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Selection of substances for the 4th Watch List under the Water Framework Directive

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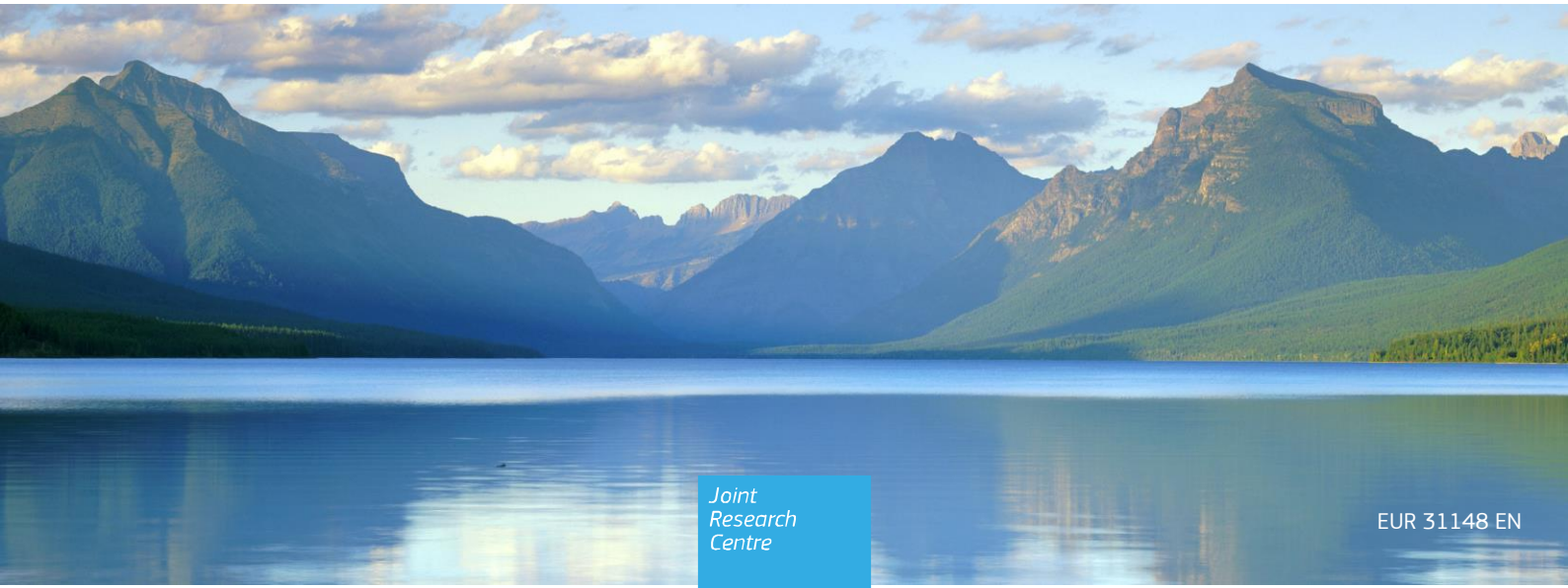

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Abstract

The 1st Watch List (WL) for substances in surface waters under the Environmental Quality Standards Directive (EQSD - Directive 2013/39/EU) was established by Commission Implementing Decision (EU) 2015/495 in March 2015. The list was first updated in June 2018 by the Commission Implementing Decision (EU) 2018/840 and in August 2020 by Commission Implementing Decision (EU) 2020/1161.

The period of continuous monitoring for any WL substance should not exceed four years (Article 8b of the EQSD). Thus, in 2022 the three substances added in 2018, i.e. the insecticide metaflumizone and the antibiotics amoxicillin and ciprofloxacin, should be removed. A maximum total of thirteen substances or groups of substances may be listed in the 4th WL, i.e. one more than the maximum allowed in 2020. The six substances or groups of substances added during the third WL update (EU 2020/1161) should be carried over to the 4th WL to ensure that enough high-quality monitoring data are collected for their risk assessment. Therefore, seven additional substances or groups of substances may be added to establish the 4th WL.

The purpose of this report is to propose candidate substances for the 4th WL, which have been selected based on three pillars of information. The overall selection process, including the rationale for each substance selected, is described.

Briefly, after comments received following the Working Group meetings, the seven candidates for the 4th Watch list are two plant protection products (PPP), two antibiotics, one insecticide, one pharmaceutical and its transformation product, and three sunscreen agents.

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Executive summary

The 1st Watch List (WL) of substances in surface waters under the Environmental Quality Standards Directive (EQSD - Directive 2008/105/EC as amended by Directive 2013/39/EU; thus indirectly under the Water Framework Directive 2006/60/EC) was established by Commission Implementing Decision (EU) 2015/495 in March 2015. The list was first updated in June 2018 by the Commission Implementing Decision (EU) 2018/840. During the WL update, the Commission concluded that the substances diclofenac, oxadiazon, 2,6-di-tert-butyl-4-methylphenol, tri-allate and 2-ethylhexyl-4-methoxycinnamate should be removed from the WL since the monitoring data quality was good enough to perform the risk assessment, while new substances were included, i.e. the insecticide metaflumizone and the antibiotics amoxicillin and ciprofloxacin (EU 2018/840). Only these three substances were kept during the second update of the WL (2020), and six substances/groups of substances were added to the list (EU 2020/1161), i.e. the antibiotics sulfamethoxazole and trimethoprim, the antidepressant venlafaxine and its metabolite o-desmethylvenlafaxine, a group of ten azole compounds used as antifungal pharmaceuticals or food protection products, and the fungicides dimoxystrobin and famoxadone.

The period of continuous monitoring for any WL substance should not exceed four years (Article 8b of the EQSD). Thus, in 2022 the three substances added in 2018, i.e. the insecticide metaflumizone and the antibiotics amoxicillin and ciprofloxacin, should be removed. A maximum total of thirteen substances or groups of substances may be listed in the 4th WL, i.e. one more than the maximum allowed in 2020. The six substances or groups of substances added during the third WL update (EU 2020/1161) should be carried over to the 4th WL to ensure that enough high-quality monitoring data are collected for their risk assessment. Therefore, seven additional substances or groups of substances may be added to establish the 4th WL.

The purpose of this report is to propose candidate substances for the 4th WL

Three pillars of information were used to select the candidate substances (Chapter 2). The first pillar is the outcome of the last review of substances for the 3rd WL, the second is information from Member States (MS) and stakeholders, and the third is literature search and/or other information.

The overall selection process, including the rationale for each substance selected, is described in Chapter 3. Accordingly, three criteria for the identification of candidate WL substances were used by the JRC.

To prioritise substances for inclusion in the WL, it is important to consider three criteria: first, the need for more monitoring data to perform a risk assessment; second, the existence of reliable information on the toxicity of the substances that points to a possible risk when considering the available monitoring data; and third, sufficiently sensitive analytical methods exist for the substances, taking account also of the relevant matrix for the relevant matrix for and stability of the substances (including potential degradation products).

Particularly crucial are the availability of a reliable Predicted No Effect Concentration (PNEC) to define the safety threshold value, and of relevant analytical methods for monitoring in the appropriate environmental matrix. Although the PNEC is based on (eco)toxicity data, hazard properties were also taken into account to support the selection, i.e. the persistence, bioaccumulation, carcinogenicity, mutagenicity, toxicity to reproduction, endocrine disruption and contribution to antimicrobial resistance (AMR). Using these criteria, the JRC classified the selected substances into three categories: priority 1, suitable candidates (Table 6) for the 4th WL; priority 2, suitable candidates for the 4th WL but for which a reliable PNEC or analytical method are missing (Table 7); and priority 3 (Table 8) good candidates for future WL updates, but which cannot be proposed now mainly because more time is needed to investigate them.

The preferred monitoring matrix for candidate substances was decided according to their partitioning coefficient (log K_{OW}). Substances with log K_{OW} > 5 should preferably be measured in sediments, or suspended particulate matter (SPM); those with a log K_{OW} < 3 should be monitored preferably in water, while for substances with a log K_{OW} between 3 and 5, the choice of sediment or SPM is optional depending on the degree of contamination. Biota monitoring is also recommended for substances with the potential to accumulate through food chains and thus expose top predators via their diet

In the first round of comments, the JRC proposed, based on the selection criteria, the substances from the priority 1 category as the most suitable candidates for inclusion in the next WL, while seeking further information (on the PNECs, and analytical methods) for substances in the priority 2 and 3 groups from MS and stakeholders.

Following comments after the WG Chemicals group meeting held on 10th February 2022, the list of candidates was modified.

In particular, two substances/groups of substances from the priority 2 and 3 categories were added, i.e. sunscreen agents and metformin with its metabolite guanylurea, respectively.

The sunscreen agents were not selected originally due to uncertainty regarding the PNEC value, but further information was received which helped to make them suitable candidates (see Table 6). Likewise, PNEC value was made available for metformin.

In the light of discussions in the WG Chemicals meeting on 4 May and the Strategic Coordination Group meeting on 17 May 2022, two synthetic hormones (levonorgestrel, norethisterone) that had been included in the priority 1 category were moved to the priority 2 category because of the difficulty of monitoring them.

Other substances excluded from the priority 1 category as a result of the earlier comments received were 4-chloroaniline and 3,4-dichloroaniline, four pyrethroids and a group of siloxanes. On the first two groups of substances, although relevant, the experts expressed concern regarding the PNEC values and the sensitivity of the available analytical methods, respectively. In the pyrethroid group, particularly for lambda-cyhalothrin, it would be very difficult to reach the low PNEC values without an advanced analytical system.

Furthermore, four pyrethroids are shortlisted in the current review of the list of priority substances under the WFD and cypermethrin is an existing priority substance, suggesting that the four pyrethroids considered for the WL are also likely to pose a risk to the environment. Consequently, it would be worth considering whether they should be covered as a group in the priority substances list (applying a cumulative approach).

For siloxanes, the JRC concluded that it would be appropriate to wait for the outcome of the ongoing process for their restriction/ban, under REACH, and then to possibly include the linear siloxanes which are currently under investigation for PBT/vPvB properties.

Some substances were moved from the priority 3 category to the priority 2 category, e.g. rodenticides and metazachlor, on the basis of information received. Further information will be gathered on the PNECs and/or analytical methods for the substances and groups of substances finally placed in those two categories, including on the two synthetic hormones, and they will be considered for inclusion in the next WL. In addition to validating a sufficiently sensitive analytical method for the hormones, consideration will be given to the possible use of bioassays (effect-based methods) as screening methods to be implemented alongside chemical analysis.

Regarding copper and copper oxides, some experts agreed to refine the QS value for these substances considering that exceedances at EU level were observed using the lower existing PNEC value. They might then be proposed for short-listing as Priority Substances.

Table S1 summarises the list of substances in the priority 1 category after the discussions with experts in May 2022.

Table S1. List of the most suitable WL candidate substances, fulfilling the selection criteria, modified following comments from MS and Stakeholder groups (after the WG Chemicals meetings held on 10th February and 4th May 2022, and the SCG meeting on 17th May 2022). In bold, the seven substances finally identified for inclusion in the 4th Watch List. The table shows for candidate substances the group/class, CAS number, use, PNEC value and matrix (environmental compartment). PPP: Plant Protection Product.

Substance/group Name	CAS Number	Use	PNEC	Matrix
Azoxystrobin	**131860-33-8**	**Fungicide used as PPP and biocide**	**0.2 µg/l(1)**	**Water**
Clindamycin	**18323-44-9**	**Human medicine** **Antibiotic (lincosamides)**	**0.044 µg/l(2)**	**Water**
Diflufenican	**83164-33-4**	**Herbicide used as PPP**	**0.01 µg/l(1)**	**Water**
Fipronil	**120068-37-3**	**Insecticide**	**0.00077 µg/l(1)**	**Water**

		Biocidal and veterinary uses		
Metformin and its transformation product guanylurea	**657-24-9 and 141-83-3**	**Pharmaceutical** **Type 2 diabetes treatment**	**156 µg/l([1])** **100([2])**	**Water**
Ofloxacin	**82419-36-1**	**Human medicine** **Antibiotic (fluoroquinolones)**	**0.026 µg/l([3])**	**Water**
Sunscreen agents	**70356-09-1 (avobenzone)**	**UV filters**	**3 µg/l([4])**	**Water**
	6197-30-4 (octocrylene)		**0.266 µg/l([5])**	
	131-57-7 (oxybenzone)		**0.67 µg/l([5])**	
Cefalexin	15686-71-2	Human medicine Antibiotic (cephalosporins)	0.08 µg/l([6])	Water
Free cyanide	57-12-5 (CN-); 74-90-8 (HCN)	Industrial and biocide	0.26 µg/l([7])	Water

([1]) https://www.oekotoxzentrum.ch/expertenservice/qualitaetskriterien/qualitaetskriterienvorschlaege-oekotoxzentrum/.
([2]) https://www.umweltbundesamt.de/sites/default/files/medien/5750/publikationen/2020_12_09_texte_233-2020_umweltqualitaetsnormen_binnengewaesser.pdf.
([3]) https://www.rivm.nl/bibliotheek/rapporten/601711003.pdf
([4]) https://www.ivl.se/download/18.694ca0617a1de98f47393d/1628417290890/FULLTEXT01.pdf
([5]) https://echa.europa.eu/
([6]) https://www.amrindustryalliance.org/wp-content/uploads/2018/09/AMR_Industry_Alliance_List-of-Predicted-No-Effect-Concentrations-PNECs.pdf
([7]) JRC Factsheet 2015- 2018/WFD-UK TAG report, 2012

1 Introduction

The surface water Watch List (WL) under the Water Framework Directive (WFD) is a mechanism for obtaining high-quality Union-wide monitoring data on emerging pollutants and substances that may pose a significant risk at Union level to or via the aquatic environment, but for which available monitoring data are insufficient to draw conclusions on the actual risk posed. According to Article 8b of the Environmental Quality Standards Directive (EQSD - Directive 2008/105/EC as amended by Directive 2013/39/EU), the WL should be updated every two years. When updating the WL, the Commission should remove any substance for which a risk-based assessment can be concluded without additional monitoring data. New substances or groups of substances can be added to the WL during each update. The maximum number of substances or groups of substances that the Commission is allowed to include in the list increases by one at each update to a maximum of 14 substances or groups of substances. The duration of a continuous WL monitoring period for any individual substance may not exceed four years.

The first WL was established by Commission Implementing Decision (EU) 2015/495 in March 2015 and replaced in June 2018 by the list in Commission Implementing Decision (EU) 2018/840, which was updated in August 2020 by Commission Implementing Decision (EU) 2020/1161. During the first WL update, the Commission concluded that the substances diclofenac, oxadiazon, 2,6-di-tert-butyl-4-methylphenol, tri-allate and 2-ethylhexyl-4-methoxycinnamate should be removed from the WL since the monitoring dataset was good enough to perform a risk assessment, while the insecticide metaflumizone and the antibiotics amoxicillin and ciprofloxacin were identified as suitable candidates, and then included (EU 2018/840). Only these three substances were kept in the second update of the WL (EU 2020/1161), and six substances/groups of substances were added to the list, i.e. the antibiotics sulfamethoxazole and trimethoprim, the antidepressant venlafaxine and its metabolite o-desmethulvenlafaxine, a group of ten azole compounds used as antifungal pharmaceuticals or food protection products and the fungicides dimoxystrobin and famoxadone.

As the continuous WL monitoring period for any individual substance may not exceed four years, in the current WL update the three substances included during the first WL update (EU 2018/840) should be removed and a maximum of thirteen substances or groups of substances can be listed in the 4th WL. The insecticide metaflumizone and the antibiotics amoxicillin and ciprofloxacin will be removed while the six substances/groups of substances included in the 3rd WL should be carried over to the 4th WL to ensure that enough high-quality monitoring data are collected for their risk assessment.

The purpose of the present report is to propose candidate substances to be included in the new WL (4th WL).

The report is structured as follows:

Chapter 2 Process for selecting candidate substances for the WL.

This chapter describes the overall process for selecting candidate substances for the WL. Section 2.1.1 gives information about exposure monitoring data, while the section 2.1.2 provides a description of the sources of information and databases for ecotoxicology data and hazard properties. Section 2.1.3 provides a description of the sources of information and databases for analytical methods.

Chapter 3 Selection of new candidate substances for the fourth WL.

Section 3.1 describes the criteria followed for the selection of candidates for the 4th WL. Section 3.2 presents the list of substances fulfilling the criteria and provides available PNEC values and analytical methods. Section 3.3 explains the rationale for the selection.

Chapter 4 Conclusion

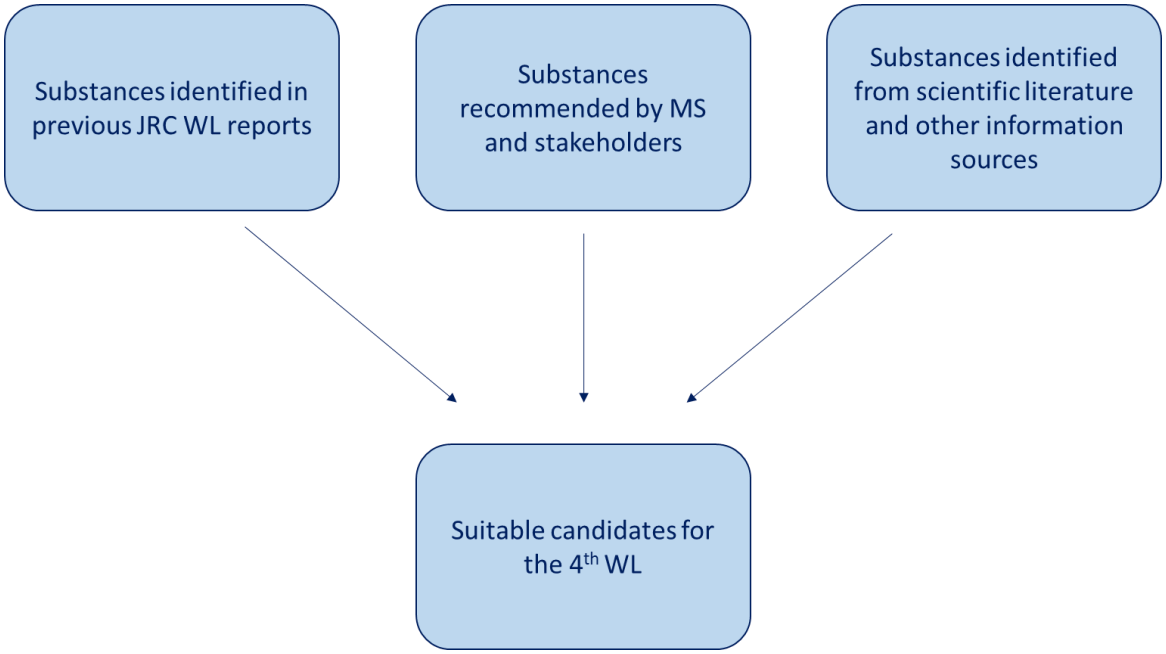
This chapter describes the conclusions and the recommendations for the next WL.

The report also includes annexes and factsheets that show all supportive information: **Annex I**: Tables containing additional information for all substances; **Annex II**: Factsheets for the candidate substances is provided in a separated document.

2 Process for selecting candidate substances for the Watch List

To select the substances, three pillars as sources of information were considered (three upper boxes in Figure 1). One pillar is the outcome of the selection of substances for the 3rd Watch List under the Water Framework Directive (WFD) (Gomez Cortes et al. 2020), another pillar consists of recommendations from MS and stakeholders as established in Article 8b of the Environmental Quality Standards Directive (EQSD), and the third pillar is literature search and other information (COM/2019/128 final). The pillars are shown in boxes on Figure 1, while the criteria for selecting suitable candidates amongst the possible substances for inclusion in the WL are described in Chapter 3.1.

Figure 1. Overall process for the selection of candidate substances for the Watch List (WL)



2.1 Sources of information on exposure, toxicity, hazard and analytical methods

A search for information on exposure of each substance in the aquatic environment was carried out in order to avoid proposing substances for which enough monitoring data are already available. For the freshwater compartment, environmental quality standards (EQS) or predicted no-effect concentration (PNEC) values were collected or derived considering toxicity effects to aquatic freshwater organisms ($PNEC_{fw,eco}$). For highly hydrophobic substances, the EQS or PNEC values were also considered for sediment-dwelling organisms ($PNEC_{eco,sed}$). EQS or PNEC values should protect freshwater and marine ecosystems from possible adverse effects of chemicals.

Hazard properties of the substances, such as Persistence (P), Bioaccumulation (B), Toxicity (T), Carcinogenicity (C), Mutagenicity (M), Reproductive Toxicity (R) and Endocrine Disruption (ED), were also investigated, as were the substances' usage and authorisation or approval status.

2.1.1 Exposure information

Exposure information was searched for all the potential WL candidates from various sources but was not always found or was often very limited. Furthermore, not only data availability but also the quality of the collected data (if any) is crucially important to assess the risk that a given substance might pose. A summary of the monitoring data for each candidate substance in provided in Section 3.3 (Rationale for the selection) while details can be found in Annex II.

Generally, the relevant sources of monitoring data include the JRC Prioritisation dataset developed in 2014 (Carvalho et al., 2016; https://circabc.europa.eu/w/browse/52c8d8d3-906c-48b5-a75e-53013702b20a), the WISE dataset managed by the EEA (https://www.eea.europa.eu/data-and-maps/data/waterbase-water-quality-icm-1), the Naiades dataset (http://www.naiades.eaufrance.fr/acces-donnees#/physicochimie), various reports and publications, and datasets retrieved from or provided directly to the JRC by several MS.

In relation to statistical analyses of Measured Environmental Concentrations (MECs), the JRC acknowledges that despite the constantly improving sensitivity of analytical techniques, any set of MECs may contain a proportion of non-detected or non-quantified samples, called censored concentrations (Gardner 2011; Helsel 2012; Shoari and Dubé, 2018).

Thus, the usage of non-quantified samples in exposure datasets is a challenge when not all the limits of quantification (LOQs) of applied analytical methods are adequate in relation to the PNEC. In this report, the term "Scenario 2" (Sc2) indicates a dataset which comprises all disaggregated raw data (all reported quantified and non-quantified samples). Instead, the Scenario 3 (Sc3) is a dataset containing quantified monitoring data plus non-quantified data for which ½ LOQ ≤ PNEC. The Sc3 is a more relevant data scenario for making a risk assessment according to the sub-group on review (SG-R) of the priority substances list (Carvalho et al., 2016). When the substitution approach is feasible (EFSA, 2010; Shoari and Dube, 2018), then the non-quantified samples in Sc2 and Sc3 are commonly set equal to half of the LOQ as stipulated in Directive 2009/90/EC. Other substitutions are also possible (for example at LOQ). If the level of censoring is high, then comprehensive mathematical techniques should be used for estimation of summary statistics (Gardner 2011; Helsel 2012; Shoari and Dube, 2018).

In this report, the analyses of MECs and calculations of Risk Quotients (RQ) are mainly based on Scenario 2 data which are usually insufficient or have low quality, therefore should be considered as preliminary and tentative. For this reason, the derived statistical parameters (mean, median and percentiles of MECs) are estimated assuming substitution of non-quantified data (censored data) either with half of the LOQs as applied in the JRC prioritisation dataset (2014) or with the LOQ as suggested in the WISE dataset of the EEA (i.e. the worst case scenario).

2.1.2 Hazard information

Hazard information was collected from various sources (Table 1) for all the potential candidates.

First, EQS were collected from reports or online databases, or from literature, in particular if the methodology in the TGD EQS (2018) had been followed.

Second, PNEC values were collected, with a particular focus on the substances where no EQS value was available. Furthermore, PNEC values were searched for in the literature, with preference given to those used already in European monitoring campaigns or prioritisation exercises.

Third, PNECs were collected from the European Chemicals Agency (ECHA) dossiers (http://echa.europa.eu/) and European Food Safety Authority (EFSA) risk assessment reports (http://www.efsa.europa.eu/), when available.

Fourth, for pharmaceuticals, the Swedish FASS database (https://www.fass.se) was considered. In the case of antimicrobials, PNEC values were retrieved from the antimicrobial resistance (AMR) industry alliance list (https://www.amrindustryalliance.org/wp-content/uploads/2018/09/AMR_Industry_Alliance_List-of-Predicted-No-Effect- Concentrations-PNECs.pdf).

Fifth, literature was also screened for PNEC values.

Finally, for those substances where information was not available from any of the sources listed above, PNECs were calculated by the JRC using studies that were considered reliable or reliable with restrictions (as explained in the TGD-EQS (2018)).

Then, information about the PBT properties was retrieved from ECHA (industrial chemicals, pharmaceuticals and biocides) or EFSA (plant protection products, PPP), while Fass (SE) and Janusinfo, Stockholm County Council was the source for human pharmaceuticals. Carcinogenicity (C), Mutagenicity (M) and Reproductive Toxicity (R) categorisations (in accordance with the Globally Harmonised System of Classification and Labelling of Chemicals (GHS)) were extracted from ECHA dossiers. For ED substances, the Endocrine Disruptor Strategy (EDS) database and categorisation of the European Commission was used (EDS database, EC). Information retrieved from TDEX (the endocrine disruption exchange) as well as from research projects and peer reviewed articles was also considered for evaluating the ED properties of the substances. Concerning PPP, the information on CMR and PTB was retrieved from EFSA dossiers when available.

ECHA's Annex III inventory was used to identify substances for which there is an indication of concern.

Table 1. Sources for EQS/PNEC values and hazard information.

Source	Description
AgriTox ANSES FR 2019	Plant protection products http://www.agritox.anses.fr/php/data-criteria.php
AMR Industry alliance	Anti-Microbial pharmaceuticals https://www.amrindustryalliance.org/wp-content/uploads/2018/09/AMR_Industry_Alliance_List-of-Predicted-No-Effect-Concentrations-PNECs.pdf
ECHA	All substances https://echa.europa.eu/home
ECOSAR	Pharmaceuticals https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model
EDS database, EC	All substances https://ec.europa.eu/environment/chemicals/endocrine/strategy/substances_en.htm
TDEX the endocrine disruption exchange	All substances https://endocrinedisruption.org/
Swiss ECOTOX centre	All substances https://www.ecotoxcentre.ch/expert-service/quality-standards/proposals-for- acute-and-chronic-quality-standards/
ECOTOX Database US EPA	All substances https://cfpub.epa.gov/ecotox/search.cfm
EFSA	All substances http://dar.efsa.europa.eu/dar-web/provision
EU Pesticides database	Plant protection products https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.selection&language=EN
FASS	Pharmaceuticals https://www.fass.se/LIF/startpage
INERIS	All substances https://substances.ineris.fr/fr/
Janusinfo, Stockholm County Council	Pharmaceuticals https://www.janusinfo.se/environment
JRC	All substances
Norman	https://www.norman- network.com/nds/ecotox/lowestPnecsIndex.php?checkSelect=0
OSPAR	All substances
Research articles and reports	All substances
RIVM	All substances https://www.rivm.nl/
UBA	All substances ETOX (Information System Ecotoxicology and Environmental Quality Targets): https://webetox.uba.de/webETOX/index.do?language=en

2.1.3 Analytical methods

A literature review of available analytical methods was carried out for all the candidate substances (Table 2). The JRC searched for analytical methods in reports and peer-reviewed papers. In these latter, the JRC verified that technical details are described. Where possible, the JRC uses the same terminology, preferably LOQ, to express the sensitivity of the method. In cases where the information is retrieved from peer-reviewed articles that use LOD (limit of detection) or MQL (method quantification limit), this is indicated. Furthermore, the matrix for which the analytical method has been validated, if other than water, is specified in the report and in the substance' factsheets (Annex II).

Table 2. Sources for analytical methods.

Source	**Description**
Companies	Plant protection products and industrial products
ECHA	Publicly available assessment reports of the approved biocidal substances https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances and other substances https://echa.europa.eu
EFSA	Plant protection products http://www.efsa.europa.eu/en http://dar.efsa.europa.eu/dar-web/provision
Research articles and reports	All substances
USGS	Plant protection products and industrial products https://www.usgs.gov/
US EPA	Plant protection products https://www.epa.gov/

3 Selection of substances for the Watch List (WL)

The first potential candidates for the 4th Watch List (WL) were identified during the selection of substances for the 3rd WL under the Water Framework Directive (WFD) (Gomez Cortes et al. 2020). This chapter describes a set of criteria for the identification of candidate substances to update the WL and presents a list of substances that fulfil the selection criteria.

3.1 Criteria for identification of candidate substances for WL update

The JRC proposes three criteria for the identification of new WL substances.

Respecting the requirements of Article 8b of the Environmental Quality Standards (EQS) Directive (Directive 2008/105/EC as amended by Directive 2013/39/EU), the following **pillars** of information were drawn upon to identify potential candidates for inclusion in the WL:

1. Substances shortlisted for, but not included in the 3rd WL because of limitations at the time concerning the reliability of the PNEC or the availability of a suitable analytical method.
2. Recommendations from MS and stakeholders.
3. Substances of emerging concern identified based on research projects and articles.

Additionally, to be selected as suitable candidates for the WL, the identified potential candidates should fulfil the following **three criteria**:

1. More monitoring data are needed to perform the risk assessment
2. A reliable PNEC value is available pointing to a possible risk.
3. An adequately sensitive analytical method is available.

