PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

The Pharmaceutical Supply Chain Initiative (PSCI):

MANAGING ACTIVE PHARMACEUTICAL INGREDIENTS (API) IN MANUFACTURING EFFLUENT: PART 4

JUL 18

PSCI CAPABILITY PROGRAMME WEBINAR

AGENDA

Welcome

PiE, AMR & PNEC first principles

PNEC resources on PSCI website

How to locate PNECs & use them

Questions

SPEAKERS

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

FRANK MASTROCCO

Pfizer

Director of Environmental Toxicology for Global EHS – Product Stewardship Group

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Johnson & Johnson

Toxicology Fellow Environmental Health, Safety & Sustainability

ANNABEL BUCHAN

Carnstone

PSCI Secretariat

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PSCI Webinar Series:
Managing active pharmaceutical ingredients (API) in manufacturing effluent

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- Jan. 2016 - **Part 1** gave a general introduction to the importance of the topic, the maturity ladder concept, how to calculate discharge concentrations, and steps sites can take to reduce API process losses.
  - Deck: https://pscinitiative.org/resource?resource=293
  - Recording: https://pscinitiative.org/resource?resource=292
  - Guidance Paper: https://pscinitiative.org/resource?resource=289
- June 2016 - **Part 2** a case study to show how to put the theory into practice; estimating actual API losses from the manufacturing process (PEC), establishing the acceptable discharge concentration (PNEC), and making low capital investment housekeeping steps to reduce the loss
  - Deck: https://pscinitiative.org/resource?resource=295
  - Recording: https://pscinitiative.org/resource?resource=296
- Oct. 2016 - **Part 3**, a look at more advanced steps to reduce loss, including reverse - osmosis.
  - Deck (No Recording): https://pscinitiative.org/resource?resource=297

Industry Guidance Paper

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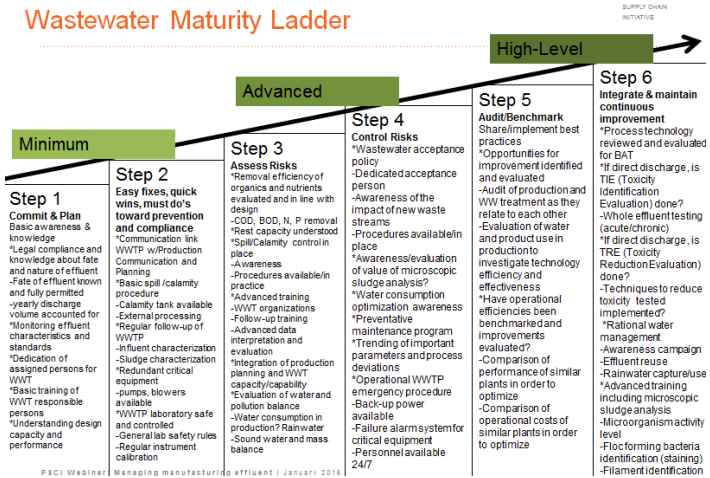
Wastewater Maturity Ladder



Environmental Toxicology and Chemistry

Critical Review | Open Access

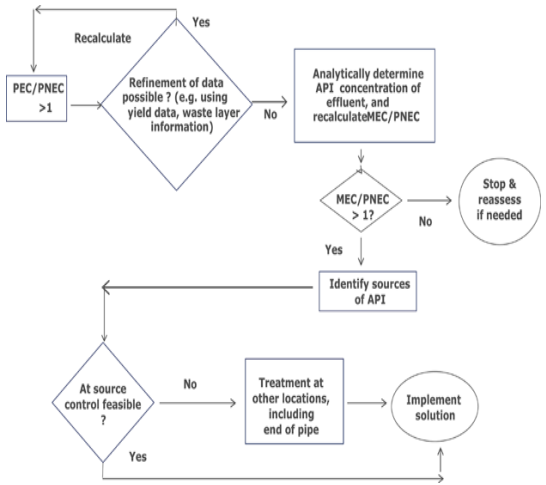
A risk-based approach to managing active pharmaceutical ingredients in manufacturing effluent

