Medicines for Europe note on the list of substances found in urban wastewater, compiled by Bio Innovation Service for the Extended Producer Responsibility feasibility report informing the Urban Wastewater Treatment Directive Impact Assessment

7 July 2025

The list of substances used in the Impact Assessment[1] of the Urban Wastewater Treatment Directive (UWWTD) to determine toxic load percentages of different sectors in urban wastewater is fundamentally limited in accuracy, raising serious concerns about its validity and reliability. The list was compiled by the consultancy Bio Innovation Service,[2] which prepared the 2022 **feasibility report on the introduction of an Extended Producer Responsibility** [3] informing the Impact Assessment, largely based on Joint Research Centre (JRC) data on concentrations and Predicted No-Effect Concentration (PNEC)[4] values of chemicals found in urban wastewater.

Medicines for Europe strongly believes that **this list should not have been utilised by the European Commission as a justification for the introduction of an Extended Producer Responsibility (EPR) system** targeting human medicines under the revised Urban Wastewater Treatment Directive.

Specifically, several scientific limitations and methodological flaws are inherent to this list, resulting in an **overestimation of the contribution of pharmaceuticals to the toxic load in urban wastewater.** This overestimation leads to the erroneous claim that 66% of toxic load found in urban wastewater is due to pharmaceutical residues, thereby seriously calling into question the **validity, proportionality and fairness** of the UWWTD EPR model.

In particular:

- The substance list is based on the "*total pollution proxy substances*" dataset of 1,337 chemicals developed in wastewater effluents complied by Pistocchi et al. (2022).[5] The authors themselves acknowledge transparently **significant data limitations in the study.**

- Notably, **concentration data were only available for 51.5% of the substances considered, and PNEC values were only available for 45% of them**.[6] In the UWWTD EPR feasibility study missing concentration rates for 25% of pharmaceuticals and missing PNEC values for 37% of the substances are indicated.[7] This fundamental lack of data undermines its scientific validity and renders it entirely unsound as a basis for calculating toxic loads or allocating costs under the EPR scheme.

[1] European Commission (2022), Impact Assessment Accompanying the document "Proposal for a Directive of the European Parliament and of the Council concerning urban wastewater treatment (recast)"

[2] BioInnovation - List of micropollutants - urban wastewater, Electronic Access to Commission Documents (EASE).

[3] BioInnovation Service et al. (2022), Feasibility of an EPR system for micro-pollutants - Publications Office of the EU.

[4] The Predicted No Effect Concentration is the concentration of a substance below which no adverse effects on the environment (in this case the aquatic ecosystem) are expected.

[5] Pistocchi et al. (2022), European scale assessment of the potential of ozonation and activated carbon treatment to reduce micropollutant emissions with wastewater - ScienceDirect.

6 Ibid.

[7] BioInnovation Service et al. (2022), Feasibility of an EPR system for micro-pollutants - Publications Office of the EU, p. 90.

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- The **PNEC values assigned in the Bio Innovation list to attribute toxicity raise serious scientific concerns.** Although the list does not explicitly state the unit used for PNECs, it can be inferred from the study of Pistocchi et al., which identifies several of these PNECs, that they are expressed in nanograms per litre (ng/L). **Assuming PNECs derived by Bio Innovation are expressed in ng/L, these values are partially orders of magnitude lower than PNECs provided and accepted in the scientific community.**

- Differences in PNEC values are a well-known issue (Belanger et al., 2021). Pistocchi et al. state that "*When a substance appears among the top contributors only for the PNEC criterion (e.g. Telmisartan), it is possible that the threshold is excessively conservative and should be reconsidered*." Pistocchi used seven different threshold criteria (one of them being the PNEC) for comparison of toxicity. **This has not been considered in the Feasibility study**.

- **It is noteworthy that several PNEC values derived for the pharmaceuticals on the list are significantly lower than those found in established and commonly accepted environmental risk assessments and scientific literature**. Using a lower PNEC value - as done in the Bio Innovation list - suggests that a substance is far more toxic to aquatic life and implies that only very low concentrations can be safely tolerated by freshwater ecosystems than may actually be the case. Some examples are presented below (more information is provided in Table 1 of the Annex)**.**

Telmisartan

  - Telmisartan is a pharmaceutical used in high blood pressure medication.
  - Based on the Bio Innovation list, telmisartan alone accounts for a calculated toxic load (% toxic load (PNEC)) of 3,623, which corresponds to **~41% of the total toxic load attributed to all substances assessed (Total toxic load = 8,830)**. In this regard, **Telmisartan would contribute the most to the total toxic load of all substances on this list**.
  - This figure is based on an assigned PNEC value of **0.55 ng/L from JRC, the validity of which could not be backed up in scientific literature.** Publicly available and accepted ecotoxicological data derive a PNEC of **49 µg/L (= 49,000 ng/L)** (Norman database; FASS SE database; UBA, 2023, *for more details see* Table 1 of the Annex)**, a value that is approximately 90,000 times higher.**
  - A lower PNEC of 26 ng/L was derived by another study, however reliability of this data is unclear (Zhou et al., 2019).
  - Using the widely used PNEC of 49 µg/L based on accepted scientific ecotoxicological data, this would **significantly reduce telmisartan's contribution to the toxic load.**
  - The **Stockholm Region** has similarly concluded that telmisartan poses **insignificant environmental risk in the Stockholm region.**[8]

[8] Janusinfo Region Stockholm, Telmisartan - Janusinfo.se (accessed in June 2025).