Banned substances fulfilling the criteria above were not considered as potential candidates for the WL following the final recommendation cited in the document on the development of the 1st Watch List (Carvalho et al. 2015). To prioritise substances for inclusion in the WL, the relevant matrix and stability of the substances were taken into account, and the level and availability of reliable PNECs and relevant analytical methods for monitoring in the appropriate environmental matrix.

The selection of candidate substances took into consideration also the hazard properties, including, for antibiotics, their possible contribution to the development of antimicrobial resistance (AMR).

The preferred monitoring matrix for hydrophobic substances with high octanol/water partition coefficient values (log K_{OW}) is sediment or biota as recommended in the WFD Common Implementation Strategy (CIS) Guidance document No. 25 on sediment and biota monitoring (EC 2010, Guidance document No. 25). Compounds with log K_{OW} > 5 should preferably be measured in sediments, or suspended particulate matter (SPM), while compounds with a log K_{OW} < 3 should preferably be measured in water. Then, for compounds with a log KOW between 3 and 5, either the sediment matrix or SPM may be used depending on the degree of contamination.

Moreover, for substances with a potential to accumulate through food chains and thus to expose top predators via their diet (log K_{OW} > 3, biomagnification factor (BMF) > 1 or bioconcentration factor (BCF) ≥ 100 and not readily biodegradable), biota monitoring is also recommended (EC 2018 Guidance document No. 27).

3.2 List of substances fulfilling the criteria

Tables 3, 4 and 5 summarise potential candidates identified by the JRC for the next WL. The substances were selected according to the above criteria. To facilitate discussion, the substances were grouped according to their use/type of substance (class). The tables include the group, name of the substance, CAS number, use, recommended monitoring matrix, hazard properties, PNEC value, available analytical method, and status. Information about the available monitoring data, measured environmental concentration (MEC), predicted environmental concentration (PEC) and initial risk assessment of potential candidates is summarised in each substance factsheet in Annex II.

Table 3 presents the substances selected according to pillar 1, i.e. identified in the previous update of the WL (Gomez Cortes et al. 2020) as good candidates but not shortlisted for inclusion in the 3rd WL. Table 4 presents

the substances selected according to pillar 2, i.e. those proposed by MS and stakeholders during the final stages of the previous review (Gomez Cortes et al. 2020). Finally, Table 5 presents substances of emerging concern identified based on research projects and articles (pillar 3).

Additional information regarding the aforementioned substances is shown in Annex I (additional tables) and Annex II (substance' factsheets).

The tables were updated following receipt of comments from MS and Stakeholder experts' comments after the WG Chemicals meetings held on 10 February and 4 May 2022.

3.2.1 Substances from pillar 1

Table 3. Potential candidates for the WL identified during the previous WL review but not selected for the 3rd WL (Gomez Cortes et al. 2020). The table shows for each candidate substance the name of the substance, CAS number, use and status, hazard properties, PNEC value, available analytical method and limit of quantification. dw: dry weight; ww: wet weight; lw: lipid weight; AF: assessment factor; PNEC: predicted no effect concentration (selected values in bold); LOQ: limit of quantification; LOD: limit of detection; PPP: plant protection product; P: persistent; B: bioaccumulative; T: toxic; M: mutagenic; C: carcinogenic; R: toxic to reproduction; ED: endocrine disruptor. .

Name	**CAS No**	**Use /Status**	**Hazard properties**	**PNEC water (µg/L)**	**Available Analytical Method (LOQ µg/L)**
4-chloroaniline	106-47-8	Industrial (ECHA) Use in the production of urea insecticides and herbicides, pigments, pharmaceuticals and cosmetic products (WHO, 2003) Approved	PT, possible M, C (ECHA) Not in Annex III inventory (ECHA) Officially recognised in the EU as Carcinogenic (Harmonised C&L) It is very toxic to aquatic life with long lasting effects (ECHA)	**0.05** (prioritisation exercise RBSP-ECOSTAT, UBA, 2014) 0.22 (NL legal standard AA- EQS, RIVM, 2009) 0.57 (MPCeco, water, RIVM, 2009) 1 (INERIS, 2011)	Isocratic reversed-phase HPLC (RPHPLC) (LOD 0.036) (Börnick et al., 2001) LC-MS/MS (0.00013) (Rimayi et al., 2019)
3,4-dichloroaniline	95-76-1	Industrial (ECHA) It is exclusively used as an intermediate in the chemical industry for the synthesis of 3,4-dichlorophenylisocyanate, the herbicide propanil and an azo dye for polyester fabrics (UC = 3 and for the production of phenylureaherbicides (diuron, linuron) and the bactericide trichlorocarbanilide by further sites (EU, RAR, DE 2006).	P, vP, T Endocrine disruptor (INERIS) Not in Annex III inventory (ECHA) It is very toxic to aquatic life with long lasting effects (ECHA)	**0.02** (monitoring exercise INERIS, 2012) additional AF of 10 since it is ED according to INERIS 0.2 (water) and 0.039 mg/kg ww (sediment) (Risk Assessment Report, JRC, 2006) 3 (NL QS, RIVM, 1998)	Isocratic reversed-phase HPLC (RPHPLC) (LOD 0.033) (Börnick et al., 2001) LC-MS/MS (LOD 0.0052) (USGS, 2012)
Free cyanide	CN^- 57-12-5 HCN 74-90-8	Industrial product Inorganic biocide NOT APPROVED as PPP (2004/129/EC) No authorisation in place APPROVED as BIOCIDE (ECHA)	T (ECHA) HCN does not display properties of environmental persistence or bioaccumulation, although it is highly toxic to aquatic organisms. It does not meet the criteria for classification as PBT	**0.26** (JRC Factsheet 2015-2018/WFD-UK TAG report, 2012) 5 (freshwater ECHA dossier) **0.5** (JRC Dossier https://circabc.europa.eu/faces/jsp/extension/wai/navigation/container.jsp, 2015) 0.04 (PNECaqua, ECHA)	Continuous Flow Analysis (CFA) method according to ISO 14403-2:2012 modified (0.14-0.30) (Fraunhofer Institute, 2018)
Benzimidazoles:	31431-	Human medicine	PBT, possible R (modelling exercise)	0.088 (FASS SE database)	LC-IonTrap-MS

Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method (LOQ µg/L)
Anthelmintics: Mebendazole	39-7	Antiparasitic Products, Insecticides and Repellents – Anthelmintics 1-10 tonne registered substance (ECHA) Authorised	P(3/3uncertain) B(3/1) T(1/3) Stockholm County Council. Suspected P suspected CMR in Annex III inventory (ECHA) Very toxic to aquatic life (ECHA)		(0.00037) (Zrnčić et al., 2014)
Gemfibrozil	25812-30-0	Human medicine Cardiovascular System – Lipid-modifying agents Authorised	PBT, possible C and R (modelling exercise) P(3/3) T(2/3) Stockholm County Council No information about ED properties This substance is suspected of causing cancer, is suspected of damaging fertility or the unborn child and is harmful to aquatic life with long lasting effects (ECHA)	0.8519 (JRC derivation, prioritisation exercise, 2016) 1.56 (Zhou et al., 2019)	SPE followed by UHPLC- QqLIT-MS (river water 0.0034) (Mandaric et al., 2017)
Norethisterone	68-22-4	Human medicine Genito-Urinary System and Sex Hormones - Sex hormones and modulators of the genital system Authorised This substance is manufactured and/or imported in the EEA in 1-10 tonnes per year	ED PBT, possible C, R, ED (modelling exercise) P(3/3) B(3/3) T(3/3) Stockholm County Council Potentially persistent, low potential for bioaccumulation and very high chronic toxicity. Moderate/high environmental risk (Janusinfo, SE) This substance may damage fertility or the unborn child, is very toxic to aquatic life, is very toxic to aquatic life with long lasting effects, is suspected of causing cancer and may cause harm to breast- fed children. (ECHA) R, a majority of data submitters agree this substance is Toxic to Reproduction (ECHA)	**0.0005** (Janusinfo SE, Fass, SE) 0.0354 (Prioritisation exercise, 2016) 0.51 (freshwater, ECHA) 10 µg/kg sediment dw (sediment freshwater, ECHA) 0.0148 (Zhou et al., 2019)	LC-MS/MS (0.00001) (Vulliet et al., 2011)
Levonorgestrel	797-63-7	Human medicine Genito-Urinary System and Sex Hormones	PT, ED Levonorgestrel very high chronic toxicity.	0.00001 (Janusinfo SE, Fass, SE, 2017)	HPLC-MS/MS (LOQ 0.00009) (Avar et al., 2015)

Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method (LOQ µg/L)
		- Sex hormones and modulators of the genital system Annex III: criteria for 1 - 10 tonne registered substances (ECHA) Authorised	High risk of environmental impact (Janusinfo, SE) This substance may damage fertility or the unborn child, is suspected of causing cancer, is harmful in contact with skin, is harmful if inhaled, may cause harm to breast-fed children and is harmful if swallowed R, a majority of data submitters agree this substance is Toxic to Reproduction (ECHA) Substances predicted as likely to meet criteria for category 1A or 1B carcinogenicity, mutagenicity, or reproductive toxicity	**0.000016 µg/L** (FASS text of Bayer AG, 2020)	LC-MS/MS (MDL 0.00033) (Vulliet et al., 2011) 0.000025 (Teigeler et al., 2021)
diCopper (I) oxide (Cu_2O) Copper (II) oxide (CuO) Copper	1317-39-1 1317-38-0 7440-508	Industrial (ECHA) Copper and Copper oxide are known to be on the EEA market in nanomaterial form Biocide (ECHA) Fungicide APPROVED as BIOCIDE This substance is manufactured and/or imported in the EEA in 1 000 - 10 000 tonnes per year This substance is used by consumers, in articles, by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing. Cu_2O substance is approved for use as a biocide in the EEA and/or Switzerland, for preventing fouling. APPROVED as PPP (copper oxide) app 01/01/2019	P two PBT criteria (EU Pesticides database) Very toxic to aquatic life with long lasting effects Copper is under assessment as Endocrine Disrupting ED (ECHA) 2 Candidate for Substitution (CfS) criteria fulfilled (persistent, toxic)	**1** (French legislation, INERIS) 1.6 (Cu, Cu_2O and CuO, statistic approach, INERIS) 2.4 (NL legal standard AA- EQS) 7.8 (Cu, Cu_2O and CuO, freshwater, ECHA) Relevant toxicity for classification): *Surface waters:* Fish (chronic, SSD HC5) = 1.11µg/L (RAC=0.37µg/L), Acipenser transmontanus (prolonged, EC_{10}) = 1.12µ/L (RAC=0.112µg/L) *Sediment:* Tubifex tubifex (prolonged, NOEC) = 16.17mg/kg ($RAC_{higher\ tier}$=3.234µ/L)	ICP-MS (0.02) (US EPA)

Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method (LOQ µg/L)
		exp 31/12/2025 2009/37/EC Reg. (EU) No 2018/1981 Reg. (EU) No 232/2015 Reg. (EU) No 540/2011 (Reg.(EU) No 84/2018) CuO is known to be on the EEA market in nanomaterial form (ECHA)			

3.2.2 Substances from pillar 2

Table 4. Substances suggested by individual MS and during internal consultation for the 3rd WL report (Gomez Cortes et al. 2020) as good candidates for future revisions of the WL. The table shows for each candidate substance the name of the substance, CAS number, use and status, hazard properties, PNEC value (selected values in bold), available analytical method and limit of quantification. Abbreviations, dw: dry weight; ww: wet weight; lw: lipid weight; AF: assessment factor; PNEC: predicted no effect concentration; LOQ: limit of quantification; LOD: limit of detection; PPP: plant protection product; P: persistent; B: bioaccumulative; T: toxic; R: toxic to reproduction; ED: endocrine disruptor; SVHC substance of very high concern.

Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method (LOQ (µg/L))
Etofenprox (Pyrethroids)	80844-07-1	PPP and Biocide Insecticide Approved as PPP Expiration 31/12/2022 Candidate for substitution Authorised as PPP in: AT, BG, CY, CZ, DE, EL, ES, FR, HU, IT, MT, PL, RO, SK Approved for use as a biocide in the EEA and/or Switzerland, for: wood preservation, controlling insects, ants, etc. (ECHA) Authorised as Biocide in: AT, HR, CY, CZ,	2 PBT criteria (BT not P) (EU Pesticides database) R Under assessment as ED (ECHA) Very toxic to aquatic life, is very toxic to aquatic life with long lasting effects (ECHA)	$PNEC_{fw}$ 0.001 µg/L (JRC derivation (Loos et al. 2018)) **0.0054 µg/L** (JRC derivation, modelling) $PNEC_{sed}$ 6.3 µg/kg ww (AT, 2013 assessment report)	Water: GC-APCI-MS/MS 12.5 pg/L (Rösch et al. 2019) LLE GC-MS/MS: 0.5ng/lm (UFZ (KGM 2021 – monitoring in small streams from 2L water)

Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method (LOQ (µg/L))
		DK, ER, DE, EL, HU, IT, LT, LU, NO, PL, RO, SK, SI, ES, SE, CH			
Lambda-cyhalothrin (Pyrethroids)	91465-08-6	PPP and Biocide Insecticide Approved as PPP Expiration 31/03/2023 Candidate for substitution Authorised as PPP in: AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK This substance is approved for use as a Biocide in the EEA and/or Switzerland, for: controlling insects, ants, etc. (ECHA) Expiration of approval: 30/09/2023 Authorised as Biocide in: AT, BE, CZ, DK, FR, DE, EL, HU, IE, IT, LU, NL, NO, PL, RO, SK, SI, ES, SE, CH, UK	2 PBT criteria (BT not P) (EU Pesticides database) Very toxic to aquatic life with long lasting effects. It is harmful in contact with skin (ECHA)	$PNEC_{fw}$ 0.00019 µg/L (DK and INERIS) **0.000022** µg/L (AA-EQS, Ecotoxcentre, CH, 2018) 0.00002 µg/L (NL QS) $PNEC_{sed}$ 0.93 µg/kg ww (DK) 1.05 µg/kg dw (DK, INERIS 2011) $PNEC_{biota}$ 0.04 µg/kg (INERIS) Chronic quality standard, $2.2*10^{-5}$ µg/L (Ecotoxcentre, CH)	Water (LOD): GS-MS/MS 0.0005 µg/l (USGS, 2009) GC-APCI-MS/MS 12.5 pg/L (Rösch et al., 2019) Sediment (LOD) GC-MS/MS 0.2 µg/kg 2009) (USGS)
Cyfluthrin (Pyrethroids)	68359-37-5	Biocide Acaricide/insecticide Not approved as PPP Expiration 30/04/2014 This substance is approved for use as a Biocide in the EEA and/or Switzerland for: controlling insects, ants, etc.. (ECHA)	Very toxic to aquatic life with long lasting effects (ECHA)	$PNEC_{fw}$ **0.000041 µg/L** (Cyfluthrin Assessment Report, 2018) 0.001 µg/L (JRC prioritisation, 2014) $PNEC_{sed}$ 0.027 µg/kg (Cyfluthrin Assessment Report, 2018)	Water (LOD): GC-MS/MS 0.001 µg/L (USGS, 2009) Sediment (LOD): GC-MS/MS 0.5 µg/kg (USGS, 2009)
Esbiothrin or Allethrin (Pyrethroid)	260359-57-7 584-79-2	Insecticides Not approved as PPP (Allethrin) Not approved as Biocide (Esbiothrin)	T potentially P (Allethrin) PT, R (Esbiothrin) Very toxic to aquatic life, is very toxic to aquatic life with long lasting effects (ECHA)	Esbiothrin: $PNEC_{fw}$ 0.41 µg/L (Norman network, deterministic approach) $PNEC_{sed}$ 17.1 µg/kg dw (Norman network) $PNEC_{biota,fw}$	Water (LOD): GC-MS/MS 0.001 µg/L (USGS, 2009) Sediment (LOD): GC-MS/MS 0.2 µg/kg dw (USGS, 2009)

Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method (LOQ (µg/L))
				1.71 µg/kg ww (Norman network) Allethrin: $PNEC_{fw}$ 0.024 µg/L (Norman network, deterministic approach) $PNEC_{sed}$ 0.88 µg/kg dw (Norman network) $PNEC_{biota,fw}$ 1.47 µg/kg ww (Norman network) For the biocide esbiothrin no final assessment report is publicly available on the ECHA website, only the BPC opinion. PNEC-values for both substances are the same in the biocidal evaluation, becuuse of read-across. $PNEC_{water}$ = 0,054 µg/L $PNEC_{sed}$ = 1,7 µg/kg ww (UBA)	
Siloxanes D4, D5, D6	556-67-2 (D4)	Industrial Cosmetic Widespread use (silicone materials) This substance is registered under the REACH Regulation and is manufactured in and / or imported to the European Economic Area, at ≥ 10 000 to < 100 000 tonnes per annum	PBT (officially recognised in the EU); Suspected Toxic for Reproduction vPvB (ECHA) Under assessment as Persistent Organic Pollutant SVHC candidate list Some uses of this substance are restricted under Annex XVII of REACH	$PNECf_w$ **0.088 µg/L** (Homem et al., 2017) 1.5 µg/L (ECHA) 0.44 µg/L (UK, 2009; RIVM, 2012; SE, 2018)0.2 µg/L (RIVM, 2012, NL EQS for sec pois) $PNEC_{sed}$	Magnetic solid-phase extraction (MSPE) /GC–MS 0.01 µg/L (Costa dos Reis et al., 2018)

Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method (LOQ (µg/L))
				3000 µg/kg dw (ECHA) 0.54 µg/kg (EA, 2009) 0.015 µg/kg dw (SE, 2018) 1.3 µg/kg dw (Homem et al 2017) $PNEC_{biota}$ 0.83 mg/kg (SE, 2018) 41 mg/Kg (ECHA, cited in SE, 2018)	
	541-02-6 (D5)	Industrial Cosmetic Widespread use (silicone materials) This substance is registered under the REACH Regulation and is manufactured in and / or imported to the European Economic Area, at ≥ 10 000 to < 100 000 tonnes per annum	PBT (officially recognised in the EU) vPvB Some uses of this substance are restricted under Annex XVII of REACH SVHC	$PNEC_{fw}$ **0.87 µg/L** (Homem et al., 2017) 1.2 µg/L (ECHA) $PNEC_{sed}$ 2.2 mg/kg dw (EA, 2009) 11 mg/kg dw (ECHA) $PNEC_{biota}$ 0.83 mg/kg (SE, 2018) 13 mg/kg (EA, 2009) 16 mg/kg (ECHA, cited in SE, 2018)	Magnetic solid-phase extraction (MSPE) /GC–MS 0.01 µg/L (Costa dos Reis et al., 2018)
	540-97-6 (D6)	Industrial Cosmetic Widespread use (silicone materials) This substance is registered under the REACH Regulation and is manufactured in and / or imported to the European Economic Area, at ≥ 1 000 to < 10 000 tonnes per annum.	PBT (officially recognised in the EU) vPvB SVHC This substance may cause long lasting harmful effects to aquatic life	$PNEC_{fw}$ **0.2 µg/L** (Homem et al., 2017) 0.53 µg/L (EA, 2009) $PNEC_{sed}$ 13 mg/kg dw (ECHA) ≥4.84 mg/kg dw (Homem et al., 2017) 7.5 mg/kg (EA, 2009) $PNEC_{biota}$ > 50 mg/kg (EA, 2009)	Magnetic solid-phase extraction (MSPE) /GC–MS 0.01 µg/L (Costa dos Reis et al., 2018)

Name	**CAS No**	**Use /Status**	**Hazard properties**	**PNEC water (µg/L)**	**Available Analytical Method (LOQ (µg/L))**
Alkylphenols	98-54-4 (4-Tert-Butylphenol)	Industrial This substance is registered under the REACH Regulation and is manufactured in and / or imported to the European Economic Area, at ≥ 10 000 tonnes per annum. It is used in adhesives and sealants and coating products. Other release to the environment of this substance is likely to occur from: indoor use (e.g. machine wash liquids/detergents, automotive care products, paints and coating or adhesives, fragrances and air fresheners). Substance included in the Community Rolling Action Plan (CoRAP) SVHC Precautionary measures suggested by manufacturers and importers of this substance. Guidance on the safe use of the substance provided by manufacturers and importers of this substance. (ECHA)	Suspected to be Toxic to Reproduction (Harmonised C&L). Officially recognised in the EU as Endocrine Disrupting (Candidate list of SVHCs). Very toxic to aquatic life with long lasting effects, causes serious eye damage, is suspected of damaging fertility and causes skin irritation (ECHA).	$PNEC_{fw}$ 10 µg/L (ECHA) $PNEC_{fw}$ **6.4 µg/L** (EU Assessment Report 2008) $PNEC_{sed}$ 270 µg/kg (DW; ECHA) Secondary Poisoning 46.67 mg/kg food (ECHA)	Water GC-MS (IVL, 2005, LOD < 0.001 – 0.04 µg/L Water, < 0.06 - 3 ng/g dw Sediment)
	121158-58-5 (Phenol, dodecyl-, branched)	Industrial This substance is registered under the REACH Regulation and is manufactured in and / or imported to the European Economic Area, at ≥ 1 000 to < 10 000 tonnes per annum. Substance included in the Community Rolling Action Plan (CoRAP). Precautionary measures suggested by manufacturers and importers of this substance. Guidance on the safe use of the substance provided by	Officially recognised in the EU as Toxic to Reproduction (Harmonised C&L, Candidate list of SVHCs). Officially recognised in the EU as Endocrine Disrupting (Candidate list of SVHCs). This substance may damage fertility and is very toxic to aquatic life with long lasting effects (ECHA). This substance may damage	$PNEC_{fw}$ **0.074 µg/L** (ECHA) $PNEC_{sed}$ 226 µg/kg (DW; ECHA) Secondary poisoning 4 mg/kg (food)	Sediment GC-MS LOD = 0.004 - 0.006 µg/L Water GC-MS LOD = 0.001- 0.039 ng/g dw Sediment

Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method (LOQ (µg/L))
			fertility or the unborn child, is suspected of damaging fertility or the unborn child and causes skin irritation.		
	80-46-6 (p-(1,1-dimethylpropyl)phenol)	Industrial This substance is registered under the REACH Regulation and is manufactured in and / or imported to the European Economic Area, at ≥ 100 to < 1 000 tonnes per annum.	Officially recognised in the EU as Endocrine Disrupting (Candidate list of SVHCs). Very toxic to aquatic life with long lasting effects	$PNEC_{fw}$ **2 µg/L** (Seki et al 2002 in Environment Agency, 2008) $PNEC_{fw}$ 10 µg/L (ECHA) $PNEC_{sed}$ 1.509 mg/kg (DW; ECHA) $PNEC_{sed}$ 0.105 mg/kg ww (Environment Agency, 2008) Secondary Poisoning (No potential for bioaccumulation)	Sediment/Water HPLC, LOD 10.9 µg/L (Seki et al., 2002), LOD 2.1 µg/L (Panter et al., 2006)
Phenol-benzotriazoles	3846-71-7 (UV-320)	Industrial Cosmetics and sunscreens 1-10 tonne registered substance (ECHA) SVHC now requiring authorisation before it is used (Annex XIV of REACH).	PBT It is harmful to aquatic life with long lasting effects and is suspected of causing cancer (C).	PNECfw 0.01416 µg/L (predicted QSAR Norman database) $PNEC_{sed}$ 0.82 µg/kg dw (predicted QSAR Norman database)	LC/LC-MS/MS freshwater LOD 0.03 ng/L; sediment LOD 0.6 µg/g DW; biota fish LOD 0.1 µg/g DW (Brorström-Lundén et al., 2011)

Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method (LOQ (µg/L))
				$PNEC_{biota,sec\ pois}$ 5.18 µg/kg ww (predicted QSAR Norman database)	GC-MS/MS); sediments LOQ 3 ng/g (Carpinteiro et al. 2012).
	3864-99-1 (UV-327)	Industrial 1-10 tonne registered substance (ECHA) SVHC now requiring authorisation before it is used (Annex XIV of REACH).	vPvB under assessment (ECHA)	PNECfw 91.1 µg/L (Wallberg et al. 2014) $PNEC_{fw}$ 0.00668 µg/L (predicted QSAR Norman database) $PNEC_{sed}$ 4.003 µg/kg dw (predicted QSAR Norman database) $PNEC_{biota,sec\ pois}$ 24.8 µg/kg ww (predicted QSAR Norman database)	LC/LC-MS/MS freshwater LOD 0.07 ng/L; biota fish LOD 1.2µg/g DW (Brorström-Lundén et al., 2011) Headspace (HS) solid-phase microextraction (SPME) followed by GC–MS/MS; Freshwater LOQ 0.2 ng/mL (Carpinteiro et al 2010) GC-MS/MS; sediments LOQ 3 ng/g (Carpinteiro et al 2012) On-line SPE-UPLC-MS/MS; Coastal marine water LOD 1.3 ng/L and LOQ 4.5 ng/L (Montesdeoca-Esponda et al. (2012) Microwave-assisted extraction (MAE) combined with on-line solid phase extraction followed by UHPLC-MS/MS; marine sediments LOD 84.1 ng/kg LOQ 280 ng/kg. (Montesdeoca-Esponda et al. 2013)

Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method (LOQ (µg/L))
					UPLC-MS/MS, MLOQ freshwater water 0.05-1.5 ng/L, sediment 0.01-0.2 ng/g (dry weight) and biota 0.004-1.35 ng/g (lipid weight). (Lu et al. 2016)
	25973-55-1 (UV-328)	This substance is registered under the REACH Regulation and is manufactured in and / or imported to the European Economic Area, at ≥ 100 to < 1 000 tonnes per annum. This substance is used in the following products: coating products, air care products, adhesives and sealants, lubricants and greases, polishes and waxes and washing & cleaning products. SVHC now requiring authorisation before it is used (Annex XIV of REACH).	Officially recognised in the EU as Persistent, Bioaccumulative and Toxic (Candidate list of SVHCs). Potentially a persistent organic pollutant POP	$PNEC_{fw}$ 10 µg/L (ECHA) PNECfw 0.00594 µg/L (predicted QSAR Norman database) PNECsed 451 mg/kg dw (equilibrium partitioning ECHA) PNECsed 5.4 mg/kg dw (predicted QSAR Norman database) $PNEC_{biota,sec\ pois}$ 13.2 mg/kg food (ECHA) $PNEC_{biota,sec\ pois}$ 3.42 mg/kg ww (ECHA) $PNEC_{biota,\ hh}$ 18.18 mg/kg food (ECHA)	LC/LC-MS/MS freshwater, LOD 0.1 ng/L; sediment LOD 0.7µg/g DW; biota fish LOD 0.3µg/g DW (Brorström-Lundén et al., 2011) Headspace (HS) solid-phase microextraction (SPME) followed by GC–MS/MS; Freshwater LOQ 0.1 ng/ml GC-MS/MS; sediments LOQ 3 ng/g. (Carpinteiro et al 2012) On-line SPE-UPLC-MS/MS; Coastal marine water LOD 1.1 ng/L and LOQ 3.7 ng/L. (Montesdeoca-Esponda et al. 2012) MAE-SPE-UHPLC-MS/MS; marine sediments LOD 78.4 ng/kg LOQ 260 ng/kg. (Montesdeoca-Esponda et al. 2013) UPLC-MS/MS; MLOQ freshwater water 0.05-

Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method (LOQ (µg/L))
					1.5 ng/L, sediment 0.01-0.2 ng/g (dry weight) and biota 0.004-1.35 ng/g (Lu et al. 2016)
	36437-37-3 (UV-350)	Industrial Cosmetics and sunscreens 1-10 tonne registered substance (ECHA) SVHC now requiring authorisation before it is used (Annex XIV of REACH).	Under assessment as very Persistent, very Bioaccumulative (vPvB) It may cause long lasting harmful effects to aquatic life and may cause damage to organs through prolonged or repeated exposure	PNECfw 0.01342 µg/L (predicted QSAR Norman database) $PNEC_{sed}$ 0.77 mg/kg dw (predicted QSAR Norman database) $PNEC_{biota,sec\ pois}$ 4.05 mg/kg ww (predicted QSAR Norman database)	UPLC-MS/MS (MLOQ) freshwater water 0.05-1.5 ng/L, sediment 0.01-0.2 ng/g (dry weight) and biota 0.004-1.35 ng/g (lipid weight). (Lu et al. 2016)
	2440-22-4 (UV-P)	This substance is registered under the REACH Regulation and is manufactured in and / or imported to the European Economic Area, at ≥ 1 000 to < 10 000 tonnes per annum. Industrial UV absorber in a wide variety of polymers, plastics, elastomers, adhesives, polycarbonates, polyurethanes, and some cellulose esters and epoxy (ECHA). Substance included in the Community Rolling Action Plan (CoRAP).	Under assessment as Persistent, Bioaccumulative and Toxic (PBT list).	PNECfw 260 ng/L (ECHA) PNECfw 260 ng/L (NICNAS, 2017) PNECfw 0.53413 µg/L (predicted QSAR Norman database) PNECsed 36.25 µg/kg sediment dw (predicted QSAR Norman database) PNECsed 136 µg/kg sediment dw (ECHA) $PNEC_{biota,sec\ pois}$ No potential for bioaccumulation (ECHA) $PNEC_{biota,sec\ pois}$ 17.25 µg/kg ww (predicted QSAR Norman database)	LC/LC-MS/MS freshwater LOD 0.08 ng/L; sediment LOD 0.3 µg/g DW; biota fish LOD 0.3 µg/g DW. (Brorström-Lundén et al., 2011) HS-SPME followed by GC–MS/MS; freshwater LOQ 0.5 ng/ml (Carpinteiro et al 2010). GC-MS/MS sediments LOQ 15 ng/g. (Carpinteiro et al. 2012). On-line SPE-UPLC-MS/MS; Coastal marine water LOD 0.9 ng/L and LOQ 3 ng/L. (Montesdeoca-Esponda et al. 2012) MAE-SPE-UHPLC-MS/MS; marine sediments LOD 55.1 ng/kg LOQ 183 ng/kg.

