National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Environmental risk limits for pharmaceuticals

Derivation of WFD water quality standards for carbamazepine, metoprolol, metformin and amidotrizoic acid

RIVM Letter report 270006002/2014
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Abstract

Surface water risk limits for pharmaceuticals

RIVM proposes water quality standards for three pharmaceuticals in surface water: carbamazepine (epilepsy), metoprolol (heart failure) and metformin (diabetes). During the past years, these pharmaceuticals have been found in surface water in the Netherlands. They were included in the so-called 'watchlist' of substances which can negatively affect water quality. The proposed quality standards can be used to better estimate possible risks for man and the environment. They serve as advisory values for the Ministry of Infrastructure and Environment, which is responsible for standard setting.

Methodology
For water quality standards, four exposure routes are taken into account: direct effects on ecosystems, secondary poisoning of fish-eating animals, consumption of fish by man and the abstraction of surface water for drinking water. The route with the most strict quality standard determines the final quality standard. The WFD methodology further distinguishes between standards protecting against prolonged and short-term exposure.

Availability of data
For another watchlist pharmaceutical, amidotrizoic acid (an X-ray contrast medium), the derivation of environmental quality standards turned out to be not possible. RIVM was not able to use the relevant data for this substance. In general, a lack of access to original study reports hampered a sound derivation of quality standards, also for the other compounds. RIVM makes a plea that pharmaceutical companies and competent authorities provide all information needed to derive environmental quality standards for pharmaceuticals.

Monitoring
Pharmaceuticals enter the environment through sewage. Monitoring data in surface waters in the Netherlands show that the proposed quality standards are not exceeded. However, these monitoring data concern large rivers and not the smaller water bodies with a lower dilution of the sewage effluent. At this moment, water boards are collecting monitoring data to assess if the proposed water quality standards are exceeded in these smaller water bodies.

This research was conducted by order of the Ministry of Infrastructure and Environment.

Keywords:
environmental risk limits, carbamazepine, metoprolol, metformin, amidotrizoic acid

Publiekssamenvatting

Oppervlaktewaternormen voor geneesmiddelen

Het RIVM doet een voorstel voor waterkwaliteitsnormen voor drie geneesmiddelen in oppervlaktewater. Het betreft carbamazepine (epilepsie), metoprolol (hartkwalen) en metformine (diabetes). Deze geneesmiddelen zijn de afgelopen jaren in Nederlands oppervlaktewater aangetroffen. Ze zijn opgenomen op een 'watchlist' van stoffen die de waterkwaliteit negatief kunnen beïnvloeden. De normvoorstellen kunnen worden gebruikt om de risico's voor mens en milieu beter in te schatten en dienen als advieswaardes voor het ministerie van Infrastructuur en Milieu (IenM), dat verantwoordelijk is voor het vaststellen van normen.

Methodologie
Voor waterkwaliteitsnormen worden de effecten van een stof op vier 'routes' onderzocht: schade aan ecosystemen, doorvergiftiging naar visetende dieren, consumptie van vis door mensen en oppervlaktewater voor de drinkwaterproductie. De route met de strengste norm bepaalt de uiteindelijke norm. Verder maakt de gebruikte Kaderrichtlijn water onderscheid tussen normen voor chronische en acute blootstelling.

Beschikbaarheid van gegevens
Voor een ander geneesmiddel op de 'watchlist', amidotrizoinezuur (röntgencontrastmiddel), was het niet mogelijk een norm af te leiden. Het RIVM kon niet beschikken over de benodigde gegevens. Ook voor de andere geneesmiddelen werd de normafleiding beïnvloed door een gebrek aan toegang tot originele onderzoeksgegevens. Het RIVM pleit ervoor dat de geneesmiddelenfabrikanten en de toelatingsautoriteiten alle gegevens ter beschikking stellen die nodig zijn om milieukwaliteitsnormen af te leiden.

Monitoring
Geneesmiddelen komen hoofdzakelijk via het riool in het oppervlaktewater terecht. Meetgegevens in Nederlandse oppervlaktewateren laten zien dat de voorgestelde normen niet worden overschreden. De metingen zijn echter gedaan in grote rivieren en niet in kleinere waterlichamen, waar minder verdunning van afvalwater optreedt. Waterbeheerders verzamelen momenteel meetgegevens om na te gaan in hoeverre de voorgestelde normen in deze kleinere wateren worden overschreden.

Het onderzoek is uitgevoerd in opdracht van het ministerie van Infrastructuur en Milieu.

Trefwoorden:
milieurisicogrenzen, carbamazepine, metoprolol, metformine, amidotrizoinezuur

Contents

Summary

RIVM proposes water quality standards for three pharmaceuticals in surface water: carbamazepine (epilepsy), metoprolol (heart failure) and metformin (diabetes). During the past years, these pharmaceuticals have been detected frequently in Dutch surface waters used for drinking water abstraction. Based on indicative risk limits they were included in the so-called 'watchlist' of substances which can negatively affect water quality. As a follow-up, the Dutch Ministry of Infrastructure and the Environment ordered RIVM to propose water quality standards to put the results of a nationwide monitoring campaign into perspective.

The proposed standards are based on ecotoxicity data from the national and European authorisation dossiers and additional information obtained from the open literature. The methods used are in accordance with the methodology of the Water Framework Directive (WFD) and national frameworks for risk limit derivation. The proposed quality standards serve as advisory values for the Ministry of Infrastructure and Environment, which is responsible for standard setting.

The WFD distinguishes two types of water quality standards: (1) a long-term standard, expressed as an annual average concentration (AA-EQS) and normally based on chronic toxicity data. This standard should protect the ecosystem against adverse effects resulting from long-term exposure; and (2) a standard for short-term concentration peaks, referred to as a maximum acceptable concentration EQS (MAC-EQS). For the AA-EQS, four exposure routes are taken into account: direct effects on ecosystems, secondary poisoning of fish-eating animals, consumption of fish by man and the abstraction of surface water for drinking water. The route with the most strict quality standard determines the final quality standard.

For amidotrizoic acid (an X-ray contrast medium), the derivation of environmental quality standards turned out to be not possible. RIVM was not able to use the relevant data for this substance. In general, a lack of access to original study reports hampered the derivation of quality standards, also for the other compounds. RIVM makes a plea that pharmaceutical companies and competent authorities transparently provide all information needed to derive environmental quality standards.

An overview of the proposed quality standards for the other compounds is presented in Table 1. All values are expressed on the basis of dissolved concentrations, but in view of the relatively low sorptive capacity of the compounds they are applicable to the total fraction as well.

Pharmaceuticals enter the environment through sewage. Monitoring data in surface waters in the Netherlands show that the proposed quality standards are not exceeded. However, these monitoring data concern large rivers and not the smaller water bodies with a lower dilution of the sewage effluent. At this moment, water boards are collecting monitoring data to assess if the proposed water quality standards are exceeded in these smaller water bodies.

Table 1. Derived AA-EQS, MAC-EQS, NC, , SRC, $QS_{dw, hh}$ values for three pharmaceuticals.

Compound	**Fresh or salt water**	**Quality standard (µg/L)**				
		AA-EQS	NC	MAC-EQS	SRC_{eco}	$QS_{dw, hh}$
Carbamazepine	Fresh	0.50	0.005	1600	1430	54
	Salt	0.05	0.0005	160	1430	n.a.
Metoprolol	Fresh	62	0.62	760	12100	9.8
	Salt	6.2	0.062	76	12100	n.a.
Metformin	Fresh	780	7.8	780	n.d.	196
	Salt	78	0.78	78	n.d.	n.a.

n.a. = not applicable
n.d. = not determined due to a lack of data

1 Introduction

1.1 Background and aim

In this report, a proposal is made for water quality standards for four pharmaceuticals: carbamazepine, metoprolol, metformin, and amidotrizoic acid. The Water Framework Directive (WFD) requires member states to identify substances that may potentially harm water quality. In 2012, an inventory was made on occurrence and potential risks of substances in Dutch surface waters, based on information of water owners and drinking water companies [1]. Based on that research, the aforementioned compounds were identified as being potentially relevant for the quality of surface waters in the Netherlands and included in a so-called Dutch watchlist [1]. This list contains (new) substances for which monitoring data indicate that they might become a problem for the ecological and/or drinking water function of Dutch surface waters, but for which too little information is available at this stage for standard setting and/or inclusion in national legislation under the WFD. The Dutch watchlist has no legal status, but is meant to focus further research, e.g. concerning monitoring or (eco)toxicological risks. To further underpin future policy decisions regarding these substances, Smit and Wuijts [1] advised to collect monitoring data on a nationwide scale and to derive water quality standards according to the methodology of the WFD [2] to compare the monitoring data to. The Dutch Ministry of Infrastructure and the Environment commissioned RIVM to propose such standards.

1.2 Standards considered

Under the WFD, two types of EQSs are derived to cover both long- and short-term effects resulting from exposure:

- an annual average concentration (AA-EQS) to protect against the occurrence of prolonged exposure, and
- a maximum acceptable concentration (MAC-EQS) to protect against possible effects from short term concentration peaks.

In Dutch, these two WFD-standards are indicated as '*JG-MKN*' and '*MAC-MKN*', respectively[1].

Next to the AA-EQS and MAC-EQS, the WFD also considers a standard for surface water used for drinking water abstraction. Below, a short explanation on the respective standards is provided and the terminology is summarised in Table 2. Note that all standards refer to dissolved concentrations in water.

- Annual Average EQS (AA-EQS) – a long-term standard, expressed as an annual average concentration (AA-EQS) and normally based on chronic toxicity data which should protect the ecosystem agains adverse effects resulting from long-term exposure.

  The AA-EQS should not result in risks due to secondary poisoning and/or risks for human health aspects. These aspects are therefore also addressed in the AA-EQS, when triggered by the characteristics of the compound (i.e. human toxicology and/or potential to bioaccumulate).

[1] JG = Jaargemiddelde = annual average; MKN = milieukwaliteitsnorm = environmental quality standard.

Separate AA-EQSs are derived for the freshwater and saltwater environment.

- Maximum Acceptable Concentration EQS (MAC-EQS) for aquatic ecosystems – the concentration protecting aquatic ecosystems from effects due to short-term exposure or concentration peaks. The MAC-EQS is derived for freshwater and saltwater ecosystems, and is based on direct ecotoxicity only.

- Quality standard for surface water that is used for drinking water abstraction ($QS_{dw, hh}$). This is the concentration in surface water that meets the requirements for use of surface water for drinking water production. The $QS_{dw, hh}$ specifically refers to locations that are used for drinking water abstraction.

The quality standards in the context of the WFD refer to the absence of any impact on community structure of aquatic ecosystems. Hence, not the potential to recover after transient exposure, but long-term undisturbed function is the protection objective under the WFD. Recovery in a test situation, after a limited exposure time, is therefore not included in the derivation of the AA- and MAC-EQS.

Table 2. Overview of the different types of WFD-quality standards for freshwater (fw), saltwater (sw) and surface water used for drinking water (dw) considered in this report.

Type of QS	Protection aim	Terminology for temporary standard[1]	Notes	Final selected quality standard
long-term	Water organisms	$QS_{fw, eco}$ $QS_{sw, eco}$	Refers to direct ecotoxicity	lowest water-based QS is selected as AA-EQS_{fw} and AA-EQS_{sw}
	Predators (secondary poisoning)	$QS_{biota, secpois, fw}$ $QS_{biota, secpois, sw}$	QS for fresh- or saltwater expressed as concentration in biota, converted to corresponding concentration in water	
		$QS_{fw, secpois}$ $QS_{sw, secpois}$		
	Human health (consumption of fishery products)	$QS_{biota, hh food}$	QS for water expressed as concentration in biota, converted to corresponding concentration in water; valid for fresh- and saltwater	
		$QS_{water, hh food}$		
short-term	Water organisms	MAC-$QS_{fw, eco}$ MAC-$QS_{sw, eco}$	Refers to direct ecotoxicity; check with $QS_{fw, eco}$ and $QS_{sw, eco}$	MAC-EQS_{fw} MAC-EQS_{sw}
dw	Human health (drinking water)		Relates to surface water used for abstraction of drinking water	$QS_{dw, hh}$

1: Note that the subscript "fw" refers to the freshwater, "sw" to saltwater; subscript "water" is used for all waters, including marine.

