Environmental risk classification of pharmaceutical products

Guidance document

A deliverable from
IVL Swedish Environmental Research Institute

ivl
Swedish Environmental
Research Institute

Contents

Guidance document

Introduction

There is a growing focus and awareness of the environmental consequences of pharmaceuticals. Consequently, there is an increasing demand on environmental pharmaceutical data from several parts of the society. The Swedish environmental pharmaceutical classification system, Fass, has been running since October 2005. The system is based on environmental risk assessments (ERAs) of individual active pharmaceutical ingredients (APIs), in terms of emissions from patient excretion in Swedish aquatic environments.

The Swedish Environmental Research Institute (IVL) has developed a model for the assessment of emissions of API from production, which is described in this guidance document. The model could be used to extend the current environmental information with environmental classification of pharmaceutical production. The project is funded by Lif (de forskande läkemedelsföretagen) and SIVL (Stiftelsen IVL).

The overall ambition is to develop an environmental risk assessment model for pharmaceutical products to enable sustainability criteria in public procurement. Later on, the methodology could further be used in other green economic incentives in the pricing and reimbursement system. In this project, with the help from you, IVL will test the model to map what information can be gathered and how it could be used in a procurement situation.

The model is based on a quantitative assessment of the emissions of API from production, formulation and when relevant, packaging sites put in relation to expected safe levels of API in the environment. The emissions or level of API that will end up in the environment can be summarized by calculating the Predicted Environmental Concentration (PEC). This value will then be compared to the API level in the environment where no impact is expected, the so called Predicted No Effect Concentration (PNEC). The risk quotient between them (PEC/PNEC) then defines the environmental risk classification of the API.

Along the value chain of the production of the pharmaceutical product, a unique PEC/PNEC-value will be calculated for each site where production, formulation and, when relevant, packaging occurs. The PNEC-value will be the same for all sites, whereas the PEC-value will be unique for each site. The site with the highest risk phrase will then represent the final product.

Please note that the PEC-value is not intended to reflect the quantity of the product produced for the Swedish market, but rather the global overall production. The PEC-calculation should thus not be adjusted for how much of the produced pharmaceutical that finally ends up in Sweden, but rather represent the value for the total amount produced at the production site.

A template for the calculations and the requested data is provided in Appendix 1. During this project all the documents and calculations received are regarded as confidentially data. In Appendix 2 fictious example data is used to demonstrate how to fill in the requested data.

PEC-local calculation

The PEC-local calculation is based on the PEC-calculation used in the Fass system today with some alterations made in order to reflect local emissions from production rather than emissions after use (FASS guideline, 2012 v3.0). In the PEC-local calculation, local emission of API into the wastewater, removal rate in sewage treatment facilities, wastewater volume through which the API is released to the environment, and a dilution factor by which the wastewater is diluted in the recipient is taken into consideration. The formula is presented below:

$$PEC_{local}\ (\mu g/L) = A * 10^9 * \frac{(100 - R)}{V * D * 100}$$

where:

A = Emission(s) of product API:
Emissions of product API is the amount of API (kg) that disappears through the wastewater per year. Local emissions of API can occur from different manufacturing process steps, such as in the production of the API, the formulation process and also during packaging. Emissions from all relevant process steps should be included. If more than one production site is involved in the production at different locations, the result for each location should be reported. Please provide data and information to justify the reported value of A.

The API emissions can be calculated via theoretical yield minus produced amount. The amount of API is usually calculated by mass balance/yield analysis calculations. Based on the path of synthesis and the amount of input of raw material the theoretical yield can be calculated. By comparing that number to the amount that has been produced, it is possible to estimate the amount of substance that has been lost to the environment.

As an example, figure 1 illustrates different emission steps of API from the operating facility via several wastewater treatment facilities before it finally reaches the recipient (Figure from PSCI Webinar, Managing active pharmaceutical ingredients in manufacturing effluent, Part 2 (June 2016)).