Dipyridamole

- Dipyridamole is a drug with an antiplatelet effect that is used to prevent thrombosis and embolisms.
- Based on the Bio Innovation list, dipyridamole contributes the third highest amount to the total toxic load, corresponding to **~8.8% of the total toxic load for all substances**.
- This figure is based to an assigned PNEC value of 5.3 ng/L from JRC. The same value, which is based on predicted ecotoxicological data was used in the Selection of substances for the 4th Watch List under the Water Framework Directive (Gomez Cortes et al., 2022).
- However, data published in the Norman Database indicate a PNEC of 23.6 µg/L (= 23,600 ng/L) (Norman database, *for more details see* Table 1 of the Annex), a value that is **approximately 4,500 times higher.**

Candesartan

- Candesartan is used as an angiotensin II receptor blocker (ARB) mainly used for medication of high blood pressure and heart failure.
- Based on the Bio Innovation list, candesartan contributes the fourth highest amount to the total toxic load, corresponding to **~4.6% of the total toxic load for all substances**.
- This figure is based to an assigned PNEC value of 3.1 ng/L from JRC. However, data from the ECHA Registration Dossier and Norman database indicate a PNEC of 100 µg/L (= 100,000 ng/L) (ECHA REACH Dossier, Norman database, *for more details see* Table 1 of the Annex), a value that is **approximately 32,000 times higher.**

Amiodarone

- Amiodarone is an antiarrhythmic medication used to treat and prevent a number of types of cardiac dysrhythmias.
- Based on the Bio Innovation list, amiodarone contributes the fifth highest amount to the total toxic load, corresponding to **~3.86% of the total toxic load for all substances**.
- This figure is based on an assigned PNEC value of 1.1 ng/L from JRC. Contrary, the FASS database suggest a PNEC of 1.2 µg/L (= 1,200 ng/L) based on ecotoxicological data that was confirmed by the Norman database (Norman database, FASS SE database, *for more details see* Table 1 of the Annex). In the selection of substances for the 5th Watch List under the Water Framework Directive, a PNEC value of 0.24 µg/L (= 240 ng/L) was proposed (Gomez Cortes et al., 2025). These values are **approximately 200 - 1,000 times higher**.
- Another study predicted a lower value of 9 ng/L based on computer-generated data (Escher et al., 2011). However, Trawiński & Skibiński (2022) assessed the reliability of different computational models for ecotoxicity evaluations of amiodarone and other iodinated pharmaceuticals and noted that "***computational methods were generally not able to correctly predict properties of the studied compounds*** *[…]. This finding clearly indicates necessity of experimental verification of such computational estimations by the in vivo experiments*."

- Notably, these **four substances alone would account for 58% of the total toxic load from all sectors according to the data from Bio Innovation**. The observed discrepancies in PNEC values of several orders of magnitude massively inflate the perceived environmental impact of these substances.

- **It is assumed that the PNEC values from JRC result from the use of computer-generated predictive models** such as QSAR (Quantitative Structure-Activity Relationship), **rather than robust, empirical ecotoxicity data required by both pharmaceutical and chemical regulators in Europe. EMA guidelines** on environmental risk assessment of medicinal products for human use currently **do not permit the use of predictive models** to replace experimental studies (EMA, 2024).[9] **ECHA guidelines** allow the use of such models under specific conditions to fill data gaps when reliable experimental data are unavailable (ECHA, 2008).[10]

- **Concentration data for substances in wastewater also raise significant questions.** The feasibility study's **assumption of uniform concentrations for each substance across all wastewater treatment plants** ignores real-world differences due to factors such as geography, weather, seasonality, consumption patterns and methodology.