For the purpose of national water quality policy, e.g. discharge permits or specific policy measures, two additional risk limits are derived:

- Negligible Concentration (NC) – the concentration in fresh- and saltwater at which effects to ecosystems are expected to be negligible and functional properties of ecosystems are safeguarded fully. It defines a safety margin which should exclude combination toxicity. The NC is derived by dividing the AA-EQS by a factor of 100, in line with [3, 4].

- Serious Risk Concentration for ecosystems (SRC_{eco}) – the concentration in water at which possibly serious ecotoxicological effects are to be expected. The SRC_{eco} is valid for the freshwater and saltwater compartment.

Quality standards for sediment and suspended matter in surface water will not be derived in this report, because for these compounds they are not relevant for compliance check within the context of national water quality policy.

2 Methods

2.1 General

The methodology is in accordance with the European guidance document for derivation of environmental quality standards under the WFD [2]. This document is further referred to as the WFD-guidance. Additional guidance for derivation of quality standards that are specific for the Netherlands, such as the NC and SRC, can be found in [5]. This guidance document was prepared for derivation of quality standards in the context of the former project "International and national environmental quality standards for substances in the Netherlands (INS)", and is further referred to as the INS-guidance. It should be noted that the WFD-guidance deviates from the INS-guidance for some aspects. This specifically applies to the treatment of data for freshwater and marine species (see section 4.1) and the derivation of the MAC (see section 4.4). This also holds for the quality standard for surface waters intended for the abstraction of drinking water ($QS_{dw, hh}$, see section 4.3). Where applicable, the WFD-guidance is followed and the INS-guidance is used for situations which are not covered by the former.

2.2 Data collection and evaluation

The derivation of the quality standards for the pharmaceuticals is based on data available in the public domain and on data from industry. An on-line literature search was performed via SCOPUS and data were retreived from the fass.se website. Publicly available reports from quality standard derivations by other institutions in other countries were also used. The original publications used in these reports were re-assessed.

Because a lot of data is generated for the marketing authorisation of pharmaceuticals, all marketing authorisation holders for products containing these four pharmaceuticals in the Netherlands were invited to share data. Positive reactions were received from a number of marketing authorisation holders. With their permission, the dossier data was accessed and evaluated using the internal database system of the Medicines Evaluation Board. These studies were evaluated, according to the procedure below (see 2.3), but only the endpoints are presented in this report because of confidentiality claims of the data owners. This is a deviation from the normal procedure as described in the WFD- and INS-guidance, and it is recognised that transparency is reduced to some extent. However, not being able to use the data was considered an even less desirable option.

2.3 Data evaluation

Ecotoxicity studies were screened for relevant endpoints (i.e. those endpoints that have consequences at the population level of the test species) and thoroughly evaluated with respect to the validity (scientific reliability) of the study. A detailed description of the evaluation procedure is given in section 2.2.2 and 2.3.2 of the INS-Guidance and in the Annex to the EQS-guidance under the WFD. In short, the following reliability indices were assigned, based on Klimisch et al [6]:

Ri 1: Reliable without restriction 'Studies or data … generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to GLP) or in which the test parameters documented are

based on a specific (national) testing guideline … or in which all parameters described are closely related/comparable to a guideline method.'

Ri 2: Reliable with restrictions 'Studies or data … (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable.'

Ri 3: Not reliable 'Studies or data … in which there are interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g., unphysiologic pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for an assessment and which is not convincing for an expert judgment.'

Ri 4: Not assignable 'Studies or data … which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.).'

All available studies are summarised in data-tables, which are available in the Annexes to this report. These tables contain information on species characteristics, test conditions and endpoints, except for studies for which data confidentiality was claimed (see above). Explanatory notes are included with respect to the assignment of the reliability indices.

2.4 Status of the results

The results presented in this report have been discussed by the members of the scientific advisory group for standard setting in the Netherlands (*WK-normstelling water en lucht*), supplemented with representatives from industry. It should be noted that the proposed quality standards in this report are scientifically derived values, based on (eco)toxicological, fate and physico-chemical data. They serve as advisory values for the Dutch Ministry of Infrastructure and Environment, that is responsible for setting Environmental Quality Standards. The presented quality standards should thus be considered as advisory values that do not have an official status.

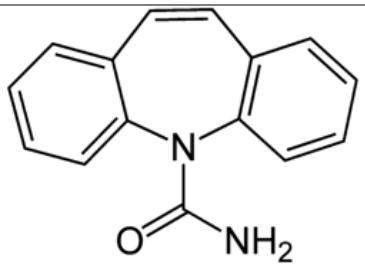
3 Carbamazepine

3.1 Introduction

Carbamazepine has been selected by Smit and Wuijts [1] after it was put forward by the Association of River Waterworks (RIWA) as a drinking water relevant compound. The compound is frequently detected in surface water used for drinking water abstraction at concentrations higher than 0.1 µg/L, which is the target set by the International Association of Waterworks in the Rhine Catchment Area (IAWR) for toxicologically relevant substances [7]. Rijkswaterstaat, the governmental board responsible for main rivers and large waterbodies, also put forward carbamazepine as a potentially relevant compound, because together with its degradation products it is one of the drugs that is most frequently found in surface water. The compound has been considered for the revision of the list of priority substances under the WFD, but in the end it was not included in Directive 2013/39/EU. Carbamazepine is included in the monitoring programme ("Rijnstoffenlijst 2011") of the International Commission for the Protection of the Rhine [8] because of its relevance for drinking water production.

3.2 Identity

Table 3. Identity of carbamazepine

Name	Carbamazepine
Chemical name	5*H*-Dibenz[b,f]azepine-5-carbamide
CAS number	298-46-4
EC number	206-062-7
Molecular formula	$C_{15}H_{12}N_2O$
Molar mass	236.27
Structural formula	
SMILES code	NC(=O)N1C2=C(C=CC=C2)C=CC2=C1C=CC=C2

3.3 Information on uses and emissions

Carbamazepine is an active pharmaceutical ingredient used for the treatment of epilepsy, trigeminal neuralgia, bipolar depression, excited psychosis, and mania. A total of 28 products with carbamazepine are registered in the Netherlands [9]. Although it is suggested that due to the ageing population carbamazepine use might increase from 8400 kg in 2007 to 8990 kg by 2020 [10], currently the estimated number of users in the Netherlands shows a decrease from almost 56000 in 2006 to around 44000 in 2012 (GIPdatabank.nl). Novartis provided data from the IMS database, showing that total consumption of carbamazepine in the EU decreased from 387 tons in 2008 to 351 tons in 2013. In the Netherlands, carbamazepine consumption decreased from 9.7 tons in 2008 to 8.6 tons in 2013 (personal communication Novartis). Estimated emissions to surface water in the Netherlands were 1090, 1093 and 1067 kg/y in 2005, 2007 and 2008, respectively [11].

3.4 Existing or proposed water quality standards, risk limits, etc.

For the evaluation of carbamazepine as a candidate for the Dutch watchlist, Smit and Wuijts [1] collected relevant environmental risk limits from readily available datasources.

Table 4. Existing environmental risk limits for carbamazepine

Country	Value [µg/L]	Remark	Reference
Switzerland	0.5	AA-EQS, NOEC *Ceriodaphnia dubia*, with AF 50	[12]
Switzerland	2550	MAC-EQS, EC50 *Lemna minor* with AF 100	[12]
EU	0.5	Draft AA-EQS, NOEC *C. dubia*, with AF 50	[13]
Norway	4.92	PNEC	[14]
Sweden	17	PNEC, industry MSDS	[15]
	0.1	target value for pharmaceuticals in surface water for abstraction of drinking water	[7]

3.5 Physico-chemical properties and fate in the environment

Table 5. Physico-chemical properties of carbamazepine

Parameter	Unit	Value	Remark	Reference
Molecular weight	[g/mol]	236.27		[12]
Water solubility	[mg/L]	17.66	Estimated	[12]
		112	Experimental value	
pK_a	[-]	15.37	Estimated; value is too high to be relevant in environmental conditions.	[12]
		13.94		[12]
log K_{OW}	[-]	2.25	Estimated	[12]
		2.45	Experimental value	
Vapour pressure	[Pa]	1.17×10^{-5}	at 25°C, estimated	[12]
		1.84×10^{-7}	at 25°C; unknown if experimental or estimated	[13]
Melting point	[°C]	190.2	Experimental value	[12]
Boiling point	[°C]	410.02	Estimated	[12]
Henry's law constant	[Pa/m^3.mol]	1.1×10^{-5} - 1.6×10^{-4}	Estimated	[12]

Log K_{OC} values of 2.23 – 3.12 are reported [12]. In the European datasheet, K_{OC} values for sludge range from 3.5 - < 57 L/kg and for soil from 116.3 – 1250 L/kg [13].

The derived quality standards are based on dissolved concentrations. In view of the sorption data, these concentrations can be assumed to be valid for the total fraction as well.

Carbamazepine has a number of metabolites or degradation products, which are also found in the environment in concentrations >10% of the parent compound [16]. Within the scope of the present quality standard derivation, the degradation products are not taken into account. Within the scope of a similar quality standard derivation in Germany and Switzerland, toxicity tests on the metabolites might be performed upon request.

3.6 Bioconcentration and biomagnification

Schwaiger et al. [17] report organ-BCFs for *Cyprinus carpio*, with a highest BCF of 12 L/kg for the liver. These data are confimed by the study of Garcia et al. [18], who report 42-days kinetic organ-BCFs for *Pimephales notatus* and *Ictalurus punctatus*, with the highest organ-BCFs of 4.6 L/kg for the liver of *P. notatus* and 7.1 for plasma in *I. punctatus*. Furthermore, a plasma-BCF in the range of 0.8 – 4.2 L/kg is reported (Fick, 2010 in [13]). A calculated BCF of 63.2 L/kg at pH 4-10 is also reported (ACD Daten Bank, 2004 in [13]). In view of these data, the risk of secondary poisoning seems to be negligible. Although whole-body BCFs are more relevant for deriving quality standards for secondary poisoning than organ-based BCFs, it can be assumed that the highest organ-based BCF is worst-case for the whole-body BCF. For derivation of the quality standard for human consumption of fishery products, the worst-case measured BCF in liver of 12 L/kg is used with a BMF of 1.

3.7 Human toxicological threshold limits and carcinogenicity

Certain evidence of reproductive adverse effects at clinical doses is reported by Novartis [13]. The compound is self-classified as Repr. 1B, Repr. 2 and Carc. 2 by some industry notifiers in the ECHA database (www.echa.europe.eu; accessed on January 9, 2014). Epidemiological data show that carbamazepine causes teratogenicity in humans (e.g., spina bifida). Genotoxicity is reported as negative [19].

A provisional drinking water standard of 50 µg/L is reported by [20], based on the lowest therapeutic dose for humans of 100 mg/day [21]. For a 60 kg adult this dose corresponds to 1.66 mg/kg_{bw}/day. With a safety margin of 100, a provisional ADI of 16.6 µg/kg_{bw}/day and a provisional drinking water standard of 50 µg/L have been derived.

A LOAEL of 100 mg/d, corresponding to 1.43 mg/kg_{bw}/day for an adult of 70 kg is reported [22]. This results in a human toxicological threshold limit of 15.9 µg/kg_{bw}/day by using a factor of 3 for extrapolation of LOAEL to NOAEL, a factor of 3 to protect sensitive groups, and a factor of 10 for possible carcinogenicity [22].

