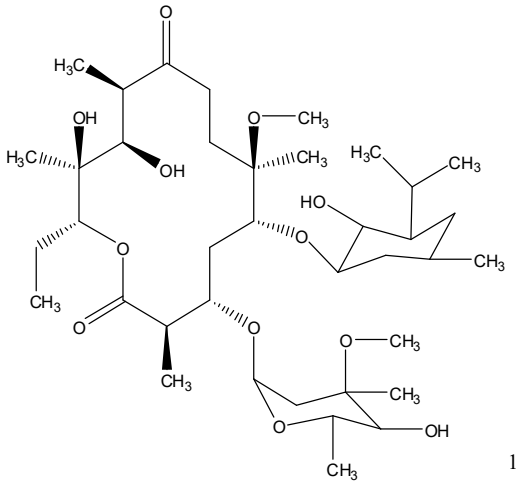
Miljøministeriet
Miljøstyrelsen

Fastsættelse af kvalitetskriterier for vandmiljøet

Clarithromycin

CAS nr. 81103-11-9



[1]

Vandkvalitetskriterium	$VKK_{ferskvand}$	0,13 µg/l
Vandkvalitetskriterium	$VKK_{saltvand}$	0,013 µg/l
Korttidsvandkvalitetskriterium	$KVKK_{ferskvand}$	0,13 µg/l
Korttidsvandkvalitetskriterium	$KVKK_{saltvand}$	0,013 µg/l
Sedimentkvalitetskriterium	$SKK_{ferskvand}$	Ikke relevant
Sedimentkvalitetskriterium	$SKK_{saltvand}$	Ikke relevant
Biota-kvalitetskriterium, sekundær forgiftning	$BKK_{sek.forgiftn.}$	4,7 mg/kg vådvægt
Biota-kvalitetskriterium, human konsum	HKK	171,8 µg/kg vådvægt

December 2022

[1] Denne anvendte strukturformel i JRC, 2022 indeholder ikke O-methyl gruppen på C6, som gør stoffet til Clarithromycin, og N-dimethylgruppen som findes i alle Erythromyciner. Clarithromycin er kemisk en 6-O-Methyl-Erythromycin.

Dansk resumé og konklusioner

Clarithromycin er et organisk stof, der tilhører gruppen af semisyntetiske macrolider. Stoffet anvendes som et antibiotikum overfor bakterielle infektioner i de øvre og nedre luftveje, infektioner på huden og i de ydre sanseorganer (ører, næse), samt til bekæmpelse af større infektioner på huden. Clarithromycin er tillige godkendt til forebyggende behandling mod udbredte infektioner af *Mycobacterium avium Complex* (MAC) hos AIDS-patienter.

Stoffets fysisk-kemiske egenskaber, dets fordeling imellem forskellige miljøer, dets skæbne via abiotisk og biotisk nedbrydning, samt dets biologiske effekter i det eksterne miljø er sammenfattet og vurderet af det Fælles Europæiske Forskningscenter JRC (JRC, 2022)[2], der på det fremlagte datagrundlag har bearbejdet data og beregnet miljøkvalitetskrav. Arbejdet og rapporteringen har været kommenteret af Europa-Kommissionens videnskabelige komite for sundhed og miljø, SCHEER (SCHEER, 2022)[3].

Clarithromycin har et kemisk nært beslægtet nedbrydningsprodukt (metabolit) 14-hydroxy-Clarithromycin (14-HC), der har tilsvarende antimikrobielle egenskaber. Stoffet 14-HC er derfor vurderet sammen med stoffet Clarithromycin. Dette stof indeholder en hydroxyl-gruppe, der funktionelt kan dissociere, og på dette grundlag er der italesat og vurderet de ændringer, som denne egenskab har på de miljøkemiske egenskaber for stoffet 14-HC.

Metodikken, der anvendes til udarbejdelse af miljøkvalitetskrav, er harmoniseret i EU og baserer sig på Europa-Kommissionens vejledning til fastsættelse af kvalitetskriterier i vandmiljøet (EC, 2018)[4].

Indledningsvist indeholder rapporten en sammenfatning af grundlag og viden om forekomsten af stoffet Clarithromycin i relevante eksterne miljøer. Baseret på indrapporterede koncentrationer af Clarithromycin i det eksterne miljø, viser den gennemførte screening følgende: de påviste og dokumenterede koncentrationer af stoffet i de europæiske staters ferske indlands overfladevande, sat i forhold til tentative kvalitetskriterier baseret på oplysninger om forventet nul-effekt niveau (PNEC: Predicted No Effect Concentration), viser potentiel tilstedeværelse af en risiko for, at Clarithromycin ikke kan overholde de tentative kriterier.

En tilsvarende vurdering af risiko for europæiske marine overfladevande kan ikke foretages, idet screeningen viser at de tilvejebragte data fremstår opdelte og utilstrækkelige. Det konkluderes derfor, at datagrundlaget ikke er fuldt udviklet til at vurdere den konkrete risiko for marine overfladevande.

---

[2] Joint Research Center (JRC) of the Commission of the European Union: Clarithromycin – Final Dossier after SCHEER final opinion – dated September 2022

[3] Scientific committee on Health, Environmental and Emerging Risks (SCHEER) of the Commission of the European Union: final opinion on clarithromycin (Publication date 6 May 2022), available on-line at: https://health.ec.europa.eu/publications/draft-environmental-quality-standards-priority-substances-under-water-framework-directive-2_en

[4] European Commission (EC): Technical Guidance for Deriving Environmental Quality Standards – Guidance Document No. 27. Updated version 2018

Stoffet er prioriteret til fastlæggelse af relevante kvalitetskriterier på baggrund af screeningen for stoffets tilstedeværelse og koncentration i det eksterne miljø.

Relevante data for stoffets økotoksikologiske effekter er præsenteret og beskrevet i rapporten fra JRC (JRC, 2022). Der er fastsat kvalitetskriterier for relevante specifikke miljøer og biota for akutte påvirkninger og kroniske effekter, samt for afledte effekter gennem fødekæder og relevante indtag og konsum. Kvalitetskriterier er fastsat på baggrund af resultater, datakvalitet og bredde af de udførte undersøgelser i forhold til undersøgte akutte og kroniske effekter på specifikke organismer, trofiske niveauer og forskellige miljøer.

Clarithromycin og metabolitten 14-HC er undersøgt for økotoksikologiske effekter i en række studier, der rummer både akutte og kroniske effekter overfor arter indenfor såvel det ferske som det marine miljø på flere end de grundlæggende 3 taksonomiske grupper (alger, krebsdyr og fisk). Studierne er indledningsvist gennemgået for relevans og troværdighed (kvalitet), og tildelt en score i henhold til kriterier fastsat af Klimisch et al. (1997)[5] – R1: troværdig uden restriktioner; R2 – troværdig med restriktioner; R3 – ikke troværdige; R4 – ikke anvendelige. Alene studier med score R1/R2 er medtaget i udarbejdelsen af kvalitetskriterierne.

I dette reducerede datamateriale af studier med høj kvalitet og troværdighed (R1/R2) for stofferne Clarithromycin og 14-HC, findes der fortsat relevante og solide studier af såvel akutte som kroniske effekter, men alene på 2 taksonomiske grupper, idet effekter på fx fisk ikke foreligger. Det samlede datagrundlag er stærkt begrænset for det ferske miljø, og datagrundlaget for de marine miljøer er begrænset til et enkelt studie på alger. Der mangler generelt studier af effekter overfor fisk og sedimentlevende organismer.

En følge af et meget begrænset datagrundlag er blandt andet, at forholdet mellem koncentrationer for akutte effekter (EC_{50}) og kroniske effekter (EC_{10}) vil kunne være meget små. I sådanne tilfælde vil en beregnet maksimalt tilladelig koncentration baseret på EC_{50} kunne være lavere end et beregnet vandkvalitetskriterium baseret på EC_{10}, alene som følge af forskelle mellem de anvendte matematiske usikkerhedsfaktorer. Dette giver ikke nogen toksikologisk mening og fører til, at den maksimalt tilladelige koncentration administrativt sættes lig vandkvalitetskriteriet. I rapporten er der redegjort for konsekvenserne af det meget begrænsede datagrundlag for Clarithromycin.

På dette grundlag er der foretaget vurderinger i henhold til fremgangsmåden fastsat i Europa-Kommissionens vejledning til fastsættelse af kvalitetskriterier i vandmiljøet (EC, 2018).

Grundlag og metode for fastsættelse af kvalitetskriterier er generelt beskrevet for de konkrete miljøer og medier.

Korttidsvandkvalitetskriterium (KVKK)
Datagrundlaget for fastsættelse af KVKK er som udgangspunkt studier af de akutte effektniveauer for et stof, og herfra etablering af en acceptabel maksimal koncentration i relevante ydre miljøer, der over kort tid ikke fører til uønskede effekter i disse miljøer.

[5] Klimisch, H. J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regulatory toxicology and pharmacology, 25(1), 1-5.

Det samlede reducerede datasæt omfatter for den anvendte deterministiske metode relevante studier af akutte effekter, der alene indeholder få studier for fersk- og saltvand fra to (alger og invertebrater) af de trofiske niveauer. Datasættet er derfor svagt og en usikkerhedsfaktor er på baggrund heraf sat til 100 for ferskvand og 1.000 for saltvand jf. vejledningen (EC, 2018). Der tillægges yderligere en faktor 2 for at tage højde for kombinerede effekter af Clarithromycin og metabolitten 14-HC.

Med udgangspunkt i laveste EC_{50} værdi på 12 µg/l for studier af vækstrate i kulturer af ferskvandsalgen *Anabaena flos-aquae* kan der med afsæt i den deterministiske tilgang fastlægges følgende KVKK-værdier:

$KVKK_{ferskvand}$ = 12 µg/l / 2 / 100 = 0,06 µg/l (reguleret til 0,13 µg/l svarende til $VKK_{ferskvand}$)
$KVKK_{saltvand}$ = 12 µg/l / 2 / 1.000 = 0,006 µg/l (reguleret til 0,013 µg/l svarende til $VKK_{saltvand}$)

Vandkvalitetskriterium (VKK)
Datagrundlaget for fastsættelse af VKK er som udgangspunkt studier af de kroniske effektniveauer for et stof, og herfra etablering af en acceptabel koncentration i relevante ydre miljøer, der ikke fører til uønskede langtidseffekter i disse miljøer.

Det samlede reducerede datasæt omfatter for den deterministiske metode relevante studier af akutte effekter, der alene indeholder få studier for fersk- og saltvand fra to (alger og invertebrater) af de trofiske niveauer. Datasættet er derfor svagt og en usikkerhedsfaktor er på baggrund heraf sat til 10 for ferskvand og 100 for saltvand jf. vejledningen (EC, 2018).

Der tillægges yderligere en faktor 2 for at tage højde for kombinerede effekter af Clarithromycin og metabolitten 14-HC.

Med udgangspunkt i laveste EC_{10} værdi på 2,6 µg/l for studier af vækstrate i kulturer af ferskvandsalgen *Anabaena flos-aquae* kan der med afsæt i den deterministiske tilgang fastlægges følgende VKK-værdier:

$VKK_{ferskvand}$ = 2,6 µg/l / 2 / 10 = 0,13 µg/l
$VKK_{saltvand}$ = 2,6 µg/l / 2 / 100 = 0,013 µg/l

Kvalitetskriterium for sediment (SKK)
I henhold til retningslinjer i Europa-Kommissionens vejledning til fastsættelse af kvalitetskriterier i vandmiljøet (EC, 2018), skal der kun udarbejdes kriterier for sediment med henblik på at beskytte dyrelivet mod sekundær forgiftning, såfremt der er evidens for, at et stof har potentiale for at kunne adsorbere til suspenderede stoffer og sediment. Clarithromycin har en estimeret log Kow værdi på 2,17, og opfylder derved ikke krav om fastsættelse af kriterium for sediment ved at værdien ikke overskrider den udløsende værdi på 3.

Der er ikke tilvejebragt data fra undersøgelser af toksicitet for stoffet Clarithromycin i sediment.

Kvalitetskriterium for biota, sekundær forgiftning ($BKK_{sek.\ forgiftn.}$)
I henhold til retningslinjer i Europa-Kommissionens vejledning til fastsættelse af kvalitetskriterier i vandmiljøet (EC, 2018), skal der kun udarbejdes kriterier for biota med henblik på at beskytte dyrelivet mod sekundær forgiftning, i fald der er evidens for, at et stof har potentiale for at kunne

bioakkumulere. For stoffet Clarithromycin er der konstateret feltbaserede organ-specifik Bio Akkumulations Faktor (BAF) på 22 – 436 l/kg for en søpølse *Apostichopus japonicus*. Disse oplysninger udløser beregning af kvalitetskriterier for biota baseret på indtag, der kan føre til sekundær forgiftning ($BKK_{sek.\ forgiftn.}$).

Der er bestemt et forventet NOAEL-niveau (No Observable Adverse Effect Level) på 4 mg/kg kropsvægt for en hund for stoffet Clarithromycin ved indtag såvel akut som kronisk. Dette er baseret på et velunderbygget datagrundlag for bestemmelse af oral toksikologi, og effekter som påvirkning af udvikling og reproduktion for en række pattedyr. Beregningsgrundlaget i Method A i Europa-Kommissionens tekniske vejledning (EC, 2018) er anvendt.

Det daglige energibehov (DEE) bestemmes ved anvendelse af NOAEL-værdien på 4 mg/kg kropsvægt/dag for hund og en antaget kropsvægt på 10 kg for hund.

log DEE [kJ/d]= 0,8136 + 0,7149 x log (10.000 g) = 3,673[6]
DEE = 4709,77

Den energinormaliseret føde-koncentration kan bestemmes på baggrund af NOAEL, DEE og kropsvægten:

$K_{energi\ normaliseret}$ [mg/kJ] = 4 mg/kg x (10 kg / 4709,77) = 0,00849 mg/kJ

Den energinormaliseret værdi skal konverteres til en koncentration i det kritiske fødeemne. For Clarithromycin bestemmes $BKK_{sek.\ forgiftn.}$ for fisk, da den Trofisk Magnificerings Faktor (TMF) er på 1. Der anvendes et standard vandindhold på 73,7% og et energiindhold på 21 kJ/g_{tv}.

K_{fisk} [mg/kg_{vv}] = 0,00849 mg/kJ x 21000 kJ/kg x (1-0,737) = 46,8 mg/kg_{vv}

Der anvendes en usikkerhedsfaktor på 10 baseret dels på anvendelse af et kronisk studie (faktor 1) og dels på ekstrapolation til det eksterne miljø fra toksikologiske studier i laboratorier (faktor 10), som leder frem til følgende kvalitetskriterier for biota:

$BKK_{sek.\ forgiftn.\ ferskvand}$ = 46,8 mg/kg / 10 = 4,7 mg/kg vådvægt (fisk)

Clarithromycin har en lav biomagnifikation over trofiske niveauer (TMF = 1), og på dette grundlag konkluderes, at en parallel standard for saltvand ikke skal udledes jf. den tekniske vejledning (EC, 2018).

Kvalitetskriterium for human konsum af vandlevende organismer (HKK)
Kvalitetskriteriet for biota til human konsum skal sikre mennesker mod sundhedsskadelige påvirkninger fra indtag af forurenede fiskeriprodukter. Principielt er kvalitetskriteriet (HKK) fastsat på baggrund af toksikologiske studier af pattedyr og fastlæggelse af en tærskelværdi for humant indtag som en NO(A)EL, oftest bestemt som et acceptabelt eller tolerabelt dagligt indtag eller referencedosis. På grundlag af en beregningsformel med standard human konsum af vandlevende organismer kan der bestemmes et kvalitetskriterium for biota til human konsum.

[6] I JRC-rapporten (2022) angives log DEE formlen for fugle og ikke pattedyr. $BKK_{sek.\ forgiftn.}$ er beregnet, hvor den korrekte formel for pattedyr er anvendt.

Clarithromycin er klassificeret i henhold til forordning om klassificering, mærkning og emballering af stoffer og blandinger (CLP-forordningen, EF nr. 1272, 2008). Klassificering som H302, "Farlig ved indtag" kræver udarbejdelse af kvalitetskriterium for human konsum.

