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

Cytostatics in Dutch surface water

Use, presence and risks to the aquatic environment

RIVM Letter report 2018-0067
C. Moermond et al.

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

Cytostatics in Dutch surface water

Use, presence and risks to the aquatic environment

RIVM Letter report 2018-0067
C. Moermond et al.

Colophon

DOI 10.21945/RIVM-2018-0067

C. Moermond (auteur/coördinator), RIVM
B. Venhuis (auteur/coördinator),RIVM
M. van Elk (auteur), RIVM
A. Oostlander (auteur), RIVM
P. van Vlaardingen (auteur), RIVM
M. Marinković (auteur), RIVM
J. van Dijk (stagiair; auteur) RIVM

Contact:
Caroline Moermond
VSP-MSP
caroline.moermond@rivm.nl

This investigation has been performed by order and for the account of the Ministry of Infrastructure and Water management (IenW), within the framework of Green Deal Zorg en Ketenaanpak medicijnresten uit water.

This is a publication of:
National Institute for Public Health and the Environment
P.O. Box 1 | 3720 BA Bilthoven
The Netherlands
www.rivm.nl/en

Synopsis

Cytostatics in Dutch surface water

Cytostatics are important medicines to treat cancer patients. Via urine, cytostatic residues end up in waste water that is treated in waste water treatment plants and subsequently discharged into surface waters. Research from RIVM shows that for most cytostatics, their residues do not pose a risk to the environment. They are sufficiently metabolised in the human body and removed in waste water treatment plants. For some other cytostatics, the risk assessment could not be performed due to a lack of environmental information.

Besides for cytostatics, environmental risks of immunotherapy and hormone therapy (with two example compounds) were assessed. The use of these tumour specific therapies has increased due to their advantages compared to classical cytostatics. The active ingredients in immunotherapy are fully metabolized in the human body and thus are no risk to the environment. Two substances used in hormone therapy were assessed. They also do not pose a risk to the environment.

For this research project, use data on cytostatics from four Dutch hospitals were used, since these data are not recorded on a national scale. With these data, the amount of cytostatic residues entering surface waters was estimated. The environmental risk was assessed by comparing these data with information on toxicity to aquatic organisms. No assessment of the consequences of the presence of these compounds for drinking water treatment was made.

Keywords: cytostatics, hormone therapy, immunotherapy, water quality, surface water, risk assessment, environmental risk, ecotoxicity

Publiekssamenvatting

Cytostatica in het Nederlands oppervlaktewater

Cytostatica (medicatie bij chemokuren) zijn belangrijk voor de behandeling van kanker. Restanten van cytostatica komen via de urine in het afvalwater terecht, dat wordt gezuiverd en op oppervlaktewater geloosd. Naar aanleiding van vragen uit de zorgsector heeft het RIVM de milieurisico's van deze stoffen onderzocht. Uit dit onderzoek blijkt dat restanten van de meeste cytostatica geen risico voor het milieu in oppervlaktewater vormen. Ze worden voldoende afgebroken door het menselijk lichaam en in de rioolwaterzuiveringsinstallatie verwijderd. Van sommige andere cytostatica kon vanwege een gebrek aan milieugegevens geen beoordeling worden gemaakt.

Behalve naar cytostatica is gekeken naar milieurisico's van restanten van medicatie voor immuun- en hormoontherapie. Dit zijn twee tumorspecifieke anti-kankertherapieën die de laatste jaren steeds vaker gebruikt worden vanwege hun voordelen ten opzichte van de klassieke cytostatica. De werkzame stoffen in immuuntherapie worden door het menselijk lichaam volledig afgebroken en vormen dus geen risico. Ook de twee onderzochte stoffen die gebruikt worden bij hormoontherapie, vormen geen risico voor het oppervlaktewater.

Voor dit onderzoek zijn gebruiksgegevens van cytostatica in vier ziekenhuizen gebruikt, omdat deze gegevens in Nederland niet centraal worden bijgehouden. Hiermee is berekend hoeveel van deze stoffen in het oppervlaktewater terecht kan komen. Het risico voor het milieu is vervolgens bepaald door deze gegevens te vergelijken met gegevens over giftigheid voor waterorganismen. Er is niet gekeken naar gevolgen van de aanwezigheid van deze stoffen voor de drinkwaterzuivering.

Kernwoorden: cytostatica, hormoontherapie, immuuntherapie, waterkwaliteit, oppervlaktewater, risicobeoordeling, milieurisico, ecotoxicologie

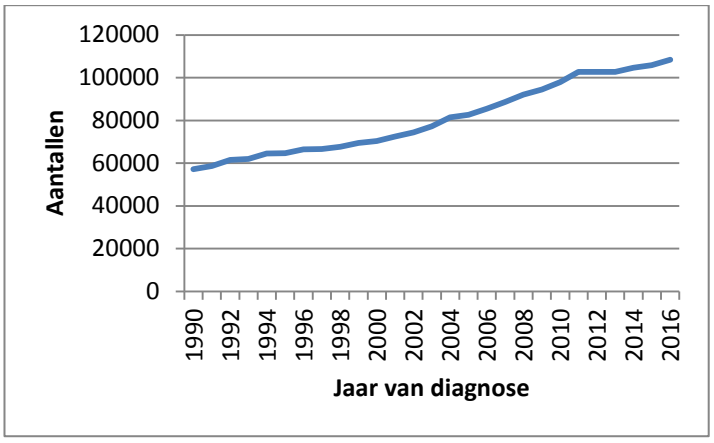
Contents

Samenvatting

Inleiding

Na gebruik worden medicijnen door de patiënt uitgescheiden. Met de urine en feces komen ze via het toilet terecht in het afvalwater en vervolgens in de rioolwaterzuiveringsinstallatie (RWZI). In de RWZI worden medicijnen over het algemeen niet volledig verwijderd, waardoor emissie plaatsvindt naar het oppervlaktewater. Hier kunnen medicijnresten een risico vormen voor de in het milieu aanwezige organismen. Vanwege deze zorgen is de Nederlandse overheid gestart met een plan van aanpak om de hoeveelheid medicijnresten in oppervlaktewater terug te brengen: de 'Ketenaanpak Medicijnresten uit Water' (https://jamdots.nl/view/239/medicijnresten-uit-water). Binnen deze aanpak wordt door alle partijen in de keten samengewerkt, van zorg tot drinkwaterbedrijven. Er is speciale aandacht voor medicijnen die een risico kunnen vormen voor aquatische ecosystemen of die terecht kunnen komen in het drinkwater.

Kanker is momenteel de meest voorkomende levensbedreigende ziekte in Nederland. Voor de behandeling van kanker zijn oncolytica, geneesmiddelen tegen kanker, essentieel en levensreddend. Een deel van de oncolytica zijn cytostatica (ook wel chemotherapeutica genoemd). Cytostatica remmen de celdeling en daarmee ook de groei van tumoren. Deze stoffen zijn zeer giftig voor de patiënt en zijn/haar omgeving. Vanwege deze eigenschappen is er vanuit de werkgroep Medicijnresten van de Green Deal Zorg, bezorgdheid geuit over het risico dat cytostatica kunnen vormen voor de ecologie van het oppervlaktewater. Verwacht wordt dat de emissie van cytostatica naar het oppervlaktewater toe zal nemen, omdat het aantal diagnoses van kanker ook toeneemt over de jaren (Figuur 1).



Figuur 1. Kanker incidentie (diagnose van nieuwe gevallen) per jaar voor alle invasieve tumoren in de periode van 1990-2016 in Nederland1.

[1] www.cijfersoverkanker.nl

In opdracht van het ministerie van IenW zijn de risico's van cytostatica voor het watermilieu in kaart gebracht. Daarvoor is het gebruik van cytostatica geïnventariseerd en is een literatuurstudie uitgevoerd naar de ecotoxicologische risico's van 11 cytostatica. Deze 11 cytostatica zijn geselecteerd op basis van uitgifte gegevens in 2016, de mate waarin de cytostatica in de patiënt worden afgebroken of omgezet en de mate waarin ze worden verwijderd in de RWZI (Tabel 1). Deze gegevens worden in onderstaande paragrafen verder beschreven. In de tabel zijn alleen de gegevens van de selecteerde stoffen gepresenteerd. In de hoofdtekst zijn ook gebruiksgegevens van andere cytostatica opgenomen.

Ter vergelijking is er ook gekeken naar twee andere behandelvormen: immuuntherapie en hormoontherapie. Dit zijn twee tumor-specifieke anti-kanker therapieën die in de laatste jaren zijn ontwikkeld en in toenemende mate gebruikt worden vanwege hun therapeutische voordelen ten opzichte van de klassieke cytostatica. Immuuntherapie wordt uitgevoerd met behulp van antilichamen. Deze antilichamen worden in het menselijk lichaam volledig afgebroken en leiden niet tot een milieurisico. Bij hormoontherapie worden anti-hormonen gebruikt die niet volledig door het menselijk lichaam worden afgebroken. Daarom is voor twee voorbeeldstoffen, tamoxifen en fulvestrant, ook een risicobeoordeling voor het watermilieu uitgevoerd.

Gebruik van cytostatica

De uitgifte van geneesmiddelen via openbare apotheken wordt in Nederland bijgehouden in de GIP databank[2]. Echter, deze databank bevat geen gegevens over geneesmiddelen die via ziekenhuisapotheken zijn verstrekt. Om toch het aantal uitgiften van cytostatica in 2016 in kaart te brengen zijn acht Nederlandse ziekenhuizen gecontacteerd. Hiervan bleken vier ziekenhuizen (twee regionale en twee academische ziekenhuizen) bereid hun gegevens, geanonimiseerd, te delen.

De gebruikte stoffen hebben verschillende werkingsmechanismes. Van de actieve stoffen zijn capecitabine en hydroxycarbamide de meest uitgegeven cytostatica in massa (kg); deze middelen worden in tablet- of capsulevorm verstrekt en zijn minder potent dan een aantal andere middelen. Een aantal van de middelen wordt ook voor andere aandoeningen dan kanker verstrekt, het gebruik voor deze indicaties valt buiten de scope van dit rapport. Volgens de Nederlandse Vereniging van Ziekenhuis Apothekers (NVZA, persoonlijke mededeling) neemt het gebruik van cytostatica toe, zowel van de 'klassieke' cytostatica als van nieuwe middelen, vanwege de toename van het aantal patiënten met kanker.

[2] www.gipdatabank.nl

Tabel 1. Gebruikte hoeveelheid (in kg actieve ingrediënt), metabolisme, verwijdering in de RWZI en de risicobeoordeling van elf geselecteerde cytostatica en twee stoffen gebruikt bij hormoontherapie. PEC = Predicted Environmental Concentration; PNEC = Predicted No Effect Concentration. Bij een risicoquotiënt hoger dan 1 is er sprake van een risico voor het watermilieu.

Stofnaam	Gebruik in 2016 [kg][a]	uitgescheiden als moederstof [%]	onveranderd in effluent [b] [%]	PEC [ng L^{-1}]	Indicatieve PNEC [ng L^{-1}]	Risico-quotiënt [PEC/PNEC]
Cytostatica (vier deelnemende ziekenhuizen)						
Capecitabine	170	3	45	477	n.a.	
Carboplatin	1,3	32	75	5,3	n.a.	
Cisplatin	0,2	23	37	0,28	25	0,01
Cyclofosfamide	7,1	25	98	28	482000	<0,001
Cytarabine	3,8	10	57	9,8	n.a.	
Etoposide	0,8	50	82	2,5	830	0,003
5-fluorouracil (intraveneus)	3,6	20	58	10	55	0,18
Som 5-fluorouracil (intraveneus)[c]	nvt	Nvt	nvt	11	55	0,20
5-fluorouracil (dermaal)[d]	108,3[d]	100[e]	58	33	55	0,6
Gemcitabine	3,6	10	100	19	n.a.	
Hydroxycarbamide	100	50	100	562	n.a.	
Ifosfamide	4,4	50	99	10	303000	<0,001
Methotrexate	3,2	90	12	1,0	80	0,01
Hormoontherapie (Nederland)						
Fulvestrant	4,1	8	5	0,018	0,57	0,03
Tamoxifen	179	30	47	6,8	67	0,10

[a] Voor cytostatica: gebaseerd op de door vier ziekenhuizen geleverde verkoopdata, niet geëxtrapoleerd naar Nederland. Behalve voor 5-fluorouracil crème (zie voetnoot d). Getallen zijn afgerond en alleen voor indicatief gebruik. Voor hormoontherapie: gebaseerd op de gegevens van de GIP databank voor heel Nederland. Gebruik van cytostatica en hormoontherapie in absolute getallen is dus niet met elkaar te vergelijken.

[b] Schatting met behulp van het model SimpleTreat.

[c] De som van 5-fluorouracil als metaboliet van capecitabine en 5-fluorouracil als actieve ingrediënt.

[d] 5-fluorouracil gebruikt als crème, gebaseerd op gegevens van de GIP databank voor heel Nederland. Gebruik van de crème (dermaal) en de vloeistof (intraveneus; gebaseerd op 4 ziekenhuizen) in absolute getallen is dus niet met elkaar te vergelijken.

[e] voor de berekeningen wordt uitgegaan van 100% uitscheiding. Volgens het Farmacotherapeutisch Kompas[10] wordt circa 10% opgenomen via de huid. Van de overige 90% is onbekend wat ermee gebeurt en in hoeverre dit wordt afgespoeld onder de douche of uit de kleding wordt gewassen.

n.a. = niet afgeleid vanwege een gebrek aan gegevens.

Cytostatica worden aan de patiënt toegediend via een infuus, injectie of als tablet/capsule. Een uitzondering hierop is 5-fluorouracil, dat ook gebruikt wordt als crème bij huidkanker. Overgebleven cytostatica worden in het ziekenhuis afgevoerd als medisch afval en op een speciale manier verwerkt. In de thuissituatie dienen overgebleven tabletten, capsules of tubes crème bij de apotheek te worden ingeleverd. Wanneer dat gebeurt, is er geen belasting van het milieu vanwege overgebleven middelen. De belangrijkste milieubelasting vindt plaats vanwege de uitscheiding van de actieve stof en/of metabolieten met de urine of feces. Bij crème kan ook milieubelasting plaatsvinden via het wassen van handen na aanbrengen, via douchen of via wassen van kleding, maar de mate waarin dat gebeurt is onduidelijk.

Metabolisme en verwijdering in de RWZI
Na toediening kunnen cytostatica in het lichaam van de patiënt worden omgezet in metabolieten. Deze metabolieten kunnen inactief zijn (zonder farmacologische werking) of nog actief, in meer of mindere mate dan de oorspronkelijke stof. De mate waarin cytostatica worden omgezet in metabolieten, verschilt sterk per stof (Tabel 1).

Via het afvalwater komen de cytostatica resten terecht in de RWZI. Hier vindt een gedeeltelijke verwijdering van deze stoffen plaats. Er zijn maar beperkt experimentele gegevens beschikbaar over verwijdering van cytostatica of hun metabolieten in Nederlandse RWZI's. De verwijdering van cytostatica in de RWZI is daarom gemodelleerd.

Risicobeoordeling
Om een risicobeoordeling uit te kunnen voeren is de verwachte concentratie (Predicted Environmental Concentration; PEC) van de cytostatica in het oppervlaktewater berekend. PECs werden op verschillende manieren berekend: in oppervlaktewater nabij het effluent van de RWZI waarop individuele ziekenhuizen lozen, maar ook omgerekend naar een worst case situatie voor heel Nederland. Voor drie ziekenhuizen die emitteren naar een gemeentelijke RWZI werden lokale PECs berekend. De verdunning van deze RWZI effluenten in het ontvangende water werd met een realistische factor berekend. PECs werden op een alternatieve manier berekend door het verbruik van vier ziekenhuizen op te schalen naar heel Nederland en gebruik te maken van het totale RWZI effluent debiet in Nederland. Deze methode leverde de hoogste PEC waarden. Hierbij werd aangenomen dat het RWZI effluent niet verdund werd in het ontvangende water. In beide methoden werd de verwijdering van cytostatica in de RWZI realistisch gemodelleerd.

In de PEC-berekeningen die zijn gebruikt voor de risicobeoordeling is uitgegaan van worst case aannames met betrekking tot gebruik, geen metabolisme, realistisch gemodelleerde verwijdering in de RWZI en geen verdunning van effluent in het ontvangende oppervlaktewater. Hierbij is de berekeningsmethode waarbij is opgeschaald naar heel Nederland gebruikt. Als er bij deze worst case PEC geen risico wordt berekend, zal dat risico er in de andere situaties ook niet zijn. De verkregen PEC voor de cytostatica capecitabine en hydroxycarbamide was het hoogst (Tabel 1).

Met behulp van ecotoxiciteitsgegevens voor waterorganismen zijn indicatieve waardes berekend voor de PNEC (Predicted No Effect Concentration), een veilige concentratie waarbij geen effecten worden verwacht op het aquatisch ecosysteem. Hoewel er van sommige middelen tientallen producten zijn geregistreerd, was er maar voor één middel milieu-informatie uit het toelatingsdossier beschikbaar. Daarom zijn ook gegevens uit de openbare wetenschappelijke literatuur gebruikt. Met behulp van deze gegevens konden in totaal voor zes cytostatica indicatieve PNECs worden afgeleid. Deze zijn gebaseerd op chronische blootstelling.

Vervolgens is een risicoquotiënt (RQ) berekend door de PEC te delen door de PNEC (Tabel 1). Een RQ hoger dan 1 geeft een potentieel risico aan. Het hoogste risicoquotiënt werd gevonden voor 5-fluorouracil. Aangezien capecitabine in het lichaam wordt omgezet tot 5-fluorouracil is er ook een RQ berekend voor de som van 5-fluorouracil als metaboliet van capecitabine en als toegediende actieve stof. Deze RQ is 0,20. De RQ voor de crème is hoger: 0,60. Hierbij is ervan uitgegaan dat 100% van de crème in water terecht komt (via opname door de huid en uitscheiding, via afspoelen onder de kraan of douche of via het wassen van kleding). Het is onbekend in hoeverre dit daadwerkelijk gebeurt. De som RQ voor beide toedieningsvormen is 0,80, dus nog steeds lager dan 1. Dit betekent dat er geen risico is.

De risicobeoordeling is gebaseerd op een worst case aanname met betrekking tot metabolisme, zoals ook in de toelatingsbeoordeling gebruikelijk is. Hierbij wordt ervan uitgegaan dat 100% van de toegediende stof onveranderd wordt uitgescheiden en er dus geen metabolisme plaats vindt. De risicobeoordeling voor 100% moederverbinding is bedoeld om ook het risico van de metabolieten af te dekken. Deze benadering geldt niet zonder meer voor zogenaamde ‘prodrugs’; inactieve geneesmiddelen die na toediening via metabolisme geactiveerd worden. Capecitabine en cisplatine zijn voorbeelden van prodrugs. De cytotoxische werking van de gevormde actieve metabolieten berust op hun grote chemische reactiviteit in de cel. Vanwege deze reactiviteit zijn ze vrijwel niet persistent buiten de cel en dus over het algemeen niet relevant voor de milieubeoordeling.

Meetgegevens in oppervlaktewater

Informatie over het vóórkomen van cytostatica in Nederlands oppervlaktewater is versnipperd. Alleen voor capecitabine, cyclofosfamide en ifosfamide zijn in het Waterkwaliteitsportaal monitoringsgegevens beschikbaar, maar geen van deze cytostatica werd daadwerkelijk aangetoond. Kwalitatieve meetgegevens van Roex et al. [1, 2] in ziekenhuiseffluent, rioolwater, RWZI influent en effluent in Utrecht en Nieuwegein laten zien dat een aantal cytostatica wordt aangetroffen. De door VEWIN beschikbaar gestelde ‘RIWA-database Nieuwegein’ bevat monitoringsdata van een aantal cytostatica in de grote rivieren. Cyclofosfamide en ifosfamide werden gedurende meerdere jaren op een aantal verschillende plaatsen gemonitord, en geregeld aangetroffen boven de rapportagegrens van 0.1 ng/L. De maximumconcentratie was 4 ng/L voor cyclofosfamide en 3 ng/L voor ifosfamide, beide ruim beneden de indicatieve PNECs van respectievelijk 482.000 ng/L en 303.000 ng/L. Gemcitabine, methotrexaat, etoposide

en 5-fluorouracil zijn op een kleiner aantal locaties/momenten geanalyseerd maar niet aangetoond boven de rapportagegrens (respectievelijk 10 ng/L, 50 ng/L, 100 ng/L en 1 µg/L). Deze rapportagegrenzen zijn lager dan de indicatieve PNECs die in dit rapport zijn afgeleid, behalve voor 5-fluorouracil. Wanneer 5-fluorouracil niet wordt aangetoond (rapportagegrens 1 µg/L), kan dus toch de indicatieve PNEC van 55 ng/L zijn overschreden. Voor de andere niet-aangetoonde cytostatica geldt dat wanneer ze niet worden aangetoond, er geen risico verwacht wordt voor het zoetwater ecosysteem van de individuele stoffen.

Tabel 2. Metingen van cyclofosfamide en ifosfamide met een rapportagegrens (RG) van 0,1 ng/L. Bron: RIWA-database Nieuwegein.

Stof	Locatie	Jaar	Aantal monsters (aantal boven RG)	Maximum [ng/L]
Cyclophosphamide	Andijk	2010-2017	97 (37)	2
	Brakel	2010-2017	91 (37)	4
	Heel	2011-2016	53 (23)	0,7
	Keizersveer	2011-2016	95 (23)	0,3
	Nieuwegein	2010-2017	96 (45)	2
	Nieuwersluis	2010-2017	97 (57)	4
	Stellendam	2010-2017	14 (6)	4
Ifosfamide	Andijk	2010-2017	98 (10)	2
	Brakel	2010-2017	92 (8)	1
	Heel	2011-2016	53 (3)	0,8
	Keizersveer	2011-2016	43 (4)	0,8
	Nieuwegein	2010-2017	97 (12)	3
	Nieuwersluis	2010-2017	98 (18)	2
	Stellendam	2010-2017	14 (2)	0,7

Mutageniteit/genotoxiciteit

Van cytostatica is bekend dat ze giftig zijn voor mensen vanwege hun mutageniteit en genotoxiciteit. In tegenstelling tot de risicobeoordeling voor mensen, is bij de risicobeoordeling voor het milieu het beschermdoel een populatie van organismen, niet het individuele organisme. Daarom wordt de impact van genotoxiciteit en mutageniteit alleen meegenomen in de milieurisicobeoordeling wanneer testen laten zien dat reproductie of andere populatie-relevante eindpunten beïnvloed worden. Testen op cellijnen zijn bijvoorbeeld niet direct te vertalen naar milieueffecten, omdat de blootstelling aan cellen anders is dan aan gehele organismen in het milieu en DNA schade niet direct vertaald kan worden naar weefselschade of andere chronische toxiciteits-effecten. Dit levert een onzekerheid op, die voor de huidige beoordeling acceptabel wordt bevonden. De onzekerheid wordt meegenomen in de afleiding van de PNEC door het toepassen van een veiligheidsfactor. Daarnaast is er het door de Tweede Kamer in 1989 vastgestelde ecologische beschermdoel waarbij 95% van alle soorten beschermd dienen te worden [3], dat ook opgenomen is als beschermdoel in de Kaderrichtlijn Water.

Hormoontherapie
Voor de risicobeoordeling van fulvestrant en tamoxifen, beide gebruikt als hormoontherapie, zijn gebruiksgegevens uit de GIP databank[2] gecombineerd met gegevens over metabolisme en verwijdering in de RWZI (Tabel 1) om een PEC te berekenen. De PNEC is op dezelfde manier afgeleid als voor de cytostatica. Ook bij deze twee stoffen blijft de RQ onder de 1, wat betekent dat ze geen risico vormen voor het water-ecosysteem.

Conclusies
Op basis van de voor deze rapportage geanalyseerde gegevens kan voor een aantal cytostatica en twee voorbeeldstoffen die gebruikt worden bij hormoontherapie, worden geconcludeerd dat deze geen risico voor het Nederlandse zoetwatermilieu vormen. Hierbij moet worden opgemerkt dat voor een aantal cytostatica niet voldoende gegevens over ecotoxiciteit beschikbaar waren om een conclusie over risico's te kunnen trekken. Er is niet gekeken naar mengseltoxiciteit.

Aanbevelingen
Een gebrek aan ecotoxiciteitsgegevens heeft ervoor gezorgd dat niet van alle geselecteerde cytostatica een milieubeoordeling kon worden uitgevoerd. Voor toekomstige milieubeoordelingen wordt aanbevolen de informatie uit registratiedossiers beter beschikbaar te maken. Voor stoffen waarvoor nog nooit een milieubeoordeling is uitgevoerd, zou de producenten gevraagd kunnen worden deze alsnog uit te voeren, wanneer de eigenschappen van de stof hier aanleiding toe geven.

Binnen de ketenaanpak 'Medicijnresten *uit* water' worden maatregelen geïdentificeerd en uitgewerkt om de hoeveelheid medicijnresten in water te verminderen. Deze maatregelen kunnen langs de gehele medicijnketen worden genomen, van ontwikkeling tot voorschrijven en gebruik en de afvalfase. Waterbeheerders werken momenteel aan pilotprojecten met betrekking tot het verbeteren van rioolwaterzuiveringsinstallaties.

Specifieke maatregelen om de emissies van cytostatica en de twee beschouwde vormen van hormoontherapie te verminderen lijken niet nodig. Zoals voor alle medicijnresten geldt, dienen restanten of ongebruikte medicijnen niet door de gootsteen of de wc te worden gespoeld.

Omdat het dermale gebruik van 5-fluorouracil de laatste jaren sterk toeneemt, verdient het aanbeveling om te onderzoeken welke fractie werkzame stof uit deze crème daadwerkelijk in het milieu terecht komt. Deze informatie kan dan gebruikt worden om de milieubeoordeling te verfijnen. Ook verdient het aanbeveling om de analytische technieken waarmee deze stof in oppervlaktewater kan worden aangetoond, te verbeteren zodat de stof tot op het niveau van de PNEC (55 ng/L) gedetecteerd kan worden.

Er zijn weinig monitoringsgegevens van cytostatica in oppervlaktewater in Nederland. Het wordt aanbevolen de stoffen met het hoogste risicoquotiënt (5-fluorouracil, etoposide en tamoxifen) en de stoffen met de hoogste gemodelleerde concentratie (capecitabine en

hydroxycarbamide) in monitoringsprogramma’s op te nemen. Ook een betere bepaling van RWZI verwijderingsrendementen en mogelijke terugvorming van de moederstof door hydrolyse kan helpen de risicobeoordeling te verbeteren.

1 Introduction

1.1 General

After use, pharmaceutical residues end up in the waste water system via the toilet. Subsequent treatment purifies the waste water from nutrients and partly from contaminants. Pharmaceutical residues are generally not fully removed in waste water treatment plants (WWTPs). Thus, WWTP effluent with pharmaceutical residues is discharged into surface waters, which raises concern. In 2016, RIVM reported that out of 80 monitored active pharmaceutical ingredients in The Netherlands in 2014, 29 were regularly detected in surface water and five posed a risk to the aquatic ecosystem [4]. These five pharmaceuticals are not expected to be the only pharmaceuticals posing a risk to the aquatic ecosystem, but for many pharmaceuticals it is not possible to perform an environmental risk assessment as information on their occurrence and the effects they can cause is sparsely, if at all, available. Because of the large amount of pharmaceutical active substances authorised for the Dutch market, around 2000 in 2016, it is not possible to monitor occurrence of all these different substances in relevant surface water bodies. For example, information on the presence of hormones and antidepressants was lacking in 2014, but these compounds can also be assumed to pose a risk to aquatic ecosystems [4].

Because of these concerns, the Dutch government has developed a so-called 'chain approach' to reduce the emission of pharmaceuticals to surface waters (the 'Ketenaanpak Medicijnresten *uit* Water'; see Figure 2), together with many stakeholders from the health and water sectors. Within this 'chain approach', source measures as well as end-of-pipe measures are identified and, where feasible and effective, implemented.

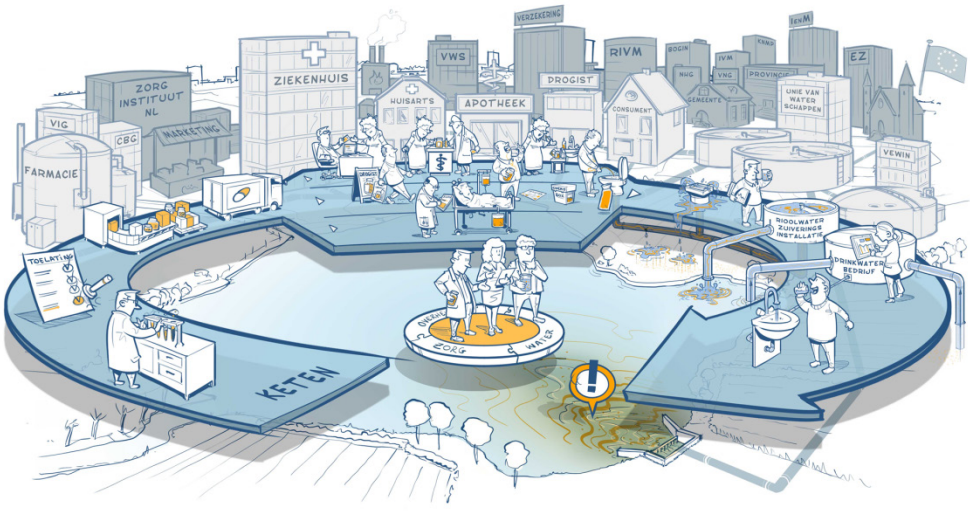


Figure 2. The Dutch chain approach 'Pharmaceutical residues out of water'. For more information, please visit https://jamdots.nl/view/239/medicijnresten-uit-water.

Within the chain approach, special attention is paid to groups of substances that may pose a risk to the aquatic ecosystem or may complicate drinking water purification. When possible, a source measure is designed for these specific groups of pharmaceuticals, such as urine collection bags for X-ray contrast media, or placement of an on-site waste water purification system at hospital sites.

In 2016, 54 stakeholders signed the 'Green Deal the Netherlands on its way to sustainable care' (https://milieuplatformzorg.nl/green-deal/). In 2017, the number of stakeholders involved in this Green Deal has increased to over 100. Within this Green Deal, a working group on Pharmaceutical residues in Water has been installed. This working group includes, amongst others, representatives from hospitals and other care facilities. Within this working group, questions were raised by hospital representatives whether the known toxicity of cytostatics to humans implies that there is also a risk to the environment.

The growing awareness of the lack of environmental information on this group of pharmaceuticals, has urged the Ministry of Infrastructure and Water Management to request RIVM to provide an overview of the use of cytostatics and their possible risks to the environment.

1.2 Concerns about cytostatic residues in the aquatic environment

Cancer is currently the most common life-threatening disease of the Netherlands. In the treatment of cancer, oncolytic drugs are essential and life-saving medicines. Among the oncolytic drugs, there is the group of cytostatic drugs, often referred to as chemotherapeutics. Cytostatic drugs interfere with cell proliferation impeding the growth of tumours. However, cytostatic drugs are essentially toxic to all cells. As emissions of cytostatic residues to the surface waters are expected to increase with the increase of people treated for cancer, the working group on Pharmaceutical residues within the Green Deal has expressed its concern about the risks posed by cytostatic residues to the ecology of the surface waters. This report sets out to address concerns about cytostatics in the aquatic environment. It should not be used to impede access to the best possible treatment for cancer patients.

Concerns about toxic effects of cytostatic substances, including their possible genotoxicity and mutagenicity, have already been raised years ago. In 2008, Van Heijnsbergen et al. [5] concluded that cytostatics would probably not be present at detectable levels in Dutch surface waters and risks were not probable, with a possible exception for 5-fluorouracil. This estimation was founded on the usage data reported by the Dutch GIP databank. However, this databank reflects only a fraction of the actual use of cytostatics, as it only contains the small fraction of cytostatics reimbursed through the medicines reimbursement system (GVS) and not the bulk of use reimbursed through the medical specialist care (medisch specialistische zorg). Actual use is thus expected to have been much higher than described by Van Heijnsbergen et al. [5] except for 5-fluorouracil, where they used an erroneous high value (see Section 5.1.2).

Within the PHARMAS project[3], experimental research and modelling studies were performed to identify risks for humans and/or the environment due to the presence of pharmaceuticals. Their conclusion in 2014 was that in the majority of European rivers, concentrations of cytostatics would be below 1 ng/L and that there were no risks to human health (via drinking water) or the environment [6].

In the project Cytothreat[4], specific attention was paid to obtaining ecotoxicity data for cytostatics. For three out of four tested cytostatics, a risk to the environment could not be excluded. The pharmaceuticals with a possible effect were 5-fluorouracil, imatinib and cisplatin [7]. Risks were unlikely for etoposide.

Concerns are also raised about the possible genotoxicity and mutagenicity of these compounds, and associated risks to the environment and human health.

Oncolytics and cytostatics
Patients with cancer may be treated with oncolytics, which is the term used for all chemical cancer treatments. Oncolytics include cytostatics, immunotherapy, hormone therapy and targeted therapy. Cytostatics are thus a subset of the possible pharmaceutical treatments against cancer. Cytostatics are used for the so-called chemotherapy and are substances that are used in the treatment of tumours and which directly influence cell division.

Although an environmental risk assessment has to be performed for all new medicinal products since 2006, only for methotrexate (limited) data on ecotoxicity is available in its registration dossier. Thus, environmental risks of cytostatics are largely unknown.