Novartis has provided a derivation of the ADI for carbamazepine, based on the same information, and arrives at the same ADI of 15.9 µg/kg_{bw}/day (Novartis, personal communication)

Inéris [23] used a LOAEL of 100 mg/kg_{bw}/day for carcinogenicity in rats with a factor of 3000 (3 for extrapolation to NOAEL, 10 for intraspecies variability, 10 for interspecies variability, 10 for toxic mechanism). This results in an ADI of 33 µg/kg_{bw}/day.

A human toxicological threshold limit of 0.34 µg/kg/day is reported by Schriks et al. [24] based on a maximum tolerated dose (MTD) of 250 mg/kg bw/d for carcinogenicity in rats. Apparently, a safety factor of 740,000 is used, which is not further explained in the Schriks publication.

For the teratogenic mode of action in humans, which is a severe effect for which the ADI should offer enough protection, various reviews estimate a LOAEL of 3.0 mg/kg_{bw}/day (based on a lowest therapeutic dose of 200 mg/day for an adult) [19, 25]. With a total factor of 900 (3 for extrapolation to NOAEL, 3 for sensitive groups in the population, 10 for possible carcinogenicity, 10 for the limited amount of data), this results in an ADI of 3.3 µg/kg_{bw}/day [25]. [19] arrive at an ADI of 10 µg/kg_{bw}/day using a total factor of 300 (10 for extrapolation to NOAEL, 3 for sensitive groups, 3 for extrapolation of subchronic to chronic, 3 for limited database).

Concludingly, due to the lack of original data which can be assessed for reliability, a pragmatic approach regarding the derivation of an ADI is needed. Teratogenicity is an important endpoint, but dose-response data are hardly available. Because there is no genotoxicity, a limit value can be used for carcinogenicity. Based on the information presented above, a rounded ADI-value of 16 µg/kg_{bw}/day will be used to assess if human exposure via fish will be the most critical route for risk limit derivation.

3.8 Aquatic toxicity data

An overview of the aggregated ecotoxicity data for carbamazepine for freshwater and marine species is given in Table 6. There are too few data to perform a meaningful statistical comparison between freshwater and marine species. Since there are no further indications of a difference in sensitivity between freshwater and marine organisms and the behaviour of carbamazepine is not expected to differ between freshwater and marine systems, the toxicity data may be combined [2]. Detailed toxicity data for carbamazepine are tabulated in separate Excel tables, which are taken up as annexes to this report. Only valid studies were used to construct the aggregated data table, with geometric means if per species more data were available for the same endpoint.

Table 6. Aggregated toxicity data for carbamazepine to fresh water organisms. All data with (s) *are salt water data.*

Chronic[a]		**Acute**[a]	
Taxonomic group	**NOEC/EC10 (mg/L)**	**Taxonomic group**	**L(E)C50 (mg/L)**
Bacteria		**Bacteria**	
Vibrio fisheri (s)	8.9[a]	*Vibrio fisheri* (s)	64.0[f]
Cyanobacteria		**Cyanobacteria**	
Synechococcus leopolensis	17.5	*Synechococcus leopolensis*	33.6
Algae		**Algae**	
Cyclotella meneghiniana	10	*Chlorella vulgaris*	36.6
Chlorella pyrenoidosa	0.5[b]	*Cyclotella meneghiniana*	31.6
Chlorella vulgaris	11.8	*Desmodesmus subspicatus*	74
Dunaliella tertiolecta (s)	10[b]	*Dunaliella tertiolecta* (s)	296[g]
Scenedesmus obliquus	0.5[b]		
Pseudokirchneriella subcapitata	0.5[b]	**Macrophyta**	
		Lemna minor	25.5
Rotifera		**Rotifera**	
Brachionus calyciflorus (s)	0.377	*Brachionus koreanus* (s)	138.6
Crustacea		**Cnidaria**	
Ceriodaphnia dubia	**0.025**[c]	*Hydra attenuata*	**15.52**[h]
Daphnia magna	0.4[d]		
Daphnia pulex	0.1	**Crustacea**	
		Ceriodaphnia dubia	77.7
Pisces		*Daphnia magna*	70.0[i]
Danio rerio	12.5[e]		
		Pisces	
		Danio rerio	35.4
		Oncorhynchus mykiss	19.9
		Oryzias latipes	35.4

[a] geometric mean of 14.2 and 5.59 mg/L for bioluminescence.
[b] most relevant edpoint: growth rate; most relevant exposure time: 96 h.
[c] most sensitive exposure time: 7 days
[d] lowest NOEC for reproduction and growth
[e] lowest relevant endpoint: NOEC for hatching
[f] geometric mean of 52.2 and 78.4 mg/L for bioluminescence, most relevant exposure time: 15 min.
[g] most relevant exposure time: 96 h
[h] lowest endpoint: EC50 for growth, morphology, feeding
[i] geometric mean of 67.5, 111, 76.3, 97.88, and 30 mg/L for immobilisation

The lowest reliable chronic toxicity value is the NOEC of 0.025 mg/L for reproduction in *Ceriodaphnia dubia* by Ferrari et al. [26]. Lamichhane et al. [27] report a nominal NOEC of 0.104 mg/L for the same species, and an EC10 of 0.054 mg/L could be calculated using the data from that study with a correction

for actual measured concentrations (see the detailed tables in the Annex to this report). Because this endpoint is derived for a different exposure time (14 days) than that by Ferrari et al., the lowest of the two is used. An industry report shows a NOEC of 17 mg/L for the same species with the same duration and the same endpoints (confidential data by Novartis). Because the difference between these values is a factor of 1000, it is not possible to use the geometric mean of these values. As there is no reason to invalidate the Ferrari (and Lamichhane) studies, this study will be used for the derivation of the quality standard.

In addition to the data in the aggregated data table, data are available from a subchronic study (10 days exposure) to *Hyalella azteca* and *Chironomus riparius*. Because this study is neither acute (i.e. 4-day exposure according to OECD 235) nor chronic (28-day exposure according to OECD 218), it is not included in the aggregated data table. The available data for the sub-lethal endpoint (growth) for these species, an EC10 of 2.6 mg/L for *C. riparius* and an EC10 of 2.4 mg/L for *H. azteca*, shows that these species are most likely not more sensitive than the species already present in the chronic dataset.

Toxicity tests with fish or amphibian embryos are regarded as chronic studies, even if the exposure time is only 48 or 96 hours, since more than one life-stage and/or the most sensitive life-stage is tested during these studies. Because the endpoint resulting from the amphibian embryo study is a higher-than value, it is not taken up into the aggregated data table.

In addition to the information presented above, chronic data for *Cyprinus carpio* are available from a report by Schwaiger et al. [17] and a publication by Triebskorn et al. [28]. This is the same experiment, with more details reported in the Schwaiger report than in the Triebskorn publication [17]. In the Schwaiger report, the detailed data show clearly that there is no effect on histopathological or blood parameters up to the highest test concentration (LOEC > 0.1 mg/L; NOEC ≥ 0.1 mg/L). Even when there seems to be an effect (for instance on plasma enzymes), the effect is not dose-related and seems more an artefact of the many variables studied, than a real physiological effect. However, Triebskorn et al. [28] does report a LOEC of 0.001 mg/L for effects on the kidney. Looking at the detailed data in Schwaiger et al., this does not seem a reliable endpoint and may again be merely an artefact of the amount of variables studied. Moreover, there is still debate if these endpoints are population relevant; where for blood parameters this does not seem to be the case, in the Diclofenac dossier for the European Commission [29], histopathological changes for *Oncorhynchus mykiss* in the same Triebskorn/Schwaiger study were accepted as relevant endpoints and included in the proposed quality standard derivation. These histopathological changes for diclofenac were much more pronounced and did show a dose-reponse relationship. However, recently a review of these studies was published, suggesting that also for diclofenac the findings were not clear [30], but the discussion within the EU is still on-going.

In view of the uncertainty regarding the studies discussed above, we decided not to use the data from the Triebskorn/Schwaiger study for derivation of the EQS for carbamazepine. The results were either not relevant for the ecolotoxicological risk limits derived here (blood parameters) or not reliable (no clear dose-response relationship for kidney histopathological effects).

Galus et al. [31] tested toxicity of carbamazepine to *Danio rerio* at 0.0005 and 0.01 mg/L. Effects on egg production were shown, but these were not dose-related and could be an artefact of the egg collection method. Also the histopathological changes in the kidney for both male and female did not seem to be dose-related. No incidence of effects was shown for histopathological changes in the liver. The gonads of female fish were affected at both concentrations, with a higher effect at the highest concentration (no effects on gonads in male fish). The study has some methodological shortcomings (2 grams of fish per liter, renewal only every 3 days), and thus results will be used as supporting information, but not as critical endpoints.

3.9 Derivation of Environmental Risk Limits

3.9.1 Derivation of $QS_{fw, eco}$ and $QS_{sw, eco}$

The acute base set is complete. Chronic data are available for six taxonomic groups, with the lowest NOEC-value of 0.025 mg/L for *Ceriodaphnia dubia*. Because there are no chronic data of the acutely most sensitive taxonomic group (Cnidaria), an assessment factor of 50 should be applied. Thus, the $QS_{fw, eco}$ is 0.025 /50 = 0.0005 mg/L = 0.50 µg/L.

For salt water systems, the $QS_{sw, eco}$ can be derived based on the same value of 0.025 mg/L for *C. dubia*. With an assessment factor of 500 (no additional specific marine taxonomic groups in the chronic dataset), this results in a $QS_{sw, eco}$ of 25 / 500 = 0.050 µg/L.

As indicated above, the data for the insect *C. riparius* could not be used since this species was tested only semi-chronically. Valid acute and chronic data on this species and/or *H. azteca* might reduce the uncertainty regarding the most sensitive taxon, in view of which a safety factor of 50 had to be applied in the present derivation. A further reduction of the uncertainties regarding this risk limit derivation could well be possible, if more data were present that would allow for using statistical extrapolation by means of a species sensitivity distribution (SSD).

3.9.2 Derivation of $QS_{water, hh food}$

A quality standard for human consumption of fishery products needs to be derived because of the reported reprotoxic effects [13].

The $QS_{water, hh food}$ represents the concentration in water that will be protective for humans upon consumption of fishery products. The $QS_{water, hh food}$ is valid for freshwater and marine waters. First, the maximum permissible concentration in fish ($QS_{biota, hh food}$) is calculated based on an ADI of 16×10^{-3} mg/kg_{bw}/day (see 3.7), assuming a body weight of 70 kg, a daily intake of 115 g fish, and a maximum contribution to the ADI of 10%.

The $QS_{biota, hh food}$ is then $(0.1 \times 16 \times 10^{-3} \times 70) / 0.115 = 0.97$ $mg/kg_{biota\ ww}$.

Subsequently, the $QS_{water, hh food}$ is converted to equivalent concentrations in water using the BCF of 12 L/kg and BMF of 1 kg/kg as derived in section 3.6. The resulting $QS_{water, hh food}$ is calculated as 0.97 / (12 × 1) = 0.081 mg/L = 81 µg/L.

3.9.3 *Choice of AA-EQS*

For freshwater ecosystems, a $QS_{fw, eco}$ of 0.50 µg/L and a $QS_{water, hh food}$ of 81 are derived. The lowest of these is the overall AA-EQS_{fw}, which means that the AA-EQS_{fw} is set at 0.50 µg/L.

For saltwater ecosystems, a $QS_{sw, eco}$ of 0.050 µg/L and a $QS_{water, hh food}$ of 81 resp. 17 µg/L are derived. The lowest of these is the overall AA-EQS_{sw}, which means that the AA-EQS_{sw} is set at 0.050 µg/L.

The comparisons above show that the quality standard for human consumption of fishery products, is not the most critical quality standard and the safety margin between these quality standards is more than a factor of 100.

3.9.4 *Derivation of MAC-EQS_{fw} and MAC-EQS_{sw}*

Because there are no acute toxicity data for insects, the requirements to perform an SSD are not met.