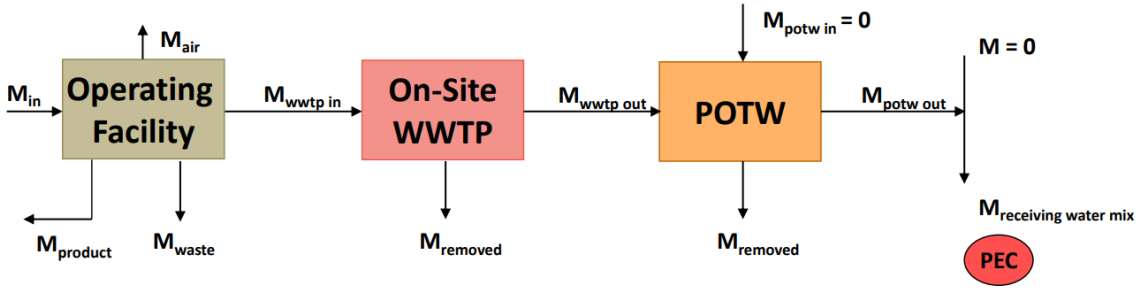

Figure 1. Illustration of emissions of API (A) by mass balance. Picture from PSCI Webinar, Managing active pharmaceutical ingredients in manufacturing effluent, Part 2 (June 2016). M=mass of API, WWTP = Wastewater Treatment Plant, POTW = Publicly Owned Treatment Plant (off-site).

If the company perform representative sampling and chemical analysis of effluents, this may also be used as basis for the emission calculations. In order to ensure the quality of the data, the sampling and analyses should be performed according to ISO 5667-10 (Water quality – Sampling – Part 10: Guidance on sampling of wastewaters). If measured concentrations are used in the calculation, information regarding sampling place and method should be provided in the background information.

R = Removal rate:
If the wastewater is treated before entering the recipient(s) and API is removed in the process, it is possible to use a removal rate (%) in the calculation of PEC-local. If a removal rate is used, a brief description of the wastewater treatment facility and how the rate is obtained should be provided as justification. Both on-site and off-site treatment of the wastewater could be included in the calculation if it is not an antimicrobial substance. For antimicrobial substances only on-site treatment is allowed to be included in the calculation. If no data is available, the default value of R = 0 should be used.

V = Wastewater volume:
Report the wastewater volumes through which API is released to the environment, for all relevant sites both on-site and off-site (L/year). Please provide data and information to justify the chosen wastewater volume.

D = Dilution factor:
Describe the localization(s) of the water body that receives the (treated) wastewater from the API production, formulation of tablet and any other relevant sites of API emissions. The description should preferably be on region/city/name of recipient, or at least at a national level (country). Based on that information, extract the relevant dilution factor from Keller et al (2014). Companies are, however, encouraged to use their own value for dilution. The dilution factor should represent the annual median dilution, except for areas with large seasonal variations, where average low flow data should be used for the calculations. Please provide data and information to justify the chosen dilution factor.

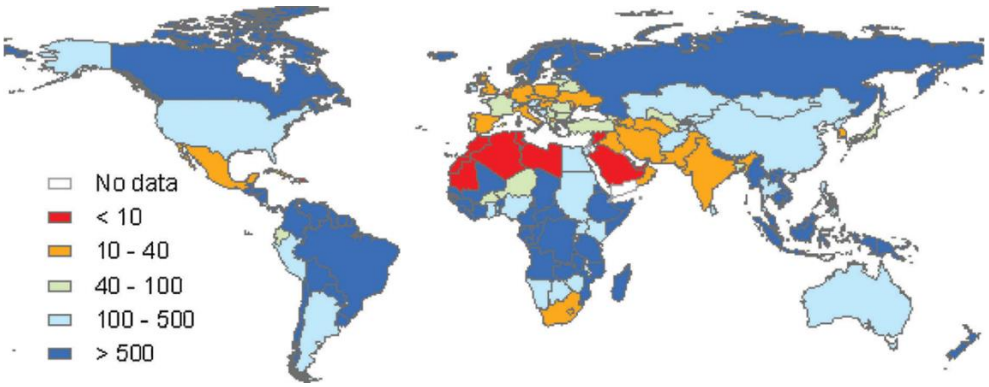

Figure 2. Modelled dilution factors per country from Keller et al (2014).

PNEC-calculation

The PNEC-calculation is based on the EMA guideline for environmental risk assessment (2006) and the requirements and requested data are described in the Fass guideline (2012 v3.0).

A PNEC value should ideally be based on ecotoxicological data from three trophic levels (usually algae, crustaceans and fish) and contain data on long-term studies. If long-term data is lacking, short-term ecotoxicological data may be used instead. Depending on the number of long-term data available different assessment factors (AF) are applied to the calculation in order to account for the extrapolation between laboratory and field studies. An AF of 1000 is normally applied to the most sensitive of three short-term toxicity endpoints. However, the AF may be reduced to 100, 50 or 10, depending on the number of long-term NOEC (No Observed Effect Concentration) endpoints available, providing long-term data are available for the species with the lowest acute value.