1.3 Aim

The aim of the current project was to provide an overview of the potential risks to the environment following the use of cytostatics. An inventory was made of the use of cytostatics in a number of Dutch hospitals. This data was combined with information on metabolic transformation of the cytostatics in patients, removal in waste water treatment plants, monitoring data in Dutch surface waters and the availability of data regarding ecotoxicity, resulting in a selection of eleven cytostatics which were further assessed.

For the selected cytostatic compounds, further detailed data were gathered on ecotoxicity in order to derive safe environmental concentrations. Using this information, risks to aquatic ecosystems following exposure to individual cytostatics were estimated. No laboratory experiments were performed, and the risks to humans (via drinking water) were not assessed.

In addition, it is described how excess cytostatics are managed by healthcare professionals and patients, where treatment is taking place

[3] www.pharmas-eu.net
[4] www.cytothreat.eu

(in the hospital or at home), and trends regarding the development and use of new forms of cancer treatments are discussed.

Within the current project, the focus lies primarily on cytostatics and not on the entire group of oncolytic drugs. Considering the increase in innovative cancer treatments, a short discussion on immunotherapy and hormone therapy is provided. For hormone therapy, two exemplary pharmaceuticals are further assessed regarding environmental risks.

2 Use of cytostatics

2.1 Method

In the Netherlands, the use of reimbursed medicines is made public by the national government via the GIP databank[5]. This databank has been accessed to obtain information on the use of cytostatics in the Netherlands. This databank only reflects a small fraction of cytostatics, as it only contains the fraction reimbursed through the medicines reimbursement system (GVS) and not the bulk of use reimbursed through the medical specialist care (medisch specialistische zorg). For example, the GIP databank reports that cisplatin was dispensed 146 times in 2014, which is an underestimation since cisplatin is not only dispensed by public pharmacies but predominantly by clinical pharmacies. In addition, data on for example doxorubicin, daunorubicin and paclitaxel could not be found despite the fact that these cytostatics are commonly used. Thus, the coverage of GIP databank regarding cytostatics is insufficient for estimating the total use of cytostatics in the Netherlands. However, the GIP databank did provide a useful 2012-2015 overview[6] for cytostatics and the number of patients treated with cytostatics with a coverage of 77% of the data.

To obtain data on the volume of cytostatic use in the Netherlands, pharmaceutical distributors/wholesalers were contacted. However, these sources could only provide general information, which was not useful for this project.

Subsequently, eight hospitals in the Netherlands, who treat cancer patients, were contacted to request purchasing records on cytostatics from the clinical and outpatient pharmacies preferably from 2012 and 2016. Four out of eight hospitals (two general hospitals and two academic centres) provided data under the condition that the data be presented anonymously. Several hospitals could not provide data since they recently switched administrative systems and were not able to provide us timely with a list of cytostatics. Nursing homes were not contacted individually as cytostatics dispensed to residents of nursing homes are included in the data from the hospitals.

The layout and content of the purchasing records varied per hospital. After receipt, the purchasing records were processed to obtain comparable data. The data on cytostatics was extracted and the overall amount (kg) dispensed was calculated per cytostatic and they were ranked on dispensed amount. Subsequently, the lists of the four hospitals were combined to obtain an overall ranking of dispensed cytostatics.

The list with the 10 most dispensed compounds (in kilograms) from the outpatient pharmacy was compared with the list from the clinical pharmacy. This comparison could only be made for data obtained from

[5] www.gipdatabank.nl
[6] https://www.gipdatabank.nl/databank#/g/00-totaal/R_04_addon/vg/bijlageOncolytica

the general hospitals, since in the data obtained from the academic centres the distinction between outpatient and clinical pharmacy data was not made. A similar ranking was also made to compare purchasing records from 2012 with 2016. Here, the comparison was made for the academic hospitals only, as the data received from the general hospitals was incomplete.

The obtained data contained the purchasing records of two academic hospitals and two general hospitals. As this is a fraction of the total dispensed amount of cytostatics in the Netherlands, the list with the 25 most dispensed cytostatics (in kilograms) was discussed with the Dutch Association of Hospital Pharmacists (NVZA) to verify if this list matches with their general impression of the dispensed cytostatics for the Netherlands as a whole. The NVZA also provided information on the way any excess cytostatics are discarded and on the question whether there is a general hospital policy regarding cytostatics that are eliminated via the waste water.

2.2 Results

2.2.1 Most dispensed cytostatics in hospitals

In Table 1, the 25 most dispensed cytostatics (in kg) are presented. This table is based on the quantities purchased by the clinical and outpatient pharmacies of two academic centres and two general hospitals. The number of patients that use the cytostatics was not included in the received data. Therefore, the list also contains cytostatics that are used in a high dose rather than being used frequently. For example, there are not many patients who receive treosulfan but the patients who do, receive around 25 gram every 3-4 weeks for a maximum of six cures/treatments[7]. On the other hand, cytostatics that are used by a large number of patients but in low dosage are missing from this list (e.g., vincristine[8]). Some of these cytostatics are also used for other indications than cancer. For these treatments, they are dispensed via public pharmacies (see Section 2.2.3).

The list in Table 1 was discussed with the Dutch Association of Hospital Pharmacists (NVZA). It was concluded that the table is representative for the use of cytostatics in the Netherlands. This was further supported by the purchasing records from a third academic hospital, which was in accordance with the data received from the other two academic hospitals. The data from the third academic hospital was not timely received and was only used for comparison.

To obtain an indicator of relative potency for the cytostatics, the amount (kg) of each cytostatic in table 1 was divided by the number of patients receiving that treatment in the Netherlands in 2015. The result was subsequently normalised to the smallest outcome. Thus, the cytostatics with the highest normalized value for kg/patient will be regarded as the most potent cytostatics in this list.

[7] https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/t/treosulfan
[8] https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/v/vincristine

Table 1. The ranking of dispensed cytostatics by kg active ingredient for the clinical and outpatient pharmacies of the four participating hospitals, the number of patients receiving treatment in 2015 in the Netherlands, and the normalised kg/patient.

	Cytostatic	Amount (kg)[a,b]	Patients 2015[c]	Normalised kg/patient[d]
1	Capecitabine	170	9236	1
2	Hydroxycarbamide	100	4363	1
3	Cyclophosphamide	7.1	9774	31
4	Ifosfamide	4.4	-	-
5	Cytarabine	3.8	848	5
6	Gemcitabine	3.6	3408	22
7	5-fluorouracil	3.6[e]	-	-[f]
8	Methotrexate	3.2[e]	68152	-[f]
9	Temozolomide	2.0	680	8
10	Carboplatin	1.3	-	-
11	Etoposide	0.8	2710	77
12	Paclitaxel	0.6	6171	234
13	Pemetrexed	0.6	3190	121
14	Oxaliplatin	0.4	5305	301
15	Azacitidine	0.4	392	22
16	Procarbazine	0.3	226	17
17	Dacarbazine	0.2	-	-
18	Irinotecan	0.2	1731	197
19	Mercaptopurine	0.2[e]	6281	-[f]
20	Cisplatin	0.2	4189	476
21	Doxorubicin	0.2	562	64
22	Docetaxel	0.2	6672	758
23	Treosulfan	0.2	-	-
24	Mitomycin	0.1	4386	997
25	Melphalan	0.1	1151	262

[a] Based on the provided purchasing records.
[b] Data are rounded off and are for indicative purpose only.
[c] Data from GIP databank oncolytics overview 2012-2015.
[d] The normalised kg/patient are used as an indicator of relative potency.
[e] This only reflects the dispensed amount via the hospital pharmacies. These substances are also used for other indications and for these uses, they are dispensed via the public pharmacy.
[f] Not calculated; also dispensed by public pharmacies (Section 2.2.3).

The list contains cytostatics with a large variety of mechanisms of action, of which alkylating agents (n=6) and pyrimidine analogues (n=5) are most frequently observed. Alkylating agents alkylate DNA, which induces breakage of DNA or formation of cross connections in the DNA. Consequently, DNA cannot uncoil and separate which is needed for DNA replication and cell division. The pyrimidine analogues mimic the structure of the naturally occurring pyrimidines, which disturb the DNA/protein synthesis or enzyme activity that is needed for cell division/function.

Most cytostatics in this list are available as an injection or infusion liquid and thus are primarily used in hospitals. However, the two most dispensed cytostatics (in kg) come as tablets or capsules. Table 1 concerns the cytostatics dispensed by hospital pharmacies; four of these are also prescribed within the hospitals for other indications than cancer. Hydroxycarbamide is also prescribed for sickle cell disease, while cyclophosphamide, methotrexate and mercaptopurine are also prescribed for several autoimmune diseases. The intended therapeutic use is of no consequence to the excretion profiles of pharmaceuticals administered by the same route. Some of the cytostatics in Table 1 are also dispensed by public pharmacies, which is discussed in Section 2.2.3.

2.2.2 Comparison between clinical and outpatient pharmacies

The ten most dispensed cytostatics from the hospitals' outpatient pharmacies were compared with those from the clinical pharmacies (Table 2). In hospital outpatient pharmacies (not to be confused with public pharmacies), patients collect the medicine that they will use at home whereas a clinical pharmacy is responsible for the medication administered to the patient in the hospital itself. Therefore, oral cytostatics (tablets or capsules) are mainly dispensed by the outpatient pharmacy while injection and infusion liquids are only distributed via the clinical pharmacy. This is reflected in Table 2: all cytostatics provided by the outpatient pharmacy are available as tablet or capsule while most cytostatics distributed by the clinical pharmacy are available as injection or infusion liquid. The NVZA explained in an interview that tablets/capsules are sometimes purchased by the clinical pharmacy but, due to changing Dutch legislations, are dispensed by the outpatient pharmacy.

Table 2. Comparison of the 10 most dispensed cytostatics (in kg) in the clinical versus outpatient pharmacies.

	Clinical pharmacy	Outpatient pharmacy	
1	Gemcitabine	Capecitabine	1
2	Cyclophosphamide	Hydroxycarbamide	2
3	5-fluorouracil	Temozolomide	3
4	Cytarabine	Cyclophosphamide	4
5	Carboplatin	Procarbazine	5
6	Hydroxycarbamide	Etoposide	6
7	Pemetrexed	Chloorambucil	7
8	Paclitaxel	Lomustine	8
9	Capecitabine	Fludarabine	9
10	Methotrexate	Melphalan	10

There are large differences between the amounts (in kg) of specific cytostatics dispensed by the outpatient and clinical pharmacies. In general, cytostatics were dispensed in much higher amounts in clinical pharmacies compared to outpatient pharmacies. However, capecitabine and hydroxycarbamide were dispensed in much higher amounts (in kg) by outpatient pharmacies when compared to clinical pharmacies (300 and 80 times more respectively). Some cytostatics were only dispensed by clinical pharmacies, e.g. gemcitabine and 5-fluorouracil (IV fluid),

and some only by outpatient pharmacies, e.g. temozolomide and procarbazine.

2.2.3 Cytostatics dispensed by public pharmacies

Public pharmacies generally do not dispense cytostatics with the exception of 5-fluorouracil cream, mercaptopurine, tioguanine, and methotrexate. 5-Fluorouracil cream is used as a treatment for skin cancer. According to GIP databank, public pharmacies in the Netherlands dispensed 108.3 kg of 5-fluorouracil in 2016. Since the cream is used as a cancer treatment this amount is taken into account in further calculations. Mercaptopurine, tioguanine and methotrexate dispensed by public pharmacies are used as anti-inflammatory drugs. The quantities dispensed are significant but outside of the scope of this report. Hence, they are not further taken into account in this report.

2.2.4 Trends in the use of cytostatic drugs

The NVZA (personal communication) notices an increase in the use of immunotherapy and hormone therapy. However, the use of classic cytostatic drugs also increases with the increasing number of cancer patients. Hence, the new therapies are additional to existing treatments rather than replacing existing therapies.

It was not possible to identify reliable trends on the use of cytostatic drugs in the data obtained from the participating hospitals for 2012 and 2016. This is due to the limited number of participating hospitals and the sometimes contradictory trends in purchasing records between hospitals. The observed changes per hospital probably reflect general changes in usage as well as specific changes in the hospitals (e.g. patient population, regulations). For instance, the participating hospitals dispensed more capecitabine and hydroxycarbamide (in kg) because these are no longer dispensed via public pharmacies since January 1st, 2015.

For public pharmacies, the GIP databank shows a steady increase in the use of 5-fluorouracil cream. In 2012 public pharmacies dispensed 74.4 kg 5-fluorouracil, which increased to 108.3 kg in 2016.

2.3 Emission routes of cytostatics

Two main emission routes to the environment can be identified. The first route is after use by the patient through excretion. The second route is through the potential discharge of unused (excess) medication.

The first emission route is by patients excreting residues of the administered cytostatic in e.g. urine, faeces, transpiration and vomit. This may occur in the hospital or elsewhere, much depending on the administration route and the time spent in the hospital (from several hours to being hospitalized for a longer period of time). Dutch hospitals generally do not collect their cancer patients' excrements or treat their waste water prior to discharge in the sewage. In the Netherlands, there are currently 4-5 hospitals that use an on-site treatment system to purify waste water before it is discharged. Urine bags from catheterized cancer patients are discarded as medical waste. The same applies to incontinence material that is used in the hospital and vomit, which is

collected in disposables in a hospital setting. The waste water emission route is considered to contribute most to the emission of cytostatics to the environment.

The second emission route concerns the potential discharge of unused or excess cytostatics. To obtain an impression of how cytostatics are handled, two hospital pharmacists and an environmental advisor (suggested by the NVZA) were interviewed. This showed that hospital staff adheres to strict safety protocols when handling hazardous substances such as cytostatics. When cytostatics are administered via an infusion or injection, often the entire content of a packaging unit is prepared (e.g. an ampoule). Any excess cytostatic produced by the pharmacy or leftover after treatment is discarded as medical waste in accordance with the Waste Framework Directive (2008/98/EC)[9]. For treatment at home, patients receive the exact number of tablets/capsules needed for the treatment period. Any excess medication should be handed in at the (local) pharmacy or as small chemical waste at the municipality. When adhering to these disposal routes, the emission of unused cytostatics to the environment through this route is negligible since hospital waste is incinerated. The willingness of pharmacies to accept unused medicines, including cytostatics, is critical for success.

Besides these main routes, 5-fluorouracil cream may end up in waste water via washing of hands, body, and clothes.

[9] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008L0098&from=EN

3 Emission of cytostatics to surface water

3.1 Method

To estimate emissions of cytostatics in surface waters, the amount of cytostatics used (Chapter 2) was combined with information on metabolism in the patient and removal in the waste water treatment plant.

3.1.1 Human metabolism in the patient and excretion

The websites of the Farmacotherapeutisch Kompas[10] and the BC Cancer association[11] provide information on metabolism and excretion levels of the unchanged drug and metabolites. When no data or insufficient data was found in those databases, additional information was obtained from publicly available literature.

3.1.2 Physico-chemical properties of cytostatics and removal in WWTPs

In order to model the behaviour of substances in a waste water treatment plant (WWTP), physico-chemical properties of the substances are needed, as well as data on environmental fate and behaviour. The search and collection strategy for these parameters is described in Annex 1. This Annex also contains, for each substance, two tables and a description of how the collected data were used to derive selected parameter values needed for WWTP modelling. The descriptive text also contains the structural formula and identity characteristics of each substance. Of these two tables in the Annex, the first presents the collected physico-chemical parameters and data on adsorption to activated (waste water) sludge. The second table presents data on removal and stability of the substance in tests with activated sludge.

3.1.3 Monitoring data for effluents and surface water

The Dutch 'Waterkwaliteitsportaal' (water quality portal)[12] and the Watson database of the Dutch emission registration[13] were screened to obtain data on detected levels of cytostatics in Dutch WWTP influent and effluent waters and in surface water.

3.2 Human metabolism and excretion

Data on metabolism and excretion was collected for the 25 most dispensed cytostatics (in kg) in order to estimate the quantities of unchanged cytostatics and metabolites entering the waste water system. Table 3 gives an overview of the most relevant data on metabolism and excretion.

[10] www.farmacotherapeutischkompas.nl
[11] http://www.bccancer.bc.ca/
[12] https://www.waterkwaliteitsportaal.nl/
[13] http://www.emissieregistratie.nl/erpubliek/erpub/wsn/default.aspx

Table 3. Metabolism and excretion of the 25 most dispensed cytostatics in the Netherlands. Administration routes: IV = intravenous, IT = intrathecal, ID = intradermal. Source: Farmacotherapeutisch Kompas10, Geneesmiddeleninformatiebank18, and BC Cancer association11. The order of cytostatics in this table is based on the amount dispensed, as reported in Table 1.

Drug Name	**Metabolites**		**Excretion**			
	Active	Inactive	$T_{½}$ elimination	Via urine[a]	Via faece[s]	As parent drug
Capecitabine	Yes	Yes	45–70 min	84-96%	-	3%
Hydroxycarbamide	Unknown	Yes	3-4 hour	25-80%	-	50%
Cyclophosphamide	Yes	Yes	4–8 hour	5-25%	31-66%	25%
Ifosfamide	Yes	Yes	4-8 hour	65%	-	50%
Cytarabine	Yes	Yes	1–3 hour (IV), 100-263 hour (IT)	80%	-	10%
Gemcitabine	Yes	Yes	0,7–12 hour	92-98%	-	10%
5-fluorouracil IV	Yes	Yes	10–20 minutes (IV)	7-20% (IV)	-	20% (IV)
5-fluorouracil ID	Unknown	Unknown	10% systemic uptake (ID)	Unknown	Unknown	unknown
Methotrexate	Yes	Yes	3–17 hour	80-90%	10%	90%
Temozolomide	Yes	Yes	1,8 hour	38%	-	10%
Carboplatin	Yes	Unknown	5 days	65%	-	32%
Etoposide	Yes	Yes	6 hour (oral), 6–12 hour (IV)	44-67%	16-44%	50%
Paclitaxel	Yes	Unknown	3–53 hour	14%	26%	19%
Pemetrexed	Unknown	Unknown	3,5 hour	70-90%	-	90%
Oxaliplatin	Yes	Yes	11–16 days	50%	-	50%
Azacitidine	Unknown	Unknown	41 minutes	50-95%	<1%	Unknown
Procarbazine	Yes	Yes	1 hour	70%	-	20%
Dacarbazine	Yes	Yes	5 hour	100%	-	50%
Irinotecan	Yes	Yes	14 hour	22%	33%	50%
Mercaptopurine	Yes	Yes	60–120 minutes, active metabolites 5 hour	7-40%	-	40%
Cisplatin	Yes	Yes	32–53 minutes (unbound); >5 days (irreversibly-bound complexes)	>90%	-	23% [8]
Doxorubicin	Yes	Yes	20 – 48 hour	3-10%	40-50%	50%

Drug Name	**Metabolites**		**Excretion**			
	Active	Inactive	$T_{½}$ elimination	Via urine[a]	Via faece[s]	As parent drug
Docetaxel	Unknown	Unknown	11 hour	5-6%	80%	14%
Treosulfan	Unknown	Unknown	1,6 hour	9-38%	-	25% [9]
Mitomycin	Unknown	Yes	50 minutes	10%	-	10%
Melphalan	No	Yes	0,52 hour	20-35%	20-50%	16%

[a] Parent drug and/or metabolites.

When the parent drug is metabolized, it may be transformed into an active or an inactive metabolite. Active metabolites may have a lower, equal or even higher potency compared to the parent drug. The t½ elimination represents the time required to excrete 50% of the administered dose from the patient. In addition, Table 3 shows the percentage of parent drug and metabolites excreted via urine and faeces. Further, it shows how much of the unchanged parent drug is excreted in a worst case scenario. It should be noted that specific metabolites of etoposide, irinotecan and doxorubicin (phase-2 conjugates) may potentially transform back into the parent drug during waste water treatment through hydrolysis.

Very little data could be found on fate of dermal 5-fluorouracil. The systemic uptake reportedly is about 10%[10]. Kinetics data on the 90% of the dose that remains on or in the skin could not be found. Thus, it is also unknown which part of the cream is washed off when rinsing hands after application, when taking a shower, or which part is washed out of clothes.

3.3 Removal in waste water treatment plants

In the Watson database[13], effluent concentrations of cyclophosphamide and ifosfamide in the Netherlands were reported from monitoring campaigns during 2006-2013. Influent concentrations were monitored during 2007-2010. No monitoring data is available for the period 2014-2016. Cyclophosphamide was detected in influent streams in 2009 (0.055 µg/L) on one out of twelve locations. Cyclophosphamide could not be detected in effluent streams of this location in the same year. It was however detected in effluent streams in the years 2006, 2012 and 2013 in respectively five, two and one WWTP(s). In these years no measurements were performed in influent streams.

Literature was searched for studies in which measured concentrations of cytostatics in both influent and effluent of a WWTP were reported. The results are compiled in Table 54 in Annex 3 and summarized in Table 4.

This table shows that for many cytostatics, no data on removal in WWTPs is available. A high effluent/influent ratio means that the substance is not removed in the WWTP very well; a low effluent/influent ratio means that the substance is removed almost completely. The main removal processes are degradation and sorption to sludge.

Table 4. Ranges of measured WWTP effluent/influent ratios as reported in public literature. For details, see Table 54 in Annex 3. The order of cytostatics in this table is based on the amount dispensed, as reported in Table 1.

	Cytostatic	Range of effluent/influent ratios
1	Capecitabine	0.0047–0.42
2	Hydroxycarbamide	No data
3	Cyclophosphamide	0.82-1.13
4	Ifosfamide	0.34[c]-1.21
5	Cytarabine	0.43-1.52
6	Gemcitabine	0.75-1.7
7	5-fluorouracil	<0.14[b]
8	Methotrexate	<0.017-0.88[d]
9	Temozolomide	No data
10	Carboplatin	0.28-0.40[a]
11	Etoposide	0.10-0.23
12	Paclitaxel	No data
13	Pemetrexed	No data
14	Oxaliplatin	No data
15	Azacitidine	No data
16	Procarbazine	No data
17	Dacarbazine	No data
18	Irinotecan	No data
19	Mercaptopurine	No data
20	Cisplatin	0.12-0.46[a]
21	Doxorubicin	No data
22	Docetaxel	No data
23	Treosulfan	No data
24	Mitomycin	No data
25	Melphalan	No data

[a] Only two ratios available.
[b] Only one ratio available.
[c] The ratio of 0.34 is an outlier, all other ratios found (6) are between 0.68 and 1.2.
[d] There is only one high ratio (0.88), in all other cases, the substance is not detected at all or only in the influent.

3.4 Monitoring data in surface water

Measured concentrations of cytostatics in Dutch surface waters were obtained via the Waterkwaliteitsportaal[12], which collects data for the European Water Framework Directive (WFD) from all Dutch WWTPs (waste water treatment plants). The concentration of only three cytostatics (capecitabine, cyclophosphamide and ifosfamide) was monitored in Dutch surface waters in 2014-2016, but all concentrations were below the detection limit (0.01–0.05 µg/L for all compounds).

The Dutch national association of drinking water companies (VEWIN) provided information from the 'RIWA-database Nieuwegein'. In this database, records for cytostatics are available from 2002-2017. Most of these records concern measurements which are below the limit of quantification (10 ng/L for cyclophosphamide, ifosfamide, and

gemcitabine; 50 ng/L for methotrexate, 100 ng/L for etoposide and 1 µg/L for 5-fluorouracil). For cyclophosphamide and ifosfamide however, a more extensive dataset was available with measurements with a lower limit of quantification for a sub-set of monitoring locations (Table 5).

Table 5. Measurements of cyclophosphamide and ifosfamide with a limit of quantification of 0.1 ng/L. Source: RIWA-database Nieuwegein.

Compound	Location	Year	Total # Samples (# > 0.1 ng/L)	Max value [ng/L]
Cyclophosphamide	Andijk	2010-2017	97 (37)	2
	Brakel	2010-2017	91 (37)	4
	Heel	2011-2016	53 (23)	0.7
	Keizersveer	2011-2016	95 (23)	0.3
	Nieuwegein	2010-2017	96 (45)	2
	Nieuwersluis	2010-2017	97 (57)	4
	Stellendam	2010-2017	14 (6)	4
Ifosfamide	Andijk	2010-2017	98 (10)	2
	Brakel	2010-2017	92 (8)	1
	Heel	2011-2016	53 (3)	0.8
	Keizersveer	2011-2016	43 (4)	0.8
	Nieuwegein	2010-2017	97 (12)	3
	Nieuwersluis	2010-2017	98 (18)	2
	Stellendam	2010-2017	14 (2)	0.7

Table 5 shows that cyclophosphamide is detected in about one-third of all sampling locations. Ifosfamide is detected less frequently but has been detected at all sampling locations. Maximum values for both active ingredients do not exceed 4 ng/L. The sampling locations in this RIWA database are larger Dutch rivers. No sampling locations of smaller surface waters close to WWTPs are included in this dataset.

Roex [1] and Roex et al [2] have screened the waste water of two academic hospitals for the presence of cytostatics. Concentrations in passive samplers were calculated back into aquatic concentrations. According to the authors this provides only an indication of the actual concentrations [1]. In Radboud UMC Nijmegen (Figure 3; [1]), nine cytostatics were monitored at 4 different locations; hospital waste water, sewage in between the hospital and WWTP, WWTP influent and WWTP effluent. Four of the cytostatics were detected in hospital waste water, three in sewage and two in WWTP influent and effluent (cytarabine and ifosfamide). The increased cytarabine and ifosfamide concentrations in WWTP influent relative to sewage are not understood. However, the limited influent/effluent ratio suggests the possibility of hydrolysing phase-2 metabolites, liberating the unchanged cytostatic. In UMC Utrecht [2], the cytostatics were only found in waste water, not in

influent or effluent of the WWTP (Figure 4).

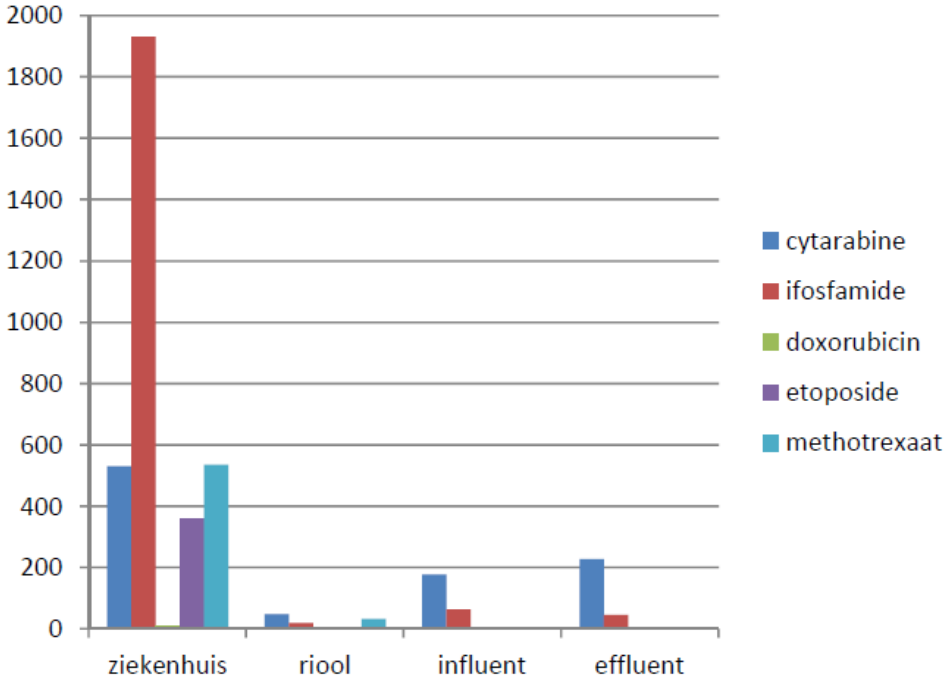


Figure 3. Concentrations of cytostatics in passive samplers in Nijmegen in ng/L [1]. Also analysed but not detected were cyclophosphamide, cisplatin, carboplatin, and vincristin. According to the authors, quantities can only be seen as indicative.

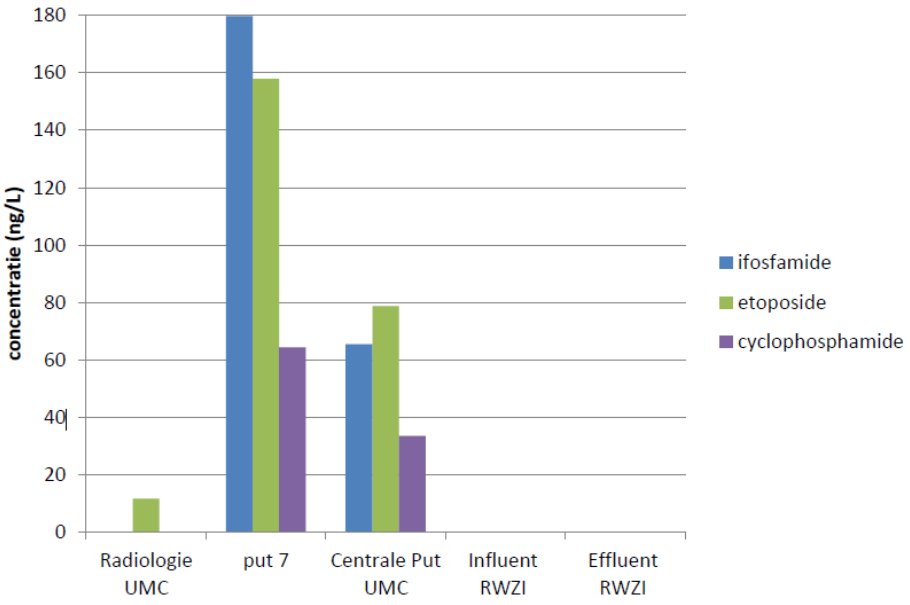


Figure 4. Concentrations of cytostatics in passive samplers in Utrecht in ng/L [2]. Also analysed but not detected were methotrexate, cytarabine, cyclophosphamide, cisplatin, carboplatin, and vincristin. According to the authors, quantities can only be seen as indicative.

Booker et al. [10] provide a review of monitoring data in the EU. The highest concentrations reported in surface water are 41 ng/L for ifosfamide, 13 ng/L for cytarabine and 10 ng/L for cyclophosphamide.

4 Selection of cytostatics for risk assessment

The 25 most dispensed cytostatics were used to select a final list of ten cytostatics. This selection was made in such a way that it contained a diverse set of cytostatics. For this purpose, the cytostatics dispensed in the highest quantity were selected, as well as very potent cytostatics that might be used in lower quantities. In addition, human metabolic transformation (Section 3.1.1) was taken into account as cytostatics that are poorly metabolized may be more relevant in terms of environmental concentrations than cytostatics that are extensively metabolized. The same is valid for removal in waste water treatment plants (Section 3.1.2). Furthermore, to fill the selection up to ten compounds, the availability of environmental information was taken into account.

Detailed information on the selected compounds is presented in Annex 1.

The most relevant cytostatics are presented in Table 6, which contains eleven instead of ten substances. 5-Fluorouracil was added to the list, since it is not only dispensed as a cytostatic by itself for IV (intravenous) and ID (intradermal) application, but it is also a metabolite of the prodrug capecitabine. In the next chapters, the amount of 5-fluorouracil used for risk assessment is reported in two different ways: the intravenous amount (the amount of intravenous 5-fluorouracil used plus the amount that is excreted as metabolite of capecitabine) and the dermal amount (the amount used as cream).

Table 6. Most relevant cytostatics for environmental risk assessment in the Netherlands, in alphabetic order.

Substance
Capecitabine
Carboplatin
Cisplatin
Cyclophosphamide
Cytarabine
Etoposide
5-fluorouracil
Gemcitabine
Hydroxycarbamide
Ifosfamide
Methotrexate

5 Predicted Environmental Concentrations

To perform an environmental risk assessment, a risk quotient is calculated based on the Predicted Environmental Concentration (PEC) divided by a 'safe environmental concentration', usually the Predicted No Effect Concentration (PNEC). A PEC/PNEC ratio > 1 shows that the predicted environmental concentration is higher that the safe environmental concentration, indicating potential risk to the environment. The derivation of the PEC is described in this chapter, using the data on use (Chapter 2) as a basis, combined with data on metabolism (Section 3.1.1) and removal in sewage treatment plants (Section 3.1.2). The derivation of the PNEC is described in Chapter 6, the resulting risk quotients are presented in Chapter 7.

The relevant PEC is calculated for a point in the receiving water near the discharge location of a WWTP. Thus, first the concentration of a given cytostatic substance in the influent of a WWTP should be known or calculated. This is based on the use and metabolism of the compound. The influent concentration is then corrected for removal in the WWTP and dilution of the WWTP effluent by the receiving surface water system.

All calculations are based on the medicine use in the year 2016.

5.1 Data on cytostatics use

As anonymity was agreed with the hospitals they are referred to as hospital 1, 2, 3 and 4. Two of these were large academic hospitals and two were 'general' hospitals. No further specification will be given in the report.

Point of departure for the PEC calculation is total use data in weight (kg) per year of the selected cytostatics in the four hospitals. The data collected in this study do not allow for an easy and direct translation to substance concentrations in the environment. There is no distinction in the data between the amount administered to patients within the hospital and the amount given by the pharmacy for outpatient treatment. Ambulatory patients will emit the majority of their cytostatic treatment at home. It is unknown where patients live and hence, to which WWTP they will ultimately emit. As nearly all hospitals serve a wider region, a large proportion of patients will not live in the city or village where the hospital is located. In other words; it is unknown which fraction of the patients will emit to the same WWTP as the hospital.

