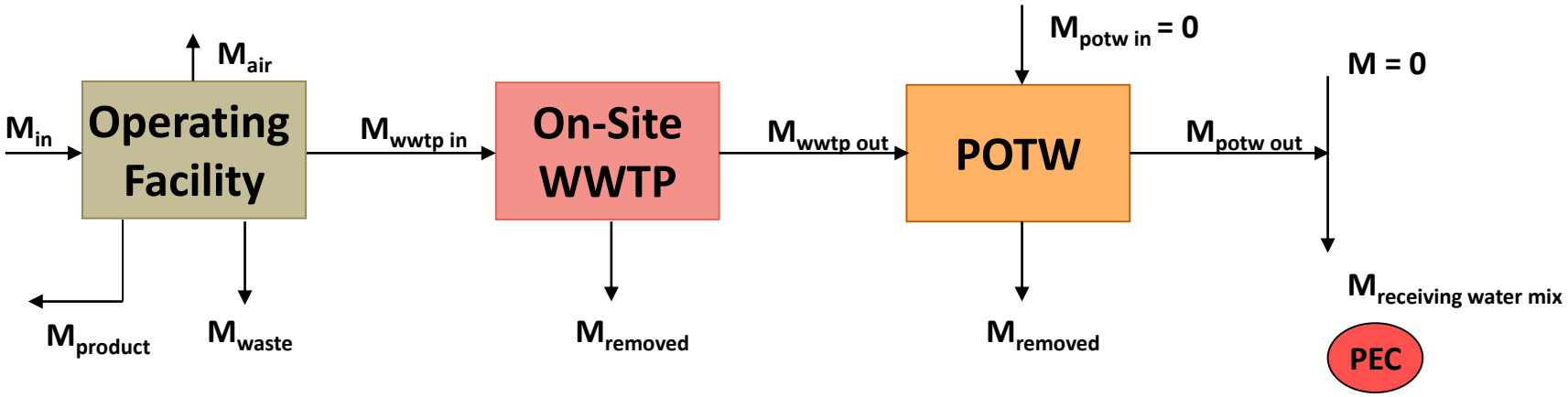
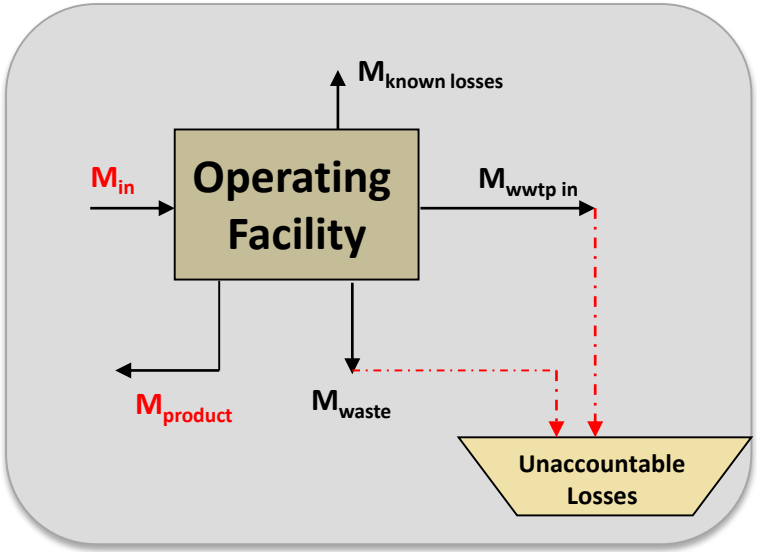
API Mass Balance Fundamental

- Mass going in = Mass going out
- "Law of Conservation"