- The study by Pistocchi et al. acknowledges that "***the concentration*** *that we assume in raw wastewater comes from available measurements, and* ***may not be always representative of the actual concentrations***" and that "*Importantly,* ***the uncertainty affecting the concentration of substances in wastewater may be even larger than the attribution of physicochemical properties*****".**[11]

- Similarly, the feasibility study recognises that "*The concentration data compiled in the JRC database is the best available data,* ***but it may not be deemed representative of average concentration in the EU.*** *This limitation affects both the allocation by substance quantity in waste water and the allocation by hazardousness****"***. (Bio Innovation Service, 2022)

- This confirms the findings of the comprehensive literature review carried out by Ramboll, which could not **identify any data that allow making absolute statements about the percentage of micropollutants in wastewater.**[12]

- Given these fundamental inconsistencies, Medicines for Europe believes that the focus of the current EPR system on pharmaceuticals is based on **scientifically flawed assumptions, leading to a disproportionate and unjustified allocation of responsibility and associated costs to the pharmaceutical sector.**

[9] European Medicines Agency (2024), Guideline on the environmental risk assessment of medicinal products for human use.

[10] European Chemicals Agency (2008), Guidance on information requirements and chemical safety assessment, Chapter R10 Chapter R.10: Characterisation of dose [concentration]-response for environment.

[11] Pistocchi et al. (2022), European scale assessment of the potential of ozonation and activated carbon treatment to reduce micropollutant emissions with wastewater - ScienceDirect.

[12] Ramboll Literature Review "Micropollutants in Urban Wastewater" (2025), Micropollutants in Urban Wastewater – summary here: Summary for-publication-May-2025.pdf.

Annex - Ramboll analysis of PNEC values for the top ten pharmaceutical substances contributing to toxic load, based on the list compiled by Bio Innovation Service

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Table 1: Top ten pharmaceutical substances that contribute to toxic load according to the list compiled by Bio Innovation Service and comparison of PNEC values.

Toxicity ranking (total toxic load in %)[13]	Pharmaceutical substance (CAS)	Toxic load (according to Bio Innovation list)	PNEC			
			Bio Innovation list	Norman Database, Lowest PNEC[14]	FASS Database	Other sources
1 (41.03%)	Telmisartan (CAS: 144701-48-4)	3623.170455	0.55 (JRC, ng/L assumed)	49 µg/L (=49,000 ng/L) (*see FASS*)	49 µg/L (=49,000 ng/L) (based on NOEC of 490 µg/L for algae (*desmodesmus subspicatus*))[15]	49 µg/L (=49,000 ng/L) (based on NOEC of 490 µg/L for algae (*desmodesmus subspicatus*)) (UBA, 2023),
3 (8.76%)	Dipyridamole (CAS: 58-32-2)	773.5849057	5.3 (JRC, ng/L assumed)	23.6 µg/L (=23,600 ng/L) (based on NOEC for algae)	No data found	0.00534 µg/L (=5.3 ng/L) (predicted) (Gomez Cortes et al., 2022)[16], 21 µg/L (=21,000) (QSAR, *green algae*) (Escher et al., 2011),
4 (4.62%)	Candesartan (CAS: 139481-59-7)	408.3699597	3.1 (JRC, ng/L assumed)	100 µg/L (=100,000 ng/L) (based on NOEC of 1 mg/L for *Pimephales promelas*)[17]	No data found	0.1 mg/L (= 100,000 ng/L) (ECHA REACH Dossier[18])
5 (3.86%)	Amiodarone (CAS: 1951-25-3)	340.5747315	1.1 (JRC, ng/L assumed)	1.2 µg/L (= 1,200 ng/L) (no details)	1.2 µg/L (= 1,200 ng/L) (based on NOEC of 12 µg/L for *Pseudokirchneriella subcapitata*)[19]	0.24 µg/L (=240 ng/L) (Gomez Cortes et al., 2025)[20]

[13] The toxicity load was calculated by dividing the toxicity of a substance by the total toxic load of 8,830, which was allocated to 100% in the Bio Innovation study. Substances were consequently ranked according to their total toxic load. A similar calculation was performed by Cosmetics Europe: UWWTD-CE-Analysis-List-of-substances-used-in-the-EPR-feasibility-report-April-2025.pdf, pages 6-11.

[14] The term Lowest PNECs refers to quality targets which are suggested by experts for prioritisation purposes. They are obtained experimentally or predicted by QSAR models. The Ecotoxicology Database provides a transparent tool to help experts in:

i. the identification of the reliable ecotoxicity studies, based on the CRED (Criteria for Reporting and Evaluating ecotoxicity Data) classification system;
ii. the online derivation of Quality Targets for each matrix and regulatory framework based on selected 'reliable' ecotoxicity studies, using a built-in software tool implementing the requirements of the EC guidelines;
iii. the compilation of all existing Quality Targets from different regulatory frameworks;
iv. the final selection of the Lowest PNEC value for substance prioritisation purposes, agreed upon as a result of Europe-wide expert consultations.

(Source: https://www.norman-network.com/nds/ecotox/, last accessed 30.06.2025)

[15] Dossier on Micardis® from Boehringer Ingelheim (last accessed 30.06.2025)

[16] PNEC cited in the selection of substances for the 4th Watch List under the Water Framework Directive.