Two calculation methods were used to calculate PECs for the selected substances, called Method 1 and Method 2 (see Annex 4 for details).

5.1.1 Method 1: cytostatics are discharged in the same WWTP as the hospital

It is assumed that the total amount of substance given out by one hospital is emitted through the WWTP to which this hospital is connected. As part of the substances will be administered and emitted in

other locations, this is a worst case estimate. A limitation of this method is that three of the hospitals (numbers 2, 3, and 4) are situated in cities having more than one hospital with an oncology department. For these locations, only the worst case contribution of one hospital to the specific WWTP was estimated, not taking into account additional contributions of the other hospitals. In addition, there is one location (city) where only one hospital is connected to the WWTP of that city. Method 1 was used for hospitals 1, 3 and 4. The situation for hospital 2 was too complex (more hospitals with oncology and more than one WWTP) to model.

5.1.2 *Method 2: cytostatic use extrapolated to all hospitals*

In the second method we extrapolate the use data from four hospitals to all hospitals having an oncology department in the Netherlands. As academic hospitals may have a different cytostatic use pattern than general hospitals, the cytostatic use in the two academic hospitals and in the two general hospitals was summed and determined two scaling factors:

1. the ratio of the number of beds in all academic hospitals to the number of beds in the two academic hospitals in this study.
2. the ratio of the number of beds in all non-academic hospitals with an oncology department to the number of beds in the two general hospitals in this study.

Assumptions made with this approach are:

- the amount (kg) of dispensed substance in a hospital is proportional to the number of patients served (in the region) by the hospital;
- the number of patients served (with cytostatic treatment) by a hospital is proportional to the size of the hospital, which can be expressed as the number of beds of the entire hospital;
- the size of the oncology department of a hospital is proportional to the total number of beds of a hospital;
- the total number of beds of hospitals that have an oncology department is proportional to the total amount of substance used in the Netherlands.

A public list of all hospitals in the Netherlands was used that contained the number of beds and type of hospital (academic, general, top clinical, etc.) [11]. This list was checked for current existence / discontinuance of hospitals, compared with another data source and appended by own research with an indication (Y/N) whether or not an oncology department exists for each of the hospitals. The two academic hospitals for which cytostatic use data are available, have a total of 1995 beds, while all academic hospitals have 7996 beds, giving a scaling factor of 4.01. The two general hospitals for which cytostatic use data are available, have a total of 2100 beds, all non-academic hospitals with oncology departments have 34144 beds, giving a scaling factor of 16.26.

The amounts of cytostatics were summed for the 2 academic hospitals and multiplied by their respective scaling factor. The same was done with the data for the two general hospitals. These resulting amounts were again summed, resulting in one extrapolated amount per active

substance for The Netherlands. The resulting amounts are shown in Table 7.

Table 7. Extrapolated quantities of cytostatic active substances used in The Netherlands in 2016 using method 2.

Substance	kg y^{-1}
Capecitabine	2010[a]
Carboplatin	13
Cisplatin	1
Cyclophosphamide	54
Cytarabine	33
Etoposide	6
5-fluorouracil intravenous	33
5-fluorouracil intradermal	108
Gemcitabine	36
Hydroxycarbamide	1072
Ifosfamide	19
Methotrexate	16

[a] Capecitabine is a prodrug. The reported amount is equivalent to 728 kg of its active ingredient 5-fluorouracil.

The amount of 5-fluorouracil (33+108 kg) is significantly less than reported earlier by Heijnsbergen et al. for 2006 (306 kg) [5]. Unfortunately, Heijnsbergen et al. arrived at that amount by multiplying the incomplete data from the GIP databank (dermal only) with what they perceived as an average daily IV dose (450 mg). As a result, dispensing was grossly underestimated and the daily dose was grossly overestimated. GIP databank[5] uses 50 mg as a defined daily dose (DDD) for dermal 5-fluorouracil, resulting in a dermal use of 34 kg in 2006 (and not 306 kg as reported by Heijnsbergen et al. [5]) and 108 kg in 2016.

5.2 Metabolism

PEC values were calculated using the worst case fraction of parent compound that is excreted unchanged ($F_{excreted}$) as shown in Table 3 as well as with $F_{excreted}$ = 1. The latter option is included since the ecotoxicity of metabolites is generally not known and their possible contribution to the overall toxicity of a substance is neglected when removal by metabolism is included in the calculation. The assumption of $F_{excreted}$ = 1 is that any metabolite excreted is equally ecotoxic as the parent. This approach is also followed within the environmental risk assessment of the European authorisation process of human pharmaceuticals [12, 13]. As capecitabine is a prodrug of 5-fluorouracil [14], the sum of total 5-fluorouracil emission to surface water was calculated. This was done by adding the fraction of unchanged 5-fluorouracil excreted by patients being administered capecitabine (0.54% [15]) to the fraction of unchanged 5-fluorouracil excreted by patients being administered 5-fluorouracil. The distinction made by setting $F_{excreted}$ to 1 was applied only to the latter fraction.

5.3 Removal in WWTP

The behaviour of the selected substances was modelled using SimpleTreat, version 4.0.9 [16, 17] with the substance related input values in Annex 1 as input. SimpleTreat operational settings used for simulations are shown in Annex 2. It is noted that with respect to biological degradation in the WWTP, input values were selected to be on the 'safe' side. This means that, depending on how much information was available, care was taken not to overestimate the potential for removal in order to arrive at a reasonable worst case PEC.

The relevant SimpleTreat output for PEC calculations is the substance mass fraction emitted to effluent, which is presented in Table 8.

Table 8. SimpleTreat calculations and measured effluent/influent ratios for the selected pharmaceuticals.

Substance	SimpleTreat fraction emitted to effluent [-]	collected effluent/influent ratios [-]
Capecitabine	0.45	0.0047–0.42
Carboplatin	0.75	0.28-0.40[a]
Cisplatin	0.37	0.12-0.46[a]
Cyclophosphamide	0.98	0.82-1.13
Cytarabine	0.57	0.43-1.52
Etoposide	0.82	0.10-0.23
5-fluorouracil	0.58	<0.14[b]
Gemcitabine	1.0	0.75-1.7
Hydroxycarbamide	1.0	no data found
Ifosfamide	0.99	0.34[c]-1.21
Methotrexate	0.12	<0.017-0.88[d]

[a] Only two ratios available.
[b] Only one ratio available.
[c] The ratio of 0.34 is an outlier, all other ratios found (6) are between 0.68 and 1.2.
[d] There is only one high ratio (0.88), in all other cases, the substance is not detected at all or only in the influent.

A high effluent/influent ratio means that the substance is not removed in the WWTP very well; a low effluent/influent ratio means that the substance is removed almost completely. The main removal processes are degradation and sorption to sludge.

The modelled emission fraction is in reasonable agreement with the range of measured values or on the upper range (corresponding with reasonable worst case) for capecitabine, cisplatin, cyclophosphamide, gemcitabine, methotrexate and ifosfamide. The highest measured ratio for methotrexate (0.88) is an exception in the range of values found. The assumption that there is potential for biodegradation may not be valid for all WWTPs, however, here we used the finding of high removal in the majority of cases to support the findings in laboratory studies showing high potential for removal. The modelled estimate for cytarabine is within the observed range. The carboplatin estimate is on the safe side (but only two measured ratios were available) as well as that for etoposide. The estimate for 5-fluorouracil is also on the safe

side but only one measured ratio was found for this substance. The experimental results on degradation of 5-fluorouracil in standardised degradation tests with activated sludge show strong differences: the substance was found to be not degraded at all or degraded very well. The reason is likely a concentration dependency of the biological degradation process, possibly linked to microbial inhibition at higher concentrations.

For the calculation of the predicted environmental concentration, the removal in WWTP is based on modelled data and not based on the measured removal rates. The amount of data found regarding measured concentrations is limited for most substances. Note that both influent and effluent should be monitored at the same location, at the time the influent batch reaches the effluent. There is a great variety in types of WWTPs and the activated sludges used in these WWTPs. Hence, the capability of removing certain substances varies between WWTPs. It should also be noted that there are very few studies that report a consistent monitoring program. This makes it difficult to derive a solid picture based on these limited, measured data.

5.4 Dilution in receiving water

Effluent rates of all (341) Dutch WWTPs were received from Statistics Netherlands (CBS). For method 1 the effluent rate for 2016 for the specific WWTP to which hospital 1, 3 and 4 were connected was used. The connection of these hospitals to the specific WWTP was confirmed by the local responsible district water board (Waterschap).

For method 1, a yearly mean flow rate for the specific (known) receiving waters of the three WWTPs connected to hospital 1, 3 and 4 was used to calculate dilution factors. The flow rates were calculated by Deltares using the Dutch nationwide Sobek model (LSM 1.2). This model is a 1D schematised hydrodynamic surface water model of the main waterways in the Netherlands. Flow rates computed for 1967, a year which had been selected in previous projects as average with respect to Dutch river water discharge [18] were used. For each WWTP discharge location a daily flow rate was modelled (for the entire year) from which the yearly arithmetic mean was calculated. From the WWTP effluent rate and yearly mean flow rate of the receiving water a dilution factor was calculated as

$$DILUTION = \frac{EFFLUENT_{\mathrm{WWTP}} + FLOW}{EFFLUENT_{\mathrm{WWTP}}}$$

In which DILUTION is the dilution factor, $EFFLUENT_{\mathrm{WWTP}}$ is the effluent discharge rate of the WWTP and FLOW the flow rate of the receiving water. Dilution factors for hospitals number 1, 3 and 4 are 1100, 6.4 and 1100.

For method 2, the total summed flow rate of all Dutch WWTPs was used and recalculated to a daily flow rate. This effluent flow is then discharged into surface water. Since this method does not make use of a specific WWTP, two generalised dilution factors were chosen: a factor of 10 and a factor of 1. The dilution factor of 10 is used in several

European regulatory risk assessment frameworks: REACH, Biocides (both ECHA) and human pharmaceuticals (EMA) as a realistic worst case estimate [12, 19]. It is however known that in periods of low discharge in smaller receiving waters, the majority, if not all, of the water flow may consist of effluent [20, 21]. As a very low dilution factor applies to these situations, a factor of 1 (no dilution) was selected as worst case.

5.5 Resulting PEC values

Table 9 shows the resulting PEC values for method 1 as well as method 2. Detailed calculations are provided in Annex 4. For method 1, calculations could only be performed for 3 out of 4 hospitals. Results are given for two situations: with and without metabolism of the parent compound. The resulting PEC values for surface water are considered local PECs, since they are calculated for the receiving water close to a specific WWTP. It is noted that based on the data currently available (see Sections 5.1-5.4), the PECs are not fully realistic values, but should be regarded as the best possible estimates.

The ranges for the outcomes of method 1 are large. There are several explanations for the differences in outcome among the hospitals: the use (amount given out) of the compound, the flow rate of the specific WWTP, but also the dilution rate in the receiving water, which is 1100, 6.4 and 1100, respectively.

The results of method 2, which gives extrapolated amounts at country level for the Netherlands, are also shown in Table 9. These PECs can be typified as an average concentration estimate at the regional scale and are presented for a receiving water with a dilution factor of 10 (default value) and no dilution (worst case situation).

With a dilution factor of 10, the results of method 2 are in the same order of magnitude as the highest, worst case values, calculated with method 1. When no dilution is assumed, which may be realistic in some cases [20, 21], the calculations of method 2 are higher than those of method 1. In order to perform a worst case estimation, the results of method 2 with no dilution are used for the risk assessment.

For 5-fluorouracil cream, only method 2 could be used as the cream is dispensed via public pharmacies. The result of method 2 with a dilution factor of 10 is 3.3 ng/L. This value is in good agreement with the value of 5.1 ng/L that is the outcome of the calculation method used in the regulatory risk assessment [12, 13]; see Section 8.3 for more information on this method.

Table 9. Local PEC (method 1; range for hospitals 1, 3 and 4) and regional PEC (method 2; based on extrapolated total amounts used in the Netherlands) for selected cytostatics. MET = metabolism. Detailed calculations and data for individual hospitals using method 1 are reported in Annex 4.

Substance	*Method 1*		*Method 2*			
			Dilution factor 10		*Dilution factor 1*	
	No MET	*Incl. MET*	*No MET*	*Incl. MET*	*No MET*	*Incl. MET*
	PEC [ng/L]	PEC [ng/L]	PEC [ng/L]	PEC [ng/L]	PEC [ng/L]	PEC [ng/L]
Capecitabine	0.51 – 94	0.015 – 2.8	48	1.4	477	14
Carboplatin	0.016 – 0.12	0.005 – 0.037	0.53	0.17	5.3	1.7
cisplatin	0.00091 – 0.0038	0.00021 – 0.00086	0.03	0.01	0.28	0.06
cyclophosphamide	0.11 – 13	0.027 – 3.2	2.8	0.69	28	6.9
cytarabine	0.045 – 0.48	0.0045 – 0.048	0.98	0.10	9.8	0.98
etoposide	0.011 – 0.36	0.0054 – 0.18	0.25	0.13	2.5	1.3
5-fluorouracil intravenous	0.040 – 0.35	0.0081 – 0.07	1.0	0.20	10	2.0
sum 5-fluorouracil intravenous	0.042 – 0.58	0.0093 – 0.31	1.1	0.32	11	3.2
5-fluorouracil dermal	-[a]	-[a]	3.3	-[b]	33	-[b]
gemcitabine	0.064 – 0.40	0.0064 – 0.04	1.9	0.19	19	1.9
hydroxycarbamide	1.0 – 133	0.49 – 67	56	28	562	281
ifosfamide	0.0029 – 10	0.0015 – 5.1	1.0	0.50	10.0	5.0
methotrexate	0.0031 – 0.042	0.0028 – 0.038	0.10	0.092	1.0	0.92

[a] method 1 not possible since the cream is only dispensed via public pharmacies.
[b] 100% emission to the environment is assumed (see Section 3.2).

6 Concentrations (PNECs)

6.1 Introduction

Although an environmental risk assessment has to be performed for all new medicinal products since 2006, only for methotrexate (limited) data on ecotoxicity is available in its registration dossier and no safe concentrations are available to determine the environmental risk of these substances.

A safe concentration is a concentration below which no unacceptable effects occur, based on the sensitivity of an ecosystem to prolonged exposure to a specific substance. Chronic exposure of a safe concentration may also cause effects that may not be very visible, but which are able to disturb ecosystem functioning. A risk to the environment is defined as an exceedance of the safe concentration. For a further explanation and an overview of different types of safe concentrations we refer to Chapter 3 in Moermond et al. [4].

The term 'Predicted No Effect Concentration (PNEC)' is used within the regulatory risk assessment of chemicals and also within the pharmaceutical framework. Its derivation is similar to the derivation of an Annual Average Environmental Quality Standard (AA-EQS), as used within the Water Framework Directive.

For the purpose of this report, only indicative PNECs are derived. To obtain a real PNEC (in Dutch: gedegen norm), all data should have been quality assessed. This was not possible within the current budget and not deemed necessary to obtain an indication of the environmental risk of cytostatics.

6.2 Method

6.2.1 Data search and evaluation

To derive safe aquatic concentrations, toxicity data for aquatic organisms are needed. A comprehensive literature search was performed where different approaches were combined. In all cases, focus was on the active pharmaceutical ingredient based on the assumption that the toxicity of metabolites is covered by that of the active ingredient, i.e. the total residue approach (see Section 6.2.3). Details on literature search and evaluation methods are reported in Annex 5.

The most critical studies (with the most sensitive results) were assessed for reliability and scored as 'reliable', ' reliable with restrictions', 'unreliable', or 'unassignable' (scores R1, R2, R3, R4, respectively; see [22] and [23]). Only studies with scores R1 or R2 were used.

(European) Public Assessment Reports, (E)PARs, are made available by EMA and CBG-MEB to disseminate endpoints regarding effectiveness and safety, assessed during application for marketing authorisation of medicinal products. EPARs were available for four of the eleven

cytostatics (Annex 5), but only the EPAR for the product containing methotrexate as API contained environmental effect data for algae and daphnids. The EPAR reported only acute toxicity because it is based on an earlier version of the current guideline (in place since 2006). The PARs found on the CBG-MEB site did not contain any environmental data. Overall, except for methotrexate, (E)PARs did not contribute to the collection of environmental effect data.

A complete overview of the gathered ecotoxicological data can be found in the attached excel files (see links 1 and 2). For each cytostatic, the most critical reliable endpoints are tabulated in the next sections.

6.2.2 *Derivation of indicative PNECs*

In line with the most commonly used methodology for the derivation of PNECs and EQSs [24], indicative PNECs were only derived if a base set of ecotoxicity data was available. This base set includes ecotoxicological data for at least three trophic levels, i.e. primary producers (algae or cyanobacteria), primary consumers (aquatic invertebrates, e.g. daphnids) and secondary consumers (fish). To extrapolate from data obtained from individual organisms to a concentration that protects the ecosystem and account for uncertainties, an assessment factor is applied to this value, the choice of which depends on the availability of ecotoxicity data, as described in the WFD guidance [24].

6.2.3 *Prodrugs and metabolites*

A number of the cytostatics assessed are prodrugs of the actual active compound (capecitabine, cisplatin, cytarabine, gemcitabine, ifosfamide and cyclophosphamide). To exert their cytostatic function the inactive prodrugs need to be transported into cells where they are transformed into active metabolites. The environmental risk assessment for the authorisation of pharmaceuticals [12], focusses on the active compound, in case of prodrugs the active metabolite is assessed. In the case of cytostatics, almost no information on ecotoxicity and environmental behaviour of on metabolites is available. However, the environmental relevance of these metabolites seems limited:

- Capecitabine: the assessment of capecitabine is covered by the assessment of its active metabolite 5-fluorouracil, which is also used as a cytostatic.
- Cisplatin, capecitabine and gemcitabine are transformed into active metabolites after passive diffusion into cells. The bioactivation processes will be similar in environmental testing organisms such as algae. Active metabolites are very reactive and probably are not persistent outside the cell environment. Thus, they are unlikely excreted into the environment.
- Ifosfamide and cyclophosphamide are oxidised by mammalian liver enzymes. These enzymes could be present in environmental organisms, but it is unknown to which extent. The active principle of these compounds is a triphosphate metabolite, which is very reactive and for that reason unlikely to be persistent. For cyclophosphamide, one study [25] reports a NOEC for a metabolite in algae that is lower than the NOEC for the parent compound. This result is unexpected as cyclophosphamide requires specific conditions for its activation and carboxy-cyclophosphamide is the waste product formed when those

conditions are not met. According to the BC cancer association database carboxy-cyclophosphamide is inactive in humans[11].

Thus, the PNECs are based on the parent compound (or prodrug) and not on the active metabolites. It can be assumed that excreted metabolites are less active and thus will be covered using a 'total residue approach', where it is assumed that no metabolism occurs and thus, 100% parent compound is excreted. This worst case assumption is also used in the environmental risk assessment for the marketing authorization of pharmaceuticals [12].

6.2.4 *Genotoxicity/ mutagenicity*

In the problem formulation phase, hospital representatives asked whether the known toxicity of cytostatics to humans implies that there is also a risk to the environment.

Considering the mode of action of cytostatics, genotoxicity and mutagenicity received special attention and corresponding data were taken into account where appropriate. The approach taken in this report to characterise environmental risks, follows closely the approach used in the Water Framework Directive. This methodology accounts for most of the known hazards of genotoxic substances.

The starting point for a risk assessment is the protection goal. In general, the goal of the environmental risk assessment is the protection of an ecosystem. In European environmental policy (e.g., the Water Framework Directive), the Environmental Quality Standards (EQS)s aim to protect ecosystems, with typically 95% of all species protected [24]. This protection goal was also defined in 1989 in Dutch environmental policy as the concentration which protects at least 95% of the species in an ecosystem, thereby protecting the functioning of the ecosystem [3]. In various European regulatory frameworks for chemical products, we find that species, populations, ecosystems and biodiversity (but not individual organisms) are the protection goals, see e.g. the EFSA Opinion on protection goals [26]. For medicinal products, neither Directive 2001/83/EC, as amended, nor the technical guideline specify the environmental protection goals [12]. However, the way the assessment is performed follows the general approach taken in other product authorisation and environmental protection frameworks.

To assess the environmental risks in agreement with the protection goals, in all frameworks the assessment of substances is based on effects on population relevant effects such as survival, growth and reproduction for a wide range of test species (producers, primary consumers, secondary consumers). As such, genotoxicity or mutagenicity are only taken into account when they affect reproduction within the time frame of testing. As already noted by Würgler and Kramers [51], the loss of individuals due to changes in somatic cells caused by genotoxicity is not considered critical for populations as long as there is a reproductive surplus. Reproduction can be affected by toxicity to the individuals exposed (juveniles and adults) resulting in lower reproduction rates. In theory it is also possible that (non-lethal) mutations in germ cells occur, without affecting the reproduction of this parent generation or survival of the first offspring. If these mutations

affect the survival or reproduction of later generations (provided they are non-reversible), the viability of the population is compromised. The rate at which this happens should be judged against the background of spontaneous mutations [51]. In exceptional cases (for small populations with a low reproduction rate), this could, over many generations, lead to (local) extinction[27].

As introduced earlier in this chapter, in this report indicative PNECS are derived from a base set of toxicity data, to assess the potential impact of (predicted) exposure concentrations. In all tests where genotoxic properties of the substance affect mortality, growth or reproduction, this will be accounted for in the endpoints. In theory it is possible that non-reversible mutations are induced, that could affect populations in the long run, but that went unnoticed in these tests. In that event, the PNECs may not protect for these adverse effects.

With respect to the selected cytostatics, information on genotoxicity has been generated by various in vitro assays commonly applied in human health risk assessment, e.g. the bacterial reverse mutation test with bacteria (i.e. Ames test), and mammalian cell gene mutation assays, chromosomal aberration and micronuclei tests. Often there are also higher tier in vivo genetic toxicology tests in rodents or mammalian organs/cells available. A few examples are discussed here. Gajski et al. [52] investigated the genotoxic potential of 5-fluorouracil, cisplatin, and etoposide towards zebrafish liver (ZFL) cell line, human hepatoma (HepG2) cells and human peripheral blood lymphocytes (HPBLs). They showed that all three cytostatics induced time and dose dependent decreases in cell viability, also for zebrafish liver cells. However, the exposure concentrations causing the effect (0.001 – 0.1 mg/L) cannot be compared to environmental exposure of the whole organism in surface water since the cells were exposed directly in culture medium. Parella et al. [53] assessed genotoxic potential of five cytostatics, including 5-fluorouracil, capecitabine, cisplatin and etoposide, using in vitro assays, but also by applying the in vivo comet assay on cells from of *Daphnia magna* and *Ceriodaphnia dubia*. It was shown that the comet assay was the most sensitive tool for genotoxicity assessment. The results of the comet assay could not be linked to results from chronic toxicity studies: the ratio between the chronic toxicity NOEC and the comet NOEC ranged from 9 to 1000 [53]. However, these tests may provide insight in the mechanisms underlying toxicity, and are used to develop novel ecotoxicity approaches, such as Adverse Outcome Pathway concept. For the current environmental risk assessment practice their usability and added value is limited.

For the purpose of this report, focusing on the environment (excluding human use functions such as drinking water, recreational water, or production of food), some uncertainty as to whether mutagenicity and/or genotoxicity may drive the environmental risk of the selected substances will remain. However, it is unknown how likely this scenario is (depending on the substance and the species tested and species present at the relevant location), and if it would occur at the relevant exposure concentrations at the location of interest – long enough for the impact to take place. How to effectively address the impact of

genotoxicity on populations has been assessed before, see e.g. Würgler and Kramers [28] and Roex et al. [29].

In conclusion, since the protection goal of environmental risk assessment concerns the population of a species and not individuals (in contrast to human risk assessment), the impact of genotoxicity and mutagenicity on population survival is only taken into account when it is shown to affect reproduction or other population-relevant endpoints. Tests on cell lines cannot be translated into environmental effects since exposure at cell level is different from that at whole organism level and effects in DNA damage are not related to chronic toxicity effects per se. For the purpose of this assessment, this uncertainty is found to be acceptable and is accounted for in the derivation of the PNEC, because a mandatory ecotoxicological base set of studies is used and assessment factors are applied, combined with the policy goal where 95% of the species are protected at the no-effect level.

6.3 Ecotoxicity data and indicative PNEC derivations per compound

In this section, the ecotoxicity data per compound are summarized. Detailed information can be found in(see link 1). These data form the basis for the derivation of indicative PNECs.
As explained above, the reported PNECs should be considered indicative and not equivalent to PNECs or AA-EQS limit values.

6.3.1 Capecitabine

Capecitabine is a prodrug of 5-fluorouracil. Normally, focus of the environmental risk assessment would be on the active substance. However, as data are present for the prodrug these have been included in the report. This also allows a comparison with 5-fluorouracil.

Reliable acute data were available for two trophic levels, and chronic data for three trophic levels (see table below). Neither the chronic nor the acute data sets contained ecotoxicity data for fish. Thus, as the base set of algae, crustaceans and fish was not available for the chronic nor the acute data sets, no indicative PNEC could be derived for capecitabine.

Table 10. Acute ecotoxicity data for capecitabine, aggregated to one value per species.

Taxon/species	L(E)C50 [mg/L]	Endpoint	Reference
Rotifera			
Brachionus calyciflorus	>500	mortality	[30]
Crustacea			
Ceriodaphnia dubia	1230	immobilization	[30]
Daphnia magna	224	immobilization	[30]
Thamnocephalus platyurus	197.7	mortality	[30]

Table 11. Chronic ecotoxicity data for capecitabine, aggregated to one value per species.

Taxon/species	NOEC/ EC10 [mg/L]	Endpoint	Reference
Rotifera			
Brachionus calyciflorus	3.3	population growth	[30]
Crustacea			
Ceriodaphnia dubia	0.5	reproduction	[30]
Daphnia magna	2.8	reproduction	[30]
Amphibia			
Xenopus laevis	2.0	embryonic malformations	[31]

6.3.2 *Carboplatin*

Hardly any ecotoxicity data were available for carboplatin. Harris et al., [32] examined as part of the PHARMAS project toxicity on zebrafish embryos for 72 h. The study was considered reliable with restrictions, but only LOEC values were reported instead of EC50 values. NOECs could not be derived as the test concentrations were not specified. Because of the lack of ecotoxicity data, no safe environmental concentration could be derived for carboplatin.

6.3.3 *Cisplatin*

For cisplatin, acute ecotoxicity data were available for six trophic levels, and chronic data for seven trophic levels (see Table 12 and Table 13). Chronic data were available for algae, aquatic invertebrates and fish. Therefore, an AF of 10 was applied to the lowest NOEC of 0.25 µg/L reported for *Daphnia magna*, resulting in an indicative PNEC of 0.025 µg/L.

It should be noted that there is uncertainty if cisplatin remains stable during ecotoxicity testing. Parrella et al. [30] measured cisplatin levels and reported that soon after dissolution, the absorbance pattern of the test solution changed and after 8 h a stable mixture was obtained. It was interpreted as hydrolysis of cisplatin and the reverse (anation) reaction where H_2O is replaced by Cl^-. There are also reports that cisplatin does remain stable in the test solution [33]. Other studies did not measure actual cisplatin concentrations, but daily renewed the test solution [32]. All these studies were considered for the derivation of the safe environmental concentration, since if complexes are formed in the test solutions, this will occur in the aquatic environment too.

Table 12. Acute ecotoxicity data for cisplatin, aggregated to one value per species.

Taxon/species	L(E)C50 [mg/L]	Endpoint	Reference
Bacteria			
Pseudomonas putida	1.20	growth	[34]
Cyanobacteria			
Synechococcus leopoliensis	0.67	growth rate	[33]
Algae			
Pseudokirchneriella subcapitata	1.52	growth rate	[33]
Rotifera			
Brachionus calyciflorus	6.52	mortality	[30]
Crustacea			
Ceriodaphnia dubia	2.5	immobilization	[30]
Daphnia magna	0.94	immobilization	[30]
Thamnocephalus platyurus	8.44	mortality	[30]
Pisces			
Danio rerio	81.3	mortality	[35]

Table 13. Chronic ecotoxicity data for cisplatin, aggregated to one value per species.

Taxon/species	NOEC/ EC10 [mg/L]	Endpoint	Reference
Bacteria			
Pseudomonas putida	0.030	growth	[34]
Cyanobacteria			
Synechococcus leopoliensis	0.05	growth rate	[33]
Algae			
Pseudokirchneriella subcapitata	0.610	growth rate	[33]
Rotifera			
Brachionus calyciflorus	0.108	population growth	[30]
Crustacea			
Ceriodaphnia dubia	0.00175	reproduction	[30]
Daphnia magna	0.00025	reproduction	[30]
Pisces			
Danio rerio	10	hatching rate	[36]
Amphibia			
Xenopus laevis	≥10	survival, growth, malformations	[31]

6.3.4 *Cyclophosphamide*

Acute data were available for seven trophic levels, and chronic data for six trophic levels (see Table 14 and Table 15). Chronic data were available for algae, aquatic invertebrates and fish. Therefore, an AF of 10 was applied to the lowest NOEC of 4.82 mg/L reported for *Brachionus calyciflorus*, resulting in an indicative PNEC of 0.482 mg/L = 482 µg/L. For the metabolite carboxy-cyclophosphamide a NOEC of 9.8 mg/L is reported for *Synechococcus leopoliensis* [25], which is lower than the NOEC for the parent compound for this species, but higher than the lowest NOEC for *Brachionus calyciflorus*.

Table 14. Acute ecotoxicity data for cyclophosphamide, aggregated to one value per species.

Taxon/species	L(E)C50 [mg/L]	Endpoint	Reference
Bacteria			
Pseudomonas putida	>1000	Growth	[34]
Vibrio fischeri	>100	bioluminescence	[37]
Cyanobacteria			
Synechococcus leopoliensis	>320	growth rate	[25]
Algae			
Pseudokirchneriella subcapitata	>100	growth rate	[37, 38]
Macrophyta			
Lemna minor	>100	growth rate (frond area)	[37]
Rotifera			
Brachionus calyciflorus	1924	Mortality	[39]
Crustacea			
Daphnia magna	>100	immobilization	[37]
Thamnocephalus platyurus	1396	mortality	[39]
Pisces			
Danio rerio	2193	mortality	[40]

Table 15. Chronic ecotoxicity data for cyclophosphamide, aggregated to one value per species.

Taxon/species	NOEC/ EC10 [mg/L]	Endpoint	Reference
Bacteria			
Pseudomonas putida	1000	growth	[34]
Cyanobacteria			
Synechococcus leopoliensis	≥320	growth rate	[25]
Algae			
Pseudokirchneriella subcapitata	≥100	growth rate	[38]
Rotifera			
Brachionus calyciflorus	4.82	reproduction	[39]
Crustacea			
Ceriodaphnia dubia	19.5	reproduction	[39]
Daphnia magna	56	reproduction	[38]
Pisces			
Danio rerio	637*	affected embryos (teratogenic & lethal effects)	[40]

* It should be noted that the EC10 of 637 mg/L for fish was derived in this report based values for affected embryos [40]. This includes teratogenic, but also lethal effects (67% lethality at highest dose). Considering the high test concentrations, a test that only assesses sublethal effects could yield a lower EC10. The derived EC10 is substantially higher than the NOEC of ≤261 mg/L.

6.3.5 Cytarabine

Hardly any ecotoxicity data were available for cytarabine. Zounková et al. [41] report an EC50 of 17 mg/L for the bacterium *Pseudomonas putida*, an EC50 of 200 mg/L for the aquatic invertebrate *Daphnia magna* and a NOEC of 10 mg/L for *Pseudomonas putida*. The base set

(algae, crustaceans, fish) is not complete, not for the acute data nor for the chronic data. Thus, it is not possible to derive a safe environmental concentration.

6.3.6 *Etoposide*

For etoposide it is reported that during four days static exposure the actual concentrations substantially dropped, yielding a geometric mean test concentration that was 19% lower than the nominal test concentration [33]. It was further reported that above 300 mg/L, crystallization occurs in the test medium [35]. Therefore, studies that did not daily renew the test solution or did not measure the actual test concentrations were not considered reliable. Consequently, these were not used for the derivation of the safe environmental concentrations.

A full set is available for acute and chronic ecotoxicity data representing primary producers, aquatic invertebrates and fish, therefore an AF of 10 is applied to the lowest NOEC of 8.3 µg/L, resulting in an indicative PNEC of 0.83 µg/L.

Table 16. Acute ecotoxicity data for etoposide, aggregated to one value per species.

Taxon/species	L(E)C50 [mg/L]	Endpoint	Reference
Bacteria			
Pseudomonas putida	630	growth	[34]
Algae			
Pseudokirchneriella subcapitata	30.43	growth rate	[33]
Rotifera			
Brachionus calyciflorus	>200	mortality	[30]
Crustacea			
Ceriodaphnia dubia	>120	immobilization	[30]
Daphnia magna	>120	immobilization	[30]
Thamnocephalus platyurus	43.3	mortality	[30]
Pisces			
Danio rerio	>300	mortality	[35]

Table 17. Chronic ecotoxicity data for etoposide, aggregated to one value per species.