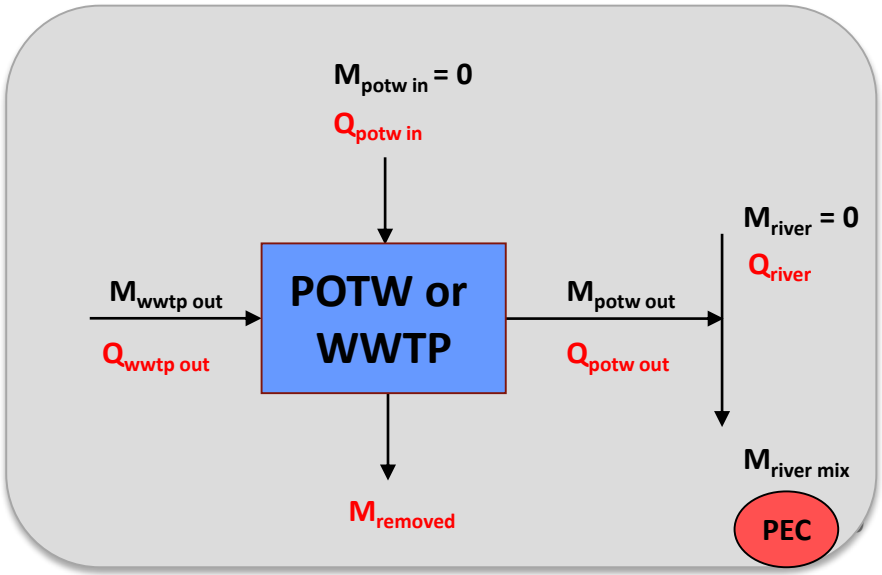


Key Factors Affecting the PEC

- At the Operating Facility
  - Product Yield
  - Batch Size & Cycle
  - Known losses and solid waste
  - "Unaccountable" API Loss



- At the POTW or WWTP
  - Wastewater Flows
  - Treatment Efficiency
  - Receiving Water Flow



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Estimating API Removal Efficiency

Model Based on Physical/Chemical Characteristics and WWTP Attributes*

% API Removal = [B+((100-B) x (P + S))] x WO

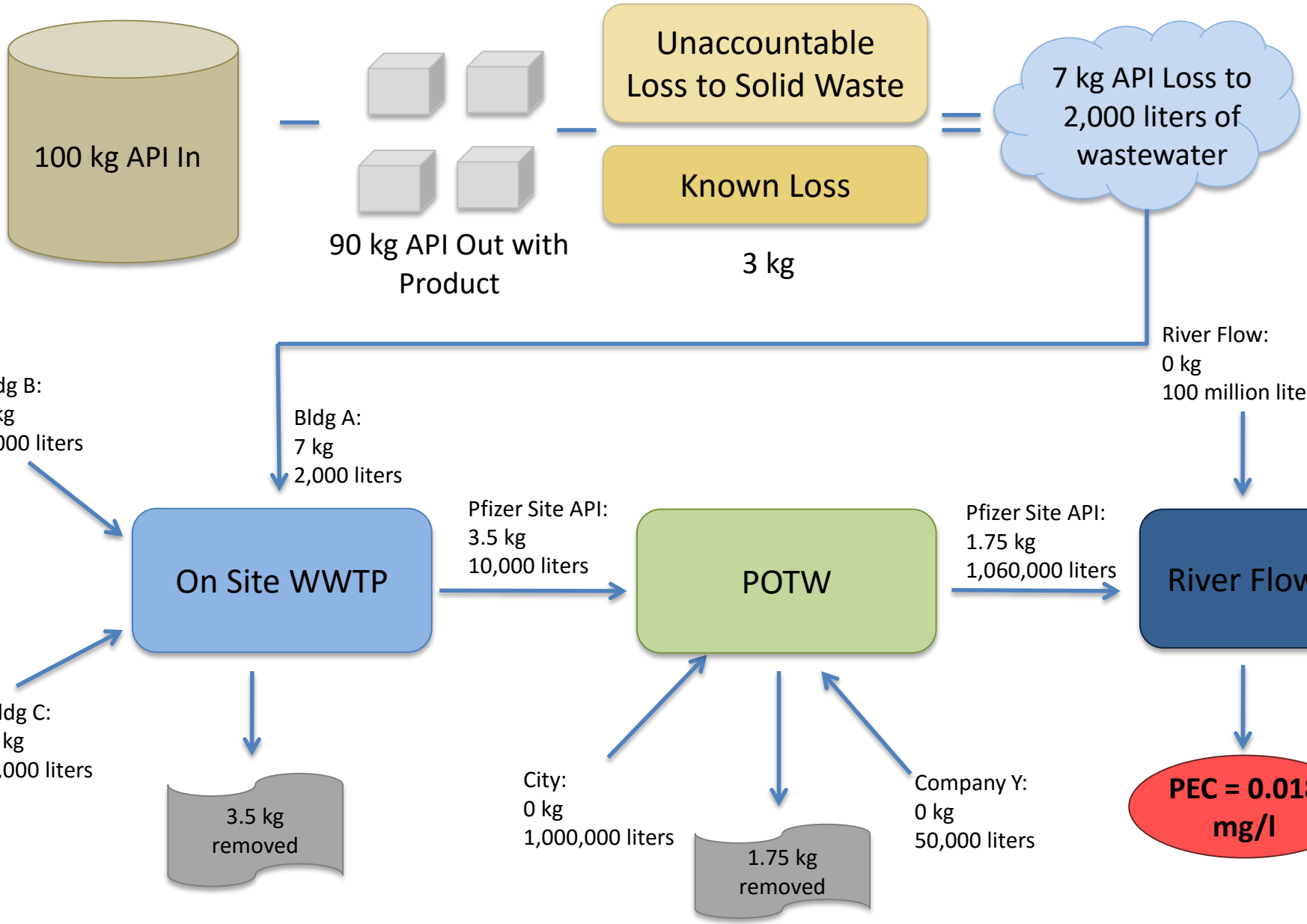
Variable	Indicates	Notes
B	% Biodegradation	shown as % removal in activated sludge testing studies
W	Treatment Process Factor	none = 0.0, primary = 0.4, secondary = 0.8, tertiary = 0.9 – 1.1, zero discharge = 1.2
O	Operation Factor	poor to excellent range 0.5 – 1.0
P	Log Octanol Factor	LogP 0 - <2.0 = 0.5, LogP 2.0 – 4.0 = 0.7, LogP > 4.0 = 0.9
S	Solubility Factor	> 10 mg/L = 0.1, < 10 mg/L = 0.2, < 1.0 mg/L = 0