Name	**CAS No**	**Use /Status**	**Hazard properties**	**PNEC water (µg/L)**	**Available Analytical Method (LOQ (µg/L))**
					Montesdeoca-Esponda et al. (2013)
Diflufenican	83164-33-4	PPP Herbicide Approved Expiration 31/12/2022 Candidate for substitution	2 PBT criteria (EU Pesticides Database) PT (EFSA 2007) This substance is very toxic to aquatic life and is very toxic to aquatic life with long lasting effects (ECHA)	$PNEC_{fw}$ 0.01 µg/L (INERIS, 2012) Chronic quality standard **0.01 µg/L** (Ecotoxcentre, CH 2018) 0.009 µg/L (German AA-EQS; UBA suggestion MAC: 0.06 µg/L)	LC-MS-MS LOQ: 0.05 µg/L (EFSA 2006, 2018)
Azoxystrobin	131860-33-8	PPP and Biocide Fungicide Approved as PPP Expiration 31/12/2024 This substance is approved for use as a biocide in the EEA and/or Switzerland, for: preservation films, preservation of fibres, leather, rubber, or polymers, preservation for construction materials. Expiration 31/10/2025	PT, vP (ECHA/BPC/168/2017) It is very toxic to aquatic life and is very toxic to aquatic life with long lasting effects.	PNECfw 0.95 µg/L (INERIS, 2011) Chronic quality standard **0.2 µg/L** (Ecotoxcentre, CH 2016)	LOD: 0.018 µg/l (DK) GS/MS LOQ: 0.1 µg/L (UK, 2017 2017 evaluation dossier)
Fipronil	120068-37-3	Biocide Insecticide Not approved as PPP Expiration 30/09/2017 Candidate for substitution This substance is approved for use as a biocide in the EEA and/or Switzerland, for: controlling insects, ants, etc.. Expiration 30/09/223 Veterinary use	P, vP and T It is very toxic to aquatic life with long lasting effects	PNECfw 0.012 µg/L (Assessment report, 2011) Chronic quality standard **0.00077 µg/L** (Ecotoxcentre, CH 2021) 0.00007 µg/L (RIVM, 2007; Margriet Beek, 2008) 0.019 µg/L (BASF DocID 2018/70005257) $PNEC_{sed}$ 3.0210^{-2} µg/Kg (Assessment report, 2011) 0.73 µg/kg dry weight (BASF DocID 2018/70005257)	HPLC-MS/MS LOQ = 0.05 ng/L (Li et al. 2019) LC-MS/MS: 0.0033 µg/L (UFZ KGM 2019)

Name	**CAS No**	**Use /Status**	**Hazard properties**	**PNEC water (µg/L)**	**Available Analytical Method (LOQ (µg/L))**
Oxypurinol (Allopurinol)	2465-59-0 315-30-0	Pharmaceutical metabolite Gout	PT (allopurinol) (suspected Janusinfo, SE)	No information in FASS, SE Allopurinol: 20.6 µg/l (PNEC-predicted, NORMAN) Oxypurinol: 14 µg/L (AA-EQS, UBA, 2020) 57.6 µg/L (PNEC-predicted, NORMAN)	LC-MS/MS-analysis LOQ surface water = 5 ng/L (allopurinol) 25 ng/L (oxypurinol) (Funke et al 2015)
Clindamycin	18323-44-9	Pharmaceuticals Antibiotic Human Lincosamides	Suspected PT There is broad agreement in that a majority of data submitters agree this substance is Toxic to Reproduction (66.67% of REACH registrations) Risk cannot be excluded (Janusinfo SE)	$PNEC_{fw}$ 0.1 µg/L (PNEC-ENV; AMR Industry Alliance) $PNEC_{fw}$ 1 µg/L (PNEC-MIC; AMR Industry Alliance) **0.044 µg/L** (AA-QS, UBA, 2020)	LC-MS/MS (0.01 µg/L) (Oertel et al 2014) UPLC-MS/MS (Rodriguez-Mozaz et al. 2020) MQL 25.59 ng/L UPLC-MS/MS LOQ 3.4 ng/L (Sanseverino et al 2022)
Metformin	657-24-9	Pharmaceuticals Antidiabetic	PT (suspected. Janusinfo, SE) It is slowly degraded in the environment, has low potential for bioaccumulation and has moderate chronic toxicity (Janusinfo, SE) Suspected ED (UBA, 2020)	EQS **156** µg/L (Swiss ECOTOX centre) 5 µg/L (AA-QSfreshwater, eco, UBA, 2020) $PNEC_{fw}$ 10 µg/L (PNEC Astra-Zeneca) $PNEC_{fw}$ 1030 µg/L (Fass, Janusinfo, SE)	SPE-LC-MS/MS 0.0005 µg/L (Papageorgiou et al., 2019) HILIC-ESI-MS/MS detection 0.005 µg/L (UBA, 2019) SPE-UHPLC-MS/MS (0.00024 µg/L) (Ek Henning 2020) SPE-LC-MS/MS Metformin (0.017 µg/L) Guanylurea (0.028 µg/L) (Kosma et al. 2016)
Gabapentin	60142-96-3	Pharmaceuticals antiepileptic	R(suspected, ECHA)	Not available, risk cannot be excluded (Janusinfo, Fass, SE)	HPLC-MS/MS LOQ = 5 ng/L (Fonseca et al. 2020)

Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method (LOQ (µg/L))
				1 mg/L (AA-QS, UBA, 2020) 10 µg/L (JD-UQN proposal, NORMAN)	
Propranolol	525-66-6	Pharmaceuticals Beta-blocker used for the treatment of hypertension, angina, certain types of anxiety, and the prevention of migraine	It is degraded in the environment, has low potential for bioaccumulation and it has very high chronic toxicity (Janusinfo, SE)	PNECfw 0.23 µg/L (Astra-Zeneca) 0.23 µg/L (Fass, SE) 0.411 µg/L (PNEC-chronic, NORMAN) 0.1 µg/L (AA-QS, UBA, 2020)	LC-MS/MS LOQ = 0.0072 ng/L (Roveri et al. 2021)
Dipyridamole	58-32-2	Pharmaceuticals	PT (suspected, Janusinfo SE)	0.00534 µg/L (PNEC-predicted, NORMAN)	
Rodenticides:	Bromadiolone 28772-56-7	Biocides for controlling rodents Rodenticide Not approved as PPP Expiration 31/05/2021 Candidate for substitution This substance is approved for use as a biocide in the EEA and/or Switzerland, for: controlling rodents. (ECHA)	PBT Toxic to Reproduction (R) It is very toxic to aquatic life with long lasting effects	PNECfw 0.017-0.38 µg/L (SE, AR 2010) $PNEC_{sed}$ 0.83 mg/kg ww (SE AR, 2010) $PNEC_{biota}$ 0.0013-0.0000056 mg/kg bw/day (SE AR, 2010)	LC-MS/MS 0.05-0.5 µg/L
	Brodifacoum 56073-10-0	Biocides for controlling rodents Rodenticide Not approved as PPP This substance is approved for use as a biocide in the EEA and/or Switzerland, for: controlling rodents Biocides for controlling rodents Rodenticide Not approved as PPP Expiration 30/12/2019 Candidate for substitution This substance is approved for use as a biocide in the EEA and/or Switzerland,	PBT Toxic to Reproduction (R) It is very toxic to aquatic life with long lasting effects	$PNEC_{fw}$ 0.04 µg/L (IT, AR 2010) 0.001 µg/l (PNEC predicted, NORMAN) $PNEC_{biota}$ 0.2 µg/kg bw/d (birds) (IT AR, 2010) 0.01 µg/kg/bw (mammals) (IT AR, 2010)	x

Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method (LOQ (µg/L))
		for: controlling rodents.			
	Difenacoum 56073-07-5		P, vP, BT Toxic to Reproduction (R) It is very toxic to aquatic life with long lasting effects	PNECfw 0.06 µg/L (FI, AR 2009) $PNEC_{sed}$ 2.51 mg/kg ww (FI AR, 2010) PNECbiota 0.03 µg/kg bw/day (FI AR, 2010)	x

3.2.3 Substances from pillar 3

Table 5. Potential candidates identified by the JRC from scientific literature. The table shows for each candidate substance the name of the substance, CAS number, use and status, hazard properties, PNEC value (selected values in bold), available analytical method and limit of quantification. Abbreviations, dw: dry weight; ww: wet weight; lw: lipid weight; AF: assessment factor; PNEC: predicted no effect concentration; LOQ: limit of quantification; LOD: limit of detection; PPP: plant protection product; P: persistent; B: bioaccumulative; T: toxic; M: mutagenic; C: carcinogenic; R: toxic to reproduction; ED: endocrine disruptor; AMR: antimicrobial resistance; SVHC. Substance of very high concern.

Group	Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method
Antibiotics	Cefalexin	15686-71-2	Human and veterinary medicine Antibiotic Cephalosporins Authorised	AMR	PNECfw **0.08 µg/L** (PNEC-ENV; AMR Industry Alliance) 4 µg/L (PNEC-MIC; AMR Industry Alliance)	Ultra-high-performance-ESI-(QqLIT) MS/MS analysis (Gros et al 2013) MQL = 8.47 ng/L (river water) UPLC-MS/MS (Rodriguez- Mozaz et al. 2020) MQL 25.64 ng/L
	Ofloxacin	82419-36-1	Human medicine Antibiotic Fluoroquinolones	AMR Hazard 9* P 3 B 3* T 3 Risk See below	PNECfw **0.026 µg/L** (PNEC-ENV;	Ultra-high-performance-ESI-(QqLIT) MS/MS

Group	Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method
			Authorised		RIVM, 2011) 10 µg/L (PNEC-ENV; AMR Industry Alliance) 0.5 µg/L (PNEC-MIC; AMR Industry Alliance)	analysis (Gros et al. 2013) MQL = 2.56 ng/L (river water) UPLC-MS/MS (Rodriguez- Mozaz et al. 2020) MQL 34.32 ng/L UPLC-MS/MS (Sanseverino et al 2022) LOQ 20.5 ng/L
Pharmaceuticals	Irbesartan	138402-11-6	Human medicine Blood pressure Angiotensin II	Slowly degraded in the environment, high potential for bioconcentration in biota and low toxic chronic toxicity (Janusinfo, SE)	Chronic quality standard 700 µg/L (Ecotoxcentre, CH 2013)	HPLC-MS/MS LOQ = 5 ng/L (Fonseca et al. 2020)
	Midazolam	59467-70-8	Human medicine Benzodiazepines	This substance is toxic to aquatic life with long lasting effects (ECHA)	No PNEC in Fass 0.115 µg/L (PNEC-predicted, NORMAN)	LC-MS/MS LOQ 0.0059 ng/L (Roveri et al. 2021)
Cytostatic drugs	Cyclophosphamide	50-18-0	Cytostatic drugs Chemotherapy Anticancer	C, a majority of data submitters agree this substance is Carcinogenic M, a majority of data submitters agree this substance is Mutagenic R, a majority of data submitters agree this substance is Toxic to Reproduction (ECHA)	Not available in FASS, SE 57.6 µg/L (PNEC-predicted, NORMAN)	
	Daunorubicin	20830-81-3	Cytostatic drugs Chemotherapy		Not available in FASS, SE	

Group	Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method
	Doxorubicin	23214-92-8	Anticancer Cytostatic drugs Chemotherapy Anticancer	C, a majority of data submitters agree this substance is Carcinogenic	Not available in FASS, SE	
	Fluorouracil	51-21-8	Cytostatic drugs Chemotherapy Anticancer	M, a majority of data submitters agree this substance is Mutagenic R, a majority of data submitters agree this substance is Toxic to Reproduction	Not available in FASS, SE 58.5 µg/L (PNEC-predicted, NORMAN)	
	Mycophenolic acid	24280-93-1	Cytostatic drugs Chemotherapy Anticancer	R, a majority of data submitters agree this substance is Toxic to Reproduction	PNECfw 132.0 ng/L (FASS SE) 2.83 µg/L (PNEC-predicted, NORMAN)	
Illicit drugs	Cocaine and metabolite Benzoylecgonine	50-36-2 519-09-5	Illicit drug	T (COC)	COC PNECfw 2.28 µg/L (Sanderson et al. 2004, Mendoza et al. 2014) 2.28 µg/L (Lopez-Garcia et al. 2021) PNEC$_{sed}$ 3.65 ng/g (Lopez-Garcia et al 2021) BE PNECfw 6810 µg/L (ECOSAR, Mendoza et al. 2014)	LC-MS/MS freshwater LOD 0.02 ng/L (Mastroianni et al. 2016) Sediment LOQ 0.16 ng/g dw (Lopez-Garcia, 2021)

Group	Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method
					2.33 µg/L (Lopez-Garcia et al. 2021) PNECsed 373 ng/g (Lopez-Garcia et al. 2021)	
	Methamphetamine 3,4-methylene dioxymethamphetamine (MDMA) Ephedrine	537-46-2 4846-07-5 (in Nicola's database) 42542-10-9 321-97-1	Illicit drug		MA PNECfw 1.97 µg/L (ECOSAR, Mendoza et al. 2014) 9.74 µg/L (Lopez-Garcia et al. 2021) MA sediment 15.57 ng/g (Lopez-Garcia et al. 2021) MDMA PNECfw 0.216 µg/L (ECOSAR, Mendoza et al. 2014) 47.60 µg/L (Lopez-Garcia et al. 2021) MDMA sediment 76.11 ng/g (Lopez-Garcia et al. 2021) EPH PNECfw 3.62 µg/L (Sanderson et al.	MA LC-MS/MS freshwater LOD 0.05 ng/L (Mastroianni et al. 2016) Sediment LOQ 0.03 ng/g dw (Lopez-Garcia, 2021) MDMA LC-MS/MS freshwater LOD 0.10 ng/L (Mastroianni et al. 2016) Sediment LOQ 0.06 ng/g dw (Lopez-Garcia, 2021) EPH LC-MS/MS freshwater LOD 0.16 ng/L (Mastroianni et al. 2016) Sediment LOQ 0.21

Group	Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method
					2004, Mendoza et al. 2014) 69.90 µg/L (Lopez-Garcia et al. 2021) EPH sediment 111.77 ng/g (Lopez-Garcia et al. 2021)	ng/g dw (Lopez-Garcia, 2021)
	Cannabinol Tetrahydrocannabinol	521-35-7 1972-08-3	Illicit drug	THC T, Potentially B, C and M under examination	CBN PNECfw 0.2 µg/L (Thomas 1975, Mendoza et al. 2014) 0.08 µg/L (Lopez-Garcia et al. 2021) CBN sediment 0.13 ng/g (Lopez-Garcia et al. 2021) THC PNECfw 0.07 µg/L (Lopez-Garcia et al. 2021) THC sediment 0.12 ng/g (Lopez-Garcia et al. 2021)	CBN LC-MS/MS freshwater LOD 2.72 ng/L (Mastroianni et al. 2016) Sediment LOQ 13 ng/g dw (Lopez-Garcia, 2021) THC LC-MS/MS freshwater LOD 3.55 ng/L (Mastroianni et al. 2016) Sediment LOQ 13 ng/g dw (Lopez-Garcia, 2021)
PPP and biocides	Metazachlor and metabolites	67129-08-2	PPP Herbicide Approved as PPP Herbicide Expiration 31/07/2022	It is very toxic to aquatic life with long lasting effects, is suspected of causing cancer	Missing PNEC value 0.08 µg/L (MPC fw, eco RIVM, 2013) 0.02 µg/L (AA-QSwater,	LC-MS/MS 0.0017 µg/L (LOQ) (UFZ KGM 2019, Halbach et al 2021)

Group	Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method
					eco INERIS, 2011 and NORMAN) UBA RAK 1.67 µg/L DE EQS: 0.4 µg/L	
Sunscreen agents	Avobenzone	70356-09-1	Full-spectrum ultraviolet A (UVA) blocker, and constitutes one of the most widely used UV filters in cosmetic products worldwide (CoRAP 2017). This substance has a very high tonnage between 1.000 and 10.000 tpa. Environmental exposure of the substance is expected from wide dispersive uses (ECHA CoRAP 2017). In cosmetic products, the ingredient avobenzone is currently regulated as a UV-filter in sunscreen products in a concentration, in ready for use preparation, up to 5 % (Annex VI, 2020).	Ahn and colleagues (Ahn et al. 2019) suggested that avobenzone functions as a metabolic disrupting obesogen. Under assessment as Persistent, Bioaccumulative and Toxic (PBT list) and very Persistent, very Bioaccumulative (vPvB)	PNECfw 27 µg/L(ECHA) **PNECfw 3 µg/L** (QSAR, SE 2011) PNECfw 0.12255 µg/L (Norman database) PNECsed 11.96 mg/kg sediment dw (ECHA) $PNEC_{biota,\ sec\ pois}$ 68.04 mg/kg fish (ECHA) $PNEC_{biota,\ hh}$ 2.25 mg/kg bw/day (ECHA)	Freshwater and Marine water: LC-MS/MS) with positive electrospray ionisation (ESI) 0.0125 µg/L (Bratkovics and Sapozhnikova 2011). Fish tissue analysis: Gel permeation chromatography (GPC) GC-MS analysis (Balmer et al. 2004).
	Oxybenzone	131-57-7	UV-filter in sunscreens It is manufactured and/or imported in the European Economic Area in 100 - 1 000 tonnes per year. This substance is used by consumers, in articles, by professional workers (widespread uses), in formulation or re-packing and at industrial sites (ECHA's InfoCard, 2020): This substance is used in cosmetics and	This substance is currently undergoing an endocrine disruptor (ED) assessment under REACH. Furthermore, according to the classification provided by companies to ECHA in REACH registrations this substance is very toxic to aquatic life and is toxic to	**PNECfw 670 ng/L** Marine water PNECfw 670 ng/L (ECHA) PNECfw 1.54 µg/L (model	Freshwater and Marine water: LC-MS/MS with positive electrospray ionisation (ESI) 0.5 ng/l (Bratkovics and Sapozhnikova 2011). Biota

Group	Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method
			personal care products, coating products, fillers, putties, plasters, modelling clay and finger paints. In cosmetic products, the ingredient Benzophenone-3 (CAS No 131-57-7, EC No 205-031-5) with the chemical names Oxybenzone, 2-Hydroxy-4-methoxybenzone, (2-Hydroxy-4-methoxyphenyl) phenyl methanone and 2-Benzoyl-5-methoxyphenol is currently regulated as a UV-filter in sunscreen products in a concentration, in ready for use preparation, up to 6 % (Annex VI/4). Furthermore, Benzophenone-3 is also allowed in a concentration up to 0.5 % to protect product formulation in all other cosmetic products (Annex VI/4). Review of new scientific evidence is currently ongoing (SCCS, 2020).	aquatic life with long lasting effects. Under assessment as Endocrine Disrupting (ED list)	Norman database) PNECsed 66 µg/kg sediment dw (equilibrium partitioning ECHA) $PNEC_{biota,\ sec\ pois}$ not required (ECHA) $PNEC_{biota,\ hh}$ 2 mg/kg bw/day (ECHA)	GC-MS 0.013-0.06 ng/g (Balmer et al. 2004). Sediment UPLC-MS/MS with positive electrospray ionisation (ESI) 0.4 ng/g dw (Tsui et al. 2017).
	Octocrylene	6197-30-4	UV-filter used in sunscreens, and other cosmetic products. It is also used in articles of paper and plastic (MST, 2015) This substance is manufactured and/or imported in the European Economic Area in 1000 - 10 000 tonnes per year. In cosmetic products, the ingredient Octocrylene (CAS No 6197-30-4, EC No 228-250-8) with the chemical name 2-Cyano- 3,3-diphenyl acrylic acid, 2-ethylhexyl ester is currently regulated as a UV-filter in sunscreen products in a concentration up to 10 % (as acid) (Annex VI/10). The Scientific Committee on Consumer Safety (SCCS) is currently	It is currently under ECHA's evaluation as a potential PBT substance (CoRAP, 2014). It is considered as a suspected endocrine disruptor with concern for human health and the environment. Under assessment as Persistent, Bioaccumulative and Toxic (PBT)	**PNECfw 266 ng/L** PNECfw 2.75 ng/L (Norman database) PNECfw 13 ng/L (QSAR value INERIS) PNECsed 1.302 mg/kg sediment dw (equilibrium partitioning ECHA) $PNEC_{biota,\ sec\ pois}$ 71.63 mg/kg fish	Freshwater and Marine water: LC-MS/MS with positive electrospray ionisation (ESI) 25 ng/L (Bratkovics and Sapozhnikova 2011). Biota GC-MS 3-11 ng/g (Balmer et al. 2004). Sediment UPLC-MS/MS with positive electrospray ionisation (ESI) 0.09 ng/g dw (Tsui et

Group	Name	CAS No	Use /Status	Hazard properties	PNEC water (µg/L)	Available Analytical Method
			evaluating the safety of octocrylene as a UV-filter in cosmetic products up to the maximum concentration of 10% (as acid), following a call for data occurred in 2019 (SCCS 2020SCCS 2020).		(ECHA) $PNEC_{biota,\ hh}$ 0.8 mg/kg bw/day (ECHA)	al. 2017).

3.3 Rationale for the selection

This chapter includes the rationale for the selection of candidate substances fulfilling the criteria described in Section 3.1 from those listed in Section 3.2. The substances are here classified in three categories according to their hazard properties, outcome of the tentative risk assessment, availability of analytical method and PNEC value, and authorisation at EU-level:

- Priority 1 category, suitable candidates for the 4th WL (Table 6). This group includes substances that may represent a risk to the aquatic environment and for which monitoring data at EU level are insufficient or of low quality to evaluate the risk. A reliable PNEC value is available as well as sensitive analytical methods (LOQ below the PNEC) to monitor the substance in an appropriate matrix.

- Priority 2 category, almost suitable candidates for the 4th WL but for which there is lack of information on PNEC value or analytical methods. This group includes substances that may pose a risk to the aquatic environment and for which monitoring data at EU level are insufficient or of low quality to evaluate the risk. If a reliable PNEC value and/or adequately sensitive analytical method (LOQ below the PNEC) to monitor the substance in an appropriate matrix, could allow these substances to be proposed for the 4th WL (Table 7).

- Priority 3 category, candidates for further updates of the WL. This group includes good candidates that may represent a risk for the aquatic environment at EU level but for which more information is needed before including them in the WL (Table 8).

Following the first round of comments after the WG Chemicals meeting held on 10th February 2022, the list of substances most suitable for inclusion in the WL was revised compared to the original list. In addition more information from MS and stakeholders was received for substances listed in the priority 2 and 3 categories and these lists were updated accordingly. Table 6 shows substances or groups of substances identified after that February meeting as most suitable for inclusion in the WL with respective names and uses. In bold the seven substances or groups of substances recommended to WG Chemicals for inclusion in the 4th WL. They include two pesticides (azoxystrobin and fipronil), two antibiotics (clindamycin and ofloxacin), a human pharmaceutical and its transformation product (metformin and guanylurea), the group of sunscreen agents (avobenzone, octocrylene and oxybenzone) and two synthetic hormones (levonorgestrel and norethisterone). The sunscreen agents were not initially selected due to uncertainty regarding their PNEC values, but further information was received which helped make them suitable candidates. Metformin is a pharmaceutical for type 2 diabetes treatment, and many MS commented that this substance has been found in water. Since the PNEC value is available, this substance could be included in the list and it should be measured together with its degradation product guanylurea.

Table 7 (priority 2 category) lists other suitable candidates for the WL but for which some information is missing.

4-Chloroaniline and 3,4-dichloroaniline, the pyrethroids and the siloxanes were moved from priority 1 category to priority 2 category, since uncertainties were pointed out by experts following the February WG Chemicals meeting, regarding the PNEC value, analytical methods and/or monitoring matrix. For the first two groups of substances, although relevant, the experts expressed concern regarding the PNEC value and the sensitivity of the available analytical methods, respectively. In the pyrethroid group, particularly for lamba-cyhalothrin, it would be very difficult to reach the low PNEC values without an advanced analytical system.

For siloxanes, the JRC would propose postponing their inclusion until the next WL is established, mainly for two reasons. One is to wait for the outcome of the ongoing process for their restriction/ban, under REACH, which could be finalised next year. The other is to include, together with the current group, the linear siloxanes, which are now under investigation for PBT/vPvB properties. The preferable matrix would be suspended particulate matter (SPM).

Additional information was provided for some substances on PNEC value, analytical methods and monitoring data, therefore they were moved from priority 3 category to priority 2. The pharmaceuticals allopurinol (and its metabolite oxypurinol), gabapentin, gemfibrozil, irbesartan, and propranolol originally included in the priority 3 category were moved to the priority 2 category, along with the PPP metazachlor and the rodenticides (bromadiolone, bromadiolone, brodifacoum and difenacoum).

Table 8 (priority 3 category) lists other good candidates that are not further considered in this exercise due to lack of information; they will be considered in future updates of the WL. Following the comments, some substances in the priority 3 category were moved to the priority 2 category, leaving only pharmaceuticals. We need urgently to fill in the gap for the lacking information since these substances may pose a risk to aquatic organisms.

After a second round of comments received during the WG Chemicals meeting held on 4th May 2022 and the WFD Common Implementation Strategy (CIS) Strategic Coordination Group (SCG) meeting on 17th May 2022, synthetic hormones were removed from the list of most suitable candidates for the 4th WL and placed in the priority 2 category. These substances will be considered for the next WL update (2024) to allow time for refining the LOQ and validating the analytical method. Bioassays will be also considered as screening methods. Diflufenican, a herbicide used as a PPP and supported by several MS, was included in the final recommendation list instead.

The substance copper and copper oxides were listed in this report, although not as candidates for the selection but as potential candidates for the Priority Substance list. The JRC recommends establishing a group to refine the QS value. Currently, based on the PNEC value of 1 µg/L, there is a concern at EU level.

Table 6. List of most suitable WL candidate substances, fulfilling the selection criteria, modified following comments from MS and Stakeholders groups (after the WG Chemicals meetings held on 10 February. The table shows the substance/group name, CAS number and use (PPP = plant protection product). In bold, the seven substances/groups originally recommended for inclusion in the 4th WL.

Substance/group Name	CAS Number	Use
Azoxystrobin	**131860-33-8**	**Fungicide used as PPP and biocide**
Clindamycin	**18323-44-9**	**Human medicine** **Antibiotic (lincosamides)**
Fipronil	**120068-37-3**	**Insecticide** **Biocide and veterinary uses**
Metformin and its transformation product guanylurea	**657-24-9 and 141-83-3**	**Pharmaceutical** **Type 2 diabetes treatment**
Ofloxacin	**82419-36-1**	**Human medicine** **Antibiotic (fluoroquinolones)**
Sunscreen agents	**70356-09-1 (avobenzone)**	**UV filters** **Industrial and cosmetics**
	6197-30-4 (octocrylene)	
	131-57-7 (oxybenzone)	
Synthetic hormones	**797-63-7 (levonorgestrel)**	**Pharmaceutical**
	68-22-4 (norethisterone)	
Diflufenican	83164-33-4	Herbicide used as PPP
Cefalexin	15686-71-2	Human medicine Antibiotic (cephalosporins)

Free cyanide	57-12-5 (CN-); 74-90-8 (HCN)	Industrial and biocide

Table 7. List of substances assessed by the JRC as suitable candidates for the next Watch List (WL) but for which information on analytical method or PNEC value is missing. The table shows for each candidate the substance/group name, CAS number and use (PPP = plant protection product).