[17] Reference cited in the Norman database: AstraZeneca Environmental Risk Assessment (2023), Candesartan-cilexetil.pdf (last accessed 30.06.2025)

[18] ECHAChem Database REACH dossier of Candesartan (CAS 139481-59-7) (last accessed 30.06.2025)

[19] Dossier on Cordarone® from Sanofi AB, (last accessed 30.06.2025)

[20] PNEC established during the selection of substances for the 5th Watch List under the Water Framework Directive by JRC.

Toxicity ranking (total toxic load in %)[13]	Pharmaceutical substance (CAS)	Toxic load (according to Bio Innovation list)	PNEC			
			Bio Innovation list	Norman Database, Lowest PNEC[14]	FASS Database	Other sources
8 (2.27%)	17b-Estradiol (CAS: 50-28-2)	200	0.1 (JRC, ng/L assumed)	0.000009 µg/L (=0.009 ng/L) [21]	0.4 ng/L (based on AA-EQS)[22]; 0.000286 µg/L (0.286 ng/L) (based on NOEC of 0.00286 µg/L for fish)[23]	2 ng/L (fish, Caldwell et al., 2012), 0.0004 µg/L based on Review of the 1st Watch List under the Water Framework Directive (Loos et al., 2018)
14 (0.75%)	Terbinafine (CAS: 91161-71-6)	66.08745767	11 (JRC, ng/L assumed)	0.053 µg/L (=53 ng/L) *(FASS, data not publicly available)*	No data found	No data found
16 (0.45%)	Venlafaxine (CAS: 93413-69-5)	39.70573036	38 (JRC, ng/L assumed)	0.88 µg/L (= 880 ng/L) (UBA, 2020)	No data found	0.03835 µg/L (=38.5 ng/L) (Gomez Cortes et al., 2020)[24] 6.1 ng/L (based on NOEC of 0.305 µg/L for fish, Gomez Cortes et al., 2020; Zhou et al., 2019))[25]
17 (0.44%)	Azithromycin (CAS: 83905-01-5)	38.58700658	19 (JRC, ng/L assumed)	0.0019 µg/L (=1.9 ng/L)[26]	0.019 µg/L (=19 ng/L) (based on NOEC of 0.19 µg/L for algae *Microcystis aeruginosa*)[27]	0.019 µg/L (=19 ng/L) (Loos et al., 2018)[28]
19 (0.43%)	Vancomycin2H (CAS: 1404-90-6)	37.87664474	3.8 (JRC, ng/L assumed)	8 µg/L (= 8,000 ng/L)[29]	No data found	7,940,000 ng/L (based on EC_{50} for algae, Zhou et al., 2019)
21 (0.37%)	Ketoconazole (CAS: 65277-42-1)	32.78463649	8.1 (JRC, ng/L assumed)	0.00814 µg/L (=8.14 ng/L)[30]	No data found	0.05 µg/L (= 50 ng/L) (Gomez Cortes et al., 2025)[31]

[21] Data source could not be verified.

[22] Dossier on Lenzetto from Gedeon Richter Nordics, (last accessed 30.06.2025)

[23] Dossier on Estradot® from Sandoz AS, (last accessed 30.06.2025)

[24] PNEC established during the selection of substances for the 3rd Watch List under the Water Framework Directive by JRC.

[25] PNEC established during the selection of substances for the 3rd Watch List under the Water Framework Directive by JRC.

[26] Data source could not be verified.

[27] Dossier on Azithromycin from Pfizer (API: Azithromycin (anhydrous)) (last accessed: 30.06.2025)

[28] Review of the 1st Watch List under the Water Framework Directive

[29] Data could not be found in cited publication.

[30] Data source could not be verified.

[31] PNEC established during the selection of substances for the 5th Watch List under the Water Framework Directive by JRC.

Additional data retrieved from literature

All data was collected 30/06/2025 - 04/07/2025.