Ved anvendelse af beregningsgrundlaget fastsat i Europa-Kommissionens tekniske vejledning (EC, 2018), og en ADI (Acceptable Daily Intake) på 1,4 µg/kg kropsvægt/dag med en indregnet sikkerhedsfaktor på 100, er der beregnet følgende kvalitetskriterium for human konsum af vandlevende organismer:

HKK = (0,2 x 1,4 µg/kg kropsvægt/dag) / 0,00163 = 171,8 µg/kg biota vådvægt

Vandkvalitetskriterium baseret på $BKK_{sek.\ forgiftn.}$ og HKK
Der er beregnet et kvalitetskriterium for sekundær forgiftning af vandlevende organismer (biota) for beskyttelse af dyrelivet ($BKK_{sek.\ forgiftn.}$), og for samme vandlevende organismer er der beregnet et kvalitetskriterium for human konsum (HKK). Bestemmelserne i Europa-Kommissionens tekniske vejledning (EC, 2018) fastslår, at der derfor skal vurderes, hvilken af disse værdier der skal være afgørende for et kvalitetskriterium for biota.

Vurderingsgrundlaget er en konvertering af begge værdier til en sammenlignelig koncentration i vandsøjlen ved beregning baseret på tilvejebragte data om Bio Akkumulations Faktor (BAF). Med en BAF-værdi på 91,2 l/kg for fisk svarer værdien for BKK til en koncentration af stoffet Clarithromycin i vand på 51,4 µg/l. Med en BAF-værdi på 91,2 l/kg for fisk svarer værdien for HKK til en koncentration af stoffet Clarithromycin i vand på 1,88 µg/l.

Kvalitetskriteriet for biota til human konsum (beskyttelse af mennesker) medfører derved et noget lavere kvalitetskriterium for biota end fastsat for at beskytte dyrelivet mod sekundær forgiftning ($BKK_{sek.\ forgiftn.}$), når disse omregnes til en koncentration i vandsøjlen.

Kvalitetskriterium for human konsum af drikkevand ($HKK_{Drikkevand}$)
Kvalitetskriteriet for drikkevand skal sikre mennesker mod sundhedsskadelige påvirkninger fra et almindeligt dagligt indtag af drikkevand. For stoffet Clarithromycin er der hverken fastsat en gældende EU kvalitetsstandard for drikkevand eller en retningsgivende koncentrationsværdi fra verdenssundhedsorganisationen WHO.

Kvalitetskriteriet for human konsum af drikkevand ($HKK_{Drikkevand}$) er fastsat i henhold til beregningsgrundlaget fastsat i Europa-Kommissionens tekniske vejledning (EC, 2018). Principielt er kriteriet fastsat på baggrund af toksikologiske studier af pattedyr og fastlæggelse af en tærskelværdi for humant indtag som en NO(A)EL, oftest bestemt som et acceptabelt eller tolerabelt dagligt indtag eller referencedosis, og på grundlag af standard human konsum af drikkevand.

Ved anvendelse af beregningsgrundlaget fastsat i Europa-Kommissionens tekniske vejledning (EC, 2018), og en ADI (Acceptable Daily Intake) på 1,4 µg/kg kropsvægt/dag med en indregnet sikkerhedsfaktor på 100, er der beregnet følgende kvalitetskriterium for human konsum af drikkevand:

$HKK_{Drikkevand}$ = (0,2 x 1,4 mg/kg kropsvægt/dag x 70) / 2 = 9,8 µg/l

Indikativt kvalitetskriterium baseret på at hindre spredning af Antimikrobiel Resistens
Mikrobiel resistens overfor antibiotika (AMR) er globalt et alvorligt og stigende problem, der blev italesat af de Forenede Nationers Generalforsamling med vedtagelse af en deklaration om gennemførelse af fælles handlinger for at takle denne udfordring (UN, 2016)[7]. Udfordringen omfatter specifikt bekymringer om tiltagende forekomster af antibiotika resistente bakterier (AMB) og øget spredning af antibiotika resistente gener (AMG) imellem bakterier knyttet til mennesker, dyr og det eksterne miljø.

Fastsættelse af et kvalitetskriterium for at hindre spredning af Antimikrobiel Resistens i det eksterne miljø, sker på baggrund af et mål om videst muligt at hindre miljøforhold, som vil kunne skabe grundlag for en selektiv opformering af bakterier og genetisk materiale (AMB og AMG), der indeholder Antimikrobiel Resistens. Kvalitetskriteriet er indikativt, idet det faglige grundlag på nuværende tidspunkt fortsat skal modnes og kræver yderligere forskning og faglig indsigt.

Bengtsson-Palme og Larsson (2016)[8] har i et større studie om sikkerhed mod selektiv opformering af resistente bakterier, foreslået anvendelse af den mindste koncentration, der vurderes at kunne frembringe inhibering af mikrobiel vækst – Minimum Inhibitory Concentration (MIC). Til denne koncentrationsværdi tilføjes en usikkerhedsfaktor på 10 for at sikre, at et kvalitetskriterium til hindring af selektive miljøforhold med deraf følgende potentiel spredning af Antimikrobiel Resistens, er baseret på en stofkoncentration væsentligt under MIC-værdien.

I studiet er der frembragt data om MIC-værdier fra den offentlige database EUCAST etableret af den Europæiske Komité for Test af Antimikrobiel Følsomhed, og på grundlag heraf beregnet PNEC-MIC-værdier for en lang række antibiotiske stoffer. For stoffet Clarithromycin er der tilvejebragt et datagrundlag for beregning af PNEC-MIC med en værdi på 0,25 µg/l.

Denne PNEC-MIC værdi for Antimikrobiel Resistens er højere end PNEC (0,13 µg/l) for økotoksikologiske effekter. Det pointeres dog, at den foreslåede PNEC-MIC ikke tager højde for tilstedeværelse af multiresistente bakterier eller kombinationseffekter afledt af flere samtidigt tilstedeværende antibiotika, samt for miljøer med andre miljøfremmede stoffer, biocider og metaller, der også vil kunne bidrage til selektion af Antimikrobiel Resistens (AMR). Det anbefales at anvende den laveste af de to PNEC-værdier.

Fremgangsmåden understøttes og anbefales af den Internationale sammenslutning af Medicinalvareproducenter (IFPMA, 2022)[9].

Effekter af stoffets ionisering ved relevante pH værdier i det eksterne miljø
Stoffet Clarithromycin er et ikke-ladet molekyle, der dog som en meget svag syre kan protolysere med en pKa værdi på 8,99. Stoffet forekommer derfor under miljørelevante forhold med pH værdier mellem 5 og 9, som et ikke-ladet stof.

[7] Forenede Nationer (UN, 2017): Deklaration vedtaget af FN's Generalforsamling den 22. september 2017. Tilgængelig online her: https://digitallibrary.un.org/record/842813
[8] Bengtsson-Palme, Johan og Larsson, D.G. Joakim: Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. Environment International 86 (2016).
[9] Tell, J. et al.: Science-based Targets for Antibiotics in Receiving Waters from Pharmaceutical Manufacturing Operations. Integrated Environmental Assessment and Management – Vol. 15, no. 3, pp. 312-319 (2019)

Konklusion
Følgende kvalitetskriterier for vandmiljøet er udregnet for Clarithromycin:

Vandkvalitetskriterium

$VKK_{ferskvand}$	0,13 µg/l
$VKK_{saltvand}$	0,013 µg/l

Korttidsvandkvalitetskriterium

$KVKK_{ferskvand}$	0,13 µg/l
$KVKK_{saltvand}$	0,013µg/l

Sedimentkvalitetskriterium

$SKK_{ferskvand}$	Ikke relevant
$SKK_{saltvand}$	Ikke relevant

Biotakvalitetskriterium, sekundær forgiftning

$BKK_{sek.forgiftn.}$	4,7 mg/kg vådvægt (fisk)

Biotakvalitetskriterium, human konsum

HKK	171,8 µg/kg biota vådvægt

EQS DATASHEET

ENVIRONMENTAL QUALITY STANDARD

Clarithromycin

List of Content

List of Tables

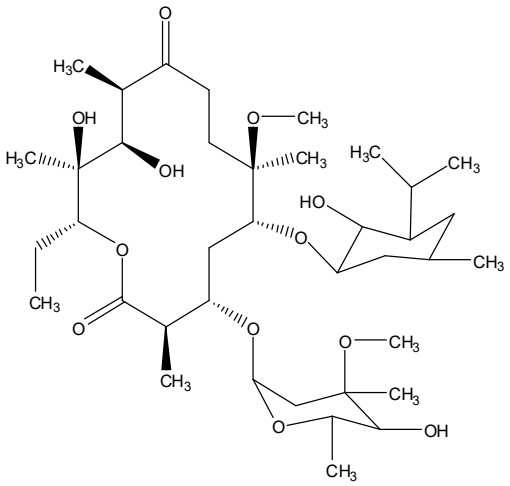
List of Figures

Changes on the Dossier after the SCHEER final Opinion (2022)

Following the final SCHEER opinion published on the 6th of May 2022 (SCHEER, 2022)[10], the JRC updated the Clarithromycin dossier in Section 6.4 "Secondary poisoning".
According to the SCHEER opinion (2022): "*the SCHEER agreed the clarithromycin chemical characteristics should trigger a secondary poisoning standard. On 27th April 2022 the JRC reported to the SCHEER that the $QS_{biota,ww}$ of 15.7 µg.kg^{-1} proposed in the dossier was incorrect. The revised calculations would now lead to $QS_{Biota,\ sec\ pois,\ fw}$ 4.7 or 1.6 mg kg^{-1} $_{ww}$ dependent on whether an AF of 10 or 30 is selected. The SCHEER awaits further confirmation of the final decision on AF"*.
In this dossier, the JRC selected the NOAEL of 4 mg.kg^{-1}.d^{-1} for dogs as starting point for $QS_{biota,\ secpois}$ derivation. Since animals were continuously exposed to clarithromycin for 6 months (Accord Healthcare Limited, 2018), the JRC proposed an AF of 10, according to the EQS Technical Guidance (EC, 2018), obtaining **a $QS_{biota,\ secpois,\ fw}$ of 4.7 mg kg^{-1} $_{ww}$.**

[10] SCHEER final opinion on clarithromycin: https://health.ec.europa.eu/publications/draft-environmental-quality-standards-priority-substances-under-water-framework-directive-2_en

1 Chemical identity

Common name	Clarithromycin
Chemical name (IUPAC)	(3R,4S,5S,6R,7R,9R,11R,12R,13S,14R)-6-{[(2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy}-14-ethyl-12,13-dihydroxy-4-{[(2R,4R,5S,6S)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy}-7-methoxy-3,5,7,9,11,13-hexamethyl-1-oxacyclotetradecane-2,10-dione
Synonym(s)	6-O-Methylerythromycin
Chemical class (when available/relevant)	Antibiotic
CAS number	81103-11-9
EU number	658-034-2
Molecular formula	$C_{38}H_{69}NO_{13}$
Molecular structure	
Molecular weight (g.mol^{-1})	747.95

2 Existing evaluations and Regulatory information

Annex III EQS Dir. (2008/105/EC)	Not Included
Existing Substances Reg. (793/93/EC)	Not applicable
Pesticides (91/414/EEC)	Not included in Annex I
Biocides (98/8/EC)	Not included in Annex I
PBT substances	Not investigated
Substances of Very High Concern (1907/2006/EC)	No
POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	No
Endocrine disrupter	Not applicable
Classification and Labelling Regulation	No

3 Proposed Quality Standards (QS)

Uses
Clarithromycin is a semisynthetic macrolide antibiotic indicated for the treatment of infections of the upper and lower respiratory tract, skin and skin structures (e.g., otitis media), disseminated mycobacterial and *H. pylori* infections caused by susceptible bacterial organisms. Clarithromycin is also approved for prophylactic use in prevention of disseminated mycobacterium avium complex (MAC) disease in AIDS patients.

3.1 Environmental Quality Standard (EQS)

Add any comment on possible residual uncertainty.

	Value	Comments
Proposed AA-EQS for [freshwater] [µg.L^{-1}] Corresponding AA-EQS in [marine water] [µg.L^{-1}]	0.13 0.013	Critical QS is $QS_{-freshwater}$ **See Section 6.2**
Proposed MAC-EQS for [freshwater] [µg.L^{-1}] Proposed MAC-EQS for [marine waters] [µg.L^{-1}]	0.13 0.013	**See Section 6.2**

3.2 Specific Quality Standard (QS)

Protection objective	Unit	Value	Comments
Predators (secondary poisoning)	[µg.$kg^{-1}_{biota\ ww}$]	4.7 x 10^3 µg.kg^{-1}	**See Section 6.4**
	[µg.l^{-1}]	51.4 (freshwaters)	
Human health via consumption of fishery products	[µg.$kg^{-1}_{biota\ ww}$]	171.8	**See section 7**
	[µg.l^{-1}]	2.02 (freshwaters)	
Human health via consumption of water	[µg.l^{-1}]	9.8 (freshwaters)	

4 Measured Environmental Concentrations

4.1 Freshwater

Note: This section has been updated by the JRC after the final adoption of QS values by the SCHEER committee in the plenary meeting on 6 May 2022. The term Predicted No Effect Concentration (PNEC) is utilised sometimes in the text as a more general term in risk assessment and for keeping approach used in the prioritisation exercise, started 2014 (Carvalho et al., 2016), consequently assuming that the PNEC is equal to the freshwater AA-EQS=0.13 µg/L.

4.1.1 Data availability and data scenarios

To update of information on exposure in the clarithromycin's dossier, the JRC has used disaggregated data existing at the beginning of current prioritisation exercise, which started in 2014 (Carvalho et al., 2016), and also recent data (after 2014) which were officially reported to the EEA (Watch List and WISE database) by the EU Member States (MS).
The currently available disaggregated raw data for measured environmental concentrations (MECs) in inland surface water compartment are summarised in Table 4.1 showing the source, dataset and corresponding periods of monitoring. A short description of each of the referred datasets is provided thereafter below.

Table 4.1: Source, dataset and available disaggregated raw monitoring data for measured environmental concentrations (MECs) in inland surface water compartment.

Source/Dataset	Available disaggregated raw data
JRC, Prioritisation dataset (2014)	4748 samples (about 43.9% quantified) from 391 sites in 1 MS (2006 – 2014)
EEA, Watch List (2019)	7336 samples (about 56.7% quantified) from 621 sites in 25 MS (2015 - 2019)
EEA, WISE (2020)	5567 samples (about 51.5% quantified) from 531 sites in 25 MS (2008, 2012, 2015 – 2019)
Data received or retrieved after the 18th meeting of WFD CIS WG Chemicals (held in October 2020)	CWPharma project (2020) https://www.lansstyrelsen.se/4.f2dbbcc175974692d268b9.html 40 quantified and 15 non-quantified samples from 25 sites in 6 MS taken with LOQ=0.001 µg/L. Assuming a substitution by ½ LOQ for non-quantified samples mean=0.026 µg/L (mean=0.036 µg/L only for quantified samples) and 95th percentile=0.1 µg/L.

The Prioritisation dataset includes monitoring data collected at the beginning of the second prioritisation exercise (Carvalho et al., 2016; https://circabc.europa.eu/w/browse/52c8d8d3-906c-48b5-a75e-53013702b20a) which are taken from following sources:

- SoE - monitoring data reported by MS under the State of the Environment (SoE) WISE (Water Information System for Europe) managed by the European Environment Agency (EEA).
- MSDAT – monitoring data directly submitted to the JRC by EU member states following a request of DG ENV to the EU Water Directors (on 21 March 2014). In addition, some monitoring data have been submitted on behalf of the European drinking water companies.
- EMPODAT - a database of geo-referenced monitoring data managed by NORMAN (Network of reference laboratories, research centres and related organisations for monitoring of emerging environmental substances) https://www.norman-network.net/). The EMPODAT data were provided to the JRC in March 2015.
- JDS - monitoring data from the third Joint Danube Survey (JDS) from the year 2013 https://www.icpdr.org/
- IPCheM - the Information Platform for Chemical Monitoring data, managed by the JRC was downloaded in January 2015 (https://ipchem.jrc.ec.europa.eu).