Substance/group Name	**CAS Number**	**Use**
Alkylphenols	4-Tert-Butylphenol, 98-54-4	Industrial products with different applications
	phenol, dodecyl-, branched, 121158-58-5	
	p-(1,1-dimethylpropyl)phenol, 80-46-6	
Allopurinol and its metabolite oxypurinol	315-30-0 and 2465-59-0	Human medicine Treatment of gout.
Chloroanilines	4-Chloroaniline, CAS 106-47-8	Industrial intermediates used in pigments, dyes, pesticides, drugs and others
	3,4-dichloroaniline, CAS 95-76-1	
Gabapentin	60142-96-3	Human medicine Antiepileptic
Gemfibrozil	25812-30-0	Human medicine Treatment of abnormal blood lipid levels
Illicit drugs	Cannabinol (521-35-7)	Illicit drugs / Pharmaceuticals
	Cocaine (50-36-2) and its metabolite benzoylecgonine (519-09-5)	
	Ephedrine (321-97-1)	
	Methamphetamine (537-46-2, 4846-07-5)	
	3,4-methylenedioxymethamphetamine (MDMA) (42542-10-9)	
	Tetrahydrocannabinol (1972-08-3)	
Irbesartan	138402-11-6	Human medicine Angiotensin II receptor blocker used to treat hypertension
Metazachlor	657-24-9	Herbicide use as PPP
Phenolbenzotriazoles	UV 320, 3846-71-7	UV-Filters
	UV 327, 3864-99-1	
	UV 328, 25973-55-1	
	UV 350, 36437-37-3	
	UV P, 2440-22-4	
Propranolol	525-66-6	Human medicine

		Beta-blocker Treatment of hypertension, angina, certain types of anxiety, and the prevention of migraine
Pyrethroids	Cyfluthrin, 68359-37-5	Insecticides used as PPP and biocides
	Esbiothrin, 260359-57-7	
	Etofenprox, 80844-07-1	
	Lambda-cyhalothrin, 91465-08-6	
Rodenticides	Brodifacoum, 56073-10-0	Rodenticides used as biocides
	Bromadiolone, 28772-56-7	
	Difenacoum, 56073-07-5	
Siloxanes	D4, 556-67-2	Industrial and cosmetic products
	D5, 541-02-6	
	D6, 540-97-6	

Table 8. List of substances assessed by the JRC as suitable candidates for the next Watch List (WL) but for which information on analytical method or PNEC value is missing. The table shows for each candidate the substance/group name, CAS number and use (PPP = plant protection product).

Substance/group Name	**CAS Number**	**Use**
Cytostatic drugs	Cyclophosphamide	Human medicines Cancer treatment Chemotherapy
	Daunorubicin	
	Doxorubicin	
	Fluorouracil	
	Mycophenolic acid, 24280-93-1	
Dipyridamole	58-32-2	Human medicine Prevention of thromboembolic events
Mebendazole	31431-39-7	Human medicine Anthelmintic
Midazolam	59467-70-8	Human medicine Benzodiazepines Anxiety treatment

The rationale and justification for the selection and classification are presented below. The substances have been grouped according to their use.

3.3.1 Industrial products

3.3.1.1 Alkylphenols

Alkylphenols are chemical substances extensively used at industrial sites for over 50 years and are of concern due to effects they may have on endocrine systems.

The three alkylphenols selected by the JRC (**4-tert-butylphenol, CAS 98-54-4; phenol, dodecyl-, branched, CAS 121158-58-5** and **p-(1,1-dimethylpropyl)phenol, CAS 80-46-6**) were suggested by MS during the revision of the report "Selection of substances for the 3rd Watch List under the Water Framework Directive" and after the WG Chemicals meeting on 15-16th January 2020 for inclusion in the 4th WL. They are registered under the REACH Regulation, officially recognised as endocrine disrupting (ED) and very toxic to aquatic life. Overall, the general toxicity data indicate that aquatic organisms appear more sensitive to the longer chain alkylphenols than the shorter chain alkylphenols. However, the longer chain alkylphenols appear to exhibit similar toxicities (Environment Agency, 2005).

Considering their toxicity and endocrine disrupting properties, emissions of alkylphenols into the environment should be minimised. At present, there is no available monitoring data for phenol, dodecyl-, branched in the ongoing prioritisation exercise while the quality of existing data is low for 4-tert-butylphenol and p-(1,1-dimethylpropyl)phenol.

4-Tert-butylphenol is used in adhesives, sealants and coating products. Release to the environment of this substance is likely to occur from indoor use (e.g. machine wash liquids/detergents, automotive care products, paints and coating or adhesives) and outdoor use in long-life materials with low release rate (e.g. metal, wooden and plastic construction, building materials).

Due to its water solubility (610 mg/L at 20°C), the release of this substance is expected primarily to the aquatic compartment. Release to air and to soil can be also expected, but to a limited extent. With a log K_{ow} of 3.29, the calculated fish bioconcentration factor (BCF) of 125 suggests a potential for bioaccumulation. However, 4-tert-butylphenol is unlikely to bioaccumulate in the food chain because it is rapidly eliminated from the organism. A PNEC of 6.4 µg/L has been selected for risk assessment, however it is provisional because an ongoing request to perform a chronic fish test may lead to changes in the aquatic PNEC (Assessment Report, 2008). In vitro and in vivo data showing the estrogenic effects of 4-tert-butylphenol, if considered in the risk assessment, could also contribute to a change in the final PNEC derivation.

Within the JRC prioritisation dataset (2014) Sc2 (inland whole water), this substance is monitored in 2 MS with 18163 samples available from 1711 sites of which only 1.4% quantified; the quality of monitoring is low and the data are not EU-representative. No data are available in the WISE (2020).

The initial risk assessment indicated that the risk this substance may pose to the aquatic environment is low (RQ<1) but since the data are not EU-representative, have low quality or are insufficient, the JRC suggests to include it in the WL aiming to collect a sufficient amount of EU-representative monitoring data of good quality to complete the risk evaluation.

Phenol, dodecyl-, branched is used at industrial sites and in manufacturing, primarily as an additive in lubricants and fuels. Release to the environment of this substance can occur from industrial use, as an intermediate step during manufacturing of another substance (use of intermediates) and in thermoplastic manufacture.

This substance is detected in the influent and effluent of sewage treatment plants, sludge, fresh and sea water, sediments as well as in biota (BauA Report, 2018). It is not readily or inherently biodegradable in the aquatic environment, and can accumulate in aquatic organisms (the measured fish BCF is 823). Phenol, dodecyl-, branched is expected to partition mainly to soil and sediment (log K_{ow} > 5) when released to the environment, where it is likely to be persistent. A BCF of 823 indicates a moderate bioaccumulation potential. Therefore, the measurement in biota was also mentioned, but sediment was indicated as matrix of choice.

There are no available monitoring data in WISE (2020) or the JRC prioritisation dataset (2014).

The initial collected information indicated that this substance may pose risk to the aquatic environment, but since there are no available monitoring data, the JRC suggests including it in the WL aiming to collect a sufficient amount of EU-representative monitoring data of good quality to assess the possible risk.

p-(1,1-Dimethylpropyl)phenol is used in polymers, perfumes and fragrances, and for the manufacture of chemicals and plastic products. Release to the environment of p-(1,1-dimethylpropyl)phenol can occur from industrial use, as an intermediate step in further manufacturing of another substance (use of intermediates) and in thermoplastic manufacture.

p-(1,1-dimethylpropyl)phenol is expected to biodegrade relatively quickly in the environment. It is fairly soluble in water, and its log K_{ow} is indicative of a moderate bioaccumulation potential in fish. The substance is expected to partition mainly to soil and sediment when released to the environment. The predicted $PNEC_{freshwater}$ is 2 µg/L, based on effects on *Oryzias latipes*, but additional long-term toxicity test for fish would be helpful for PNEC calculation. Considering that no sediment toxicity data are available, $PNEC_{sediment}$ was derived from the surface water PNEC by using equilibrium partitioning assumptions. The JRC would recommend measurement in sediment but also measurement in water could be accepted.

Within the JRC prioritisation dataset (2014) Sc2 (inland whole water), this substance is monitored in 1 MS with 1298 samples available from 106 sites. All reported samples are non-quantified and were measured with LOQ = 0.5 µg/L. The quality of monitoring is low and the data are not EU-representative. No data are available in the WISE (2020).

The initial risk assessment indicated that the risk this substance may pose to the aquatic environment is low (RQ<1) but since the data are not EU-representative, have low quality or are insufficient, the JRC suggests to include it in the WL aiming to collect a sufficient amount of EU-representative monitoring data of good quality to complete the risk evaluation.

Conclusion alkylphenols: the alkylphenols 4-tert-butylphenol, phenol, dodecyl-, branched, and p-(1,1-dimethylpropyl)phenol are suitable for inclusion in the 4th WL and listed in the priority 2 category. These substances should be monitored in sediment. The PNEC is uncertain for the first one and no sediment toxicity date are available for the others.

3.3.1.2 4-Chloroaniline and 3,4-dichloroaniline

4-Chloroaniline (CAS 106-47-8) and **3,4-dichloroaniline (CAS 95-76-1)** are industrial chemicals (aromatic amines) primarily used as chemical intermediates in the synthesis of pigments, dyes, pesticides, drugs and rubber products, as well as in laboratory chemicals. These substances are manufactured in and/or imported into the European Economic Area (EEA) for industrial use, in particular the manufacture of other substances (ECHA1). Due to their high solubility in water, they can be easily released into surface waters through runoff either as the parent substance or as transformation products and metabolites (e.g. aromatic amines can be found as degradation products and intermediates of various pesticides).

In addition to industrial products, 4-chloroaniline is formed as a metabolite of diflubenzuron. The latter is authorised for phytosanitary use for salmon farms in Norway, which is the largest supplier of fish, in particular salmon, to the European Union.

Both substances (4-chloroaniline and 3,4-dichloroaniline) are persistent. 4-Chloroaniline is classified as carcinogenic (ECHA) and 3,4-dichloroaniline is a suspected ED (INERIS 2012, DRC-11-112070-03826B). These substances are selected under criterion 1.

There are available monitoring data for both substances from the JRC prioritisation dataset (2014) and WISE (2020). The additional raw data, received or retrieved by the JRC, are described in Annex II.

4-Chloroaniline

Within the prioritisation dataset (2014) in Sc2 (inland whole water), 26925 samples are available from 5 MS (2323 sites) with only 0.8% quantified samples. The quality of data is almost acceptable but the data are not EU-representative since one MS holds about 90% of all samples. Seemingly these data could support derivation of MEC-statistics but they do not represent the current exposure because cover the period up to 2014.

Scarce recent data were found in WISE (2020), in Sc2 (inland whole water) there are 53 samples (0% quantified) from 8 sites in 1 MS (2018). LOQs = 1.5 µg/L. The data quality is low and the data are missing any EU coverage.

3,4-Dichloroaniline

Within the prioritisation dataset (2014) in Sc2 (inland whole water), 13348 samples are available from 9 MS. Only 0.7% are quantified samples and the data quality is poor since 71.5% of non-quantified samples were measured with LOQ > PNEC (lowest PNEC = 0.02 µg/L). The data are not EU-representative as 79% of all samples originate from 2 MS.

In the WISE (2020), in Sc2 (coastal water) 109 samples (0% quantified) from 1 site in 1 MS (taken in 2018) are available (LOQs = 0.05 µg/L). Data quality is low and the data are not EU-representative.

Additional raw monitoring data were received after the 22th meeting of the WFD CIS WG Chemicals held on 10th February 2022 (see Annex II for further details).

Although the quality of the available data is not good, a tentative risk assessment was carried out for both substances indicating a potential risk to the aquatic environment.

These substances were initially selected as priority 1 category but following comments from MS and Stakeholder experts, in particular regarding uncertainties on the PNEC value, the JRC decided that more information is needed before including them in the WL. For this reason, they were moved to priority 2.

Conclusion chloroanilines: 4-chloroaniline and 3,4-dichloroaniline are selected as suitable candidates for the 4th WL and listed in the priority 2 category, since uncertainties in the PNEC value were identified.

3.3.1.3 Free cyanide

Free cyanide (CAS CN- 57-12-5; CNH CAS 74-90-8) is approved for use as a biocide in the European Economic Area (EEA) for wood preservation, controlling rodents, controlling insects and ants (ECHA). Furthermore, the cyanide is used as a raw material in many products leading to the release into aquatic environments through effluents (Destanoğlu et al. 2015) as cyanide ions (Jaszczak et al. 2017). Free cyanide has been identified as the most toxic form derived from hydrogen cyanide (HCN), sodium cyanide (NaCN) and potassium cyanide (KCN). This substance was identified as a good candidate for the 1st WL (Carvalho et al. 2015), however it was not recommended due to the lack of an appropriate analytical method. In 2015, a project was launched by the stakeholder in collaboration with the Fraunhofer Institute entitled "Monitoring programme for the determination of the natural background concentrations of free cyanide in surface waters". The overall goal of this study was to validate a method to determine the natural background of free cyanide (Fraunhofer Institute, 2018). The project could successfully develop a sensitive method for the free cyanide measurements with LOQ below 0.3 µg/L.

There are available data for cyanide anion within the JRC prioritisation dataset. In Sc2 (inland dissolved fraction; see Annex II), data from 2 MS with 340 samples are available (18.5% quantified samples). The data quality is low since about 64% of non-quantified samples have LOQ/LOD ≥ PNEC (PNEC = 0.5 µg/L) and the data are not Union-representative (monitored only in 2 countries). Therefore, there is an insufficient amount of good quality and representative data for free cyanide to develop a EU-wide risk assessment for inland surface water (dissolved fraction).

Additional monitoring data, received from MS after the WG Chemicals meeting on 15-16th January 2020, have been included in the factsheet (Annex II). However, these supplementary data are insufficient to complete the risk assessment. Moreover, there are no available data for cyanide anion in coastal/transitional water (dissolved fraction).

There are also monitoring data available from WISE (2021). In Sc2 (inland surface water; dissolved fraction), there were 158 samples available (4.4% quantified) from 61 sites in 3 MS (for 2015 and 2019). For non-quantified samples, the range of LOQs is 0.002 – 0.57 µg/L. The available data are not EU-representative.

On the other hand, the available monitoring data allow making a tentative initial risk assessment which showed a risk in several MS (confirmed by risk quotients; the physical-chemical properties also indicate a potential risk). Therefore, to complete the risk evaluation, collection of more data is recommended through inclusion of free cyanide (anion) in the WL.

Conclusion free cyanide: Free cyanide is selected as a suitable candidate for the 4th WL in the priority 1 category. An analytical method is available, with a Limit of Quantification (LOQ) < 0.3 µg/L (PNEC value for freshwater is 0.5 µg/L), thus confirming sufficient sensitivity of the analytical method to reach a value below the PNEC in freshwater. Free cyanide is suitable for inclusion in the next WL to be monitored in inland surface (preferable) and coastal waters (both in dissolved fraction).

3.3.1.4 Group of phenolbenzotriazoles used as UV filters

The benzotriazoles UV 320 (CAS N. 3846-71-7), UV 327 (CAS N. 3864-99-1), UV 328 (CAS N. 25973-55-1), UV 350 (CAS N. 36437-37-3) and UV P (CAS N. 2440-22-4), were proposed by MS during the revision of the report

"Selection of substances for the 3rd Watch List under the Water Framework Directive" and after the WG Chemicals meeting on 15-16 January 2020 for inclusion in the 4th WL. Other UV filters, such as UV-234, UV-327, UV-360 and UV-928, found in SPM with similar concentrations (Wick et al., 2016), were suggested by MS following the WG Chemicals meeting held on 10 February 2022, and could be considered for the future updates of the WL.

Analytical methods are available for these substances in different matrices (water, sediment and biota) and are listed in the substances' factsheets (Annex II). Ecotoxicity data are available for the UV filters, but most of the PNEC values are based on modelling data (QSAR).

UV 320

UV 320 is used in industrial UV-protection agents as well as in adsorbents used for the manufacture of rubber and plastic products. It is a UV-stabiliser for plastics, polyurethanes and rubber, and constituent in formulations used for coating of surfaces, e.g. cars or special industrial wood coatings. It is also used in cosmetics and sunscreens (not in Europe) (ECHA, 2014). It is persistent, bioaccumulative, and toxic (PBT). It is suspected carcinogen (C).

This substance is highly hydrophobic and bioaccumulative (log K_{ow} > 5 and BCF > 100), so the recommended matrixes for its monitoring are sediment and biota (Water Framework Directive (WFD) CIS Guidance document No. 25).

There are no available monitoring data in the JRC prioritisation dataset (2014) or WISE (2020). For this reason, the JRC suggests to include it in the WL to collect a sufficient amount of EU-representative monitoring data of good quality to carry out the risk evaluation.

UV 327

UV 327 is an industrial product used in UV-protection agents for rubber and constituent in formulations used for coating of surfaces, especially for cars and special industrial wood coatings. It is a UV-stabiliser for a wide range of plastics and articles (polycarbonates, acrylic polymers, polyester (saturated and unsaturated), styrene mono- and copolymers, polyvinyl chloride, polyolefins, polyvinylbutyle, and polyurethanes). It is under assessment as very persistent, very bioaccumulative (vPvB).

It is highly hydrophobic and bioaccumulative (log K_{ow} > 5 and BCF > 100), so the recommended matrices for its monitoring are sediment and biota (EC 2010, CIS Guidance document No. 25).

There are no available monitoring data in the JRC prioritisation dataset (2014) or WISE (2020). For this reason, the JRC suggests to include it in the WL to collect a sufficient amount of EU-representative monitoring data of good quality to carry out the risk evaluation.

UV 328

UV 328 is an industrial product used in coating, air care, adhesives and sealants, lubricants and greases, plastics, polishes and waxes and washing and cleaning products (ECHA 2021).

It is persistent, bioaccumulative and toxic (PBT). This substance is under assessment as a Persistent Organic Pollutant (POP).

It is highly hydrophobic and bioaccumulative (log K_{ow} > 5 and BCF > 100), so the recommended matrices for its monitoring are sediment and biota (EC 2010, CIS Guidance document No. 25).

There are no available monitoring data in the JRC prioritisation dataset (2014) or WISE (2020). For this reason, the JRC suggests to include it in the WL to collect a sufficient amount of EU-representative monitoring data of good quality to carry out the risk evaluation.

UV 350

UV 328 is an industrial UV absorber (ECHA 2014). It is under assessment as very persistent, very bioaccumulative (vPvB).

UV 350 is highly hydrophobic and bioaccumulative (log $_{Kow}$ > 5 and BCF > 100), so the recommended matrices for its monitoring are sediment and biota (EC 2010, CIS Guidance document No. 25).

There are no available monitoring data in the JRC prioritisation dataset (2014) or WISE (2020). For this reason, the JRC suggests to include it in the WL to collect a sufficient amount of EU-representative monitoring data of good quality to carry out the risk evaluation.

UV P

UV P is an industrial UV absorber in a wide variety of polymers, plastics, elastomers, adhesives, polycarbonates, polyurethanes, and some cellulose esters and epoxides (ECHA 2017). It is under assessment as persistent, bioaccumulative and toxic (PBT).

UV P is less hydrophobic compared to the other UV filters in this group (log K_{ow} between 3 and 5 and BCF > 100), so the recommended matrices for its monitoring are water, sediment or biota (EC 2010, CIS Guidance document No. 25).

There are no available monitoring data in the JRC prioritisation dataset (2014) or WISE (2020). For this reason, the JRC suggests to include it in the WL to collect a sufficient amount of EU-representative monitoring data of good quality to carry out the risk evaluation.

Conclusion phenolbenzotriazoles: The UV filters are selected as suitable candidates for the WL, in the priority 2 category to be monitored in water, sediment, or biota. They could be included in the WL if reliable PNEC values (based on ecotoxicity data) become available.

3.3.1.5 Group of siloxanes

The siloxanes **octamethylcyclotetrasiloxane D4 (CAS N. 556-67-2)**, **decamethylcyclopentasiloxane D5 (CAS N. 541-02-6)** and **dodecamethylcyclohexasiloxane D6 (CAS N. 540-97-6)**, were proposed by MS for inclusion in the WL during the revision of the report "Selection of substances for the 3rd Watch List under the Water Framework Directive" and after the WG Chemicals meeting on 15-16th January 2020. The use of siloxane-based compounds is widespread in personal care, pharmaceutical, household and industrial products.

A study by Homem et al. (2017) indicates that D4 and D5 may be harmful tin the water compartment, and D5 and D6 in the sediment compartment showed risk quotients higher than 1.

D4

The siloxane D4 is a monomer used in the manufacture of polymeric materials and personal care products (e.g. antiperspirants, deodorants, skin care products, and as conditioners for hair care products) (ECHA). It is a SVHC. It is persistent, very persistent, bioaccumulative, very bioaccumulative and toxic (PBT, vPvB). It is suspected toxic to reproduction (R). This substance is highly hydrophobic and bioaccumulative (log K_{ow} > 5 and BCF > 100), so the recommended matrices for its monitoring are sediment and biota (EC 2010, CIS Guidance document No. 25).

There are no available monitoring data in the JRC prioritisation dataset (2014) or WISE (2020), but data obtained from the literature indicate that D4 may pose a risk to the aquatic environment. For this reason, the JRC suggests to include it in the WL to collect a sufficient amount of EU-representative monitoring data of good quality to carry out the risk evaluation.

D5

The siloxane D5 is used as an intermediate in the formation of silicone polymers, personal care products, household products and in industrial/institutional cleaning (ECHA).

It is classified as a SVHC. It is persistent, very persistent, bioaccumulative and very bioaccumulative and toxic (P, vP, B, vB). D5 does not meet the T criteria, but it is considered T as D4 may be present as an impurity (ECHA, 2015 ANNEX XV).

This substance is highly hydrophobic and bioaccumulative (log K_{ow} > 5 and BCF > 100), so the recommended matrices for its monitoring are sediment and biota (EC 2010, CIS Guidance document No. 25).

There are no available monitoring data in the JRC prioritisation dataset (2014) or WISE (2020), but data obtained from the literature indicate that D5 may pose a risk to the aquatic environment. For this reason, the JRC suggests to include it in the WL to collect a sufficient amount of EU-representative monitoring data of good quality to carry out the risk evaluation.

D6

The siloxane D6 is used as an intermediate in the formation of silicone polymers and personal care products (EA, 2009). It is classified as a SVHC). It is persistent, very persistent, bioaccumulative and very bioaccumulative

and toxic (P, vP, B, vB). D6 does not meet the T criteria, but it is considered T as D4 may be present as impurity (ECHA, 2015 ANNEX XV).

This substance is highly hydrophobic and bioaccumulative (log K_{ow} > 5 and BCF > 100), so the recommended matrices for its monitoring are sediment and biota (EC 2010, CIS Guidance document No. 25).

There are no available monitoring data in the JRC prioritisation dataset (2014) or WISE (2020). For this reason, the JRC suggests to include it in the WL to collect a sufficient amount of EU-representative monitoring data of good quality to carry out the risk evaluation.

These substances could be banned under REACH with a transitional period of several years. Their concentrations in the environment would probably decrease, however since these substances are P, vP they will still be present in the environment for a long time. One remaining issue, apart from their use as intermediates, is the presence of D4, D5 and D6 as constituents (having a function) in polymers; these uses are in some cases derogated from the existing restrictions. Then, there is the reversibility of monomers from polymers, which may also lead to exposure. For this reason, even if additional restrictions are imposed, exposure is still likely.

The JRC has listed D4, D5 and D6 but there are other siloxanes, such as the linear ones L3 (CAS N. 107-51-7), L4 (CAS N. 141-62-8) and L5 (CAS N. 141-63-9) for which PBT assessment is ongoing and that could be listed in future updates of the WL.

The JRC would propose postponing the inclusion of these substances until the next WL is established, mainly for two reasons. One is to wait for the outcome of the ongoing process for their restriction/ban, under REACH, which could be finalised next year. The other is to include, together with the current group, the linear siloxanes which are now under investigation for PBT/vPvB properties. The preferred matrix would be suspended particulate matter (SPM).

Conclusion siloxanes: The siloxanes D4, D5 and D6 were initially selected as suitable candidates for the WL in priority 1 category, to be monitored most preferably in SPM. However, after consultation, the JRC decided not to shortlist them for the 4th WL in view of their possible further restriction/ban and for the ongoing investigation for the linear siloxanes as PBT/vPvB. In case, the latter would be classified as PBT/vPvB, they could be listed for the next WL as group together with the cyclic siloxanes. Therefore, these substances were moved to priority 2 category.

3.3.1.6 Group of sunscreen agents

The sunscreen agents avobenzone (CAS 70356-09-1), octocrylene (CAS 6197-30-4) and oxybenzone (CAS 131-57-7), were identified by the JRC under criterion 3 (Stien et al. 2020). Sunscreens are widely used, a rough estimation of the annually sales of sunscreen agents in the EU (low estimation) is provided as follows: 45 million citizens in the EU (of 450 million) buy 0.2 L sunscreen a year => 9000 tonnes a year. Because of how they are used, most applied sunscreen agent washes or wears off directly – without any treatment at all - into the bathing waters. A smaller remaining part of the sunscreens are in most cases washed off when showering later in the day and this part ends up in urban wastewater treatment plants (UWWTP) where it may be removed to a greater or lesser extent.

Currently there are no available experimental data for standard long-term toxicity of these substances to fish and aquatic invertebrates, so the PNEC values for the freshwater compartment are based on modelling data. The PNEC values for the sediment compartment are derived using equilibrium partitioning (see Annex II, substance' factsheets).

Following the WG Chemicals meeting held on 10th February 2022, additional comments and information were provided for this group of substances, which helped make them suitable candidates for the 4th WL.

Avobenzone

Avobenzone is a full-spectrum ultraviolet A (UVA) blocker. It constitutes one of the most widely used UV filters in cosmetic products worldwide and is also used in plastic articles (ECHA). The maximum threshold as UV filter allowed in cosmetic products is 5% (EU Cosmetics Regulation Annex VI, Allowed UV Filters).

It is suspected persistent, bioaccumulative and toxic (PBT)/very persistent, very bioaccumulative (vPvB) (ECHA). This substance is highly hydrophobic and has the potential to bioaccumulate (log K_{ow} > 5 and BCF > 100), so the recommended matrices for its monitoring are sediment and biota (EC 2010, CIS Guidance document No. 25).

There are no available monitoring data in the JRC prioritisation dataset (2014) or WISE (2020). For this reason, the JRC suggests to include it in the WL to collect a sufficient amount of EU-representative monitoring data of good quality to carry out the risk evaluation.

Octocrylene

Octocrylene is a UV-filter used in sunscreens, cosmetics and personal care products. It is also used in paper and plastic articles (ECHA's InfoCard, 2021). The maximum threshold as UV filter allowed in cosmetic products of 10% (EU Cosmetics Regulation Annex VI, Allowed UV Filters).

Octocrylene is under assessment as persistent, bioaccumulative and toxic (PBT) (ECHA). It is highly hydrophobic and since it has potential to bioaccumulate (log K_{ow} > 5 and BCF > 100), the recommended matrices for its monitoring are sediment and biota (Water Framework Directive (WFD) CIS Guidance document No. 25 on sediment and biota monitoring (2010) and on sediment sampling, storage and extraction).

There are no available monitoring data in the JRC prioritisation dataset (2014) or WISE (2020). For this reason, the JRC suggests to include it in the WL to collect a sufficient amount of EU-representative monitoring data of good quality to carry out the risk evaluation.

Oxybenzone

Oxybenzone is a UV-filter used in sunscreens, cosmetics, personal care products and other industrial articles (ECHA). The maximum threshold as UV filter allowed in cosmetic products of 6% and no more than 0.5% to protect the product formulation (EU Cosmetics Regulation Annex VI, Allowed UV Filters).

It is under assessment as an endocrine disruptor (ED) (ECHA). It has a potential to bioaccumulate and is less hydrophobic than avobenzone and octocrylene (log K_{ow} between 3 and 5). The recommended matrices for its monitoring are water or sediment (EC 2010, CIS Guidance document No. 25).

There are no available monitoring data in the JRC prioritisation dataset (2014) or WISE (2020). Some raw data were received from one MS (see Annex II). For this reason, the JRC suggests to include it in the WL to collect a sufficient amount of EU-representative monitoring data of good quality to carry out the risk evaluation.

Conclusion sunscreen agents: The sunscreen agents, avobenzone, octocrylene and oxybenzone were not selected originally due to uncertainty regarding their PNEC values. Further information was received for these substances and the JRC could thus propose them as among the most suitable candidates for the 4th WL.

3.3.2 Pharmaceuticals

3.3.2.1 Antibiotics

Antibiotics are chemical agents that kill or inhibit the growth of microorganisms and are widely used in the treatment of bacterial diseases. They could be toxic to aquatic life and can contribute to the spread of antimicrobial resistance (AMR) even at low, sub-lethal or sub-inhibitory concentrations, representing a risk to human health (Sanseverino et al., 2018). Antibiotics are released to the environment mainly through wastewater treatment plants (WWTP) and surface runoff and their concentrations in water, considered the main reservoir, range between 0.01 to 1 µg/L (Monteiro et al. 2010, Larsson 2014, Kümmerer et al. 2003) with higher values reported for effluents of antibiotic manufacturing sites (Larsson et al. 2007). The selection of antibiotics is in line with the European One Health Action Plan against antimicrobial resistance (COM/2017/0339 final).

The antibiotics proposed by the JRC (**clindamycin, CAS 18323-44-9; cefalexin, CAS 15686-71-2;** and **ofloxacin, CAS 82419-36-1**) belong to three different classes: lincosamides, cephalosporins and fluoroquinolones, respectively. Lincosamides act by inhibiting protein synthesis through the 50S ribosomal subunit, cephalosporins inhibit the bacterial cell wall peptidoglycan synthesis, and fluoroquinolones target DNA gyrase and topoisomerase IV and inhibit their control of supercoiling within the cell which results in impaired DNA replication.