Telmisartan

FASS Database

PNEC	Derivation (translated from Swedish)	Source
1000 µg/L	Ecotoxicological studies Algae (Pseudokirchneriella subspicata) (OECD201) (NOTOX Project 490915) : EC50 72 h (growth rate) > 100.0 mg/L NOEC 72 h = 100.0 mg/L Crustacean (Daphnia magna , waterflea): Acute toxicity EC50 48 h (immobilization) > 100.0 mg/L (OECD202) (Ciba-Geigy Test No: 948032) Chronic toxicity NOEC 21 days (reproduction, survival and parental length) = 100 mg/L; no effect up to the highest concentration tested (OECD 211) (NOTOX Project 485928) Fish: Acute toxicity (Danio rerio, zebra fish) LC50 96 h (mortality) > 100.0 mg/L (OECD203) (Ciba-Geigy Test No. 811678) Chronic toxicity (Pimephales promelas, fathead minnow) NOEC 30 days (hatchability, survival, length and weight) = 10.0 mg/L; no effect up to the highest concentration tested (OECD 210) (NOTOX Project 485928) Other ecotoxicity data: Bacterial respiration inhibition EC 50 3 h > 750 mg/L (activated sludge respiration inhibition) (OECD209) (Ciba-Geigy Test No. 948033) Sediment-dwelling organisms (Chironomus riparius , non-biting midge) NOEC 28 days (emergence rate and development rate) = 10.0 mg/L (OECD 218) (Report No BR0137/B) PNEC derivation: PNEC = 1000 µg/L PNEC (µg/L) = lowest NOEC/10, where 10 is the assessment factor used if three chronic toxicity studies from three trophic levels are available. The NOEC for fish early life stage toxicity has been used for this calculation.	FASS SE Dossier on Read Love from STADA Nordic (APIs: Hydrochlorothiazide and Telmisartan)
49 µg/L	The PNEC has been derived from the lowest NOEC (Desmodesmus subspicatus, 72h (growth rate)) of 0.49 mg/L. An assessment factor of 10 is used based on the availability of A NOEC for algal growth inhibition in combination with chronic toxicity studies for the other trophic levels in accordance with ECHA Guidelines (ECHA, 2008). Algae (Green algae, Desmodesmus subspicatus) (OECD 201, GLP) (Ref.II): EC50 72h (growth rate) = 9.88 mg/L NOEC 72h (growth rate) = 0.49 mg/L EC50 72h (biomass) = 1.75 mg/L NOEC 72h (biomass) = 0.25 mg/L Crustacean (Water flea, Daphnia magna): Acute toxicity (FDA, TAD 4.08, GLP), (Ref.III)	FASS SE Dossier on Micardis® from Boerhinger Ingelheim (APIs: Hydrochlorothiazide and Telmisartan)

PNEC	Derivation (translated from Swedish)	Source
	EC50 48h (mortality)= 18 mg/L NOEC 48h (mortality)= 5.4 mg/L Chronic toxicity (OECD 211, GLP, (Ref.IV) NOEC 21d (mortality)= 1.2 mg/L LOEC 21d (mortality)= 3.9 mg/L Fish (Rainbow trout, Oncorhynchus mykiss)(OECD 203, GLP), (Ref.V): Acute toxicity LC50 96h (mortality)= 3.74 mg/L NOEC 96h (mortality)= 1.92 mg/L Fish (Zebrafish, Danio rerio)(OECD 210, GLP), (Ref.VI): Chronic toxicity (OECD 210) NOEC 35d (dry weight) = 1.0 mg/L LOEC 35d (dry weight) = 3.1 mg/L Other ecotoxicity data MIC (minimal inhibitory concentration) for bacillus subtilis was determined to 20 mg/L. No EC50 could be derived. For the four other species tested (2 bacteria, 1 fungus, 1 blue-green algae), no inhibition of growth was observed up to 1000 mg/L (FDA, TAD 4.02, GLP), (Ref.VII). No inhibition of activated sludge was observed at concentrations up to 1 000 mg/L (OECD 209, GLP), (Ref.VIII).	

Other sources

- 26 ng/L (based on EC50 for fish, Zhou et al., 2019)
- The following table presents ecotoxicity data collected by Gunnarsson et al. (2019). However, these data were not used to derive own PNEC values due to the high level of uncertainty that would be associated with this approach in the absence of a thorough environmental hazard assessment.

NOEC (µg/L)	Species	Source[a]
490	Algae	https://www.fass.se/LIF/product?userType=2&nplId=19990907000037
1200	Daphnia	https://www.fass.se/LIF/product?userType=2&nplId=19990907000037
1000	Fish	https://www.fass.se/LIF/product?userType=2&nplId=19990907000037

[a] Primary sources were not checked for correctness of data.

Dipyridamole

FASS Database

No data found

Other Sources

- 75,800 ng/L (based on EC50 for Crustaceans, Zhou et al., 2019)
- **A PNEC of 0.00534 µg/L (=5.3 ng/L) (predicted) was recommended in the Selection of substances for the 4th Watch List under the Water Framework Directive** (Gomez Cortes et al., 2022)
- The following table presents ecotoxicity data collected by Gunnarsson et al. (2019). However, these data were not used to derive own PNEC values due to the high level of uncertainty that would be associated with this approach in the absence of a thorough environmental hazard assessment.

NOEC (µg/L)	Species	Source[a]
2360	Algae	https://www.fass.se/LIF/product?nplId=20120414000053&userType=0

[a]Primary sources were not checked for correctness of data.

