Grey Water Footprint of Amoxicillin Production

A study on the Grey Water Footprint of amoxicillin production for amoxicillin-based medicine sold for oral human use in the Netherlands.

M.C.J. (Max) de Vries
Bachelor Thesis Civil Engineering
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UNIVERSITY OF TWENTE.

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Assignment period:
April 22, 2020 – July 10, 2020

UNIVERSITY OF TWENTE.

Preface

This report is written as part of my bachelor research for the study Civil Engineering at the University of Twente. In this report the Grey Water Footprint (GWF) of amoxicillin production for amoxicillin-based medicine sold for oral human use in the Netherlands is calculated. The study contains the process of my research and my findings concerning the GWF of amoxicillin production.

During this research project I realised that Civil Engineering is much broader than I thought, since even the pharmaceutical industry has common ground with Civil Engineering. By doing research related to the pharmaceutical industry I realised even more that sustainable processes are of great importance to human health and that monitoring water quality standards is even more important than I thought beforehand. To my opinion this research project really emphasises the need to control water quality standards, both for human health concerns and environmental concerns in general.

Furthermore, I would like to thank everybody that helped me during my bachelor thesis project. Especially I want to thank my supervisor, Lara Wöhler. After my first bachelor thesis project to the Republic of South Africa was cancelled due to COVID-19, Lara helped me with finding a new thesis project. Afterwards she helped me during the entire research and I am very grateful for that.

For any questions regarding this research report, I am available via m.c.j.devries@student.utwente.nl

Max de Vries

Enschede, 10th July 2020

Abstract

Antibiotic production worldwide contributes heavily to water pollution and the increase of antibiotic resistance. One of the most consumed antibiotics worldwide is amoxicillin. To combat antibiotic resistance and water pollution in general, pollutant loads of pharmaceutical manufacturing sites should be reduced. One crucial step hereto is knowing about the severity of the pollution. This research therefore estimates the grey water footprint (GWF) of amoxicillin production of amoxicillin-based medicine sold for oral human use in the Netherlands. This GWF is an indicator of freshwater pollution which is linked to the production process of amoxicillin in this research. Besides the GWF of the overall production process, this research assesses other GWFs as well: 1) The GWF of 1 gram amoxicillin produced, 2) the average GWF of amoxicillin production per capita in the Netherlands and 3) the average GWF of amoxicillin production per amoxicillin user in the Netherlands. Afterwards the average GWF of amoxicillin consumption per capita in the Netherlands and the average GWF of amoxicillin consumption per amoxicillin user in the Netherlands is calculated as well. This completes the entire GWF of amoxicillin per capita and per amoxicillin user in the Netherlands.

The supply chain of amoxicillin was researched in order to find the manufacturing locations of amoxicillin. After researching the supply chain and the production process of obtaining amoxicillin, a literature study was conducted of amoxicillin concentrations at pharmaceutical production sites. This led to one report that mentioned an amoxicillin manufacturing site, concentrations of amoxicillin and discharges at the pharmaceutical Wastewater Treatment Plant (WWTP) which were all valuable for the GWF calculations. Eventually the environmental standards were researched, which led to guidelines set by governments and companies and one regulation which emphasises the maximum allowable concentration of amoxicillin in wastewater. Afterwards the GWFs were estimated considering several scenarios based on different input data.

45 amoxicillin products for oral use are authorised for the Dutch market, which are sold by 10 different companies that are authorised to sell those products. 12 companies produce those 45 products to the market authorisation holders. After conducting literature research, it turned out that the Active Pharmaceutical Ingredient (API) amoxicillin, which is used for making the end product, is produced in China, India, Mexico and Spain. The only place were information was found regarding concentrations of the API amoxicillin in pharmaceutical wastewater combined with discharges was China. Those concentrations combined with environmental standards set by Predicted No-Effect Concentration (PNEC) values and regulations led to a GWF of $8{,}26*10^8$ m^3/day for the production process. The GWF per gram amoxicillin produced is 14,5 m^3/gram, the GWF per capita in the Netherland is 14,8 m^3/year and the GWF per amoxicillin user in the Netherlands is 229,3 m^3/year. The GWFs regarding amoxicillin consumption found were significantly higher than the GWFs of amoxicillin production. This was due to low removal rates in domestic WWTPs.