The Watch List (WL) dataset includes monitoring data from several reporting cycles of the WL (2015-2019) and this dataset is in detail described in a dedicated report (Marinov and Lettieri, 2020; https://circabc.europa.eu/ui/group/9ab5926d-bed4-4322-9aa7-9964bbe8312d/library/deabbcb4-c001-4855-b503-04f27996ca7d/details).

The monitoring data from the WISE dataset, managed by the EEA, has been received in November 2020 (information about WISE data could be found on https://www.eea.europa.eu/data-and-maps/data/waterbase-water-quality-icm-1).

Further, the JRC acknowledged the point raised by the stakeholders that despite the constant improving of sensitivity of analytical techniques, any set of measured concentrations may contain a portion of non-detected or non-quantified samples, called often “less than” values or censored concentrations (Helsel 2006; Gardner 2011; Helsel 2012; Shoari and Dubé, 2018; Merrington et al., 2021). The censored or less than values are measurements for which the observed concentration is less than the limit of detection (LOD) or limit of quantification (LOQ) and for them, the true sample concentration is somewhere between zero and the reporting limit (Helsel, 2006; Gardner, 2011). Three approaches exist for tackling the censored data problem: i) ignoring less than data, ii) substituting less than data and, the third one iii) comprehensive mathematical techniques (Helsel 2006; Gardner 2011; Helsel 2012; Shoari and Dube, 2018). The practice of analysing datasets with censored data in regulatory agencies, US EPA and EFSA is summarised in Shoari and Dube (2018) showing that either substitution or mathematical techniques are applied according to levels of censoring.

Accordingly, the JRC has adopted to deal with the uncertainty from censored data, when deriving statistics of MECs, by using the Kaplan-Meier nonparametric method and/or as alternative, if feasible, the substitution approach. The latter follows the guideline of the European Food Safety Authority (EFSA, 2010) which suggests making the calculations of statistics twice, once for a lower bound by substituting non-detects with null and once for an upper bound by substituting non-detects with the LOD or LOQ. If the difference between the upper and lower bound of the estimated parameter is negligible, then substitution with the LOD or LOQ is recommended (this is the worst-case scenario but other scenarios are also possible, i.e. ½ LOQ). When the difference is not negligible or the upper bound estimate is in the range of (eco)toxicological threshold, then alternative estimation techniques should be used. A similar approach is applied also by the US EPA (Shoari and Dube, 2018). As a software tool dealing with dataset including censored data (in

particular deriving statistics by the Kaplan-Meier method which is especially useful because avoids assumptions about the data distribution) the JRC is using ProUCL v5.1 of US EPA (https://www.epa.gov/land-research/proucl-software).
Moreover, in monitoring datasets the usage of non-quantified samples is a challenge when not all Limit of Quantifications (LOQs) of applied analytical methods are adequate to the Predicted No Effect Concentration (PNEC). For this reason, and also following the experience from the latest review of the Priority Substances (PS) list (Carvalho et al, 2016), three data scenarios are considered in this dossier (Table 4.2).

Table 4.2: Scenarios considered in the data analyses and risk assessment (the scenario indicated as Sc3 was called Sc2-PNEC-QC in the last monitoring-based prioritisation exercise (Carvalho et al., 2016)).

Data scenario	Description
Scenario 1 (Sc1)	**Only quantified** monitoring samples
Scenario 2 (Sc2)	**All monitoring samples** (quantified and non-quantified). In Sc2 the non-quantified samples are set equal to half of LOQ as stipulated in Directive 2009/90/EC
Scenario 3 (Sc3)	**Quantified** monitoring samples **plus non-quantified** samples when **½ LOQ ≤ PNEC** (or EQS) Sc3 is a more relevant data scenario for making a risk assessment according the sub-group on review (SG-R) of the priority substances list in the prioritization exercise 2016.

Scenario 1 (Sc1) includes only quantified samples, thus clearly overestimating the risk. If application of the substitution approach for censored data is feasible, then in both Scenario 2 (Sc2) and Scenario 3 (Sc3) the non-quantified samples are set to half LOQ[11]. However, Sc2 comprises all monitoring records, thus could lead to non-confirmed exceedances when ½LOQ>PNEC, while Sc3 takes into account quantified monitoring samples and non-quantified samples only when ½LOQ≤PNEC, thus avoiding any non-confirmed exceedances. According to the sub-group on review (SG-R) of the priority substances list, Sc3 is the most relevant scenario to assess whether the substance poses a risk at EU-level (Carvalho et al., 2016). Anyway, information for Sc1 and Sc2 scenarios is also presented for completeness.
Then, the records from the datasets, shown in Table 4.1, have been combined in a single dataset (called thereafter COMBI dataset). However, it should be noted that duplicated records are possible between the individual datasets in particular between the Watch List and WISE datasets. Thus, after removal of duplicates from COMBI dataset, the latter is used for making a union wide risk assessment. A summary information about the numbers of participating MS, monitoring sites and collected samples is presented in Table 4.3 for Sc1 and Sc2 data scenarios (info about Sc3 is given after the data quality check). Furthermore, the detailed statistics per country for Sc2 and Sc3 scenarios is provided in a complementary Excel file entitled ***MEC_Clarithromycin_dossier*** (including the number of sites, number of samples, fraction from all samples, number of quantified

11 Under the QA/QC Directive and EQS Directive, MS are required to replace the non-quantified samples by half LOQ to assess compliance with the EQS for individual substances. However, the amended EQSD mentions that "when the calculated mean value of a measurement, when carried out using the best available technique not entailing excessive costs, is referred to as "less than limit of quantification", and the limit of quantification of that technique is above the EQS, the result for the substance being measured shall not be considered for the purposes of assessing the overall chemical status of that water body".

samples, info about LOQ values, statistics of MECs, etc.). It evidenced that two MS are overrepresented in the combined dataset holding together about 83.45% of all samples (MS#06 contributed with 43.75% while MS#07 with 39.7%).

Table 4.3: Available disaggregated data for the measured environmental concentrations (MECs) in inland surface water compartment across EU MS (jointly data from all countries after the elimination of duplicated records) for the period 2006 – 2019 in Sc1 and Sc2 of the combined dataset (called thereafter COMBI dataset)

Scenario	Member States (MS)	Sites	Samples	Quantified samples (% from all samples)
Sc1	22	684	6047	100
Sc2	25	1032	11971	50.5

4.1.2 Quality of data

The quality of measured concentrations is essential for making a proper risk assessment. The applied general requirements for data quality check and the procedures for treatment of outliers and duplicates are described in two JRC reports (Carvalho et al, 2016; Loos et al., 2018).
The records in the COMBI dataset fulfil the general requirements for appropriate data reporting (where, when, what, how was measured, etc.). The dataset is free of duplicates and outliers. Therefore, a special attention is paid here on the sensitivity of the applied analytical methods (LOQ-PNEC criterion), union representativeness of data and uncertainty (bias) related to non-quantified (censored) concentrations.
For instance, considering the data from all MS together, Figure 4.1 shows the range of LOQs of non-quantified samples per country while Figure 4.2 informs how many non-quantified samples fulfilled the LOQ-PNEC condition (½ LOQ≤PNEC) in each of the reporting MS. It was found that MS have monitored with sufficiently sensitive analytical methods and all non-quantified samples fulfilled the LOQ-PNEC criterion. The detailed information about the LOQ values per MS for non-quantified samples in Sc2 dataset is provided in the accompanying Excel file (*MEC_Clarithromycin_dossier)*.

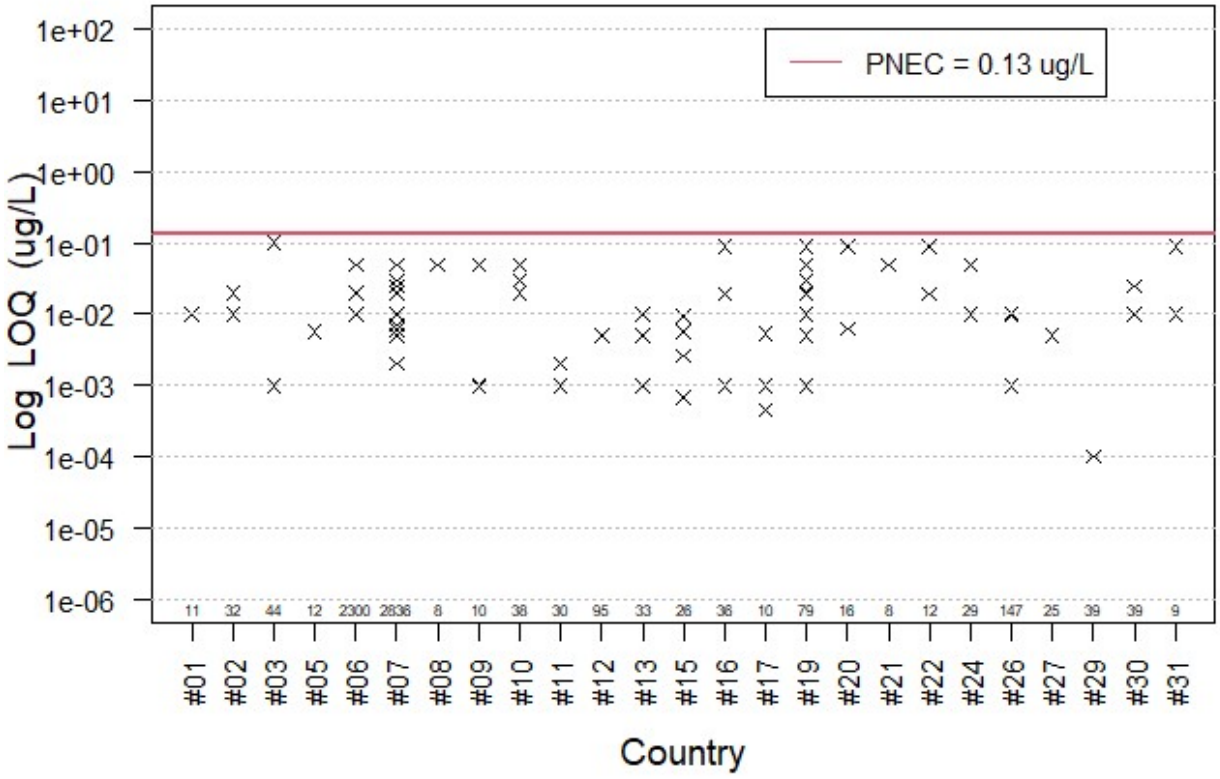


Figure 4.1: Range of LOQs for non-quantified samples in Sc2 of combined dataset per country. The lowermost line of the figure shows the overall number of non-quantified samples in each reporting MS. For confidentiality, the countries' names are coded. The red line indicates the PNEC value.

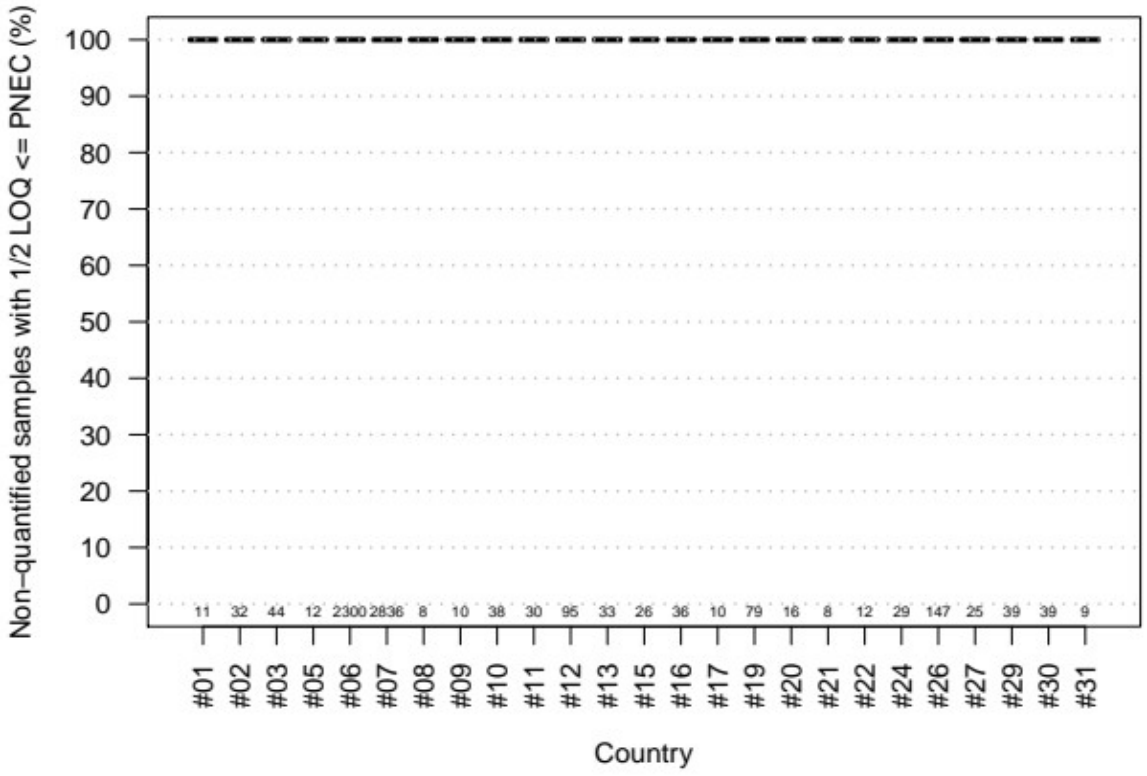


Figure 4.2: Number of non-quantified samples fulfilled LOQ-PNEC condition (½ LOQ≤PNEC) as percentage from reported non-quantified samples per country in Sc2 of the combined dataset. The lowermost line of the figure shows the overall number of non-quantified samples in each reporting MS. For confidentiality, the countries' names are coded.

After the LOQ-PNEC check the decisive Sc3 data scenario is developed using PNEC=0.13 µg/L (in fact, since the good data quality Sc3=Sc2). The basic information for Sc3 scenario is presented in Table 4.4. Moreover, the detailed statistics for Sc3 dataset is provided in the complementary Excel file. It was concluded that there are sufficient amount of data with a good quality for making a union-wide risk assessment.

Table 4.4: Available disaggregated data for measured environmental concentrations (MECs) across EU MS (jointly data from all countries after the elimination of duplicated records) for the period 2006 – 2019 in Sc3 of the combined dataset (PNEC=0.13 µg/L).

Scenario	Member States (MS)	Sites	Samples	Quantified samples (% from all)
Sc3	25	1032	11971	50.5

Then, the plots of histogram (Figure 4.3) and cumulative frequency (Figure 4.4) have been prepared for measured concentrations in Sc3 of the combined dataset (data from all MS together) undertaking a substitution by half of LOQs for censored data. The cumulative frequency (Figure 4.4) is

compared to a log-normal distribution with the same mean and standard deviation. It was found that the empirical distribution is not far away from the log-normal.

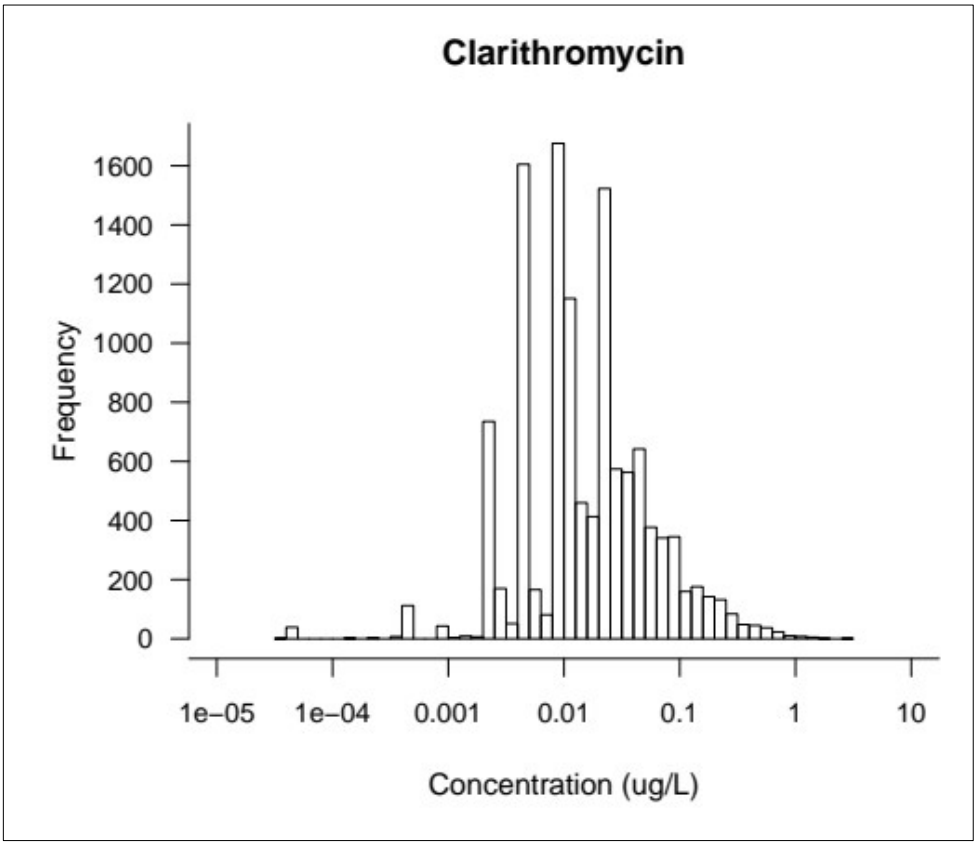


Figure 4.3: Histogram of concentrations (data from all MS together) for Sc3 scenario of the combined dataset undertaking a substitution by half of LOQs for censored data

.