Taxon/species	NOEC/ EC10 [mg/L]	Endpoint	Reference
Bacteria			
Pseudomonas putida	200	growth	[34]
Cyanobacteria			
Synechococcus leopoliensis	≥351	growth rate	[33]
Algae			
Pseudokirchneriella subcapitata	13.61	growth rate	[30]
Rotifera			
Brachionus calyciflorus	1	reproduction	[30]
Crustacea			
Ceriodaphnia dubia	0.096	reproduction	[30]
Daphnia magna	0.00834	reproduction	[30]
Pisces			
Danio rerio	200	mortality	[36]

6.3.7 *5-fluorouracil*

For 5-fluorouracil a substantial amount of ecotoxicity data was found. Acute data were available for eight trophic levels, and chronic data for seven trophic levels (see Table 18 and Table 19). The lowest NOEC was 0.55 µg/L and was reported for the aquatic invertebrate Ceriodaphnia dubia based on reproduction [30]. Applying an assessment factor of 10 results in an indicative PNEC of 0.055 µg/L.

There are no PNECs reported for 5-fluorouracil on the FASS.se website. Straub calculated a PNEC of 0.2 µg/L based on NOECs from long-term tests with fish [42], daphnia [43], green algae [34, 44], and cyanobacteria [45].

Table 18. Acute ecotoxicity data for 5-fluorouracil, aggregated to one value per species.

Taxon/species	L(E)C50 [mg/L]	Endpoint	Reference
Bacteria			
Pseudomonas putida	0.034[a]	growth	[34, 41]
Vibrio fischeri	0.14[b]	bioluminescence	[46, 47]
Cyanobacteria			
Anabaena flos-aquae	0.024	growth rate	[45]
Synechococcus leopoliensis	2.8[c]	growth rate	[33, 48]
Algae			
Pseudokirchneriella subcapitata	0.26[d]	growth rate	[32, 33, 48]
Macrophyta			
Lemna minor	2.45	growth rate (frond area)	[37]
Rotifera			
Brachionus calyciflorus	>200	mortality	[30]
Crustacea			
Ceriodaphnia dubia	501	mortality	[30]
Daphnia magna	22.4[e]	immobility	[34]
Thamnocephalus platyurus	0.28	mortality	[30]

Taxon/species	L(E)C50 [mg/L]	Endpoint	Reference
Pisces			
Danio rerio	2222	mortality	[49]
Pimephales promelas	2240	mortality	[50]
Amphibia			
Xenopus laevis	1063[f]	mortality	[51, 52]

[a] geometric mean of 0.027 and 0.044 mg/L.
[b] geometric mean of 0.122 and 0.16 mg/L.
[c] geometric mean of 1.2 and 3.006 mg/L.
[d] geometric mean of 0.13, 0.32 and 0.44mg/L.
[e] geometric mean of 15, 20.84 and 36 mg/L.
[f] geometric mean of 25 values in the range of 310 to 2130 mg/L.

Table 19. Chronic ecotoxicity data for 5-fluorouracil, aggregated to one value per species.

Taxon/species	NOEC/ EC10 [mg/L]	Endpoint	Reference
Bacteria			
Pseudomonas putida	0.0095[a]	growth	[34, 41]
Vibrio fischeri	0.0046[b]	bioluminescence	[46, 47]
Cyanobacteria			
Anabaena flos-aquae	0.002	growth rate	[45]
Synechococcus leopoliensis	0.20[c]	bioluminescence	[33, 48]
Algae			
Pseudokirchneriella subcapitata	0.029[d]	growth rate	[33, 48]
Rotifera			
Brachionus calyciflorus	0.129	population growth	[30]
Crustacea			
Ceriodaphnia dubia	0.00055	reproduction	[30]
Daphnia magna	0.0028	fecundity, mortality and length parental daphnids	[43]
Pisces			
Danio rerio	0.1	body length and dry body weight	[49]
Amphibia			
Xenopus laevis	5	embryonic malformations	[31]

[a] geometric mean of 0.03 and 0.003 mg/L.
[b] geometric mean of 0.0015 and 0.014 mg/L.
[c] geometric mean of 0.13 and 0.319 mg/L.
[d] geometric mean of 0.02 and 0.043 mg/L.

6.3.8 Gemcitabine

For gemcitabine it was not possible to derive a safe environmental concentration since the base set (algae, crustaceans, fish) was not complete. Reliable ecotoxicity data were reported by Zounková et al., [41], i.e. an EC50 of 100 mg/L for the bacterium *Pseudomonas putida*, an EC50 of 110 mg/L for the aquatic invertebrate *Daphnia magna* and a NOEC of 10 mg/L for *Pseudomonas putida*. For the daphnia reproduction study, an EC50 and LOEC of >1 mg/L were reported, but as no effects

were determined at the highest test concentration of 1.0 mg/L, the NOEC can be set at ≥1 mg/L.

6.3.9 *Hydroxycarbamide*

For hydroxycarbamide it was not possible to derive a safe environmental concentration since the base set (algae, crustaceans, fish) was not complete. Reliable information was only available for one zebrafish embryo chronic toxicity test reporting LOECs up to 72 hours for mortality. A 72 hour NOEC could be set at 3042 mg/L based on this study for *Danio rerio* [32].

6.3.10 *Ifosfamide*

For ifosfamide, acute data was available for seven trophic levels and chronic data for five trophic levels (see Table 20 and Table 1Table 21). As the acute and chronic sets represented primary producers, aquatic invertebrates and fish, an AF of 10 was applied to the lowest NOEC of 3.03 mg/L for *Ceriodaphnia dubia* [39], resulting in an indicative PNEC of 303 µg/L.

Table 20. Acute ecotoxicity data for ifosfamide, aggregated to one value per species.

Taxon/species	L(E)C50 [mg/L]	Endpoint	Reference
Bacteria			
Vibrio fischeri	>100	bioluminescence	[37]
Cyanobacteria			
Synechococcus leopoliensis	>320	growth rate	[25]
Algae			
Pseudokirchneriella subcapitata	>100	growth rate	[37]
Macrophyta			
Lemna minor	>100	growth rate (frond area)	[37]
Rotifera			
Brachionus calyciflorus	996.3	mortality	[39]
Crustacea			
Ceriodaphnia dubia	196.4	mortality	[39]
Daphnia magna	>100	immobilization	[37]
Thamnocephalus platyurus	771.5	mortality	[39]
Pisces			
Danio rerio	835	mortality	[40]

Table 21. Chronic ecotoxicity data for ifosfamide, aggregated to one value per species.

Taxon/species	NOEC/ EC10 [mg/L]	Endpoint	Reference
Cyanobacteria			
Synechococcus leopoliensis	≥320	growth rate	[25]
Algae			
Pseudokirchneriella subcapitata	≥320	growth rate	[25]
Rotifera			
Brachionus calyciflorus	5.75	population growth	[39]
Crustacea			
Ceriodaphnia dubia	3.03	reproduction	[39]
Pisces			
Danio rerio	204*	affected embryos (teratogenic & lethal effects)	[40]

* It should be noted that the EC10 of 204 mg/L for fish was derived in this report based on values for affected embryos [40]. This includes teratogenic, but also lethal effects (77% lethality at highest dose). Considering the high test concentrations, a test that only assesses sublethal effects could yield a lower EC10. The derived EC10 is substantially higher than the NOEC of 65 mg/L.

6.3.11 Methotrexate

Methotrexate was shown to rapidly degrade in a *Lemna minor* growth inhibition test [37]. This affected the toxicity exerted with a more frequent renewal of test solution leading to increased toxicity, i.e. the 7-day EC50 amounted to 0.16, 0.11 and 0.08 mg/L in a setup without solution exchange (=static conditions), with solution exchange at days 3 and 5, and with daily solution exchange, respectively. Therefore, studies that did not daily renew the test solution or did not measure the actual test concentrations were not considered reliable and were not used for the derivation of the safe environmental concentrations.

Acute data were available for six taxa, and chronic data for one taxon (see Table 22 and Table 23).The acute data set did not contain a LC50 value for fish. Gustafson et al. [53] reported LC25 values that ranged from >454 to >45 mg/L as well as from 148 to 182 mg/L. The LC50 values are expected to be lower, but it is unlikely that they will be below the 7-day EC50 of 0.08 mg/L reported for the common duckweed *L. minor.* Thus, the most sensitive species of the acute data set, is not present in the chronic data set, and instead of an AF of 100 an AF of 1000 is applied to the NOEC of 0.08 mg/L, resulting in an indicative PNEC of 80 ng/L.

Table 22. Acute ecotoxicity data for methotrexate, aggregated to one value per species.

Taxon/species	L(E)C50 [mg/L]	Endpoint	Reference
Bacteria			
Vibrio fischeri	>100	bioluminescence	[37]
Algae			
Pseudokirchneriella subcapitata	9.51	growth rate	[37]
Macrophyta			
Lemna minor	0.08	growth rate (frond area)	[37]
Crustacea			
Daphnia magna	>1000	immobility	[54]
Amphibia			
Xenopus laevis	107[a]	malformations	[51, 52]

[a] geometric mean of 90 and 127 mg/L.

Table 23. Chronic ecotoxicity data for methotrexate, aggregated to one value per species.

Taxon/species	NOEC/ EC10 [mg/L]	Endpoint	Reference
Pisces			
Danio rerio	3.1	embryonic malformations	[53]

[a] geometric mean of 45.4; 45.4; 4.54; 4.54; 0.454 and 0.0454 mg/L from ring test.

6.4 Overview of derived indicative PNECs

In Table 24, the indicative PNECs for the selected cytostatics are reported. For six compounds an indicative PNEC could be derived, for five compounds not enough ecotoxicity data were available.

The derived values for the PNECs show a large difference among the cytostatics, with a maximum factor of 20,000 difference in sensitivity. The most toxic compounds, cisplatin and methotrexate, are also amongst the more potent compounds for humans (Table 1); for 5-fluorouracil the relative potency to humans could not be established.

For five compounds no indicative PNEC could be derived due to a lack of data. Although an environmental risk assessment has to be performed for all new medicinal products since 2006, only for methotrexate (limited) data on ecotoxicity is available in its registration dossier. For other compounds, public literature is the only source for ecotoxicity data. For carboplatin no NOEC was available in literature at all, for capecitabine, cytarabine, gemcitabine and hydroxycarbamide the necessary base set of toxicity data was not complete but one or more NOECs were available. Thus, for these compounds no risk assessment can be performed due to a lack of data.

Table 24. Indicative PNECs for the selected cytostatics. n.d. = not enough data to derive a PNEC.

Substance	*Indicative PNEC* [ng/L]
Capecitabine	n.d.
Carboplatin	n.d.
Cisplatin	25
Cyclophosphamide	482000
Cytarabine	n.d.
Etoposide	830
5-fluorouracil	55
Gemcitabine	n.d.
Hydroxycarbamide	n.d.
Ifosfamide	303000
Methotrexate	80

7 Environmental risk evaluation of cytostatics

To evaluate risks of cytostatics to the environment, PECs are compared with indicative PNECs, resulting in a risk quotient. When the PEC is higher than the PNEC, i.e., the expected concentration exceeds the safe concentration, the risk quotient (RQ) is > 1.

Table 25 shows the worst case PEC values from Section 5.5, based on excretion of 100% unchanged parent compound and no dilution of WWTP effluent in the receiving water. When these worst case values, with all the uncertainties as discussed in Chapter 4, do not result in a risk to the aquatic ecosystem, the other PEC values can also be assumed to be safe. These PEC values are compared with PNECs as derived in Chapter 6, resulting in risk quotients (RQs). For capecitabine, cytarabine, gemcitabine and hydroxycarbamide no risk quotient can be calculated due to a lack of data.

As discussed in Section 6.1, the PNECs can only be seen as indicative values.

Table 25. Worst case PECs (Section 5.5), indicative PNECs (Section 6.3) and risk quotients for the selected cytostatics. n.d. = not enough data to derive a PNEC.

Substance	PEC [ng/L]	Indicative PNEC [ng/L]	*RQ*
Capecitabine	477	n.d.	
Carboplatin	5.3	n.d.	
Cisplatin	0.28	25	0.01
Cyclophosphamide	28	482000	<0.001
Cytarabine	9.8	n.d.	
Etoposide	2.5	830	0.003
5-fluorouracil (intravenous)	10	55	0.18
sum 5-fluorouracil (intravenous)[a]	11	55	0.20
5-fluorouracil (dermal)	33	55	0.60
Gemcitabine	19	n.d.	
Hydroxycarbamide	562	n.d.	
Ifosfamide	10.0	303000	<0.001
Methotrexate	1.0	80	0.01

[a] the sum of intravenous 5-fluorouracil is the sum of 5-fluorouracil excreted as metabolite of capecitabine and 5-fluorouracil administered as 5-fluorouracil.

The results from Table 25 show that for the six cytostatics for which an indicative PNEC could be derived, no risk is to be expected based on worst case PEC calculations. The compound with the highest risk was 5-fluorouracil. As capecitabine is transformed to 5-fluorouracil in the patient's body, the RQ of the sum of 5-fluorouracil as metabolite of capecitabine and 5-fluorouracil as active ingredient was also calculated. This RQ was 0.20. The RQ for 5-fluorouracil cream is higher: 0.60. To calculate this value, it was assumed that 100% of the cream ends up in waste water (via washing of hands after application, showering, or washing clothes). It is unknown to what extent this assumption is correct. The sum RQ for both application routes is 0.80, which is still

below 1. This means that also for 5-fluorouracil, no risk to the environment may be expected.

For five cytostatics, no indicative PNECs could be derived. For capecitabine, the lowest NOEC is a factor of 1000 above the PEC; for cytarabine the NOEC is a factor of 1 million above the PEC, for gemcitabine the NOEC is a factor of 50,000 above the PEC and for hydroxycarbamide the NOEC is a factor of 5 million above the PEC. Thus, for these compounds the risk assessment cannot be concluded due to a lack of data but no immediate concern is expected. For carboplatin, no NOEC was available at all.

It should be noted that potential risks of metabolites were not taken into account. For the worst case risk assessment described above, it was assumed that no metabolism has occurred and thus, 100% parent compound is excreted. This worst case assumption is also used in the environmental risk assessment for the marketing authorization of pharmaceuticals [12]. The underlying assumption is that when metabolites are formed, the total ecotoxicity is reduced. This approach does not automatically apply to so-called 'prodrugs'; inactive drugs that after administration require metabolism for their activation. Some cytostatics are prodrugs (e.g. cyclophosphamide, capecitabine). Their active metabolites' cytotoxic effects follow on their high chemical reactivity in the cell. However, the environmental relevance of these metabolites seems limited. For more explanation, see Section 6.2.3.

Since compounds in WWTP effluent always occur together with many other compounds, mixture toxicity effects could be possible. Information on mixture toxicity is somewhat inconsistent and shows that this may be compound- and species specific [25, 33]. Further assessment of mixture toxicity was outside the scope of this report.

For cyclophosphamide and ifosfamide, the 'RIWA-database Nieuwegein' obtained from VEWIN shows that these compounds are detected regularly in surface waters in the Netherlands (see Section 3.1.3). The maximum concentration for cyclophosphamide was 4 ng/L and for ifosfamide 3 ng/L. This is well below the indicative PNECs of 482,000 ng/L and 303,000 ng/L, respectively. Gemcitabine, methotrexate, etoposide and 5-fluorouracil were analysed less frequently but not detected. However, their LOQs were higher than those for cyclophosphamide and ifosfamide (10 ng/L, 50 ng/L, 100 ng/L and 1 µg/L, respectively. The LOQ of these compounds, except for 5-fluorouracil, is below the indicative PNECs derived in this report. Thus, when the compounds are not detected, there is no risk to the environment. Also, when monitoring data from other countries are compared to these values (see Section 3.1.3), no risk is identified. For 5-fluorouracil, the LOQ was 1 µg/L. The indicative PNEC of 55 ng/L is well below this value. This means that when 5-fluorouracil is not detected, the indicative PNEC could still be exceeded.

8 Other oncolytics and risks to the environment

8.1 Method

Classic cytostatic drugs are not tumour specific and frequently result in significant toxic effects to non-cancerous tissues. Currently there is a focus on research, development and use of more tumour cell-specific oncolytics such as immunotherapeutic and hormone therapy. These therapies are reported to cause less damage to healthy cells and to be more effective [55, 56].

An evaluation of the environmental risks was made for immunotherapy and hormone therapy. Two example compounds were further analysed on their usage, excretion, emission to the environment and environmental fate and risks.

Data on usage in the Netherlands was obtained from the GIP databank[5]. In contrast to cytostatics, data from the GIP databank regarding hormone treatment was assumed to be complete since these pharmaceuticals are mainly reimbursed through the general reimbursement system (see Section 2.1). The GIP databank was contacted to ascertain whether their records would cover most of the use. Information on human metabolism and excretion of the drugs was obtained from Farmacotherapeutisch Kompas[10] and BC Cancer Association[11].

The use data and metabolism data, together with information on WWTP removal, was used to derive a PEC concentration. WWTP data was obtained from publicly available peer-reviewed scientific literature. When no (sufficient) data was available, an estimation of removal in WWTPs was made with SimpleTreat. Parameters needed for SimpleTreat (see description in Annex 2) were obtained from literature, the fass.se website and the website of the producer (Astrazeneca.com). QSARs were used when parameters could not be obtained from literature.

Furthermore, information on ecotoxicological effects of the drugs was obtained from publicly available, peer reviewed scientific literature. Ecotoxicity data was used to derive indicative PNECs (see Section 6.1 for methodology).

8.2 Immunotherapy

Immunotherapy targets the patient's immune system. It stimulates or alters the immune system in order to attack cancer cells. Immunotherapy includes treatment with monoclonal antibodies, immune checkpoint inhibitors and cancer vaccines.

Immunotherapeutic drugs are readily metabolized in the patient and therefore unlikely to result in significant risk to the environment. The European Medicines Agency therefore exempts immunotherapeutic drugs from an ERA [12]. Therefore, no ecotoxicological risk assessment for immunotherapy was performed in this report.

8.3 Hormone therapy

Hormone therapy uses anti-hormones to slow down or stop the growth of hormone-sensitive tumours. Anti-hormones block the body's ability to produce hormones or by interfere with the effects of endogenous hormones on cancer cells. Tumours that are hormone insensitive do not have hormone receptors rendering anti-hormone treatment not useful.

Concerns were raised that anti-hormone therapy might pose a significant risk to the environment due to their potential of acting as an endocrine disrupting chemical [57, 58]. In this chapter the two anti-hormones Fulvestrant and Tamoxifen will be discussed as an example.

8.3.1 Fulvestrant

Fulvestrant is a drug used in the treatment of breast-cancer. It is an anti-estrogenic drug that binds to the estrogen-receptor (ER) and blocks the activating function, resulting in growth-inhibition of ER positive tumour cells. The use of fulvestrant in the Netherlands has been increasing in the past few years, as can be seen in Figure 5.

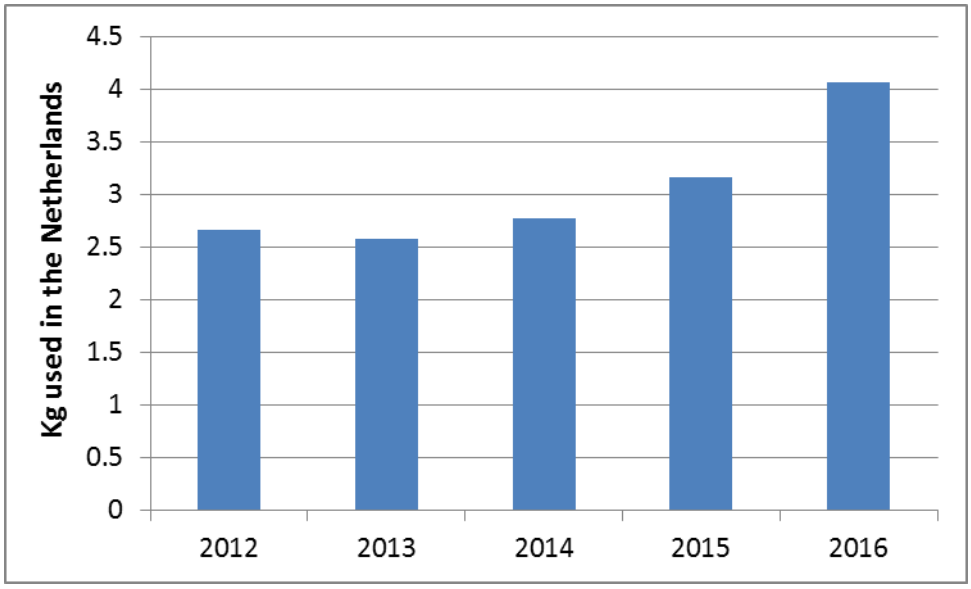


Figure 5. Use of fulvestrant in the Netherlands in the years 2012-2016 (source: GIP Databank5).

In Table 26 an overview of collected data for fulvestrant is shown. The drug is administered via intramuscular injection and is rapidly and extensively metabolized in the patient. Excretion is mainly via the faeces and approximately 8% of the administered dose is excreted as unchanged fulvestrant[59].

Fulvestrant has not been analysed for in Dutch surface waters (data on Waterkwaliteitsportaal[12]) nor in Dutch WWTP influents/effluents[13]. A literature search also did not return any monitoring data for fulvestrant.

Table 26. Data summary for the anti-hormones fulvestrant and tamoxifen.

	Fulvestrant	Tamoxifen
ATC-code	L02BA03	L02BA01
Amount of DDD in 2016[a]	490,510	8,962,800
$T_{½}$ elimination (d) [b]	50	7
Excretion as parent drug (%) from initial dose[b]	8	30
WWTP removal of parent drug (%) [c]	95	53
PEC (ng/L)	0.018	6.78
PNEC (ng/L)	0.57	67
Risk quotient	0.03	0.10

[a] From GIP databank[2].
[b] From Farmacotherapeutisch Kompas[10] and BC Cancer Association[11].
[c] Modelled using Simple Treat (see Annex 2).

Because for the anti-hormones, actual use of the compounds is recorded in the GIP databank, it was not necessary to use the same estimation methods for the Predicted Environmental Concentration (PEC) as for the cytostatics. Instead, the PEC was calculated using the method that is used for the marketing authorization of pharmaceuticals [12, 13]. With the amount of defined daily doses used in 2016 according to the GIP databank[5] (see Table 26), a defined daily dose of 8.3 mg/day as published by the WHO[14], 17.0 million inhabitants in the Netherlands (CBS), and a fraction removal in the WWTP of 0.95 as modelled with Simple Treat (See Annex 2), a PEC of 1.8×10^{-5} µg/L (0.018 ng/L) is calculated. For this calculation, the total residue approach is followed, i.e. no metabolism in the patient is assumed. Fulvestrant is metabolized into a number of metabolites, of which 17-ketofulvestrant is the only metabolite which is pharmacologically active. Around 8% of fulvestrant is excreted as parent compound, the amount of 17-ketofulvestrant excreted is not reported in any publicly available documentation. Furthermore, a number of metabolites may be hydrolysed back into the parent compound during WWTP passage. Hence, a total residue approach was followed as a worst case assumption, similar to the assumption made in AstraZeneca's dossier for marketing authorisation [59].

Both AstraZeneca and EMA have published an environmental risk assessment of fulvestrant [59]. Their PEC values are 0.5 and 0.46 ng/L respectively, based on the prevalence of the disease and not on actual use of the compound. These PECs are higher than the PEC calculated above based on use in the Netherlands. The AstraZeneca and EMA PECs are nearly equal; however, a lower WWTP removal rate used by AstraZeneca (50%, while EMA used 96%) is counteracted by a twice lower value for total consumption.

For fulvestrant, ecotoxicity data are reported in an Excel sheet(see link 2). Acute as well as chronic toxicity data are available for algae, crustaceans and fish. Thus, the PNEC can be derived by applying an assessment factor of 10 on the lowest toxicity value, which was a NOEC 0.0057 µg/L for the fish *Pimephales promelas*. This study was provided

[14] https://www.whocc.no/atc_ddd_index/

by AstraZeneca for their marketing authorisation [60]. The PNEC thus becomes 5.7 x 10^{-4} µg/L = 0.57 ng/L.

The PEC/PNEC ratio of fulvestrant is 0.03, indicating that the use of fulvestrant does not pose a risk to the environment.

8.3.2 *Tamoxifen*

Tamoxifen is a drug used to treat many types of cancer but is primarily indicated for the treatment of ER positive breast cancer. It is an anti-estrogenic drug that binds to the ER, inducing a conformational change in the receptor resulting in reduced tumour growth. Over the past few years, the number of users of tamoxifen in the Netherlands has been increasing (Figure 6), leading to an increased emission in the environment as well.

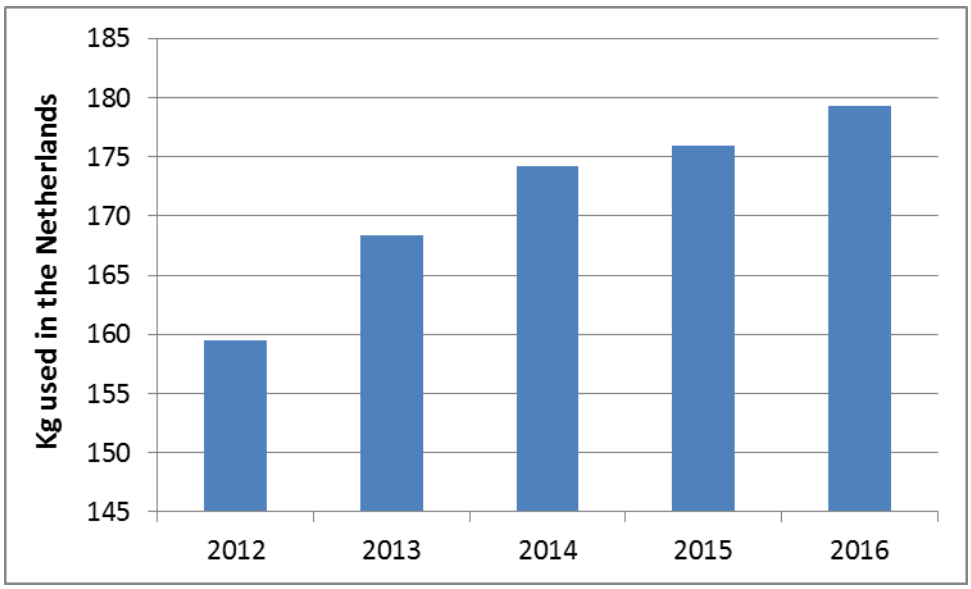


Figure 6. Number of users of tamoxifen in the Netherlands in the years 2012-2016 (source: GIP Databank5).

In Table 26 an overview of the collected data is given for tamoxifen. Tamoxifen is administered in tablet-from and is rapidly metabolized, giving rise to several metabolites which have a similar pharmacological profile as tamoxifen [60]. Excretion is mainly via the faeces and up to 30% of the administered dose can be excreted as the parent drug.

Tamoxifen was monitored in Dutch surface waters in 2014 (on one location) and 2016 (on twenty locations), but not detected (Waterkwaliteitsportaal[12]). The detection limit for those measurements were between 0.1 - 1 µg/L. The 'RIWA-database Nieuwegein', provided by VEWIN, contains measurements in 2016 and 2017 at three locations in larger rivers, but tamoxifen was not detected (LOQ 50 ng/L).

In 2010, effluent streams of eleven Dutch WWTPs were monitored, but no concentrations of tamoxifen could be detected. To date, no monitoring for tamoxifen in influent streams is performed (Watson-Database[13]). The highest reported concentration Tamoxifen in literature

is 4.2 x 10^{-2} µg/L, which was measured in influent streams of a WWTP in Spain [61].

Because the metabolites of tamoxifen have a similar pharmacological profile as their parent compound, a total residue-approach was used to obtain a PEC. As for fulvestrant, the PEC was calculated using the method that is also used for the marketing authorization of pharmaceuticals [12, 13]. With the amount of defined daily doses used in 2016 according to the GIP databank[5] (see Table 26), a defined daily dose of 20 mg/day as published by the WHO[14], 17.0 million inhabitants in the Netherlands (CBS), and a fraction removal in the WWTP of 0.53 as modelled with Simple Treat (See Annex 2), a PEC of 6.8 x 10^{-3} µg/L = 6.8 ng/L is calculated.

In the AstraZeneca dossier on the environmental risks of tamoxifen a PEC of 3.6 x 10^{-2} µg/L is reported [60]. The difference between the two PEC values can be explained by taking into account WWTP removal; in this report 53% removal of Tamoxifen was taken into account based on SimpleTreat calculations and AstraZeneca assumed a 0% removal rate as a worst case scenario [60].

For tamoxifen, ecotoxicity data are reported in an Excel sheet (see link 2). Acute as well as chronic data are available for a number of taxa, including algae, crustaceans and fish. Thus, the PNEC can be derived by applying an assessment factor of 10 on the lowest toxicity value, which was a NOEC of 0.67 µg/L for *Daphnia pulex*. This study was provided by AstraZeneca for their marketing authorisation [60]. The PNEC thus becomes 6.7 x 10^{-2} µg/L = 67 ng/L.

The PEC/PNEC ratio of tamoxifen is 0.10. This indicates that the use of tamoxifen does not pose a risk to the environment. Also, when compared to the highest measured value of 42 ng/L (in Spain, see above), no risk is identified.

9 Conclusions and recommendations

9.1 Use and emission of cytostatics

Purchasing records for four Dutch hospitals show a high level of consistency among the most dispensed cytostatics (in kg). This was supported by data from a fifth hospital that were received after the closing term. Expert judgement by the NVZA confirmed the ranking would also apply to the Netherlands as a whole. Therefore, it was considered valid to select the cytostatics for environmental risk assessment for the Dutch situation from the data received from the four hospitals. Trends in the use of cytostatics could not be identified with the obtained data.

Data on human metabolism show that the level of degradation is highly variable. For example, some cytostatics are extensively metabolised (97%), whereas others undergo little metabolism (10%) and are mainly excreted as their parent drug. Regarding removal in waste water treatment plants (WWTPs), results show that some cytostatics are almost completely removed while others are not removed at all. A number of metabolites may be hydrolysed back into the parent compound during WWTP passage.

9.2 Risks of cytostatics to the environment

Eleven cytostatics were selected for further environmental risk assessment. This selection was based on the amount of cytostatics dispensed, metabolic conversion, and the modelled data on removal in waste water plants.

For these eleven cytostatics, a predicted environmental concentration (PEC) was calculated using a number of methods. The worst case PECs (using worst case data on assumption on STP removal, assuming no metabolism and no dilution into surface water) were selected. To obtain a risk characterisation, these worst case PEC values were compared to indicative predicted no-effect concentrations (PNECs), which are based on ecotoxicity studies. This results in a risk quotient (PEC/PNEC), where a risk quotient above 1 means that the predicted environmental concentration exceeds the safe concentration. For six cytostatics an indicative PNEC could be derived and the PEC/PNEC ratio was well below 1. The cytostatic with the highest risk quotient was 5-fluorouracil, with a risk quotient of 0.2 for the intravenous fluid and 0.6 for the cream. Thus, it can be concluded that no risk is to be expected for the six cytostatics for which an indicative PNEC could be derived.

However, for five of the eleven cytostatics not enough data was available to finalize the risk assessment, despite the fact that since 2006 an environmental risk assessment should be submitted for marketing authorisation of new products. From these five, for capecitabine, cytarabine, gemcitabine and hydroxycarbamide, the lowest NOECs are more than a factor of 1000 above the PEC. Thus, for these compounds the risk assessment cannot be concluded due to a lack of data but no

immediate concern is expected. For carboplatin, no NOEC was available at all.

Limited monitoring data are available for cytostatics in the Netherlands. When cyclophosphamide or ifosfamide were detected, their concentrations were well below the indicative PNEC. For other cytostatics, the limit of quantification was above the indicative PNEC. Thus, when they are not detected, their concentrations do not exceed the indicative PNEC. Only for 5-fluorouracil, the limit of quantification is relatively high (1 µg/L). When this compound is not detected, the indicative PNEC of 55 ng/L may still be exceeded.

Since compounds in WWTP effluent always occur together with many other compounds, mixture toxicity effects could be possible. Information on mixture toxicity is somewhat inconsistent and shows that this may be compound- and species specific. Further assessment of mixture toxicity was outside the scope of this report.

Cytostatics are known to be toxic to humans, with greatest concern for their mutagenic/genotoxic potential. For the environment, the protection goal of environmental risk assessment concerns the population of a species and not individuals (in contrast to human risk assessment). Thus, the impact of genotoxicity and mutagenicity on population survival is only taken into account when it is shown to affect reproduction or other population-relevant endpoints. Tests on cell lines cannot be translated into environmental effects since exposure at cell level is different from that at whole organism level.

9.3 Risks of other oncolytics to the environment

Besides for cytostatics, environmental risks were assessed for two other oncolytics classes: immunotherapy and hormone therapy. The antibodies used in immunotherapy are completely metabolized in the patient and thus do not result in a risk to the environment.

For hormone therapy, literature suggests that the active substances used may pose a risk to the environment due to their endocrine disrupting potential. Thus, for two example compounds (fulvestrant and tamoxifen) a risk assessment was performed. This risk assessment shows that a risk to the aquatic environment may not be expected for these hormone therapies. However, it should be noted that mixture effects of a substances with a similar mode of action are not taken into account. For instance, the anti-estrogenic effects of fulvestrant and tamoxifen could be additive.

9.4 Recommendations

A lack of (ecotoxicity) data for a number of cytostatics hampered the risk assessment. Making ecotoxicity data from registration dossiers better available would be of help in future risk assessments. A system like the e-ERA system as proposed by pharmaceutical industry[15] could

[15] https://www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/pharmaceuticals-in-the-environment-pie/

help in providing harmonized data, also for compounds for which currently no information is available.