Clindamycin was suggested by MS during the revision of the report "Selection of substances for the 3rd Watch List under the Water Framework Directive" and after the WG Chemicals meeting on 15-16th January 2020 for consideration as WL candidate. Clindamycin is used for the treatment of anaerobic infections of the respiratory tract, skin and soft tissues, dental, peritonitis (Brook et al. 2005, Darley and MacGowan 2004). In case of hypersensitivity to penicillins, it is used to treat infections caused by sensitive aerobic bacteria. Clindamycin is particularly useful to treat bone and joint infections caused by Staphylococcus aureus.

Clindamycin is a semi-synthetic derivative of lincomycin, a natural antibiotic that is produced by the actinobacterium Streptomyces lincolnensis. It is used in both human and veterinary medicine. The effect is bacteriostatic to bactericidal by binding to the 23S region of the 50S ribosome subunits and thus inhibiting protein synthesis. The two main metabolites clindamycin sulfoxide (CAS No. 22431-46-5) and N-desmethylclindamycin (CAS No. 22431-45-4) are pharmacologically active (UBA, 2020).

The existing monitoring data in the JRC prioritisation dataset (2014) came from 1 MS with 436 samples (about 30% quantified). The quality of monitoring is acceptable but the data are not EU-representative. No data are available in the WISE (2020).

The tentative initial risk assessment indicated that this substance may pose risk to the aquatic environment (RQ>1), for this reason the JRC suggests to include it in the WL to collect a sufficient amount of EU-representative monitoring data of good quality to complete the risk evaluation.

Cefalexin is a first-generation cephalosporin used to treat a number of susceptible bacterial infections. No monitoring data are available for this substance in the dataset of the prioritisation exercise (2014) or in WISE (2020). However, according to literature data, it presents a potential risk to the ecosystem's health. Cefalexin was indeed identified together with ciprofloxacin and azithromycin as a marker of antibiotic pollution in a study analysing urban wastewater effluents in Portugal, Spain, Cyprus and Germany (Rodriguez-Mozaz et al. 2020). Cefalexin was selected as it could occasionally pose risk to the environment due to a risk quotient (RQ) exceeding the threshold of 0.1 (Rodriguez-Mozaz et al. 2020). Following the risk ranking criterion, cefalexin showed a high risk (RQ > 1) in a study performed in Argentina where this antibiotic was detected in river water with a maximum concentration of 0.29 µg/L (Valdés et al. 2021).

The initially collected information indicated that this substance may pose a risk to the aquatic environment, but since there are not available monitoring data, the JRC suggests to include it in the WL aiming to collect a sufficient amount of EU-representative monitoring data of good quality to assess the possible risk.

Ofloxacin is an antibacterial agent used for the treatment of bacterial infections affecting, among others, the respiratory tract, kidney, skin, soft tissue, and the urinary tract. Its maximal concentration in European inland surface water is between 2 and 5 µg/L (Sanseverino et al., 2018) and literature data show maximal concentrations in inland surface water all over the world between 0.005 and 8.8 µg/L (Sanseverino et al. 2018).

Monitoring data from 3 MS with 227 samples (69% quantified) are available in the prioritisation dataset (2014). The sensitivity of monitoring is good but generally the data are not representative for making a Union-wide risk assessment. There are no available monitoring data in WISE (2020).

The tentative initial risk assessment indicated that this substance may pose a risk to the aquatic environment (RQ>1). For this reason, the JRC suggests to include it in the WL to collect a sufficient amount of EU-representative monitoring data of good quality to complete the risk evaluation.

The proposed antibiotics can be monitored using the same analytical method (UPLC-MS/MS) with limits of quantification ranging from 0.00256 and 0.03432 µg/L, depending on the substance.

For each antibiotic proposed by the JRC, both PNEC and PNEC-MIC (Predicted No-Effect Concentration - Minimum Inhibitory Concentrations) have been collected in order to determine ecotoxicological and resistance selection. Indeed, the Environmental Risk Assessment (ERA) for antibiotics is only based on ecotoxicological tests and PNEC-MIC represents the only derivation of PNEC for antibiotics that addresses the resistance. For its derivation, the MIC is extracted from literature data and an assessment factor of 10 should be applied as described by Bengtsson-Palme and Larsson (2016), taking into account that the minimum antibiotic selective concentration must be lower than the inhibitory concentration. Moreover, considering that the resistance gene transfer is the main driver for the evolution of multidrug resistance in bacteria, measurement of resistance genes by quantitative polymerase chain reaction (qPCR) and sequencing methods could be adopted as an endpoint for the evaluation in the risk assessment, as proposed in the 3rd WL Report by the JRC (Gomez Cortes et al. 2020).

Conclusion antibiotics: The antibiotics clindamycin, cefalexin and ofloxacin are listed as among the most suitable candidates for the WL. Following MS and Stakeholders comments, the JRC proposes clindamycin and ofloxacin for the 4th WL.

3.3.2.2 Cytostatic drugs

As anticancer home treatment via oral chemotherapy has been developed (Besse et al. 2012), household discharge became an important source of cytostatic drugs in the aquatic environment (Besse et al. 2012, Zhang et al. 2013). Up to 7.5% of the overall amount of released cytostatics has been quantified in the hospital effluent, meaning that the remaining part is excreted into household toilets (Ort et al. 2010). Drug manufacturing plants and their effluents constitute another source of cytostatic drugs, but it remains uncertain whether the discharged quantities are significant compared with those released to the environment through human excretion (Lenz et al. 2007, Mahnik et al. 2006, Zhang et al. 2013).

Advanced treatment technologies employed at WWTPs are unable to entirely retain cytostatic drugs within the treatment line (Balcerzak and Rezka 2014). For example, in activated sludge incubation experiments, no degradation of cyclophosphamide and its related compound ifosfamide was observed within 24h at concentrations of ~1×10−4 mg/L (Buerge et al. 2006), their aerobic biodegradation reached 38% after 3 days and 65% after 4 days, while anaerobic biodegradation accounted for < 60% after 50 days (Balcerzak and Rezka 2014). Additionally, the drugs could maintain their function even for years (O'Keefe 2011).

Chemico-physical parameters of cytostatic drugs determine their levels in water environments. A great number of these molecules are hydrophilic with K_{ow} < 2 or even negative values for some of them (e.g. cyclophosphamide K_{ow} 0.63, ifosfamide K_{ow} 0.86). In sewage sludge, cyclophosphamide and ifosfamide were detected at < 2 × 10−5 mg/g, while their concentrations per litre in a WWTP influent were up to 103 times higher (Besse et al. 2012, Buerge et al. 2006, Popowicz and Koszelnik 2015, Zhang et al. 2013). In contrast, water solubility of cytostatic drugs varies widely, from insoluble compounds such as methotrexate and pemetrexed, up to highly soluble molecules with values of 104 and 105 mg/L for platinum cytotoxic drugs, cyclophosphamide, 5-fluorouracil, gemcitabine, temozolomide, capecitabine or cytarabine. The combination of low log K_{ow} and a high water solubility results in an elevated mobility of numerous cytotoxic drugs in the aquatic environment, including cisplatin, carboplatin and oxaliplatin (Ghafuria et al. 2017 and 2018). On the other hand, the bioconcentration factor (BCF) indicating the risk of biomagnification in aquatic organisms is low for most cytotoxic drugs (from 1 to 4 for all alkylating agents, antimetabolites and cytotoxic antibiotics) (Jureczko and Kalka 2020), although high values have been reported for some of them (e.g. BCF 827 for tamoxifen and bicalutamide, BCF 2535 for lapatinib, BCF 7649 for mitotane, or extremely high BCF 13783 for estramustine) (Kosjek and Heath 2011, Zhang et al. 2013).

The aforementioned parameters and the chemical structure of cytostatic compounds determine their behaviour and mode of action (MoA) which could be a basis for a grouping approach used in monitoring. Currently, PNECs are available for few substances based on QSAR modelling.

Some monitoring data are available in the JRC prioritisation dataset (2014) only for cyclophosphamide (no data were found in WISE (2020) for the cytostatic drugs). In Sc2 (inland whole water), cyclophosphamide is monitored in 3 MS with 763 samples available from 153 sites of which only 1.2% are quantified. About 86% of non-quantified samples were measured with LOQ = 0.001 µg/L (median = 0.0005 µg/L; MEC(P95) = 0.005 µg/L). The data are not EU-representative.

Conclusion cytostatic drugs: These substances are listed in the priority 3 category due to the lack of reliable PNECs but the JRC considers them substances of concern

3.3.2.3 Illicit drugs

Illicit drugs make part of pharmaceutically active compounds used for therapeutic purposes. They are released to the water environment from WWTPs collecting wastewaters from several sources such as manufacturing and clinical sites, through landfill leachates, due to transformation of other compounds, and to a minor extent from a natural production and excretion. Their ubiquitous presence due to continuous use, large volumes of production and incomplete removal in WWTPs has been linked to potentially hazardous effects on aquatic organisms and on humans upon consumption of contaminated drinking water (Wang et al. 2019, Fontes et al. 2020, Valdez-Carrillo et al. 2020, Davoli et al. 2019, Deng et al. 2020). Even though most illicit drugs are detected at low concentrations (ng/L to µg/L), such levels have been reported to elicit behavioural changes, immobilisation, growth inhibition, reproductive toxicity, mortality, endocrine disruption, genotoxicity and

carcinogenicity (Godoy and Kummro 2015) in nontarget biota including algae, crustaceans, molluscs and fishes (Cortez et al. 2018, Capaldo et al. 2019, Chen et al. 2019). These effects can be enhanced by a combined action of different molecules; for example, exposure of zebra mussels (Dreissena polymorpha) and zebrafish (Danio rerio) to cocaine and its metabolite benzoylecgonine resulted in genotoxicity and apoptosis (Parolini et al. 2015 and 2018).

No monitoring data are available in the JRC prioritisation dataset (2014) or in WISE (2020) for the illicit drugs considered by the JRC: cocaine, CAS 50-36-2; methamphetamine, CAS 537-46-2, 4846-07- 5; 3,4-methylenedioxymethamphetamine (MDMA), CAS 42542-10-9; ephedrine, CAS 321-97-1; cannabinol, CAS 521-35-7 and tetrahydrocannabinol, CAS 1972-08-3.

The initially collected information indicated that these substances may pose risk to the aquatic environment, but since there are no available monitoring data, the JRC suggests to include them in the WL aiming to collect a sufficient amount of EU-representative monitoring data of good quality to assess the possible risk. PNEC values for these substances are provisional and ecotoxicological data should be collected for a reliable PNEC calculation. The illicit drugs proposed by the JRC can be monitored using the same analytical method (LC-MS/MS).

The most commonly detected illicit drugs are hydrophilic with low K_{ow} up to values slightly exceeding 2, although some are rather hydrophobic (e.g. estimated cannabinol K_{ow} 7.23, tetrahydrocannabinol K_{ow} 6.97) (Mastroianni et al. 2016). When considering water solubility, a range of different values have been obtained: from extremely low solubility for cannabinol (estimated 0.0021) to 2800 for tetrahydrocannabinol and over 104 for ephedrine (Mastroianni et al. 2016). These parameters show that some illicit drugs will be available in water, other molecules characterised by hydrophobicity and low water solubility will be likely to bioaccumulate in aquatic biota or adhere to the organic matter without being detected at realistic levels in the water compartment (cannabinol BCF 31100).

Despite it being troublesome to identify the sources of illicit drugs, standardised approaches for their monitoring in water environments have been developed (EMCDDA 2013, Sulej-Suchomska et al. 2020, Hahn et al. 2021, Genc et al. 2021).

Illicit drugs were not supported by the majority of the MS experts that sent their comments after the CIS WG Chemicals meeting held in February 2022. However these substances are present in the aquatic environment and may pose a risk to the aquatic organisms. Some MS have included them in their monitoring programmes but there is no information on their presence or concentrations at EU level. In the last years, an increase of synthetic molecules used as illicit drugs has been observed. In January 2022, the Commission proposed a stronger mandate for the EU Drugs Agency as the illicit market proliferates[1]. All these substances will be released into water and it would be easier to protect the health of aquatic organisms and humans from the indirect effects of their use if their presence and concentrations at EU level could be monitored and mapped.

Conclusion illicit drugs: The JRC considers illicit drugs as suitable candidates for the WL with priority 2

3.3.2.4 Metformin and its transformation product guanylurea

Metformin (CAS 657-24-9) was suggested by MS for inclusion in the WL during the revision of the report "Selection of substances for the 3rd Watch List under the Water Framework Directive" after the WG Chemicals meeting on 15-16th January 2020. This substance was initially listed in the priority 3 category for the 4th WL but after comments received following the WG Chemicals in February 2022 the JRC decided to shortlist it in the priority 1 category together with its transformation product guanylurea (CAS 141-83-3).

Metformin is a human medicine widely used alone or in combination with other medicines for the treatment of type 2 diabetes. Medicines containing metformin have been authorised nationally in the EU since the 1960s. Recent studies indicated estrogenic effects of metformin at environmentally relevant concentrations (UBA 2020).

Many MS commented that this substance has been found in water. Since the PNEC value is available, this substance could be included in the list and should be measured together with its degradation product guanylurea.

[1] https://ec.europa.eu/commission/presscorner/detail/en/IP_22_302

There are available monitoring data for both substances in the JRC prioritisation exercise (2014).

- Regarding metformin, 2090 samples from 2 MS (103 sites) are available in Sc2 (inland surface water). About 97% of all samples are quantified. The sensitivity of monitoring seems good, although data are insufficient and not EU-representative.
- For guanylurea, 106 samples from 2 MS (5 sites) are available in Sc2 (inland surface water). About 96% of all samples are quantified. The sensitivity of monitoring appears good but data are insufficient and not EU-representative.

No data were found in WISE (2020).

Some additional disaggregated recent data for metformin were received from three MS (see Annex II). To complete the risk evaluation, it is preferable to collect a sufficient amount of EU-representative monitoring data of a good quality.

Conclusion metformin: Metformin and its transformation product guanylurea have been identified as among the most suitable candidates for inclusion in the 4th WL to be monitored in inland surface waters.

3.3.2.5 Synthetic hormones

Levonorgestrel (CAS 797-63-7) and **norethisterone (CAS 68-22-4)**, also known as norethindrone, are synthetic progestational hormones belonging to the 19-nortestosterone-derived class of progestins. The first was suggested by MS for inclusion in the WL during the revision of the report "Selection of substances for the 3rd Watch List under the Water Framework Directive" after the WG Chemicals meeting on 15-16th January 2020, while the latter was identified by the JRC in the previous update of the WL but not selected for the 3rd WL.

Synthetic progestins mimic the effects of the natural hormone progesterone, which is involved in regulating the menstrual cycle, pregnancy, and embryogenesis in humans and other species. In mammals, they are known to interact not only with the progesterone receptor (PR) but also with other steroid hormone receptors such as the androgen, estrogen and glucocorticoid receptors (AR, ER and GR). For example, norethisterone has (anti)androgenic or (anti)estrogenic activities (Fent 2015). Levonorgestrel and norethisterone are used alone or in combination with estradiol (E2) or ethinylestradiol (EE2) in contraceptive pills, menopausal hormone replacement therapy and for the treatment of various hormonal and gynaecological disorders. When used in combination with estrogens, the content of levonorgestrel and norethisterone in the medicines is usually higher than that of E2 or EE2.

Levonorgestrel and norethisterone have been detected in the aquatic environment together with other progestins (Fent 2015). The presence of these substances in the aquatic environment raises concern due to their ability to act as endocrine disrupters (ED) by mimicking and/or disrupting the activity of endogenous progestogens, which play critical roles in modulating sexual development and maturation in fish (Vulliet 2011, Fent 2015 and Runalls 2013).

Norethisterone and levonorgestrel have been detected in surface (river) water and wastewater (Fent 2013). Both substances can be analysed in the environment by LC-MS/MS (Vuillet 2011, Avar 2015), with LOQ < PNEC which is the major limitation for hormone monitoring in the aquatic environment.

A tentative risk assessment of progestins for fish was carried out by K. Fent (Fent 2015) and the highest risk was identified for norethindrone and levonorgestrel. This study suggests that norethindrone and levonorgestrel pose a clear risk to fish reproduction at environmental concentrations. Levonorgestrel is an agonist of the progesterone receptor (PR), and norethisterone is a potent agonist of the PR. Levonorgestrel is also able to bind AR with lower affinity, while norethisterone interacts with AR and ER in a weaker manner compared to the PR.

Alternative methods such as bioassays or effect-based methods (EBM) could be used to overcome the monitoring difficulties posed by the low PNEC values. The use of EBM would provide a measure of the overall effects of substances binding to the PR receptor. There are commercially available EBM with different sensitivity that could be used as screening methods to monitor these substances in water, such as the binding assays LanthaScreen TR-FRET; Progesterone Receptor Coactivator Assay Kit, PolarScreen Progesterone Receptor Competitor Assay Kit, or the cell-based assays GeneBLAzer PR DA Assay Kit, and PR-CALUX.

Levonorgestrel is persistent (P), toxic (T), and its toxicity to reproduction is suspected (ECHA). Even if it is below the limit value for high potential to bioaccumulate, the substance binds to Sex Hormone Binding Globulin (SHBG), so it is assumed to contribute to the exceptionally high bioconcentration ability (and thus potency) observed in fish for levonorgestrel. There are no available data in the JRC prioritisation dataset (2014) and WISE (2020),

but the use of levonorgestrel (sales data Sweden 2019) has been judged to entail a high risk of environmental impact (Janusinfo, SE), and ranked with a high-risk quotient in a recently published study by Gunnarsson et al. 2019). Levonorgestrel acts through the progesterone (PR) and androgen receptors (AR) (PR agonist and weak AR agonist).

Norethisterone fulfils the persistent/very persistent (P/vP) and toxic (T) criteria and is suspected to be toxic to reproduction (ECHA). Several studies have also described androgenic effects of norethisterone in fish indicating that it activates the androgen receptors (AR) in these organisms (Paulos 2010, Ellestad 2014).

Some monitoring data are available for this substance from the JRC prioritisation exercise (2014) (only 20 samples from one MS). The data quality is good (100% quantified samples), however the amount is insufficient and not EU-representative. Considering also aggregated data received after the WG Chemicals meeting on 15-16th January 2020, the tentative initial risk assessment showed a risk in some MS. Therefore, to complete the risk evaluation, it is preferable to collect a sufficient amount of EU-representative monitoring data of a good quality. Norethisterone acts through the progesterone (PR), AR and estrogen receptors (ER) (potent PR agonist, weak AR agonist and weak ER agonist).

Conclusion synthetic hormones: Levonorgestrel and norethisterone were initially identified as among the most suitable candidates for inclusion in the 4th WL to be monitored in inland surface waters. However, they were not shortlisted since the analytical method is not sensitive enough for monitoring levonorgestrel. These substances will be considered in the following WL update (2024).

3.3.2.6 Other pharmaceuticals

The selection of pharmaceuticals for monitoring is in line with the Commission Communication on the Strategic Approach to Pharmaceuticals in the Environment (COM/2019/128 final). This section includes different types of pharmaceuticals commonly found in surface waters, ground waters and soils across the EU that have been evaluated for inclusion in the WL. It does not include antimicrobials, hormones, cytostatic and illicit drugs. The rationale for the selection of those pharmaceuticals is covered in previous sections. Additional information regarding the hazard properties, monitoring data, available PNEC value and analytical method relevant to the pharmaceuticals covered in this section is provided in Annex I of this report.

List of other pharmaceuticals:

Allopurinol (CAS 315-30-0) and its metabolite **oxypurinol (CAS 2465-59-0)** used for the treatment of gout. The mother substance and the metabolite inhibit the formation of uric acid. Oxypurinol is found in surface waters in concentrations up to 22 µg/L. With an AA-QS of 14 µg/L, negative impacts on aquatic biocenosis cannot be excluded (UBA, 2020).

The phosphodiesterase inhibitor **dipyridamole (CAS 58-32-2),** used to prevent thromboembolic events.

The antiepileptic **gabapentin (CAS 60142-96-3).**

Gemfibrozil (CAS 25812-30-0) used for the treatment of abnormal blood lipid levels.

The angiotensin II receptor blocker **irbesartan (CAS 138402-11-6),** used to treat hypertension.

The anthelmintic **mebendazole (CAS 31431-39-7).**

The benzodiazepine **midazolam (CAS 59467-70-8)** used to treat anxiety.

The beta-blocker **propranolol (CAS 525-66-6)** used for the treatment of hypertension, angina, certain types of anxiety, and the prevention of migraine.

Information regarding the PNEC values and concentration in surface water was provided by MS and Stakeholders after the meeting of WFD CIS WG Chemicals in February 2022 so the following substances were moved from the priority 3 category to the priority 2 category: allopurinol and oxypurinol, gabapentin, gemfibrozil, irbesartan, and propranolol.

Conclusion other pharmaceuticals: The pharmaceuticals listed above were identified by the JRC under criteria 1, 2 and 3. Following the additional information received after the WG Chemicals meeting (10th February

2022), the substances allopurinol and oxypurinol, gabapentin, gemfibrozil, irbesartan, and propranolol were listed in the priority 2 category.

3.3.3 Plant protection products

3.3.3.1 Azoxystrobin

The fungicide azoxystrobin (131860-33-8) was proposed by MS for inclusion in the WL during the revision of the report "Selection of substances for the 3rd Watch List under the Water Framework Directive" and after the WG Chemicals meeting on 15-16th January 2020.

This substance is approved for use as a PPP until 31/12/2024 in 27 MS (EU pesticides database), and as a biocide in the EEA and/or Switzerland for preservation of films, fibres, leather, rubber or polymers and construction materials until 31/10/2025 (ECHA). Azoxystrobin is persistent (P), very persistent (vP) and toxic (T).

Some monitoring data are available for this substance. In the JRC prioritisation (2014), 21361 samples from 8 MS (2102 sites) are available in Sc2 dataset (inland surface whole water). About 6.4% of samples are quantified. The data quality seems acceptable since only five non-quantified samples were measured with LOQ > 2*PNEC (PNEC = 0.2 µg/L). However, 2 MS are overrepresented in the dataset holding about 84.5% of all samples. . In addition, these data do not represent the current exposure in inland surface water because cover the period up to 2014.

Regarding the present situation, in the latest version of WISE dataset (2021), for Sc3=Sc2 (inland surface water; Total and Dissolved) 3677 samples (85.4% quantified) are available from 406 sites in 2 MS (period 2016 - 2018). The range of LOQs is 0.002 – 0.05 µg/l. The sensitivity of monitoring seems sufficient but the WISE data are not EU-representative. Five MS provided additional recent data for Azoxystrobin directly to the JRC (two of them are already presented in WISE data). FR dominates the additional dataset since it reported more than 130000 samples with LOQs from 0.001 to 0.1 µg/L. In three of the reporting five MS, only the maximum concentrations have exceeded the PNEC=0.2 µg/L. The additional raw data, received or retrieved by the JRC, are described in Annex II.

The tentative initial risk assessment indicated that the risk this substance may pose to the aquatic environment is not high (RQ<1), but optionally azoxystrobin could be considered for inclusion in the WL aiming to collect a satisfactory amount of EU-representative monitoring data of good quality to complete the risk evaluation at EU level.

Conclusion azoxystrobin: Azoxystrobin is recommended to be included in the 4th WL and to be monitored in inland surface waters.

3.3.3.2 Copper and copper oxides

Copper and copper oxides were included in the WL report in 2018, however they were not selected because the available monitoring data set was assumed to be of good quality and sufficient to perform the risk assessment. Below are some reflections on these substances and a conclusion regarding the recommended course of action.

Copper and copper oxides, are widely used. Recently their role in antimicrobial resistance (AMR) has been highlighted by several scientific investigations. Considering the monitoring dataset on copper in the dissolved fraction, all ionic forms seem to be captured allowing the risk assessment to be performed. In the factsheet in Annex II, all the properties and the monitoring dataset are described in detail. They are summarised below.

Copper occurs in nature in four oxidation states: elemental copper (Cu) (0) (solid metal), Cu (I) cuprous ion (Cu2O; CAS 1317-39-1), Cu (II) cupric ion (CuO; CAS 1317-38-0), and rarely Cu (III). In water, Cu (II) is the most prevalent form of copper (Kiaune and Singhasemanon 2011). Two forms of copper oxide (i.e. Cu (I) oxide and Cu (II) oxide) are approved in the European Economic Area (EEA) and/or Switzerland for use as active ingredients in PPP and biocides. Copper (I) oxide is approved as a biocide for preventing fouling, while Cu (II) oxide is approved as a biocide for wood preservation. Dicopper oxide is manufactured and/or imported in the European Economic Area at levels of 1000-10000 tonnes per year, while copper oxide is manufactured and/or imported in the European Economic Area at levels of 1000+ tonnes per year (ECHA). These substances may be washed into the aquatic environment from agricultural and urban application sites and may also enter the water when used as a biocide in antifouling paint formulations.

Besides, Cu (II) oxide is known to be on the EEA market in the nanomaterial form (ECHA). Metal nanoparticles can induce toxicity by mechanisms that are different from those of soluble ions. A Danish investigation into the environmental risk posed by engineered nanomaterials found that release patterns and hazard properties of copper nanomaterials may cause concern in the future (The Danish Environmental Protection Agency, 2015).

Cu, CuO and Cu_2O are considered toxic or very toxic to aquatic life with long-lasting effects (ECHA). Cu is also under assessment as an endocrine disruptor (ED list, ECHA). Further, copper (compounds) is categorised as candidate for substitution (CfS) due to its toxicity to and persistence in the environment (especially in surface waters, sediment and soil) (EU 2009).

Moreover, the environmental pollution caused by heavy metals such as copper can co-select for AMR (Sanseverino et al. 2018). Indeed, copper together with other heavy metals, such as zinc and silver, has been shown to drive antibiotic resistance. Consequently, it could have an environmental role in resistance development (Poole 2017, Niegowska et al. 2021).

Monitoring data for inland surface water (dissolved fraction) are available in the JRC prioritisation dataset (2014) and WISE (2020) (see Annex II). However, copper was measured and reported by MS as a total including ionic forms of Cu (Cu2O and CuO).

For Cu total inland dissolved fraction (Sc3 scenario; JRC prioritisation dataset (2014)), 69535 samples from 24 MS (4935 sites) are available, of which about 69.1% are quantified. The data quality seems acceptable due to the large amount of quantified records (see Annex II). Additionally, recent data for Cu total inland dissolved fraction (Sc3 scenario; WISE (2020)), are available for 60441 samples from 19 MS (3987 sites), of which about 79.2% are quantified. Also for this dataset, the data quality seems acceptable due to the large number of quantified records (see Annex II). Comparison with the lowest available PNEC (1 µg/L) would show exceedances in all reporting MS and an overall risk quotient based on the 95th percentile RQ>1 (7.2 according to JRC prioritisation dataset (2014) and 4.1 according to WISE (2020); see Annex II) considering together data from individual MS. If needed, the JRC could undertake an update of the existing PNEC value, possibly considering the bioavailability of Cu (actually the application of bioavailability is not needed for the ionic forms of Cu).

Conclusion copper and copper oxides: At present, copper and copper oxides should be considered as potential candidate for the PS list, and a sub-group of experts should be established to derive a provisional QS value.

3.3.3.3 Diflufenican

The herbicide **diflufenican (83164-33-4)** was proposed by MS for inclusion in the WL during the revision of the report "Selection of substances for the 3rd Watch List under the Water Framework Directive" and after the WG Chemicals meeting on 15-16th January 2020. This substance is approved for use as a PPP until 31/12/2022 in 27 MS (EU pesticides database). Diflufenican is persistent (P) and very toxic (T) to aquatic life (EU Pesticides database and ECHA).

Some monitoring data are available for this substance from the JRC prioritisation exercise (2014) and WISE (2020). In the JRC prioritisation (2014), 47162 samples from 8 MS are available in Sc2 inland whole water (8.8% quantified samples). The data quality is low with respect to the sensitivity of the applied analytical methods (only 8.2% of non-quantified samples have LOQs ≤ PNEC (0.01 µg/L)). The data are not EU-representative since 2 MS hold about 96% of all samples.

Within the WISE database (2020), 1166 samples are available in Sc2 (inland surface water; total; 28.6% quantified) from 69 sites in 3 MS (2015-2018) with the LOQs ranging from 0.004 – 0.05 µg/L. The quality of data is acceptable but the data are not EU-representative.

The tentative initial risk assessment indicated that this substance may pose a risk to the aquatic environment. For this reason, the JRC suggests to include it in the WL to collect a sufficient amount of EU-representative monitoring data of good quality to complete the risk evaluation.

Conclusion diflufenican: Diflufenican is listed among the most suitable candidates for inclusion in the 4th WL to be monitored in inland surface waters.

3.3.3.4 Fipronil

The insecticide fipronil (CAS 797-63-7) was proposed by the MS for inclusion in the WL during the revision of the report "Selection of substances for the 3rd Watch List under the Water Framework Directive" and after the WG Chemicals meeting on 15-16th January 2020.

This substance is not approved anymore as a PPP (30/09/2017), however it is approved for use as a biocide in the EEA and/or Switzerland for controlling insects, ants, etc. (the approval expires on 30/09/2023).