Daniel J. Caldwell, Birgit Mertens, Kelly Kappler, Thomas Senac, Romain Journel, Peter Wilson, Roger D. Meyerhoff, Neil J. Parke, ... See all authors

First published: 16 July 2015 | https://doi.org/10.1002/etc.3163 | Cited by: 6

Abstract

The present study describes guidance intended to assist pharmaceutical manufacturers in assessing, mitigating, and managing the potential environmental impacts of active pharmaceutical ingredients (APIs) in wastewater from manufacturing operations, including those from external suppliers. The tools are not a substitute for compliance with local regulatory requirements but rather are intended to help manufacturers achieve the general standard of "no discharge of APIs in toxic amounts." The approaches detailed in the present study identify practices for assessing potential environmental risks from APIs in manufacturing effluent and outline measures that can be used to reduce the risk, including selective application of available treatment technologies. These measures either are commonly employed within the industry or have been implemented to a more limited extent based on local circumstances. Much of the material is based on company experience and case studies discussed at an industry workshop held on this topic. *Environ Toxicol Chem* 2016;35:813–822. © 2015 The Authors. *Environmental Toxicology and Chemistry* Published by Wiley Periodicals, Inc. on behalf of SETAC.



Decision tree providing guidance on the actions to be taken in case the risk assessment PNEC/PEC > 1

How does Antimicrobial Resistance (AMR) occur?

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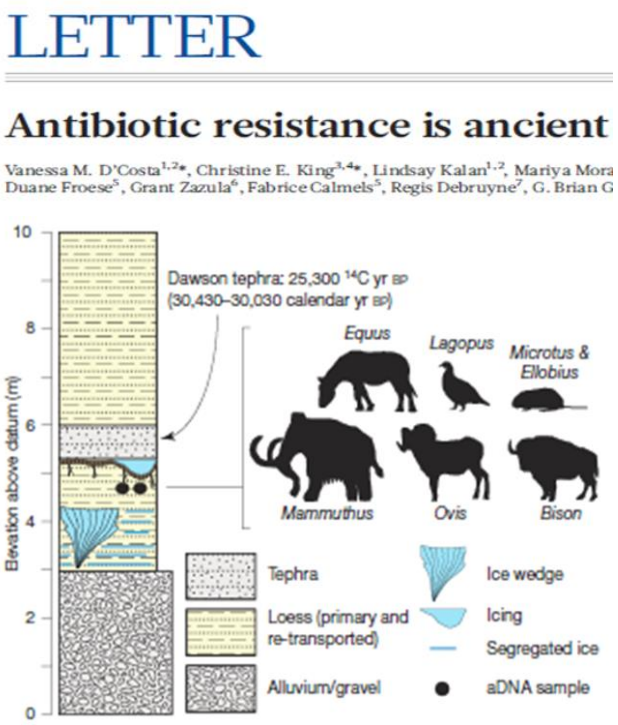
- Microorganism-mediated AMR can be intrinsic or acquired.
- Resistance occurs naturally (intrinsic), as bacteria, fungus, and viruses are exposed to antimicrobial substances produced by competitive species.
- Excessive use in humans and animals is well-known to accelerate the process.
- Environmentally-mediated (acquired) AMR results from external pressures sufficient to trigger a resistance response in the microorganism. Resistance can also be acquired through gene-transfer amongst bacteria
- Current environmental focus is on manufacturing.
- The link between the environment and human health is still unclear.