Within the national chain approach 'Medicijnresten *uit* water' (https://jamdots.nl/view/239/medicijnresten-uit-water), measures are identified and taken to reduce the effects of pharmaceutical residues in the aquatic environment. Possible measures can be taken along the medicinal product chain, from development, prescription and use, to the waste stage. Water managers are currently working on pilot projects to improve the functionality of waste water treatment plants.

The currently identified risk quotients for cytostatics warrant no additional measures. As for all pharmaceutical residues, leftover or unused medication should not be disposed of through the sink or toilet.

Because the intradermal use of 5-fluorouracil is strongly increasing, more attention could be paid to the actual amount of this substance entering the environment. It is recommended to determine the fraction washed off under the shower or by rinsing hands after application, and the fraction washed out of clothes. This information could be used to refine the risk assessment. Besides this, the analytical methods to determine this substance in surface water could be improved. Currently, the limit of detection and limit of quantification are well above the PNEC of 55 ng/L. It is recommended to use analytical techniques that can detect 5-fluorouracil at the PNEC level.

For many cytostatics, no monitoring data were available. To assess whether the modelled predicted concentration reflects actual concentrations, it is recommended to include the compounds with the highest risk ratios (5-fluorouracil, etoposide and tamoxifen) in monitoring programs for surface water, as well as the compounds with the highest predicted environmental concentration (capecitabine and hydroxycarbamide). Monitoring of influent/effluent ratios in the WWTP could provide information on removal rates, but also on the possible hydrolysis of metabolites, which would liberate the parent compound again.

10 References

1. Roex E. 2015. Monitoring van geneesmiddelen in afvalwater met behulp van passive sampling. Deltares. Utrecht, The Netherlands: Deltares. Report nr. 1220617-000. 26 p.
2. Roex E, Cinjee A, Beeltje H. 2016. Geneesmiddelen in het afvalwater van UMC Utrecht en rwzi Utrecht, gemeten met passive sampling. Deltares. Utrecht, The Netherlands: Deltares. Report nr. 1221520-000. 24 p.
3. Anonymous. 1989. Nationaal Milieubeleidsplan (NMP). Notitie "Omgaan met risico's". Vergaderjaar 1988-1989, 21 137, nr 5. . Tweede Kamer der Staten-Generaal. Den Haag, the Netherlands:
4. Moermond CTA, Smit CE, van Leerdam RC, Van der Aa NGFM, Montforts MHMM. 2016. Geneesmiddelen en waterkwaliteit. RIVM. Bilthoven, the Netherlands: Report nr. 2016-0111.
5. van Heijnsbergen E. 2008. Cytostatica in het aquatisch milieu. Utrecht University. Utrecht, the Netherlands.
6. Vidaurre R. 2014. Pharmas. European policy brief. Webpage: http://www.pharmas-eu.net/images/stories/download/PHARMAS_policy_brief_May2014.pdf. Accessed 23/03/2018.
7. Knasmüller S, Mišík M, Filipič M. 2014. Fate and effects of cytostatic pharmaceuticals in the environment and the identification of biomarkers for an improved risk assessment on environmental exposure. CytoThreat Deliverable Report. European Commission. Brussels, Belgium: Report nr. Workpackage 8, D.8.5. PEC/PNEC values for selected cytostatics and determination safe levels in the environment. 15 p. http://www.cytothreat.eu/index.php/project-deliverables.
8. Reece PA, Stafford I, Davy M, Freeman S. 1987. Disposition of unchanged cisplatin in patients with ovarian cancer. Clin Pharmacol Ther 42 (3): 320-325.
9. Hilger RA, Harstrick A, Eberhardt W, Oberhoff C, Skorzec M, Baumgart J, Seeber S, Scheulen ME. 1998. Clinical pharmacokinetics of intravenous treosulfan in patients with advanced solid tumors. Cancer Chemother Pharmacol 42 (2): 99-104.
10. Booker V, Halsall C, Llewellyn N, Johnson A, Williams R. 2014. Prioritising anticancer drugs for environmental monitoring and risk assessment purposes. Science of The Total Environment 473-474: 159-170. doi https://doi.org/10.1016/j.scitotenv.2013.11.145. http://www.sciencedirect.com/science/article/pii/S0048969713014496.
11. Anonymous. 2013. Lijst van Nederlandse ziekenhuizen. Webpage: https://nl.wikipedia.org/wiki/Lijst_van_Nederlandse_ziekenhuizen. Accessed 2018-03-02.
12. EMA. 2006. Guideline on the environmental risk assessment of medicinal products for human use. European Medicines Agency. London, United Kingdom: Report nr. EMEA/CHMP/SWP/4447/00 corr 2. 12 p.

13. EMA. 2016. Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'. European Medicines Agency,. London, United Kingdom: Report nr. EMEA/CHMP/SWP/44609/2010 Rev. 1. 12 p.
14. Straub JO. 2010. Combined environmental risk assessment for 5-fluorouracil and capecitabine in Europe. Integrated Environmental Assessment and Management 6 (SUPPL. 1): 540-566. doi 10.1897/IEAM-2009-073.1. https://www.scopus.com/inward/record.uri?eid=2-s2.0-77956368457&doi=10.1897%2fIEAM-2009-073.1&partnerID=40&md5=7e8fa3a9a16d762eb2d2e2d6b57612ff.
15. Judson IR, Beale PJ, Trigo JM, Aherne W, Crompton T, Jones D, Bush E, Reigner R. 1999. A human capecitabine excretion balance and pharmacokinetic study after administration of a single oral dose of ^{14}C-labelled drug. Investig New Drugs 17: 49-56.
16. RIVM. 2017. SimpleTreat 4.0 (computer program). Version 4.0.9. Bilthoven, the Netherlands: National Institute for Public Health and the Environment. https://www.rivm.nl/en/Topics/S/Soil_and_water/SimpleTreat.
17. Struijs J. 2014. SimpleTreat 4.0: a model to predict fate and emission of chemicals in wastewater treatment plants. Background report describing the equations. National Institute for Public Health and the Environment. Bilthoven, The Netherlands: Report nr. 601353005/2014. 65 p.
18. Wuijts S, Bak-Eijsberg CI, Van Velzen EH, Van der Aa NGFM. 2012. Effecten klimaatontwikkeling op de waterkwaliteit bij innamepunten voor drinkwater Analyse van stofberekeningen. National Institute for Public Health and the Environment. Bilthoven, The Netherlands: Report nr. 609716004/2012. 51 p.
19. ECHA. 2017. Guidance on Biocidal Products Regulation. Volume IV Environment - Assessment and Evaluation (Parts B + C). Version 2.0. European Chemicals Agency. Helsinki, Finland: Report nr. ECHA-17-G-231-EN. 416 p. https://www.echa.europa.eu/documents/10162/23036412/bpr_guidance_ra_vol_iv_part_b-c_en.pdf/e2622aea-0b93-493f-85a3-f9cb42be16ae.
20. De Greef J, De Nijs T. 1990. Risk Assessment of New Chemical Substances. Dilution of Effluents in The NetherlandsRisk Assessment of New Chemical Substances. National Institute of Public Health and Environmental Protection. Bilthoven, The Netherlands: Report nr. 670208001. 42 p.
21. Link M, von der Ohe PC, Voß K, Schäfer RB. 2017. Comparison of dilution factors for German wastewater treatment plant effluents in receiving streams to the fixed dilution factor from chemical risk assessment. Science of The Total Environment 598: 805-813. doi https://doi.org/10.1016/j.scitotenv.2017.04.180. http://www.sciencedirect.com/science/article/pii/S0048969717310240.

22. Klimisch HJ, Andreae M, Tillmann U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regulatory Toxicology and Pharmacology 25 (1): 1-5. doi 10.1006/rtph.1996.1076. https://www.scopus.com/inward/record.uri?eid=2-s2.0-0031080387&doi=10.1006%2frtph.1996.1076&partnerID=40&md5=0f5625e23c5226bab3107beb6882a424.
23. Moermond CTA, Kase R, Korkaric M, Ågerstrand M. 2016. CRED: Criteria for reporting and evaluating ecotoxicity data. Environmental Toxicology and Chemistry 35 (5): 1297-1309. doi 10.1002/etc.3259. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84977904183&doi=10.1002%2fetc.3259&partnerID=40&md5=92c1b6c23edb02933706d8fdfaf59a1d.
24. European Commission. 2011. Common Implementation Strategy for the Water Framework Directive (2000/60/EC). Technical Guidance For Deriving Environmental Quality Standards. European Commisson. Brussels, Belgium: Report nr. Guidance Document No. 27. Technical Report - 2011 – 055. 203 p.
25. Česen M, Eleršek T, Novak M, Žegura B, Kosjek T, Filipič M, Heath E. 2016. Ecotoxicity and genotoxicity of cyclophospamide, ifosfamide, their metabolites/transformation products and their mixtures. Environmental Pollution 210: 192-201. doi 10.1016/j.envpol.2015.12.017. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84961135879&doi=10.1016%2fj.envpol.2015.12.017&partnerID=40&md5=f54b3adf84c7bbda7bae4abeef266dbe.
26. EFSA. 2016. Guidance to develop specific protection goals options for environmental risk assessment at EFSA, in relation to biodiversity and ecosystem services. . EFSA Journal 14 (6): 4499.
27. Lande R. 1998. Risk of population extinction from fixation of deleterious and reverse mutations. Genetica 102 (0): 21-27.
28. Wurgler FE, Kramers PGN. 1992. Environmental effects of genotoxins (eco-genotoxicology). Mutagenesis 7 (5): 321-327. doi 10.1093/mutage/7.5.321. https://www.scopus.com/inward/record.uri?eid=2-s2.0-0026657955&doi=10.1093%2fmutage%2f7.5.321&partnerID=40&md5=333da30766dcbcd7cd7dba64727c64e0.
29. Roex EWM, Traas TP, Slooff W. 2001. Ecotoxicological hazard assessment of genotoxic substances. Bilthoven, The Netherlands: RIVM.
30. Parrella A, Lavorgna M, Criscuolo E, Russo C, Fiumano V, Isidori M. 2014. Acute and chronic toxicity of six anticancer drugs on rotifers and crustaceans. Chemosphere 115 (1): 59-66. doi 10.1016/j.chemosphere.2014.01.013. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84921627666&doi=10.1016%2fj.chemosphere.2014.01.013&partnerID=40&md5=f56788b746538144c00adf7444fe190c.

31. Isidori M, Piscitelli C, Russo C, Smutná M, Bláha L. 2016. Teratogenic effects of five anticancer drugs on Xenopus laevis embryos. Ecotoxicology and Environmental Safety 133: 90-96. doi 10.1016/j.ecoenv.2016.06.044. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84978296352&doi=10.1016%2fj.ecoenv.2016.06.044&partnerID=40&md5=2552550817698439c0799afe125ef4ba.
32. Harris C, Legradi J, Harris G, Legler J, Sumpter J. 2014. PHARMAS Deliverable Report 2.2: Data on genotoxic effects of anticancer drugs on fish, invertebrates and algae. Brunel University. Uxbridge, UK:
33. Brezovšek P, Eleršek T, Filipič M. 2014. Toxicities of four anti-neoplastic drugs and their binary mixtures tested on the green alga Pseudokirchneriella subcapitata and the cyanobacterium Synechococcus leopoliensis. Water Research 52: 168-177. doi 10.1016/j.watres.2014.01.007. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84892838737&doi=10.1016%2fj.watres.2014.01.007&partnerID=40&md5=6ece0a328948e3187ea0dde55d0664ab.
34. Zounková R, Odráška P, Doležalová L, Hilscherová K, Maršálek B, Bláha L. 2007. Ecotoxicity and genotoxicity assessment of cytostatic pharmaceuticals. Environmental Toxicology and Chemistry 26 (10): 2208-2214. doi 10.1897/07-137R.1. https://www.scopus.com/inward/record.uri?eid=2-s2.0-35348926800&doi=10.1897%2f07-137R.1&partnerID=40&md5=6f64142125b9417fac2cb491eee7be20.
35. Kovács R, Bakos K, Urbányi B, Kövesi J, Gazsi G, Csepeli A, Appl ÁJ, Bencsik D, Csenki Z, Horváth Á. 2016. Acute and sub-chronic toxicity of four cytostatic drugs in zebrafish. Environmental Science and Pollution Research 23 (15): 14718-14729. doi 10.1007/s11356-015-5036-z. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84937698611&doi=10.1007%2fs11356-015-5036-z&partnerID=40&md5=4f8aa5c45e12dfdcd828669601df6c09.
36. Horváth A, Csenki Z, Kovács R, Bakos K, Kovács B. 2012. CytoThreat Deliverable Report 5.1 Experimental report on acute toxicity of cytostatics in adult zebrafish and in embryos (FET test). Szent istván university. Gödöllő, Hungary
37. Białk-Bielińska A, Mulkiewicz E, Stokowski M, Stolte S, Stepnowski P. 2017. Acute aquatic toxicity assessment of six anti-cancer drugs and one metabolite using biotest battery – Biological effects and stability under test conditions. Chemosphere 189: 689-698. doi 10.1016/j.chemosphere.2017.08.174. https://www.scopus.com/inward/record.uri?eid=2-s2.0-85030150683&doi=10.1016%2fj.chemosphere.2017.08.174&partnerID=40&md5=a5b626214da7ba469d5bd839ad01ffe9.

38. Grung M, Källqvist T, Sakshaug S, Skurtveit S, Thomas KV. 2008. Environmental assessment of Norwegian priority pharmaceuticals based on the EMEA guideline. Ecotoxicology and Environmental Safety 71 (2): 328-340. doi 10.1016/j.ecoenv.2007.10.015. https://www.scopus.com/inward/record.uri?eid=2-s2.0-51249095222&doi=10.1016%2fj.ecoenv.2007.10.015&partnerID=40&md5=9ea9e8f6eaebcbb9c693b953f2188d2c.
39. Russo C, Lavorgna M, Česen M, Kosjek T, Heath E, Isidori M. 2018. Evaluation of acute and chronic ecotoxicity of cyclophosphamide, ifosfamide, their metabolites/transformation products and UV treated samples. Environmental Pollution 233: 356-363. doi 10.1016/j.envpol.2017.10.066. https://www.scopus.com/inward/record.uri?eid=2-s2.0-85032262519&doi=10.1016%2fj.envpol.2017.10.066&partnerID=40&md5=f758764715312c1e6005f8ab2b4c5cb5.
40. Weigt S, Huebler N, Strecker R, Braunbeck T, Broschard TH. 2011. Zebrafish (Danio rerio) embryos as a model for testing proteratogens. Toxicology 281 (1-3): 25-36. doi 10.1016/j.tox.2011.01.004. https://www.scopus.com/inward/record.uri?eid=2-s2.0-79851510179&doi=10.1016%2fj.tox.2011.01.004&partnerID=40&md5=aac4b4be75f54e84016d59bf325de945.
41. Zounková R, Kovalova L, Blaha L, Dott W. 2010. Ecotoxicity and genotoxicity assessment of cytotoxic antineoplastic drugs and their metabolites. Chemosphere 81 (2): 253-260. doi 10.1016/j.chemosphere.2010.06.029. https://www.scopus.com/inward/record.uri?eid=2-s2.0-77956191509&doi=10.1016%2fj.chemosphere.2010.06.029&partnerID=40&md5=949e5b7394ced6cc9f8a6e2a5a3653b4.
42. Egeler P, Seck C. 2008. 5-Fluorouracil: A study on the toxicity to early-life stages of Danio rerio (zebrafish). ECT Oekotoxicologie. Flörsheim/Main (DE) and Battelle UK, Ongar (UK) Report nr. ECT 08AZ1FV.
43. Jergentz S, Goth M, Seck C. 2009. Fluorouracil: A study on the chronic toxicity to Daphnia magna according to the OECD Guideline 211. ECT Oekotoxicologie. Flörsheim/Main (DE) and Battelle UK, Ongar (UK) Report nr. 08AZ1DB.
44. Cleuvers M. 2002. Aquatische Okotoxikologie ausgew ihlter Arzneimittel; Algentest und akuter Daphnientest. UWSF- Z Umweltchem Okotox 14 (2): 85-89. doi dx.doi.org110.1065/uwsf2002.04.025.
45. Junker T, Seck C. 2009. 5-Fluorouracil: A study on the toxicity to blue-green algae (Anabaena flos-aquae). ECT Oekotoxikologie. Flörsheim/Main (DE) and Battelle UK, Ongar (UK). Report nr. ECT report 08AZ1AB.
46. Backhaus T, Grimme LH. 1999. The toxicity of antibiotic agents to the luminescent bacterium Vibrio fischeri. Chemosphere 38 (14): 3291-3301. doi 10.1016/S0045-6535(98)00560-8. https://www.scopus.com/inward/record.uri?eid=2-s2.0-0033151442&doi=10.1016%2fS0045-6535%2898%2900560-8&partnerID=40&md5=7ee9e7897c820b00d06f87197678b98b.

47. Załeska-Radziwiłł M, Affek K, Rybak J. 2014. Ecotoxicity of chosen pharmaceuticals in relation to micro-organisms-risk assessment. Desalination and Water Treatment 52 (19-21): 3908-3917. doi 10.1080/19443994.2014.887503. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84902807050&doi=10.1080%2f19443994.2014.887503&partnerID=40&md5=1497261a696ddc553e09e76d5824f76f.
48. Elersek T, Stanič K, Bricelj M, Filipič M, Bergoč P. 2012. CytoThreat Deliverable Report 4.1: Toxicity of cytostatics to algae. SME: Institute of Environmental Egineering. Maribor, Slovenia
49. Horváth A, Csenki Z, Kovács R, Bakos K, Kovács B, Garaj-Vrhovac V, Gajski G, Gerić M, Baebler S, Rotter A, Demšar T, Filipič M, Novak M. 2014. CytoThreat Deliverable Report 5.4. LC50 and NOEC values for vertebrates for the selected cytostatics. Szent istván university. Gödöllő, Hungary
50. DeYoung DJ, Bantle JA, Hull MA, Burks SL. 1996. Differences in sensitivity to developmental toxicants as seen in Xenopus and Pimephales embryos. Bulletin of Environmental Contamination and Toxicology 56 (1): 143-150. doi 10.1007/s001289900021. https://www.scopus.com/inward/record.uri?eid=2-s2.0-0029656113&doi=10.1007%2fs001289900021&partnerID=40&md5=16c0622fbb9e72b5e899b3c32b4c69d5.
51. Dawson DA, Bantle JA. 1987. Development of a reconstituted water medium and preliminary validation of the Frog Embryo Teratogenesis Assay—Xenopus (FETAX). Journal of Applied Toxicology 7 (4): 237-244. doi 10.1002/jat.2550070403. https://www.scopus.com/inward/record.uri?eid=2-s2.0-0023277877&doi=10.1002%2fjat.2550070403&partnerID=40&md5=82604ab7d7f752720a37582c1b9d50e3.
52. Bantle JA, Burton DT, Dawson DA, Dumont JN, Finch RA, Fort DJ, Linder G, Rayburn JR, Buchwalter D, Gaudet-Hull AM, Maurice MA, Turley SD. 1994. Fetax interlaboratory validation study: Phase II testing. Environmental Toxicology and Chemistry 13 (10): 1629-1637. doi 10.1002/etc.5620131012. https://www.scopus.com/inward/record.uri?eid=2-s2.0-0028094973&doi=10.1002%2fetc.5620131012&partnerID=40&md5=60a1889e1ecf3c4336eb2323679f752a.
53. Gustafson AL, Stedman DB, Ball J, Hillegass JM, Flood A, Zhang CX, Panzica-Kelly J, Cao J, Coburn A, Enright BP, Tornesi MB, Hetheridge M, Augustine-Rauch KA. 2012. Inter-laboratory assessment of a harmonized zebrafish developmental toxicology assay - Progress report on phase I. Reproductive Toxicology 33 (2): 155-164. doi 10.1016/j.reprotox.2011.12.004. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84862803324&doi=10.1016%2fj.reprotox.2011.12.004&partnerID=40&md5=6eb0a28246e73710bfeaf22261b191a1.
54. EMA. 2017. Assessment report Jylamvo - Procedure No. EMEA/H/C/003756/0000. Report nr. EMA/78284/2017.

55. Jakesz R, Hausmaninger H, Kubista E, Gnant M, Menzel C, Bauernhofer T, Seifert M, Haider K, Mlineritsch B, Steindorfer P. 2002. Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer—Austrian Breast and Colorectal Cancer Study Group Trial 5. Journal of Clinical Oncology 20 (24): 4621-4627.
56. Morrissey KM, Yuraszeck T, Li CC, Zhang Y, Kasichayanula S. 2016. Immunotherapy and novel combinations in oncology: current landscape, challenges, and opportunities. Clinical and translational science 9 (2): 89-104.
57. Besse JP, Latour JF, Garric J. 2012. Anticancer drugs in surface waters. What can we say about the occurrence and environmental significance of cytotoxic, cytostatic and endocrine therapy drugs? Environment International 39 (1): 73-86. doi 10.1016/j.envint.2011.10.002. https://www.scopus.com/inward/record.uri?eid=2-s2.0-80355131689&doi=10.1016%2fj.envint.2011.10.002&partnerID=40&md5=77718868c3abd687a4277ed2d45f905b.
58. Hoffmann F, Kloas W. 2012. The antiestrogens tamoxifen and fulvestrant abolish estrogenic impacts of 17α-ethinylestradiol on male calling behavior of Xenopus laevis. PloS one 7 (9): e44715.
59. AstraZeneca. Environmental Risk Assessment Data Fulvestrant.
60. AstraZeneca. Environmental Risk Assessment Data Tamoxifen.
61. Ferrando-Climent L, Rodriguez-Mozaz S, Barceló D. 2014. Incidence of anticancer drugs in an aquatic urban system: from hospital effluents through urban wastewater to natural environment. Environmental Pollution 193: 216-223.
62. US EPA. 2012. EPI Suite™ (computer program). Version 4.11. Washington, DC, U.S.A.: U.S. Environmental Protection Agency (EPA) Office of Pollution Prevention Toxics and Syracuse Research Company (SRC).
63. ChemAxon Ltd. 2016. MarvinSketch (computer program). Version 16.10.24.0. Budapest, Hungary: ChemAxon. http://www.chemaxon.com/.
64. BioByte. 2006. BioLoom for Windows (computer program). Version 1.5. Claremont, CA, USA: BioByte Corporation.
65. Elsevier B.V. 2018. Scopus ®. Document search. Webpage: https://www.scopus.com/.
66. Roche. 2015. Safety Data Sheet for Capecitabine. Webpage: https://www.roche.com/sustainability/what_we_do/for_communities_and_environment/environment/safety_data_sheets-row.htm. Accessed 11 January 2018.
67. Franquet-Griell H, Gómez-Canela C, Ventura F, Lacorte S. 2017. Anticancer drugs: Consumption trends in Spain, prediction of environmental concentrations and potential risks. Environmental Pollution 229: 505-515. doi 10.1016/j.envpol.2017.06.011. https://www.scopus.com/inward/record.uri?eid=2-s2.0-85020787193&doi=10.1016%2fj.envpol.2017.06.011&partnerID=40&md5=190b445963e1b5ee4ed27540622ac9a2.

68. EMA. 2013. Capecitabine SUN. Assessment report for initial marketing authorisation application. Procedure No. EMEA/H/C/002050/0000. EMA. London, United Kingdom: Report nr. EMA/370014/2013. 22 p. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002050/WC500145306.pdf.
69. Kosjek T, Perko S, Žigon D, Heath E. 2013. Fluorouracil in the environment: Analysis, occurrence, degradation and transformation. Journal of Chromatography A 1290: 62-72. doi 10.1016/j.chroma.2013.03.046. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84876708401&doi=10.1016%2fj.chroma.2013.03.046&partnerID=40&md5=249e6433e18b6ac98123df50b41b36af.
70. Franquet-Griell H, Medina A, Sans C, Lacorte S. 2017. Biological and photochemical degradation of cytostatic drugs under laboratory conditions. Journal of Hazardous Materials 323: 319-328. doi 10.1016/j.jhazmat.2016.06.057. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84999035128&doi=10.1016%2fj.jhazmat.2016.06.057&partnerID=40&md5=52f48172413b6fec8cad285e779a7ada.
71. Negreira N, López de Alda M, Barceló D. 2014. Study of the stability of 26 cytostatic drugs and metabolites in wastewater under different conditions. Science of the Total Environment 482-483 (1): 389-398. doi 10.1016/j.scitotenv.2014.02.131. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84896449399&doi=10.1016%2fj.scitotenv.2014.02.131&partnerID=40&md5=251dc5c69f0b0fb0d6258c9e587d94b7.
72. Lenz K, Hahn S, Koellensperger G, Stefánka Z, Stingeder G, Weissenbacher N, Mahnik SN, Fürhacker M. 2005. Presence of cancerostatic platinum compounds in hospital wastewater and possible elimination by adsorption to activated sludge. Science of the Total Environment 345 (1-3): 141-152. doi 10.1016/j.scitotenv.2004.11.007. https://www.scopus.com/inward/record.uri?eid=2-s2.0-20344388300&doi=10.1016%2fj.scitotenv.2004.11.007&partnerID=40&md5=4e8b8375d7362e92a867ba042fb3fb71.
73. Hahn S, Stefánka Z, Lenz K, Stingeder G. 2005. Novel separation method for highly sensitive speciation of cancerostatic platinum compounds by HPLC–ICP–MS. Analytical and Bioanalytical Chemistry 381: 405-412.
74. Lenz K, Koellensperger G, Hann S, Weissenbacher N, Mahnik SN, Fürhacker M. 2007. Fate of cancerostatic platinum compounds in biological wastewater treatment of hospital effluents. Chemosphere 69 (11): 1765-1774. doi 10.1016/j.chemosphere.2007.05.062. https://www.scopus.com/inward/record.uri?eid=2-s2.0-35448957704&doi=10.1016%2fj.chemosphere.2007.05.062&partnerID=40&md5=4f21c957fdeed35b1355135c74fcc221.
75. Falter R, Wilken R-D. 1999. Determination of carboplatinum and cisplatinum by interfacing HPLC with ICP-MS using ultrasonic nebulisation. Science of the Total Environment 225: 167-176.
76. Merck. 2014. SAFETY DATA SHEET according to Regulation (EC) No. 1907/2006. Carboplatin. 9 p. www.merckgroup.com.

77. Lenz K, Mahnik SN, Weissenbacher N, Hann S, Koellensperger G, Mader R, Fürhacker M. 2004. Adsorption of selected cytostatic agents to suspended solids in wastewater and activated sludge. Osterreichische Wasser- und Abfallwirtschaft 56 (9-10): 127-131. https://www.scopus.com/inward/record.uri?eid=2-s2.0-8644226107&partnerID=40&md5=f1a3fbf006e4b4b63fd0df61760e04b4.
78. Curtis L, Turner A, Vyas N, Sewell G. 2010. Speciation and Reactivity of Cisplatin in River Water and Seawater. Environ Sci Technol 44: 3345-3350.
79. Turner A, Mascorda L. 2015. Particle–water interactions of platinum-based anticancer drugs in river water and estuarine water. Chemosphere 119: 415-422.
80. Lenz K, Mahnik SN, Weissenbacher N, Mader RM, Krenn P, Hann S, Koellensperger G, Uhl M, Knasmüller S, Ferk F, Bursch W, Fürhacker M. 2007. Monitoring, removal and risk assessment of cytostatic drugs in hospital wastewater. 141-149 pp.
81. Fürhacker M, Lenz K, Mahnik S, Weissenbacher N, Mader R, Knasmüller S, Ferk F, Uhl M, Bursch W, Köllensperger G, Hann S. 2006. Chemische Analyse, Risikobewertung und Entfernung von ausgewählten Zytostatika aus Abwasserströmen aus Krankenhäusern Teil II "Risikoabschätzung und Risikomanagement". Lebensministerium Wien, Austria:
82. Hahn S, Koellensperger G, Stefánka Z, Stingeder G, Fürhacker M, Buchberger W, Mader RM. **2003**. Application of HPLC-ICP-MS to speciation of cisplatin and its degradation products in water containing different chloride concentrations and in human urine. J Anal At Spectrom 18 (1391-1395)
83. Vidmar J, Martinčič A, Milačič R, Ščančar J. 2015. Speciation ofcisplatin in environmental water samples by hydrophilic interaction liquid chromatography coupled to inductively coupled plasma massspectrometry. Talanta 138: 1-7.
84. Kiffmeyer T, Götze HJ, Jursch M, Lüders U. 1998. Trace enrichment, chromatographic separation and biodegradation of cytostatic compounds in surface water. Fresenius' Journal of Analytical Chemistry 361 (2): 185-191. https://www.scopus.com/inward/record.uri?eid=2-s2.0-0000582243&partnerID=40&md5=1c103d1e4aafc4eec921ec8bdfb85ba6.
85. Opiolka S. 1999. Dampfdrücke von Zytostatika. Gefahrstoffe - Reinhaltung der Luft 59 (11/12): 443-444.
86. Opiolka S. 2000. Verhalten von Zytostatika in der Umwelt, insbesondere in Abwässern, Gewässern und Kläranlagen. Institut für Energie- und Umwelttechnik e.V. (IUTA),. Duisburg, Germany: Report nr. MURL: LUA 112-1781 WV 8/98, A.-Nr. 16141, 30.04.98. 229 p.

87. Mioduszewska K, Dołżonek J, Wyrzykowski D, Kubik Ł, Wiczling P, Sikorska C, Toński M, Kaczyński Z, Stepnowski P, Białk-Bielińska A. 2017. Overview of experimental and computational methods for the determination of the pKa values of 5-fluorouracil, cyclophosphamide, ifosfamide, imatinib and methotrexate. TrAC - Trends in Analytical Chemistry 97: 283-296. doi 10.1016/j.trac.2017.09.009. https://www.scopus.com/inward/record.uri?eid=2-s2.0-85030848654&doi=10.1016%2fj.trac.2017.09.009&partnerID=40&md5=9610bc1f7c874eb483b9e4e436c9b5ae.
88. Ternes TA, Herrmann N, Bonerz M, Knacker T, Siegrist H, Joss A. 2004. A rapid method to measure the solid-water distribution coefficient (K d) for pharmaceuticals and musk fragrances in sewage sludge. Water Research 38 (19): 4075-4084. doi 10.1016/j.watres.2004.07.015. https://www.scopus.com/inward/record.uri?eid=2-s2.0-5644255828&doi=10.1016%2fj.watres.2004.07.015&partnerID=40&md5=3fc11696ef4b1b2d5eebaefcced8bfaf.
89. Kümmerer K, Steger-Hartmann T, Baranyai A, Bürhaus I. 1996. Examination of the biodegradation of the antineoplastics cyclophosphamide and ifosfamide with the closed bottle test (OECD 301 D). Zentralblatt fur Hygiene und Umweltmedizin 198 (3): 215-225. https://www.scopus.com/inward/record.uri?eid=2-s2.0-0030072652&partnerID=40&md5=6680cbdb26cb8ea7ea4ff49a43c075d4.
90. Lutterbeck CA, Wilde ML, Baginska E, Leder C, MacHado EL, Kümmerer K. 2016. Degradation of cyclophosphamide and 5-fluorouracil by UV and simulated sunlight treatments: Assessment of the enhancement of the biodegradability and toxicity. Environmental Pollution 208: 467-476. doi 10.1016/j.envpol.2015.10.016. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84962704786&doi=10.1016%2fj.envpol.2015.10.016&partnerID=40&md5=f005d349780509b4b0ecf214f048c821.
91. Steger-Hartmann T, Kümmerer K, Hartmann A. 1997. Biological degradation of cyclophosphamide and its occurrence in sewage water. Ecotoxicology and Environmental Safety 36 (2): 174-179. doi 10.1006/eesa.1996.1506. https://www.scopus.com/inward/record.uri?eid=2-s2.0-0031105636&doi=10.1006%2feesa.1996.1506&partnerID=40&md5=20ca253a43b504c7f56a86dedb4681fe.
92. Steger-Hartmann T, Kümmerer K, Schecker J. 1996. Trace analysis of the antineoplastics ifosfamide and cyclophosphamide in sewage water by two-step solid-phase extraction and gas chromatography-mass spectrometry. Journal of Chromatography A 726 (1-2): 179-184. doi 10.1016/0021-9673(95)01063-7. https://www.scopus.com/inward/record.uri?eid=2-s2.0-0002837142&doi=10.1016%2f0021-9673%2895%2901063-7&partnerID=40&md5=3ecd0a61dfbce3543d286db45d680778.