Using the assessment factor method, the $MAC_{fw, eco}$ is derived with the lowest value of 15.5 mg/L for *Hydra attenuata*. The standard deviation of the log-transformed acute data is below 0.5, and thus an assessment factor of 10 can be applied, resulting in a MAC-EQS_{fw} of 1.6 mg/L.

It is noted that the difference between the AA-EQS and MAC-EQS is more than a factor of 1000, which is due to the high acute-to-chronic ratio. When monitoring data are compared with the standards according to the procedures under the WFD, exceedance of the MAC-EQS will automatically lead to exceedance of the AA-EQS. This means that the MAC-EQS for imidacloprid is of little relevance from the viewpoint of compliance check. However, it may be used for other purposes as well, such as actual risk assessment of incidental peaks.

The saltwater species *Brachionus koreanus* is not considered as a specifically marine taxon in a sense that the life form or feeding strategy differ from those of related freshwater species. Therefore , the MAC-EQS_{sw} should be derived using an additional assessment factor of 10 (), which results in a MAC-EQS_{sw} of 1.6 / 10 = 0.16 mg/L.

3.9.5 *Derivation of NC_{fw} and NC_{sw}*

The NC is a factor of 100 below the AA-EQS. The NC_{fw} is 0.50 / 100 = 0.005 µg/L (5 ng/L), the NC_{sw} is 0.0005 µg/L (0.5 ng/L).

3.9.6 *Derivation of $SRC_{fw, eco}$ and $SRC_{sw, eco}$*

Because more than three chronic toxicity values are available, the SRC_{eco} is taken as the geometric mean of all chronic toxicity data. Thus, the SRC_{eco} is 1.43 mg/L. This value is valid for freshwater and saltwater.

3.9.7 *$QS_{dw, hh}$*

Within the WFD, it is assumed that the level of purification of waters intended for drinking waters should be reduced. Thus, a simple treatment of water abstracted for use as drinking water is assumed [2].

Carbamazepine is considered difficult to remove by current methods for surface water treatment (only 0-40% removed; [32]{Ter Laak, 2010 #38. Thus, in line

with the WFD methodology for the calculation of the $QS_{dw, hh}$ 0% removal is assumed.

With an ADI of 15.5 × 10^{-3} mg/kg_{bw}/day = 15.5 µg/kg_{bw}/day (see section 3.7), assuming a body weight of 70 kg, a daily intake of 2 L water, and a maximum contribution to the ADI of 10%, the $QS_{dw, hh}$ becomes (15.5 x 0.1 x 70) / 2 = 54 µg/L.

Because this $QS_{dw, hh}$ is higher than the QS_{fw}, this means that the QS_{fw} is also protective for drinking water abstraction when human-toxicological information is used as a basis. However, the proposed target value for pharmaceuticals according to the DMR-memorandum [7] is 0.1 µg/L, which is lower than the QS_{fw}.

3.10 Comparison with monitoring data

In Table 7, an overview is given of monitoring data of carbamazepine.

Table 7. Monitoring data of carbamazepine in the Netherlands

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark (location)	Reference
2003		0.227				263 measurements; RIWA data	[24]
2006	<	0.12	0.06	0.0539	0.081	28 (Brakel)	[33]
	0.03	0.12	0.065	0.0692	0.12	12 (Lobith)	
	0.04	0.15	0.08	0.0821	0.112	117 (Nieuwegein)	
	0.05	0.13	0.09	0.0893	0.118	15 (Nieuwersluis)	
	<	0.08	0.07	0.0635	0.08	13 (Andijk)	
2007	<	0.07	0.05	<	0.06	29 (Brakel)	[33]
	0.027	0.14	0.06	0.0716	0.136	13 (Lobith)	
	<	0.12	0.08	0.067	0.11	13 (Nieuwegein)	
	0.05	0.1	0.08	0.0757	0.095	14 (Nieuwersluis)	
	0.04	0.07	0.05	0.05	0.07	13 (Andijk)	
2008	<	0.06	*	<	*	8 (Luik)	[33]
	<	0.07	<	<	0.062	27 (Brakel)	
	<	0.09	<	<	0.086	13 (Keizersveer)	
	0.026	0.12	0.057	0.061	0.109	13 (Lobith)	
	0.05	0.08	0.07	0.0669	0.08	13 (Nieuwegein)	
	0.05	0.11	0.08	0.08	0.106	13 (Nieuwersluis)	
	0.04	0.06	0.05	0.05	0.06	13 (Andijk)	
2009	0.059	*	0.03	*	*	7 (Luik)	[33]
	<	<	<	<	<	122 (Heel)	
	<	0.13	0.06	0.059	0.11	29 (Brakel)	
	0.03	0.12	0.06	0.0687	0.12	15 (Keizersveer)	
	0.039	0.16	0.078	0.0824	0.144	13 (Lobith)	
	<	0.08	0.06	0.0565	0.076	13 (Nieuwegein)	
	0.07	0.12	0.08	0.0831	0.112	13 (Nieuwersluis)	
	<	0.07	0.05	0.0481	0.066	13 (Andijk)	
2009		0.61		0.21		16 occasions during screening	[34]

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark (location)	Reference
2010	<	0.07	0.014	0.0189	0.0654	10 (Namêche)	[33]
	<	0.057	0.016	0.0193	0.0539	10 (Luik)	
	<	<	<	<	<	53 (Heel)	
	<	0.1	0.055	0.0513	0.083	26 (Brakel)	
	0.02	0.1	0.06	0.0562	0.096	13 (Keizersveer)	
	0.033	0.11	0.0475	0.0565	0.102	12 (Lobith)	
	<	0.1	0.065	0.0679	0.1	12 (Nieuwegein)	
	<	0.11	0.08	0.0754	0.106	13 (Nieuwersluis)	
	<	0.14	<	0.055	0.128	13 (Andijk)	
	0.04	0.06	0.05	0.0508	0.06	12 (Stellendam)	
2011	<	<	<	<	<	149 (Heel)	[33]
	<	0.19	0.08	0.0817	0.139	30 (Brakel)	
	<	0.13	0.11	0.0862	0.127	12 (Keizersveer)	
	0.016	0.17	0.088	0.0877	0.154	13 (Lobith)	
	<	0.16	0.07	0.0765	0.148	13 (Nieuwegein)	
	<	0.088	0.064	0.0578	0.0864	13 (Nieuwersluis)	
	<	0.09	<	<	0.082	13 (Andijk)	
	0.03	0.07	0.06	0.0564	0.07	11 (Stellendam)	
2012	<	<	<	<	<	153 (Heel)	[33]
	<	0.045	0.028	0.0273	0.041	13 (Brakel)	
	<	0.09	<	<	0.09	14 (Keizersveer)	
	<	0.11	0.06	0.0505	0.08	292 (Lobith)	
	<	0.064	0.042	0.0398	0.0616	13 (Nieuwegein)	
	0.03	0.064	0.052	0.0486	0.0632	13 (Nieuwersluis)	
	<	0.047	0.03	0.0288	0.0446	13 (Andijk)	
	0.03	0.07	0.05	0.0486	0.065	14 (Stellendam)	

Other screening monitoring studies by waterboards showed concentrations between 0.02 and 0.73 µg/L [1].

Rademaker and De Lange [35] summarize monitoring data from various sources. Over 2003-2005, carbamazepine was found in 99 out of 153 samples (65%), the highest concentration was 0.26 µg/L, the average was 0.067 µg/L.

Concludingly, the measured concentrations, with annual averages of 0.0.03 - 0.09 µg/L over 2011/2012, are a factor of > 6 lower than the proposed AA-EQS of 0.50 µg/L. The maximum value over 2011/2012 of 0.19 µg/L is almost a factor of 1000 lower than the MAC-EQS of 1.6 mg/L. However, these monitoring data mainly concern larger rivers. There is an on-going monitoring programme of regional waters, results of which will be published soon.

Data from the Watson-database over 2012, regarding measurements in effluents of various sewage treatment plants, show an average carbamazepine concentration of 0.619 µg/L, with a maximum value of 0.774 µg/L and a 90th percentile of 1.17 µg/L. Thus, the average value in effluents does exceed the derived AA-EQS value. Depending on the dilution of the effluent, the concentration in the receiving waters might also exceed the AA-EQS value.

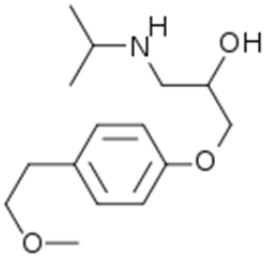
4 Metoprolol

4.1 Introduction

Similar to carbamazepine, metoprolol has been selected by Smit and Wuijts [1] for the Dutch watchlist after it was put forward by RIWA as a drinking water relevant compound. The compound is frequently detected in surface water used for drinking water abstraction at concentrations higher than 0.1 µg/L, which is the target set by the IAWR for toxicologically relevant substances [7].

4.2 Identity

Table 8. Identity of metoprolol

Name	Metoprolol
Chemical name	1-[4-(2-methoxyethyl)phenoxy]-3-(propan-2-ylamino)propan-2-ol
CAS number	37350-58-6 (base); 98418-47-4 (succinate); 56392-17-7 (tartrate)
EC number	253-483-7
Molecular formula	$C_{15}H_{25}NO_3$
Molar mass	267.37 (base); 652.81 (succinate); 684.82 (tartrate)
Structural formula	
SMILES code	COCCc1ccc(OCC(O)CNC(C)C)cc1

4.3 Information on uses and emissions

Metoprolol is a selective β1 receptor blocker used in treatment of several diseases of the cardiovascular system, especially hypertension. Metoprolol competes with adrenergic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart. Beta(1)-receptor blockade results in a decrease in heart rate, cardiac output, and blood pressure (http://www.drugbank.ca/drugs/DB00264). The active substance metoprolol is employed either as metoprolol succinate or metoprolol tartrate (where 100 mg metoprolol tartrate corresponds to 95 mg metoprolol succinate), respectively as prolonged-release or conventional-release formulation. In the Netherlands, 67 products containing metoprolol are registered [9]. The estimated number of users in the Netherlands has increased from about 800000 in 2006 to almost 975000 in 2010 [36]. The estimated use of metoprolol was 22681 kg in 2007, while the use is expected to increase to 28061 kg in 2020 [10]. The compound is not included in the Pollutant Release and Transfer Register [11].

4.4 Existing or proposed water quality standards, risk limits, etc.

For the evaluation of metoprolol as a candidate for the Dutch watchlist, Smit and Wuijts [1] collected relevant environmental risk limits from readily available data sources (see Table 9).

Table 9. Existing environmental risk limits for metoprolol

Country	Value [µg/L]	Remark	Reference
CH	64	AA-EQS, based on direct ecotoxicity for *Daphnia magna* with AF of 50.	[37]
CH	76	MAC-EQS, based on direct ecotoxicity to *Desmodesmus subspicatus* with AF of 100.	[37]
F	7.3	PNEC, EC50 *D. subspicatus* with AF 1000	[38]
S	58.3	PNEC, industry MSDS	[15]
	0.1	target value for pharmaceuticals in surface water for abstraction of drinking water	[7]

4.5 Physico-chemical properties and behaviour in the environment

Table 10. Physico-chemical properties of metoprolol

Parameter	Unit	Value	Remark	Reference
Molecular weight	[g/mol]	267.37		
Water solubility	[mg/L]	16900	Experimental value	[39]
		200000	metoprolol base	Dossier data AstraZeneca
pK_a	[-]	9.09; 14.41	Estimated	[39]
log K_{OW}	[-]	1.88	Experimental value	EpiWin
		1.69	Calculated	EpiWin
		-0.9	Experimental value at pH 7; OECD 107	Dossier data AstraZeneca
log K_{OC}	[-]	1.475; 2.057	Calculated	[39]
Vapour pressure	[Pa]	3.84×10^{-5}	Calculated	[39]
Melting point	[°C]	116.15	Calculated	[39]
Boiling point	[°C]	362.44	Calculated	[39]
Henry's law constant	[Pa/m^3.mol]	1.42×10^{-8} 2.15×10^{-6}	Calculated	[39]

The derived quality standards are based on dissolved concentrations. In view of the expected low sorption, these concentrations are valid for the total fraction as well.