The substance is persistent (P), very persistent (vP) and toxic (T) with a very low chronic EQS derived by the Ecotoxcentre, CH (2021).

Some monitoring data are available for this substance from the JRC prioritisation exercise (2014). 6657 samples from 3 MS are available in Sc2 inland whole water (1% are quantified samples). The sensitivity of monitoring data quality is low and the data are not EU-representative. Additional raw data, received or retrieved by the JRC, are described in Annex II. The tentative initial risk assessment indicated that this substance could pose a risk to the aquatic environment. The JRC suggests to include it in the WL to collect a sufficient amount of EU-representative monitoring data of good quality to complete the risk evaluation.

Conclusion fipronil: Fipronil is recommended to be included in the 4th WL to be monitored in inland surface waters.

3.3.3.5 Group of pyrethroid insecticides

The pyrethroid insecticides **etofenprox (CAS 80844-07-1)**, **esbiothrin (CAS 260359-57-7)**, **cyfluthrin (CAS 68359-37-5)**, and **lambda-cyhalothrin (CAS 68359-37-5)** were proposed by MS for inclusion in the WL during the revision of the report "Selection of substances for the 3rd Watch List under the Water Framework Directive" and after the WG Chemicals meeting on 15-16th January 2020.

Pyrethroid insecticides act on the sodium channel in the nerve membranes of the invertebrate nervous system causing pronounced repetitive activity and a prolongation of the transient increase in sodium permeability of the nerve membranes. This results in continual nerve impulse transmission leads to tremors and death. These substances are used in PPP and/or biocidal products.

The preferred monitoring matrix for pyrethroid insecticides with high octanol/water partition coefficient values (log K_{ow} > 5) is sediment as recommended in the WFD CIS Guidance document No. 25 (EC 2010). However, analytical methods for monitoring these substances in water are also available and described together with those for sediment in the factsheets (Annex II).

Pyrethroids have very low PNEC values for the freshwater compartment. Following the WFD CIS WG Chemicals in February 2022, several MS were in favour of listing these substances in the 4th WL. At the same time, they expressed concern regarding the sensitivity of the available analytical methods for their monitoring in water. Particularly for lambda-cyhalothrin, it would be very difficult to reach the low PNEC values without an advanced analytical system.

Four other pyrethroids are shortlisted in the current review of the list of priority substances under the WFD and cypermethrin is an existing priority substance, suggesting that the four pyrethroids listed here are also likely to pose a risk to the environment. Consequently, it would be worth considering whether they should be covered as a group in the priority substances list (applying a cumulative approach).

Etofenprox

Etofenprox is a non-ester pyrethroid insecticide. It is approved for use as a PPP, (EU Pesticides database) and as biocide (ECHA). Etofenprox is bioaccumulative (B), very toxic (T) to aquatic life with long-lasting effects and under assessment as endocrine disrupting substance (ED) (ECHA).

Some monitoring data are available in the JRC prioritisation database (2014). In Sc2 (inland whole water), data from 3 MS (91 sites) and 1116 samples (10 quantified samples) are available, although the quality is low since LOQs of non-quantified samples are ≥ 0.02 µg/L (considerably higher than the lowest PNEC). The data are not EU- representative. The tentative initial risk assessment indicated that this substance could pose a risk to the

aquatic environment. For this reason, the JRC suggests to include it in the WL to collect a sufficient amount of EU- representative monitoring data of good quality to complete the risk evaluation.

Esbiothrin

Esbiothrin is a type I pyrethroid insecticide used for the control of mosquitoes including Culex, Aedes and other small biting flies in domestic living areas (excluding kitchens). This substance is not approved as s biocide following the biocidal product committee's (BPC) opinion adopted on 16th June 2020 (ECHA), or as a PPP (EU Pesticides database).

It is persistent (P) and toxic (T), but no monitoring data are available in the JRC prioritisation dataset (2014) or WISE (2020) to determine the risk. The JRC considers this substance a good candidate for the WL, in casethe use of the substance will be approved at EU level and that a reliable PNEC value will be available.

Cyfluthrin

Cyfluthrin is a type II pyrethroid insecticide. The intended uses of cyfluthrin-based products are to control flying and crawling insects, such as house flies, litter beetles, fleas and red mites in animal housings (spray application for use by professionals), as well as cockroaches (adults, nymphs), ants and termites indoors (ready to use spray foam for use by non-professionals in households). The spray application is done by spraying a strip on window frames and to ceilings using a low pressure Knapsack (backpack) sprayer, while the foam product is applied to cracks and crevices around skirting and door frames, supplied with a directional tube applicator (ECHA). It is not approved for use as a PPP (EU pesticides database). It is very toxic to aquatic life with long-lasting effects (ECHA).

Some monitoring data are available in the JRC prioritisation dataset (2014). 14579 samples from 5 MS are available in Sc2 inland whole water (2.3 % quantified samples). The data quality is low since LOQs of non-quantified samples are ≥ 0.005 µg/L (considerably higher than the PNEC). The data are not EU-representative since one MS holds about 88.2% of all samples. The tentative initial risk assessment indicated that this substance could pose a very high risk to the aquatic environment. The JRC suggests to include it in the WL to collect a sufficient amount of EU-representative monitoring data of good quality to complete the risk evaluation.

Lambda-cyhalothrin

Lambda-cyhalothrin is a type II pyrethroid, a quick-acting insecticide used to control a wide spectrum of agricultural crop and public health pests (in veterinary medicine) (JRC factsheet, Carvalho et al, 2016).

It is approved for use as a PPP (EU Pesticides database) and as biocide (ECHA). Lambda-cyhalothrin is bioaccumulative (B) and very toxic (T) to aquatic life (EU Pesticides database and ECHA). There are data from the priority substances prioritisation exercise (Carvalho et al, 2016). 21729 samples from 6 MS are available in Sc2 inland whole water (0.6% quantified samples). The data quality is low since LOQs of non-quantified samples are ≥ 0.002 µg/L (considerably higher than the lowest PNEC). The data are not EU-representative since one MS holds about 90.2% of all data. The tentative initial risk assessment indicated that this substance could pose a high risk to the aquatic environment. The JRC suggests to include it in the WL to collect a sufficient amount of EU- representative monitoring data of good quality to complete the risk evaluation.

Conclusion pyrethroid insecticides: Etofenprox, cyfluthrin and lambda-cyhalothrin were initially listed in the priority 1 category. After consultation with MS and Stakeholder experts, the JRC moved them to the priority 2 category, because the sensitivity of the analytical methods would be insufficient to reach the low PNEC values without an advanced analytical system. Furthermore, four pyrethroids are shortlisted in the current review of the list of priority substances under the WFD. Consequently, it would be worth considering whether they should be covered as a group in the priority substances list (applying a cumulative approach). The preferred matrix for monitoring this group of substances is sediment or SPM.

3.3.3.6 Other PPP and biocides

The biocides **bromadiolone (CAS 28772-56-7)**, **brodifacoum (CAS 56073-10-0)** and **difenacoum (CAS 56073-07-5)** approved in the EEA and/or Switzerland for controlling rodents were identified by MS for inclusion in the WL during the revision of the report "Selection of substances for the 3rd Watch List under the Water Framework Directive" and after the WG Chemicals meeting on 15-16th January 2020. These substances are PBT and have high K_{oc} and BCF values, therefore their monitoring is suggested in SPM, sediment or biota.

The herbicide metazachlor (CAS 67129-08-2) used as a PPP and its metabolites were identified by the JRC under criterion 3.

Following the WG Chemicals meeting held on 10th February 2022 additional information was provided for the aforementioned substances, therefore they were moved from the priority 3 category to the priority 2 category (Annex II, substances' factsheets).

Conclusion other PPP and biocides: The rodenticides and metazachlor were initially listed in the priority 3 category but following comments from MS and stakeholder experts, they were moved to the priority 2 category, on the basis of the information they provided such as PNEC value, analytical method and monitoring data.

4 Conclusions

In 2022, the Watch List (WL), according to Directive 2008/105/EC (Article 8b), has to be revised and, except for six substances or groups of substances included in 2020, all existing substances must be removed. Seven additional substances or groups of substances could be included in the WL update 2022.

Based on the criteria described in section 3.1 for inclusion in the next WL (2022), several substances were identified as potential candidate substances for the next WL. Following the receipt of comments and further information from MS and stakeholders in the CIS WG Chemicals, the JRC identified ten substances/groups of substances as the most suitable candidates. Among them, seven substances or groups of substances were recommended for inclusion in the 4th WL (Table 6). They were two pesticides (azoxystrobin and fipronil), two antibiotics (clindamycin and ofloxacin), the pharmaceutical for type 2 diabetes treatment (metformin), a group of sunscreen agents (avobenzone, octocrylene and oxybenzone), and two hormones. At a later stage, the two hormones were replaced by the pesticide diflufenican (Table S1). Briefly, the most suitable candidates are listed as follows, in bold the seven substances finally proposed by the JRC to be included in the 4th WL:

- **Azoxystrobin** is a fungicide approved for use as PPP and as a biocide for preservation films, preservation of fibres, leather, rubber, or polymers, and construction materials. It is persistent and toxic.

- **Clindamycin** is an antibiotic belonging to lincosamides class. It is used in human and veterinary medicines. It was identified due to its widespread use and release into water, toxicity to aquatic life and possible contribution to the spread of antimicrobial resistance (AMR), which is in line with the EU One Health Action Plan, (COM/2017/0339 final).

- **Diflufenican** is a herbicide approved for use as a PPP, until at least 31/12/2022. It is persistent and very toxic to aquatic life.

- **Fipronil** is an insecticide approved for use as a biocide in the EEA and/or Switzerland for controlling insects, ants, etc. It is also used in veterinary medicines for the control of parasites. This substance is persistent and toxic to aquatic organisms with a very low PNEC value.

- **Metformin**, and its degradation product guanylurea. Metformin is a human medicine widely used for type 2 diabetes treatment and frequently detected in water.

- **Ofloxacin** is a fluoroquinolone antibiotic identified in the context of action to address in a more holistic way the rising threat from AMR. The environment, and particularly water, has been identified as a potential reservoir of resistance whose role needs to be better understood (EU One Health Action Plan, (COM/2017/0339 final).

- **Sunscreen agents** (avobenzone, oxybenzone, octocrylene), are widely used as UV filters in cosmetics, personal care and industrial products. Most of the sunscreen agents washed or wear off directly into bathing waters, or when showering.

- Synthetic hormones (levonorgestrel and norethisterone) are synthetic progestins with endocrine disrupting (ED) properties, which act at very low concentrations and may pose a risk to aquatic organisms.

- Cefalexin is an antibiotic belonging to the class of cephalosporins used in human and veterinary medicine and it has been identified in line with the EU One Health Action Plan (COM/2017/0339 final).

- Free cyanide is one of the most toxic cyanide forms in the aquatic environment. This substance was identified as a potential risk during the priority substances prioritisation exercise (2011), but questions were raised about the form of cyanide covered by the available monitoring data. Thanks to the efforts of stakeholders, a method is now available and the selection of this substance would result in monitoring data collected across Europe. However, the potential natural background should be considered.

References

AMR Industry Alliance Antibiotic Discharge Targets. List of Predicted No-Effect Concentrations (PNECs). (2018).

Assessment Report P-TERT-BUTYLPHENOL, CAS No: 98-54-4, Summary Assessment Report, EINECS No: 202-679-0, Norway, 2008

Avar, P., Maasz, G., Takács, P., Lovas, S., Zrinyi, Z., Svigruha, R., Takátsy, A., Tóth, L. G., and Pirger, Z. (2016) HPLC-MS/MS analysis of steroid hormones in environmental water samples. Drug Test. Analysis, 8: 123– 127. Doi: 10.1002/dta.1829.

BauA Report_SUBSTANCE EVALUATION CONCLUSION as required by REACH Article 48 and EVALUATION REPORT for Phenol, dodecyl-, branched EC No 310-154-3 CAS No 121158-58-5, 2018

Balcerzak W., Rezka P. Occurrence of anti-cancer drugs in the aquatic environment and efficiency of their removal – the selected issues. Tech. Trans. Environ. Eng., 1 (2014).

Balmer, ME., Buser, H-R., Muller, M.D., Poiger, T. 2004. Occurrence of the Organic UV Filter Compounds BP-3, 4-MBC, EHMC, and OC in Wastewater, Surface Waters, and in Fish from Swiss Lakes. BUWAL Project: 3189.041.01.14. Final Report. March 2004.

BASF. (2011). BASF study summary, active substance: Fipronil (BAS 350 I), Document III Section A1 to A7 (BASF DocID 2018/70005257).

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

Besse J.P., Latour J.F., Garric J.. Anticancer drugs in surface waters. What can we say about the occurrence and environmental significance of cytotoxic, cytostatic and endocrine therapy drugs? Environ. Int., 39 (2012), pp. 73-86

Bratkovics, S., Sapozhnikova, Y. 2011. Determination of seven commonly used organic UV filters in fresh and saline waters by liquid chromatography-tandem mass spectrometry. Anal. Methods, 2011, 3, 2943. DOI: 10.1039/c1ay05390f.

Brook I, Lewis MA, Sándor GK, Jeffcoat M, Samaranayake LP, Vera Rojas J (2005). Clindamycin in dentistry: more than just effective prophylaxis for endocarditis? Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 100(5): 550–8

Börnick, H., Grischek, T. & Worch, E. Determination of aromatic amines in surface waters and comparison of their behavior in HPLC and on sediment columns. Fresenius' Journal of Analytical Chemistry 371, 607- 613, doi:10.1007/s002160101011 (2001).

Brorström-Lundén E, Remberger M, Kaj L, Hansson K, Andersson H, Haglund P, Andersson R, Liljelind P, Grabic R. (2011). Screening of benzothiazoles, benzenediamines, dicyclohexylamine and benzotriazoles 2009 1-64. IVL Report B2023. IVL Swedish Environmental Research Institute Ltd. Available on-line at: https://www.ivl.se/download/18.343dc99d14e8bb0f58b7618/1454339575630/B2023.pdf

Buerge I.J., Buser H.R., Poiger T., Müller M.D. Occurrence and fate of the cytostatic drugs cyclophosphamide and ifosfamide in wastewater and surface waters. Environ. Sci. Technol., 40 (23) (2006), pp. 7242-7250.

Carpinteiro I, Abuin B, Rodriguez I, Cela R, Ramil M. (2010). Headspace solid-phase microextraction followed by gas chromatography tandem mass spectrometry for the sensitive determination of benzotriazole UV stabilizers in water samples. Analytical and Bioanalytical Chemistry 397(2):829-839. https://doi.org/10.1007/s00216-010-3584-0

Carpinteiro, I., Abuin, B., Ramil, M., Rodriguez, I., & Cela, R. (2012). Matrix solid-phase dispersion followed by gas chromatography tandem mass spectrometry for the determination of benzotriazole UV absorbers in sediments. Analytical and bioanalytical chemistry, 402(1), 519-527. https://doi.org/10.1007/s00216-011-5386-4

Carvalho, R. N., Ceriani, L., Ippolito, A. & Lettieri, T. Development of the first Watch List under the Environmental Quality Standards Directive, EUR2714, Publications Office of the European Union, Luxembourg, doi: 10.2788/101376. (2015).

Capaldo A, Gay F, Laforgia V (2019) Changes in the gills of the European eel (*Anguilla anguilla*) after chronic

exposure to environmental cocaine concentration. Ecotoxicol Environ Saf 169:112–119. https://doi.org/10.1016/j.ecoenv.2018.11.010

Carvalho, R. N. et al. Monitoring-based exercise: second review of the priority substances list under the Water Framework Directive (https://circabc.europa.eu/w/browse/52c8d8d3-906c-48b5-a75e- 53013702b20a). (2016).

Carvalho RN, 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.

Casado, J., Brigden, K., Santillo, D. & Johnston, P. Screening of pesticides and veterinary drugs in small streams in the European Union by liquid chromatography high resolution mass spectrometry. Science of The Total Environment 670, 1204-1225, doi:https://doi.org/10.1016/j.scitotenv.2019.03.207 (2019).

CH, 2016. EQS - Vorschlag des Oekotoxzentrums für: Metformin und Haupttransformationsprodukt Guanylharnstoff

Chitescu, C. L., Kaklamanos, G., Nicolau, A. I. & Stolker, A. A. M. High sensitive multiresidue analysis of pharmaceuticals and antifungals in surface water using U-HPLC-Q-Exactive Orbitrap HRMS. Application to the Danube river basin on the Romanian territory. Science of The Total Environment 532, 501-511, doi:https://doi.org/10.1016/j.scitotenv.2015.06.010 (2015).

Cortez FS, da Silva Souza L, Guimarães LL, Almeida JE, Pusceddu FH, Maranho LA, Pereira CDS (2018) Ecotoxicological effects of losartan on the brown mussel Perna perna and its occurrence in seawater from Santos Bay (Brazil). Sci Total Environ 637-638:1363–1371. https://doi.org/10.1016/j.scitotenv.2018.05.069

Corcellas, C., Eljarrat, E. & Barceló, D. First report of pyrethroid bioaccumulation in wild river fish: A case study in Iberian river basins (Spain). Environment International 75, 110-116, doi:https://doi.org/10.1016/j.envint.2014.11.007 (2015).

Costa Dos Reis L, Vidal L & Canals A (2018) Determination of siloxanes in water samples employing graphene oxide/Fe(3) O(4) nanocomposite as sorbent for magnetic solid-phase extraction prior to GC-MS. Journal of separation science 41: 4177-4184.

The Danish Environmental Protection Agency. Ministry of Environment and Food. Environmental assessment of nanomaterial use in Denmark. Environmental project No. 1788, 2015. (2015).

Darley ES, MacGowan AP (2004). Antibiotic treatment of gram-positive bone and joint infections. J Antimicrob Chemother. 53(6): 928–35.

Destanoğlu, O., Gümüş Yılmaz, G. & Apak, R. Selective Determination of Free Cyanide in Environmental Water Matrices by Ion Chromatography with Suppressed Conductivity Detection. Journal of Liquid Chromatography & Related Technologies 38, 1537-1545, doi:10.1080/10826076.2015.1076460 (2015).

EA Environment Agency (2009) Environmental Risk Assessment Report: Octamethylcyclotetrasiloxane ISBN: 978-1-84911-031-0.

EC COM(2012) 252. Communication from the Commission to the council. The combination effect of chemicals Chemical mixtures. Brussels, 31.5.2012.EFSA (European Food Safety Authority), 2008. Opinion of the Scientific Panel on Plant Protection Products and their Residues to evaluate the suitability of existing methodologies and, if appropriate, the identification of new approaches to assess cumulative and synergistic risks from pesticides to human health with a view to set MRLs for those pesticides in the frame of Regulation (EC) 396/2005. The EFSA Journal 2008, 704, 1-85.

EFSA, 2006. Draft Assessment Report (DAR) - public version. Initial risk assessment by the rapporteur Member States United Kingdom for the existing active substance DIFLUFENICAN in the third stage (part A) of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC. March 2006.

EFSA, 2013. Scientific Opinion on the relevance of dissimilar mode of action and its appropriate application for cumulative risk assessment of pesticides residues in food. EFSA Journal, 11(12): 3472.EFSA (European Food Safety Authority). 2010. Management of left-censored data in dietary exposure assessment of chemical substances. EFSA J 8:1–96.

EFSA, 2018. Renewal Assessment Report prepared according to the Commission Regulation (EU) N° 1107/2009. Rapporteur Member State: United Kingdom, Co-Rapporteur Member State: Czech Republic

Ellestad, L. E. et al. Environmental Gestagens Activate Fathead Minnow (Pimephales promelas) Nuclear Progesterone and Androgen Receptors in Vitro. Environmental Science & Technology 48, 8179-8187, doi:10.1021/es501428u (2014).

Environment Agency. Prioritisation of Alkylphenols for Environmental Risk Assessment, 2005 Environment Agency_Environmental risk evaluation report: 4-tert-pentylphenol (CAS no. 80-46-6), (2008).

EU 2006. Risk Assessment Report 3,4-DICHLOROANILINE CAS No: 95-76-1 EINECS No: 202-448-4 RISK ASSESSMENT. EUR 22235 EN. ISSN 1018-5593 Luxembourg: Office for Official Publications of the European Communities, 2006 © European Communities, 2006.

EU 2008. Commission Implementing Decision (EU) 2018/840 of 5 June 2018 establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council and repealing Commission Implementing Decision (EU) 2015/495 (notified under document C(2018) 3362). (2018).

EU 2008. European Union Risk Assessment Report_ P-TERT-BUTYLPHENOL, 2008.

EU 2008. Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council. Official Journal of the European Union, L348/84-97, 24.12.2008. (2008).

EU 2009. Commission Directive 2009/90/EC of 31 July 2009 laying down, pursuant to Directive 2000/60/EC of the European Parliament and of the Council, technical specifications for chemical analysis and monitoring of water status. Official Journal of the European Union, L201/36, 1.8.2009. (2009).

EU 2009. Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC.

EU 2009. Directive 2009/90/EC of 31 July 2009 laying down, pursuant to Directive 2000/60/EC of the European Parliament and of the Council, technical specifications for chemical analysis and monitoring of water status, Official Journal of the European Union, L 201/36-38, 1.8.2009

EU 2013. Directive 2013/39/EU of the European Parliament and of the Council of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy. Official Journal of the European Union, L226/1-17, 24.8.2013. (2013).

EU 2015. Commission Implementing Decision (EU) 2015/495 of 20 March 2015 establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council. Official Journal of the European Union, L 78/40-42, 24.3.2015. (2015).

EU 2017. COM/2017/0339 final: Communication from the Commission to the Council and the European Parliament: A European One Health Action Plan against Antimicrobial Resistance (AMR) https://eur-lex.europa.eu/legal-content/GA/TXT/?uri=CELEX:52017DC0339. (2017).

EU 2019. COM/2019/128 final: COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL AND THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE: European Union Strategic Approach to Pharmaceuticals in the Environment (https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=COM:2019:128:FIN). (2019).

EU 2020. Commission Implementing Decision (EU) 2020/1161 of 4 August 2020 establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council (notified under document number C(2020) 5205) (2020).Fent, K. Progestins as endocrine disrupters in aquatic ecosystems: Concentrations, effects and risk assessment. Environment International 84, 115-130, doi:https://doi.org/10.1016/j.envint.2015.06.012 (2015).

Fraunhofer Institute. Monitoring program for the determination of the natural background concentrations of free cyanide in surface waters. Report on work package 4: Cyanide monitoring program. Fraunhofer Institute for Molecular Biology and Applied Ecology (IME). Division Applied Ecology, 57392 Schmallenberg, Germany. (2018).

Fonseca E, Hernández F, Ibáñez M, Rico A, Pitarch E, Bijlsma L, Occurrence and ecological risks of

pharmaceuticals in a Mediterranean river in Eastern Spain, Environment International, Volume 144, 2020, 106004, ISSN 0160-4120, https://doi.org/10.1016/j.envint.2020.106004.

Fontes MK, de Campos BG, Cortez FS, Pusceddu FH, Nobre CR, Moreno BB, Pereira CDS (2020) Mussels get higher: a study on the occurrence of cocaine and benzoylecgonine in seawater, sediment and mussels from a subtropical ecosystem (Santos Bay, Brazil). Sci Total Environ 757:143808. https://doi.org/10.1016/j.scitotenv.2020.143808.

Funke J, Prasse C, Lütke Eversloh C, Ternes TA. Oxypurinol - A novel marker for wastewater contamination of the aquatic environment. Water Res. 2015 May 1;74:257-65. doi: 10.1016/j.watres.2015.02.007. Epub 2015 Feb 18. PMID: 25753675.

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

Ghafuria Y., Yunesian M., Nabizadeh R., Mesdaghinia A., Dehghani M.H., Alimohammadi M. Platinum cytotoxic drugs in the municipal wastewater and drinking water, a validation method and health risk assessment. Hum. Ecol. Risk Assess., 24 (3) (2017), pp. 784-796

Ghafuria Y., Yunesian M., Nabizadeh R., Mesdaghinia A., Dehghani M.H., Alimohammadi M. Environmental risk assessment of platinum cytotoxic drugs: a focus on toxicity characterization of hospital effluents. Int. J. Environ. Sci. Technol., 15 (9) (2018), pp. 1983-1990

Gomez Cortes L., Marinov D., Sanseverino I., Navarro Cuenca A., Niegowska M., Porcel Rodriguez E. and Lettieri T., Selection of substances for the 3rd Watch List under the Water Framework Directive, EUR 30297 EN, Luxembourg: Publications Office of the European Union, 2020, ISBN 978-92-76-19426-2, doi:10.2760/194067, JRC121346.

Godoy AA, Kummrow F, Pamplin PAZ (2015) Ecotoxicological evaluation of propranolol hydrochloride and losartan potassium to Lemna minor L. (1753) individually and in binary mixtures. Ecotoxicology 24(5):1112–1123. https://doi.org/10.1007/s10646-015-1455-3

Gros M., Rodríguez-Mozaz S., Barceló D. (2013). Rapid analysis of multiclass antibiotic residues and some of their metabolites in hospital, urban wastewater and river water by ultra-high-performance liquid chromatography coupled to quadrupole-linear ion trap tandem mass spectrometry. J. Chromatogr. A, 1292: 173-188.

Guidance document No. 27. Technical Guidance For Deriving Environmental Quality Standards. Updated version 2018. (2018).

Guidance document No. 25 on chemical monitoring of sediment and biota under the Water Framework Directive. ISBN 978-92-79-16224-4; doi: 10.2779/43586. (2010).

Gunnarsson, L. et al. Pharmacology beyond the patient – The environmental risks of human drugs. Environment International 129, 320-332, doi:https://doi.org/10.1016/j.envint.2019.04.075 (2019).

Halbach K., Möder M, Schrader S., Liebmann L., Schäfer RB, Schneeweiss A, Schreiner VC, Vormeier P, Weisner O, Liess M, Reemtsma T, Small streams–large concentrations? Pesticide monitoring in small agricultural streams in Germany during dry weather and rainfall, Water Research, Volume 203,2021,117535, ISSN 0043-1354, https://doi.org/10.1016/j.watres.2021.117535.

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

Ek Henning, H., Putna.Nimane, I., Kalinowski, R., Perkola, N., Bogusz, A., Kublina, A., Haiba, E., Barda, I., Karkovska, I., Schütz, J., Mehtonen, J., Siimes, K., Nyhlén, K., Dzintare, L., Äystö, L., Sinics, L., Laht, M., Lehtonen, M., Stapf, M., Stridh, P., Poikāne, R., Hoppe, S., Lehtinen, T., Kõrgma, V., Junttila, V., Leisk, Ü. (2020). Pharmaceuticals in the Baltic Sea Region – emissions, consumption and environmental risks. Report no. 2020:28, Länsstyrelsen Östergötland, Linköping. Available at: https://www.lansstyrelsen.se/4.f2dbbcc175974692d268b9.html

Hladik, M. & USGS. Methods Development for the Analysis of Pyrethroid Pesticides in Environmental Samples.

FINAL REPORT FOR CALFED Recipient Agreement No. ERP-02-P42. (2007).

Hladik, M. L. & Kuivila, K. M. Assessing the Occurrence and Distribution of Pyrethroids in Water and Suspended Sediments. Journal of Agricultural and Food Chemistry 57, 9079-9085, doi:10.1021/jf9020448 (2009).

Hladik, M. L., Smalling, K. L. & Kuivila, K. M. Methods of Analysis—Determination of Pyrethroid Insecticides in

Water and Sediment Using Gas Chromatography/Mass Spectrometry. Techniques and Methods 5–C2. U.S. Department of the Interior. U.S., Geological Survey, Reston, Virginia. (2009).

Hladik, M. L. & Calhoun, D. L. Analysis of the herbicide diuron, three diuron degradates, and six neonicotinoid insecticides in water—Method details and application to two Georgia streams: U.S. Geological Survey Scientific Investigations Report 2012–5206, 10 p. Available at http://pubs.usgs.gov/sir/2012/5206. (2012).

Homem V, Capela D, Silva JA, Cincinelli A, Santos L, Alves A & Ratola N (2017) An approach to the environmental prioritisation of volatile methylsiloxanes in several matrices. Science of The Total Environment 579: 506-513

INERIS 2011. Validation groupe d'experts: Mars 2011. Version 4: 29/03/2011 DRC-11-112070-04123A.

INERIS, 2012. Validation groupe d'experts: Avril 2012. Version 2: 28/06/2012. DRC-11-112070-04504B.

INERIS, 2012. Validation groupe d'experts. Avril 2012. Version 2: 03/07/2012. DRC-11-112070-03826B.

INERIS, 2014. Validation groupe d'experts : Juillet 2014. Version 2 : 17/02/2016. DRC-15-136849-12771B.

IVL, 2005. Screening tertiary butylphenols, methylphenols and long-chain alkylphenols in the Swedish environment. IVL Swedish Environmental Research Institute, Stockholm. Report No. B1594

Jaszczak, E., Polkowska, Ż., Narkowicz, S. & Namieśnik, J. Cyanides in the environment—analysis—problems and challenges. Environmental Science and Pollution Research 24, 15929-15948, doi:10.1007/s11356- 017-9081-7 (2017).