LETTER

Antibiotic resistance is ancient

Vanessa M. D'Costa[1,2]*, Christine E. King[3,4]*, Lindsay Kalan[1,2], Mariya Mora
Duane Froese[5], Grant Zazula[6], Fabrice Calmels[5], Regis Debruyne[7], G. Brian G

Stakeholders challenge manufacturing controls – Focus on antimicrobial resistance

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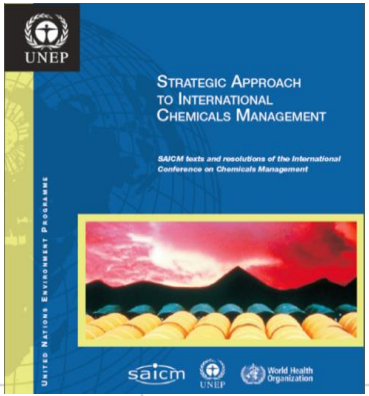

O'Neill Report: Expert group commissioned by UK government to review state of affairs and recommend changes to avert antibiotic resistance. (2015)

"Failing to solve this problem does most harm in the short-term to the health of people living near manufacturing sites who are exposed to polluted water. In a way, they are paying a price for the supply of cheap antibiotics upon which much of the world relies. But in the long-term, we know that resistance spreads and this will contribute to the global problem."

RECOMMENDATIONS:

1. **ESTABLISH MINIMUM STANDARDS TARGETING THE EMISSION OF MANUFACTURING WASTE**
2. **ENCOURAGE THE PHARMACEUTICAL INDUSTRY TO DRIVE HIGHER STANDARDS THROUGHOUT THEIR SUPPLY CHAINS**

SAICM: UNEP proposes persistent pharmaceuticals as a new, emerging policy issue

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

Industry Alliance Roadmap for Progress on Combating Antimicrobial Resistance – September 2016

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1) We support measures to reduce environmental impact from production of antibiotics, and will:

i. Review our own manufacturing and supply chains to assess good practice in controlling releases of antibiotics into the environment.

ii. Establish a common framework for managing antibiotic discharge, building on existing work such as PSCI, and start to apply it across our own manufacturing and supply chain by 2018.

iii. Work with stakeholders to develop a practical mechanism to transparently demonstrate that our supply chains meet the standards in the framework.

iv. Work with independent technical experts to establish science-driven, risk-based targets for discharge concentrations for antibiotics and good practice methods to reduce environmental impact of manufacturing discharges, by 2020.

https://www.ifpma.org/wp-content/uploads/2018/06/Roadmap-for-Progress-on-AMR-FINAL.pdf

IFPMA International Federation of Pharmaceutical Manufacturers & Associations

Industry Alliance Roadmap
Manufacturing Work Group Position Summary

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- Manufacturing is one potential source of antibiotics in the environment
- The Manufacturing Work Group of the AMR Industry Alliance has an environmental framework that provides a set of minimum requirements to conduct site risk evaluating
- Alliance members with commercial supply of antibiotics are being asked to commit to report progress in implementing the requirements of the framework across their supply chain
- Wide spread adoption is key - innovators and generics - to reduce overall manufacturing contribution to antibiotics in the environment

SIGNATORY COMPANIES

Allergan
AstraZeneca
Cipla
gsk
SINOCHEM | DSM
DSM Sinochem Pharmaceuticals
Johnson & Johnson
Pfizer
SANOFI
MERCK
NOVARTIS
WOCKHARDT
Roche
SHIONOGI

Measuring Drug Susceptibility

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- **Minimum Selective Concentration** (MSC) is the lowest concentration of an antibiotic that selects for a resistance mutation.
- **Minimal Inhibitory Concentration** (MIC) is the lowest concentration of an antibiotic that prevents visible microorganism growth after overnight incubation.
- MIC is the measure used to gauge clinical effectiveness so is widely available, whereas, MSC is a much more difficult endpoint to measure and availability is limited.
- Therefore, the popular approach to establishing AMR target limits for Environmental Risk Assessment (ERA) is based on the MIC per the approach published in Bengtsson-Palme & Larsson*. These Predictive No-Effect Concentration (PNEC-MIC) values incorporate added conservatism acknowledging that the MSC is likely lower than the MIC.
- To consider effects other than AMR, the 'environmental' toxicity PNEC should also be considered and the current recommendation is to use the lower of the **PNEC-MIC** or **PNEC-ENV** in the ERA.