93. Buerge IJ, Buser HR, Poiger T, Müller MD. 2006. Occurrence and fate of the cytostatic drugs cyclophosphamide and ifosfamide in wastewater and surface waters. Environmental Science and Technology 40 (23): 7242-7250. doi 10.1021/es0609405. https://www.scopus.com/inward/record.uri?eid=2-s2.0-33845284543&doi=10.1021%2fes0609405&partnerID=40&md5=fd7c6d8dd09c8dcab1537c996967de55.
94. Kümmerer K, Al-Ahmad A. 1997. Biodegradability of the anti-tumour agents 5-fluorouracil, cytarabine, and gemcitabine: Impact of the chemical structure and synergistic toxicity with hospital effluent. Acta Hydrochimica et Hydrobiologica 25 (4): 166-172. https://www.scopus.com/inward/record.uri?eid=2-s2.0-0031295578&partnerID=40&md5=b9f050cf33d016ef28b2daf6f4485b4f.
95. Struijs J. 2015. Application of SimpleTreat 4.0 in European substance regulations. Umwelt Bundesamt. Dessau-Roßlau, Germany: Report nr. Texte 13/2015. 43 p. http://www.umweltbundesamt.de/publikationen/application-of-simpletreat-40-in-european-substance.
96. Manallack DT. 2007. The pK(a) Distribution of Drugs: Application to Drug Discovery. Perspectives in Medicinal Chemistry 1: 25-38. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2754920/.
97. Checa A, Soto VG, Hernández-Cassou S, Saurina J. 2005. Fast determination of pKa values of reverse transcriptase inhibitor drugs for AIDS treatment by using pH-gradient flow-injection analysis and multivariate curve resolution. Analytica Chimica Acta 554 (1-2): 177-183. doi 10.1016/j.aca.2005.08.084. https://www.scopus.com/inward/record.uri?eid=2-s2.0-27744528256&doi=10.1016%2fj.aca.2005.08.084&partnerID=40&md5=38196ff90dc4e925a89d0cc7ee10f845.
98. Prankerd RJ. **2007**. Critical compilation of pK_a values. Profiles of Durg Substances, Excipients, and Related Methodology, Vol 33. Amsterdam, The Netherlands: Elsevier, Inc. Academic Press. ISBN 978-0-12-260833-9. 726 p.
99. Mahnik SN, Lenz K, Weissenbacher N, Mader RM, Fürhacker M. 2007. Fate of 5-fluorouracil, doxorubicin, epirubicin, and daunorubicin in hospital wastewater and their elimination by activated sludge and treatment in a membrane-bio-reactor system. Chemosphere 66 (1): 30-37. doi 10.1016/j.chemosphere.2006.05.051. https://www.scopus.com/inward/record.uri?eid=2-s2.0-33750976959&doi=10.1016%2fj.chemosphere.2006.05.051&partnerID=40&md5=70ec395e0043fcc26efece09589cdc2b.
100. Mahnik SN, Rizovski B, Fürhacker M, Mader RM. 2004. Determination of 5-fluorouracil in hospital effluents. Analytical and Bioanalytical Chemistry 380: 31-35.
101. Roche. 2015. Safety Data Sheet. Fluorouracil. According to Regulation (EU) nr. 1907/2006. Roche. 9 p. https://www.roche.com/sustainability/what_we_do/for_communities_and_environment/environment/safety_data_sheets-row.htm.

102. Yu JT, Bouwer EJ, Coelhan M. 2006. Occurrence and biodegradability studies of selected pharmaceuticals and personal care products in sewage effluent. Agricultural Water Management 86 (1-2): 72-80. doi 10.1016/j.agwat.2006.06.015. https://www.scopus.com/inward/record.uri?eid=2-s2.0-33750624076&doi=10.1016%2fj.agwat.2006.06.015&partnerID=40&md5=080be63dcba110003bedebfffc9b2835.
103. Sandoz. 2017. Gemcitabin Sandoz. Koncentrat till infusionsvätska, lösning 40 mg/ml. Regulatory environmental endpoint data contained in fass database. www.fass.se: FASS. Swedish environmental classification. 4 p. Accessed: 24-11-2017
104. Bristol-MSC. 2010. Safety Data Sheet for Hydroxyurea. Webpage: http://www.msdsexplorer.com/PDFsFiles/4923.pdf. Accessed 29 January 2018.
105. Kümmerer K, Steger-Hartmann T, Meyer M. 1997. Biodegradability of the anti-tumour agent ifosfamide and its occurrence in hospital effluents and communal sewage. Water Research 31 (11): 2705-2710. doi 10.1016/S0043-1354(97)00121-8. https://www.scopus.com/inward/record.uri?eid=2-s2.0-0042548456&doi=10.1016%2fS0043-1354%2897%2900121-8&partnerID=40&md5=c71821076dadf984be7114b41edec50f.
106. Muñoz M, Bonjoch J, Prat J, Pujol M, Girona V, De Bolós J. 1996. Degradation kinetics of ifosfamide in aqueous solution. International Journal of Pharmaceutics 139 (1-2): 249-253. doi 10.1016/0378-5173(96)04629-7. https://www.scopus.com/inward/record.uri?eid=2-s2.0-0030576588&doi=10.1016%2f0378-5173%2896%2904629-7&partnerID=40&md5=612afa5d7f37d390020016a250f8bb36.
107. Kosjek T, Negreira N, de Alda ML, Barceló D. 2015. Aerobic activated sludge transformation of methotrexate: Identification of biotransformation products. Chemosphere 119: S42-S50. doi 10.1016/j.chemosphere.2014.04.081. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84922754265&doi=10.1016%2fj.chemosphere.2014.04.081&partnerID=40&md5=4b66ed23e73b5b080d804c69c415f221.
108. Shalaeva M, Kenseth J, Lombardo F, Bastin A. 2008. Measurement of dissociation constants (pKa values) of organic compounds by multiplexed capillary electrophoresis using aqueous and cosolvent buffers. Journal of Pharmaceutical Sciences 97 (7): 2581-2606. doi 10.1002/jps.21287. https://www.scopus.com/inward/record.uri?eid=2-s2.0-52449106452&doi=10.1002%2fjps.21287&partnerID=40&md5=da4a3fc663a0bf9bc39c9d1512ff766b.
109. Lutterbeck CA, Baginska E, Machado ÊL, Kümmerer K. 2015. Removal of the anti-cancer drug methotrexate from water by advanced oxidation processes: Aerobic biodegradation and toxicity studies after treatment. Chemosphere 141: 290-296. doi 10.1016/j.chemosphere.2015.07.069. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84955514091&doi=10.1016%2fj.chemosphere.2015.07.069&partnerID=40&md5=1b4fe50d3aee7cc99fb06b0d7a9e4b01.

110. Henschel KP, Wenzel A, Diedrich M, Fliedner A. 1997. Environmental hazard assessment of pharmaceuticals. Regulatory Toxicology and Pharmacology 25 (3): 220-225. doi 10.1006/rtph.1997.1102. https://www.scopus.com/inward/record.uri?eid=2-s2.0-0031171238&doi=10.1006%2frtph.1997.1102&partnerID=40&md5=d626afa6edc95bfe3346b676dc6a0066.
111. Bristol-MSC. 2009. Safety Data Sheet for Paclitaxel. Webpage: http://www.msdsexplorer.com/PDFsFiles/4923.pdf. Accessed 29 January 2018.
112. Pfizer. 2016. Safety Data Sheet for Paclitaxel. Webpage: https://www.pfizer.com/sites/default/files/products/material_safety_data/Paclitaxel_inj_(hospira)_2-Aug-2016.pdf. Accessed 29 January 2018.
113. EMA. 2015. Abraxane. European Public Assessment Report. International non-proprietary name: PACLITAXEL. Procedure No. EMEA/H/C/000778/II/0067. EMA. London, United Kingdom: Report nr. EMA/76768/2015. 69 p.
114. Franquet-Griell H, Pueyo V, Silva J, Orera VM, Lacorte S. 2017. Development of a macroporous ceramic passive sampler for the monitoring of cytostatic drugs in water. Chemosphere 182: 681-690. doi 10.1016/j.chemosphere.2017.05.051. https://www.scopus.com/inward/record.uri?eid=2-s2.0-85019549249&doi=10.1016%2fj.chemosphere.2017.05.051&partnerID=40&md5=ab1910c5cb518a6e521cd1cd93700ba1.
115. Isidori M, Lavorgna M, Russo C, Kundi M, Žegura B, Novak M, Filipič M, Mišík M, Knasmueller S, de Alda ML, Barceló D, Žonja B, Česen M, Ščančar J, Kosjek T, Heath E. 2016. Chemical and toxicological characterisation of anticancer drugs in hospital and municipal wastewaters from Slovenia and Spain. Environmental Pollution 219: 275-287. doi 10.1016/j.envpol.2016.10.039. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84994052004&doi=10.1016%2fj.envpol.2016.10.039&partnerID=40&md5=7c7f0f19d3b5e535fed8096127227eda.
116. Negreira N, de Alda ML, Barcelo´ D. 2014. Cytostatic drugs and metabolites in municipal and hospital wastewaters in Spain: Filtration, occurrence, and environmental risk. Science of the Total Environment 497-498: 68-77. doi 10.1016/j.scitotenv.2014.07.101. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84905574596&doi=10.1016%2fj.scitotenv.2014.07.101&partnerID=40&md5=b5a788b7ff2cb6c9b1f7c318a4326f0c.
117. Azuma T, Arima N, Tsukada A, Hirami S, Matsuoka R, Moriwake R, Ishiuchi H, Inoyama T, Teranishi Y, Yamaoka M, Mino Y, Hayashi T, Fujita Y, Masada M. 2016. Detection of pharmaceuticals and phytochemicals together with their metabolites in hospital effluents in Japan, and their contribution to sewage treatment plant influents. Science of the Total Environment 548-549: 189-197. doi 10.1016/j.scitotenv.2015.12.157. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84955497567&doi=10.1016%2fj.scitotenv.2015.12.157&partnerID=40&md5=a95566492f7579d5d8259e6f3dd614a7.

118. Ghafuri Y, Yunesian M, Nabizadeh R, Mesdaghinia A, Dehghani MH, Alimohammadi M. 2018. Platinum cytotoxic drugs in the municipal wastewater and drinking water, a validation method and health risk assessment. Human and Ecological Risk Assessment 24 (3): 784-796. doi 10.1080/10807039.2017.1400372. https://www.scopus.com/inward/record.uri?eid=2-s2.0-85038619378&doi=10.1080%2f10807039.2017.1400372&partnerID=40&md5=bcc5c2270d61ef3eaf8fbe007bb22539.
119. Martín J, Camacho-Muñoz D, Santos JL, Aparicio I, Alonso E. 2011. Simultaneous determination of a selected group of cytostatic drugs in water using high-performance liquid chromatography-triple-quadrupole mass spectrometry. Journal of Separation Science 34 (22): 3166-3177. doi 10.1002/jssc.201100461. https://www.scopus.com/inward/record.uri?eid=2-s2.0-81755166687&doi=10.1002%2fjssc.201100461&partnerID=40&md5=4ceff011bfdda8bf6236d7b563c389f6.
120. Martín J, Camacho-Munõz D, Santos JL, Aparicio I, Alonso E. 2014. Occurrence and ecotoxicological risk assessment of 14 cytostatic drugs in wastewater. Water, Air, and Soil Pollution 225 (3) doi 10.1007/s11270-014-1896-y. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84893670599&doi=10.1007%2fs11270-014-1896-y&partnerID=40&md5=fc3657fd3db2adaa323baa88274816b1.
121. Rabii FW, Segura PA, Fayad PB, Sauvé S. 2014. Determination of six chemotherapeutic agents in municipal wastewater using online solid-phase extraction coupled to liquid chromatography-tandem mass spectrometry. Science of the Total Environment 487: 792-800.
122. Prinsen GF, Becker BPJ. 2011. Application of SOBEK hydraulic surface water models in the netherlands hydrological modelling instrument. Irrigation and Drainage 60 (Suppl. 1): 35-41.
123. Prinsen GF, Sperna Weiland F, Ruijgh E. 2015. The Delta Model for Fresh Water Policy Analysis in the Netherlands. Water Resources Management 29: 645-661.
124. VWS. 2016. De Staat van Volksgezondheid en Zorg. Webpage: https://www.staatvenz.nl/kerncijfers/ziekenhuisbedden. Accessed March 2, 2018.

Annex 1 Identity, physico-chemical and environmental fate properties of selected substances

Data sources
Data on identity, physico-chemical and environmental fate properties of selected cytostatics were collected using the databases and QSAR/software programs: EPISuite [62], Marvin Sketch [63] and Bio-Loom [64]. Details for each parameter are provided below.

In addition, scientific literature was searched using Scopus [65], GoogleScholar and via retrospective searching. The third data source were lists of endpoints published as a result of an environmental risk assessment performed in a regulatory context. To this end, the www.fass.se database and the EMAs EPAR (European public assessment report) database was searched for environmental risk assessments or lists of endpoints for all substances under investigation.

CAS nr, SMILES code and K_{ow} estimates were obtained from EpiSuite or Bio-Loom. Molecular weight, water solubility, vapour pressure are EpiSuite estimates, appended with experimentally determined values from literature, if available. The majority of experimentally determined values that were retrieved, were taken from material safety data sheets (MSDS) from which, generally, no further details on method, temperature, pH, etc. is provided. Nevertheless, experimental values were given preference over estimated values. If no experimental water solubility was available, the EPISuite K_{ow} based estimate (at 25°C) was used. If no experimental vapour pressure was available, the EPISuite estimated subcooled liquid vapour pressure (at 25°C) was entered in SimpleTreat simulations. SimpleTreat corrects water solubility and vapour pressure to 15°C, the (model) temperature of the WWTP. For SimpleTreat vapour pressure entries, a lower limit of 10^{-8} Pa was used meaning that lower estimates below were assigned this limit value.

For pK_a values, a QSAR estimate by MarvinSketch was always generated, which was appended with experimentally determined values, if these were found in the literature.

Information on degradation was obtained mainly from public literature and from ERAs published by pharmaceutical companies (Roche, AstraZeneca) or lists of endpoints (EMA, fass.se).

Legend to the tabulated parameters

M_w	molecular weight
S_w	water solubility
P_v	vapour pressure
pK_a	dissociation constant
K_{ow}	octanol-water partition coefficient
ClogP	K_{ow} estimate generated by Bio-Loom software [64]
MlogP	experimentally determined log K_{ow} value, proposed by Bio-Loom software [64]
KOWWIN	K_{ow} estimate generated by EPISuite software [62].

K_{oc}	organic carbon normalised adsorption coefficient, preferably derived experimentally and preferably derived using activated sludge. Two QSAR estimated K_{oc} values are shown for each compound: one using the MCI (molecular connectivity indices), the other based on K_{ow}. Both values generated using EpiSuite.
K_d	normalised adsorption coefficient, preferably derived experimentally and preferably derived using activated sludge.
f_{oc}	fraction organic carbon of matrix used in adsorption study.

Tables

For each compound, identity parameters, structural formula and a conclusion on dissociation behaviour and biodegradability in the waste water treatment plant are presented. Next, two tables with the collected data are shown for each compound. The first table contains physico-chemical properties and data on adsorption, the second table contains data on degradation obtained in standard tests with activated sludge (e.g. ready biodegradability tests) and other information on stability, if available. Values marked **bold** are selected values used for SimpleTreat simulations.

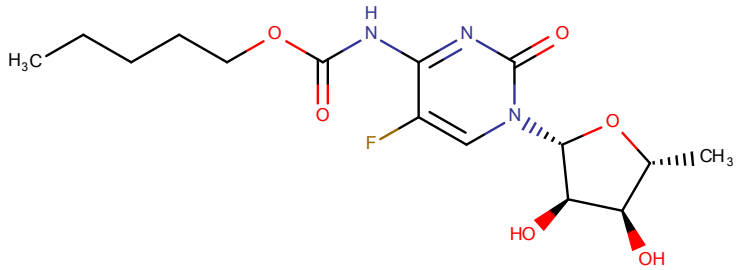
A summary with SimpleTreat settings on sorption and degradation for each substance is presented in Table 27.

Table 27. Selected SimpleTreat parameters for sorption and degradation.

	substance	QSAR selection [a] SimpleTreat	pK_a [b]	K_{oc} [L kg^{-1}]	K_{oc} type [c]	K_{ow} [d] [-]	SimpleTreat biodegradation setting [e]	rate constant [f] [h^{-1}]
1	capecitabine	acid	8.8	272	exp		inherently in MITI II and Zahn-Wellens	0.1
2	carboplatin	acid	6.13	2399	exp		not biodegradable	0
3	cisplatin	neutral		12589	exp			
4	cyclophosphamide	neutral		158	exp		not biodegradable	0
5	cytarabine	base	4.02	117	ST	0.00513	inherently in MITI II and Zahn-Wellens	0.1
6	etoposide	acid	9.8	27.2	ST	3.98	not biodegradable	0
7	5-fluorouracil	acid	8.02	5.01	ST	0.141	biodegradable in OECD 303A	0.1
8	gemcitabine	neutral		1.39	ST	1.13	not biodegradable	0
9	hydroxycarbamide	acid	10.14	1.38	ST	0.0158	not biodegradable	0
10	ifosfamide	acid	9.1	62	exp		not biodegradable	0
11	methotrexate	acid	3.25	21.7	ST	0.0141	biodegradable in OECD 303A	1

[a] In case an experimentally determined adsorption constant on waste water sludge was not available, the SimpleTreat QSAR for adsorption to sludge were used.
[b] This pK_a value is used in SimpleTreat in conjunction with the Koc QSAR selection.
[c] Indication whether the selected K_{oc} is experimental = exp, or calculated = ST, using SimpleTreat QSARs
[d] K_{ow} value used as input in SimpleTreat in absence of an experimentally determined Koc value.
[d] The selected biodegradation setting, based on the outcome of the available information (Annex 1).
[e] The default rate constant for biodegradation provided by SimpleTreat.

Capecitabine



CAS nr. 154361-50-9
SMILES: CCCCCOC(=O)NC1=NC(=O)N(C=C1F)[C@@H]1O[C@H](C)[C@@H](O)[C@H]1O

Conclusions for SimpleTreat simulation based on collected data.

- Molecule reacts as an acid at the lowest pK_a value (NB measured pK_a is 8.8) and changes from neutral to 1- around pH 7. Select SimpleTreat: QSAR: acid with pK_a = 8.8.
- Potential for primary degradation exists in inherent tests; the substance is unlikely to be readily biodegradable. Select 'inherently in MITI II test' in SimpleTreat.

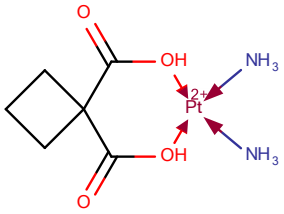
Table 28. Capecitabine: physico-chemical properties and data on environmental fate and behaviour.

Parameter	Value	Unit	T (°C)	pH	Remark	Source
M_w	**359.36**	g mol^{-1}				[62]
S_w	**2.60E+04**	mg L^{-1}	**20**		experimentally determined	[14, 66]
	1821	mg L^{-1}	25		K_{ow} method	[62]
	1.00E+06	mg L^{-1}			fragment method	[62]
P_v	**1.35E-08**	Pa	**25**		subcooled liquid VP	[62]
pK_a	1.9					[67]
	8.8					[66]
	8.77					[68]
	6.63				for R-NH $\rightarrow$ RN-	[63]
log K_{ow}	**0.96**					[10]
	~4.5			7.4	outlier; differs 3-4 orders of magnitude with other and calculated values	[66]
	0.84				ClogP; for molecule with esterified C5 chain. Bio-Loom entry for capecitabine lacks this chain	[64]
	0.56				KOWWIN	[62]
K_d	**272**	L kg^{-1}			activated sludge	[66]
K_d	272	L kg^{-1}			activated sludge; study like OECD 302, not a batch adsorption test	Haner, 2006, cited in [14]
K_d	insignificant				activated sludge; study like OECD 302, not a batch adsorption test	Studer 2005, cited in [14]
K_{oc}	46.68	L kg^{-1}			MCI method; QSAR	[62]
	1.491	L kg^{-1}			Kow method; QSAR	[62]

Table 29. Capecitabine: data on removal in WWTP related systems.

Study type	Parameter	Result	Unit	Remark	Source
OECD 302C (MITI II)		inherent		evidence for prior abiotic primary degradation as a rate-limiting process	[66]
OECD 302B		not inherent		58% after 28 days; also data after 7,14,21 d	ETT, 2004, cited in [14]
like OECD 302C		-		41% after 21 days; also data after 14d	[14]
like OECD 302C		not inherent		29% after 28 days; also data after 56, 84d	Häner 2006, cited in [14]
batch study	DT50	77	h	1 mg/L CAP; 0.67 g act sludge/L; >99% in 12 d	[69]
batch study	DT50	205	h	1 mg/L CAP; 0.14 g act sludge/L; 78% in 16 d	[69]
batch study	DT50	not degraded		1 mg/L CAP; 0.014 g act sludge/L; 47% in 16 d	[69]
batch reactor (2 d)	DT50	0.53	d	2 d incubation in primary effluent; ~1 g TSS/L, aerated; 16 cytostatics in mixture each at 50 µg/L	[70]
batch reactor (10 d)	DT50	0.96	d	5 times a 2 d cycle; one cycle = fill-react-settle-decant-fill; with: primary effluent; ~1 g TSS/L, aerated; 16 cytostatics in mixture each at 50 µg/L	[70]
hydrolysis	DT50	0.96	d	dark; 22°C. pH not reported	[70]
photolysis	DT50	0.20	d	290-400 nm; simulated sunlight	[70]
stability	%left after 1 d	55	%	not stable; stability test in 0.45 µm filtered raw waste water; 1 mg/L; pH 7, 4°C	[71]
stability	%left after 1 d	40	%	not stable; stability test in 0.45 µm filtered raw waste water; 1 mg/L; pH 7, 25°C	[71]
QSAR Biowin 1		0.7345		ready	[62]
QSAR Biowin 3		2.9679		not ready	[62]
QSAR Biowin 5		0.1952		not ready	[62]
QSAR Biowin 7		NO		not ready	[62]

Carboplatin



CAS nr. 41575-94-4
SMILES: N[Pt]2(N)OC(=O)C1(CCC1)C(=O)O2

Conclusions for SimpleTreat simulation based on collected data.

- At pH 7, molecule is charged 1- for approximately 50% and 2- for 50%. Select SimpleTreat QSAR: acid with pK_a = 6.13. It is noted that the molecule is actually a divalent acid.
- The geometric mean of the upper and lower K_{oc} value from a batch adsorption experiment with activated sludge is selected for use in the SimpleTreat simulation (2399 L kg^{-1}). The reported Freundlich constant from this experiment can not be used since the fraction organic carbon of the activated sludge was not reported.
- The experimental information available on degradation of carboplatin in waste water matrices shows it to: hydrolyse slowly [72], be relatively stable in water and in water with Cl^- [73], adsorb to a lesser extent than cisplatin [74, 75], and is relatively stable in (filtered) waste water [71]. SimpleTreat setting: carboplatin is not biodegradable in the WWTP. In the WWTP simulation, the major removal process will be adsorption.

Table 30. Carboplatin: physico-chemical properties and data on environmental fate and behaviour.

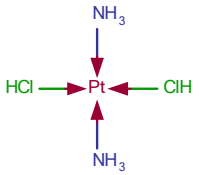
Parameter	Value	Unit	T (°C)	pH	Remark	Source
M_w	**369.24**	g mol^{-1}				[62]
S_w	**1.70E+04**	mg L^{-1}	**20**			[76]
	1.17E+04	mg L^{-1}	25		K_{ow} method	[62]
	1.00E+06	mg L^{-1}			fragment method	[62]
P_v	**1.32E-05**	Pa	**25**		subcooled liquid VP	[62]
pK_a	**6.13**				for R-COOH → $R\text{-}COO^-$; charge is 1- below pK_a, 2- above pK_a	[63]
log K_{ow}	**-2.30**				MlogP	[64]
	-2.34			7.4	ClogP	[64]
	-0.46				KOWWIN	[62]
K_{oc}	891	L kg^{-1}	25		activated sludge; analysis based on ICP-MS (Pt); lower value from range, OECD 106; 25°C	[74]
K_{oc}	6457	L kg^{-1}	25		activated sludge; analysis based on ICP-MS (Pt); upper value from range, OECD 106; 25°C	[74]
geomean K_{oc}	**2399**	L kg^{-1}				
K_d	376	L kg^{-1}			activated sludge from municipal WWTP; f_{oc} not reported; lower value from range, OECD 106 sludge	[77]
K_d	1301	L kg^{-1}			activated sludge from municipal WWTP; f_{oc} not reported; higher value from range, OECD 106 sludge	[77]
geomean K_d	699	L kg^{-1}				
K_d	470	L kg^{-1}			general hospital-waste water; f_{oc} not reported	[77]
K_{oc}	10	L kg^{-1}			MCI method; QSAR	[62]
K_{oc}	1.63	L kg^{-1}			K_{ow} method; QSAR	[62]

Adsorption data not expressed as adsorption constant were found in Falter and Wilken [75]and Lenz et al [72].

Table 31. Carboplatin: data on removal in WWTP related systems.

Study type	Parameter	Result	Unit	Remark	Source
stability	% left after 1 d	90	%	stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7; 4°C	[71]
stability	% left after 1 d	83	%	stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7; 25°C	[71]
QSAR Biowin 1		0.3878		not ready	[62]
QSAR Biowin 3		2.1711		not ready	[62]
QSAR Biowin 5		-0.2595		not ready	[62]
QSAR Biowin 7		NO		not ready	[62]

Cisplatin



CAS nr. 15663-27-1
SMILES: [NH3][Pt]([NH3])(Cl)Cl

Conclusions for SimpleTreat simulations based on collected data.

- Adsorption of cisplatin was studied in river, estuarine and sea water[78, 79] as well as waste water sludge [72, 74, 75, 77, 80, 81]. The geometric mean of the upper and lower K_{oc} value from a batch adsorption experiment with activated sludge is selected for use in the SimpleTreat simulation (12589 L kg^{-1}). The reported Freundlich constant from this experiment can not be used since the fraction organic carbon of the activated sludge was not reported.
- Cisplatin does not dissociate, the SimpleTreat setting 'neutral' is selected. However, since an experimental K_{oc} is used, effectively, no QSAR will be used for partitioning calculations.
- Cisplatin, *cis*-$PtCl_2(NH_3)_2$, in aqueous solution reacts by replacement of Cl^- to form monoaquacisplatin *cis*-$PtCl(OH_2)(NH_3)_2^+$, and diaquacisplatin *cis*-$PtCl(OH_2)2(NH_3)_2^{2+}$. The aqua complexes are the reactive species that cause toxicity and their formation rate is inversely related to chloride concentration. Excretion of cisplatin occurs mainly via urine and an estimate of 40% for excretion of monocisaquaplatin was reported (one patient) [82], the remaining fraction of the portion excreted being unchanged parent, which is then partly converted to monocisaquaplatin before entering the WWTP. Although analysis of the various cisplatin species is analytically possible e.g. [82, 83], a complete picture of the ratios of parent and reaction products resulting from transformation along the pathway from patient, waste water, treatment plant, to surface water caused by various environmental conditions is out of scope at present. However, the assumption that excreted cisplatin will enter the WWTP as a mixture of parent and aqua complexes is reasonable. Assuming no degradation in the WWTP [84]means that removal is mainly caused by adsorption which matches the observations of Lenz et al., cited above. For the SimpleTreat simulation 'no biodegradation' is assumed.

Table 32. Cisplatin: physico-chemical properties and data on environmental fate and behaviour.

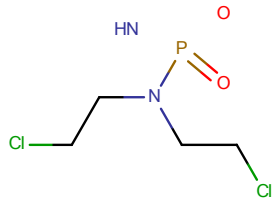
Parameter	Value	Unit	T (°C)	pH	Remark	Source
M_w	**300.05**	g mol^{-1}				[62]
S_w	**2530**	mg L^{-1}			experimental match, temperature not reported. 20°C used for simulation	[62]
	9.1E+05	mg L^{-1}	25		K_{ow} method	[62]
	1.4E+05	mg L^{-1}			fragment method	[62]
P_v	**0.0018**	Pa	**20**		experimentally determined; OECD 104	[85, 86]
	3.17E-15	Pa	25		subcooled liquid VP	[62]
pK_a					does not dissociate	
log K_{ow}	-2.19				experimentally determined	[62]
	-2.75				KOWWIN	[62]
	-2.50				ClogP	[64]
	-2.53				MlogP	[64]
K_{oc}	3020	L kg^{-1}	25		activated sludge; analysis based on ICP-MS (Pt); lower value from range, OECD 106; 25°C	[74]
K_{oc}	52481	L kg^{-1}	25		activated sludge; analysis based on ICP-MS (Pt); upper value from range, OECD 106; 25°C	[74]
geomean K_{oc}	**12589**	L kg^{-1}				
K_d	3186	L kg^{-1}			activated sludge from municipal WWTP; f_{oc} not reported; lower value from range, OECD 106 sludge	[77]
K_d	3186	L kg^{-1}			activated sludge from municipal WWTP; f_{oc} not reported; higher value from range, OECD 106 sludge	[77]
geomean K_d	4430	L kg^{-1}				
K_d	1634	L kg^{-1}			general hospital-waste water; f_{oc} not reported	[77]
K_{oc}	43.9	L kg^{-1}			MCI method; QSAR	[62]
K_{oc}	0.141	L kg^{-1}			K_{ow} method; QSAR	[62]
% left after 5 d	54	%			undiluted waste water; 25 µg/L; 5 d incubation; then concentration measurements in 0.3 µm filtered water phase	[75]
% left after 5 d	20	%			river water (Rhine); 25 µg/L; 5 d incubation; then concentration measurements in 0.3 µm filtered water phase	[75]
% adsorption	88±7	%			waste water; pH 7; 24 h; 2.8 µg/L; analysis based on ICP-MS (Pt)	[72]
% adsorption	96±8	%			act. sludge; pH 7; 24 h; 2.8 µg/L; analysis based on ICP-MS (Pt)	[72]
%elimination	25, 33, 36,	%			waste water; n=5; 24 h incubation; analysis based on ICP-MS (Pt)	[72]

Parameter	Value	Unit	T (°C)	pH	Remark	Source
%elimination	80, 87 85, 93, 93, 95, 96	%			act. sludge; *n*=5; 2.5 µg/L; 48 h incubation; analysis based on ICP-MS (Pt)	[72]

Table 33. Cisplatin: data on removal in WWTP related systems.

Study type	Parameter	Result	Unit	Remark	Source
OECD screening test (301E type)	degradation	0±2	%	not degraded; WWTP effluent, 1:50 diluted in mineral medium, aerated, stirred, (inoculum not washed); dry matter content not determined	[84]
QSAR Biowin 1		0.6047		ready	[62]
QSAR Biowin 3		2.5361		not ready	[62]
QSAR Biowin 5		- 0.1898		not ready	[62]
QSAR Biowin 7		NO		not ready	[62]

Cyclophosphamide



CAS nr. 50-18-0
SMILES: ClCCN(CCCl)P1(=O)NCCCO1

Conclusions for SimpleTreat simulations based on collected data.

- The molecule is a very weak acid; charged neutral up to pH 13. Select SimpleTreat QSAR: neutral.
- The selected K_{oc} value (158 L kg^{-1}) is experimentally determined in primary sludge.
- Cyclophosphamide is not readily biodegradable, no primary degradation seems to occur in activated sludge .Select 'not biodegradable' in SimpleTreat.

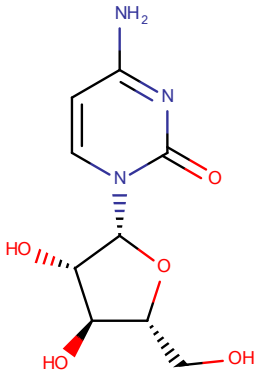
Table 34. Cyclophosphamide: physico-chemical properties and data on environmental fate and behaviour.

Parameter	Value	Unit	T (°C)	pH	Remark	Source
M_w	**261.09**	g mol^{-1}				[62]
S_w	**4.00E+04**	mg L^{-1}	**20**		experimentally determined	[62]
	5943	mg L^{-1}	25		K_{ow} method	[62]
	57921	mg L^{-1}			fragment method	[62]
	40	mg L^{-1}			source, method and temperature not reported	[70]
P_v	**0.0033**	Pa	**20**		experimentally determined; OECD 104	[85, 86]
	0.0103	Pa	**25**		subcooled liquid VP	[62]
pK_{a1}	2.3				pK_{a1} for 1+ to 0	[87]
	2.84					[63]
pK_{a2}	11.1				pK_{a2} for 0 to 1-	[87]
	13.43				RNH → RN-	[63]
log K_{ow}	0.63				pH not reported	[10]
	0.63					[64]
	0.97				experimentally determined	[62]
	0.63				KOWWIN value	[62]
K_{oc}	**158**	L kg^{-1}			f_{oc} = 0.35; primary sludge	[88]
K_{oc}	7.1	L kg^{-1}			f_{oc} = 0.34; secondary sludge	[88]
K_d	55	L kg^{-1}			f_{oc} = 0.35; primary sludge	[88]
K_d	2.5	L kg^{-1}			f_{oc} = 0.34; secondary sludge	[88]
K_{oc}	94.23	L kg^{-1}			MCI method; QSAR	[62]
K_{oc}	20.49	L kg^{-1}			K_{ow} method; QSAR	[62]

Table 35. Cyclophosphamide: data on removal in WWTP related systems.

Study type	Parameter	Result	Unit	Remark	Source
OECD 301D		not ready		no degradation after 28 days, nor 57 days (research gat translation)	[89]
OECD 301D		not ready		25-35% after 28 d; 4.5 mg/L CP; act sludge from municipal WWTP (73000 IE)	[90]
OECD 302B		not inherent		0% after 28 days	[91]
	elimination rate			plateau reached after 7 days; test concentration 1 mg /L; 95% CI:0-	
OECD 303A		4	%	11%	[86]
OECD 303A	elimination rate	0±5	%	result: not biodegraded; 150 mg /L	[84]
lab scale WWTP		not degradable			[92]
undiluted activated sludge		no degradation		exposure duration 24 h; concentration parent 90 ng parent/L	[93]
biodegradation	DT50	0.30	d	incubation in activated sludge: 5 times a 2 day cycle	[70]
stability	% left after 1 d	95	%	stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7, 4°C	[71]
stability	% left after 1 d	90	%	stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7, 25°C	[71]
hydrolysis	DT50	1.20	d	dark; 22°C. pH not reported	[70]
photolysis	DT50	0.07	d	290-400 nm; simulated sunlight	[70]
QSAR Biowin 1		0.4005		not ready	[62]
QSAR Biowin 3		2.2758		not ready	[62]
QSAR Biowin 5		0.1944		not ready	[62]
QSAR Biowin 7		NO		not ready	[62]

Cytarabine



CAS nr. 147-94-4
SMILES: Nc2ccn(C1OC(CO)C(O)C1O)c(=O)n2

Conclusions for SimpleTreat simulation based on collected data.

