AMR Alliance Science-Based PNEC Targets for Risk Assessments

The members of the AMR Industry Alliance have developed a unified approach to establishing discharge targets for antibiotic manufacturing, based on Predicted No-Effect Concentrations (PNECs) for use in environmental risk assessments of antibiotics. The discharge target can be derived using these PNECs and site-specific parameters. The publication of the PNEC table fulfills the commitment of the AMR Industry Alliance to publish science-driven, risk-based targets for discharge concentrations of antibiotics. The pharmaceutical industry, as member companies of the Alliance, have collated, shared, analyzed, and published existing antibiotic data with respect to antimicrobial resistance and ecotoxicity.

The PNEC is the concentration in the environment at which minimal impact is expected. The PNEC table contains two values: the PNEC-Environment (PNEC-ENV) and the PNEC-Minimum Inhibitory Concentration (PNEC-MIC). Both PNEC-ENV and PNEC-MIC values are important parameters relevant for water quality.

The PNEC-ENV values are based on ecotoxicology data generated by Alliance member companies and relevant peer-reviewed literature and are intended to be protective of the species within the ecosystems of receiving water bodies. The PNEC-ENV is derived from effect concentrations determined in ecotoxicity studies by applying an assessment factor (AF) consistent with standard environmental risk methodologies. The AF is a safety factor that accounts for uncertainties in the extrapolation from a limited number of test species to complex ecosystems in the receiving environment. Cyanobacteria are considered most sensitive test species to antibiotics; therefore, data sets are considered complete if cyanobacteria data are available, following the OECD 201 Guideline or equivalent.[1]

The PNEC-MIC values are determined based on the approach published by Bengtsson-Palme and Larsson (2016) and are intended to minimize the risk of AMR development.[2] The PNEC-MIC is derived from publicly available minimum inhibitory concentration data, e.g., from the EUCAST database, and is based on the 1% lowest MIC, adjusted for the number of species tested. An AF is then applied to account for differences between MICs and minimal selective concentrations. This table will be updated periodically as new reliable and robust data becomes available.

The lowest of the two PNEC values (PNEC-ENV and PNEC-MIC) shall be used to conduct an antibiotic manufacturing emission risk assessment. At this time, the PNEC-MIC value is adopted as the best-available proxy to mitigate the risk of resistance promotion (PNEC-res); therefore, if no compound-specific PNEC-MIC value is available, a default PNEC-MIC of 0.05 µg/L, based on a statistical analysis of available data, has to be used.[3] In the event that compound-specific MIC data is available in EUCAST, but no PNEC-MIC is listed in this Table, member companies may contact AMRIA to request a PNEC-MIC be derived from the data available in EUCAST (info@amrindustryalliance.org).

If no PNEC-MIC data are available in EUCAST but a member company has appropriate MIC data generated in accordance with EUCAST criteria[4], a request may be made to AMRIA (info@amrindustryalliance.org) to set a PNEC-MIC. For quality and consistency purposes, AMRIA will only evaluate MIC data that has also been submitted to EUCAST.

In order to seek certification, a PNEC-MIC value must be included in this table.

The publication of this table is an important step in the journey of evaluating antibiotic discharge concentrations using science-driven, risk-based targets, allowing Alliance member companies to work toward achieving these target values in the receiving water body. The AMR Industry Alliance believes working toward achieving these antibiotic discharge concentration targets will reduce ecological impacts and minimize the risk for the selection and evolution of AMR in the environment. It is important to note that these values are recommended based on currently available information and thus may change as new reliable and relevant information generated based on recognized protocols comes to light.

[1] Tell J, Caldwell DJ, Häner A, Hellstern J, Hoeger B, Journel R, Mastrocco F, Ryan JJ, Snape J, Straub JO, Vestel J (2019): Science-based targets for antibiotics in receiving waters from pharmaceutical manufacturing operations. Integr Environ Assess Manag 15(3):312–319. https://doi.org/10.1002/ieam.4141

[2] Bengtsson-Palme J, Larsson D.G.J (2016): Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. Environment International 86: 140–149. http://dx.doi.org/10.1016/j.envint.2015.10.015

[3] Vestel J, Caldwell DJ, Tell J, Constantine L, Häner A, Hellstern J, Journel R, Ryan JJ, Swenson T, Xei W (2022): Default predicted no-effect target concentrations for antibiotics in the absence of data for the protection against antibiotic resistance and environmental toxicity. Integr Environ Assess Manag 18(4):863–867. https://doi.org/10.1002/ieam.4560

[4] EUCAST MIC Determination of non-fastidious and fastidious organisms. https://www.eucast.org/bacteria/methodology-and-instructions/mic-determination/