Data from pharmaceutical companies were not available in this research, which meant that data was used from literature and estimations. This limited the research in a way that the results are based on assumptions instead on factual data. To assess a realistic range in which the GWF is likely to be located and to address uncertainties, different scenarios were designed. Those were developed with ranges of removal rates, concentrations and wastewater flows to determine loads. Added to that, scenarios regarding different maximum concentrations were designed as well. The conclusion of this study was that the GWF of amoxicillin production was relatively low compared to the GWF of amoxicillin consumption, but high when compared to the total Dutch Water Footprint per capita. Compared to a regular product like beef, the GWF was substantially higher. This resulted in the fact that pollution should be drastically lowered to comply with environmental standards in such a way that risks for antibiotic resistance are negligible.

Samenvatting [NL]

De productie van antibiotica draagt wereldwijd sterk bij aan watervervuiling en de toename van de antibioticaresistentie. Een van de meest gebruikte antibiotica ter wereld is amoxicilline. Om antibioticaresistentie en watervervuiling tegen te gaan, moet vervuiling van farmaceutische productielocaties worden verminderd. Een cruciale stap hierbij is het kennen van de ernst van vervuiling. Dit onderzoek berekent daarom de Grey Water Footprint (GWF) van amoxicillineproductie van op amoxicilline gebaseerde medicijnen die in Nederland voor oraal menselijk gebruik worden verkocht. Deze GWF is een indicator van watervervuiling en in dit onderzoek is deze gekoppeld aan de productie van amoxicilline. Naast de GWF van het totale productieproces worden in dit onderzoek ook andere GWFs beoordeeld: 1) de GWF van 1 gram geproduceerde amoxicilline, 2) de gemiddelde GWF van amoxicillineproductie per hoofd van de bevolking in Nederland en 3) de gemiddelde GWF van amoxicillineproductie per amoxicillinegebruiker in Nederland. Daarna wordt ook de gemiddelde GWF van amoxicillineconsumptie per hoofd van de bevolking in Nederland en de gemiddelde GWF van amoxicillineconsumptie per amoxicillinegebruiker in Nederland berekend. Hiermee is de totale GWF van amoxicilline per hoofd van de bevolking en per amoxicillinegebruiker in Nederland bekend.

De productieketen van amoxicilline is onderzocht om de productielocaties van amoxicilline te vinden. Na onderzoek van de productieketen en het productieproces van amoxicilline is een literatuurstudie uitgevoerd naar amoxicillineconcentraties in farmaceutische productielocaties. Dit heeft geleid tot gegevens die de hoeveelheid amoxicilline in water verduidelijkten. Daarna werden milieunormen onderzocht, wat leidde tot richtlijnen en eisen van overheden en bedrijven die de maximaal toelaatbare concentratie van amoxicilline in het afvalwater benadrukken. Daarna werden de GWFs berekend op basis van diverse scenario's.

45 amoxicillineproducten voor oraal gebruik zijn toegestaan op de Nederlandse markt. Deze worden verkocht door 10 verschillende bedrijven die deze producten mogen verkopen en deze producten worden geproduceerd door 12 (andere) bedrijven. Na literatuuronderzoek is gebleken dat de werkzame stof amoxicilline, die wordt gebruikt voor het maken van het eindproduct, wordt geproduceerd in China, India, Mexico en Spanje. China was de enige plek waar informatie werd gevonden met betrekking tot concentraties van amoxicilline in farmaceutisch afvalwater in combinatie met amoxicilline lozingen. Deze concentraties in combinatie met milieunormen hebben geleid tot een GWF van $8,26*10^8$ m^3/dag voor het productieproces. De GWF per gram geproduceerde amoxicilline is 14,5 m^3/gram, de GWF per hoofd van de bevolking in Nederland is 14,8 m^3/jaar en de GWF per gebruiker van amoxicilline in Nederland is 229,3 m^3/jaar. De gevonden GWFs met betrekking tot de consumptie van amoxicilline waren significant hoger dan de GWFs met betrekking tot amoxicillineproductie. Dit was het gevolg van lage verwijderingspercentages van amoxicilline in rioolwaterzuiveringsinstallaties.