Antimicrobial substances

For antimicrobial substances only removal rates (%) for on-site wastewater treatment is allowed in the PEC-local calculation. The reason is that public wastewater treatment facilities have been shown to be a hot spot for the development of antimicrobial resistance and rather increase the risk than diminish it (Access to Medicine Foundation, 2021).

For antimicrobial substances two PNEC-values should be determined: an ecotoxicological PNEC-value and a PNEC-value for resistance, called PNEC-R. For both PNEC-values an assessment factor of 10 should be used.

The ecotoxicological PNEC-value should be derived from an OECD 201 test on cyanobacteria, or equivalent and reflect ecotoxicological effect-limits in the recipient. The PNEC-R value on the other hand, should be based on resistance selection of bacteria in the wastewater after the on-site treatment facility.

There is no standardized way to determine PNEC-R, but one commonly accepted method is a model developed by Bengtsson-Palme and Larsson (2016), which uses sample size adjusted data on lowest minimum inhibitory (growth) concentration (MIC) data from the European Committee on Antimicrobial Susceptibility Testing database (EUCAST). Another way to determine the PNEC-R value could be based on the minimum selective concentration (MSC). MSC is defined as the minimum concentration at which the presence and expression of resistance genes provide bacteria an advantage due to fitness over nonresistance strains of the same species or strain (Le Page et al, 2017). When several PNEC and/or PNEC-R values are found for antimicrobial substances, the lowest of them should be used in the following risk calculation. When no data are found a default value of 0.05 µg/L should be used (Vestel et al, 2021). For all antimicrobial studies an AF of 10 should be used.

Please note that there exist several databases with ecotoxicological-PNEC as well as PNEC-R values for different APIs. Information from such databases or the scientific literature may also be used in order to obtain a PNEC-value. The Norman network holds a database containing nearly 95 000 substances with lowest PNEC values at their home page: https://www.norman-network.com/nds/ecotox/ and the AMR Industry Alliance has a list of 125 PNEC and PNEC-mic values for antibiotic substances, which is found here:

https://www.amrindustryalliance.org/wp-content/uploads/2018/09/AMR_Industry_Alliance_List-of-Predicted-No-Effect-Concentrations-PNECs.pdf.

Both the ecotoxicological PNEC- as well as the PNEC-R values should be presented. The lowest of the two should be used in the following risk calculation. Please note that if no PNEC-data is presented for the API an environmental risk phrase cannot be obtained.

Environmental risk phrase

Based on the PEC-local/PNEC-ratio an environmental risk phrase will be obtained for each site (see Table 1).

Table 1. PEC-local/PNEC ratio and corresponding Environmental risk phrase.

PEC-local/PNEC ratio	**Environmental risk phrase**
PEC-local/PNEC ≤ 0.1	Emissions from production of *name of the product* has been considered to result in insignificant environmental risk.
0.1 < PEC-local/PNEC ≤ 1	Emissions from production of *name of the product* has been considered to result in low environmental risk.
1 < PEC-local/PNEC ≤ 10	Emissions from production of *name of the product* has been considered to result in moderate environmental risk.
PEC-local/PNEC > 10	Emissions from production of *name of the product* has been considered to result in high environmental risk.
If there is no data to calculate the PEC-local/PNEC.	Risk of environmental impact during production of *name of the product* cannot be excluded, since no ecotoxicity data are available.
If there is some, but not sufficient data to calculate the PEC-local/PNEC.	Risk of environmental impact during production of *name of the product* cannot be excluded, since there is not sufficient ecotoxicity data available.

Complex value chains

The model is based on emissions of API from production, formulation, and packaging sites in different parts of the world. When all production processes are placed at a single site and owned or within control of the reporting company the data is usually feasible to acquire, and the calculation is simple to perform (see Figure 3).