- pK_a is valid for ring NH^+ --> ring N. Molecule is neutral at pH values > pK_a. Select SimpleTreat QSAR 'base', with pK_a = 4.02.
- Based on experimental data, cytabine is not readily biodegradable, but 50% transformation was observed after a lag phase and it was found to be inherently biodegradable, meeting the 10 d window in a Zahn-Wellens test [94]. The potential for degradation was confirmed in three OECD 303 simulation tests, in which the elimination rate ranged from 60 to 74%. Using the hierarchy for selection of biodegradation rate constants [95], a rate constant of 0.1 h^{-1} at 293 K is selected for the SimpleTreat simulation. This corresponds with the rate proposed for an inherently biodegradable substance and for a substance with an elimination rate of 50% in the 303A simulation test.
- No experimental data K_{oc} data available. The SimpleTreat QSAR for adsorption is used.

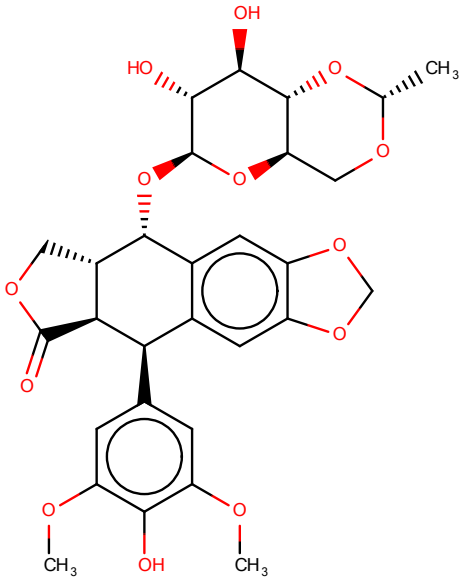
Table 36. Cytarabine: physico-chemical properties and data on environmental fate and behaviour.

Parameter	Value	Unit	T (°C)	pH	Remark	Source
M_w	**243.22**	g mol^{-1}				[62]
S_w	**1.76E+05**	mg L^{-1}	**25**			[62]
	1.00E+06				K_{ow} method; fragment method	[62]
P_v	**1.15E-07**	Pa	**25**		subcooled liquid VP	[62]
pK_a	4.24					[64]
	4.22					[63]
	4.22					[70]
	4.3					[96]
	4.02					[97]
	-0.06				value strongly deviating from others. not used for further analysis	[63]
	4.3					[98]
log K_{ow}	-2.51				experimental match	[62]
	-2.20				ClogP	[64]
	-2.29				MlogP	[64]
K_{oc}	10	L kg^{-1}			MCI method; QSAR	[62]
	0.03613	L kg^{-1}			K_{ow} method; QSAR	[62]

Table 37. Cytarabine: data on removal in WWTP related systems.

Study type	Parameter	Result	Unit	Remark	Source
OECD 301D		not ready		50%, only after adaptation period of 20 days. 80% after prolongation test to 40 days.	[94]
OECD 302B		inherent		>95% after few days; 10 d window met	[94]
OECD 303A	elimination rate	65	%	plateau reached after 12 days; test concentration 1 mg /L; 95% CI:51-71%	[86]
OECD 303A	elimination rate	74	%	plateau reached after 10 days; test concentration 1 mg /L; 95% CI:59-80%	[86]
OECD 303A	elimination rate	60±8	%	no lag phase, but plateau not reached after 14 d (slow, continuous increase in elimination rate); test concentration 12.5 mg/L	[84]
Batch reactor (2 d)	DT50	0.16	d	2 d incubation in primary effluent; ~1 g TSS/L, aerated; 16 cytostatics in mixture each at 50 µg/L	[70]
Batch reactor (10 d)	DT50	0.036	d	5 times a 2 d cycle; one cycle = fill-react-settle-decant-fill; with: primary effluent; ~1 g TSS/L, aerated; 16 cytostatics in mixture each at 50 µg/L	[70]
hydrolysis	DT50	1.60	d	dark; 22°C. pH not reported	[70]
photolysis	DT50	0.012	d	290-400 nm; simulated sunlight	[70]
QSAR Biowin 1		0.7606		ready	[62]
QSAR Biowin 3		3.1329		ready	[62]
QSAR Biowin 5		0.5850		ready	[62]
QSAR Biowin 7		YES		ready	[62]

Etoposide



CAS nr. 33419-42-0
SMILES: COc1cc(cc(OC)c1O)C6C2C(COC2=O)C(OC4OC3COC(C)OC3C(O)C4O)c7cc5OCOc5cc67

Conclusions for SimpleTreat simulations based on collected data.

- Dissociation of phenyl-OH to phenyl-O- at pK_a 9.8. In SimpleTreat, the QSAR 'acid' is selected, with pK_a 9.8.
- BIOWIN QSARs do not predict ready biodegradability for etoposide. However, the collected experimental data show that is not very stable in filtered waste water [71] and degraded relatively rapidly in a batch reactor set up [70]. The OECD 303A tests [86] also indicate that degradation in activated sludge is possible. Unfortunately, no data on ready or inherent biodegradability were retrieved. Based on the elimination rates of 29-36% in the simulation tests and using the selection hierarchy in Struijs [95], a half life of 0.03 h^{-1} is selected in the SimpleTreat simulation.
- In the absence of experimental adsorption data, the SimpleTreat QSAR based on a log K_{ow} value of 0.60 (K_{ow} = 3.981) is used to model sorption to sludge.

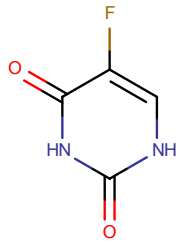
Table 38. Etoposide: physico-chemical properties and data on environmental fate and behaviour.

Parameter	Value	Unit	T (°C)	pH	Remark	Source
M_w	**588.57**	g mol^{-1}				[62]
S_w	**58.7**	mg L^{-1}	**25**		K_{ow} method	[62]
	159.94	mg L^{-1}			fragment method	[62]
	200	mg L^{-1}			no reporting of source, type of determination, temperature, pH, etc.	[70]
P_v	**0.0026**	Pa	**20**		experimentally determined; OECD 104	[85, 86]
	2.30E-17	Pa	25		subcooled liquid VP	[62]
pK_a	**9.8**					[70]
	9.33				Ø-OH → Ø-O-	[63]
log K_{ow}	0.6				no source or method reported	
	0.03				ClogP	[64]
	0.60				MlogP and experimental database match in EpiSuite 4.11	[62, 64]
	0.04				KOWWIN	[62]
K_{oc}	199.1	L kg^{-1}			MCI method; QSAR	[62]
K_{oc}	1.927	L kg^{-1}			K_{ow} method; QSAR	[62]

Table 39. Etoposide: data on removal in WWTP related systems.

Study type	Parameter	Result	Unit	Remark	Source
Batch reactor (2 d)	DT50	0.06	d	2 d incubation in primary effluent; ~1 g TSS/L, aerated; 16 cytostatics in mixture each at 50 µg/L	[70]
Batch reactor (10 d)	DT50	1.20	d	5 times a 2 d cycle; one cycle = fill-react-settle-decant-fill; with: primary effluent; ~1 g TSS/L, aerated; 16 cytostatics in mixture each at 50 µg/L	[70]
OECD 303A	elimination rate	36	%	plateau reached after 11 days; test concentration 0.5 mg /L; 95% CI:28-45%	[86]
OECD 303A	elimination rate	29	%	plateau reached after 9 days; test concentration 1.5 mg /L; 95% CI:22-35%	[86]
stability	%left after 1 d	98	%	stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7; 4°C	[71]
stability	%left after 3 d	75	%	stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7; 4°C	[71]
stability	%left after 1 d	55	%	stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7; 25°C	[70]
hydrolysis	DT50	1.20	d	dark; 22°C. pH not reported	[70]
photolysis	DT50	0.44	d	290-400 nm; simulated sunlight	[70]
QSAR Biowin 1		0.2677		not ready	[62]
QSAR Biowin 3		2.0730		not ready	[62]
QSAR Biowin 5		0.6515		ready	[62]
QSAR Biowin 7		NO		not ready	[62]

5-Fluorouracil



CAS nr. 51-21-8
SMILES: C1=C(C(=O)NC(=O)N1)F

Conclusions for SimpleTreat simulations based on collected data.

- the molecule is predominantly neutral below pK_a 1 (~pH 8), charged 1- between pKa_1 and pK_{a2} (~pH 13) and 2- above pH 13. Select SimpleTreat QSAR 'acid' with pK_a 8.02.
- A reliable, experimentally determined K_{oc} is not available. The value of >4786 L/kg reported by Fürhacker et al. [81] is very high and unexplained. The molecule is not hydrophobic, has no positively charged (nitrogen) atoms and is therefore not expected to sorb to a high extent. Since only water phase concentrations were measured in this test, the results are likely caused by the concentration dependent degradation of 5-fluorouracil; see discussion in the next indent. The few other studies investigating adsorption in waste water or activated sludge [77, 99] confirm this picture. Low adsorption was also confirmed in a sediment-water simulation study (OECD 308), cited by Straub [14] (Mamouni, 2005).
  For SimpleTreat simulations, the K_{oc} QSAR for monovalent acids is used with the selected K_{ow} of 0.141 as input.
- The biodegradation of 5-fluorouracil shows contrasting results, which are likely caused by concentration dependency. At high concentrations, the substance does not degrade and is not readily and not inherently biodegradable, as shown by data from Gröner, as cited in [14] and [90, 94]. Test concentrations ranged from 4.5 to 854 mg/L in these studies. In stability tests in filtered, raw waste water, 5-fluorouracil (1 mg/L) is also stable for up to at least nine days [71]. In an inherent type test with drinking water and activated sludge complete mineralisation was observed (0.4 and 11 mg FU/L) (Mamouni, cited in[14]). In WWTP simulation studies (OECD 303), resulting plateau elimination rates were 38, 92 and 100%. Concentration dependency was investigated by Kosjek et al. [69] (data in Supplementary information) in batch studies with activated sludge, showing an increase in removal half life with increasing FU concentration and with decreasing activated sludge concentration. Half life values ranged from 5 to 28 h, corresponding with removal rate constants for of 0.025 to 0.14 h^{-1}. An additional finding is a half life of approximately 2.5 d (k=0.012 h^{-1}) for removal of 5 µg FU/L from activated sludge [99]. Based on a limited search, concentration measurements of FU range roughly from 2-500 µg/L in waste water

samples from oncology departments and from 0.08-122 µg/L in hospital waste waters [81, 99, 100]. WWTP influent concentrations will be lower due to dilution with waste water from other sources. Kosjek et al. [69] reports 4.7 to 92 ng/L in WWTP influent.
Note that the rate constants given above are not fully corresponding with the standardised, built-in half life values in SimpleTreat, as these apply to full degradation as measured in the standardised ready and inherent tests. Hence, even the highest observed removal rate constant (0.14 h^{-1}) for removal is likely optimistic as input value for biodegradability. However, the observed elimination rates in the OECD 303A studies give an indication. Using the selection hierarchy described in Struijs [95], an elimination rate of 50% corresponds with a rate constant of 0.1 h^{-1}. Assuming that elimination rates of near 100% will be reached more easily at low µg/L concentrations compared to the mg/L range tested in the 303A studies, it is assumed that 50% is a realistic, but conservative estimate.
For the SimpleTreat simulation we select 'Method 3: chemical is biodegradable in activated sludge simulation test (OECD 303A) with a rate constant of.1 h^{-1}.

Table 40. 5-fluorouracil: physico-chemical properties and data on environmental fate and behaviour.

Parameter	Value	Unit	T (°C)	pH	Remark	Source
M_w	**130.08**	g mol^{-1}				[62]
S_w	**1.11E+04**	mg L^{-1}	**22**		experimentally determined value	[62]
	2.59E+04	mg L^{-1}	25		K_{ow} method	[62]
	1.89E+04	mg L^{-1}			fragment method	[62]
P_v	**0.0014**	Pa	**20**		experimentally determined value; OECD 104	[85, 86]
	6.80E-03	Pa	25		subcooled liquid VP	[62]
pK_{a1}	**8.02**					[14]
	8.0±0.1					[98]
	8					[96]
	7.18					[63]
	7.5				pK_{a1}; 0 to 1-	[87]
pK_{a2}	9				pK_{a2}; 1- to 2-	[87]
	12.01					[63]
	13.0±0.1					[98]
	13					[96], [14], citing Clarke 2009
log D_{ow}	-1			7.4		[14]
log K_{ow}	-0.89				experimentally determined value	[62]
	-0.58				ClogP	[64]
	-0.85				MlogP	[64]
	-0.81				KOWWIN	[62]
	-0.69					[101]
K_d	insignificant				observation during OECD 302B; 3h	[94]
K_d	insignificant				no adsorption or decline in aqueous concentration observed during 24 h; batch adsorption study with municipial waste water; 8-18 g SS/L; 14C labelled FR at 5 and 500 µg/L	[99]
K_d	insignificant				no adsorption observed; 24 h; batch adsorption study with waste water; 237 mg/L DOC and 364 mg/L TOC; 14C labelled FR at 5 µg/L	[77]
%adsorption	2-5	%			activated sludge; batch set up; 24 h incubation; 5 µg 14C-FU/L; constant 2-5% of substance found in sludge; steady decrease in water phase; 25% $^{14}CO_2$ at end of test.	[99]
%adsorption	6.6	%			maximum percentage adsorbed to pond sediment in OECD 308 study	Mamouni et al.

Parameter	Value	Unit	T (°C)	pH	Remark	Source
						2005[b], cited in [14]
%adsorption	9	%			maximum percentage adsorbed to river sediment in OECD 308 study	Mamouni et al. 2005[b], cited in [14]
K_d	>4786	L kg^{-1}			activated sludge; batch adsorption study with determination of adsorption kinetics; analysis only in water phase; K_d value could not be determined (>); degradation is expected to play a role	[81]
K_{oc}	6.99	L kg^{-1}			MCI method; QSAR	[62]
K_{oc}	2.77	L kg^{-1}			Kow method; QSAR	[62]

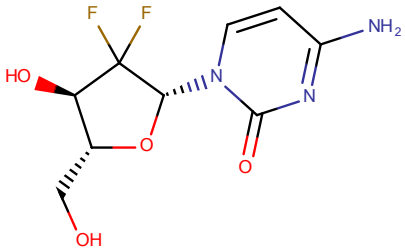
Table 41. 5-fluorouracil: data on removal in WWTP related systems.

Study type	Parameter	Result	Unit	Remark	Source
OECD 301F		not ready		no degradation; 21 days; 10 and 100 mg FU/L	Gröner 1983[a], cited in [14]
OECD 301D		not ready		0% after 28 and after 40 days; 20±1°C; 9.02 mg FU/L	[94]
OECD 301D		not ready		35-44% in 28 d; 4.5 mg/L FU	[90]
OECD 302B		not inherent		act. sludge from municipal WWTP; 2% after 28 d; 854 mg FU/L	[94]
OECD 302B		not inherent		hospital waste water effluent; 17% after 28 d; 175 mg FU/L	[94]
OECD 302B		not inherent		no degradation; 21 days; 812 mg FU/L; unadapted act. sludge	Gröner 1983[a], cited in [14]
OECD 302B		not inherent		no degradation; 21 days; 270 mg FU/L; pre-adapted act. sludge	Gröner 1983[a], cited in [14]
inherent test	CO_2 production	65-100	%	^{14}C-labelled; result obtained after 4 days; 0.2 and 11 mg FU/L in drinking water with 4 g AS/L	Mamouni et al. 2005[b], cited in [14]
inherent test	CO_2 production	97.5-100	%	^{14}C-labelled; result obtained after 14 days; 0.2 and 11 mg FU/L in drinking water with 4 g AS/L	Mamouni et al. 2005[b], cited in [14]
OECD 303A	elimination rate	38	%	elimination rate reaches maximally 38%; duration prolonged until 30 days; test concentration 2.5 mg /L	[86]
OECD 303A	elimination rate	92	%	elimination rate of 92% reached after 3 days; test concentration 10 mg /L	[86]
OECD 303A	elimination rate	100±4	%	plateau reached after 2 days, achieving a rate of 90-100%; 5 mg/L	[84]
biodegradation study	removal	50	%	after 50 d at 25°C; 1 µg/L; 1:10000 diluted act. sludge in medium	[102]
stability study	DT50 removal	2.5	d	activated sludge; batch set up; 24 h incubation; 5 µg ^{14}C-FU/L; steady decrease in water phase; 25% $^{14}CO_2$ at end of test	[99][c]
batch study	DT50	5	h	1 µg/L FU; 0.67 g act. sludge/L	[69]
batch study	DT50	8	h	1 mg/L FU; 0.67 g act sludge/L; 100% in 40 h	[69]
batch study	DT50	11	h	1 mg/L FU; 0.14 g act sludge/L; 100% in 48 h	[69]
batch study	DT50	16	h	1 mg/L FU; 0.014 g act sludge/L; 100% in 48 h	[69]
batch study	DT50	23	h	10 mg/L FU; 0.67 g act. sludge/L	[69]
batch study	DT50	28	h	20 mg/L FU; 0.67 g act. sludge/L	[69]
batch study	DT50	not degraded		100 mg/L FU; 0.67 g act. sludge/L	[69]
OECD 309	DT50 CO_2 production	9-10	d	OECD 309 study, natural river water; 20°C; dark; 0.019 and 11 mg FU/L	Mamouni et al. 2005[b], cited in

Study type	Parameter	Result	Unit	Remark	Source
					[14]
OECD 308	DT50system	~2	d	OECD 308 study; comparable results for water and pond system; resulting graph shown cited in Straub, 2010	Mamouni et al. 2005[b], cited in [14]
OECD 308	DT50 CO_2 production	~2	d	OECD 308 study; comparable results for water and pond system; resulting graph shown cited in Straub, 2010	Mamouni et al. 2005[b], cited in [14]
stability	%left	95	%	after 1 d; stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7; 4°C	[71]
stability	%left	90	%	after 3 d; stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7; 4°C	[71]
stability	%left	100	%	after 1-9 d; stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7; 25°C	[71]
stability	%left	<40	%	after 1 month; stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7; 25°C	[71]
QSAR Biowin 1		0.6856		ready	[62]
QSAR Biowin 3		2.9117		ready	[62]
QSAR Biowin 5		0.3487		not ready	[62]
QSAR Biowin 7		NO		not ready	[62]

[a] Internal communication within Roche company, cited in Straub [14].
[b] Original source could not be retrieved. SETAC poster, cited in Straub [14].
[c] The data published in this study are likely the same as in the study by Fürhacker et al. 2006 [81], which is cited in Straub [14], but could not be retrieved via the internet.

Gemcitabine



CAS nr. 95058-81-4
SMILES: Nc2ccn(C1OC(CO)C(O)C1(F)F)c(=O)n2

Conclusions for SimpleTreat simulations based on collected data.

- Molecule is fully neutral at pH 7; around pH 11, dissociation of the alkyl-OH group occurs. Select SimpleTreat QSAR: neutral.
- Log D_{ow} value at pH 5 and 7 are valid as log K_{ow} value, since molecule is neutral at those pH value. Log K_{ow} = 0.053 (K_{ow} 1.130) is used in SimpleTreat for K_{oc} estimation.
- The hydrolysis rate reported by Franquet-Griell et al. [70] does not correspond with the stability data reported by Negreira et al [71]. The substance is not readily and not inherently biodegradable in standardised tests[94, 103]. The potential for ultimate degradation is shown by Franquet-Griell et al. [70] after 10 d cyclic incubation in primary effluent. In the SimpleTreat simulation, the selection 'not biodegradable' is made.

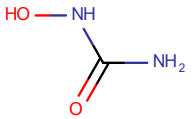
Table 42. Gemcitabine: physico-chemical properties and data on environmental fate and behaviour.

Parameter	Value	Unit	T (°C)	pH	Remark	Source
M_w	**263.2**	g mol^{-1}				[62]
S_w	5.13E+04	mg L^{-1}			source, temperature and method not reported	[70]
	5.19E+04	mg L^{-1}	25		K_{ow} method	[62]
	1.00E+06	mg L^{-1}	20		fragment method	[62]
P_v	**6.87E-06**	Pa	25		subcooled liquid VP	[62]
pK_a	-0.94				ring-NH+ → ring-N	[63]
	11.52				R-OH → R-O-	[63]
	3.6				source and method not reported; value deviates strongly from qsar estimate	[70]
log D_{ow}	0.053			5	FDA 3.02 study; log D_{ow}	[103]
	0.053			7	FDA 3.02 study; log D_{ow}	[103]
	0.052			9	FDA 3.02 study; log D_{ow}	[103]
log K_{ow}	-0.71				ClogP	[64]
	-2.01				KOWWIN	[62]
K_{oc}	10	L kg^{-1}			MCI method; QSAR	[62]
K_{oc}	0.0683	L kg^{-1}			K_{ow} method; QSAR	[62]

Table 43. Gemcitabine: data on removal in WWTP related systems.

Study type		Result	Unit	Remark	Source
FDA 3.11		**not ready**		70% of parent remained after 28 d	[103]
301D		not ready		42% after 28 d	[94]
302B		not inherent		45% after 4 d, 50% at test end (28 d)	[94]
DT50 biodegradation 5		0.0049	d	5 times a 2 d cyclic act. sludge incubation	[70]
hydrolysis	DT50	0.28	d	dark; 22°C. pH not reported	[70]
photolysis	DT50	0.012	d	290-400 nm; simulated sunlight	[70]
stability	%left	95	%	after 1 d; stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7; 4°C	[71]
stability	%left	80	%	after 3 d; stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7; 4°C	[71]
stability	%left	90	%	after 1 d; stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7; 25°C	[71]
stability	%left	68	%	after 3 d; stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7; 25°C	[71]
QSAR Biowin 1		0.4084		not ready	[62]
QSAR Biowin 3		2.7167		not ready	[62]
QSAR Biowin 5		0.4544		not ready	[62]
QSAR Biowin 7		NO		not ready	[62]

Hydroxycarbamide



CAS nr. 127-07-1
SMILES: NC(=O)NO

Conclusions for SimpleTreat simulations based on collected data.

- Molecule is predominantly neutral at pH 7, pK_a is 10.14 for proton release of R-OH group. Select SimpleTreat QSAR: acid with a pK_a value of 10.14.
- No experimentally determined adsorption coefficients are available. The SimpleTreat QSAR for acids is used with the selected log K_{ow} of -1.80 (K_{ow} 0.0158) as input.
- Based on a reported outcome as not readily biodegradable in a MSDS [104] and the borderline QSAR predictions, the SimpleTreat selection 'not biodegradable' is made.

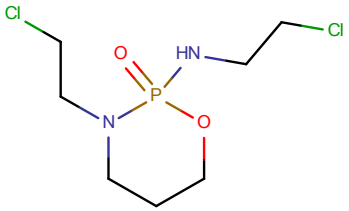
Table 44. Hydroxycarbamide: physico-chemical properties and data on environmental fate and behaviour.

Parameter	Value	Unit	T (°C)	pH	Remark	Source
M_w	**76.06**	g mol^{-1}				[62]
S_w	**2.24E+05**	mg L^{-1}	25		K_{ow} method	[62]
	1.00E+06	mg L^{-1}			fragment method	[62]
P_v	**5.85E-01**	Pa	25		subcooled liquid VP	[62]
pK_a	10.14				R-OH → R-O-	[63]
log K_{ow}	-1.80				ClogP	[64]
	-1.80				MlogP	[64]
	-1.68				KOWWIN	[62]
K_{oc}	6.11	L kg^{-1}			MCI method; QSAR	[62]
K_{oc}	0.830	L kg^{-1}			K_{ow} method; QSAR	[62]

Table 45. Hydroxycarbamide: data on removal in WWTP related systems.

Study type	Result	Unit	Remark	Source
study type not reported	not ready		ultimate aerobic biodegradation (28 days): 5 %. not readily biodegradable	[104]
QSAR Biowin 1	0.7113		ready	[62]
QSAR Biowin 3	3.0311		ready	[62]
QSAR Biowin 5	0.4859		not ready	[62]
QSAR Biowin 7	NO		not ready	[62]

Ifosfamide



CAS nr. 3778-73-2
SMILES: ClCCNP1(=O)OCCCN1CCCl

Conclusions for SimpleTreat simulations based on collected data.

- The molecule becomes predominantly neutral above pK_{a1} and becomes charged 1- around pK_{a2} and above. The SimpleTreat selection 'acid' is made with a pK_a value of 9.1.
- An experimentally determined adsorption constant of 62 L kg^{-1}is available, which is used in SimpleTreat.
- Multiple studies demonstrate that ifosfamide is not readily or inherently degradable and is not degraded in lab scale WWTP simulation set up. Stability and hydrolysis studies confirm these results. The results reported by Franquet-Griell et al [70] showing a rapid hydrolysis and relatively low DT50 in a cyclic activated sludge incubation are in contrast with these findings. The latter experiment however had a prolonged incubation time (10 d) allowing for adaptation. For the SimpleTreat simulation the option 'not biodegradable' is selected.

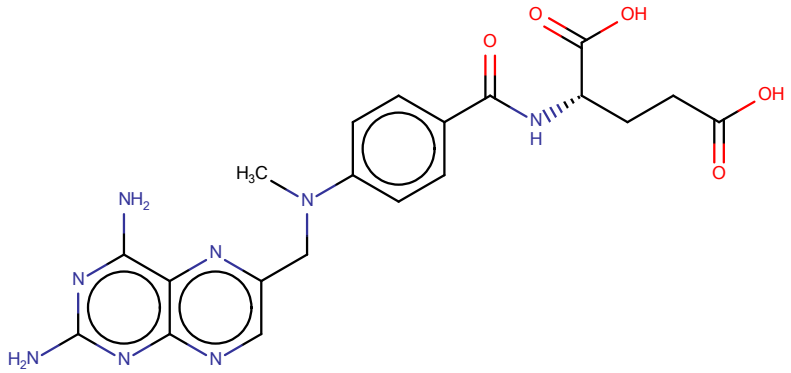
Table 46. Ifosfamide: physico-chemical properties and data on environmental fate and behaviour.

Parameter	Value	Unit	T (°C)	pH	Remark	Source
M_w	**261.09**	g mol^{-1}				[62]
S_w	**3781**	mg L^{-1}	**25**		K_{ow} method	[62]
	57921	mg L^{-1}			fragment method	[62]
P_v	**0.0145**	Pa	**25**		subcooled liquid VP	[62]
pK_a	4.75				not reported for which reaction; does not match with other values	[70]
pK_{a1}	<2.5 or 1.4					[87]
pK_{a2}	9.1				for R-NH-R → R-N- -R. proton releasing reaction of NH	[87]
pK_{a2}	14.64					[63]
log K_{ow}	0.92				ClogP	[64]
log K_{ow}	0.86				MlogP; the same experimental determined value is cited by EPISuite	[62, 64]
log K_{ow}	0.97				KOWWIN	[62]
K_{oc}	**62**	L kg^{-1}			primary sludge; f_{oc} = 0.35; 62±40	[88]
K_{oc}	4.1	L kg^{-1}			secondary sludge; f_{oc} = 0.34; 4.1±1.2	[88]
K_{oc}	94.23	L kg^{-1}			MCI method; QSAR	[62]
K_{oc}	27.46	L kg^{-1}			K_{ow} method; QSAR	[62]

Table 47. Ifosfamide: data on removal in WWTP related systems.

Study type		Result	Unit	Remark	Source
OECD 301D		not ready		no degradation after 28 and 57 days	[89]
OECD 302 B		not inherent			[105]
lab scale WWTP		not degradable			[92]
activated sludge		no degradation		24 h incubation in undiluted act. sludge; 0.120 µg parent/L	[93]
batch reactor (10 d)	DT50	0.32	d	5 times a 2 d cycle; one cycle = fill-react-settle-decant-fill; with: primary effluent; ~1 g TSS/L, aerated; 16 cytostatics in mixture each at 50 µg/L	[70]
stability	% left after 1 d	95	%	after 1 d; stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7; 4°C	[71]
stability	% left after 3 mo	90	%	after 3 months; stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7; 4°C	[71]
stability	% left	95	%	after 1 d; stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7; 25°C	[71]
stability	% left	100	%	after 3 months; stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7; 25°C	[71]
hydrolysis	DT50	1.20	d	dark; 22°C. pH not reported	[70]
hydrolysis		negligible		10% in 94 d at 25C; pH 7	[106]
hydrolysis	DT50	12.4	d	50°C	[106]
photolysis	DT50	0.69	d	290-400 nm; simulated sunlight	[70]
QSAR Biowin 1		0.4005		not ready	[62]
QSAR Biowin 3		2.2758		not ready	[62]
QSAR Biowin 5		0.1944		not ready	[62]
QSAR Biowin 7		NO		not ready	[62]

Methotrexate



CAS nr. 59-05-2
SMILES: CN(Cc2cnc1nc(N)nc(N)c1n2)c3ccc(cc3)C(=O)NC(CCC(O)=O)C(O)=O

Conclusions for SimpleTreat simulations based on collected data.

- Dissociation behaviour. The molecule has 7 species, the neutral form occurs for maximally ~40% around pH 3. Around pH 7, the 2- form is dominant for ~99%. The pK_a values for the two carboxyl groups giving rise to the 2- form are around 3 - 3.34 and 4 - 4.7.
  The SimpleTreat QSAR 'acid' with pK_a 3.25 is selected.
- Experimentally determined K_{oc} values are not available. The selected log K_{ow} of -1.85 (K_{ow} 0.0141) is used.
- Methotrexate does not fulfil the criteria for ready biodegradability in two standard tests (301D and 301F), although it is noted that 44% degradation was observed in the 301D test. Various other sources indicate that methotrexate is degraded in activated sludge, although the rate differs depending on the conditions. Negreira et al. [71] showed short term stability in filtered, raw waste water at pH 7 at both 4°C and 25°C. Three WWTP simulation tests (OECD 303A) showed a ~90-100% elimination rate after a 4 to 8 day lag phase [84, 86]. Kosjek et al. [107] showed rapid degradation in diluted activated sludge, although the concentration suspended solids was higher than required for a standardised OECD 301 test. With the information of a ~90-100% elimination rate from the OECD 303A tests, 44% degradation in a 301 test and the hierarchy for selection of SimpleTreat rate constants described by Struijs [95] a rate constant of 1 h^{-1} (at 293 K) is selected using 'Method 3' (tab 'Biodegradation') in the SimpleTreat simulation.

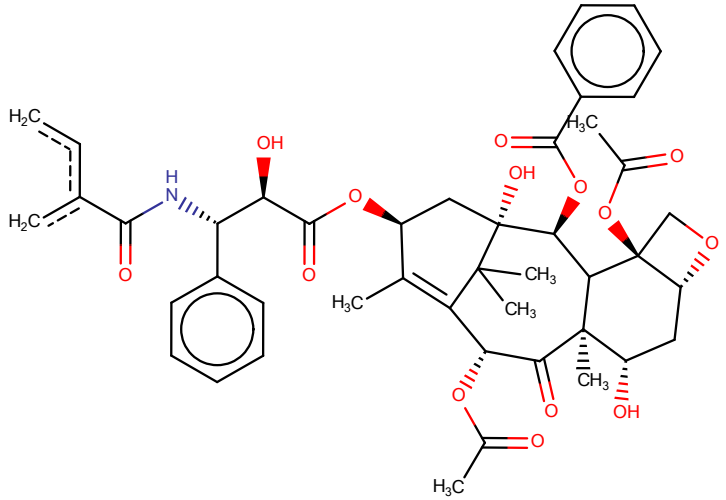
Table 48. Methotrexate: physico-chemical properties and data on environmental fate and behaviour.

Parameter	Value	Unit	T (°C)	pH	Remark	Source
M_w	**454.45**	g mol^{-1}				[62]
S_w	**2600**	mg L^{-1}	**25**		K_{ow} method	[62]
	800.81	mg L^{-1}			fragment method	[62]
P_v	**1.23E-13**	Pa	**25**		subcooled liquid VP	[62]
pK_{a1}	2.9				from 1+ to neutral	[87]
pK_{a1}	3.25				3.04-3.36; proton release from carboxyl group	[63, 98]
pK_{a1}	3.30				experimental value; multiplexed capillary electrophoresis method	[108]
pK_{a1}	4				3.12-4.7; proton release from carboxyl group	[63, 98]
pK_{a1}	3.8				pK_{a1} acid	[96]
pK_{a2}	4.6				pK_{a2} from neutral to 1-	[87]
pK_{a2}	4.7					[64]
pK_{a2}	4.8				p$K_{a\ 2}$ acid	[96]
pK_{a3}	5.71				N+ → N	[98]
pK_{a3}	5.6				pK_{a3} (base)	[96]
pK_{a3}	6.6				pK_{a3} from 1- to 2-	[87]
log K_{ow}	**-1.85**				experimentally determined	[62]
	-0.53				ClogP	[64]
	-1.28				KOWWIN	[62]
K_{oc}	1468	L kg^{-1}			MCI method; QSAR	[62]
K_{oc}	0.4102	L kg^{-1}			K_{ow} method; QSAR	[62]

Table 49. Methotrexate: data on removal in WWTP related systems.