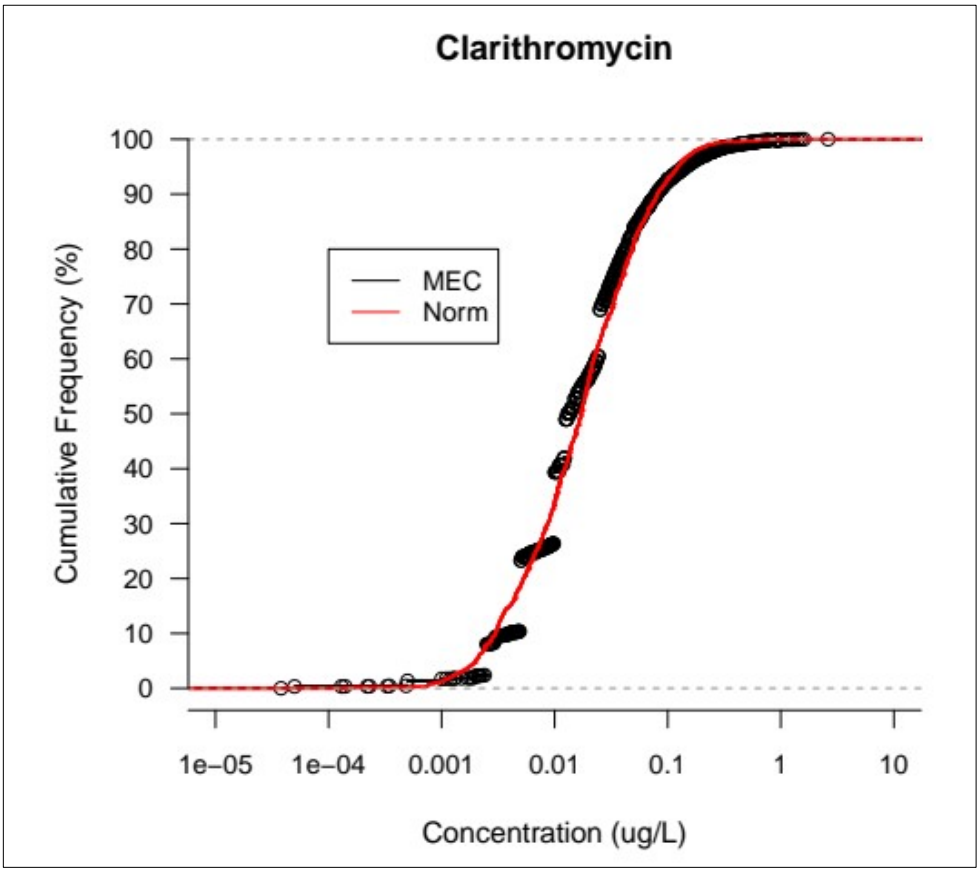


Figure 4.4: Cumulative frequency of concentrations (data from all MS together) for Sc3 scenario of the combined dataset undertaking a substitution by half of LOQs for censored data. The red line represents a cumulative frequency of log-normal distribution with the same mean and standard deviation.

4.1.3 Summary statistics of measured concentrations

The summary statistics of measured concentrations in compartment inland surface water for Sc3 (min, average, standard deviation (StDev), median, 90th percentile (P90), 95th percentile (P95), 99th percentile (P99) and max) is estimated considering together the data from all MS and using Kaplan-Meier nonparametric method (ProUCL 5.1 tool) of the US EPA (https://www.epa.gov/land-research/proucl-software). The obtained results are presented in Table 4.5. For completeness, the table shows also statistics for Sc3 with the substitution approach taking into consideration two extreme cases (lower bound 1% of LOQ and upper bound 99% of LOQ) alongside with the common "central" approach (50% of LOQ). One could observe that the mean concentration, found by Kaplan-Meier method, is between the estimates of lower bound and middle substitution (i.e. 1% and 50% of LOQ), while the median and P90 are identical to the upper bound of replacement (99% of LOQ). The nonparametric method and substitution approximation showed equal values for higher percentiles (for example P95 and P99).
According to ProUCL 5.1 tool, the assessed variance in Sc3 by KM method is about $7.78*10^{-3}$ µg/L. The 95% upper confidence limit (95% UCL) of mean concentration, estimated by KM, is 0.0371 µg/L through bootstrapping and 0.0394 µg/L according Chebyshev method (ProUCL 5.1). The 95% upper tolerance limit with 95% coverage (i.e. 95% UCL of the 95th percentile) is 0.183 µg/L by KM approach assuming normal distribution and higher, 0.42 µg/L, according Chebyshev method (ProUCL 5.1).

Table 4.5: Summary statistics of measured concentrations for **Sc3 scenario** (jointly data from all MS) estimated by Kaplan-Meier nonparametric method for dataset containing censored data (ProUCL 5.1 tool of the US EPA). For completeness, statistics for Sc3 derived by the substitution approach for censored data considering two extreme cases (lower bound 1% of LOQ and upper bound 99% of LOQ) alongside with the common "central" approach (50% of LOQ) is also presented.

Concentration (µg/L)	Kalpan-Meier method (ProUCL 5.1)	Scenario 1% LOQ	Scenario 50% LOQ	Scenario 99% LOQ
Min	3.8E-05	1.0E-06	3.8E-05	3.8E-05
Mean	0.0359	0.0332	0.0383	0.0434
StDev	0.0882	0.089	0.089	0.0865
Median	0.021	0.002	0.013	0.021
P90	0.084	0.08	0.08	0.084
P95	0.141	0.1405	0.1405	0.1405
P99	0.41	0.41	0.41	0.41
Max	2.62	2.62	2.62	2.62

In addition for completeness, Table 4.6 is comparing the summary statistics of measured environmental concentrations for Sc3 scenario (jointly data from all MS) estimated by Kaplan-Meier nonparametric method for dataset containing censored data (ProUCL 5.1 tool) with statistics for Sc1 and Sc2 data scenarios (Sc1 includes only quantified samples; in Sc2 scenario a substitution by half of LOQ is applied for censored data).

Table 4.6: Comparison statistics of measured concentrations for Sc3 scenario (jointly data from all MS) estimated by Kaplan-Meier nonparametric method for dataset containing

censored data (ProUCL 5.1 tool of the US EPA) with statistics for Sc1 and Sc2 data scenarios (Sc1 includes only quantified samples; in Sc2 scenario a substitution by half of LOQ is applied for censored data).

Concentration (µg/L)	**Scenario Sc1**	**Scenario Sc2**	**Scenario Sc3 Kalpan-Meier method (ProUCL 5.1)**
Min	3.8E-05	3.8E-05	3.8E-05
Mean	0.0654	0.0383	0.0359
StDev	0.1165	0.0874	0.0882
Median	0.032	0.013	0.021
P90	0.14	0.08	0.084
P95	0.23	0.14	0.141
P99	0.59	0.41	0.41
Max	2.62	2.62	2.62

Since two MS (#06 and #07) are overrepresented in the combined dataset holding together about 83.45% of all samples (see the supporting Excel file), for this reason Table 4.7 analyses the summary statistics if all MS are presented in the Sc3 dataset and also a hypothetical scenario of excluding the data-rich countries. The statistics are estimated by Kaplan-Meier nonparametric method for dataset containing censored data (ProUCL 5.1 tool). The derived mean concentrations in both scenarios are similar. In addition, compatible results were obtained for higher percentiles of MECs ($\geq 90^{th}$ percentile) when considering all MS or if excluding the overrepresented MS.

Table 4.7: Comparison statistics for measured environmental concentrations across EU considering either jointly data from all MS (Sc3 all MS presented) or excluding the most data-rich MS (without MS#06 and MS#07) from the combined dataset. The statistics are estimated by Kaplan-Meier nonparametric method for dataset containing censored data (ProUCL 5.1 tool of the US EPA).

Concentration (µg/L)	**Sc3 (presented all MS)**	**Scenario "data-rich MS excluded from Sc3" (without #06 and #07)**
Min	3.8E-05	3.8E-05
Mean	0.0359	0.0321
StDev	0.0882	0.103
Median	0.021	0.011
P90	0.084	0.09
P95	0.141	0.14
P99	0.41	0.454
Max	2.62	2.62

4.1.4 Temporal trend

The temporal trend is verified for the period 2006-2019 according to the annual variability of 95th percentiles (P95) of measured concentrations. The P95 of MECs are estimated by Kaplan-Meier nonparametric method of ProUCL 5.1 tool of the US EPA.
Considering data from all MS together (see Figure 4.5), no clear temporal trend of P95 was found. Generally, the 95th percentiles of MECs showed a low variability and small oscillations around the PNEC value. In the recent years (2015-2019), most of the P95 tend to exceed slightly the PNEC value.
Detailed information about P95 per country and year is provided for Sc3 dataset in the complementary Excel file (MEC_Clarithromycin_dossier).

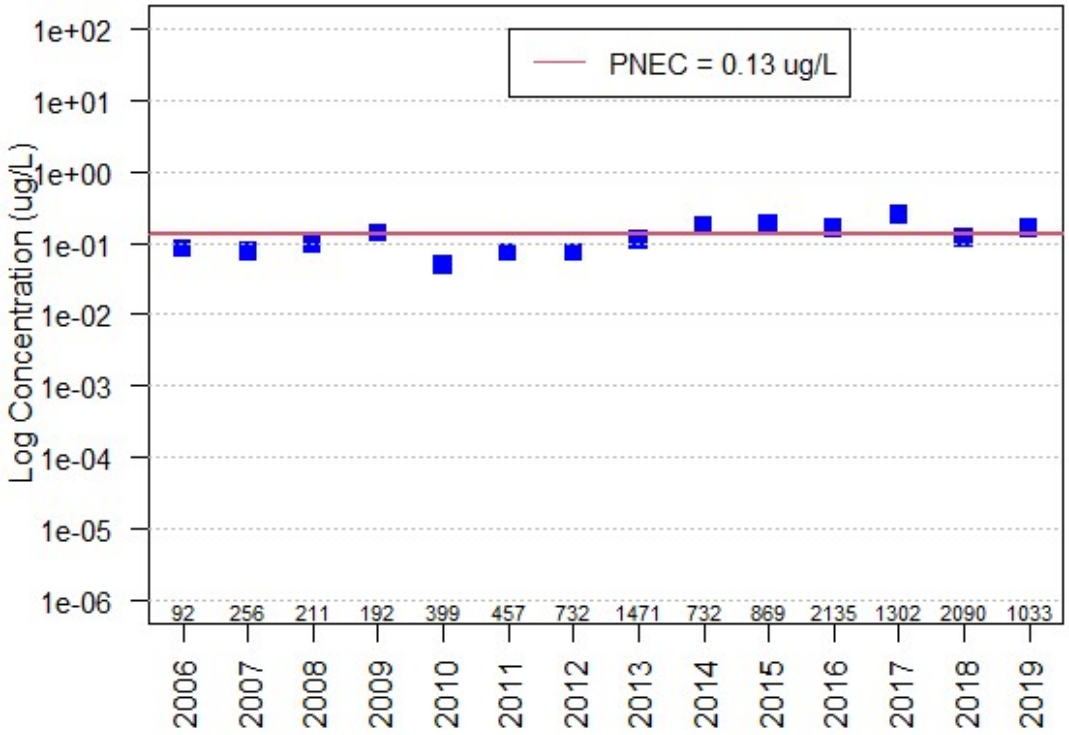


Figure 4.5: Plot for 95th percentiles (P95) of measured environmental concentrations per year for Sc3 scenario of the combined dataset considering data from all MS. It was found no clear temporal trend of P95. Generally, the 95th percentiles of MECs showed a low variability and small oscillations around the PNEC value. In the recent years (2015-2019), most of the P95 tend to exceed slightly the PNEC value. The lowermost line of the figure shows overall number of samples in each year. The red line represents the PNEC value.

4.2 Risk assessment (freshwater)

The Risk Assessment (RA) analysis, developed after the adoption EQS values by the SCHEER committee, includes two components – first, a screening of overall risk for inland surface water compartment and second, a compliance check in regard to the freshwater AA-EQS and MAC-EQS.

Screening of risk

The screening of overall risk was elaborated following the procedure adopted by the sub-group of revision of the Priority Substances list (Carvalho et al., 2016; https://circabc.europa.eu/w/browse/52c8d8d3-906c-48b5-a75e-53013702b20a). Accordingly, the risk screening is based on MECs in Sc3 data scenario of the combined dataset and utilizes PNEC equal to the freshwater AA-EQS=0.13 µg/L. The risk screening takes into account the Risk Quotient RQ(P95), the Spatial, Temporal and Extent of PNEC exceedances (STE score) and number of exceeding MS (see Table 4.8).

The Risk Quotient RQ(P95) is estimated by the 95th percentile (P95) of concentrations considering measurements in Sc3 from all MS and for the entire time period. A given country is specified as "Exceeding MS" if the 95th percentile of its own measured concentrations is higher than the freshwater AA-EQS. The STE (Spatial, Temporal and Extent of PNEC exceedances) is assessment tool developed in-house by the JRC. The STE method is widely described and discussed in Carvalho et al., 2016 (https://circabc.europa.eu/w/browse/52c8d8d3-906c-48b5-a75e-53013702b20a). The STE calculates for each substance a risk score by summing the Spatial, Temporal and Extent of PNEC exceedance factors (indexes) using P95 of MECs at monitoring sites. The range of STE scores is between 0 and 3 since the individual factors vary from 0 to 1, where a STE score of 0 indicating null concern, while a score of 3 showing an extremely high concern.

The relevant P95 of MECs (see Table 4.5) are estimated by Kaplan-Meier nonparametric method for datasets containing censored data (ProUCL 5.1 tool of the US EPA). The P95 of reporting MS, respectively exceedances in each MS, are evaluated also with the Kaplan-Meier method and ProUCL tool (see the complementary Excel file). However, the STE score is calculated in a traditional manner using the substitution by half of LOQs for non-quantified (censored) data.

Table 4.8: Risk assessment screening results. The evaluation is based on measured concentrations in Sc3 scenario of the combined dataset and **PNEC=0.13 µg/L**. The Risk Quotient RQ(P95) is estimated by the 95th percentile of concentrations considering altogether measurements from all MS whereas the P95 is estimated by Kaplan-Meier nonparametric method for datasets containing censored data (ProUCL 5.1 tool of the US EPA). The STE (Spatial, Temporal and Extent of PNEC exceedances) is assessment tool developed by the JRC (the table shows also the Spatial, Temporal and Extent of PNEC exceedance factors of the STE score). A given country is specified "Exceeding MS" if the 95th percentile of its measured concentrations is higher than the PNEC value. The P95 of reporting MS, respectively exceedances in each MS, are evaluated also with the Kaplan-Meier method and ProUCL tool

Scenario	RQ(P95)	Fspat	Ftemp	Fext	STE score	Exceeding MS (% from total)	Total number of reporting MS
Sc3	1.084	0.0369	0.2803	0.07	0.387	7 (28%)	25

The performed screening indicated a presence of risk at EU level because the overall RQ(P95)=1.084, viz. it is higher than one, and 7 out of the 25 reporting countries in Sc3 could be specified as exceeding MS (about 28% from all MS).