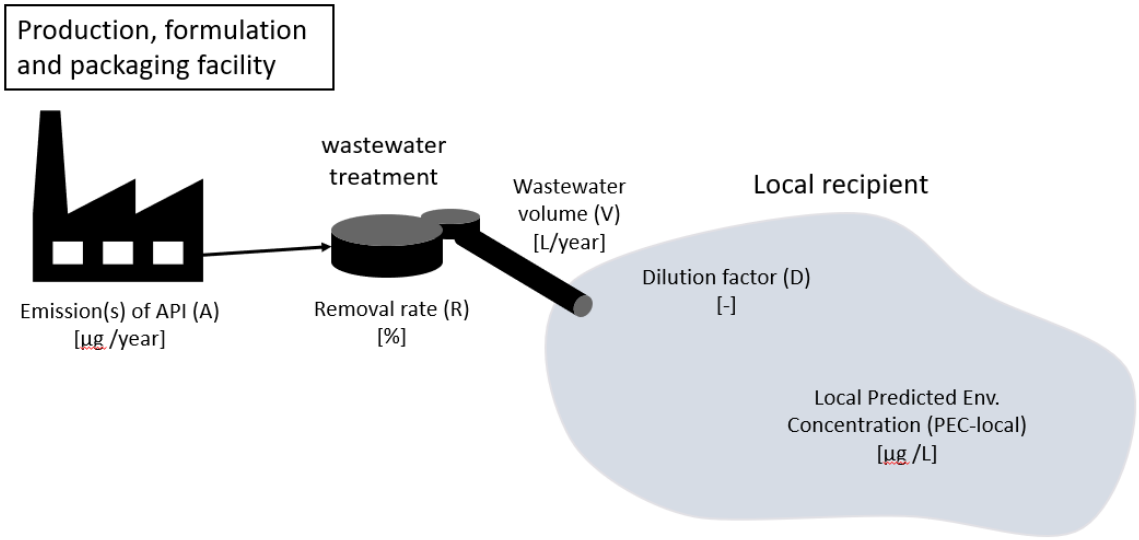

Figure 3. Illustration of a single site production process and the parameters in the PEC-local calculation.

In most cases, however, the pharmaceutical production process is far more complex with several different sites involved in various parts of the world. When there are complex value chains with several different sites involved in the process of pharmaceutical production it is important to calculate and report a PEC-local value for each site. In case of missing data from one or more site(s) that should also be reported. It is preferable to add a figure to illustrate the value chain.

For each site involved in the production of a pharmaceutical, a risk phrase should be retrieved by the ratio of each PEC-local value by the PNEC-value for the substance. Data for all sites involved in the value chain should be reported. The final risk phrase for the product will be represented by the site with the highest risk phrase in the value chain.

References

Access to Medicine Foundation, *Antimicrobial Resistance Benchmark 2021.* https://accesstomedicinefoundation.org/media/uploads/downloads/61ee758c8c1e3_Antimicrobial%20Resistance%20Benchmark%20report%202021.pdf

AMR Industry Alliance. *AMR Industry Alliance Antibiotic Discharge Targets. List of Predicted No-Effect Concentrations (PNECs).* https://www.amrindustryalliance.org/wp-content/uploads/2018/09/AMR_Industry_Alliance_List-of-Predicted-No-Effect-Concentrations-PNECs.pdf

Bengtsson-Palme J., and Larsson D.G.J., 2016, *Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation*. Environmental International, Volume 86, January 2016, p 140-149. https://reader.elsevier.com/reader/sd/pii/S0160412015300817?token=C83DB19C31D8C9678F599E2A56EB30FBA13A06B4A220B0651E1E694E383EF8887ABE2430AC008E312BA24EF053200D39&originRegion=eu-west-1&originCreation=20220701064252

Committee for Medicinal Products for Human Use (CHMP); *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use*. 1 June 2006, Ref EMEA/CHMP/SWP/4447/00. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-first-version_en.pdf

EUCAST database – European Committee on Antimicrobial Susceptibility Testing, European Society of Clinical Microbiology and Infectious Diseases. https://mic.eucast.org/search/

Fass guideline v3.0 (2012). *Environmental classification of pharmaceuticals at www.fass.se. Guidance for pharmaceutical companies*, 2012, v3.0. https://www.lif.se/contentassets/b7cf255755504f78a906f3eba8a6ae38/environmental-classification-of-pharmaceuticals-att-wwwfassse.pdf