Study type	Parameter	Result	Unit	Remark	Source
OECD 301D		not ready		44±3%	[109]
OECD 301F		not ready			[110]
batch test/activated sludge		biodegradable		1 mg/L; fully degraded with 1 to 3 days in 1:8 or 1:40 diluted activated sludge in mineral medium with or without nutrients; 330 - 1400 mg d.w. SS/L	[107]
OECD 303A	elimination rate	87	%	plateau reached in 8 days; test concentration 0.5 mg/L; 95% CI:75-100%	[86]
OECD 303A	elimination rate	90	%	plateau reached in 8 days; test concentration 20 mg/L; 95% CI: 82-100%	[86]
OECD 303A	elimination rate	98±6	%	10 and 20 mg/L; 4 d lag phase	[84]
stability	% left after 1 d	95-110	%	stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7, 4°C	[71]
stability	% left after 1 mo	95-110	%	stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7, 4°C	[71]
stability	% left after 1-9 d	100	%	stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7, 25°C	[71]
stability	% left after 3 mo	0	%	stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7, 25°C	[71]
stability	% left after 7 d	0	%	stability tested in deionised water; 1 mg/L; room temperature, pH not reported	[107]
QSAR Biowin 1		0.2140		not ready	[62]
QSAR Biowin 3		2.3452		not ready	[62]
QSAR Biowin 5		-0.5171		not ready	[62]
QSAR Biowin 7		NO		not ready	[62]

Paclitaxel (taxol)



CAS nr. 33069-62-4
SMILES:
CC(=O)OC6C(=O)C2(C)C(O)CC1OCC1(OC(C)=O)C2C(OC(=O)c3ccccc3)C7(O)CC(OC(=O)C(O)C(NC(=O)c4ccccc4)c5ccccc5)C(=C6C7(C)C)C

Conclusions for SimpleTreat simulations based on collected data.

- Paclitaxel has 6 pK_a QSAR predicted values [63] of which one at -1.18 and five from pH 11 and higher. The molecule is 98-100% neutral until pH 10, from which very weak acidic groups start to dissociate. The SimpleTreat QSAR 'neutral' is selected.
- Little information on adsorption to waste water sludge is available. Based on the selected log K_{ow} of 3.5 (K_{ow} 3162), the SimpleTreat predicted K_{oc} value is 861 L kg^{-1}, which is in same range as the K_{oc} reported for a silty soil in the Bristol-Myers Squibb MSDS of 717-1220 L kg^{-1} [111]. The SimpleTreat value is used for the simulation.
- The outcome that paclitaxel is readily biodegradable [111] is in accordance with the stability tests reported by Negreira et al. [71], although the amount of information on biodegradability and the Bristol-MSQ 'ready' endpoint is very limited. In SimpleTreat, the option 'ready biodegradable, fulfilling the 10 day window' is selected.

Table 50. Paclitaxel: physico-chemical properties and data on environmental fate and behaviour.

Parameter	Value	Unit	T (°C)	pH	Remark	Source
M_w	**853.93**	g mol^{-1}				[62]
S_w	2.50E-01	mg L^{-1}		5	experimental value, method and temperature not reported	[111]
	2.50E-01	mg L^{-1}		9	experimental value, method and temperature not reported	[111]
	0.004847	mg L^{-1}	25		K_{ow} method	[62]
	1.74E+00	mg L^{-1}	20		fragment method	[62]
P_v	**1.51E-26**	Pa	25		subcooled liquid VP	[62]
pK_a	see text					[63]
log D_{ow}	3.95				predicted', no further details reported	[112]
log K_{ow}	**3.5**			5, 7, 9	probably not a slow stirring study (OECD 123), values may be underestimate of true log *P*	[111]
	3.31				OECD 107, no further details reported	[113]
	4.73				ClogP	[64]
	3.31				KOWWIN	[62]
K_{oc}	6.48E+06	L kg^{-1}			MCI method; QSAR	[62]
K_{oc}	45.27	L kg^{-1}			K_{ow} method; QSAR	[62]

Table 51. Paclitaxel: data on removal in WWTP related systems.

Study type	Parameter	Result	Unit	Remark	Source
ready test		ready		ready biodegradability test; no study details reported in MSDS	[111]
stability	% left after 1 d	85	%	stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7, 4°C	[71]
stability	% left after 3 d	80	%	stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7, 4°C	[71]
stability	% left after 3 mo	25	%	stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7, 4°C	[71]
stability	% left after 1 d	50	%	stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7, 25°C	[71]
stability	% left after 3-9 d	25-35	%	stability in 0.45 µm filtered raw waste water; 1 mg/L; pH 7, 25°C	[71]
hydrolysis	DT50	65.6	d	pH 5	[111]
hydrolysis	DT50	18.6	d	pH 7	[111]
hydrolysis	DT50	13.9	d	pH 9	[111]
QSAR Biowin 1		0.8734		ready	[62]
QSAR Biowin 3		1.3251		not ready	[62]
QSAR Biowin 5		0.5844		not ready	[62]
QSAR Biowin 7		NO		not ready	[62]

Annex 2 SimpleTreat 4.0 settings

SimpleTreat version 4.0.9 was used for WWTP simulations using the 'municipal' facility setting. The selected operational parameters are shown in Table 52.

Table 52. Operation mode settings in SimpleTreat.

Parameter	Symbol	Value	Unit
include primary solids removal		yes	
waste water flow	*Q*	0.2	m^3 PE^{-1} d^{-1}
mass of waste water solids	SO	0.09	kg PE^{-1} d^{-1}
mass of O_2 binding material in waste water	BOD	60	g O_2 PE^{-1} d^{-1}
fraction of BOD in waste water solids	FB	0.5417	-
fraction of solids removed by primary sedimentation	FS	0.67	-
sludge loading rate	k_{SLR}	0.1	kg O_2 kg^{-1} d^{-1}
pH		7	-
concentration suspended solids in effluent	$C_{CO, SLS}$	0.0075	kg m^{-3}
aeration mode	*M*	surface (s)	-

Settings for the Emission scenario used SimpleTreat 4.0.9 are shown in Table 53.

Table 53. Emission scenario settings used in SimpleTreat.

Parameter	Symbol	Value	Unit
temperature environment (water/air) of WWTP		288.15	K
wind speed	*WS*	3	m s^{-1}
number of inhabitants	*N*	10000	persons
emission rate chemical	$Elocal_{water}$	1	kg d^{-1}

Annex 3 Collected data on measured WWTP effluent/influent concentrations

Table 54. Measured effluent/influent of selected cytostatics in European WWTPs.

Substance		effluent/ influent	Country	Note	Reference
capecitabine		0.16	ES		[114]
capecitabine		0.0047	SI	1	[115]
capecitabine	<	LOD	ES	2	[115]
capecitabine		0.42	ES	3	[116]
capecitabine		0.35	JAP	4	[117]
carboplatin		0.28	AT	5	[72]
carboplatin		0.40	IR	6	[118]
cisplatin	<	LOD	NL	7	[1]
cisplatin		0.12		8	[7]
cisplatin		0.46	IR	9	[118]
cyclophosphamide		1.13	SE		[114]
cyclophosphamide	<	LOD	SE	10	[119]
cyclophosphamide	<	LOD	SE	11	[120]
cyclophosphamide		0.82	CH	12	[93]
cyclophosphamide		0.89	SI	13	[115]
cyclophosphamide		1.03	CAN	14	[121]
cyclophosphamide		0.98	ES	15	[61]
cyclophosphamide		0.90	ES	16	[71]
cyclophosphamide	<	LOD	NL	17	[1]
cyclophosphamide		1.13	JAP	18	[117]
cytarabine		1.52	ES	19	[119]
cytarabine		0.43	ES	20	[120]
cytarabine		1.29	NL	21	[1]
etoposide		0.23	ES	22	[119]
etoposide	<	0.10	ES	23	[120]
etoposide	<	LOD	ES	24	[61]
etoposide	<	LOD	ES & SI	25	[115]
etoposide	<	LOD	NL	26	[1]
5-fluorouracil	<	LOD	SE	27	[119]
5-fluorouracil	<	LOD	SE	28	[120]
5-fluorouracil	<	0.14	SE	29	[115]
5-fluorouracil	<	LOD	SI	30	[115]
gemcitabine		0.75	ES	31	[119]
gemcitabine		1.7	SE	32	[120]
gemcitabine	<	LOD	SE	33	[115]
gemcitabine	<	LOD	SI	34	[115]
gemcitabine	<	LOD	CAN	35	[121]

Substance		effluent/ influent	Country	Note	Reference
ifosfamide		0.34	ES	36	[119]
ifosfamide		0.85	ES	37	[120]
ifosfamide		0.68	ES	38	[71]
ifosfamide	<	LOD	CAN	39	[121]
ifosfamide	<	LOD	ES	40	[61]
ifosfamide		0.71	NL	41	[1]
ifosfamide		1.09	GE	42	[105]
ifosfamide		1.05	GE	43	[105]
ifosfamide		1.21	CH	44	[93]
methotrexate	<	0.017	SI	45	[115]
methotrexate	<	0.060	ES	46	[115]
methotrexate	<	LOD	ES	47	[119]
methotrexate	<	0.0037	ES	48	[120]
methotrexate		0.88	CAN	49	[121]
methotrexate	<	LOD	NL	50	[1]
methotrexate	<	LOD	ES	51	[71]

Notes

1. 0.5 ng/L; effluent set as LOD.
2. 0.5 ng/L.
3. Mean of effluent and influent concentration in 10 WWTPs; WWTPs with non detects excluded from mean.
4. Ratio of mean of effluent and influent concentration measurements of 4 sampling moments; 1 WWTP.
5. Range 59-85% removal from 5 activated sludges after 24 h incubation; mean 27% removal in waste water treatment.
6. Ratio of mean of 12 influent concentrations in 12 WWTPs and 3 effluent concentrations in 7 WWTPs (in 4 WWTPs <LOQ = 43 ng/L).
7. LOD 20 ng/L.
8. Fraction removal 0.88.
9. Ratio of mean of 12 influent concentrations in 12 WWTPs and 3 effluent concentrations in 7 WWTPs (in 4 WWTPs <LOQ = 56 ng/L).
10. LOD 2.1-2.3 ng/L; below LOD in influent and effluent; 1 WWTP.
11. LOD 2.2 ng/L; mean influent and effluent data for 48 samples (24 h composites) from 4 WWTPs; treatments in the studied WWTPs involve pre treatment, primary (settling) and secondary (activated sludge) treatments.
12. Mean of 4 WWTPs.
13. LOD 2.3 ng/L.
14. Mean of one WWTP sampled at two occasions; in two other WWTPs all influent and effluent measurements were <LOD of 4 ng/L.
15. Average over 3 months (1 WWTP).
16. Mean of effluent and influent concentration in 7 WWTPs; WWTPs with non detects excluded from mean.
17. LOD 10 ng/L.
18. Ratio of mean of effluent and influent concentration measurements of 4 sampling moments; 1 WWTP.
19. Ratio of mean concentration from 24 h composite samples from influent and effluent; 1 WWTP; LOD 1.5 ng/L.
20. LOD 1.47 ng/L; ratio of mean influent and effluent concentration for 48 samples (24 h composites) from 4 WWTPs; cytarabine detected

in all 48 samples; treatments in the studied WWTPs involve pre treatment, primary (settling) and secondary (activated sludge) treatments.
21. LOD 10 ng/L; ratio of substance concentration on passive samplers exposed 1.5 week in WWTP influent and effluent.
22. Ratio of mean concentration from 24 h composite samples from influent and effluent; 1 WWTP; LOD 3-3.4 ng/L.
23. LOD 2.95 ng/L; LOD used as effluent value; etoposide was not detected in any of the effluent samples: 48 samples (24 h composites) from 4 WWTPs; treatments in the studied WWTPs involve pre treatment, primary (settling) and secondary (activated sludge) treatments.
24. LOD 26 ng/L; average over 3 months (1 WWTP).
25. LOD 16.5 ng/L.
26. LOD 10 ng/L.
27. LOD 21-38 ng/L; below LOD in influent and effluent; 1 WWTP.
28. LOD 29.5 ng/L; 5-fluorouracil was not detected in any of the influent and effluent samples: 48 samples (24 h composites) from 4 WWTPs; treatments in the studied WWTPs involve pre treatment, primary (settling) and secondary (activated sludge) treatments.
29. LOD 0.5 ng/L; Calculated with effluent value set as LOD; mechanical and conventional biological treatment with suspended biomass. WWTP designed for 1,700,000 PE; average load/inflow of 234,000 m^3 d^{-1}. Sludge retention time 15-20 d, HRT is 8-12 h; average biomass concentration in the biological tank is 3.5-4.0 g L^{-1}.
30. LOD 0.5 ng/L; Mechanical and conventional and biological treatment with suspended biomass. The waste water treatment plant is designed for 360,000 population equivalents (PE) with an average load/inflow of 80,000 m^3 waste water entering the WWTP per day. The sludge retention time is 7 days, while the hydraulic retention time is 21 h. The average biomass concentration in the biological tank is 3.2 g/L
31. Ratio of mean concentration from 24 h composite samples from influent and effluent; 1 WWTP; LOD 1.4- 2.6 ng/L.
32. LOD 2 ng/L; mean influent and effluent data for 4 samples (24 h composites) in which gemcitabine was detected; treatments in the studied WWTPs involve pre treatment, primary (settling) and secondary (activated sludge) treatments.
33. LOD 0.7 ng/L.
34. LOD 0.7 ng/L.
35. LOD 20 ng/L; substance not detected in 3 WWTPs in neither influent nor effluent.
36. ratio of mean concentration from 24 h composite samples from influent and effluent; 1 WWTP; LOD 1.1- 1.7 ng/L.
37. LOD 1.43 ng/L; ratio of mean influent and effluent concentration for 6 samples (24 h composites); ifosfamide detected in 6 out of 48 samples; treatments in the studied WWTPs involve pre treatment, primary (settling) and secondary (activated sludge) treatments.
38. Mean of effluent and influent concentration in 5 WWTPs; 2 WWTPs with ratio's of 3.5 and 4.7 and WWTPs with non detects excluded
39. LOD 4 ng/L; substance not detected in 3 WWTPs in neither influent nor effluent.
40. LOD 1.35 ng/L.
41. LOD 10 ng/L.

42. LOD 6 ng/L; result calculated as ratio of the median of 6 effluent and influent measurements on the same day in 1 WWTP.
43. LOD 6 ng/L; result calculated as ratio of the median of 6 effluent and influent measurements on the same day in 1 WWTP.
44. Mean of 2 WWTPs.
45. LOD 0,5 ng/L; Calculated with effluent set as LOD.
46. LOD 0,5 ng/L; Calculated with effluent set as LOD.
47. LOD 0.1 ng/L; below LOD in influent and effluent; 1 WWTP.
48. LOD 0,08 ng/L; LOD used as effluent value; methotrexate was not detected in any of the effluent samples; detected 8 (of 48) samples (24 h composites) from 4 WWTPs; treatments in the studied WWTPs involve pre treatment, primary (settling) and secondary (activated sludge) treatments.
49. One WWTP; in two other WWTPs concentrations were >LOD 12 ng/L, but <LOQ.
50. LOD 10 ng/L.
51. Not detected in effluent from 12 WWTPs; LOD 0.2-1.6 ng/L.

Annex 4. Calculation of predicted environmental concentrations

The relevant environmental concentration (PEC) is calculated for a point in the receiving water close to[16] the discharge location of a WWTP. To this end, the concentration of a given cytostatic substance in the influent of a WWTP should be known or calculated.

The total use data in weight (kg) per year of the selected cytostatics in four hospitals are used as point of departure for the calculations. It was agreed to the hospital pharmacies to treat their data confidential, therefore these hospitals are named 1, 2, 3 and 4. Two of these were large academic hospitals and two were 'general' hospitals. No further specification will be given in the report.

The data collected in this study do not allow for an easy and direct translation to substance concentrations in the environment. There is no distinction in the data between the amount administered to patients within the hospital and the amount given by the pharmacy for outpatient treatment. Ambulatory patients will emit the majority of their cytostatic treatment at home. It is unknown where patients live and hence, to which WWTP they will ultimately emit. As nearly all hospitals serve a wider region, a large proportion of patients will not live in the city or village where the hospital is located. Stated otherwise, it is unknown which fraction of the patients will emit to the same WWTP as the hospital.

Two calculation methods were used.

Method 1
The first method results in a worst case type PEC estimate: assume that the total amount of substance given out by one hospital is emitted through the WWTP to which this hospital is connected. Some of the limitations of this method are described in the previous section. As part of the substances will be administered and emitted in other locations, this is a worst case estimate. Another limitation is that 3 of the locations of our hospitals are cities in which there is more than one hospital with an oncology department. For these locations, we can therefore only estimate the worst case contribution of one hospital to the specific WWTP. In addition, there is one location (city) with one hospital which is connected to the WWTP of that city. This method could only be done for hospitals nr. 1, 3 and 4. The situation for hospital 2 was too complex (more hospitals with oncology and more that 1 WWTP) to model.

The following calculation steps were employed in method 1.

The PEC_{SW} is estimated using equation 1:

[16] this point should in principle be at the point of complete mixing, this was however not validated for this study.

$$PEC_{\mathrm{SW}} = \frac{Q \cdot F_{excr} \cdot F\mathrm{emitted}_{\mathrm{WWTP}}}{EFFLUENT_{\mathrm{WWTP}} \cdot DILUTION} \quad (1)$$

For the WWTP it is assumed that $EFFLUENT_{\mathrm{WWTP}} = INFLUENT_{\mathrm{WWTP}}$. The dilution factor is calculated using equation 2:

$$DILUTION = \frac{EFFLUENT_{\mathrm{WWTP}} + FLOW}{EFFLUENT_{\mathrm{WWTP}}} \quad (2)$$

Parameter	Description	Unit
DILUTION	dilution factor of effluent in receiving water	[-]
$EFFLUENT_{\mathrm{WWTP}}$	effluent discharge rate of WWTP	[$m^3\ d^{-1}$]
$F\mathrm{emitted}_{\mathrm{WWTP}}$	mass fraction of substance emitted by WWTP	[-]
$INFLUENT_{\mathrm{WWTP}}$	effluent discharge rate of WWTP	[$m^3\ d^{-1}$]
F_{excreted}	average mass fraction of substance emitted unchanged by patient	[-]
FLOW	flow rate of the receiving water	[$m^3\ d^{-1}$]
Q	daily substance mass emitted to sewer	[mg d^{-1}]
PEC_{sw}	predicted environmental concentration in surface water	[mg m^{-3} = µg L^{-1}]

- The amount of substance given out in one hospital is known, in mg $year^{-1}$, which is converted to mg d^{-1} by dividing by 365. This parameter is called Q.
- F_{excreted} and $F_{\mathrm{emittedWWTP}}$ are derived within this study and are reported in Table 3 and Table 8, respectively.
- Effluent rates in $m^3\ y^{-1}$ of all (341) Dutch WWTPs were kindly received from Statistics Netherlands (CBS). For method 1 we used the effluent rate for 2016 for the specific WWTP to which hospital 1, 3 and 4 were connected. The connection of these hospitals to the specific WWTP was confirmed by checking with the local responsible district water board (Waterschap).
- To employ equation nr. 2, the flow rate of the receiving water (*FLOW*) should be known. We used a yearly mean flow rate for the specific (known) receiving waters of the three WWTPs connected to hospital 1, 3 and 4. These flow rates were calculated by Deltares using the Dutch nationwide Sobek model (LSM 1.2). This model is a 1D schematised hydrodynamic surface water model of the main waterways in the Netherlands. It has a typical spatial resolution of 500 m and consists of about 21,000 calculation points, the computational time step is 10 min and it allows for computation of a whole year at national scale. The model calculated discharges, water levels and depths. See Prinsen and Becker [122] and Prinsen et al. [123] for more detailed information. We used flow rates computed for 1967, a year which had been selected in previous projects as average with respect to Dutch river water discharge. For each WWTP discharge location a daily flow rate was modelled (for the entire year) from which the arithmetic mean was calculated.

Table 55. Method 1. Local PEC for selected cytostatics, for hospital nr. 1.

Substance	*PEC no metabolism* [ng L^{-1}]	*PEC incl metabolism* [ng L^{-1}]
Capecitabine	4.1	0.12
Carboplatin	0.043	0.014
cisplatin	0.00091	0.00021
cyclophosphamide	0.13	0.032
cytarabine	0.067	0.0067
etoposide	0.011	0.0054
5-fluorouracil	0.052	0.010
sum 5-fluorouracil	0.062	0.021
gemcitabine	0.13	0.013
hydroxycarbamide	4.5	2.2
ifosfamide	0.0029	0.0015
methotrexate	0.0031	0.0028

Table 56. Method 1. Local PEC for selected cytostatics, for hospital nr. 3.

Substance	*PEC no metabolism* [ng L^{-1}]	*PEC incl metabolism* [ng L^{-1}]
capecitabine	94	2.8
carboplatin	0.12	0.037
cisplatin	0.0038	0.00086
cyclophosphamide	13	3.2
cytarabine	0.48	0.048
etoposide	0.36	0.18
5-fluorouracil	0.35	0.070
sum 5-fluorouracil	0.58	0.31
gemcitabine	0.40	0.040
hydroxycarbamide	133	67
ifosfamide	10	5.1
methotrexate	0.042	0.038

Table 57. Method 1. Local PEC for selected cytostatics, for hospital nr. 4.

Substance	*PEC no metabolism* [ng L^{-1}]	*PEC incl metabolism* [ng L^{-1}]
capecitabine	0.51	0.015
carboplatin	0.016	0.0050
cisplatin	0.0018	0.00040
cyclophosphamide	0.11	0.027
cytarabine	0.045	0.0045
etoposide	0.014	0.0068
5-fluorouracil	0.040	0.0081
sum 5-fluorouracil	0.042	0.0093
gemcitabine	0.064	0.0064
hydroxycarbamide	1.0	0.49
ifosfamide	0.10	0.050
methotrexate	0.012	0.011

Method 2
In the second method use data from 4 hospitals is extrapolated to all hospitals having an oncology department in the Netherlands. It is realised that there are potentially large uncertainties in this method too (as in method 1). As the academic hospitals may have a different cytostatic use pattern than the general hospitals, the cytostatic use in the 2 academic hospitals is summed and separately also for the 2 general hospitals. Total cytostatic use is estimated two scaling factors:

3. the ratio of the number of beds in all academic hospitals and the number of beds in the 2 academic hospitals for which we have data
4. the ratio of the number of beds in all non-academic hospitals with an oncology department and the number of beds in the 2 general hospitals for which we have data.

Assumptions made with this approach are:

- kg of substance used plus given out in a hospital is proportional to the number of patients served (in the region) by the hospital;
- the number of patients served by a hospital is proportional to the size of the hospital, which can be expressed as the number of beds of the entire hospital;
- the size of the oncology department of a hospital is proportional to the total number of beds of a hospital;
- the total number of beds of hospitals that have an oncology department is proportional to the total amount of substance used in the Netherlands.

We used a list of all hospitals in the Netherlands (2013) which included the number of beds and type of hospital (academic, general, top clinical, etc.). This list was checked for current existence of hospitals and appended by own research with an indication (Y/N) whether or not an oncology department exists for each of the hospitals.

The list contains 92 hospitals with a total of 45213 beds. For comparison, an independently reported value for the total number of beds in the Netherlands for 2013 is 45067 [124], indicating that our list is relatively robust.

The 2 academic hospitals for which we have cytostatic use data, have a total of 1995 beds, while all academic hospitals have 7996 beds, giving a scaling factor of 4.01.
The 2 general hospitals for which we have cytostatic use data, have a total of 2100 beds, all non academic hospitals with oncology departments have 34144 beds, giving a scaling factor of 16.26.

As stated, the amounts of cytostatics were summed for the 2 academic hospitals, and multiplied by the respective scaling factor. The same was done for with the data for the two general hospitals. These resulting amounts were again summed, resulting in one extrapolated amount per active substance for The Netherlands. The resulting amounts are shown inTable 58.

Table 58. Extrapolated quantities of cytostatic active substances used in The Netherlands.

Substance	mg y^{-1}	kg y^{-1}
capecitabine	2010181426	2010
carboplatin	13483332	13
cisplatin	1442661	1
cyclophosphamide	54030269	54
cytarabine	32671342	33
etoposide	5873938	6
5-fluorouracil	33136691	33
gemcitabine	35544205	36
hydroxycarbamide	1072220387	1072
ifosfamide	19147950	19
methotrexate	16069340	16
capecitabine+5-fluorouracil	2043318117	2043

PEC_{SW} was subsequently calculated using equation 2, albeit with different values for the parameters Q, $EFFLUENT_{WWTP}$ and *DILUTION*, as follows.

- Q was replaced by the total amount estimated for the Netherlands, for each active substance.
- For $EFFLUENT_{WWTP}$ the total summed effluent of all Dutch WWTPs was used, recalculated to a daily flow rate, which amounted to 5.219×10^6 m^3 d^{-1}.
- Since this method does not make use of a specific WWTP, two generalised dilution factors were chosen: a factor of 10 and a factor of 1. The dilution factor of 10 is used in several European regulatory risk assessment frameworks: REACH, Biocides (both ECHA) and human pharmaceuticals (EMA) as a realistic worst case estimate. It is however known that in periods of low discharge in smaller receiving waters, the majority, if not all, of the water flow may consist of effluent. A very low dilution factor applies to these situations, we choose a factor of 1 (no dilution) to mimic the worst case.

PEC values were calculated using $F_{excreted}$ as shown in Table 3 as well as with $F_{excreted} = 1$. The latter option is included since the ecotoxicity of metabolites is generally not known and their possible contribution to the overall toxicity of a substance is neglected when using $F_{excreted}$. Assuming that potential metabolites are equally toxic as the parent (unless more information is available) is an approach also followed within the environmental risk assessment of the European authorisation process of human pharmaceuticals. The implicit assumption is that all metabolites are equally toxic as the parent compound and assuming that the concept of additivity applies, their PEC/PNEC ratios can be summed. As capecitabine is a prodrug to 5-fluorouracil [14], we also calculated the sum of total 5-fluorouracil emission to surface water. This was done by adding the fraction of unchanged 5-fluorouracil excreted by patients administered capecitabine (0.54% [15]) to the fraction of unchanged 5-fluorouracil excreted by patients administered 5-fluorouracil. The distinction made by setting $F_{excreted}$ to 1 was applied only to the latter fraction.

Table 59 shows the calculated PECs in surface water for Method 2 for a dilution factor of 10 and 1 and with or without correction for excretion.

Table 59. Method 2: PECsw for selected cytostatics, based on the extrapolated total amounts used in the Netherlands (DIL = dilution factor in receiving water).

Substance	*DIL* 10 [ng L^{-1}]	*DIL* 10 F_{excr} = 1 [ng L^{-1}]	*DIL* 1 [ng L^{-1}]	*DIL* 1 F_{excr} = 1 [ng L^{-1}]
capecitabine	48	1.4	477	14
carboplatin	0.53	0.17	5.3	1.7
cisplatin	0.03	0.01	0.28	0.06
cyclophosphamide	2.8	0.69	28	6.9
cytarabine	0.98	0.10	9.8	0.98
etoposide	0.25	0.13	2.5	1.3
5-fluorouracil	1.0	0.20	10	2.0
sum 5-fluorouracil [a]	1.1	0.32	11	3.2
gemcitabine	1.9	0.19	19	1.9
hydroxycarbamide	56	28	562	281
ifosfamide	1.0	0.50	10.0	5.0
methotrexate	0.10	0.092	1.0	0.92

Annex 5. Data search for derivation of Predicted No Effect Concentrations.

Scientific peer reviewed literature was gathered by searching Scopus, Pubmed, Google Scholar and the EPA Ecotox database, as well as by retrospective searching. The reports of two EU FP7 projects, i.e. CytoThreat[4] and Pharmas[3] also served as sources of ecotoxicological data for several of the cytostatics. Data generated for regulatory purposes were obtained from European Public Assessment Reports (EPARs) that are available on the European Medical Agencies (EMAs) dissemination site for centralized procedures[17]; from PARs on the Dutch Medical Evaluation Board (CBG-MEB) site for decentralized, mutual recognition and national procedures[18]; from the Swedish medicines portal FASS.se; and from pharmaceutical company's websites and safety data sheets. Next to these searches the German Umweltbundesamt (UBA) was also contacted to verify the completeness of our search. The internal UBA environmental fate and effect database that contains non-public confidential endpoints, did not contain additional data (Dr. J. Bachmann, personal communication).

The most critical studies (with the most sensitive species) were assessed for reliability and scored as 'reliable', ' reliable with restrictions', 'unreliable', or 'unassignable' (scores Ri1, Ri2, Ri3, Ri4, respectively; see [22] and [23]). Only studies with scores Ri1 or Ri2 were used. In some cases a general assessment of reliability could easily be performed. Normally, according to the evaluation principles, when no information about test setup, performance and results are available, the study reliability cannot be assessed (Score Ri4) and these results cannot be used for risk assessment [23]; [24]. In the regulatory databases used here, no test details are reported and thus, these results would be not assignable. However, for the current indicative purpose, we considered the results from regulatory assessments as acceptable, as their reliability was assessed in a regulatory context using approved methodology.

EPARs and PARs are made available by EMA and CBG-MEB to disseminate endpoints regarding effectiveness and safety. EPARs were available for four of the eleven cytostatics, but only the EPAR for the product containing methotrexate as API contained environmental effect data for algae and daphnids (Table 60). The EPAR reported only acute toxicity because it is based on an earlier version of the current guideline (in place since 2006). The PARs found on the CBG-MEB site did not contain any environmental data. Overall, except for methotrexate, (E)PARs did not contribute to the collection of environmental effect data. The literature search yielded around 70 publically available reports and peer reviewed scientific papers that contained ecotoxicological data for the selected cytostatics. Furthermore, industry papers, e.g. [14],

[17] http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp&mid=

[18] https://www.geneesmiddeleninformatiebank.nl/nl/

provided endpoints of contract laboratory reports that were not available for a thorough assessment. If only endpoints were reported the data were considered unassignable and were not used (see above for details on reliability assessment). However, for the current indicative purpose, results were considered acceptable if a robust study summary was provided, that did allow verifying the quality without performing a full assessment. The data were assigned a reliability score of 2 (reliable with restrictions). It should be noted that during a formal annual average environmental quality standard (AA-EQS) or Predicted No Effect Concentration (PNEC) derivation such data would probably have been considered unassignable, as not all relevant details were available. Thus, as this report aims to get a grasps of the environmental risk of the selected cytostatics, and as for most of the substances ecotoxicological data are scarcely available, a less stringent approach was followed. The derived safe environmental concentrations in this report are to be considered indicative PNECs.

A complete overview of the gathered ecotoxicological data can be found in the attached excel files. When for a cytostatic both a NOEC (No Observed Effect Concentration) and an EC10 (concentration with 10% effect) are reported in the same study, the EC10 was considered more relevant, even if it was not the lowest value. For each cytostatic, the most critical reliable endpoints are tabulated in the next sections.

A number of authors report on studies with fish embryos during three to five days. These studies resemble the FET test (Fish Embryo Acute Toxicity test (OECD 236). The applicability of this study in regulatory frameworks as a replacement of the acute fish toxicity (AFT) test is still under discussion. Due to the indicative nature of the PNECs derived in the current report, the EC50 values from the FET data were used as acute toxicity data and NOEC values were used as chronic data. This is in accordance with the WFD guidance [24] where it is stated that a test may also be seen as a chronic test when one or more sensitive life stages are covered. In analogy, the WFD guidance considers the 96-hour Frog Embryo Teratogenesis Assay Xenopus (FETAX) test as a chronic test due to the endpoints (next to mortality also development and malformation) and the sensitive life stage (embryonic stages) assessed. Thus, endpoints from the fish embryo toxicity tests were taken up in acute data tables (LC50 values for mortality) as well as in chronic data tables (EC10/NOEC values for effects on hatching, development or malformations).

Table 60. Number of products registered per API and (E)PAR availability.

API	number and status of products		Environmental data in (E)PAR
	EMA	CBG-MEB	
Capecitabine	6 medicines with EPAR	34 products registered	not available
Carboplatin	-	7 products registered	not available
Cisplatin	3 medicine for rare diseases (orphan)	7 products registered	not available
Cyclophosphamide	1 paediatric investigation plan	9 products registered	not available
Cytarabine	1 medicine with EPAR; 2 paediatric investigation plans; 1 medicine for rare diseases (orphan); 1 withdrawn application	8 products registered	not available
Etoposide	1 medicine for rare diseases (orphan); 2 referrals	9 products registered	not available
5-fluorouracil	1 paediatric investigation plan; 1 medicine for rare diseases (orphan)	5 products registered	not available
Gemcitabine	1 medicine	43 products registered	not available
Hydroxycarbamide	1 medicine with EPAR; 1 medicine for rare diseases (orphan)	6 products registered	not available
Ifosfamide	1 medicine for rare diseases (orphan)	1 product registered	not available
Methotrexate	2 medicines with EPAR; 2 medicines for rare diseases (orphan)	123 products registered	acute ecotoxicity data for algae and daphnids

RIVM
Committed to *health and sustainability*