4.6 Bioconcentration and biomagnification

Using the worst-case log K_{OW} of 1.88, the BCF can be estimated to be 7.9 L/kg according to [2]. Risk of secondary poisoning seems negligible.

4.7 Human toxicological threshold limits and carcinogenicity

The compound is self-classified as Repr. 2 by some industry notifiers in the ECHA database (echa.europa.eu/ ; accessed on January 9, 2014).

A provisional drinking water standard is reported by [20], based on the lowest therapeutic dose of 100 mg/day [21]. For a 60 kg adult this dose corresponds to 1.66 mg/kg_{bw}/day. With a safety margin of 100, a provisional ADI of 16 µg/kg_{bw}/day and a provisional drinking water standard of 50 µg/L were derived.

However, this lowest therapeutic dose is based on metoprolol tartrate and not on metoprolol base [21]. If a correction is applied based on molecular weights (2 x 267.4 g/mol for metoprolol and 684.8 g/mol for metoprolol tartrate), the lowest therapeutic dose becomes 78 mg/day. Besides this, the current lowest dose is not 100 mg/day but 25 mg/day (for use without other medication; see also the package leaflet for Selokeen which can be found at www.astrazeneca.nl). Corrected for metoprolol base, the dose of 25 mg/day corresponds to 19.5 mg, which would correspond to a dose of 0.28 mg/kg_{bw}/day for an adult of 70 kg (which is preferred within the WFD framework). With a safety margin of 100, the provisional ADI for a 70 kg adult would become 2.8 µg/kg_{bw}/day.

It is noted that reprotoxicity is not taken into account in this provisional ADI. However, it is not possible to derive an ADI based on reproduction toxicity since the data underlying the self classification are not publicly available. A LOAEL of 64 mg/kg_{bw}/day for increased embryo mortality in rabbits and a LOAEL of 3.5 mg/kg_{bw}/day for sperm production in rats were found (FDA data on http://www.drugs.com/pro/metoprolol.html; accessed on Jan 20, 2014). However, because the study report of this study was not publicly available, reliability could not be checked. Compared with the daily intake of 19.5 mg/person and the provisional ADI of 2.8 of µg/kg_{bw}/day, the safety margin with the LOAEL is about a factor of 1000, which is sufficient to consider the provisional ADI to be safe.

4.8 Aquatic toxicity data

An overview of the aggregated ecotoxicity data for metoprolol for freshwater and marine species is given in Table 11. There are too few data to perform a meaningful statistical comparison between freshwater and marine species. Since there are no further indications of a difference in sensitivity between freshwater and marine organisms and the behaviour of metoprolol is not expected to differ between fresh and marine systems, the toxicity data may be combined {EC, 2011 #41}. Detailed toxicity data for metoprolol are tabulated in separate Excel tables in the Annex to this report. Only valid studies were used to construct the aggregated data table, with geometric means if per species more data were available for the same endpoint.

Table11. Aggregated toxicity data for metoprolol for fresh and saltwater organisms. All data with (s) *are salt water data.*

Chronic		**Acute**	
Taxonomic group	**NOEC/EC10 (mg/L)**	**Taxonomic group**	**L(E)C50 (mg/L)**
Protozoa		**Bacteria**	
Tetrahymena pyriformis	21.8	*Vibrio fisheri (s)*	144
Algae		**Protozoa**	
Pseudokirchneriella subcapitata	13.4[a]	*Tetrahymena pyriformis*	121
Crustacea		**Algae**	
Daphnia magna	**3.1**[b]	*Desmodesmus subspicatus*	**7.6**[d]
		Pseudokirchneriella subcapitata	45.5[e]
Pisces			
Danio rerio	24[c]	**Crustacea**	
		Ceriodaphnia dubia	20.0[f]
		Daphnia magna	133[g]
		Thamnocephalus platyurus	77.5[h]
		Pisces	
		Danio rerio	137
		Oncorhynchus mykiss	106

[a] Geometric mean of 19.65, 6.14, and 19.9 mg/L, NOEC/EC10 values for growth rate (preferred endpoint).
[b] NOEC for reproduction in a 9-days test
[c] EC10 for growth and development.
[d] Geometric mean of 7.3 and 7.9 mg/L, EC50 for growth rate
[e] Geometric mean of 43.4 and 47.7 mg/L, EC50 for growth rate (preferred endpoint)
[f] Geometric mean of 45.3 and 8.8 mg/L, EC50 for mortality.
[g] 48-hours EC50 value for immobility/mortality (Geometric mean of 63.9, 438, 76.2, 200, and 96.64 mg/L). Effects on heart rate and breathing are not used since these are not population relevant.
[h] Most sensitive endpoint, Thamnotoxkit.

Toxicity tests with metoprolol are either performed with metoprolol tartrate or metoprolol succinate. However, the quality standard is derived for the metoprolol base. The endpoints reported should thus reflect the metoprolol base concentrations. In some studies, it is reported clearly if the endpoints reflect the base, the tartrate salt or the succinate salt. In the latter two cases, the endpoint is recalculated into metoprolol base concentrations. If it was not reported if the data reflect the concentrations of the base or the salt, an email was sent to the authors to enquire. If no response was received, it was assumed that the data reflected the metoprolol base (the weight of which is 78% of metoprolol tartrate and 82% of metoprolol succinate).

The NOEC of 3.1 mg/L for Daphnia magna originates from a 9-day test. Although this test is neither acute nor chronic, it is included in the chronic dataset because the "true" chronic endpoint reproduction was included. In addition to the valid studies taken up in the aggregated data table (Table 11),

chronic data for *Oncorhynchus mykiss* are available from [28] with a LOEC of ≤ 0.001 mg/L for histopathological effects on the kidney and the liver and 0.005 mg/L for histopathological effects on the gills. Similar to what is observed for carbamazepine (see 3.8), a closer look reveals that these effects are not dose-related but rather seem to be an artefact of the many variables studied, than a real physiological effect. Moreover, there is still debate if these endpoints are population relevant; where for blood parameters this does not seem to be the case, in the diclofenac draft EQS derivation for the European Commission [29], histopathological changes for *O. mykiss* observed in the same experiment [40] were accepted as relevant endpoints. However, recently a review of these studies was published, suggesting that also for diclofenac the findings were not clear [30]. As for carbamazepine, it was decided not to use the histopathological endpoints for derivation of the EQS for metoprolol..

4.9 Derivation of Environmental Risk Limits

4.9.1 Derivation of $QS_{fw, eco}$ and $QS_{sw, eco}$

The acute base set is available. Chronic data are available for a protozoa (*Tetrahymena pyriformis*), algae, crustaceans, and the fish *Danio rerio*. The trophic level which is the most sensitive in the acute dataset (primary producers) is also present in the chronic dataset. The lowest NOEC is 3.1 mg/L for reproduction of *Daphnia magna* obtained in a 9-day test. There is also a 'lower than' value which is lower than this lowest NOEC (< 3.1 mg/L for growth of 2nd generation *D. magna*), also obtained in 9-day test. In view of this, and because the test duration is only semi-chronic., an assessment factor of 50 is applied to the NOEC of 3.1 mg/L for *D. magna*, resulting in an $QS_{fw, eco}$ of 0.062 mg/L = 62 µg/L.

No specific marine taxa are present in the dataset, and thus the $QS_{sw, eco}$ is derived using an additional assessment factor of 10, which results in an $QS_{sw, eco}$ of 6.2 µg/L.

4.9.2 Derivation of $QS_{water, hh\ food}$

Because of the selfclassification of Repr. 2, derivation of the $QS_{water, hh\ food}$ is triggered
[13].

A provisional ADI of 2.8×10^{-3} mg/kg_{bw}/day is derived (see section 0).

The $QS_{water, hh\ food}$ represents the concentrations in water that will be protective for humans upon consumption of fishery products. The $QS_{water, hh\ food}$ is valid for fresh and marine water. First, the maximum permissible concentration in fish ($QS_{biota, hh\ food}$) is calculated based on an ADI of 2.8×10^{-3} mg/kg_{bw}/day (see 4.7), assuming a body weight of 70 kg, a daily intake of 115 g fish, and a maximum contribution to the ADI of 10%.

The $QS_{biota, hh\ food}$ is then $(0.1 \times 2.8 \times 10^{-3} \times 70) / 0.115 = 0.17$ mg/$kg_{biota\ ww}$.

Subsequently, the $QS_{biota, hh\ food}$ is converted to an equivalent concentration in water using the BCF of 7.9 L/kg and BMF of 1 kg/kg as derived in section 4.6. The resulting $QS_{water, hh\ food}$ is calculated as $0.17 / (7.9 \times 1) = 0.022$ mg/L = 22 µg/L.

The quality standard for human consumption of fishery products is considered as highly uncertain. There is no reliable BCF, and due to a lack of data the ADI is not based on toxicological data but on the therapeutic dose. To increase the certainties surrounding these risk limits, the performance of a BCF study could be recommended, together with the public availability of toxicological study reports.

4.9.3 Choice of final EQS

The $QS_{fw, eco}$ is 62 µg/L and the $QS_{sw, eco}$ is 6.2 µg/L.

The $QS_{water, hh\ food}$ is 22 µg/L, which is lower than the $QS_{fw, eco}$. However, the derivation of this human route is too uncertain to use as a basis for an AA-EQS that relates to surface water in general. Therefore, the AA-EQS_{fw} is set to 62 µg/L on the basis of the $QS_{fw, eco}$. It is noted that for metoprolol and for pharmaceuticals in general, information from valid and relevant, publicly available, studies is urgently needed to set a reliable human-toxicological threshold limit for the general population. For saltwater the $QS_{sw, eco}$ is most critical and the final AA-EQS_{sw} is 6.2 µg/L.

4.9.4 Derivation of MAC-EQS_{fw} and MAC-EQS_{sw}

Acute toxicity data are available for five taxonomic groups. Using the assessment factor method, the MAC-$QS_{fw, eco}$ is derived using the lowest value of 7.6 mg/L for the alga *Desmodesmus subspicatus*. The standard deviation of the log-transformed acute data is below 0.5, and thus an assessment factor of 10 can be applied, resulting in a MAC-EQS_{fw} of 0.76 mg/L = 760 µg/L.

For marine systems, the MAC-EQS_{sw} can be derived using an additional assessment factor of 10, since no typically marine taxonomic group is present The MAC-EQS_{sw} is 76 µg/L.

4.9.5 Derivation of NC_{fw} and NC_{sw}

The NC is a factor of 100 below the AA-EQS. The NC_{fw} is 62 / 100 = 0.62 µg/L, the NC_{sw} is 6.2 / 100 = 0.062 µg/L.

4.9.6 Derivation of $SRC_{fw, eco}$ and $SRC_{sw, eco}$

Because more than three chronic toxicity values are available, the SRC_{eco} is taken as the geometric mean of all chronic toxicity data. The SRC_{eco} is 12.1 mg/L. . This value is valid for freshwater and saltwater.

4.9.7 $QS_{dw, hh}$

Within the WFD, it is assumed that the level of purification of waters intended for drinking waters should be reduced. Only simple treatment of water abstracted for use as drinking water is therefore assumed [2].

Metoprolol is considered difficult to remove by current methods for surface water treatment (only 0-43% removed; [41]; [42]; [32]). In line with the WFD methodology for the calculation of the $QS_{dw, hh}$ 0% removal is assumed.

With the provisional ADI of 2.8×10^{-3} $mg/kg_{bw}/day$ = 2.8 $µg/kg_{bw}/day$ (see section 0), assuming a body weight of 70 kg, a daily intake of 2 L water, and a maximum contribution to the ADI of 10%, the $MPC_{dw, hh}$ becomes (2.8 x 0.1 x 70) / 2 = 9.8 µg/L.