Le Page G., Gunnarsson L., Snape J., Tyler C.R., (2017), *Integrating human and environmental health in antibiotic risk assessment: A critical analysis of protection goals, species sensitivity and antimicrobial resistance.* Environmental International, Volume 109, December 2017, p 155-169. https://reader.elsevier.com/reader/sd/pii/S0160412017309005?token=A87F52E24A3140A2CDC7F0D5589037490BCB96747DC889B4D7F339BFBADA9BD7D5EF69D9658AA7C60ABF6EFB1B8BB6C1&originRegion=eu-west-1&originCreation=20220701065648

NORMAN – Network of reference laboratories, research centres and related organisations for monitoring of emerging environmental substances, *Norman Ecotoxicology Database.* https://www.norman-network.com/nds/ecotox/

ISO standard, ISO 5667-10:2020; *Water quality – Sampling – Part 10: Guidance on sampling of waste water*. https://www.iso.org/standard/70934.html

Keller, V.D.J., et al. (2014) *Worldwide estimation of river concentrations of any chemical originating from sewage-treatment plants using dilution factors.* Environmental Toxicology and chemistry. Vol 33, no 2 447-452.
https://setac.onlinelibrary.wiley.com/doi/epdf/10.1002/etc.2441

PSCI Webinar, *Managing active pharmaceutical ingredients in manufacturing effluent part 2* (15th June 2016). https://pscinitiative.org/resource?resource=295

Vestel J., Caldwell D.J., Tell J., Constantine L., Häner A., Hellstern J., Journel R., Ryan J.J., Swenson T., and Xei W., (2021), *Default predicted no-effect target concentrations for antibiotics in the absence of data for the protection against antibiotic resistance and environmental toxicity*. Integrated Environmental Assessment and Management, Volume 18, Number 4, p 863-867, November 2021
https://setac.onlinelibrary.wiley.com/doi/pdf/10.1002/ieam.4560

Appendix 1 – Template

Data summary

Name of pharmaceutical company: *add company name*

Name of pharmaceutical product: *add product name*

Name of active pharmaceutical ingredient (API): *add API name*

PEC-local = *add concentration for the site with the highest value* µg/L

PNEC = *add concentration* µg/L

PEC/PNEC = *add ratio*

Environmental risk phrase: **Emissions from production of **name of the product** has been considered to result in **insert risk phrase** environmental risk.**

or,

Environmental risk phrase: **Risk of environmental impact during production of **name of the product** cannot be excluded, since **add risk phrase*.**

Predicted Environmental Concentration at local production site (PEC-local)

PEC-local is calculated according to the following formula:

PEC-local (µg/L) = $(A*10^{9}*(100-R))/(V*D*100)$

Where:

A = *add total emissions of API* kg/year (total emission of API to wastewater per year)

R = *add percentage removal* % *and a justification to the value* (due to removal in waste-water treatment facilities, R = 0 if no data is available)

V = *add wastewater volume* L/year (volume of wastewater discharged per year)

D = *add dilution factor* (factor for dilution of wastewater by predicted annual median dilution or average low flow data for areas with large seasonal variations)

Based on data given above, this results in:

PEC-local = *(xx*10^{9}*(100-xx)) / (xx*xx*100) = xx µg/L*

NOTE: if more than one site is involved in the production, formulation and/or packaging of the API, a separate PEC-local calculation should be provided for each site involved. Thus, if more than one site is involved in the production process, please copy the text above and provide PEC-local data for each site. If possible, please also include an illustration of the value chain.

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies*

Algae (Latin name) (*guideline eg OECD 201*) (*Reference*):

EC_{50} *(duration) (endpoint) = xx* µg/L

EC_{10} or NOEC *(endpoint) = xx* µg/L

Crustacean (Latin name):

Acute toxicity

EC_{50} *(duration)* h (*endpoint*) = *xx* µg/L *(guideline eg OECD 202) (Reference)*

Chronic toxicity

EC_{10} or NOEC *(duration)* days (*endpoint*) = *xx* µg/L *(guideline eg OECD 211) (Reference)*

Fish (Latin name):

Acute toxicity

LC_{50} *(duration)* h *(endpoint) = xx* µg/L *(guideline eg OECD 203) (Reference)*

Chronic toxicity

EC_{10} or NOEC *(duration)* days *(endpoint) = xx* µg/L *(guideline eg OECD 210) (Reference)*

Other ecotoxicity data: *xx*

Assessment factor (AF) = *xx* e.g., 1000, 100 or 10 (justification of chosen assessment factor (AF)) *add justification*

PNEC = lowest EC_{10} or NOEC/assessment factor = *xx/xx* = *xx* µg/L

Based on data given above, this results in:

PNEC = add concentration µg/L

**if the ecotoxicological test is not standardized please specify the test with additional relevant data (e.g., medium, temperature, exposure regime, number of replicates & test geometry)*

For antimicrobial substances a PNEC-R value should also be presented.