Candesartan

Norman Database

An environmental risk assessment of AstraZeneca[32] is cited to derive a PNEC of 100 µg/L:

- Long-term tests have been undertaken for species from three trophic levels, based on internationally accepted guidelines. Therefore, the PNEC is based on the lowest NOEC value 1 mg/L (equivalent to 1,000 µg/L) which was reported for Pimephales promelas and an assessment factor of 10 is applied, in accordance with ECHA guidance (Ref. 2).

FASS Database

No data found

Other Sources

- In the ECHA REACH dossier[33] a PNEC of 0.1 mg/L was derived.
- 1,200 ng/L (based on EC50 for algae, Zhou et al., 2019)
- The following table presents ecotoxicity data collected by Gunnarsson et al. (2019). However, these data were not used to derive own PNEC values due to the high level of uncertainty that would be associated with this approach in the absence of a thorough environmental hazard assessment.

NOEC (µg/L)	Species	Source[a]
32000	Algae	https://www.astrazeneca.com/content/dam/az/our-company/Sustainability/2017/candesartan.pdf
10000	Daphnia	https://www.astrazeneca.com/content/dam/az/our-company/Sustainability/2017/candesartan.pdf
1000	Fish	https://www.astrazeneca.com/content/dam/az/our-company/Sustainability/2017/candesartan.pdf

[a]Primary sources were not checked for correctness of data.

Amiodarone

FASS Database

[32] AstraZeneca Environmental Risk Assessment (2023), Candesartan-cilexetil.pdf (last accessed 30.06.2025)

[33] ECHAChem Database REACH dossier of Candesartan, (last accessed 30.06.2025)

PNEC	Derivation (translated from Swedish)	Source
1.2 µg/L	*Algae (Pseudokirchneriella subcapitata):* EC $_{50}$ 72 h (growth rate): >12 µg/L NOEC 72 h (growth rate): 12 µg/L Test item: Amiodarone Hydrochloride (Protocol: OECD 201) (Ref II) *Crustacean (Daphnia magna):* NOEC 21 d (reproduction, mortality): 68.4 µg/L Test item: Amiodarone Hydrochloride (Protocol: OECD 211) (Ref. III) *Fish (Pimephales promelas):* NOEC 28 days (survival, growth): 623 µg/L (Protocol: OECD 210) (Ref IV) The PNEC (µg/L) = lowest EC $_{50}$ /10 was calculated using results from the most sensitive toxicity endpoint and an assessment factor of 10 (three long-term results from species representing three trophic levels), to add a safety margin to the toxicity endpoint. The most sensitive species was *Pseudokirchneriella subcapitata* for which the NOEC 72 h was 12 µg/L. PNEC = 12 µg/L/10 = 1.2 µg/L	Dossier on Amiodarone hameln from hameln pharma (API: Amiodarone), Dossier of Cordarone ® from Sanofi AB, (API: Amiodarone)

Other sources

- In the selection of substances for the 5th Watch List under the Water Framework Directive, a **PNEC value of 0.24 µg/L** (= 240 ng/L) was proposed (Gomez Cortes et al., 2025).
- Another study predicted a lower value of 9 ng/L based on computer-generated data (Escher et al., 2011). However, Trawiński & Skibiński (2022) assessed the reliability of different computational models for ecotoxicity evaluations of amiodarone and other iodinated pharmaceuticals and noted that "computational methods were generally not able to correctly predict properties of the studied compounds […]. This finding clearly indicates necessity of experimental verification of such computational estimations by the *in vivo* experiments."
- The following table presents ecotoxicity data collected by Gunnarsson et al. (2019). However, these data were not used to derive own PNEC values due to the high level of uncertainty that would be associated with this approach in the absence of a thorough environmental hazard assessment.

NOEC (µg/L)	Species	Source[a]
12	Algae	https://www.fass.se/LIF/product?userType=0&nplId=19870508000059&docType=78
623	Fish	https://www.fass.se/LIF/product?userType=0&nplId=19870508000059&docType=78

[a]Primary sources were not checked for correctness of data.

17b-Estradiol

FASS Database

As several medicals with Estradiol are available, the following table presents a selection only:

PNEC	Derivation (translated from Swedish)	Source
0.000286 µg/L	Ecotoxicological studies Algae (green algae , Desmodesmus subspicatus): NOEC 72 hours (growth rate) ≥ 3 100 µg/L, ErC 50 72 hours (growth rate) > 3100 µg/L. Guideline OECD 201. (Reference II) Crustacean (water flea, Daphnia magna): Chronic toxicity NOEC 21 days (reproduction) ≥ 139 µg/L. Guideline FDA TAD 4.09. (Reference III) Fish (rainbow trout, Oncorhynchus mykiss): Acute toxicity LC 50 96 hours (survival) ≥ 500 µg/L. Guideline FDA TAD 4.11. (Reference IV) Fish (fathead minnow, Pimephales promelas): Chronic toxicity EC 10 56 days (weight) = 0.008 µg/L. Guideline EPA FIFRA Subdev. E, 72-5. (Reference V) Fish (Japanese rice fish, Oryzias latipes): Chronic toxicity Besides the OECD studies complying with GLP documentation requirements, there is a published fish full life-cycle study, which was conducted with the Japanese rice fish (Oryzias latipes). The test setup is exploratory, but the publication was considered sufficiently reliable for derivation of the environmental quality standard (EQS) and is therefore included here. The study started with fish embryos 12 hours after fertilization and continued for up to 101 days including filial fish generation (spawned at day 98, 99, and 100) and assessed various endpoints. Fish were exposed continuously (flow-through system) at 0.939, 2.86, 8.66, 27.9, and 92.4 ng/L. Most endpoints showed no concentration-response related effects of estradiol. However, sex differentiation, induced vitellogenin (VTG; yolk protein), and reproductive impairment were observed with concentration-response relationship in the parent fish generation, coming up with a NOEC of 2.86 ng/L. There were no effects in the filial fish generation at concentrations below 8.66 ng/L. NOEC 101 days (fertility) = 2.86 ng/L = 0.00286 µg/L. Fish full life-cycle exploratory study. (Reference VI) The PNEC was calculated by dividing the lowest effect level (NOEC) of the most sensitive taxonomic group considering an appropriate assessment factor (AF). The most sensitive taxonomic group were fish and the lowest effect level was reported as NOEC = 0.00286 µg/L. The regulatory default standard AF of 10 was used, which is applicable when there are chronic aquatic toxicity studies representing the three trophic levels (algae, crustaceans, and fish). PNEC = 0.00286 µg/L / 10 = 0.000286 µg/L	Dossier on Estradot® from Sandoz AS (API: Estradiol), Dossier on Progynon® from Bayer (API: Estradiol)
0.4 ng/L	Available eco-toxicological data for 17β-estradiol, estrone and estriol and the derivation of PNEC values is presented in this section. **3.2.1 17β-estradiol** A proposed EU EQS (PNEC) value has been derived for the 17β-estradiol (Ref. 7) in connection with setting 17β-estradiol on a short-list of 19 possible new priority substances for the Water Frame Directive (Ref. 6). The data used for the derivation of the EQS value is presented in the Appendix together with the derivation, and only a short overview of the derivation is given here.	Dossier on Lenzetto from Gedeon Richter Nordics (API: Estradiol)

	Knowledge of the mode of action of 17β-estradiol - and strongly supported by the acute and chronic test toxicity data (see Appendix) - suggests that fish and amphibians are likely to be the most sensitive organisms. This is supported by the available chronic toxicity data which indicates that fish are particularly sensitive to 17β-estradiol. Two studies were located on amphibians with LOECs in the range of 1000-2740 ng/l reported for *Rana pipes* and *Xenopus laevis* . These LOECs are far above the NOECs for fish. Therefore, a SSD (Species Sensitivity Distribution) was derived for 17β-estradiol based on data for the most sensitive taxonomic groups, fish - expecting that chronic fish data used for the derivation of an SSD would also be protective of the other less sensitive group. The lowest no observed effect concentration for 17β-estradiol is a 35-50 d NOEC of 0.5 ng/l (Ref. 48) for the trout (*Onchorhynchus mykiss*). The observed effects were sperm volume, sperm density and fertilization success. The study was not carried out according to a guideline. Experiments took place in four identical flow-through 0.5 m^3 tanks (three replicates and one control - each tank with 10 males and 3 females of approximately the same size). Water inflow temperature was 6 ° C and air saturation of water was >90%. Fish were kept under natural photoperiod (experiments were carried out in Kreuzstein in Sankt Gilgen, Upper Austria during December – January). Overall, reliable chronic NOEC values were available for 11 species of fish and the SSD was based on these 11 fish species (Ref. 7). The HC5 for the SSD was found at 0.8 ng/l. Based on the available dataset and the knowledge of the mode of action, an assessment factor of 2 was considered appropriate. This gives an AA-EQS of 0.4 ng/l. This derivation of the AA-EQS was reviewed by SCHER (Ref. 8). Both the reliability and the ecological relevance of the endpoints and taxonomic groups were considered. Overall, the SCHER supported the proposed AA-EQS of 0.4 ng/l for 17β-estradiol. In conclusion, a PNEC of 0.4 ng/L is used for 17β-estradiol	

Other Sources

- **A PNEC of 0.0004 µg/L was recommended in the Review of the 1st Watch List under the Water Framework Directive (Loos et al., 2018)**
- 1.6 ng/L (based on NOEC for fish, Zhou et al., 2019)
- The following table presents ecotoxicity data collected by Gunnarsson et al. (2019) (referred as "Estradiol"). However, these data were not used to derive own PNEC values due to the high level of uncertainty that would be associated with this approach in the absence of a thorough environmental hazard assessment.