OR

Default = 0% Conservative; overestimates API released to environment

** Woodard & Curran Inc, 2010*

PEC Example: Site Building A



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PEC Data Collection & Analysis

- Review batch records to determine API losses
- Estimate ***daily*** API losses (account for batch and cleaning cycles)
- Estimate treatment plant removal efficiency using the API chemical and physical properties 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.

PIE Impact Assessment Worksheet: PEC Data Collection

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Supplier	
Location	
Facility Type	
API	
Contact	

Data	Available?	Source	Comments
Production Process Flow Diagram			
%API in finished product			
Batch records			
Cycle time			
# Batches per year			
Yield			
Equipment cleaning SOP			
Equipment cleaning frequency			
API in wastewater			
API in solvent disposal			
API in solid waste			
On-site WWTP PFD			
WWTP unit ops sizing			
WWTP wastewater flow			
WWTP monitoring records			
WWTP compliance records			
Off-site POTW PFD			
POTW unit ops sizing			
POTW wastewater flow			
POTW monitoring records			
POTW compliance records			
Receiving water identity			
Receiving water flow			

Knowledge Check 2

Question 1

Which factor has the biggest effect on the PEC?

a. Chemical properties that break down API

b. Treatment efficiency

c. Dilution

Knowledge Check 2

Question 1

Which factor has the biggest effect on the PEC?

a. Chemical properties that break down API

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Knowledge Check 2

Question 2

Fundamentally, if mass (kg) losses are known, what other parameter is needed to derive a concentration?

a. Flow
b. Pressure
c. Log D
d. Treatment Efficiency
e. Dilution

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Knowledge Check 2

Question 2

Fundamentally, if mass (kg) losses are known, what other parameter is needed to derive a concentration?

a. Flow

b. Pressure

c. Log D

d. Treatment Efficiency

e. Dilution

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Knowledge Check 2

Question 3

What API removal efficiency through the treatment plant should you assume if limited or no data is available?

a. 0%

b. 50%

c. 100%

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Knowledge Check 2

Question 3

What API removal efficiency through the treatment plant should you assume if limited or no data is available?

a. 0%

b. 50%

c. 100%

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Knowledge Check 2

Question 4

In order to derive the PEC, mass (kg) API losses to wastewater should be estimated on an:

a. Annual basis

b. Batch basis

c. Daily basis

Knowledge Check 2

Question 4

In order to derive the PEC, mass (kg) API losses to wastewater should be estimated on an:

a. Annual basis

b. Batch basis

c. Daily basis

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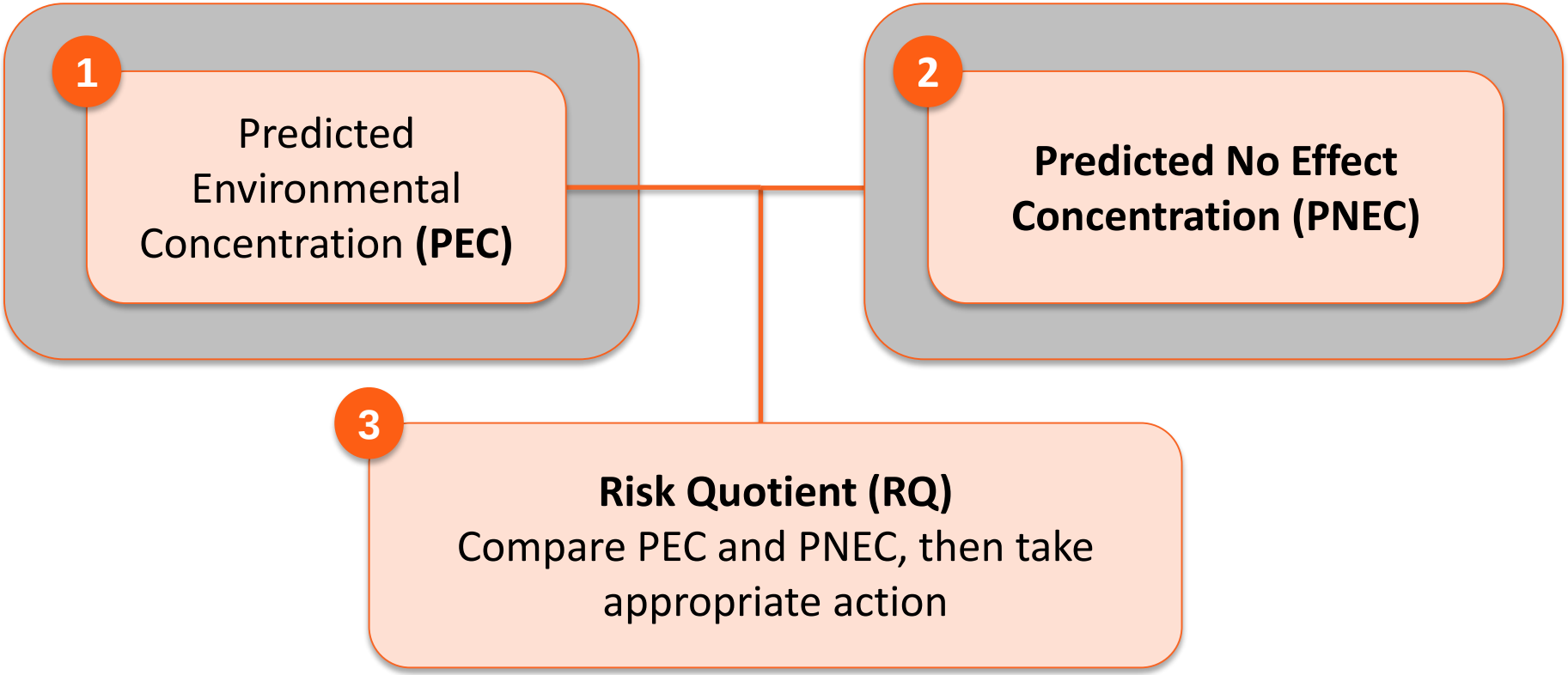
Conducting An Impact Assessment



Step 2: PNEC

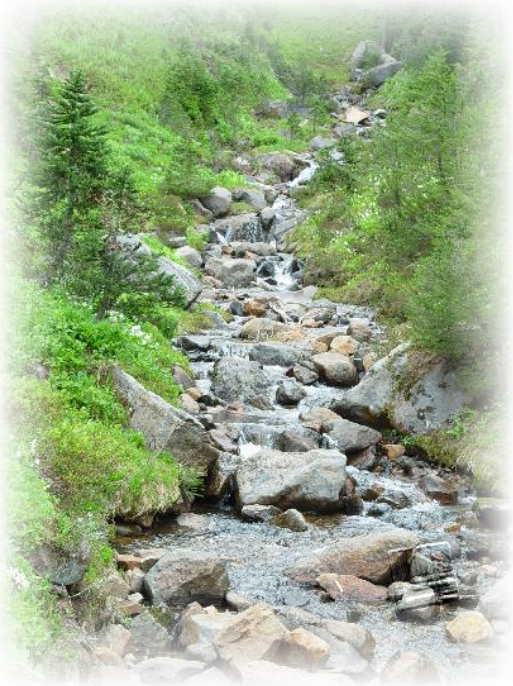
2

Predicted No Effect Concentration **(PNEC)**

→ ***The API level in the environment where no impact is expected***

Critical Factors

- Understanding of the surrounding ecosystem
- Amount of environmental toxicity study data available