JRC. Draft Dossier of substances identified in the second prioritisation process https://circabc.europa.eu/faces/jsp/extension/wai/navigation/container.jsp. (2016).

Jureczko M., Kalka J. Cytostatic pharmaceuticals as water contaminants, European Journal of Pharmacology,Volume 866, 2020, 172816, ISSN 0014-2999, https://doi.org/10.1016/j.ejphar.2019.172816.(https://www.sciencedirect.com/science/article/pii/S0014 29991930768X)

Kiaune, L. & Singhasemanon, N. in Reviews of Environmental Contamination and Toxicology Volume 213 (ed David M. Whitacre) 1-26 (Springer New York, 2011).

Kosma CI, Lambropoulou DA, Albanis TA. Analysis, occurrence, fate and risks of proton pump inhibitors, their metabolites and transformation products in aquatic environment: A review. Sci Total Environ. 2016 Nov 1;569-570:732-750. doi: 10.1016/j.scitotenv.2016.06.160. Epub 2016 Jul 2. PMID: 27380396.

Krizman-Matasic, I., Kostanjevecki, P., Ahel, M. & Terzic, S. Simultaneous analysis of opioid analgesics and their metabolites in municipal wastewaters and river water by liquid chromatography–tandem mass spectrometry. Journal of Chromatography A 1533, 102-111, doi:https://doi.org/10.1016/j.chroma.2017.12.025 (2018).

Kümmerer, K. & Henninger, A. Promoting resistance by the emission of antibiotics from hospitals and households into effluent. Clinical Microbiology and Infection 9, 1203-1214, doi:https://doi.org/10.1111/j.1469-0691.2003.00739.x (2003).

Larsson, D. G. J. Antibiotics in the environment. Upsala Journal of Medical Sciences 119, 108-112, doi:10.3109/03009734.2014.896438 (2014).

Larsson, D. G. J., de Pedro, C. & Paxeus, N. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. Journal of Hazardous Materials 148, 751-755, doi:https://doi.org/10.1016/j.jhazmat.2007.07.008 (2007).

Lettieri, T. et al. Modelling-based strategy for the prioritisation exercise under the Water Framework Directive, https://circabc.europa.eu/w/browse/85b46283-9353-4e67-bf56-e4d18b32cbaf). (2016).

Lenz K., Mahnik S.N., Weissenbacher N., Mader R.M., Krenn P., Hann S., Koellensperger G., Uhl M., Knasmuller S., Ferk F., Bursch W., Fuerhacker M. Monitoring, removal and risk assessment of cytostatic drugs in hospital wastewater. Water Sci. Technol., 56 (12) (2007), pp. 141-149.

Loos, R., Marinov, D., Sanseverino, I., Napierska, D. & Lettieri, T. Review of the 1st Watch List under the Water Framework Directive and recommendations for the 2nd Watch List. EUR 29173, Publications Office of the European Union, Luxembourg, 2018, doi:10.2760/701879. (2018).

Loos, R., Marinov, D., Sanseverino, I. & Lettieri, T. Analytical methods for substances in the Watch List under the

Water Framework Directive. Workshop Report. Publications Office of the European Union, Luxembourg, ISBN 978-92-79-96856-3, doi:10.2760/74723, JRC113172. (2018).

Loos, R. et al. EU-wide monitoring survey on emerging polar organic contaminants in wastewater treatment plant effluents. Water Research 47, 6475-6487, doi:https://doi.org/10.1016/j.watres.2013.08.024 (2013).

López-García E, Mastroianni N, Ponsà-Borau N, Barceló D, Postigo C, López de Alda M, Drugs of abuse and their metabolites in river sediments: Analysis, occurrence in four Spanish river basins and environmental risk assessment, Journal of Hazardous Materials, Volume 401, 2021, 123312, ISSN 0304-3894, https://doi.org/10.1016/j.jhazmat.2020.123312.

Lu, Z., De Silva, A. O., Peart, T. E., Cook, C. J., Tetreault, G. R., Servos, M. R., & Muir, D. C. (2016). Distribution, partitioning and bioaccumulation of substituted diphenylamine antioxidants and benzotriazole UV stabilizers in an urban creek in Canada. Environmental science & technology, 50(17), 9089-9097. https://doi.org/10.1021/acs.est.6b01796

Mandaric, L. et al. Contamination sources and distribution patterns of pharmaceuticals and personal care products in Alpine rivers strongly affected by tourism. Science of The Total Environment 590-591, 484- 494, doi:https://doi.org/10.1016/j.scitotenv.2017.02.185 (2017).

Mahnik S.N., Rizovski B., Fuerhacker M., Mader R.M. Development of an analytical method for the determination of anthracyclines in hospital effluents. Chemosphere, 65 (8) (2006), pp. 1419-1425

Massei, R. et al. Screening of Pesticide and Biocide Patterns As Risk Drivers in Sediments of Major European River Mouths: Ubiquitous or River Basin-Specific Contamination? Environmental Science & Technology 52, 2251-2260, doi:10.1021/acs.est.7b04355 (2018).

Mastroianni, N., Bleda, M. J., de Alda, M. L., & Barceló, D. (2016). Occurrence of drugs of abuse in surface water from four Spanish river basins: Spatial and temporal variations and environmental risk assessment. Journal of hazardous materials, 316, 134-142.

Mendoza A., Rodríguez-Gil J.L., González-Alonso S., Mastroianni N., López de Alda M., Barceló D., Valcárcel Y., Drugs of abuse and benzodiazepines in the Madrid Region (Central Spain): Seasonal variation in river waters, occurrence in tap water and potential environmental and human risk, Environment International, Volume 70, 2014, Pages 76-87, ISSN 0160-4120, https://doi.org/10.1016/j.envint.2014.05.009.

Monteiro, S. C. & Boxall, A. B. A. in Reviews of Environmental Contamination and Toxicology (ed David M. Whitacre) 53-154 (Springer New York, 2010).

Montesdeoca-Esponda, S., Sosa-Ferrera, Z., & Santana-Rodríguez, J. J. (2013). Microwave-assisted extraction combined with on-line solid phase extraction followed by ultra-high-performance liquid chromatography with tandem mass spectrometric determination of benzotriazole UV stabilizers in marine sediments and sewage sludges. Journal of separation science, 36(4), 781-788. https://doi.org/10.1002/jssc.201200664

Niegowska M., Sanseverino I., Navarro A., Lettieri T., Knowledge gaps in the assessment of antimicrobial resistance in surface waters, FEMS Microbiology Ecology, Volume 97, Issue 11, November 2021, fiab140, https://doi.org/10.1093/femsec/fiab140.

O'Keefe T. Cytotoxic Drug Contamination in Hospital and Municipal Wastewater and its Transfer to Surface. Water Pharma-Cycle Inc (2011).

Ort C., M.G. Lawrence, J. Reungoat, G. Eaglesham, S. Carter, J. Keller. Determining the fraction of pharmaceutical residues in wastewater originating from a hospital. Water Res., 44 (2) (2010), pp. 605-615.

Oertel R, Schubert S, Mühlbauer V, Büttner B, Marx C, Kirch W. (2014). Determination of clindamycin and its metabolite clindamycin sulfoxide in diverse sewage samples. Environ Sci Pollut Res Int. 21(20):11764-9. doi: 10.1007/s11356-013-2333-2.

Panter GH, Hutchinson TH, Hurd KS, Bamforth J, Stanley RD, Duffell S, Hargreaves A, Gimeno S & Tyler CR. Development of chronic tests for endocrine active chemicals. Part 1. An extended fish early-life stage test for oestrogenic active chemicals in the fathead minnow (Pimephales promelas). Aquatic Toxicology, 77, 279–290, 2006

Parolini M, Magni S, Castiglioni S, Zuccato E, Binelli A (2015) Realistic mixture of illicit drugs impaired the oxidative status of the zebra mussel (Dreissena polymorpha). Chemosphere 128:96–102. https://doi.org/10.1016/j.chemosphere.2014.12.092

Parolini M, De Felice B, Ferrario C, Salgueiro-González N, Castiglioni S, Finizio A, Tremolada P (2018) Benzoylecgonine exposure induced oxidative stress and altered swimming behavior and reproduction in Daphnia magna. Environ Pollut 232:236–244. https://doi.org/10.1016/j.envpol.2017.09.038

Paulos, P. et al. Reproductive responses in fathead minnow and Japanese medaka following exposure to a synthetic progestin, Norethindrone. Aquat Toxicol 99, 256-262, doi:10.1016/j.aquatox.2010.05.001 (2010).

Papageorgiou, M., Zioris, I., Danis, T., Bikiaris, D. & Lambropoulou, D. Comprehensive investigation of a wide range of pharmaceuticals and personal care products in urban and hospital wastewaters in Greece. Science of The Total Environment 694, 133565, doi:https://doi.org/10.1016/j.scitotenv.2019.07.371 (2019).

Pico, Y. et al. Contaminants of emerging concern in freshwater fish from four Spanish Rivers. Science of The Total Environment 659, 1186-1198, doi:https://doi.org/10.1016/j.scitotenv.2018.12.366 (2019).

Poole K. At the Nexus of Antibiotics and Metals: The Impact of Cu and Zn on Antibiotic Activity and Resistance. Trends Microbiol. 2017 Oct;25(10):820-832. Doi: 10.1016/j.tim.2017.04.010. Epub 2017 May 17. PMID: 28526548.

J. Popowicz, P. Koszelnik. Wpływ właściwości fizykochemicznych na metody inaktywacji I usuwania leków cytostatycznych z wód I ścieków. Acta Sci. Pol. Form. Circumiectus, 14 (3) (2015), pp. 107-125

Quinlan, E. L. et al. Temporal Dynamics of Periphyton Exposed to Tetracycline in Stream Mesocosms. Environmental Science & Technology 45, 10684-10690, doi:10.1021/es202004k (2011).

RIVM 1997. RIVM report no. 601501002. Maximum Permissible Concenrations and Negligible Concentrations for pesticides. https://www.rivm.nl/bibliotheek/rapporten/601501002.pdf.

RIVM 1998. Report no. 601501003. Maximum Permisssible Concentrations and Negligible Concentrations for aniline derivatives. https://www.rivm.nl/bibliotheek/rapporten/601501003.pdf.

RIVM 2009. RIVM Report 601714002/2009. Environmental risk limits for monochloroanilines https://www.rivm.nl/bibliotheek/rapporten/601714002.pdf.

RIVM 2012 Environmental risk limits for octamethylcyclotetrasiloxane in water. A proposal for water quality standards in accordance with the Water Framework Directive. RIVM Letter Report 601714020/2012.

RIVM 2013. Enviromental risk limits for metazachlor in water. A proposal for water quality standards in accordance with the Water Framework Directive RIVM Letter report 601714024/2013 J.W. Vonk | C.E. Smit | F.M.W. de Jong.

Rimayi, C., Odusanya, D., Weiss, J. M., de Boer, J. & Chimuka, L. Contaminants of emerging concern in the Hartbeespoort Dam catchment and the uMngeni River estuary 2016 pollution incident, South Africa. Science of The Total Environment 627, 1008-1017, doi:https://doi.org/10.1016/j.scitotenv.2018.01.263 (2018).

Rodriguez-Mozaz Sara et al., Antibiotic residues in final effluents of European wastewater treatment plants and their impact on the aquatic environment. Environment International, 2020

Rösch, A., Beck, B., Hollender, J. & Singer, H. Picogram per liter quantification of pyrethroid and organophosphate insecticides in surface waters: a result of large enrichment with liquid–liquid extraction and gas chromatography coupled to mass spectrometry using atmospheric pressure chemical ionization. Analytical and Bioanalytical Chemistry 411, 3151-3164, doi:10.1007/s00216-019-01787-1 (2019).

Roveri, V., Guimarães, L.L., Toma, W. et al. Occurrence and ecological risk assessment of pharmaceuticals and cocaine in the urban drainage channels of Santos beaches (São Paulo, Brazil): a neglected, but sensitive issue. Environ Sci Pollut Res 28, 65595–65609 (2021). https://doi.org/10.1007/s11356-021-15249-8.

Runnalls, T. J., Beresford, N., Losty, E., Scott, A. P. & Sumpter, J. P. Several Synthetic Progestins with Different Potencies Adversely Affect Reproduction of Fish. Environmental Science & Technology 47, 2077-2084, doi:10.1021/es3048834 (2013).

Sanseverino, I., Navarro Cuenca, A., Loos, R., Marinov, D. & Lettieri, T. State of the Art on the Contribution of Water to Antimicrobial Resistance, EUR 29592 EN, Publications Office of the European Union, Luxembourg, ISBN 978-92-79-98478-5, doi:10.2760/771124, JR C114775. (2018).

Sanseverino I, Gómez L, Navarro A, Cappelli F, Niegowska M, Lahm A, Barbiere M, Porcel-Rodríguez E, Valsecchi S, Pedraccini R, Crosta S, Lettieri T, Holistic approach to chemical and microbiological quality of aquatic ecosystems impacted by wastewater effluent discharges, Science of The Total Environment, Volume 835, 2022, 155388, ISSN 0048-9697, https://doi.org/10.1016/j.scitotenv.2022.155388.

SE 2011. https://www.ivl.se/download/18.694ca0617a1de98f47393d/1628417290890/FULLTEXT01.pdf

Sharma, A. et al. Different DNA damage response of cis and trans isomers of commonly used UV filter after the exposure on adult human liver stem cells and human lymphoblastoid cells. Science of The Total Environment 593-594, 18-26, doi:https://doi.org/10.1016/j.scitotenv.2017.03.043 (2017).

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

Teigeler M, Schaudien D, Böhmer W, Länge R, Schäfers C. Effects of the Gestagen Levonorgestrel in a Life Cycle Test with Zebrafish (Danio rerio). Environ Toxicol Chem. 2022 Mar;41(3):580-591. doi: 10.1002/etc.5008. Epub 2021 Mar 29. PMID: 33539028.

Alena Tierbach, Alexandra Kroll, Marion Junghans. 2021. CQC (AA-EQS) and AQC (MAC-EQS) – Proposal by the Ecotox Centre for: Fipronil. Dübendorf (CH): Swiss Centre for Applied Ecotoxicology; 112 pp.

UBA TEXTE 42/2019. Prof. Dr. Thomas Ternes, Dr. Georg Dierkes, Lise Boulard, Alexander Weizel Bundesanstalt für Gewässerkunde, Koblenz. On behalf of the German Environment AgencyMethod development for analysis of pharmaceuticals in environmental samples. Project No. (FKZ) 3715674130 Report No. (UBA-FB) 002731/ENG. http://www.umweltbundesamt.de/publikationen

UBA TEXTE 233/2020. Dr. Hannah Wünnemann, Dr. Klaus Weiß, Daniela Arndt, Dr. Michaela Baumann, Rebekka Weiß, Hermann Ferling, Karin Scholz-Göppel, Karina Bucher, Christoph Feick, Georg Hartmann, Peter Kitzing, Martin Szyja, Dr. Julia Schwaiger. Umweltqualitätsnormen für Binnengewässer Überprüfung der Gefährlichkeit neuer bzw. prioritärer Substanzen

Valdés M. Eugenia et al., Distribution of antibiotics in water, sediments and biofilm in an urban river (Cordoba, Argentina, LA). Environmental Pollution, 2021

Valdez-Carrillo M, Abrell L, Ramírez-Hernández J, Reyes-López JA, Carreón-Diazconti C (2020) Pharmaceuticals as emerging contaminants in the aquatic environment of Latin America: a review. Environ Sci Pollut Res 27:44863–44891. https://doi.org/10.1007/s11356-020-10842-9

Vulliet, E. & Cren-Olivé, C. Screening of pharmaceuticals and hormones at the regional scale, in surface and groundwaters intended to human consumption. Environmental Pollution 159, 2929-2934, doi:https://doi.org/10.1016/j.envpol.2011.04.033 (2011).

Wang Y, Liu Y, Lu S, Liu X, Meng Y, Zhang G, Guo X (2019) Occurrence and ecological risk of pharmaceutical and personal care products in surface water of the Dongting Lake, China-during rainstorm period. Environ Sci Pollut Res 26:28796–28807. https://doi.org/10.1007/s11356-019-06047-4.

WFD – UK TAG Report, Proposed EQS for Water Framework Directive Annex VIII substances: cyanide (free) (For consultation), Water Framework Directive - United Kingdom Technical Advisory Group, 2012. Available at http://www.wfduk.org/sites/default/files/Media/Cyanide_Final_.pdf.

Wick A., Jacobs B., Kunkel U., Heininger P., Ternes T.A., Benzotriazole UV stabilizers in sediments, suspended particulate matter and fish of German rivers: New insights into occurrence, time trends and persistency, Environmental Pollution, Volume 212, 2016, Pages 401-412, ISSN 0269-7491, https://doi.org/10.1016/j.envpol.2016.01.024.

Wielens Becker, R. et al. Investigation of pharmaceuticals and their metabolites in Brazilian hospital wastewater by LC-QTOF MS screening combined with a preliminary exposure and in silico risk assessment. Science of The Total Environment 699, 134218, doi:https://doi.org/10.1016/j.scitotenv.2019.134218 (2020).

Wellington, E. M. H. et al. The role of the natural environment in the emergence of antibiotic resistance in Gram-negative bacteria. The Lancet Infectious Diseases 13, 155-165, doi:https://doi.org/10.1016/S1473-3099(12)70317-1 (2013).

J. Zhang, V. Chang, A. Giannis, J. Wang. Removal of cytostatic drugs from aquatic environment: a review. Sci. Total Environ., 445–446 (2013), pp. 281-298

Zhou, S. et al. Optimization of screening-level risk assessment and priority selection of emerging pollutants – The case of pharmaceuticals in European surface waters. Environment International 128, 1-10, doi:https://doi.org/10.1016/j.envint.2019.04.034 (2019).

Zrnčić, M. et al. Analysis of anthelmintics in surface water by ultra high performance liquid chromatography coupled to quadrupole linear ion trap tandem mass spectrometry. Chemosphere 99, 224-232,

doi:https://doi.org/10.1016/j.chemosphere.2013.10.091 (2014).

List of abbreviations and definitions

AMR Antimicrobial resistance

APCI Atmospheric pressure chemical ionisation

ARB Antibiotic resistant bacteria

B Bioaccumulation

C Carcinogenicity

CMR Carcinogenic, mutagenic and toxic to reproduction

CAS Chemical Abstract Service

Eawag Swiss Federal Institute of Aquatic Science and Technology

ECHA European Chemicals Agency

ECOSAR Ecological structure activity relationships

ED Endocrine disruptor

EDS Endocrine Disruptors Strategy

EEA European Environment Agency

EEA European Economic Area

EFSA European Food Safety Authority

EFTA European Free Trade Association

EMA European Medicines Agency

EQS Environmental quality standard

EQSD Environmental quality standard Directive

ERA Environmental Risk Assessment

FASS Swedish Medicines Information Engine

GC-MS Gas chromatography mass spectrometry

INERIS Institut national de l'environnement industriel et des risques

JRC Joint Research Centre

K_{ow} N-octanol/water partition coefficient

LC-MS-MS Liquid chromatography (tandem) triple quadrupole mass spectrometry

LLE Liquid-liquid extraction

LOD Limit of detection LOQ Limit of quantification

M Mutagenicity

MDL Method detection limit

MEC Measured environmental concentration

MIC Minimum inhibitory concentration

MoA Mode of Action MS Member State

OSPAR Convention for the Protection of the Marine Environment of the North-East Atlantic

PBT Persistent, bioaccumulative and toxic

PEC Predicted environmental concentration

PNEC Predicted no-effect concentration

P Persistence

PPP	Plant protection product
PS	Priority Substance
R	Reproduction Toxicity
RIVM	National Institute for Public Health and the Environment (NL)
RQ	Risk Quotient
Sc2	and Sc3 Scenario 2 and Scenario 3
SCG	Strategic Coordination Group
SG-R	Sub-group on revision (of the priority substance list)
SoE	State of the Environment
SPE	Solid-phase extraction
SPM	Suspended particulate matter
STE	Spatial, Temporal and Extent of PNEC exceedance
SVHC	Substance of very high concern
T	Toxicity
TGD	Technical guidance document
UBA	German Environment Agency
USGS	United States Geological Survey
US EPA	The United States Environmental Protection Agency
WFD	Water Framework Directive
WG	Working Group
WL	Watch List

List of boxes

Respecting the requirements of Article 8b of the Environmental Quality Standards (EQS) Directive (Directive 2008/105/EC as amended by Directive 2013/39/EU), the following **pillars** of information were drawn upon to identify potential candidates for inclusion in the WL: 11

Conclusion alkylphenols: the alkylphenols 4-tert-butylphenol, phenol, dodecyl-, branched, and p-(1,1-dimethylpropyl)phenol are suitable for inclusion in the 4th WL and listed in the priority 2 category. These substances should be monitored in sediment. The PNEC is uncertain for the first one and no sediment toxicity date are available for the others. 41

Conclusion chloroanilines: 4-chloroaniline and 3,4-dichloroaniline are selected as suitable candidates for the 4th WL and listed in the priority 2 category, since uncertainties in the PNEC value were identified. 42

Conclusion free cyanide: Free cyanide is selected as a suitable candidate for the 4th WL in the priority 1 category. An analytical method is available, with a Limit of Quantification (LOQ) < 0.3 µg/L (PNEC value for freshwater is 0.5 µg/L), thus confirming sufficient sensitivity of the analytical method to reach a value below the PNEC in freshwater. Free cyanide is suitable for inclusion in the next WL to be monitored in inland surface (preferable) and coastal waters (both in dissolved fraction). 42

Conclusion phenolbenzotriazoles: The UV filters are selected as suitable candidates for the WL, in the priority 2 category to be monitored in water, sediment, or biota. They could be included in the WL if reliable PNEC values (based on ecotoxicity data) become available. 44

Conclusion siloxanes: The siloxanes D4, D5 and D6 were initially selected as suitable candidates for the WL in priority 1 category, to be monitored most preferably in SPM. However, after consultation, the JRC decided not to shortlist them for the 4th WL in view of their possible further restriction/ban and for the ongoing investigation for the linear siloxanes as PBT/vPvB. In case, the latter would be classified as PBT/vPvB, they could be listed for the next WL as group together with the cyclic siloxanes. Therefore, these substances were moved to priority 2 category. 45

Conclusion sunscreen agents: The sunscreen agents, avobenzone, octocrylene and oxybenzone were not selected originally due to uncertainty regarding their PNEC values. Further information was received for these substances and the JRC could thus propose them as among the most suitable candidates for the 4th WL. 46

Conclusion antibiotics: The antibiotics clindamycin, cefalexin and ofloxacin are listed as among the most suitable candidates for the WL. Following MS and Stakeholders comments, the JRC proposes clindamycin and ofloxacin for the 4th WL 48

Conclusion cytostatic drugs: These substances are listed in the priority 3 category due to the lack of reliable PNECs but the JRC considers them substances of concern 48

Conclusion illicit drugs: The JRC considers illicit drugs as suitable candidates for the WL with priority 2 49

Conclusion metformin: Metformin and its transformation product guanylurea have been identified as among the most suitable candidates for inclusion in the 4th WL to be monitored in inland surface waters. 50

Conclusion synthetic hormones: Levonorgestrel and norethisterone were initially identified as among the most suitable candidates for inclusion in the 4th WL to be monitored in inland surface waters. However, they were not shortlisted since the analytical method is not sensitive enough for monitoring levonorgestrel. These substances will be considered in the following WL update (2024). 51

Conclusion other pharmaceuticals: The pharmaceuticals listed above were identified by the JRC under criteria 1, 2 and 3. Following the additional information received after the WG Chemicals meeting (10th February 2022), the substances allopurinol and oxypurinol, gabapentin, gemfibrozil, irbesartan, and propranolol were listed in the priority 2 category. 51

Conclusion azoxystrobin: Azoxystrobin is recommended to be included in the 4th WL and to be monitored in inland surface waters. 52

Conclusion copper and copper oxides: At present, copper and copper oxides should be considered as potential candidate for the PS list, and a sub-group of experts should be established to derive a provisional QS value. 53

Conclusion diflufenican: Diflufenican is listed among the most suitable candidates for inclusion in the 4th WL to be monitored in inland surface waters. 54

Conclusion fipronil: Fipronil is recommended to be included in the 4th WL to be monitored in inland surface waters. 54

Conclusion pyrethroid insecticides: Etofenprox, cyfluthrin and lambda-cyhalothrin were initially listed in the priority 1 category. After consultation with MS and Stakeholder experts, the JRC moved them to the priority 2 category, because the sensitivity of the analytical methods would be insufficient to reach the low PNEC values without an advanced analytical system. Furthermore, four pyrethroids are shortlisted in the current review of the list of priority substances under the WFD. Consequently, it would be worth considering whether they should be covered as a group in the priority substances list (applying a cumulative approach). The preferred matrix for monitoring this group of substances is sediment or SPM. 55

Conclusion other PPP and biocides: The rodenticides and metazachlor were initially listed in the priority 3 category but following comments from MS and stakeholder experts, they were moved to the priority 2 category, on the basis of the information they provided such as PNEC value, analytical method and monitoring data. .. 56

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Table 3. Potential candidates for the WL identified during the previous WL review but not selected for the 3rd WL (Gomez Cortes et al. 2020). The table shows for each candidate substance the name of the substance, CAS number, use and status, hazard properties, PNEC value, available analytical method and limit of quantification. dw: dry weight; ww: wet weight; lw: lipid weight; AF: assessment factor; PNEC: predicted no effect concentration (selected values in bold); LOQ: limit of quantification; LOD: limit of detection; PPP: plant protection product; P: persistent; B: bioaccumulative; T: toxic; M: mutagenic; C: carcinogenic; R: toxic to reproduction; ED: endocrine disruptor. 13

Table 4. Substances suggested by individual MS and during internal consultation for the 3rd WL report (Gomez Cortes et al. 2020) as good candidates for future revisions of the WL. The table shows for each candidate substance the name of the substance, CAS number, use and status, hazard properties, PNEC value (selected values in bold), available analytical method and limit of quantification. Abbreviations, dw: dry weight; ww: wet weight; lw: lipid weight; AF: assessment factor; PNEC: predicted no effect concentration; LOQ: limit of quantification; LOD: limit of detection; PPP: plant protection product; P: persistent; B: bioaccumulative; T: toxic; R: toxic to reproduction; ED: endocrine disruptor; SVHC substance of very high concern. 16

Table 5. Potential candidates identified by the JRC from scientific literature. The table shows for each candidate substance the name of the substance, CAS number, use and status, hazard properties, PNEC value (selected values in bold), available analytical method and limit of quantification. Abbreviations, dw: dry weight; ww: wet weight; lw: lipid weight; AF: assessment factor; PNEC: predicted no effect concentration; LOQ: limit of quantification; LOD: limit of detection; PPP: plant protection product; P: persistent; B: bioaccumulative; T: toxic; M: mutagenic; C: carcinogenic; R: toxic to reproduction; ED: endocrine disruptor; AMR: antimicrobial resistance; SVHC. Substance of very high concern. 28

Table 6. List of most suitable WL candidate substances, fulfilling the selection criteria, modified following comments from MS and Stakeholders groups (after the WG Chemicals meetings held on 10 February. The table shows the substance/group name, CAS number and use (PPP = plant protection product). In bold, the seven substances/groups originally recommended for inclusion in the 4th WL. 37

Table 7. List of substances assessed by the JRC as suitable candidates for the next Watch List (WL) but for which information on analytical method or PNEC value is missing. The table shows for each candidate the substance/group name, CAS number and use (PPP = plant protection product). 38

Table 8. List of substances assessed by the JRC as suitable candidates for the next Watch List (WL) but for which information on analytical method or PNEC value is missing. The table shows for each candidate the substance/group name, CAS number and use (PPP = plant protection product). 39

Annexes

Annex I. Additional tables.

Annex II. Factsheets included in a separate document.

Annex I: Additional tables

Table AI.1. Substances fulfilling criterion 1. Potential candidates for the WL identified following the new criteria defined by the JRC (Gomez Cortes et al., 2020) but not selected for the 3rd WL. Abbreviations: MEC: measured environmental concentration; PNEC: predicted no effect concentration; PPP: plant protection product; RQ: risk quotient; SVHC: substance of very high concern.