Note:

The screening of risk according to the hypothetical scenario "exclusion the data-rich countries from Sc3 dataset" (i.e. without MS #06 and 07) showed quite similar RQ(P95)=1.077 (see Table 4.7), i.e. confirmed again the presence of risk for EU fresh waters. One of the excluded MS (#06) showed individually RQ(P95)>1 (the other excluded MS #07 has individual RQ(P95) approaching one).

Compliance check

The compliance check, which is a core part of the developed risk assessment, was performed according to the EQS Directive[12]. The compliance is based on MECs in Sc3 data scenario of the combined dataset and is considered to be fulfilled (not failed) if the annual average measured concentrations at monitoring sites in the participating MS do not exceed the AA-EQS, and when the maximum concentrations (or 99th percentile[13] of concentrations) in reporting MS do not exceed the MAC-EQS. In the compliance analysis the non-quantified concentrations in the Sc3 dataset were assumed to be equal to a half of LOQs[14] i.e. the substitution approach, adopted by Directive 2009/90/EC, was applied.

A boxplot of annual average concentrations at monitoring sites for the considered time period (Sc3 scenario) is shown on Figure 4.6 comparing to the freshwater AA-EQS=0.13 µg/L. Then, a relevant statistics about the number of monitoring sites in Sc3 dataset which annual mean concentrations exceeded the freshwater AA-EQS (given also as a percentage from the total number of sites) is presented in Table 4.9. For instance recently (onwards 2015 when more MS have reported data), yearly from 9 up to 19 sites, corresponding to 3.2%-7.1% of all monitoring sites, showed annual mean concentrations higher than the freshwater AA-EQS. This confirms the failure of compliance in regard to the freshwater AA-EQS.

[12] Directive 2008/105/EC Annex I Part B

Paragraph 1 "For any given surface water body, applying the AA-EQS means that, for each representative monitoring point within the water body, the arithmetic mean of the concentrations measured at different times during the year does not exceed the standard'' and

Paragraph 2 "For any given surface water body, applying the MAC-EQS means that the measured concentration at any representative monitoring point within the water body does not exceed the standard''.

[13] Directive 2008/105/EC Annex I Part B Paragraph 2 states that "In accordance with Section 1.3.4 of Annex V to Directive 2000/60/EC, Member States may introduce statistical methods, such as a percentile calculation, to ensure an acceptable level of confidence and precision for determining compliance with the MAC-EQS".

[14] Directive 2009/90/EC Article 5 Paragraph 1 states "Where the amounts of physico-chemical or chemical measurands in a given sample are below the limit of quantification, the measurement results shall be set to half of the value of the limit of quantification concerned for the calculation of mean values".

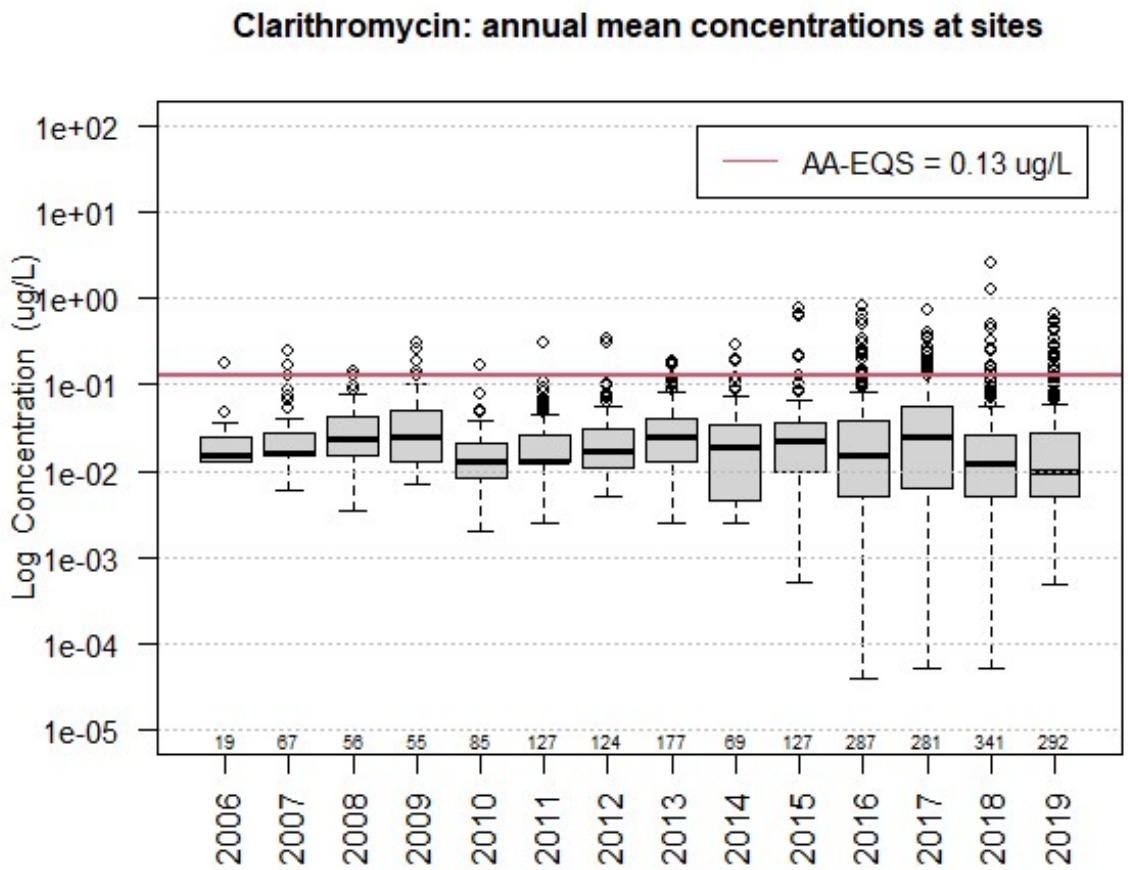


Figure 4.6: Boxplot of annual average values of measured concentrations at monitoring sites in Sc3 scenario for the considered time period. In this analysis the non-quantified concentrations are assumed to be equal to a half of LOQ (Directive 2009/90/EC). The lowermost line of the figure gives the overall number of monitoring sites in each year. The red line indicates the PNEC equal to the freshwater AA-EQS.

Table 4.9: Number of monitoring sites in Sc3 dataset which annual mean concentrations exceeded the freshwater AA-EQS (given also as a percentage from the total number of sites). In this analysis the non-quantified concentrations are assumed to be equal to a half of LOQ (Directive 2009/90/EC).

Year	Number of reporting MS	Total number of sites	Number of exceeding sites	% of exceeding sites from all
2006	1	19	1	5.3
2007	1	67	2	3.0
2008	2	56	3	5.4
2009	1	55	5	9.1
2010	1	85	1	1.2
2011	1	127	1	0.8
2012	2	124	2	1.6
2013	1	177	4	2.3
2014	1	69	3	4.3
2015	9	127	9	7.1

2016	23	287	19	6.6
2017	24	281	19	6.8
2018	21	341	11	3.2
2019	21	292	19	6.5

Regarding the compliance with the freshwater MAC-EQS=0.13 µg/L, the 99th percentiles of MECs from individual MS per year (Sc3 dataset) were compared with the MAC threshold (see Table 4.10). In the time-period after 2014, every year from 3 up to 6 MS showed P99 exceeding the freshwater MAC-EQS (corresponding to 19 - 33.3 % of the number of annually reporting MS). This allows concluding a failure of compliance in regard to the freshwater MAC-EQS.

Table 4.10: Number of reporting MS in Sc3 combined dataset which 99th percentiles of MECs exceeded annually the freshwater MAC-EQS (for each year given also as a percentage from the total number of reporting MS). In this analysis the non-quantified concentrations are assumed to be equal to a half of LOQ (Directive 2009/90/EC).

Year	Number of reporting MS	Number of exceeding MS	% of exceeding MS from all
2006	1	1	100
2007	1	1	100
2008	2	1	50
2009	1	1	100
2010	1	0	0
2011	1	1	100
2012	2	1	50
2013	1	1	100
2014	1	1	100
2015	9	3	33.3
2016	23	5	21.7
2017	24	6	25
2018	21	4	19
2019	21	6	28.6

4.3 Coastal/Transitional water

This section is not fully developed because currently there are available a small amount of disaggregated monitoring data for the compartment of coastal/transitional water (see Table 4.11). The available raw data from the EEA (Watch List and WISE database) are described in Table 4.11
Regarding the quality of monitoring data from the WL, the range of LOQs of non-quantified samples is 0.0001 - 0.05 µg/L. Most of non-quantified samples (21 out of 27) are taken with LOQs in the range 0.0001 - 0.01 µg/L but another 6 unquantified samples are monitored with LOQs from 0.02 – 0.05 µg/L which are higher than the AA-EQS$_{marinewater}$ (0.013 µg/L) and this may indicate an insufficient sensitivity of applied analytical methods.
All available samples from the WISE database are non-quantified, 10 samples are from monitoring with LOQs in the range 0.001 - 0.01 µg/L (i.e. respect the saltwater AA-EQS) but the remaining 12 samples are processed with LOQs from 0.015 – 0.026 µg/L (i.e. exceed the AA-EQS$_{marinewater}$) that may indicate an insufficient sensitivity of monitoring.
Thus, the total amount of data and sensitivity of monitoring are insufficient for making a reliable risk assessment for this compartment. However, for completeness the summary statistics of measured concentrations in Sc2 scenario (raw data) is presented in Table 4.12. In this analysis the non-quantified concentrations are assumed to be equal to ½ LOQ.

Table 4.11: Source and available disaggregated raw monitoring data for measured environmental concentrations (MEC) in coastal/transitional water.

Source/Dataset	Available disaggregated raw data
EEA, Watch List (2019)	41 samples from 6 MS (34% quantified) for the period 2015-2019
EEA, WISE (2021)	22 samples from 5 MS (all non-quantified) for the period 2019-2020 (no duplicated samples with the WL)

Table 4.12: Summary statistics of measured environmental concentrations (µg/L) in Sc2 scenario. In this analysis the non-quantified concentrations are assumed to be equal to ½ LOQ.

Concentration (µg/L)	Min	Mean	StDev	Median	P90	P95	P99	Max
	$5*10^{-5}$	0.011	0.0156	0.005	0.033	0.0556	0.066	0.071

5 Environmental Behaviour

5.1 Environmental distribution

		Reference
Water solubility (mg l^{-1})	0.33 (exp.) 0.217 (est.) 0.07 at 20°C (exp.); 0.32 at 25°C (est.); Ca. 2 (exp.), room temperature, pH 7.8	Drugbank Drugbank Nakagawa et al. 1992; US EPA (2021); Baumann et al. 2015
Volatilisation		
Vapour pressure	2.32E-25 (mm Hg) 3.1 E-23 (Pa) (est.)	PubChem, (2021) US EPA (2021)
Henry's Law constant ($Pa.m^3.mol^{-1}$)	1.76E-24 (est); 6.765 E-20 (est.)	US EPA (2021)
Adsorption		
Organic carbon – water partition coefficient (Log K_{OC})	1.37 (est.); 2.17 (est.)	US EPA (2021)
Sediment – water partition coefficient ($K_{susp\text{-}water}$)	Log Kow = 3.16	US EPA (2021)
	251	Thompson (2005)
Kd - activated sludge / water distribution coefficient	262 – 400 L/kg	
Bioaccumulation		
Octanol-water partition coefficient (Log Kow)	0.7 (geomean, pH 6.2, CLA^+) 1.8 (geomean, pH 11, CLA^0)	Sibley & Pedersen (2008)
	0.69 (pH 4, CLA^+), 0.86 (pH 6, CLA^+) 1.24 (pH 6.5, CLA^+), 1.68 (pH 8, CLA^0);	Nakagawa et al. (1992)

5.2 Abiotic and Biotic degradations

		Reference
Photolysis	DT_{50}= 40 days (photolysis method)	Vione et al. (2009)
Biodegradation	Not readily biodegradable Not rapidly biodegradable, 24% biodegradable after 28 days in the closed bottle test according to OECD 301D	PubChem, (2021) Alexy et al. (2004)
Metabolites	**14-hydroxy(R)–clarithromycin [110671-78-8]; N-desmethyl-clarithromycin [101666-68-6]**; N,N-didesmethyl-clarithromycin; 14-hydroxy(S)-clarithromycin; 14-hydroxy(R)-dimethyl-clarithromycin; descladinosyl-clarithromycin; 14-hydroxy(R)-descladinosyl-clarithromycin; clarithromycin-N-oxide	Ecotox Centre (2016) Baumann et al. (2015)

6 Effects and Quality Standards

The studies were evaluated and assessed according to Moermond et al. (2016). This assessment includes a set of 20 reliability and 13 relevance criteria, whereby the classes assigned (R1-4) match those of Klimisch et al. (1997):

R1 Reliable without restrictions: All critical reliability criteria for this study are fulfilled. The study is well designed and performed, and it does not contain flaws that affect the reliability of the study.

R2 Reliable with restrictions: The study is generally well designed and performed, but some minor flaws in the documentation or setup may be present.

R3 Not reliable: Not all critical reliability criteria for this study are fulfilled. The study has clear flaws in study design and/or how it was performed.

R4 Not assignable: Information needed to assess the study is missing. This concerns studies that do not give sufficient experimental details and that are only listed in abstracts or secondary literature (books, reviews, etc.) or studies of which the documentation is not sufficient for assessment of reliability for one or more vital parameters.

6.1 Acute aquatic ecotoxicity

6.1.1 Clarithromycin

			Reference
Algae & aquatic plants (µg l^{-1})	**Freshwater**	*Anabaena flos-aquae* / 72 h **EC_{50}: 12** (growth rate) Reliability evaluation: 1	Baumann et al. 2015 Maletzki, et al. 2012
		Anabaena flos-aquae / 72 h EC_{50}: 5.6 (biomass) Reliability evaluation: 1	Baumann et al. 2015 Maletzki, et al. 2012
		Raphidocelis subcapitata / 96 h EC_{50}: 12 (growth rate) Reliability evaluation: 4	Harada et al. 2008
		Raphidocelis subcapitata / 72 h EC_{50}: 2 (growth rate) Reliability evaluation: 4	Isidori et al. 2005
		Raphidocelis subcapitata / 72 h EC_{50}: 6.9 (growth rate) Reliability evaluation: 2	Watanabe et al. 2016
		Raphidocelis subcapitata / 96 h EC_{50}: 11 (growth rate) Reliability evaluation: 4	Yamashita et al. 2006
		Raphidocelis subcapitata / 72 h EC_{50}: 46 (biomass) Reliability evaluation: 4	Yang et al. 2008
		Raphidocelis subcapitata / 72 h EC_{50}: 230 (growth rate) Reliability evaluation: 4	Minguez et al. 2014
		Desmodesmus subspicatus / 72 h EC_{50}: 37 (growth rate) Reliability evaluation: 1	Baumann et al. 2015
		Desmodesmus subspicatus / 72 h EC_{50}: 32 (biomass) Reliability evaluation: 1	Baumann et al. 2015
		Raphidocelis subcapitata 72 h EC_{50}: 20 (growth rate) Reliability evaluation: 2	Guo et al. 2020
	Marine	*Phaeodactylum tricornutum*, 72 h EC_{50}: 2679 (growth rate) Reliability evaluation: 1	Polleichtner, C. 2020
		Skeletonema marinoi / 72 h EC_{50}: 0.152 (growth rate) Reliability evaluation: 4	Minguez et al. 2014