Deriving the PNEC

$$\text{PNEC} = \frac{\text{No Observed Effect Concentration (NOEC)}}{\text{Assessment Factor (AF)}}$$

- **No Observed Effect Concentration (NOEC):** The amount of a substance where no harm to an organism has been observed
- **Assessment Factor:** Factor used to account for uncertainties; varies inversely with strength of data set

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NOEC

- NOECs are identified through toxicity testing and toxicological studies of the material on a variety of species
- NOECs must be from reliable sources; conducted in-house or by qualified external contractors

Examples:

Species	NOEC
Fish Early Life Stage	0.45mg/l
Daphnia Full Life-Cycle	0.14mg/l
Green Algae	24mg/l

- Review all available NOECs for your substance
- Select the smallest NOEC
- Apply professional judgment and understanding of ecosystem

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Assessment Factor

- Accounts for uncertainties in the data
- More data, lower AF, less precautionary

Available Data	AF
At least one short-term L(E)C50 from each of three trophic levels of the baseset (fish, *Daphnia* and algae)	1000
One long-term NOEC (either fish or *Daphnia*)	100
Two long-term NOECs from species representing two trophic levels (fish and/or *Daphnia* and/or algae)	50
Long-term NOECs from at least three species and trophic levels (normally fish, *Daphnia* and algae)	10

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Selecting The Assessment Factor

Species	NOEC
Fish Early Life Stage	0.45mg/l
Daphnia Full Life-Cycle	0.14mg/l
Green Algae	24mg/l

Available Data	AF
At least one short-term L(E)C50 from each of three trophic levels of the baseset (fish, *Daphnia* and algae)	1000
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PNEC Example

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$$\text{PNEC} = \frac{\text{NOEC}}{\text{Assessment Factor (AF)}}$$

$$\text{PNEC} = \frac{0.14\text{mg/l}}{10} = 0.014\text{mg/l}$$

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Temple WET Center Database of PNECs

Constructed from Vestel et al. 2016

- Data
  - Acute effects data for fish, daphnids, green and blue-green algae generated to support ERAs, development, scale-up, manufacturing, and classification and labeling for handling and transport safety
  - Chronic effects data generated to support Environmental Risk Assessments for new drug/medicinal authorization applications
  - Good Laboratory Practice (GLP) and reliable non-GLP studies included
- Sources
  - Unpublished aquatic toxicity data (various pharmaceutical companies)
  - Published aquatic toxicity data (curated)
  - Data published on some companies public web sites
  - Data published by a national medicinal agency (www.fass.se) (curated)
  - Data gaps filled with peer-reviewed literature values, when available, after extensive data review

http://wet.temple.edu/

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Summary Analysis of Database

- A chronic PNEC can be predicted from the acute PNEC for all classes of pharmaceuticals, except endocrine Mode of Action and a few other noted compounds
- Using the acute data with the appropriate Assessment Factor would be a more conservative approach for risk screening than using the chronic data (i.e., generally lower PNECs)

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Uses of the Temple WET Center Database

- Increased transparency on part of industry
  - Supports EcoPharmacoStewardship framework
- Publicly accessible list of PNECs (online 3Q2016)
  - Screening PNECs to evaluate local conditions
  - Capacity building for external suppliers
- Underlying data can be provided to Environment Agencies (NOECs, study type) upon request
  - Prioritization of additional ERA activities
  - Basis for regulatory EQS

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Knowledge Check 3

Question 1

(True or False)

The more environmental toxicology data we have, the higher the Assessment Factor (AF).

a. True

b. False

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Knowledge Check 3

Question 1

(True or False)

The more environmental toxicology data we have, the higher the Assessment Factor (AF).

a. True

b. False

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Knowledge Check 3

Question 2

When selecting the No Observed Effect Concentration (NOEC), you should select:

a. The average number to account for a range of species

b. The lowest number regardless of species

c. The lowest number for the species found in the local environment

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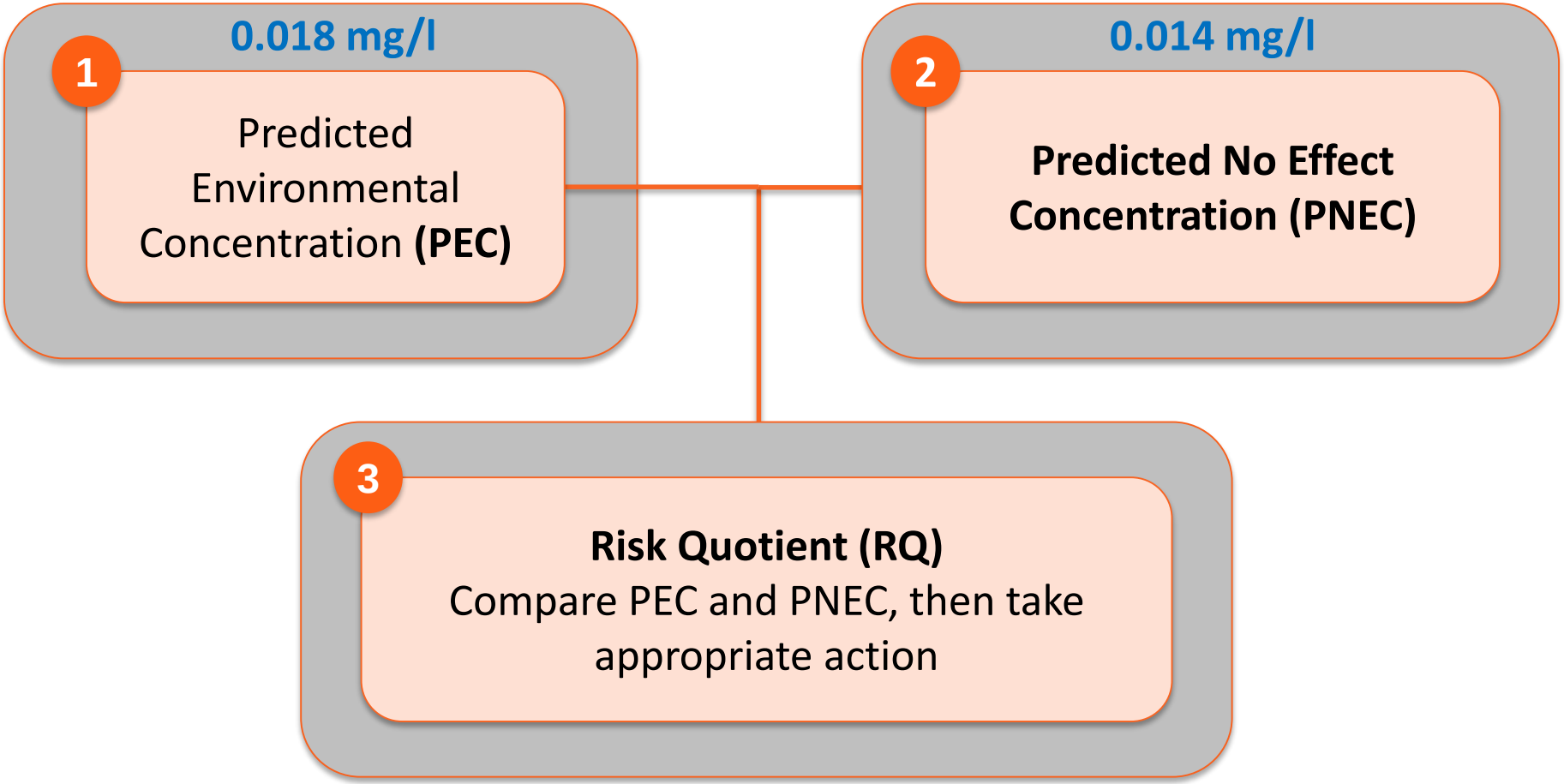
Step 3: Calculating the Risk Quotient



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Risk Quotient Indication

$$\text{Risk Quotient (RQ)} = \frac{\text{PEC}}{\text{PNEC}} = \frac{0.018\ \text{mg/l}}{0.014\ \text{mg/l}} = 1.3$$

Risk Quotient		
Less than 1	Indicates that the expected concentration is lower than the concentration where there is a potential for impact to the environment	
Greater than 1	Indicates that the expected concentration exceeds the low- or no-effect concentration indicating the potential for impact to the environment	

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What If My RQ is Greater Than 1?