PNEC-R = *add concentration µg/L, (add name of database or study). Use the default value of 0.05 µg/L if no other data is found (reference Vestel et al, 2021).*

The lowest of the two PNEC-values should be used in the following risk calculation for antimicrobial substances together with an AF of 10 (default).

Lowest PNEC/10 (for antimicrobial substances): ***add concentration µg/L***

Environmental risk classification (PEC/PNEC ratio)

According to data presented above:

<u>Environmental risk phrase for site 1:</u>

PEC-local 1 = *xx* µg/L

PNEC = *xx* µg/L

PEC-local 1/PNEC = *xx* µg/L

xx < PEC/PNEC ≤ *xx* which justifies the phrase 'Emissions from production of **name of the product** has been considered to result in *insignificant / low / moderate / high environmental risk* (choose risk phrase).'

or,

Risk of environmental impact during production of **name of the product** cannot be excluded, since *there is no / not sufficient ecotoxicity data available (choose risk phrase).*

NOTE: if more than one site is involved in the production, formulation and/or packaging of the API, a risk calculation should be provided for each site involved. Thus, if more than one site is involved in the production process, please copy the text above and provide data for each site. The final risk phrase for the pharmaceutical product is then represented by the site with the highest risk phrase.

Add the text below for products with a complex value chain with more than one PEC/PNEC-calculation:

Final environmental risk phrase for *name of the product*:

Based on the data given above the final risk phrase for **name of the product** is: ’Emissions from production of *name of the product* has been considered to result in moderate environmental risk’, which represents the site with the highest risk phrase in the value chain.

References

Please insert the list of used references from the literature here.

Appendix 2 – Example data

This is an example of how to calculate PEC, PNEC and Environmental risk using fictitious data.

Data summary

Name of pharmaceutical company: *nn*

Name of pharmaceutical product: *nn*

Name of active pharmaceutical ingredient (API): *nn*

PEC-local = 10.0 µg/L

PNEC = 1.5 µg/L

PEC/PNEC = 6.67 µg/L

Environmental risk phrase: ***Emissions from production of *name of the product* has been considered to result in moderate environmental risk***.

Predicted Environmental Concentration at local production site (PEC-local)

PEC-local is calculated according to the following formula:

PEC-local (µg/L) = $(A*10^{9}*(100-R))/(V*D*100)$

Figure 1 illustrates the value chain for **name of the product**. Since there is no emission of the API to the environment at the packaging site, there will be three PEC-local calculations.

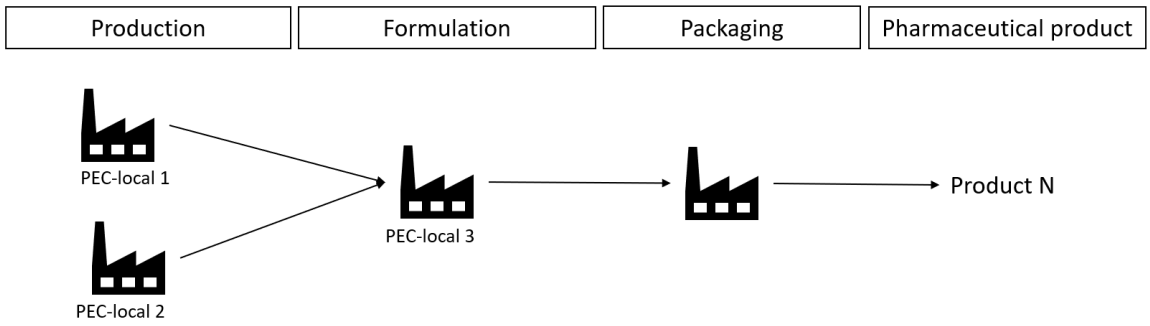

Figure 1. Illustration of the value chain for the production of **name of the product**.

PEC-local 1:

A = *10 kg/year* (total emission of API to wastewater per year). The value for A is based on the following mass balance calculations: ….