Invertebrates (µg l^{-1})	**Freshwater**	*Daphnia magna* / 48 h EC_{50}: > 2000 (immobilization) Reliability evaluation: 1	Baumann et al. 2015
		Daphnia magna / 24 h EC_{50}: 25720 (immobilization) Reliability evaluation: 4	Isidori et al. 2005
		Brachionus calyciflorus / 24 h LC_{50}: 35460 (mortality) Reliability evaluation: 4	Isidori et al. 2005
		Ceriodaphnia dubia / 48 h EC_{50}: 18660 (immobilization) Reliability evaluation: 4	Isidori et al. 2005
		Daphnia magna / 24 and 48 h EC_{50}: > 10000 (immobilization) Reliability evaluation: 4	Harada et al. 2008
		Daphnia magna / 48 h EC_{50}: > 100000 (immobilization) Reliability evaluation: 4	Minguez et al. 2014
		Daphnia magna / 48 h NOEC: ≥ 10000 (immobilization) Reliability evaluation: 4	Yamashita et al. 2006
		Thamnocephalus platyurus / 24 h LC_{50}: 33640 (mortality) Reliability evaluation: 4	Isidori et al. 2005
		Thamnocephalus platyurus / 24 h LC_{50}: 94230 (mortality) Reliability evaluation: 2	Kim et al. 2009
	Marine	*Phaeodactylum tricornutum* / 72d EC_{50}: 2679 (growth rate) Reliability evaluation: 1	Polleichtner, C .2020
		Artemia salina / 48 h EC_{50}: > 100000 (immobilization) Reliability evaluation: 4	Minguez et al. 2014
	Sediment		
Fish (µg l^{-1})	**Freshwater**	*Danio rerio* / 48 h LC_{50}: > 2000 (embryo lethality) Reliability evaluation: 1	Baumann et al. 2015
		Danio rerio / 96 h LC_{50}: > 1000000 (mortality) Reliability evaluation: 4	Isidori et al. 2005
		Oryzias latipes / 96 h LC_{50}: > 100000 (larval mortality) Reliability evaluation: 2	Kim et al. 2009
	Marine		
	Sediment		
Other taxonomic groups (µg l^{-1})		*Xenopus laevis* / 96 h EC_{50}: > 10000 (developmental toxicity) Reliability evaluation: 4	Harada et al. 2008
		Aliivibrio fischeri / 5 min EC_{50}: 12650 (luminescence) Reliability evaluation: 1	de García et al. 2014

	Aliivibrio fischeri / 5 min EC_{50}: 12760 (luminescence) Reliability evaluation: 1	de García et al. 2016
	Aliivibrio fischeri / 15 min EC_{50}: 12080 (luminescence) Reliability evaluation: 1	de García et al. 2014
	Aliivibrio fischeri / 15 min EC_{50}: 12030 (luminescence) Reliability evaluation: 1	de García et al. 2016
	Aliivibrio fischeri / 15 min EC_{50}: > 10000 (luminescence) Reliability evaluation: 4	Harada et al. 2008
	Aliivibrio fischeri / 15 min NOEC: ≥ 8200 (luminescence) Reliability evaluation: 4	Yamashita et al. 2006
	Aliivibrio fischeri / 30 min NOEC: 100000 (luminescence) Reliability evaluation: 4	Isidori et al. 2005
	Microbial organisms EC_{50}: 36400 (oxygen consumption) Reliability evaluation: 2 *(Activated sludge tests)*	de García et al. 2014

Note: Studies reported in grey were not considered for the EQS derivation

6.1.2 14-Hydroxy-Clarithromycin

			Reference
Algae & aquatic plants ($\mu g\ l^{-1}$)	**Freshwater**	*Desmodesmus subspicatus* / 72 EC_{50}:46 (growth rate) Reliability evaluation: 1[a]	Baumann et al. 2015
		Anabaena flos-aquae / 72 h **EC_{50}: 27** (growth rate) Reliability evaluation: 1[a]	Baumann et al. 2015
		Anabaena flos-aquae / 72 h EC_{50}:10 (biomass) Reliability evaluation: 1[a]	Baumann et al. 2015
		Desmodesmus subspicatus / 72 h EC_{50}: 33 (biomass) Reliability evaluation: 1[a]	Baumann et al. 2015
Invertebrates ($\mu g\ l^{-1}$)	**Freshwater**	*Daphnia magna* / 2 d $EC_{50} \geq$ 2000 (immobilization) Reliability evaluation: 1[a]	Baumann et al. 2015
Fish ($\mu g\ l^{-1}$)	**Freshwater**	*Danio rerio* / 48 h $LC_{50} \geq 2000$ (immobilisation) Reliability evaluation: 1[a]	Baumann et al. 2015

Note: Studies reported in grey were not considered for the EQS derivation.

6.2 Chronic aquatic ecotoxicity

6.2.1 Clarithromycin

			Reference
Algae & aquatic plants (µg l-1)	**Freshwater**	*Anabaena flos-aquae* / 72 h EC_{10}: **2.6** (growth rate) Reliability evaluation: 1	Baumann et al. 2015
		Anabaena flos-aquae / 72 h EC_{10}: 1.1 (biomass) Reliability evaluation: 1	Baumann et al. 2015
		Raphidocelis subcapitata / 96 h NOEC: 3.1 (growth rate) Reliability evaluation: 4	Yamashita et al. 2006
		Raphidocelis subcapitata / 72 h NOEC: 2.45 (growth rate) Reliability evaluation: 2	Watanabe et al. 2016
		Raphidocelis subcapitata / 96 h NOEC: 5.2 (growth rate) Reliability evaluation: 4	Harada et al. 2008
		Desmodesmus subspicatus / 72 h EC_{10}: 28 (growth rate) Reliability evaluation: 1	Baumann et al. 2015
		Desmodesmus subspicatus / 72 h NOEC: 25 (growth rate) Reliability evaluation: 1	Baumann et al. 2015
		Desmodesmus subspicatus / 72 h EC_{10}: 27 (biomass) Reliability evaluation: 1	Baumann et al. 2015
		Raphidocelis subcapitata 72 h EC10: 5 (growth rate) Reliability evaluation: 2	Guo et al. 2020
		Chlorella vulgaris 72 h NOEC: 40 (growth rate) Reliability evaluation: 2	Guo et al. 2020
		Lemna minor / 7 d NOEC: 800 (dry weight) Reliability evaluation: 1	Baumann et al. 2015
		Lemna minor / 7 d NOEC: > 1900 (leaf area) Reliability evaluation: 1	Baumann et al. 2015
	Marine	*Phaeodactylum tricornutum* / 72d NOEC: 100 (growth rate) Reliability evaluation: 1	Polleichtner, C. 2020

Note: Studies reported in grey were not considered for the EQS derivation

Invertebrates (µg l-1)	**Freshwater**	*Daphnia magna* / 21 d NOEC: 3.1 (reproduction) Reliability evaluation: 4[a]	Yamashita et al. 2006
		Daphnia magna / 21 d NOEC: ≥ 2100 (reproduction) Reliability evaluation: 1[a]	Baumann et al. 2015
		Brachonius calyciflorus / 48 h EC_{50}: 12210 (gender ratio, growth) Reliability evaluation: 4[a]	Isidori et al. 2005
		Danio rerio / 9 d NOEC ≥ 68000 (hatching and survival rate) Reliability evaluation: 2	Watanabe et al. 2016
		Ceriodaphnia dubia / 8 d NOEC: 4620 (reproduction) Reliability evaluation: 2[a]	Watanabe et al. 2016
		Ceriodaphnia dubia / 7 d EC_{50}: 8160 (reproduction) Reliability evaluation: 4[a]	Isidori et al. 2005

Note: Studies reported in grey were not considered for the EQS derivation

6.2.2 14-Hydroxy-Clarithromycin

			Reference
Algae & aquatic plants (µg l^{-1})	**Freshwater**	*Desmodesmus subspicatus* / 72 h EC_{10}: 24 (growth rate) Reliability evaluation: 1	Baumann et al. 2015
		Anabaena flos-aquae / 72 h **EC_{10}: 8.7 (growth rate)** **NOEC: 2.7 (growth rate)** Reliability evaluation: 1	Baumann et al. 2015
		Anabaena flos-aquae / 72 h EC_{10} = 3.1 (biomass) NOEC = 1 (biomass) Reliability evaluation: 1	Baumann et al. 2015
		Desmodesmus subspicatus / 72 h EC_{10}: 23 (biomass) Reliability evaluation: 1	Baumann et al. 2015
		Desmodesmus subspicatus / 72 h NOEC: 20 (growth rate) Reliability evaluation: 1	Baumann et al. 2015
Invertebrates (µg l^{-1})	**Freshwater**	*Daphnia magna* / 21 d (OECD 211) NOEC ≥ 850 (reproduction) Reliability evaluation: 1	Baumann et al. 2015

Note: Studies reported in grey were not considered for the EQS derivation

6.3 Tentative QSwater

According to TGD No. 27 (EC 2018), two QSs are required for the water compartment to cover both long-term and short-term exposures to a chemical. Whilst derivation of the QS typically employs chronic toxicity data, the MAC-QS always relies on acute data. When data are sparse or the ratio between acute effects and chronic no-effects is narrow, the estimated MAC-QS can sometimes be more stringent than the AA-QS. Since the effects of chronic exposure normally occur at lower concentrations than those of acute exposure, MAC-QS values below the QS make little toxicological sense. Therefore, where the derivation of the MAC-QS leads to a lower value than the AA-QS, the MAC-QS is set equal to the QS for direct ecotoxicity.
This is the case for clarithromycin. Both, the MAC-QS and the AA-Qs were derived from the same study, but with different assessment factors. The more stringent MAC-QS compared to the AA-QS is just mathematically, as the difference between the Assessment factors is larger than the difference between the EC_{50}, used for the MAC-QS and the EC_{10} used for the AA-QS, respectively.
In addition, an additional factor of 2 is proposed to account for the combined effects of the lead substance and its metabolite 14-hydroxy-clarithromycin, leading to a QS of 0.13 µg/l for freshwater and 0.013 µg/l for marine waters.

Table 6.1: Tentative QS for Clarithromycin

	Relevant study for derivation of QS	**Assessment factor**	**Tentative QS**
$MAC_{freshwater, eco}$	*Anabaena flos-aquae* / 72 h EC_{50}: 12 µg l^{-1} (growth rate)	2 x 100	0.13 µg l^{-}
$MAC_{marine\ water, eco}$		2 x 1000	0.013 µg l
$AA\text{-}QS_{freshwater, eco}$	*Anabaena flos-aquae* / 72 h EC_{10}: 2.6 µg/L (growth rate)	2 x 10	0.13 µg l^{-1}
$AA\text{-}QS_{marine\ water, eco}$		2 x 100	0.013 µg l^{-1}

Note: an additional factor of 2 is proposed to account for the combined effects of the lead substance and its metabolite 14-hydroxy-clarithromycin

6.4 Secondary poisoning

6.4.1 Secondary poisoning of top predators

		Master reference
Mammalian oral toxicity	Dog (Species not reported) / Oral / 6 months / "adverse effects" NOAEL: 4 $mg.kg^{-1}_{bw}.d^{-1}$	Accord Healthcare Limited (2018)
	Rat (Species not reported) / Oral / 6 months / "adverse effects" NOAEL: 8 $mg.kg^{-1}_{bw}.d^{-1}$	Accord Healthcare Limited (2018)
Avian oral toxicity	Not available	

Note: An assessment not possible as original publications & dossiers are not available. However, the studies were used for authorisation of CLA and therefore were assessed in a certain form.

Tentative QS_{biota}

A biota standard to protect wildlife from secondary poisoning ($QS_{biota, sec\ pois, fw}$) needs to be derived in case there is evidence of bioaccumulation potential of the substance (EC 2018). Step 1 of the evaluation lists a measured BMF>1 or BCF (BAF) ≥100 or a Log Kow ≥ 3 if no valid measured BMF or BCF (BAF) is available.
Experimental BMF were not identified in the literature. Based on whole fish concentrations of clarithromycin in marine fish off the Chinese coast and the position of these fish in the food chain, a TMF of 1 with a large 95 % CI (0.3 - 2.6) was derived (Liu 2018). Available BCF and BAF are listed in Tables 6.1 and 6.2. BCFs derived for the different organs of a sea cucumber (*Apostichopus japonicus*) ranged from 22-435 L/kg, with BCFs being lower at higher exposure concentrations. A geometric mean cannot be derived, as the weight fraction of the individual organs is unknown, but it can be expected that the mean would be > 100 L/kg. A mean field BAF of 27.00 (6.82–61.09) was derived for caged freshwater mussels (*Lasmigona costata*) based on average clarithromycin concentrations of two years (de Solla et al. (2016)).
In addition, Zhang *et al.* (2019) quantified clarithromycin in coastal and off-shore oysters and derived logBAF values with respect to measured marine concentrations. Individual logBAF and the exact reference water concentrations are not reported, however, based on visual inspection of Figure 5, values range from 1.5 – 3 in coastal corals to 3 – 4 in off-shore corals. (Liu *et al.* 2018) quantified clarithromycin in seven wild fish species collected from Laizhou Bay, North China. Individual logBAF are reported for organs, but not for whole fish, and have been derived based on mean water concentrations measured in 2012 (0.19 ng/L), thus four years before fish were sampled. However, Zhang et al. (2012, 2013) reported nearly constant concentrations in the waters of Laizhou Bay. Reported logBAF range from 4.0 ± 0.5 (muscle) to 5.1 ± 0.5 (liver). Individual organ weights are not available, but individual fish weight was reported. Liver and whole-body weight often show strong correlation in studied fish (e.g. Mahboob 2002) but may vary e.g. with season (Schwalme 1999). For the purpose of estimation of whole body BAF, a fraction of 0.01 of liver weight is assumed resulting in an estimated whole body BAF of 1260. Nevertheless, because of the difference in sampling time between the biota and water samples (four years), the logBAFs from Liu et al. (2018) cannot be considered reliable.

Finally, Zhang et al. (2020) reported a logBAFs for clarithromycin equal to 1.96 L/kg_{ww} for coral reef fish from waters off the coast of southern China. The logBAF was based on fish muscle concentrations.

Table 6.2: BCF values reported for clarithromycin.

Species	BCF [L/kg]	Tissue	Exposure	Further information	Reference
Sea Cucumber (*Apostichopus japonicus*)	310 435.9 22 284.4 186.6 115.5 30.4 173.9	Body wall Mouth Digestive tract Respiratory tract Body wall Mouth Digestive tract Respiratory tract	1 µg/L 10 µg/L Laboratory, semistatic, daily replacement of 1/3 volume	Juveniles, 4 months old (body length: 2−3 cm, wet weight: ~1.0 g) Composite-sand filtered natural sea water 14.3 ± 1.2 °C photoperiod of 12:12 (light/dark) commercial	Zhu et al. (2020)
Fish	56.49	Whole body	Estimated value		PubChem (2021)

Table 6.3: BAF values reported for clarithromycin.

Species	BAF [L/kg]	Tissue	Exposure	Further information	Reference
Fluted shell (*Lasmigona costata),* freshwater mussel	27.00 (6.82–61.09)	Whole body	Caged, field, 4 weeks, <5.2-243 ng/L (2009-2011), n=5	Grand River, Ontario, Canada, downstream of a WWTP	de Solla et al. (2016)
Marine fish*	31623 10000 39811 125893	Gills Muscle Kidney Liver	Wild catches, average water concentration: 0.19 ng/L	Laizhou Bay, North China*	(Liu *et al.* 2018) Not reliable
Coral reef fish**	91.2	Muscle	Marine concentrations: 0.29 ng/L	Zhongsha and Xisha Islands, South China	(Zhang *et al.* 2020)
fish	96.83	--	estimated	Equation recommended in EU TGD for EQS	EC (2018)

*Seven marine fish species, including javeline goby (*Acanthogobius hasta*, *n* = 3), bartail flathead (*Platycephalus indicus*, *n* = 3), tongue sole (*Cymoglossus robustus*, *n* = 3), dotted gizzard shad (*Konosirus punctatus*, *n* = 3), so-iuy mullet (*Liza haematocheilus*, *n* = 3), Chinese sea perch (*Lateolabrax maculatus*, *n* = 3), and silvery pomfret (*Pampus argenteus*, *n* = 3), were collected from the Laizhou Bay with a bottom trawl in May 2016.

**Eight species of coral reef fishes were sampled from the study area from May to July 2015: *Myripristis murdjan* (n = 6), *Melichthys vidua* (n = 5), *Lethrinus olivaceus* (n = 6), *Gnathodentex aureolineatus* (n = 7), *Parupeneus trifasciatus* (n = 9), *Lutjanus kasmira* (n = 9), *Cephalopholis urodeta* (n = 8), *Caranx ignobilis* (n = 1).