Risk Quotient		
Greater than 1	Indicates that the expected concentration exceeds the low- or no-effect concentration indicating the potential for impact to the environment	

API Release Reduction Hierarchy

1. Reduce Losses To Wastewater
   → *Re-calculate RQ*
2. Collect Wastewater at Point of Generation (POG)
   → *Re-calculate RQ*
3. Make WWTP Modifications*
   → *Re-calculate RQ*

**consider options*

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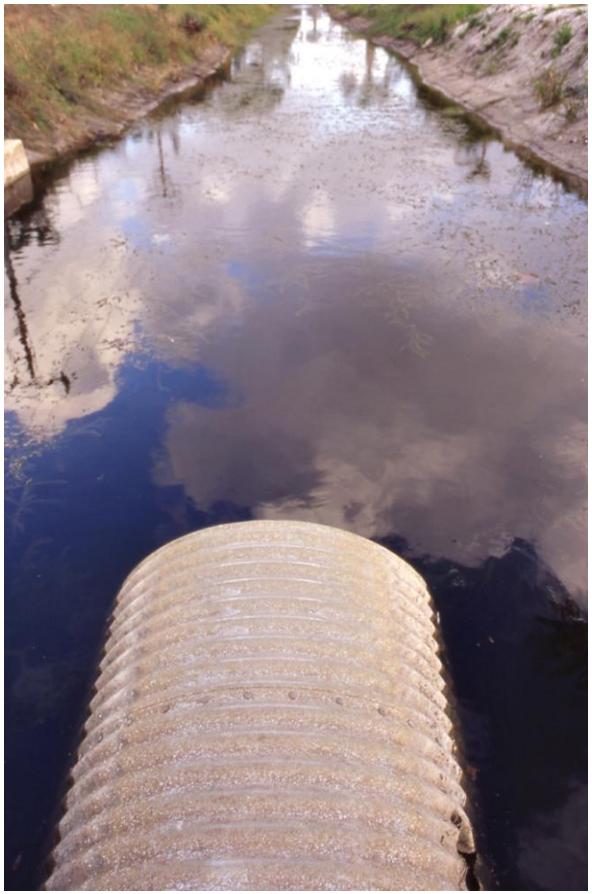
Level 1: Reduce Losses to Wastewater

Use Good Management Practices

- Eliminate direct sewer discharges of rejected/spilled material
- Use dry cleaning practices as much as practical
- Minimize wet cleaning practices



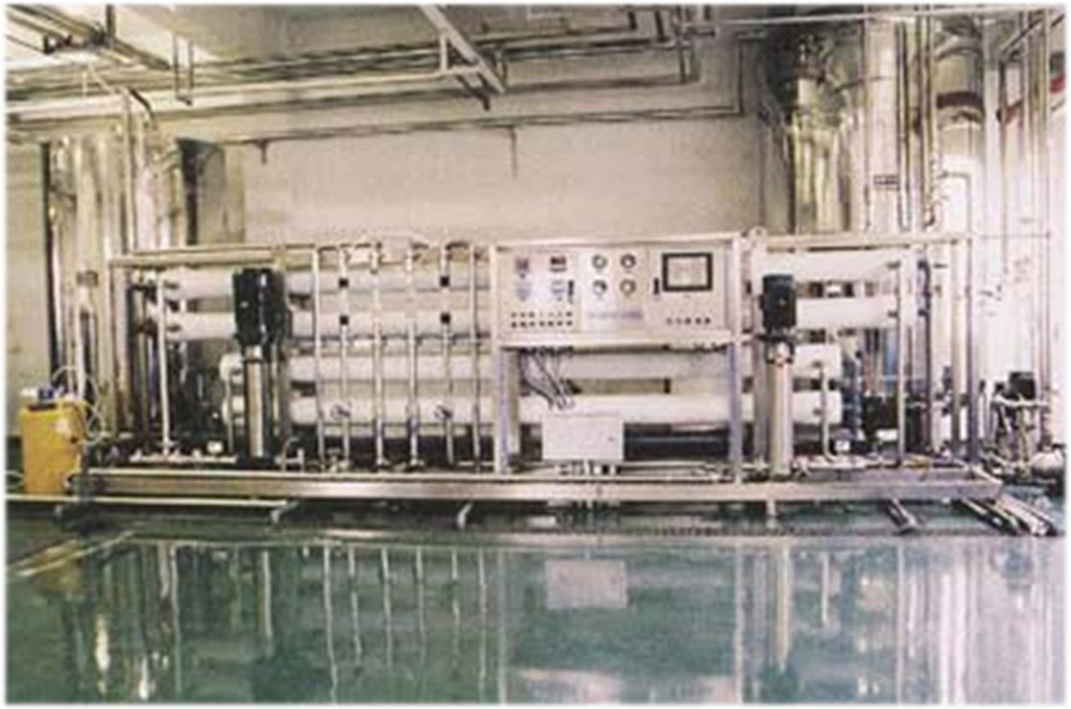
Implement these practices and then re-calculate RQ