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Active Pharmaceutical Ingredient	PNEC-ENV (µg/L)	PNEC-MIC (µg/L)	Lowest Value (µg/L)
Amikacin	18.7	16	16
Amoxicillin	0.57	0.25	0.25
Ampicillin	0.6	0.25	0.25
Avilamycin	125	8	8
Azithromycin	0.03	0.25	0.03
Aztreonam	150	0.5	0.5
Bacitracin	114.6	8	8
Bedaquiline	0.08	0.016	0.016
Benzylpenicillin	3.11	0.25	0.25
Capreomycin	N/A	2	2
Cefaclor	N/A	0.5	0.5
Cefadroxil	0.14	2	0.14
Cefaloridine	N/A	4	4
Cefalothin	N/A	2	2
Cefazolin	0.47	1	0.47
Cefdinir	N/A	0.25	0.25
Cefepime	1.3	0.5	0.5
Cefixime	0.64	0.06	0.06
Cefoperazone	N/A	0.5	0.5
Cefotaxime	0.12	0.125	0.12
Cefoxitin	N/A	8	8
Cefpirome	N/A	0.06	0.06
Cefpodoxime	1.76	0.25	0.25
Cefquinome	1.6	0.125	0.125
Cefradine (cephradine)	0.19	32	0.19
Ceftaroline	0.12	0.06	0.06
Ceftazidime	1.3	0.5	0.5
Ceftibuten	N/A	0.25	0.25
Ceftiofur	0.4	0.06	0.06
Ceftobiprole	0.23	0.25	0.23
Ceftolozane	1.9	2	1.9
Ceftriaxone	0.33	0.03	0.03
Cefuroxime	1.7	0.5	0.5
Cephalexin	0.21	4	0.21
Chloramphenicol	N/A	8	8

Active Pharmaceutical Ingredient	PNEC-ENV (µg/L)	PNEC-MIC (µg/L)	Lowest Value (µg/L)
Chlortetracycline	5	1	1
Ciprofloxacin	0.45	0.06	0.06
Clarithromycin	0.25	0.25	0.25
Clinafloxacin	N/A	0.5	0.5
Clindamycin	0.1	1	0.1
Clofazimine	N/A	0.03	0.03
Cloxacillin	20	0.125	0.125
Colistin (Polymyxin E)	9	2	2
Dapsone	N/A	0.05 (default)	0.05
Daptomycin	510	1	1
Delamanid	0.03	0.05 (default)	0.03
Doripenem	0.46	0.125	0.125
Doxycycline	25.1	2	2
Enrofloxacin	1.91	0.06	0.06
Ertapenem	14	0.125	0.125
Erythromycin	0.5	1	0.5
Ethambutol	75	2	2
Faropenem	N/A	0.016	0.016
Fidaxomicin	891	0.016	0.016
Florfenicol	38	2	2
Flucloxacillin	26.8	0.125	0.125
Flumequine	N/A	0.25	0.25
Fosfomycin	52.4	2	2
Fusidic acid	N/A	0.5	0.5
Framycetine	N/A	0.05 (default)	0.05
Gamithromycin	0.24	0.5	0.24
Gatifloxacin	N/A	0.125	0.125
Gemifloxacin	N/A	0.06	0.06
Gentamicin	0.15	1	0.15
Gepotidacin	6	1	1
Imipenem	0.41	0.125	0.125
Isoniazid	1290	0.125	0.125
Kanamycin	1.05	2	1.05
Levofloxacin	1.52	0.25	0.25
Lincomycin	0.81	2	0.81

Active Pharmaceutical Ingredient	PNEC-ENV (µg/L)	PNEC-MIC (µg/L)	Lowest Value (µg/L)
Linezolid	3.5	8	3.5
Loracarbef	N/A	2	2
Mecillinam	N/A	1	1
Meropenem	1.5	0.06	0.06
Metronidazole	N/A	0.125	0.125
Minocycline	1.1	1	1
Moxifloxacin	N/A	0.125	0.125
Mupirocin	N/A	0.25	0.25
Nalidixic acid	N/A	16	16
Narasin	N/A	0.5	0.5
Neomycin	0.03	2	0.03
Netilmicin	N/A	0.5	0.5
Nitrofurantoin	N/A	64	64
Norfloxacin	120	0.5	0.5
Ofloxacin	10	0.5	0.5
Omadacycline	N/A	1	1
Oxacillin	N/A	1	1
Oxytetracycline	47	0.5	0.5
Pefloxacin	N/A	8	8
Phenoxymethylpenicillin	0.96	0.06	0.06
Phenoxymethylpenicillin procaine	16.0	0.06	0.06
Piperacillin	4.3	0.5	0.5
Pivmecillinam	N/A	0.05 (default)	0.05
Polymyxin B	0.06	2	0.06
Pretomanid	N/A	0.05 (default)	0.05
Retapamulin	N/A	0.06	0.06
Rifampicin	4.06	0.06	0.06
Rifamycin	1	0.05 (default)	0.05
Rifaximin	0.11	0.05 (default)	0.05
Roxithromycin	6.84	1	1
Secnidazole	N/A	1	1
Sparfloxacin	N/A	0.06	0.06
Spectinomycin	N/A	32	32
Spiramycin	1.09	0.5	0.5

Active Pharmaceutical Ingredient	PNEC-ENV (µg/L)	PNEC-MIC (µg/L)	Lowest Value (µg/L)
Streptomycin	N/A	16	16
Sulfadiazine	11.21	0.05 (default)	0.05
Sulfamethoxazole	6.6	16	6.6
Sulfanilamide	230	0.05 (default)	0.05
Tedizolid	3.2	0.5	0.5
Teicoplanin	12.9	0.5	0.5
Telithromycin	N/A	0.06	0.06
Tetracycline	3.2	1	1
Thiamphenicol	N/A	1	1
Tiamulin	N/A	1	1
Ticarcillin	N/A	8	8
Tigecycline	0.1	1	0.1
Tildipirosin	0.42	4	0.42
Tilmicosin	0.8	1	0.8
Tobramycin	4.3	1	1
Trimethoprim	928	0.5	0.5
Trovafloxacin	N/A	0.03	0.03
Tylosin	0.98	4	0.98
Vancomycin	13.5	8	8
Viomycin	N/A	2	2
Virginiamycin	71.1	2	2