R = *25 %* (due to removal in waste-water treatment facilities, R = 0 if no data is available). The site is equipped with the following waste-water treatment facilities: … and the value of R is based on the following calculations …

V = *400x10^{6} L/year* (volume of wastewater discharged per year)

D = *The site is located in country C, where the dilution factor is D=36* (factor for dilution of wastewater by predicted annual median dilution or average low flow data for areas with large seasonal variations)

Based on data given above, this results in:

PEC-local 1 = *(10*10^{9}*(100-25)) / (400 000 000*36*100) = 0.52 µg/L*

PEC-local 2:

A = *100 kg/year* (total emission of API to wastewater per year). The value for A is based on the following mass balance calculations: ….

R = *50 %* (due to removal in waste-water treatment facilities, R = 0 if no data is available). The site is equipped with the following waste-water treatment facilities: … and the value of R is based on the following calculations …

V = 5*00x10^{6} L/year* (volume of wastewater discharged per year)

D = *50 based on the following calculations of average low flow data for the recipient: …* (factor for dilution of wastewater by predicted annual median dilution or average low flow data for areas with large seasonal variations)

Based on data given above, this results in:

PEC-local 2 = *(100*10^{9}*(100-50)) / (500 000 000*50*100) = 2.0 µg/L*

PEC-local 3:

A = *20 kg/year* (total emission of API to wastewater per year). The value for A is based on the following mass balance calculations: ….

R = *0 %* (due to removal in waste-water treatment facilities, R = 0 if no data is available).

V = *200x10^6 L/year* (volume of wastewater discharged per year)

D = *10 based on the following calculations of average low flow data for the recipient: …* (factor for dilution of wastewater by predicted annual median dilution or average low flow data for areas with large seasonal variations)

Based on data given above, this results in:

PEC-local 3 = *(20*10^9*(100-0)) / (200 000 000*10*100) = 10.0 µg/L*

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies*

Green Algae (Pseudokirchneriella subcapitata) (guideline OECD 201) (Reference)*:*

EC_{50} 72 h (growth rate) = 320 µg/L

NOEC (growth rate) < 100 µg/L

Giant Water Flea (Daphnia magna):

Acute toxicity

EC_{50} 48 h (immobility) = 50 µg/L (guideline OECD 202) (Reference)

Chronic toxicity

NOEC 28 days (reproduction) = 15 µg/L (guideline OECD 211) (Reference)

Zebra Fish (Danio rerio):

Acute toxicity

LC_{50} 96 h (mortality) = 1700 µg/L (guideline OECD 203) (Reference)

Chronic toxicity

NOEC 14 days (hatching rate) = 360 µg/L (guideline OECD 210) (Reference)

Other ecotoxicity data: not available

Assessment factor (AF) = 10 (tests on species from three trophic levels with chronic tests justifies an AF of 10)

PNEC = lowest EC_{10} or NOEC/assessment factor = 15/10 =1.5 µg/L

Based on data given above, this results in:

PNEC = 1.5 µg/L

**if the ecotoxicological test is not standardized please specify the test with additional relevant data (e.g., medium, temperature, exposure regime, number of replicates & test geometry.*

Environmental risk classification (PEC/PNEC ratio)

According to data presented above:

Environmental risk phrase for site 1:

PEC-local 1 = *0.52* µg/L

PNEC = *1.5* µg/L

PEC-local 1/PNEC = *0.35* µg/L

0.1 < PEC/PNEC ≤ 1 which justifies the phrase 'Emissions from production of *name of the product* has been considered to result in low environmental risk.'

Environmental risk phrase for site 2:

PEC-local 2 = *2.0* µg/L

PNEC = *1.5* µg/L

PEC-local 2/PNEC = *1.33* µg/L

1 < PEC/PNEC ≤ 10 which justifies the phrase 'Emissions from production of *name of the product* has been considered to result in moderate environmental risk.'

Environmental risk phrase for site 3:

PEC-local 3 = *10.0* µg/L

PNEC = *1.5* µg/L

PEC-local 3/PNEC = *6.67* µg/L

1 < PEC/PNEC ≤ 10 which justifies the phrase ’Emissions from production of *name of the product* has been considered to result in moderate environmental risk.’

Final environmental risk phrase for *name of the product*:

Based on the data given above the final risk phrase for **name of the product** is: **’Emissions from production of *name of the product* has been considered to result in moderate environmental risk’**, which represents the site with the highest risk phrase in the value chain.