If RQ still greater than 1, go to Level 2

Level 2: Collect Wastewater at POG

Collect Wastewater at Point of Generation (POG)

- Off-site disposal (e.g., incineration)
- Treatment (e.g., filtration, advanced oxidation)



Implement these practices and then re-calculate RQ

If RQ still greater than 1, go to Level 3

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Collecting Wastewater at POG Example

Oral contraceptive production: Initial PEC/PNEC ratio for EE2 was 151

- After first rinse, 80 L captured, 92.1% residual EE2 removed, PEC/PNEC ratio drops to 12
- Further pressure rinse 3x, 50 L (total) removed additional 5.2% of EE2, PEC/PNEC = 4
- The 130 L cleaning water collected and sent to incineration reduced EE2 mass discharged and potential risk by >97%

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Level 3: Consider WWTP Modifications

- Understand existing WWTP operations & capabilities
- Assess API removal mechanisms
- Screen treatment technologies
- Typically beyond conventional treatment (i.e. ozone, GAC, UV/H_2O_2)

What If My RQ is Less Than 1?

Risk Quotient		
Less than 1	Indicates that the expected concentration is lower than the concentration where there is a potential for impact to the environment	

- Continue to use good management practices
- Continually improve efforts to reduce API losses to wastewater

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Wastewater Maturity Ladder

Minimum

Advanced

High-Level

Step 1
Commit & Plan
Basic awareness & knowledge
*Legal compliance and knowledge about fate and nature of effluent
-Fate of effluent known and fully permitted
-yearly discharge volume accounted for
*Monitoring effluent characteristics and standards
*Dedication of assigned persons for WWT
*Basic training of WWT responsible persons
*Understanding design capacity and performance

Step 2
Easy fixes, quick wins, must do's toward prevention and compliance
*Communication link WWTP w/Production Communication and Planning
*Basic spill /calamity procedure
-Calamity tank available
-External processing
*Regular follow-up of WWTP
-Influent characterization
-Sludge characterization
*Redundant critical equipment
-pumps, blowers available
*WWTP laboratory safe and controlled
-General lab safety rules
-Regular instrument calibration

Step 3
Assess Risks
*Removal efficiency of organics and nutrients evaluated and in line with design
-COD, BOD, N, P removal
*Rest capacity understood
*Spill/Calamity control in place
-Awareness
-Procedures available/in practice
*Advanced training
-WWT organizations
-Follow-up training
-Advanced data interpretation and evaluation
*Integration of production planning and WWT capacity/capability
*Evaluation of water and pollution balance
-Water consumption in production? Rainwater
-Sound water and mass balance

Step 4
Control Risks
*Wastewater acceptance policy
-Dedicated acceptance person
-Awareness of the impact of new waste streams
-Procedures available/in place
*Awareness/evaluation of value of microscopic sludge analysis?
*Water consumption optimization awareness
*Preventative maintenance program
*Trending of important parameters and process deviations
*Operational WWTP emergency procedure
-Back-up power available
-Failure alarm system for critical equipment
-Personnel available 24/7

Step 5
Audit/Benchmark
Share/implement best practices
*Opportunities for improvement identified and evaluated
-Audit of production and WW treatment as they relate to each other
-Evaluation of water and product use in production to investigate technology efficiency and effectiveness
*Have operational efficiencies been benchmarked and improvements evaluated?
-Comparison of performance of similar plants in order to optimize
-Comparison of operational costs of similar plants in order to optimize

Step 6
Integrate & maintain continuous improvement
*Process technology reviewed and evaluated for BAT
*If direct discharge , is TIE (Toxicity Identification Evaluation) done?
-Whole effluent testing (acute/chronic)
*If direct discharge , is TRE (Toxicity Reduction Evaluation) done?
-Techniques to reduce toxicity tested implemented?
*Rational water management
-Awareness campaign
-Effluent reuse
-Rainwater capture/use
*Advanced training including microscopic sludge analysis
-Microorganism activity level
-Floc forming bacteria identification (staining)
-Filament identification

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Summary

- The pharmaceutical industry is committed to minimize environmental impacts from manufacturing effluents.
- Companies working together developed the EcoPharmacoStewardship (EPS) framework to minimise potential environmental risks.
- Although individual companies have different programs, we are working together to leverage best practices, share information and tools and increase transparency.
- Much progress has been made in the past 5 years but work continues.
- We look forward to working collaboratively with all stakeholders to further the EPS approach.

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Questions

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The Pharmaceutical Supply Chain Initiative

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