**J. Bengtsson-Palme, D.G.J. Larsson, Environment International, Volume 86, 2016, Pages 140-149, ISSN 0160-4120, https://doi.org/10.1016/j.envint.2015.10.015.*

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Sources of PNECs for Antibiotics

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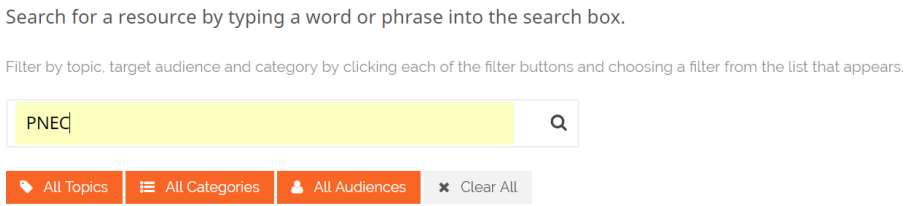
- The AMR Industry Alliance list of PNEC-ENV for 70 antibiotics will be uploaded to the IFPMA website
- PNEC-ENV for pharmaceuticals and several antibiotics are listed on the Temple WET Center website
- For PNEC-MIC values, those derived by Bengtsson-Palme & Larsson will be posted on the IFPMA website

- PSCI PNEC resource page website

PNEC Resource Page on PSCI website

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

- Go direct to: https://pscinitiative.org/resource?resource=342
- OR type “PNEC” into the Resources search tool at https://pscinitiative.org/resources



- …and click on the first result

PNEC Resource Page on PSCI website

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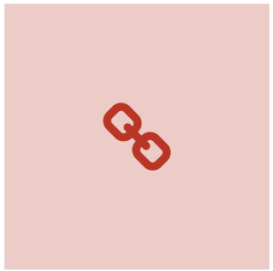
← Back to resources



Predicted-No-Effect-Concentration (PNEC) resource links

Link

June 2018 · Pharmaceuticals in the Environment · Members · Suppliers

The following are useful resources for obtaining PNEC values.

1. Estimated (in µg/L) predicted no-effect concentrations for 111 antibiotics and 11 antibiotics combinations.
   Taken from: Johan Bengtsson-Palme, D.G. Joakim Larsson, Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation, Environment International, Volume 86, 2016, Pages 140-149, ISSN 0160-4120, https://doi.org/10.1016/j.envint.2015.10.015.
2. Temple WET Center PNEC database, where you will find PNEC values for APIs other than antibiotics.
3. A third resource is under construction and will be posted here in due course.

NOTE: The PNEC values found in these resources are believed to be correct and up-to-date. PSCI suggests that you confirm with your client the accuracy and/or suitability of the PNECs found.

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Ecotoxicity Data: PNEC-ENV

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- Company provided data for which they conducted studies
- PNEC-ENV developed using standard assessment factors
- Data gaps filled with literature data (quality check done)
- Preliminary PNEC-ENV values developed for 54 APIs
  - Minimum of blue-green algae data required
  - Range 0.003 µg/L (Tiamulin) – 780 µg/L (Sulfadimethoxine)
  - ~60% < 1 µg/L
  - ~26% < 0.1 µg/L
- Comparison to Bengtsson-Palme (2016) PNEC-MIC proposed values
  - n=40
  - PNEC-ENV < PNEC-MIC 70% of instances