References

Please insert the list of references here.

Feedback questions for further development of the model

Since the method for environmental risk assessment of pharmaceutical production is under development, we would appreciate if you would answer the following questions:

1. Was the model for PEC-local easy to understand?
2. Was the information required for calculation of PEC local easy to locate?
3. Did you already have the information or was a calculation/investigation required?
4. What type of in data did you use for the PEC-local calculation and why?
5. Do you see any uncertainties with the model (in data and so on)?
6. Did you have a complex value chain for your product?
7. Was the information needed from the complex value chain analysis easy to locate?
8. Did you already have the information for the complex value chain or was an investigation/calculation needed?
9. Was there data that you were unable to locate? Why?
10. Was the Appendix with the template and/or example data helpful?
11. Do you have any suggestions for development of the template and/or example data?
12. Would you agree on sharing the summary data presented at the top of Appendix 1 to a procurement organization in a procurement situation?* If not – why?
13. Would you agree on sharing any other information presented in Appendix 1 to a procurement organization in a procurement situation, if yes what? *
14. Any other comments?

*Please note that no information will be shared in this project.

CONFIDENTIALITY AGREEMENT

Between

IVL Svenska Miljöinstitutet AB, reg. no 556116-2446,", Box 21060, 100 31 Stockholm, Sweden, hereinafter "IVL and ……..

the following Confidentiality agreement has been met, hereinafter the "Agreement".

The Company and IVL are collectively referred to as the "Parties" and individually as "Party".

1. Background, purpose etc.

1.1 IVL is currently working on a project together with the Swedish Association of the pharmaceutical industry (*Sw. Läkemedelsindustriföreningen, "**LIF**"*) in order to test a model for environmental assessment of pharmaceuticals (the "**Purpose**"). In order to perform the test the company will submit information concerning chosen pharmaceutical products.

1.2 Within the Purpose stated in section 1.1 the Company will give IVL access to Confidential Information. "Confidential information" means any information which, through marking or otherwise, has been declared by the Company to be of confidential nature, except for:

a) information which is generally known or becomes publicly known in a manner other than through IVL's breach of the content of this Agreement;

b) information which IVL can show that IVL already knew before receiving it from the Company; or

c) information received or that will be received from a third party without being bound by any confidentiality undertaking in relation to the third party.

2. Confidentiality undertaking

2.1 IVL undertakes not to disclose for a third party any Confidential Information which IVL receives from the Company. IVL undertakes to ensure that its' employees, consultants and board members do not pass on confidential information to third parties. IVL is not entitled to use Confidential Information other than for the Purpose stated in section 1.1 above.

2.2 The Parties undertake, without limitation in time, not to reveal without compelling reason:

a) the existence of this Agreement or arbitration pursuant to this Agreement (however, IVL is entitled to invoke the cooperation under this Agreement as a reference object),

b) the content of this Agreement or arbitration pursuant to this Agreement; or

c) information on negotiations, arbitration or mediation pursuant to this Agreement.

2.3 The obligations under this Agreement regarding Confidential Information shall not prevent IVL from disclosing or providing information if, and to the extent, IVL is obliged to disclose it under mandatory law, judgement or decision by an authority.

2.4 At the Company's request IVL shall as soon as possible return or destroy all copies of Confidential Information received in documented form.

3. Term of the Agreement

3.1 This Agreement enters into force when duly signed by the Parties and is valid for a period of three (3) years from the signing date.

4. Choice of law and Dispute resolution

4.1 This Agreement shall be governed by Swedish law.

4.2 Any dispute, controversy or claim arising out of or in connection with this Agreement, or the breach, termination or invalidity thereof, shall be finally settled by arbitration administered by the Arbitration Institute of the Stockholm Chamber of Commerce (the "SCC"). The Rules for Expedited Arbitrations shall apply, unless the SCC in its discretion determines, taking into account the complexity of the case, the amount in dispute and other circumstances, that the Arbitration Rules shall apply. In the latter case, the SCC shall also decide whether the Arbitral Tribunal shall be composed of one or three arbitrators. The seat of the arbitration shall be Stockholm.

_____

This Agreement has been executed in two (2) originals of which the Parties have taken one (1) each.

Place	Date	Place	Date
……	…….....	.....	.....

IVL SVENSKA MILJÖINSTITUTET AB

……...	……...
Signature	Signature
……	……
Printed name	Printed name