This does not correspond to the value derived by Versteegh et al. [20] since they used a different therapeutic dose and did not take the molecular weight of metoprolol base into account. The difference in bodyweight of 60 kg used by Versteegh et al. versus 70 kg used in this derivation, is equalled out in the calculation.

Because this $QS_{dw, hh}$ is lower than the QS_{fw}, this means that the QS_{fw} is not protective for drinking water abstraction and that for waters intended for drinking water abstraction the $QS_{dw, hh}$ should be used.

4.10 Comparison with monitoring data

Table 12 gives an overview of monitoring data in the Netherlands.

Table 12. Monitoring data of metoprolol in the Netherlands

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark	Reference
2005	0.03	0.06				autumn 2005	[20]
2006		0.2				114 measurements; RIWA data	[24]
2006	0.02	0.04				spring 2006	[20]
2006	<	0.18	0.065	0.0754	0.159	12 (Nieuwegein)	[33]
	0.06	0.2	0.105	0.118	0.2	12 (Nieuwersluis)	
	<	0.1	<	0.0164	0.086	11 (Andijk)	
2007	0.014	0.038	0.0235	0.0238	0.0362	12 (Lobith)	[33]
	<	0.11	0.08	0.0619	0.102	13 (Nieuwegein)	
	<	0.14	0.11	0.0892	0.136	13 (Nieuwersluis)	
	<	0.06	<	0.0185	0.06	13 (Andijk)	
2008	<	<	*	<	*	7 (Luik)	[33]
	<	0.068	*	0.037	*	4 (Heel)	
	<	0.04	*	0.0287	*	4 (Brakel)	
	0.035	0.13	*	0.08	*	9 (Keizersveer)	
	0.011	0.047	0.027	0.0278	0.045	13 (Lobith)	
	<	0.13	0.09	0.0775	0.124	12 (Nieuwegein)	
	0.1	0.18	0.13	0.141	0.18	11 (Nieuwersluis)	
	<	0.06	<	0.0225	0.059	10 (Andijk)	
2009	0.03	0.11	*	0.065	*	4 (Brakel)	[33]
	<	0.21	<	<	0.174	15 (Keizersveer)	
	0.039	0.12	0.059	0.0673	0.12	13 (Lobith)	
	<	0.13	0.09	0.0823	0.126	11 (Nieuwegein)	
	0.11	0.25	0.16	0.159	0.238	11 (Nieuwersluis)	
	<	0.12	0.0175	0.0365	0.12	10 (Andijk)	
2010	<	<	*	<	*	4 (Namêche)	[33]
	<	<	*	<	*	4 (Luik)	
	<	0.07	<	<	0.07	13 (Brakel)	
	0.04	0.19	0.12	0.114	0.182	13 (Keizersveer)	
	0.053	0.14	0.071	0.0773	0.124	12 (Lobith)	
	<	0.13	<	0.0517	0.118	13 (Nieuwegein)	
	0.014	0.19	0.11	0.094	0.186	13 (Nieuwersluis)	
	<	0.09	<	<	0.078	13 (Andijk)	
	<	0.1	0.07	0.07	0.1	12 (Stellendam)	

Year	Min [µg/L]	Max [µg/L]	Median [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark	Reference
2011	0.013	0.031	*	0.0205	*	4 (Heel)	[33]
	<	0.12	0.05	0.055	0.116	13 (Brakel)	
	0.06	0.29	0.18	0.178	0.278	13 (Keizersveer)	
	0.032	0.13	0.075	0.0805	0.126	13 (Lobith)	
	0.033	0.055	*	0.0428	*	6 (Nieuwegein)	
	<	0.069	*	0.0461	*	6 (Nieuwersluis)	
	<	0.025	*	0.00808	*	6 (Andijk)	
	<	0.12	0.06	0.0632	0.114	11 (Stellendam)	
2012	<	<	<	<	<	4 (Heel)	[33]
	<	0.045	0.028	0.0273	0.041	13 (Brakel)	
	<	0.09	<	<	0.09	13 (Keizersveer)	
	-	0.11	0.06	0.0505	0.08	13 (Lobith)	
	<	0.064	0.042	0.0398	0.0616	6 (Nieuwegein)	
	0.03	0.064	0.052	0.0486	0.0632	6 (Nieuwersluis)	
	<	0.047	0.03	0.0288	0.0446	6 (Andijk)	
	0.03	0.07	0.05	0.0486	0.065	11 (Stellendam)	

Monitoring data from a number of waterboards show concentrations of metropolol ranging from 0.11 to 1.1 µg/L [1]. This is higher than the values reported by RIWA [33].

The annual average over 2011/2012 is 0.01 - 0.18 µg/L, which is well below the derived AA-EQS_{fw} of 43 µg/L. The maximum over 2011/2012 is 0.29 µg/L, which is also well below the derived MAC-EQS_{fw} of 760 µg/L.

Rademaker and De Lange [35] summarise monitoring data of pharmaceuticals in the Netherlands over 2003-2005, based on a number of studies. Metropolol was found in 59 out of 120 samples (49%), the highest concentration was 0.42 µg/L, the average was 0.023 µg/L.

Data from the Watson-database over 2012, regarding measurements in various STP-effluents, show an average metoprolol concentration of 1.785 µg/L, with a maximum value of 4 µg/L and a 90th percentile of 2.8 µg/L. Without taking further dilution into account, the average value in effluents is also well below the the derived AA-EQS_{fw} value.

These monitoring data indicate that the AA-EQS_{fw} and the $QS_{dw, hh}$ will likely not be exceeded. However, these monitoring data mainly concern larger rivers.

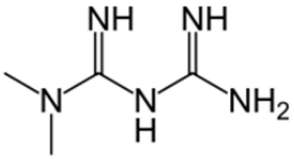
5 Metformin

5.1 Introduction

Metformin has been selected for the Dutch watchlist after it was put forward by RIWA as a drinking water relevant compound. The compound is considered toxicologically relevant and frequently detected in surface water used for drinking water abstraction at concentrations higher than 0.1 µg/L, which is the target set by the IAWR [7].

5.2 Identity

Table 13. Identity of metformin

Name	Metformin
Chemical name	N,N-dimethylimidodicarbonimidic diamide
CAS number	657-24-9
EC number	211-517-8
Molecular formula	$C_4H_{11}N_5$
Molar mass	129.2
Structural formula	
SMILES code	N=C(N)NC(=N)N(C)C

5.3 Information on uses and emissions

Metformin is registered as a human pharmaceutical in the EU and the Netherlands. Metformin has been on the market since 1967 and is primarily used for type 2 diabetes. In the Netherlands, 90 products are registered [9]. In Europe, another 12 products are registered (http://www.emea.europa.eu/).

The estimated number of users in the Netherlands was 426870 in 2006 and has increased to over 500000 in 2010 (GIP-database; [36]). In 2007, the estimated use of metformin hydrochloride was 207190 kg, while the use is expected to increase to 256103 kg in 2020 [10]. The compound is not included in the Pollutant Release and Transfer Register [11].

5.4 Existing or proposed water quality standards, risk limits, etc.

For the evaluation of metformin as a candidate for the Dutch watchlist, Smit and Wuijts [1] collected relevant environmental risk limits from readily available datasources (see Table 14Table).

Table 14. Existing environmental risk limits for metformin

Country	Value [µg/L]	Remark	Reference
S	1200	PNEC, NOEC fish ELS test with AF 10	[15]
F	64	PNEC, EC50 *Daphnia magna* with AF 1000	[38]
N	101	PNEC, background not known	[14]
	0.1	target value for pharmaceuticals in surface water for abstraction of drinking water	[7]

5.5 Physico-chemical properties and behaviour in the environment

Table 15. Physico-chemical properties of metformin

Parameter	Unit	Value	Remark	Reference
Molecular weight	[g/mol]	129.2		
Water solubility	[mg/L]	1 x 10^6	Calculated	EpiSuite
pK_a	[-]			
log K_{OW}	[-]	-1.1	Experimental; pH 7.4	[43]
		-1.4	Calculated	EpiSuite
log K_{OC}	[-]	0.77	Experimental; geometric mean sludge	[43]
		3.05	Experimental; geometric mean soil	
Vapour pressure	[mm Hg]	7.58 x 10^{-5}	Calculated	EpiSuite
Melting point	[°C]	74.45	Calculated	EpiSuite
		223-226	Experimental	EpiSuite
Boiling point	[°C]	268.97	Calculated	EpiSuite
Henry's law constant	[Pa/m^3.mol]	7.74 x 10^{-11}	Calculated	EpiSuite

The derived quality standards are based on dissolved concentrations. In view of the low sorption, these concentrations are valid for the total fraction as well.

Metformin dissipates rapidly from the water phase via adsorption to the sediment [43]. During a ready biodegradability test, no degradation of metformin was observed during 28 days [43].

When metformin is degraded, a metabolite is formed (guanylurea), which is often found to be present in surface waters and/or effluents in higher concentrations than the parent compound metformin. Guanylurea appears to be relatively persistent, but virtually no information is available on physical-chemical characteristics and ecotoxicology of this compound. The rate of degradation from metformin into guanylurea seems to vary among STPs.

5.6 Bioconcentration and biomagnification

Because of the low log K_{OW}, it can be assumed that the bioconcentration factor is < 100 L/kg, which is confirmed by EpiSuite calculations. Thus, risk for secondary poisoning is considered negligible.

5.7 Human toxicological threshold limits and carcinogenicity

No risk phrases or human toxicological threshold limits are available. However, the compound is self-classified as Repr. 2 by a number of notifiers on the ECHA website (echa.europa.eu; accessed on January 14, 2014).

According to Novartis (Dan Caldwell, personal communication), the fertility of male or female rats was not affected by metformin at doses as high as 600 mg/kg_{bw}/day. Metformin reduced the spontaneous abortion rate of women treated with metformin; it did not appear to be teratogenic. A recent meta-analysis showed that metformin did not give any serious detrimental side-effects when administered to pregnant women.

Using the lowest therapeutic dose of metformin hydrochloride (molecular weight 165.6 g/mol) of 500 mg/person/day [21], the lowest dose for metformin base can be calculated to be 390 mg/person/day.

Applying a safety factor of 100 and a human body weight of 70 kg, a provisional ADI would be 56 $\mu g/kg_{bw}$/day. Because there are no data on reprotoxicity publicly available, the uncertainty of this value is high.

5.8 Aquatic toxicity data

An overview of the aggregated ecotoxicity data for metformin for freshwater species is given in Table 16. No data are available for saltwater organisms. Detailed toxicity data for metformin are tabulated in separate Excel tables in the Annex to this report. Only valid studies were used to construct the aggregated data table, with geometric means if per species more data were available for the same endpoint.

Toxicity tests with metformin are usually performed with metformin hydrochloride. However, the quality standard is derived for the metformin base. The endpoints reported should thus reflect the metformin base concentrations. In some studies, it is reported clearly if the endpoints reflect the base, or the hydrochloride. In the latter case, the endpoint is recalculated into metformin base concentrations.

In 2011, for one product with metformin a European public assessment report (Epar), including environmental information, was published. (Jentadueto; procedure number EMEA/H/C/002279; [43]). The information in this assessment report was evaluated by the Netherlands during the authorisation procedure, according to the same reliability criteria as for the derivation of environmental risk limits. Thus, although only endpoints were published in the Epar without experimental details, these results can be used for quality standard derivation.

Table 16. Aggregated toxicity data for metformin for freshwater organisms.

Chronic		**Acute**	
Taxonomic group	**NOEC/EC10 (mg/L)**	**Taxonomic group**	**L(E)C50 (mg/L)**
Algae		**Algae**	
Desmodesmus subspicatus	≥78	*Desmodesmus subspicatus*	>320
		Pseudokirchneriella subcapitata	>77.2
Crustacea			
Daphnia magna	**11.5**[a]	**Macrophyta**	
		Lemna minor	110
Pisces			
Danio rerio	≥10	**Crustacea**	
Pimephales promelas	≥7.8	*Daphnia magna*	**64**
		Pisces	
		Danio rerio	>86

[a] Geometric mean of 17 and 7.8 mg/L.