Comparison of PNEC-ENV to PNEC-MIC

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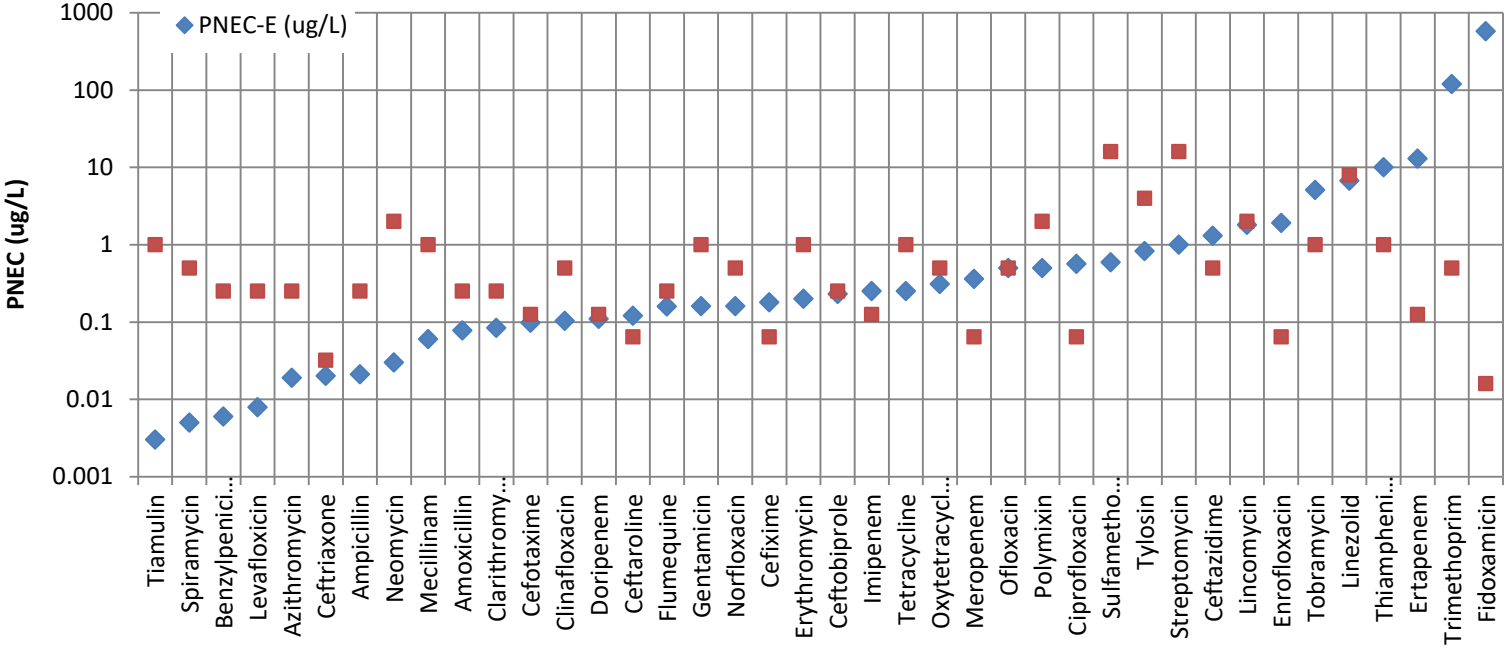

Choice of PNECs for Risk Assessment

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Active Pharmaceutical Ingredient	PNEC-ENV (µg/L)	PNEC-MIC (µg/L)	Lowest Value (µg/L) Used for Risk Assessment
Azithromycin	**0.02**	0.25	0.02
Bacitracin	100	**8**	8
Ciprofloxacin	0.45	**0.06**	0.06
Clarithromycin	**0.08**	0.25	0.08
Sulfamethoxazole	**0.6**	16	0.6

Hypothetical Risk Assessments for a 0.1 µg/L concentration of an antibiotic in mixing zone

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Active Pharmaceutical Ingredient	Hypothetical example PEC (µg/L)	Lowest PNEC (µg/L)	Risk Quotient PEC/PNEC
Azithromycin	0.1	0.02	5
Bacitracin	0.1	8	0.01
Ciprofloxacin	0.1	0.06	1.67
Clarithromycin	0.1	0.08	1.25
Sulfamethoxazole	0.1	0.6	0.17

Proposed Path Forward: Effluents

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- Continue to explore science-driven solutions to AMR issue
- No likely science-based resolution prior to 2020
- **Proposal in front of Industry Alliance**:
  - Use both approaches (PNEC-ENV and PNEC-MIC) and take lower of the two
  - Point of Compliance: End of mixing zone in receiving stream
  - Can start now
- Continue to test to fill ecotoxicity data gaps
- Review updates to EUCAST as needed following Bengtsson-Palme & Larsson approach
- Will drive significant reductions in effluents
  - Applicable to both internal sites and suppliers
- Some companies may have an alternative approach – ask your customer!

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