Reported logKow for clarithromycin vary substantially (see Chapter 5.1). According to the EU TGD for EQS derivation, the selected (log) Kow value is the average value of all reliable values determined by the shake flask, slow stirring or generator column method (EC 2018). A logKow of 3.16 is often used for clarithromycin (derived by McFarland *et al.* (1997)), however, this value was derived potentiometrically by the shift in pKa values in rapidly stirred 0.167 M NaCl solutions before and after the addition of n-octanol. At the same time, logKow derived by the shake flask method have been published by Sibley & Pedersen (2008) and Nakagawa *et al.* (1992). For the purpose of EQS derivation, a geometric mean of 0.91 was calculated based on values obtained for the environmentally relevant pH-range of approximately 5 to 9 (see section 8.1.1). This logKow would not trigger derivation of $QS_{biota,\ sec\ pois,\ fw}$. Further, there is no additional evidence of bioaccumulation or high intrinsic toxicity to mammals and birds (EC (2018). However, based on the organ-based BCF derived for a sea cucumber, derivation of $QS_{biota,\ sec\ pois,\ fw}$ would be triggered. Thus, $QS_{biota,\ sec\ pois,\ fw}$ derivation is deemed necessary and is presented in the following.

The EU TGD for EQS states that the "food item that will determine the final value for the quality standard in biota is not only dependent on the energy contents of the food items, but also on the bioaccumulation characteristics of the substance through the food chain." Thus, a "critical food item" needs to be identified. In case the TMF (dry weight) < 1.0, the risk limit should be calculated for bivalves, otherwise in fish. Whether BAF are generally lower in fish than in invertebrates cannot be assessed based on available data. Thus, based on the only TMF (=1) available by Liu (2017), calculations are based on fish in the following. The BAF from Zhang et al. (2020) of 91.2 L/kg_{ww} (derived from the logBAF of 1.96 L/kg_{ww}) was used for further calculations.

In the following, mammalian oral toxicity data relevant for the assessment of secondary poisoning is summarized. Effect data for wildlife species was not available, thus, the assessment is limited to

laboratory test species. Original study reports on non-aquatic vertebrate toxicity were not identified/available, however, summarized study data was retrieved from a "Rapporteur's Public Paediatric Assessment Report for paediatric studies" (EMA 2010), from the "electronic medicines compendium (emc)" (Accord Healthcare Limited 2020), with other details from the owner's webpage (Accord Healthcare Limited 2020), and from a specialized U.S. FDA drug database (Drugbank 2021).

The lowest NOEL was reported in rats (8 mg/kg/day) and in dogs (**4 mg/kg/day**) after 6 months exposure. Chronic studies exceeding 6 months exposure were not identified.

Neither teratogenicity nor effects on fertility or reproduction were observed at the highest tested dose levels (Accord Healthcare Limited 2020). Based fertility and reproduction studies in female rats by the same company, it was reported that a daily dosage of 150 mg/kg/ day (highest dose tested) caused no adverse effects on the oestrus cycle, fertility parturition and number and viability of offspring (Accord Healthcare Limited 2020). A lower NOEL of 50 mg/kg/day for developmental effects in rats was reported by studies available the U.S. FDA (Drugbank 2021). No adverse developmental effects were observed in mice at ≤ 250 mg/kg/day (Drugbank 2021.

For the derivation of a $QS_{biota,\ sec\ pois,\ fw}$, the NOAEL of 4 mg/kg/day in dogs is selected, presumably based on wet weight.

According to the EU TGD for EQS (EC (2018)): "If the endpoint of a toxicity test is expressed as a daily dose (e.g. mg/kg_{bw}/day), this could be expressed as a diet concentration normalised to the energy (caloric) content of the food" using the method A. To take into account daily energy expenditure, logDEE (equation 1) was first calculated as follows:

$$\log DEE[kJ/d] = 1.032 + 0.6760 * \log bw\ [g] \qquad \text{Equation 1}$$

The body weight (bw) selected was the average body weight of an adult beagle of 10 kg; according to the experts opinion. Therefore, the logDEE is equal to 3.673 kJ/d. Diet concentration was then normalised to the energy according to Equation 2:

$$C_{energy\ normalised}\ [mg/kJ] = dose * (bw / DEE) \qquad \text{Equation 2}$$

The obtained $C_{energy\ normalised}$ value was of 8.49×10^{-3} mg/kJ. Subsequently, the concentration of clarithromycin in a specific food item was calculated according to Equation 3:

$$C_{food\ item}\ [mg/kg_{\ ww}] = C_{energy\ normalised}\ [mg/kJ] * \text{energy content}_{food\ item,\ dw} * (1\text{-moisture fraction}_{food\ item})$$

$$= C_{energy\ normalised}\ [mg/kJ] * \text{energy content}_{food\ item,\ fw} \qquad \text{Equation 3}$$

Since the TMF for clarithromycin is equal to 1 (Liu et al., 2017), according to the EU TGD for EQS (Figure 8, EC, 2018), the risk limit is calculated for fish. The energy contents on a dry weight basis for fish of 21 kJ/kg_{dw} and a moisture fraction of 73.7% were thus selected for further calculations (E.C., 2018). The obtained $C_{food\ item}$ was 46.885 $mg/kg_{\ ww}$ for fish.

The suggested assessment factor would be 10 in accordance with EU TGD for EQS (Table 10, EC (2018)). The application of an AF of 10 to the $C_{food\ item}$ was 46.885 mg/kg $_{ww}$ for fish results in a **$QS_{biota,\ sec\ pois,\ fw}$ = 4.7 mg/kg_{ww}**. Using the BAF from Zhang et al. (2020) of 91.2 L/kg_{ww} (derived from the logBAF of 1.96 L/kg_{ww}), the **$QS_{fw,\ biota,\ secpois}$** is equal to **51.4 µg/L**.

Considering the low biomagnification characteristics of clarithromycin (TMF=1, Liu et al., 2017), according to the TGD for EQS (EC, 2018), a standard for marine waters was not needed to be derived.

	Relevant study for derivation of QS	**Assessment Factor**	**Tentative QS**
Biota	NOAEL: 4 $mg.kg^{-1}_{bw}.d^{-1}$	AF = 10	4.7 x 10^3 $\mu g.kg^{-1}_{biota\ ww}$ corresponding to 51.4 μgL^{-1} (freshwater)

7 Human health

Human health via consumption of fishery products
The derivation of a biota standard for human health is triggered on the basis of the hazardous properties of a substance. Clarithromycin is classified as H302, "*Harmful if swallowed*", which warrants derivation of a $QS_{biota, hh}$. The EU TGD for EQS recommends a default daily fish consumption of 0.115 kg d^{-1} in combination with a body weight of 70 kg resulting in a daily consumption of 1.6 g fish kg^{-1} body weight. The $QS_{biota, hh, food}$ (expressed as $\mu g \cdot kg_{-1\ biota}$) is calculated based on the TL_{hh} (expressed as $\mu g \cdot kg^{-1}_{bw} \cdot d^{-1}$):

$QS_{biota, hh} = 0.2 * TL_{hh} / 0.00163$

To represent TLhh, Oral Reference Doses (RfD), Acceptable Daily Intake (ADI), Tolerable Daily Intake (TDI), or No Observable Adverse Effect Level (NOAEL) can be used. For the purpose of QS derivation for clarithromycin, the published ADI (including safety factors) of 1.4 $\mu g \cdot kg^{-1}bw \cdot d^{-1}$ (Khan & Nicell 2015) was used. It was derived based on the occupational exposure limit (OEL) of 1 mg/m^3 (according to the MSDS published by Abbott) with a default safety factor of 100.
The resulting **$QS_{biota, hh}$ is 171.8 µg/kg_{biota}.**
Based on a BAF of 91.2 L/kg in fish (see section 6.4.1), this corresponds to a water concentration of 1.88 µg/L.

Human health via consumption of drinking water

According to the EU TGD for EQS, the suggested AA-$QS_{freshwater, eco}$ is compared with the EU drinking water standard (98/83/EC) or the WHO drinking water standard. In case both are available, the WHO standard is preferred (WHO 2017). In case drinking water standards are not available, a provisional standard needs to be derived based on the following formula:
$QS_{dw,hh} = 0.2 * TL_{hh} * 70 / 2$

A fraction of 0.2 of the reference doses is applied for the intake of the respective substance from drinking water. Further, a daily intake of 2 L of water and an average body weight of 70 kg are assumed. The published ADI (including safety factors) of 1.4 $\mu g \cdot kg^{-1}_{bw} \cdot d^{-1}$ (Khan & Nicell 2015) was used. As described above, the ADI was derived based on the OEL of 1 mg/m^3 (Abbott MSDS) with a default safety factor of 100.
This results in **a $QS_{dw, hh}$ of 9.8 µg/L** for clarithromycin.

8 Additional Considerations

8.1 pH-Effects

Boström and Berglund (2015) found significant differences in pH among countries with a median range from 7.0 (Sweden) to 8.3 (Cyprus). Within-country pH variations ranged from 0.4 pH units (Switzerland) to 5.9 pH units (Spain). This is in line with Bundschuh et al. (2016), who reported a mean pH of 7.8 in European rivers (without the Scandinavian countries) with a maximum pH of 12.4 and a minimum pH of 4.3.
In this context, it is important to note that around 80% of all pharmaceuticals are ionisable (Manallack 2008). This means that aquatic environmental pH can affect their chemical specification, i.e. the fraction of ionic or uncharged forms (Boström and Berglund 2015). Small changes in the test pH can significantly alter the balance between the dissociated and non-dissociated form of the substance. These altered dissociation equilibria are expected to significantly affect the partition coefficient of diclofenac (i.e. the pH dependent log Dow), and thus also its bioavailability and measurable toxicity, according to OECD guideline 23 on the test of difficult substances (OECD 2019). The reason for this is that for the most part only the neutral, uncharged form can pass the biological membranes. It is, therefore, essential that the relevant dissociation constant (i.e. the pKa) and the respective log D values are considered in the environmentally relevant pH-range of approximately 5 to 9 (see figure 8.1) prior to the commencement of testing (Chapter 5.1).
In fact, differences of more than one order of magnitude in the acute toxicity of ionic substances have been observed due to alterations of the test pH in the environmentally relevant range (Anskjær 2013), which is in line with most OECD guidelines. As seen in figure 8.1 below, the log D is changing quite considerably between pH 7 and pH 8.5, which is according to Bundschuh et al. (2016), and Boström and Berglund (2015) the pH range of more than 90 % of the surface water in Europe. And these variations can occur quite naturally, due to diurnal variation, but also due to small scale variations of abiotic and biotic factors, like lightening conditions and the potential of photosynthesis; differences between interstitial and open water; particular organic matter, Redox-Potential.

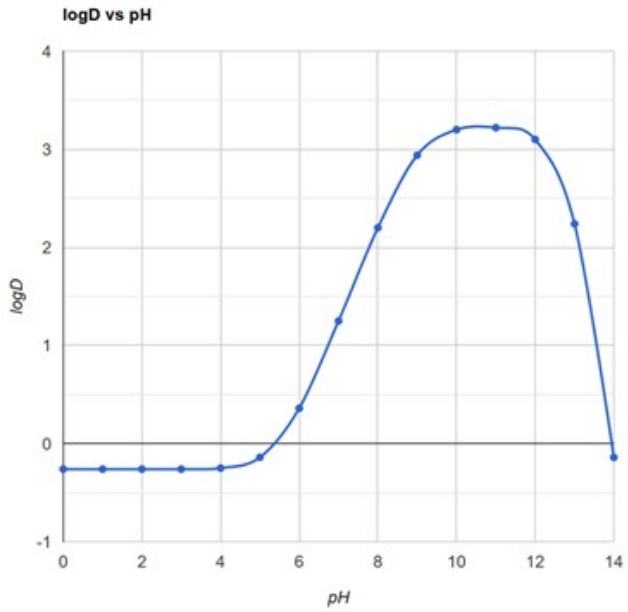


Figure 8.1: Prediction of the pH dependence of the octanol-water coefficient (log D) of Clarithromycin (Chemaxon 2020).

8.2 Contribution of Clarithromycin to antimicrobial resistance

Clarithromycin is frequently used both as human and veterinary medicine and was included in the first surface water Watch List (WL) of the European Water Framework Directive (WFD) in 2015 (EU, 2015/495), together with erythromycin and azithromycin as they belong to the same class (macrolide antibiotics), sharing the same mode of action and analytical method (JRC Report, 2015; Loos, 2015). Clarithromycin was also included in the list of priority antibiotics by the World Health Organization (WHO) in 2016 (WHO, 2017) and it is among the most studied antibiotics in the environment.

The derived PNEC value for clarithromycin (0.13 µg/L, see Table 6.1) is based on an EC_{10} of 2.6 µg/L (*Anabaena flos-aquae,* 72h, growth rate) with an assessment factor (AF) of 10. The additional AF of 2 was used since the toxic metabolite 14-hydroxy-claritromycin occurs up to about 50% in surface water and is equivalent toxic.

PNEC derivation for antibiotics is currently based on ecotoxicology data and does not consider the contribution of these substances to the spread of antibiotic resistant bacteria (ARB) and antibiotic resistance genes (ARG) in water environments; indeed, no guidelines are available for deriving the minimum levels of antibiotics that may result in the development of antibiotic resistance.

In a recent publication, Bengtsson and Larsson derived PNEC values for antibiotics by collecting Minimum Inhibitory Concentrations (MIC) from the public European Committee on Antimicrobial Susceptibility Testing database (EUCAST) (Bengtsson-Palme and Larsson, 2016). The lowest MIC value was identified and an assessment factor of 10 was then applied considering that the selective concentration must be lower than the inhibitory concentration (Bengtsson-Palme and Larsson, 2016). To date, this is the only derivation of PNEC for antibiotics that addresses the resistance. The PNEC-MIC values are intended to be protective for both humans and the environment and have also been adopted by the AMR Industry Alliance with the recommendation to use the lower of the two values: PNEC and PNEC-MIC (Tell et al., 2019). In the case of clarithromycin, the PNEC-MIC (0.25 µg/L) is above the available PNEC value for ecotoxicological effects (see Table 8.1).

However, it should be considered that the PNEC-MIC proposed by Bengtsson and Larsson does not account for multidrug resistant bacteria and does not consider the exposure of bacteria to mixtures of antibiotics. In addition, other pollutants such as biocides and metals may also contribute to the selection of ARG.

Table 8.1: PNEC and PNEC-MIC (Minimum Inhibitory Concentrations) values for clarithromycin. PNEC and PNEC-MIC were derived for clarithromycin and the lower value was selected for the risk assessment.

Clarithromycin	
PNEC (µg/L)	**PNEC-MIC (µg/L)**
0.13	0.25*

*(Bengtsson-Palme and Larsson, 2016)

The need to carry out surveillance of environmental sources of antibiotics (e.g. clarithromycin) is documented in several scientific papers. Booth et al. compared the average antibiotic concentrations in different environmental matrices (e.g. hospital wastewater treatment plan – WWTP, municipal WWTP) to the PNEC values of each antibiotic in order to derive which of them exceeded their PNEC and was most likely to induce the spread of AMR in the environment (Booth et al., 2020). Data on antibiotic concentrations were retrieved from the German database on pharmaceuticals across 47 countries and clarithromycin, together with ciprofloxacin, showed the greatest proportion of residues exceeding the PNEC, particularly in hospital WWTP, while no excess of antibiotics was detected in drinking water. Hospital effluents are indeed among the main sources of macrolides as reported in a previous study by Verlicchi et al. (Verlicchi et al., 2014). However, high levels of clarithromycin (1.6-2.4 µg/L) were also observed in Mediterranean rivers (Feitosa-Felizzola and Chiron, 2009; Valcárcel et al., 2011; Moreno-González et al., 2014).
These data underline the importance to continue monitoring how anthropogenic sources can impact the dissemination of antibiotic resistance in the environment. Further research is however required to better understand how information on resistance can be used in the process of the environmental risk assessment for antibiotics. Finally, it should be noted that this evaluation should also consider the contribution of ARG and mobile genetic elements (MGE) to the spread of resistance, considering that gene transfer is the way by which the microbial community become resistant. In this context, measurements of ARG by quantitative polymerase chain reaction (qPCR) and sequencing methods were proposed in the 3rd WL Report by the JRC as an endpoint for the evaluation of risk assessment (Gomez Cortes et al., 2020).