NOEC (µg/L)	Species	Source[a]
1700	Algae	https://www.fass.se/LIF/product?nplId=20090917000020&userType=0&docType=78&docTypeDynTab=78
200	Daphnia	https://www.fass.se/LIF/product?nplId=20090917000020&userType=0&docType=78&docTypeDynTab=78
0.003	Fish	https://www.fass.se/LIF/product?nplId=20090917000020&userType=0&docType=78&docTypeDynTab=78

[a]Primary sources were not checked for correctness of data.

Terbinafine

FASS Database

No data found

Other Sources

- No data for Terbinafine was found in Gunnarsson et al. (2019).

Venlafaxine

FASS Database

No data found

Other Sources

- No data for Venlafaxine was found in Gunnarsson et al. (2019).
- **A PNEC of 0.038 µg/L was recommended in the Review of the 1st Watch List under the Water Framework Directive (Loos et al., 2018)**

Azithromycin

FASS Database

PNEC	Derivation (translated from Swedish)	Source
0.019 µg/L	Ecotoxicological studies *Microbial growth inhibition (guideline FDA 4.02)* [6] *Aspergillus niger* minimal inhibitory concentration = >1 000 000 µg/L *Trichoderma viride* minimal inhibitory concentration = >1 000 000 µg/L *Clostridium perfringens* minimal inhibitory concentration = 2 000 µg/L *Bacillus subtilis* minimal inhibitory concentration = 2 000 µg/L *Nostoc sp.* minimum inhibitory concentration = 400 µg/L *Activated sludge microorganisms (guideline OECD 209)* [7] EC_{10} (respiration inhibition) = 1 890 µg/L EC_{50} (respiration inhibition) = 269 000 µg/L *Green alga (Pseudokirchneriella subcapitata) (guideline OECD 201)* [8] NOEC 72 h (growth rate, acute toxicity) = 1.8 µg/L EC_{50} 72 h (growth rate, acute toxicity) = 8.4 µg/L *Blue-green alga (Microcystis aeruginosa) (guideline OECD 201)* [9] NOEC 72 h (growth rate, acute toxicity) = 0.19 µg/L EC_{50} 72 h (growth rate, acute toxicity) = 1.8 µg/L NOEC 96 h (cell density, acute toxicity) = 0.19 µg/L EC_{50} 96 h (cell density, acute toxicity) = 0.68 µg/L *Daphnids (Daphnia magna) (guideline OECD 202)* [10] NOEC 48 hours (immobilization, acute toxicity) = 19 000 µg/L	Dossier on Azithromycin Krka from KRKA (API: Azithromycin (anhydrous)), Dossier on Azithromycin Sandoz from Sandoz AS (API: Azithromycin (anhydrous)), Dossier on Azithromycin STADA from STADA Nordic (API: Azithromycin (anhydrous)), Dossier on Azithromycin from Pfizer (API: Azithromycin (anhydrous))

PNEC	Derivation (translated from Swedish)	Source
	EC $_{50}$ 48 hours (immobilization, acute toxicity) = 120 000 µg/L *Daphnids (Ceriodaphnia dubia) (guideline EPA 1002.0)* [11] NOEC 7 days (reproduction, chronic toxicity) = 4.4 µg/L LOEC 7 days (reproduction, chronic toxicity) = 15 µg/L EC $_{50}$ 7 days (survival, chronic toxicity) = >1 400 µg/L *Rainbow trout (Oncorhynchus mykiss) (guideline OECD 203)* [12] NOEC 96 hours (mortality, acute toxicity) = 84 000 µg/L LC $_{50}$ 96 hours (mortality, acute toxicity) = > 84 000 µg/L *Fathead Minnow (Pimephales promelas) (guideline OECD 210)* [13] NOEC 32 days (early life stage, chronic toxicity) = 4 600 µg/L LOEC 32 days (early life stage, chronic toxicity) = >4 600 µg/L Based on the lowest NOEC for the species *Microcystis aeruginosa* and using the assessment factor [2] of 10, the PNEC is calculated to 0.19/10 = 0.019 µg/L.	

Other Sources

- **A PNEC of 0.019 µg/L was recommended in the Review of the 1st Watch List under the Water Framework Directive (Loos et al., 2018)**
- 1,870 ng/L (based on EC50 for algae, Zhou et al., 2019)
- No data for Azithromycin was found in Gunnarsson et al. (2019).

Vancomycin2H

FASS Database

- No data found.

Other Sources

- No data for Vancomycin2H was found in Gunnarsson et al. (2019).

Ketoconazole

FASS Database

- No data found.

Other Sources

- No data for Ketoconazole was found in Gunnarsson et al. (2019).

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