Group	Name	CAS No	Matrix (log K_{ow})	Status	Environmental concentrations and monitoring data	Priority (table)
Industrial products	4-chloroaniline	106-47-8	Water 1.83 at 25 °C (ECHA) 3.9 g/L at 25 °C (ECHA)	Approved	JRC prioritisation dataset (2014): In Sc2 (inland whole water) monitored in 5 MS (2323 sites); available 26925 samples; only 0.8% quantified samples; the data quality is acceptable but the data are not Union-representative since one MS holds about 90% of all samples; Median = 0.05 µg/L; MEC(P95) = 0.15 µg/L; Sc3 is expected to be similar to Sc2 if PNEC = 0.05 µg/L; RQ(P95) = 3 (PNEC = 0.05 µg/L); STE=0.97 (PNEC = 0.05 µg/L). WISE (2020): In Sc2 (inland whole water) available 53 samples (0% quantified) from 8 sites in 1 MS (2018). LOQ=1.5 µg/L. Median=MEC(P95) = 1.5 µg/L. Low quality of data.	2
	3,4-dichloroaniline	95-76-1	Water Log K_{ow} = 2.68 at 20 °C Water solubility = 730 mg/L at 20 °C (ECHA)	Approved	JRC prioritisation dataset (2014): In Sc2 (inland whole water) monitored in 9 MS; available 13348 samples; only 0.7% are quantified samples; the data quality is poor since 71.5% of non-quantified samples were measured with LOQ > PNEC (PNEC = 0.02 µg/L); the data are not EU-representative (79% of all samples originate from 2 MS); Median = 0.025 µg/L; MEC(P95) = 0.15 µg/L.; Sc3 is not developed due to the low data quality; for PNEC = 0.02 µg/L RQ(P95) = 7.5 and STE=1.6 WISE (2020): In Sc2 (coastal water) available 109 samples (0% quantified) from 1 site in 1 MS (2018). LOQs=0.05 µg/L. Median=MEC(P95) = 0.05 µg/L. Low quality of data.	2

	Free cyanide	CN- 57-12-5 CNH 74-90-8	Water	NOT APPROVED as PPP (2004/129/EC) No authorisation in place APPROVED AS BIOCIDE. This substance is approved for use as a biocide in the EEA and/or Switzerland, for: wood preservation, controlling rodents, controlling insects, ants, etc. (ECHA)	Cyanide anion (CN-) JRC prioritisation dataset (2014): In Sc2 (inland dissolved fraction) data from 2 MS with 340 samples are available (18.5% quantified samples). The data quality is low since about 64% of non-quantified samples have LOQ or LOD ≥ PNEC (PNEC = 0.5 µg/L). The data are not EU representative. Median = 1 µg/L; MEC(p95) = 11.7 µg/L. RQ(P95) = 23.4 (PNEC = 0.5 µg/L) and RQ(P95)=45 (PNEC = 0.26 µg/L). STE is not calculated due to the data scarcity. WISE (2021): In Sc2 (inland surface water; Dissolved fraction) available 158 samples (4.4% quantified) from 61 sites in 3 MS (2015 - 2019). For non-quantified samples, the range of LOQs is 0.002 – 0.57 µg/L. The sensitivity of monitoring is acceptable. The data are not EU-representative. Median= 0.003 µg/L, Mean=0.11 µg/L and MEC(P95)=0.57 µg/L. RQ(P95) = 1.14 (PNEC = 0.5 µg/L) and RQ(P95)=2.19 (PNEC = 0.26 µg/L). STE is not calculated due to the data scarcity.	1 (backup)
Other pharmaceuticals	Benzimidazoles: Anthelmintics: Mebendazole	31431-39-7		Authorised	MECs are not available in WISE 2020 and JRC prioritisation dataset (2014)	3
	Gemfibrozil	25812-30-0	Water Log K_{ow} = 4.77	Authorised	JRC prioritisation dataset (2014): In Sc2 (inland whole water) monitored in 3 MS (251 sites); available 2476 samples; only 2% quantified samples; 97% of all samples coming from one MS; the data are not EU-representative; Median = MEC(p95) = 0.0125 µg/L; Sc3 is equal to Sc2 (PNEC = 0.8519 µg/L). RQ(P95) = 0.015 (PNEC = 0.8519 µg/L); STE=0.16 (PNEC = 0.8519 µg/L). MECs are not available in WISE 2020.	3

	Norethisterone	68-22-4	Water Log K_{ow} = 2.97	Authorised This is substance is manufactured and/or imported in the EEA in 1-10 tonnes per year. This substance is used at industrial sites and in manufacturing.	The use of norethisterone (sales data Sweden 2018) has been considered to result in moderate/high environmental risk (Janusinfo, SE). PEC = 0.0020 µg /L (based on sales data in Sweden in year 2018, Janusinfo, SE) JRC prioritisation dataset (2014): In Sc2 (inland whole water) monitored in 1 MS (19 sites); available 20 samples; the sensitivity of monitoring is good (100% quantified samples). However, the data are insufficient and are not EU-representative. Median = 0.003 µg/L; MEC(p95) = 0.0034 µg/L. RQ(P95) = 0.1 (PNEC = 0.0354 µg/L) and RQ(PP95) = 0.23 (PNEC=0.0148 µg/L); STE=0 (PNEC = 0.0354 µg/L). No available data in the WISE (2020)	2
	Levonorgestrel	797-63-7	Water Log K_{ow} = 3.48	Authorised This is substance is manufactured and/or imported in the EEA in 1-10 tonnes per year. This substance is used at industrial sites and in manufacturing.	PEC/PNEC is based on sales data in Sweden in year 2019. PEC/PNEC = 141 which gives the risk high (Janusinfo, SE). No available data in the JRC prioritisation dataset (2014) and WISE (2020)	2
Plant protection products and biocides: other substances	diCopper (I) oxide (Cu_2O) Copper (II) oxide (CuO) Copper	1317-39-1 1317-38-0 7440-50-8		APPROVED as BIOCIDE This substance is manufactured and/or imported in the EEA in 1 000 - 10 000 tonnes per year. This substance is used by consumers, in articles, by	Cu2O and CuO: No available data in the JRC prioritisation dataset (2014) and WISE (2020) Cu: JRC prioritisation dataset (2014): in Inland dissolved (Sc3; PNEC = 7.8 µg/L) 97036 samples from 24 MS (7009 sites); 50% of all samples are quantified; the data quality seems good; Median = 1.7 µg/L, MEC(p95) = 6 µg/L. RQ(P95) = 0.77 (Sc3; PNEC = 7.8 µg/L) and RQ(P95) = 16 (Sc3; PNEC = 1.6 µg/L). STE=0.4 (Sc3; PNEC = 7.8 µg/L)	1 (not proposed)

				professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing. Cu_2O substance is approved for use as a biocide in the EEA and/or Switzerland, for preventing fouling. APPROVED as PPP (copper oxide) app 01/01/2019 exp 31/12/2025 2009/37/EC Reg. (EU) No 2018/1981 Reg. (EU) No 232/2015 Reg. (EU) No 540/2011 (Reg.(EU) No 84/2018) Authorised in: AT, BE, BG, CY, CZ, DE, EL, ES, FR, HR, HU, IE, IT, LT, LU, LV, MT, PL, PT, RO, SI, SK, UK (23 MS). CuO is known to be on the EEA market in nanomaterial form (ECHA).	WISE (2020): In Sc2 (inland surface water; Total and dissolved) available 92599 samples (75.6% quantified) from 5398 sites in 20 MS (2015-2018). Median= 1 µg/L, MEC(P95) = 5.4 µg/L.	

Table AI.2. Substances fulfilling criterion 2. Substances suggested by individual MS and during internal consultation for the 3rd WL report (Gomez Cortes et al. 2020) as good candidates for future revisions of the WL. Abbreviations: MEC: measured environmental concentration; PNEC: predicted no effect concentration; PPP: plant protection product; RQ: risk quotient; SVHC: substance of very high concern.

Name	CAS No	Matrix	Status	MS proposing the substance	Environmental concentration/ Monitoring	Priority (Table)
Etofenprox (Pyrethroids)	80844-07-1	Sediment/biota/water	PPP and Biocide Insecticide Approved as PPP Expiration 31/12/2022 Candidate for substitution Authorised in: AT, BG, CY, CZ, DE, EL, ES, FR, HU, IT, MT, PL, RO, SK Approved for use as a biocide in the EEA and/or Switzerland, for: wood preservation, controlling insects, ants, etc. (ECHA)	DE	JRC prioritisation dataset (2014): 1116 samples from 3 MS available in Sc2 inland whole water. Quantified samples less than 1%. MEC(p95) =0.01 µg/L RQ=9.3 (lowest PNEC) No available data in the WISE (2020)	2
Lambda-cyhalothrin (Pyrethroids)	91465-08-6	Sediment/biota/water	PPP and Biocide Insecticide Approved as PPP Expiration 31/03/2023 Candidate for substitution Authorised in: AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK This substance is approved for use as a biocide in the EEA and/or Switzerland, for: controlling insects, ants, etc. (ECHA) Expiration of approval: 30/09/2023	DE, DK	JRC prioritisation dataset (2014): 21729 samples from 6 MS available in Sc2 inland whole water. Quantified samples are about 0.6%. The data quality is low. MEC(p95) = 0.05 µg/L RQ=250 No available data in the WISE (2020)	2

			Authorised in: AT, BE, CZ, DK, FR, DE, EL, HU, IE, IT, LU, NL, NO, PL, RO, SK, SI, ES, SE, CH, UK			
Cyfluthrin (Pyrethroids)	68359-37-5	Sediment/biota/water	Biocide Acaricide/insecticide Not approved as PPP Expiration 30/04/2014 This substance is approved for use as a biocide in the EEA and/or Switzerland, for: controlling insects, ants, etc..(ECHA)		JRC prioritisation dataset (2014): 14579 samples from 5 MS are available in Sc2 inland whole water. Quantified samples are about 2.3%. The data quality is low. MEC(p95) = 0.1 µg/L RQ=2500 (lowest PNEC) No available data in the WISE (2020)	2
Esbiothrin or allethrin (Pyrethroid)	584-79-2 260359-57-7	Sediment/biota/water	Insecticide Not approved as PPP Not approveds as Biocide	DK	JRC prioritisation dataset (2014): 8477 samples from 1 MS are available in Sc2 inland whole water. Quantified samples are about 0.01%. The data quality is very low. MEC(p95) = 0.05 µg/L No available data in the WISE (2020)	2
Siloxanes D4, D5, D6	556-67-2 (D4)	Water/sediment Log K_{ow} = 6.98 (Homem et al 2017) BCF = 14900 (ECHA 2018)	Restricted SVHC candidate list	DE	No available data in JRC prioritisation dataset (2014) and WISE (2020 MEC surface water 987 ng/L MEC sediment 121 ng/g dw PEC surface water	2

					54 ng/L PEC sediment 52 ng/g dw (Homem et al. 2017)	
	541-02-6 (D5)	Water/sediment/ Log K_{ow} = 8.09 (Homem et al 2017) BCF = 16200 (ECHA)	Some uses of this substance are restricted under Annex XVII of REACH SVHC and included in the candidate list for authorisation. SVHC candidate list		No available data in JRC prioritisation dataset (2014) and WISE (2020 MEC surface water 1490 ng/L MEC sediment 5840 ng/g dw PEC surface water 493 ng/L PEC sediment 4120 ng/g dw (Homem et al. 2017)	2
	540-97-6 (D6)	Water/sediment/ Log K_{ow} = 8.87 (Homem et al 2017) BCF = 2868 (ECHA)	SVHC and included in the candidate list for authorisation.		No available data in JRC prioritisation dataset (2014) and WISE (2020) MEC surface water 151 ng/L MEC sediment 1270 ng/g dw PEC surface water 2476 ng/L PEC sediment	2

					52 ng/g dw (Homem et al. 2017)	
Alkylphenols	98-54-4 (4-Tert-Butylphenol)	Water Log K_{ow} = 3 (ECHA) 3.29 (EU Assessment Report 2008) BCF = 125 (EU Assessment Report 2008)	Substance included in the Community Rolling Action Plan (CoRAP). SVHC and included in the candidate list for authorisation. Precautionary measures suggested by manufacturers and importers of this substance. Guidance on the safe use of the substance provided by manufacturers and importers of this substance. (ECHA)	DE	JRC prioritisation dataset (2014): Sc2 inland whole water. No available data in the WISE (2020) Butylphenol: 18163 samples from 2 MS; Quantified samples about 1.4%. The data quality is low. MEC(p95) = 0.25 µg/L RQ=0.025	2
	121158-58-5 (Phenol, dodecyl-, branched)	Sediment Log K_{ow} = 7.14 at 25 °C (ECHA) BCF = 823 (ECHA)	Substance included in the Community Rolling Action Plan (CoRAP). Precautionary measures suggested by manufacturers and importers of this substance. Guidance on the safe use of the substance provided by manufacturers and importers of this substance.		Dodecylphenol: no data in the JRC prioritisation dataset (2014).	2

	80-46-6 (p-(1,1-dimethylpropyl)phenol)	Water Log K_{ow} = 3.6 at 22 °C (ECHA) BCF = 229 l/Kg ww (ECHA) 501 l/Kg (QSAR, Environment Agency, 2008)			Amylphenol: JRC prioritisation dataset (2014): 1298 samples from 1 MS; 0% quantified samples. The data quality is very low. MEC(P95) = 0.5 µg/L RQ=0.05	2
Phenol-benzotriazoles	3846-71-7 (UV-320)	Water/Sediment/Biota Log K_{ow} = 6.853 ± 1.254, 25 °C BCF >2000 (SVHC SUPPORT DOCUMENT - UV-320, 2014, ECHA)	SVHC and included in the candidate list for authorisation. SVHC requiring authorisation before it is used (Annex XIV of REACH).	DE	No available data in the JRC prioritisation dataset (2014) and WISE (2020)	2
	3864-99-1 (UV-327)	Water/Sediment/Biota Log K_{ow} = 7.544 ± 1.258, 25 °C (SVHC SUPPORT DOCUMENT - UV-327, ECHA)	SVHC and included in the candidate list for authorisation. Substance of very high concern requiring authorisation before it is used (Annex XIV of REACH).		No available data in the JRC prioritisation dataset (2014) and WISE (2020)	2
	25973-55-1 (UV-328)	Water/Sediment/Biota Log K_{ow} > 6.5 UV-328 has a tendency to bioaccumulate (SVHC SUPPORT DOCUMENT - UV-328, ECHA)	SVHC and included in the candidate list for authorisation. SVHC requiring authorisation before it is used (Annex XIV of REACH).		No available data in the JRC prioritisation dataset (2014) and WISE (2020)	2

	36437-37-3 (UV-350)	Water/Sediment/Biota Log K_{ow} = 6.951 ± 1.251 at 25 °C BCF >5000; very bioaccumulative (SVHC SUPPORT DOCUMENT - UV-350, ECHA)	SVHC and included in the candidate list for authorisation. SVHC requiring authorisation before it is used (Annex XIV of REACH).		No available data in the JRC prioritisation dataset (2014) and WISE (2020)	2
	2440-22-4 (UV-P)	Water/Sediment Log K_{ow} = 4.20 (25°C, pH=6.3) (SUBSTANCE EVALUATION CONCLUSION, CZ, 2017) ECHA: BCF <2000 L/kg.	Substance included in the Community Rolling Action Plan (CoRAP).		No available data in the JRC prioritisation dataset (2014) and WISE (2020)	2
Diflufenican	83164-33-4	Water	PPP Herbicide Approved Expiration 31/12/2022 Candidate for substitution Authorised in: AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SE, SI, SK	DK	JRC prioritisation dataset (2014): 47162 samples from 8 MS are available in Sc2 inland whole water. About 8.8% quantified samples. The data quality is low. MEC(p95)=0.026 µg/L; RQ=2.6 There are data available in the WISE (2020) WISE (2020): In Sc2 (inland surface water; Total) available 1166 samples (28.6% quantified) from 69 sites in 3 MS (2015-2018). Range of LOQs is 0.004 – 0.05 µg/L. Median= 0.04 µg/L MEC(P95) = 0.064 µg/L. The quality of data is acceptable but the data are not EU-representative. RQ(P95) = 6.4 (PNEC = 0.01 µg/L)	1

Azoxystrobin	131860-33-8	Water	PPP and Biocide Fungicide Approved as PPP Expiration 31/12/2024 Authorised in: AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SE, SI, SK This substance is approved for use as a biocide in the EEA and/or Switzerland, for: preservation films, preservation of fibres, leather, rubber, or polymers, preservation for construction materials. Expiration 31/10/2025	DK	JRC prioritisation dataset (2014): 21361 samples from 8 MS (2102 sites) are available in Sc2 dataset. About 6.4% of samples are quantified. The data quality is acceptable since only 5 non-quantified samples were measured with LOQ > 2*PNEC (PNEC=0.2 µg/L). However, 2 MS are overrepresented in the dataset holding about 84.5% of all samples. Median=0.01 µg/L; MEC(p95) = 0.04 µg/L RQ=0.04 There are data available in the WISE (2020) WISE (2020): In Sc2 (inland surface water; Total) available only 18 samples (44.4% quantified) from 2 sites in 1 MS (2018). Range of LOQs is 0.002 – 0.02 µg/L. Median= 0.002 µg/L MEC(P95) = 0.003 µg/L. The quantity of data is insufficient and the data are not EU-representative. RQ(P95) = 0.015 (PNEC = 0.2 µg/L)	1
Fipronil	120068-37-3	Water	Biocide Insecticide Not approved as PPP Expiration 30/09/2017 Candidate for substitution This substance is approved for use as a biocide in the EEA and/or Switzerland, for: controlling insects, ants, etc..	NL	JRC prioritisation dataset (2014): 6657 samples from 3 MS are available in Sc2 inland whole water. About 1% quantified samples. The data quality is low. MEC(p95) = 0.025 µg/L RQ=2.1 No data available in the WISE (2020)	1

			Authorised in: AT, BE, BG, HR, CY, CZ, DK, EE, FI, FR, DE, EL, HU, IE, IT, LU, MT, NL, NO, PL, PT, RO, SK, SI, ES, SE, CH, UK (ECHA)			
Oxypurinol (Allopurinol)	2465-59-0 315-30-0	Water	Pharmaceutical metabolite, Gout	DE	Risk of environmental impact of allopurinol cannot be excluded, since there are no sufficient ecotoxicity data available (Janusinfo and Fass, SE) PEC = 0,79 µg/L (FASS, SE) No available data in the JRC prioritisation dataset (2014) and WISE (2020)	2
Clindamycin	18323-44-9	Water	Pharmaceuticals Antibiotic	DE	JRC prioritisation dataset (2014): 436 samples from 1 MS are available in Sc2 inland whole water. About 30% quantified samples. The quality of monitoring is acceptable but the data are not EU-representative. MEC(P95) = 0.11 µg/L RQ=1.1 (lowest PNEC) No data available in the WISE (2020)	1
Metformin	657-24-9	Water Log K_{ow} = -1.43 (Janusinfo, SE)	Pharmaceuticals Antidiabetic	DE	Low risk according to AstraZeneca's Environmental Risk Summaries JRC prioritisation dataset (2014): 2090 samples from 2 MS are available in Sc2 inland whole water. About 97% quantified samples. The data quality is good but data are not Union-representative. MEC(P95) = 4.8 µg/L. RQ=0.48 (lowest PNEC) No data available in the WISE (2020)	1

Gabapentin	60142-96-3	Water	Pharmaceuticals antiepileptic	DE	JRC prioritisation dataset (2014): 1478 samples from 1 MS are available in Sc2 inland whole water. About 96% quantified samples. The data quality is good but data are not Union-representative. MEC(P95) = 3.8 µg/L) No data available in the WISE (2020)	2
Propranolol	525-66-6	Water	Pharmaceuticals Beta-blocker used for the treatment of hypertension, angina, certain types of anxiety, and the prevention of migraine	NL	PEC/PNEC = 0.016 µg/L /0.23 µg/L = 0.070 PEC/PNEC ≤ 0.1 The use of propranolol (sales data Sweden 2017) has been considered to result in insignificant environmental risk JRC prioritisation dataset (2014): 4069 samples from 4 MS are available in Sc2 inland whole water. About 13% quantified samples. The data quality is low. MEC(P95) = 0.02 µg/L; RQ=0.09. Few data available in the WISE (2020) WISE (2020): In Sc2 (inland surface water; Total) available only 24 samples (54.2% quantified) from 5 sites in 1 MS (2018). All of LOQs are equal to 0.03 µg/L. Median= 0.0325 µg/L MEC(P95) = 0.105 µg/L. The quantity of data is insufficient and the data are not EU-representative. RQ(P95)=0.46 (PNEC = 0.23 µg/L)	2

Dipyridamole	58-32-2	Water	Pharmaceuticals	NL	PEC/PNEC is based on sales data in Sweden in year 2013 PEC / PNEC = 0.21 (Janusinfo, SE) No available data in the JRC prioritisation dataset (2014) and WISE (2020) prioritisation exercise	3
Rodenticides:	Bromadiolone 28772-56-7	Water Log K_{ow} = 4.27 (FOOTPRINT, INERIS) BCF values of 339 to 575. It can be concluded that bromadiolone has potential to bioaccumulate	Biocides for controlling rodents Rodenticide Not approved as PPP Expiration 31/05/2021 Candidate for substitution This substance is approved for use as a biocide in the EEA and/or Switzerland, for: controlling rodents. (ECHA)	ES	Data available in the prioritisation dataset (inland whole water Sc2). No data available in the WISE (2020). Bromadiolone: 5368 samples from 2 MS; all non-quantified; low data quality; MEC(P95)=0.05 µg/L; RQ=2.94-0.13	2
	Brodifacoum 56073-10-0		Rodenticide Not approved as PPP This substance is approved for use as a biocide in the EEA and/or Switzerland, for: controlling rodents		Brodifacoum: 91 samples from 1 MS; all non-quantified; low data quality; MEC(P95)=0.005 µg/L; RQ=0.125	2
	Difenacoum 56073-07-5		Rodenticide Not approved as PPP Expiration 30/12/2019 Candidate for substitution This substance is approved for use as a biocide in the EEA and/or Switzerland, for: controlling rodents.		Difenacoum: 1298 samples from 1 MS; all non-quantified; low data quality; MEC(P95)=0.05 µg/L; RQ=0.83	2

Table AI.3. Substances fulfilling criterion 3. Abbreviations: MEC: measured environmental concentration; PNEC: predicted no effect concentration; RQ: risk quotient.

Group	Name	CAS No	Matrix	Status/Regulation	Environmental concentrations/ Monitoring	Priority (Table)
Antibiotics	Cefalexin	15686-71-2	water	Authorised	No available data in the JRC prioritisation dataset (2014) and WISE (2020)	1 (backup)
	Ofloxacin	82419-36-1	water	Authorised	JRC prioritisation dataset (2014): 277 samples from 3 MS; 69% quantified; the sensitivity of monitoring is good; the data quality is not acceptable since the data are not EU representative; Mean=0.051 µg/L; Median=0.01 µg/L; MEC(P95)=0.18 µg/L; RQ(P95)=0.36 (lowest PNEC) No available data in the WISE (2020)	1
Pharmaceuticals	Irbesartan	138402-11-6	Water Log K_{ow} = 1.13 at pH 7 (OECD 107) (Janusinfo, SE)	Authorised	PEC = 0.234 µg/L PEC/PNEC= 0.234/704 = 0.00033, i.e. PEC/PNEC ≤ 0.1 which justifies the phrase: "Use of Irbesartan has been considered to result in insignificant environmental risk." (FASS, SE) PEC/PNEC is based on sales data in Sweden in year 2016. PEC/PNEC = 0.000387 which gives the risk insignificant, i.e. consideration has not been given to measured levels in the environment. JRC prioritisation dataset (2014): 436 samples from 1 MS; 84.6% quantified; the data quality is good but the data are not EU representative; Mean=0.18 µg/L; Median=0.08 µg/L; MEC(P95)=0.55 µg/L; RQ(P95)=0.0008 (lowest PNEC) No available data in the WISE (2020)	2
	Midazolam	59467-70-8	Water	Authorised	PEC = 8.27*10 µg/L The PEC/PNEC ratio could not be calculated due to lack of data and therefore justifies the phrase: "Risk of	3

					environmental impact of midazolam cannot be excluded, since no ecotoxicity data are available" However, according to the European Medicines Agency guideline on environmental risk assessment of medicinal products (EMA/CHMP/SWP/4447/00), use of midazolam is unlikely to represent a risk for the environment, because the predicted (FASS, SE) No available data in the JRC prioritisation dataset (2014) and WISE (2020)	
Pharmaceuticals Chemotherapy Anti-cancer	Cyclophosphamide	50-18-0	Water	Authorised	JRC prioritisation dataset (2014): In Sc2 (inland whole water) monitored in 3 MS; available 763 samples from 153 sites; only 1.2% are quantified samples; about 86% of non-quantified samples were measured with LOQ = 0.001 µg/L; the data are not EU-representative (84.9% of all samples originate from 1 MS); Median = 0.0005 µg/l; MEC(P95) = 0.005 µg/L; RQ(P95)= (if PNEC is known) No available data in the WISE (2020)	3
	Daunorubicin	20830-81-3	water	Authorised	PEC = 0.00003 µg/L (FASS, SE) Monitoring data are not available in the JRC prioritisation dataset (2014) and WISE (2020)	3
	Doxorubicin	23214-92-8	water	Authorised	Monitoring data are not available in the JRC prioritisation dataset (2014) and WISE (2020	3
	Fluorouracil	51-21-8	water	Authorised	PEC = 0.018 µg/L (FASS, SE) Monitoring data are not available in the JRC prioritisation dataset (2014) and WISE (2020	3
	Mycophenolic acid	24280-93-1	water	Authorised	PEC = 0.3971 µg/L (FASS, SE) Monitoring data are not available in the JRC prioritisation dataset (2014) and WISE (2020	3
Illicit drugs	Cocaine and metabolite Benzoylecgonine	50-36-2 519-09-5	water		No available data in the JRC prioritisation dataset (2014) and WISE (2020)	2

	Methamphetamine, 3,4-methylene dioxymethamphetamine (MDMA) Ephedrine	537-46-2 4846-07-5 (in Nicola's database) 42542-10-9 321-97-1	water		Methamphetamine JRC prioritisation dataset (2014): 200 samples from 1 MS; 77.5% quantified; the data quality is good but the data are not EU representative; Mean=0.013 µg/L; Median=0.008 µg/L; MEC(P95)=0.041 µg/L; RQ(P95)=0.021 (lowest PNEC) No available data in the WISE (2020) MDMA and Ephedrine No available data in the JRC prioritisation dataset (2014) and WISE (2020)	2
	Cannabinol Tetrahydrocannabinol	521-35-7 1972-08-3	Cannabinoids CBN and CBD, because of the physical-chemical properties, tend to be adsorbed to the particulate matter rather than in the dissolved phase		No available data in the JRC prioritisation dataset (2014) and WISE (2020	2
PPP and Biocides	Metazachlor and metabolites	67129-08-2	water	Approved as PPP Herbicide Expiration: 31/07/2022 Authorised in: AT, BE, BG, CY, CZ, DE, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK	JRC prioritisation dataset (2014): 86815 samples from 15 MS (2006-2014); 8.7% quantified; the data quality could be improved because 4.5% of all samples are non-detected, only 45% of non-quantified samples have LOQs ≤ 0.02 µg/L and 2 MS holds 82.9% of all samples; Range of LOQs 0.002–20 µg/l; Mean=0.021 µg/L; Median=0.0125 µg/L; MEC(P95)=0.028 µg/L; RQ(P95)= N/A (missing PNEC) Available data in WISE (2020) WISE (2020): In Sc2 (inland surface water; Total and dissolve) available 46605 samples (20.2% quantified) from 2015 sites in 9 MS (2015-2018). Range of LOQs is 0.001 – 0.7 µg/L. Median= 0.005 µg/L MEC(P95) = 0.02 µg/L. The quality of data seems acceptable but it could not be evaluated in regard to PNEC since PNEC is missing.	2

Sunscreen agents	Avobenzone	70356-09-1	Water/sediment	In cosmetic products, the ingredient avobenzone is currently regulated as a UV-filter in sunscreen products in a concentration, in ready for use preparation, up to 5 % (Annex VI, 2020).	No available data in the JRC prioritisation dataset (2014) and WISE (2020)	1
	Oxybenzone	131-57-7	Water/sediment	In cosmetic products, the ingredient Benzophenone-3 (CAS No 131-57-7, EC No 205-031-5) with the chemical names Oxybenzone, 2-Hydroxy-4-methoxybenzone, (2-Hydroxy-4- methoxyphenyl) phenyl methanone and 2-Benzoyl-5-methoxyphenol is currently regulated as a UV-filter in sunscreen products in a concentration, in ready for use preparation, up to 6 % (Annex VI/4). Furthermore, Benzophenone-3 is also allowed in a concentration up to 0.5 % to protect product formulation in all other cosmetic products (Annex VI/4). Review of new scientific evidence is currently ongoing (SCCS, 2020). It is currently under assessment as a potential ED chemical under the ECHA's Community Rolling Action Plan (CoRAP, 2014).	No available data in the JRC prioritisation dataset (2014) and WISE (2020)	1
	Octocrylene	6197-30-4	Water/sediment	In cosmetic products, the ingredient Octocrylene (CAS No 6197-30-4, EC No 228-250-8) with the chemical	No available data in the JRC prioritisation dataset (2014) and WISE (2020)	1

				name 2-Cyano-3,3-diphenyl acrylic acid, 2-ethylhexyl ester is currently regulated as a UV-filter in sunscreen products in a concentration up to 10 % (as acid) (Annex VI/10). The Scientific Committee on Consumer Safety (SCCS) is currently evaluating the safety of octocrylene as a UV-filter in cosmetic products up to the maximum concentration of 10% (as acid), following a call for data occurred in 2019 (SCCS 2020). It is currently under assessment as a potential PBT chemical under the ECHA's Community Rolling Action Plan (CoRAP, 2014).		

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