9 References

Accord Healthcare Limited (2018) Summary of Product Characteristics, Clarithromycin 500 mg Film-coated Tablets https://www.accord-healthcare.com/ie/sites/default/files/spc/spc-clarithromycin-500mg-fc_tablets_mar2018_cl.pdf

Alexy, R, Kümpel T, Kümmerer, K (2004): Assessment of degradation of 18 antibiotics in the Closed Bottle Test. Chemosphere Volume 57, Issue 6:505–512. http://dx.doi.org/10.1016/j.chemosphere.2004.06.024

Anskjær GG, Rendal C, Kusk KO (2013) Effect of pH on the toxicity and bioconcentration of sulfadiazine on *Daphnia magna*. Chemosphere. 91(8):1183-8. doi: 10.1016/j.chemosphere.2013.01.029.

Baumann, M., Weiss, K., Maletzki, D., Schüssler, W., Schudoma, D., Kopf, W., & Kühnen, U. (2015). Aquatic toxicity of the macrolide antibiotic clarithromycin and its metabolites. Chemosphere, 120, 192-198.

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

Booth, A., Aga, D.S., and Wester, A.L. (2020). Retrospective analysis of the global antibiotic residues that exceed the predicted no effect concentration for antimicrobial resistance in various environmental matrices. Environ Int 141**,** 105796. 10.1016/j.envint.2020.105796

Boström, M. L. and O. Berglund (2015). Influence of pH-dependent aquatic toxicity of ionizable pharmaceuticals on risk assessments over environmental pH ranges. Water Res 72: 154-161.

Bundschuh, M.; Weyers, A.; Ebeling, M.; Elsaesser, D. and Schulz, R. (2016). Narrow pH Range of Surface Water Bodies Receiving Pesticide Input in Europe. Bulletin of Environmental Contamination and Toxicology 96 (1), 3-8. DOI: 10.1007/s00128-015-1665-7

Carvalho, R.N., Marinov, D., Loos, R., Napierska, D., Chirico, N., Lettieri, T., (2016). Monitoring-based exercise: second review of the priority substances list under the Water Framework Directive, Available at https://circabc.europa.eu/w/browse/52c8d8d3-906c-48b5-a75e-53013702b20a.

de García, S. A. O., Pinto, G. P., García-Encina, P. A., & Irusta-Mata, R. (2014). Ecotoxicity and environmental risk assessment of pharmaceuticals and personal care products in aquatic environments and wastewater treatment plants. Ecotoxicology, 23(8), 1517-1533.

de García, S. O., García-Encina, P. A., & Irusta-Mata, R. (2016). Dose–response behavior of the bacterium *Vibrio fischeri* exposed to pharmaceuticals and personal care products. Ecotoxicology, 25(1), 141-162.

de Solla, S.R., Gilroy, È.A.M., Klinck, J.S., King, L.E., McInnis, R., Struger, J., Backus, S.M. and Gillis, P.L. (2016) Bioaccumulation of pharmaceuticals and personal care products in the unionid mussel *Lasmigona costata* in a river receiving wastewater effluent. Chemosphere 146, 486-496.

Drugbank. http://www.drugbank.ca/drugs/DB01211 (Search date February 2021)

EC (2018) Technical Guidance for Deriving Environmental Quality Standards Environment, Guidance Document No. 27, Updated version 2018, Document endorsed by EU Water Directors at their meeting in Sofia on 11-12 June 2018.

Ecotox Centre. Ecotox Dossier (2016), EQS - Vorschlag des Oekotoxzentrums für: Clarithromycin und Haupttransformationsprodukte.

EFSA, 2010. Management of left-censored data in dietary exposure assessment of chemical substances. EFSA Journal 8:1–96.

EMA (2010) Rapporteur's Public Paediatric Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended; Clarithromycin, Clarithromycin_SK/W/0001/pdWS/001.

Feitosa-Felizzola, J., and Chiron, S. (2009). Occurrence and distribution of selected antibiotics in a small Mediterranean stream (Arc River, Southern France). Journal of Hydrology 364**,** 50-57. https://doi.org/10.1016/j.jhydrol.2008.10.006

Gardner, M. 2011. Improving the interpretation of 'less than' values in environmental monitoring. Water and Environment Journal, CIWEM, pp.1-6.

Gomez Cortes, L., Marinov, D., Sanseverino, I., Navarro Cuenca, A., Niegowska, M., Porcel Rodriguez, E., et al. (2020). Selection of substances for the 3rd Watch List under the Water Framework Directive. EUR 30297 EN. JRC 121346.

Harada A, Komori K, Nakada N, Kitamura K, Suzuki Y (2008): Biological effects of PPCPs on aquatic lives and evaluation of river waters affected by different wastewater treatment levels, Water Science and Technology, 58 (8):1541 – 1546.

Helsel D. 2006. Fabricating Data: How substituting values for nondetects can ruin results, and what can be done about it. Chemosphere, 65, 2434–2439

Helsel D. 2012. Statistics for Censored Environmental Data Using Minitab and R. John Wiley & Sons, Hoboken, NJ, USA

Isidori M, Lavorgna M, Nardelli A, Pascarella L, Parrella A (2005): Toxic and genotoxic evaluation of six antibiotics on nontarget organisms. Science of the Total Environment 346:87–98.

JRC Report (2015): Carvalho, R.N., Ceriani, L., Ippolito, A., and Lettieri, T. Development of the first Watch List under the Environmental Quality Standards Directive. Publications Office of the European Union. EUR 27142 EN. JRC 95018.

Khan, U. and Nicell, J. (2015) Human Health Relevance of Pharmaceutically Active Compounds in Drinking Water. The AAPS Journal 17(3), 558-585.

Kim J W, Ishibashi H, Yamauchi R, Ichikawa N, Takao Yuji, Hirano M, Koga M, Arizono K (2009): Acute toxicity of pharmaceuticals and personal care products on freshwater crustacean (*Thamnocephalus platyurus*) and fish (*Oryzias latipes*). The Journal of Toxicological Sciences 34(2):227-232.

Klimisch, H. J., Andreae, M. and Tilmann, U. (1997). "A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data." Regul Toxicol Pharmacol 25(1): 1-5.

Liu, S., Zhao, H., Lehmler, H. J., Cai, X., & Chen, J. (2017). Antibiotic pollution in marine food webs in Laizhou Bay, North China: trophodynamics and human exposure implication. Environmental science & technology, 51(4), 2392-2400.

Liu, S., Bekele, T.-G., Zhao, H., Cai, X. and Chen, J. (2018) Bioaccumulation and tissue distribution of antibiotics in wild marine fish from Laizhou Bay, North China. Science of The Total Environment 631-632, 1398-1405.

Loos, R. (2015). Analytical methods for possible WFD first Watch List substances. EUR 27046EN. JRC 94012.

Loos, R., Marinov, D., Sanseverino, I., Napierska, D., and Lettieri, T. (2018). Review of the 1st Watch List under the Water Framework Directive and recommendations for the 2nd Watch List. EUR 29173 EN, Publications Office of the European Union, Luxembourg, ISBN 978-92-79-81839-4, doi: 10.2760/614367, JRC111198

Mahboob, S. and Sheri, A.N. (2002). Relationships among Gonad Weight, Liver Weight and Body Weight of Major, Common and Some Chinese Carps under Composite Culture System with Special Reference to Pond Fertilization. Asian-Australasian Journal of Animal Sciences 2002;15(5): 740-744. https://doi.org/10.5713/ajas.2002.740

Maletzki, D. (2012). Prüfung der Toxizität auf das Cyanobakterium Anabaena flos-aquae. Chemikalienprüfung mit Clarithromycin.

Maletzki, D. (2013): Neue statistische Evaluierung der Daten zur Prüfung der Toxizität auf das Cyanobakterium Anabaena flos-aquae. Chemikalienprüfung mit Clarithromycin, Prüfungscode 2011-0074-AAAf aus dem Abschlussbericht vom 30.05.2012.

Manallack, D.T., (2008). The pK(a) distribution of drugs: application to drug discovery. Perspect. Med. Chem. 1, 25 -38.

Marinov D., and T. Lettieri, (2020). Results of the Watch List under the Water Framework Directive from the 4th reporting year and the combined dataset. Part A: Data quality, EUR xxxxxx EN, Publications Office of the European Union, Luxembourg (in press). Available at https://circabc.europa.eu/ui/group/9ab5926d-bed4-4322-9aa7-9964bbe8312d/library/deabbcb4-c001-4855-b503-04f27996ca7d/details

McArdell CS., Molnar, E.M., Suter, M.J.F. and Giger, W. 2003. Occurrence and fate of macrolide antibiotics in wastewater treatment plants and in the Glatt Valley Watershed, Switzerland, Environ Sci & Technol 37 (24):5479-5486. https://pubs.acs.org/doi/10.1021/es034368i

McFarland, J.W., Berger, C.M., Froshauer, S.A., Hayashi, S.F., Hecker, S.J., Jaynes, B.H., Jefson, M.R., Kamicker, B.J., Lipinski, C.A., Lundy, K.M., Reese, C.P. and Vu, C.B. (1997) Quantitative Structure−Activity Relationships among Macrolide Antibacterial Agents: In Vitro and in Vivo Potency against Pasteurella multocida. Journal of Medicinal Chemistry 40(9), 1340-1346.

Merrington Graham, Adam Peters, Iain Wilson, Mike Gardner, Stuart Rutherford, Stijn Baken, Christian Schlekat, Chris Cooper, Jelle Mertens, William Adams, Lara Van de Merckt, Jaap van Nes, Leondina Della Pietra, Jim Ryan, 2021. Using Exposure Data to Identify Priority Substances Under the European Water Framework Directive: The Quest to Reflect Uncertainties, ET&C, Wiley, https://doi.org/10.1002/etc.4987

Minguez, L., Pedelucq, J., Farcy, E., Ballandonne, C., Budzinski, H., & Halm-Lemeille, M. P. (2014). Toxicities of 48 pharmaceuticals and their freshwater and marine environmental assessment in northwestern France. Environmental Science and Pollution Research, 1-10.

Moermond C. T., Kase, R., Korkaric, M., & Ågerstrand, M. (2016). CRED: Criteria for reporting and evaluating ecotoxicity data. Environmental Toxicology and Chemistry. Environ Toxicol Chem. 2016 35(5):1297-309. doi: 10.1002/etc.3259

Moreno-González, R., Rodríguez-Mozaz, S., Gros, M., Pérez-Cánovas, E., Barceló, D., and León, V.M. (2014). Input of pharmaceuticals through coastal surface watercourses into a Mediterranean lagoon (Mar Menor, SE Spain): Sources and seasonal variations. *Science of The Total Environment* 490**,** 59-72. https://doi.org/10.1016/j.scitotenv.2014.04.097

Nakagawa, Y., Itai, S., Yoshida, T. and Nagai, T. (1992) Physicochemical properties and stability in the acidic solution of a new macrolide antibiotic, clarithromycin, in comparison with erythromycin. Chem Pharm Bull (Tokyo) 40(3), 725-728.

OECD (2019) OECD Environmental Health and Safety Publications, Series on Testing and Assessment No. 23: Guidance Document on Aquatic Toxicity Testing of Difficult Substances, Test Chemicals and Mixtures, Organisation for Economic Co-Operation and Development, Paris, pp. 81

PubChem: https://pubchem.ncbi.nlm.nih.gov/compound/84029?from=summary Search date February 2021

Schwalme, K. and Chouinard, G.A. (1999) Seasonal dynamics in feeding, organ weights, and reproductive maturation of Atlantic cod (*Gadus morhua*) in the southern Gulf of St Lawrence. ICES Journal of Marine Science, 56, (3), 303–319, https://doi.org/10.1006/jmsc.1999.0458

Shoari N, and Dubé J.S. 2018. Toward Improved Analysis of Concentration Data: Embracing Nondetects. Environmental Toxicology and Chemistry, Volume 37, Number 3, pp. 643–656

Sibley, S.D. and Pedersen, J.A. (2008) Interaction of the Macrolide Antimicrobial Clarithromycin with Dissolved Humic Acid. Environmental Science & Technology 42(2), 422-428.

Tell, J., Caldwell, D.J., Häner, A., Hellstern, J., Hoeger, B., Journel, R., et al. (2019). Science-based Targets for Antibiotics in Receiving Waters from Pharmaceutical Manufacturing Operations. Integrated environmental assessment and management 15**,** 312-319. 10.1002/ieam.4141

Thompson, A. (2005). The fate and removal of pharmaceuticals during sewage treatment. PhD- thesis, Cranfield University https://dspace.lib.cranfield.ac.uk/handle/1826/8539.

US EPA (2021). Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.11. United States Environmental Protection Agency, Washington, DC, USA. https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface#copyright

Valcárcel, Y., González Alonso, S., Rodríguez-Gil, J.L., Gil, A., and Catalá, M. (2011). Detection of pharmaceutically active compounds in the rivers and tap water of the Madrid Region (Spain) and potential ecotoxicological risk. Chemosphere 84**,** 1336-1348. 10.1016/j.chemosphere.2011.05.014

Verlicchi, P., Al Aukidy, M., Jelic, A., Petrović, M., and Barceló, D. (2014). Comparison of measured and predicted concentrations of selected pharmaceuticals in wastewater and surface water: a case study of a catchment area in the Po Valley (Italy). Sci Total Environ 470-471**,** 844-854. https://doi.org/10.1016/j.scitotenv.2013.10.026

Vione D., Feitosa-Felizzola J. Minero, C., and Chiron, S. (2009). Phototransformation of selected human-used macrolides in surface water: Kinetics, model predictions and degradation pathways. Water Research 43 (3) 1959-1967. https://doi.org/10.1016/j.watres.2009.01.027

Watanabe, H., Tamura, I., Abe, R., Takanobu, H., Nakamura, A., Suzuki, T., Hirose, A., Nishimura, T. and Tatarazako, N. (2016). Chronic toxicity of an environmentally relevant mixture of pharmaceuticals to three aquatic organisms (alga, daphnid, and fish). Environmental Toxicology and Chemistry 35 (4), 996-1006. https://doi.org/10.1002/etc.3285

WHO (2017). Critically important antimicrobials for human medicine, 5th revision. ISBN: 978-92-4-151222-0.

Yamashita N., Yasojiama M., Nakada N., Miyajima K., Komori K., Suzuki Y and Tanaka H. (2006): Effects of antibacterial agents, levofloxacoin and clarithromycin, on aquatic organisms Water, Sci & Tech. 53 (11) 65-72, 2006.

Yang L-H, Ying G-G, SU H-C, Jennifer L S, Adams M S, Binet M T (2008): Growth-inhibiting effects of 12 antibacterial agents and their mixtures on the freshwater microalga *Pseudokirchneriella subcapitata*. Environmental Toxicology and Chemistry, Vol. 27, No. 5:1201–1208.

Zhang, R., Zhang, G., Zheng, Q., Tang, J., Chen, Y., Xu, W., ... & Chen, X. (2012). Occurrence and risks of antibiotics in the Laizhou Bay, China: impacts of river discharge. Ecotoxicology and environmental safety, 80, 208-215.

Zhang, R., Tang, J., Li, J., Zheng, Q., Liu, D., Chen, Y., ... & Zhang, G. (2013). Antibiotics in the offshore waters of the Bohai Sea and the Yellow Sea in China: occurrence, distribution and ecological risks. Environmental Pollution, 174, 71-77.

Zhang, R., Yu, K., Li, A., Wang, Y. and Huang, X. (2019) Antibiotics in corals of the South China Sea: Occurrence, distribution, bioaccumulation, and considerable role of coral mucus. Environmental Pollution 250, 503-510.

Zhang, R., Yu, K., Li, A., Wang, Y., Pan, C. and Huang, X. (2020) Antibiotics in coral reef fishes from the South China Sea: Occurrence, distribution, bioaccumulation, and dietary exposure risk to human. The Science of the total environment 704, 135288.

Zhu, M., Wang, Z., Chen, J., Xie, H., Zhao, H. and Yuan, X. (2020) Bioaccumulation, Biotransformation, and Multicompartmental Toxicokinetic Model of Antibiotics in Sea Cucumber (*Apostichopus japonicus*). Environmental Science & Technology 54(20), 13175-13185.