5.9 Derivation of Environmental Risk Limits

5.9.1 *Derivation of $QS_{fw, eco}$ and $QS_{sw, eco}$*

An acute base set is available, which partly included unbound ('higher than') values. Regarding the chronic data, reliable unbound values are available for the algal species *Desmodesmus subspicatus* and the fish *Danio rerio* and *Pimephales promelas*. It is considered justified to assume that using the lowest unbound NOEC of ≥ 7.8 mg/L offers adequate protection. Therefore, an assessment factor of 10 is used on this value , which results in a $QS_{fw, eco}$ of 7.8 / 10 = 0.78 mg/L = 780 µg/L.

The $QS_{sw, eco}$ is derived in the same way but with an additional assessment factor of 10 due to the lack of specific marine taxonomic groups. This results in a $QS_{sw, eco}$ of 78 µg/L.

5.9.2 *Derivation of $QS_{water, hh food}$*

Derivation of the $QS_{water, hh food}$ is triggered because of potential reprotoxic effects (self classification Repr. 2, see section 5.7).

However, the data on which this classification is based are not available, and a provisional ADI of 56 µg/kg_{bw}/day could only be based on the lowest therapeutic dose (see section 5.7) . This means that the $QS_{water, hh food}$ for human consumption of fishery products cannot be derived with a high amount of certainty. Besides this, because of the low values for K_{OW} (< -1), it is not realistic to derive a BCF and thus, no $QS_{water, hh food}$ can be derived.

5.9.3 *Choice of AA-EQS*

The final AA-EQS for freshwater is based on the $QS_{fw, eco}$ and becomes 780 µg/L.

The final AA-EQS for salt water systems is based on the $QS_{sw, eco}$ and becomes 78 µg/L.

5.9.4 *Derivation of MAC-EQS$_{fw}$ and MAC-EQS$_{sw}$*

Because of the unbound values in the data set, it cannot be assessed whether the standard deviation of the log transformed acute toxicity data is lower than 0.5. The compound is not an apolar narcotic, and because of this there is no certainty that the compound acts with the same mode of action on all organisms. The unbound values indicate that the differences in sensitivity among taxa maybe larger than for apolar narcotics. Because of this, an assessment factor of 100 should be applied to the lowest LC50 value of 64 mg/L for *Daphnia magna*, which results in an MAC-QS$_{fw}$ of 0.64 mg/L = 640 µg/L. As this value is lower than the QS$_{fw, eco}$, the MAC-EQS$_{fw}$ is set equal to the QS$_{fw, eco}$ and becomes 780 µg/L.

For marine systems, the MAC-EQS$_{sw}$ is derived using an additional assessment factor of 10, since no specific marine taxonomic group is present. This results in a MAC-EQS$_{sw}$ of 78 µg/L.

5.9.5 *Derivation of NC$_{fw}$ and NC$_{sw}$*

The NC is a factor of 100 below the AA-EQS. The NC$_{fw}$ is 780 / 100 = 7.8 µg/L, the NC$_{sw}$ is 78 / 100 = 0.78 µg/L.

5.9.6 *Derivation of SRC$_{fw, eco}$ and SRC$_{sw, eco}$*

Because of the lack of data (mainly higher-than values are available), an SRC$_{eco}$ cannot be derived.

5.9.7 *QS$_{dw, hh}$*

Within the WFD, it is assumed that the level of purification of waters intended for drinking waters should be reduced. Thus, a simple treatment of water abstracted for use as drinking water is assumed [2].

A human toxicological threshold limit is not available. Using the lowest therapeutic dose of 390 mg/person/day, applying a safety factor of 100 and a human body weight of 70 kg, a provisional ADI would be 56 µg/kg$_{bw}$/day (see section 5.7).

With a provisional ADI of 56 µg/kg$_{bw}$/day, assuming a body weight of 70 kg, a daily intake of 2 L water, and a maximum contribution to the ADI of 10%, the MPC$_{dw, hh}$ becomes (56 x 0.1 x 70) / 2 = 196 µg/L.

Because this QS$_{dw, hh}$ is lower than the AA-EQS$_{fw}$, this means that the AA-EQS$_{fw}$ is not protective for drinking water abstraction. It should be noted however, that the QS$_{dw, hh}$ is only provisional and not very reliable.

5.10 Comparison with monitoring data

Table 17 summarises monitoring data of metformin in Dutch surface waters.

Table 17. Monitoring data of metformin in the Netherlands

Year	Min [µg/L]	Max [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark	Reference
2010	0.41	0.68	0.56		6 (Brakel)	[33]
	0.24	0.87	0.457		6 (Nieuwegein)	
	0.24	0.54	0.347		6 (Nieuwersluis)	
	0.14	0.57	0.348		6 (Andijk)	
2011	<	1.1	0.455	0.986	12 (Brakel)	[33]
	0.099	1.1	0.555	1.1	12 (Nieuwegein)	
	<	1.2	0.355	1.07	12 (Nieuwersluis)	
	0.083	0.53	0.365	0.524	12 (Andijk)	
2012	0.24	2.8	0.96	2.24	13 (Heel)	[33]
	0.095	1.3	0.56	1.22	13 (Brakel)	
	0.57	1.6	0.83	1.52	13 (Lobith)	
	<	3.2	0.4	2.4	13 (Nieuwegein)	
	0.088	2	0.42	1.88	13 (Nieuwersluis)	
	0.077	0.99	0.38	0.974	13 (Andijk)	

The annual average concentration over 2011 and 2012 is 0.4 - 0.6 µg/L, which is well below the proposed AA-EQS$_{fw}$ of 780 µg/L. However, these monitoring data mainly concern larger rivers.

Data from the Watson-database over 2012, regarding measurements in various STP-effluents, show an average metformin concentration of 7.9 µg/L, with a maximum value of 103 µg/L and a 90th percentile of 14.4 µg/L. Thus, the average value in effluents also does not exceed the derived AA-EQS$_{fw}$ value, even when dilution is not taken into account.

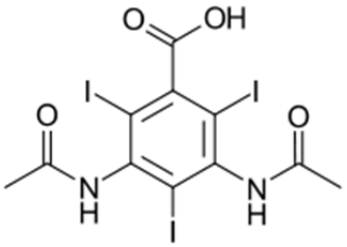
6 Amidotrizoic acid

6.1 Introduction

Amidotrizoic acid (also known as diatrizoic acid) has been selected by Smit and Wuijts [1] after it was put forward by RIWA as a drinking water relevant compound. The compound is frequently detected in surface water used for drinking water abstraction at concentrations higher than 0.1 µg/L, which is the target set by the IAWR for toxicologically relevant substances [7]. The compound is included in the monitoring programme ("Rijnstoffenlijst 2011") of the International Commission for the Protection of the Rhine [8] because of its relevance for drinking water production.

6.2 Identity

Table 18. Identity of amidotrizoic acid

Name	Amidotrizoic acid, diatrizoic acid
Chemical name	3,5-diacetamido-2,4,6-triiodobenzoic acid
CAS number	117-96-4 (acid); 737-31-5 (Na-salt); 131-49-7 (Meglumine salt)
EC number	204-223-6
Molecular formula	$C_{11}H_9I_3N_2O_4$
Molar mass	613.91
Structural formula	
SMILES code	CC(=O)Nc1c(I)c(NC(C)=O)c(I)c(C(O)=O)c1I

6.3 Information on uses and emissions

Amidotrizoic acid is registered as a human pharmaceutical in the Netherlands for use as a radio contrast fluid. It enters Dutch waters from local use, but its presence in rivers such as the river Rhine also result from use in upstream countries. In 2001, 60686 kg was sold in Germany and Switzerland [44]. Two products are registered in the Netherlands [9]. Data on use in the Netherlands are not available, the compound is included in the GIP-database [36]. Emission data are not available, the compound is not included in the Pollutant Release and Transfer Register [11].

6.4 Existing or proposed water quality standards, risk limits, etc.

For the evaluation of amidotrizoic acid as a candidate for the Dutch watchlist, Smit and Wuijts [1] collected relevant environmental risk limits from readily available datasources (see Table). It is noted that these limits are not based on ecotoxicological information.

Table 19. Existing environmental risk limits for amidotrizoic acid

Country	Value [µg/L]	Remark	Reference
DE	≤ 0.1 – 1.0	drinking water standard for iodin-containing contrast fluids	[8]
	0.1	target value for pharmaceuticals in surface water for abstraction of drinking water	[7]

6.5 Physico-chemical properties and behaviour in the environment

Table 20. Physico-chemical properties of amidotrizoic acid

Parameter	Unit	Value	Remark	Reference
Molecular weight	[g/mol]	613.91		
Water solubility	[mg/L]	8.885	Calculated	[45]
pK_a	[-]			[45]
log K_{OW}	[-]	1.37	Calculated	[45]
		-1.05	Experimental	Dictionary of Pharmacological Agents; Personal communication, Bayer.
log K_{OC}	[-]	1.000	Calculated	[45]
		0.863		
Vapour pressure	[Pa]	4.76×10^{-13}	Calculated	[45]
Melting point	[°C]	285	Calculated	[45]
Boiling point	[°C]	655	Calculated	[45]
Henry's law constant	[Pa/m^3.mol]	2.84×10^{-13}	Calculated	[45]
		3.29×10^{-11}	Calculated	

The derived quality standards are based on dissolved concentrations. In view of the low sorption, these concentrations can be assumed to be valid for the total fraction as well.

6.6 Bioconcentration and biomagnification

EpiWin estimates a BCF of 3.16 L/kg. Risk for secondary poisoning is considered negligible.

6.7 Human toxicological threshold limits and carcinogenicity

Amidotrizoic acid is not classified and no human toxicological threshold limit is available.

Bayer (personal communication) reported a NOEL of 4.5 g/kg for embryotoxicity/teratogenicity for repeated intravenous administration in rats. However, because the compound was administered intravenously, this NOEL cannot be used for the derivation of an oral ADI which is needed for EQS-derivation.

In the absence of any further data, the therapeutic dose used in humans is used. Because the compound has no therapeutic function but instead is designed not to affect humans, it can be assumed that the highest therapeutic dose is still safe.

There are two products with amidotrizoic acid registered in the Netherlands: Gastrografin 370 and Urografin 30%. Information on these compounds can be found at www.cbg-meb.nl (accessed on October 29, 2012).
For Gastrografin 370, the highest dose is 100 mL. Per mL, this product contains 100 mg sodium amidotrizoate (635.9 g/mol) and 660 mg Meglumine amidotrizoate (809.1 g/mol). This corresponds to a dose of amidotrizoic acid (613.91 g/mol) of 100 mL x 100 mg/ml x (613.9/635.9) + 100 mL x 660 mg/mL x (613.9/809.1) = 9,654 mg + 50,077 mg = 59,731 mg = 59.7 grams.

For Urografin 30%, the highest dose is 250 mL. Per mL, this product contains 40 mg sodium amidotrizoate (635.9 g/mol) and 260 mg meglumine amidotrizoate (809.1 g/mol). This corresponds to a dose of amidotrizoic acid (613.91 g/mol) of 250 mL x 40 mg/mL x (613.9/635.9) + 250 mL x 260 mg/mL x (613.9/809.1) = 9,654 mg + 49,318 mg = 58,972 mg = 59,0 grams.

With the highest dose of 59.7 grams/person/day, a safety margin of 10 (intra-individual variaton, [20]) and a human body weight of 70 kg, a provisional ADI would be 85.3 mg/kg_{bw}/day. This value is more an acute reference dose (single administration) than a chronic risk limit.
Because of the lack of data on chronic toxicity, no chronic risk limit can be derived.

6.8 Aquatic toxicity data

Only one valid chronic toxicity value is available, a NOEC of > 614 mg/L for *Tetrahymena pyriformis*. No other valid toxicity data for amidotrizoic acid are available. Bayer provided an EC10 for the bacterium *Pseudomonas putida* of ≥ 1000 mg/L and a NOEC for *Daphnia magna* of ≥ 100 mg/L. However, access to the full study reports was not granted and the validity of these values cannot be assessed.

6.9 Derivation of Environmental Risk Limits

No AA-EQS and MAC-EQS values can be derived due to a lack of data.

Derivation of quality standards for secondary poisoning and human consumption of fishery products is not triggered.

6.10 $QS_{dw, hh}$

A human toxicological threshold limit is not available and no estimate for a risk limit for chronic toxicity for humans can be made. Thus, no $QS_{dw, hh}$ can be derived.

6.11 Monitoring data

Monitoring data for amidotrizoic acid in Dutch surface waters are summarised below.

Table 21. Monitoring data of amidotrizoic acid in the Netherlands

Year	Min [µg/L]	Max [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark	Reference
2001-2008	0.01	0.61	0.208		Lobith	[44]
	0.01	0.39	0.09		Andijk	[44]
	0.01	0.84	0.202		Nieuwegein	[44]
	0.01	1.2	0.194		Nieuwersluis	[44]
	0.01	0.083			Tap water	Mons et al., 2003 in [44]
2006	<	<	<		1 (Brakel)	[33]
	0.05	0.35	0.182	0.341	12 (Lobith)	
	0.093	0.26	0.156	0.248	13 (Nieuwegein)	
	0.074	0.34	0.147	0.284	13 (Nieuwersluis)	
	0.03	0.14	0.0785	0.124	13 (Andijk)	
2007	0.032	0.097	0.0628		4 (Brakel)	[33]
	0.11	0.41	0.191	0.407	12 (Lobith)	
	0.02	0.53	0.165	0.498	13 (Nieuwegein)	
	0.028	0.33	0.119	0.278	13 (Nieuwersluis)	
	<	0.22	0.0665	0.192	13 (Andijk)	
2008	<	0.073	<		4 (Heel)	[33]
	0.072	0.45	0.207		4 (Brakel)	
	<	0.11	0.0587		9 (Keizersveer)	
	0.14	0.61	0.265	0.57	13 (Lobith)	
	0.097	0.84	0.341	0.764	13 (Nieuwegein)	
	0.15	1.2	0.355	0.944	13 (Nieuwersluis)	
	0.057	0.39	0.161	0.33	13 (Andijk)	
2009	<	0.23	0.0672		4 (Brakel)	[33]
	<	0.43	0.0902	0.39	11 (Keizersveer)	
	0.13	0.47	0.262	0.438	13 (Lobith)	
	<	0.47	0.121	0.422	13 (Nieuwegein	
	0.19	0.62	0.328		4 (Nieuwersluis)	
	<	0.32	0.0702	0.296	13 (Andijk)	
2010	0.05	0.19	0.105	0.178	13 (Brakel)	[33]
	0.07	0.37	0.15	0.33	13 (Keizersveer)	
	0.099	0.22	0.172	0.217	12 (Lobith)	

Year	Min [µg/L]	Max [µg/L]	Average [µg/L]	90th percentile [µg/L]	Remark	Reference
	0.05	0.24	0.126	0.219	12 (Nieuwegein)	
	0.05	0.17	0.129	0.166	13 (Nieuwersluis)	
	0.03	0.16	0.0913	0.156	13 (Andijk)	
	0.05	0.18	0.125	0.174	12 (Stellendam)	
2011	0.07	0.18	0.12		4 (Heel)	[33]
	0.044	0.48	0.241	0.44	13 (Brakel)	
	0.02	0.38	0.196	0.348	13 (Keizersveer)	
	0.08	0.62	0.33	0.596	13 (Lobith)	
	0.14	0.42	0.3	0.416	13 (Nieuwegein)	
	0.1	0.75	0.366	0.686	13 (Nieuwersluis)	
	0.056	0.61	0.227	0.514	13 (Andijk)	
	0.03	0.24	0.138	0.226	11 (Stellendam)	
2012	0.01	0.06	0.0292	0.057	12 (Heel)	[33]
	0.065	0.29	0.145	0.266	13 (Brakel)	
	0.04	0.1	0.0715	0.1	13 (Keizersveer)	
	0.061	0.52	0.26	0.464	13 (Lobith)	
	0.099	0.53	0.251	0.438	13 (Nieuwegein)	
	0.12	0.46	0.288	0.46	13 (Nieuwersluis)	
	0.057	0.37	0.159	0.342	13 (Andijk)	
	0.05	0.2	0.09	0.168	11 (Stellendam)	

The annual average over 2011 and 2012 was 0.09-0.4 µg/L. Waterboard Roer and Overmaas provided monitoring data for one location in the River Roer in April, August and October 2009, concentrations ranged from 0.58 to 1.3 µg/L, which is higher than measured by RIWA [1].

Data from the Watson-database over 2012, regarding measurements in various STP-effluents, show an average amidotrizoic acid concentration of 0.137 µg/L, with a maximum value of 1.6 µg/L and a 90th percentile of 0.454 µg/L.

Due to a lack of validated ecotoxicity data, it was not possible to derive scientifically underpinned quality standards according to the WFD-guidance. Therefore, a comparison with monitoring data cannot be made. If still deemed necessary from the viewpoint of water quality assessment, derivation of an indicative risk limit according to national procedures may be considered.

7 Conclusions and recommendations

In this report, water quality standards are proposed for carbamazepine, metoprolol and metformin. An overview of the proposed quality standards is presented in Table 22. The derived quality standards are expressed as dissolved concentrations. In view of the expected limited sorption, these values can be assumed to be valid for the total fraction as well. For amidotrizoic acid, quality standards could not be derived because RIVM was not able to use the underlying (eco)toxicity data.

In general, the EQS derivation for pharmaceuticals is hampered because the original study reports cannot be accessed and reported without permission of the data owners. This situation is similar to that of biocides and plant protection products, although for these substance groups elaborate summaries from European or national authorisation procedures are available. For pharmaceuticals, the endpoints for environmental parameters from the authorisation process may already be publicly available because of the UNECE Aarhus Convention (http://www.unece.org/env/pp/welcome.html). If, how and where these endpoints are published differs per product, because of different policies among the member states and/or competent authorities (and the European Medicines Agency) being responsible for the registration and authorization.

For the derivation of environmental risk limits the WFD-guidance clearly states that single endpoints are not sufficient to underpin a risk limit. Information on test conditions and performance of the underlying ecotoxicity studies needs to be available to assess the reliability of these endpoints. This means that either full study reports or detailed regulatory summaries need to be available. Therefore, the marketing authorisation holders were asked to voluntarily share the necessary data from the perspective of good stewardship. In this way, detailed ecotoxicity information became available for carbamazepine, metoprolol and metformin, but not for amidotrizoic acid.

Besides ecotoxicity data, also details on human toxicological endpoints are generally needed for the derivation of the risk limits. For the pharmaceuticals in our study, the relevant data were hard to obtain, also in case the marketing authorisation holders were willing to provide data. Because of this, it was not possible to fully assess the risks of secondary poisoning and human consumption of fishery products.

It should be recognized that the derivation of scientifically valid EQSs is of a general and societal interest. From that viewpoint RIVM makes a plea that pharmaceutical companies and competent authorities provide all information needed to derive environmental quality standards for pharmaceuticals.

The proposed water quality standards for carbamazepine and metoprolol, are in close agreement to earlier derived AA-EQS values by Switzerland using the same methodology. Although a larger dataset is available now, the critical studies are still the same. The difference between the currently proposed quality standards and other available risk limits, like PNECs, for the same compounds may be due to differences in the methodology, the data sets, the selection of key data, and/or the applied assessment factors.

Monitoring data in large surface waters show that the quality standards for the three pharmaceuticals are not exceeded. However, these monitoring data concern large rivers and not the smaller surface waters receiving effluents from sewage treatment plants. Monitoring data of effluents show that for carbamazepine, the AA-EQS is regularly exceeded. Depending on the amount of dilution of the effluent, the concentration in the receiving waters might also exceed the AA-EQS value.

Table 22. Derived AA-EQS, MAC-EQS, NC, SRC, $QS_{dw, hh}$ values for three pharmaceuticals.

Compound	**Fresh or salt water**	**Quality standard (µg/L)**				
		AA-EQS	NC	MAC-EQS	SRC_{eco}	$QS_{dw, hh}$
Carbamazepine	Fresh	0.50	0.005	1600	1430	54
	Salt	0.05	0.0005	160	1430	n.a.
Metoprolol	Fresh	62	0.62	760	12100	9.8
	Salt	6.2	0.062	76	12100	n.a.
Metformin	Fresh	780	7.8	780	n.d.	196
	Salt	78	0.78	78	n.d.	n.a.

n.a. = not applicable
n.d. = not determined due to a lack of data

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List of terms and abbreviations

AA-EQS	Annual Average Environmental Quality Standard
ACR	Acute to Chronic Ratio
ADI	Acceptable Daily Intake
BCF	Bioconcentration factor
CAR	Competent Authority Report
CLP	Classification Labelling and Packaging of substances
Ctgb	College voor de toelating van gewasbeschermingsmiddelen en biociden
DAR	Draft Assessment Report
DT50	dissipation or degradation half-life time
EC_x	Concentration at which x% effect is observed
EFSA	European Food Safety Authority
EQS	Environmental Quality Standard
ERL	Environmental risk limit
HC5	Hazardous Concentration for 5% of the species
INS	International and National Environmental Quality Standards for Substances in the Netherlands
JG-MKN	Jaargemiddelde milieukwaliteitsnorm
Koc	Organic carbon-water partitioning coefficient
Kow	Octanol-water partitioning coefficient
LCx	Concentration at which x% mortality is observed
MAC-EQS	Maximum Acceptable Concentration for ecosystems
MAC-MKN	Maximum Aanvaardbare Concentratie milieukwaliteitsnorm
MAC-$QS_{fw, eco}$	Maximum Acceptable Concentration for ecosystems in freshwater
MAC-$QS_{sw, eco}$	Maximum Acceptable Concentration for ecosystems in the saltwater compartment
Marine species	Species that are representative for marine and brackish water environments and that are tested in water with salinity > 0.5 ‰.
MKN	milieukwaliteitsnorm
NC	Negligible Concentration
NC_{fw}	Negligible Concentration in freshwater
NC_{sw}	Negligible Concentration in saltwater
NOEAEC	No Observed Ecosystem Adverse Effect Level
NOEC	No Observed Effect Concentration
pKa	Dissociation constant
PPP	Plant Protection Products
$QS_{biota, hh food}$	Quality standard for based on human health expressed as concentration in biota
$QS_{biota, secpois, fw}$	Quality standard for freshwater based on secondary poisoning expressed as concentration in biota
$QS_{biota, secpois, sw}$	Quality standard for saltwater based on secondary poisoning expressed as concentration in biota
$QS_{dw, hh}$	Quality standard for water used for abstraction of drinking water
$QS_{fw, eco}$	Quality standard for freshwater based on ecotoxicological data
$QS_{fw, secpois}$	Quality standard for freshwater based on secondary poisoning
$QS_{sw, eco}$	Quality standard for saltwater based on ecotoxicological data
$QS_{sw, secpois}$	Quality standard for saltwater based on secondary poisoning

$QS_{water, hh\ food}$	Quality standard for freshwater and saltwater based on consumption of fish and shellfish by humans
RIVM	Rijksinstituut voor Volksgezondheid en Milieu National Institute for Public Health and the Environment
SRC_{eco}	Serious Risk Concentration for ecosystems
$SRC_{fw, eco}$	Serious risk concentration for freshwater ecosystems
$SRC_{sw, eco}$	Serious risk concentration for saltwater ecosystems
SSD	Species Sensitivity Distribution
TGD	Technical Guidance Document
TWA	Time Weighted Average
WFD	Water Framework Directive (2000/60/EC)

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