Gegevens van farmaceutische bedrijven waren niet beschikbaar in dit onderzoek waardoor gegevens uit literatuur en schattingen zijn gebruikt. Dit beperkte het onderzoek op een manier dat de resultaten gebaseerd zijn op aannames in plaats van op feitelijke gegevens. Om een realistisch bereik te geven waarin de GWF zich waarschijnlijk bevindt, en om onzekerheden bloot te stellen, zijn verschillende scenario's gemaakt. Deze zijn gerelateerd aan verwijderingspercentages, beginconcentraties en afvalwaterstromen om de uiteindelijke concentratie amoxicilline te bepalen. De conclusie van dit onderzoek was dat de GWF van amoxicillineproductie relatief laag was in vergelijking met de GWF van amoxicillineconsumptie, maar hoog in vergelijking met de totale Nederlandse Water Footprint per hoofd van de bevolking. Vergeleken met een regulier product als rundvlees was de GWF aanzienlijk hoger. Dit resulteerde in de conclusie dat vervuiling drastisch moet worden verlaagd om aan milieunormen te voldoen, zodat de risico's op antibioticaresistentie verwaarloosbaar zijn.

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Medicine pill icon on front page retrieved from pngrepo.com (PNG Repo, n.d.)

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List of Abbreviations

ABR	Antibiotic Resistance
AMR	Antimicrobial Resistance
API	Active Pharmaceutical Ingredient
CBG	College ter Beoordling van Geneesmiddelen (*English: Medicines Evaluation Board*)
DDD	Defined Daily Dose
DT	Dispersible Tablet
EEA	European Economic Area
EU	European Union
GWF	Grey Water Footprint
PNEC	Predicted No-Effect Concentration
RIVM	Dutch National Institute for Public Health and the Environment
WF	Water Footprint
WHO	World Health Organisation
WWTP	Wastewater Treatment Plant

1. Introduction

The pharmaceutical industry has made significant progress since the 19th century due to the development of antimicrobials which led to containment of numerous fatal infections (Zaffiri et al., 2012). Improved hygiene along with the use of antimicrobials and other modern pharmaceuticals has substantially increased life expectancy in developed countries. One of these is the Netherlands where the average life expectancy grew from 50,8 years in 1900 to 81,8 in 2018 (CBS, 2019). Currently more people die because of antiquity than dying through infection diseases (Meessen & Stobberingh, 2017). Antimicrobials are used to treat microbial infections. There are different types of antimicrobials that can be distinguished by the microbial group they have an effect on. Substances that function against infectious bacteria are classified as antibiotics (Shield Jr, n.d.). They have a major importance in today's medicine. Besides their effectiveness of treating bacterial bourne infections, antibiotics play for example a major role to control surgical infections (Zaffiri et al., 2012).

Apart form the benefits that the pharmaceutical industry has brought to human health, the use of pharmaceutical products has led to pollution of fresh water resources (Aus der Beek et al., 2016). Urban sewage systems have turned out to be one of the most important factors of water pollution as a result of pharmaceutical residues in human excrements (Aus der Beek et al., 2016). Pharmaceuticals used in hospitals are another important element of water pollution. Also here wastewater contains pharmaceutical substances as a result of human excretion after medicine use (Aus der Beek et al., 2016). Pharmaceuticals for animal use ending up in the environment due animal excrements are a cause for water pollution as well (Wöhler et al., 2020). Abovementioned pollution is all related to pharmaceutical consumption. Nevertheless, contamination from pharmaceutical manufacturing sites contributes heavily to water pollution compared to human excrements through high concentrations of pharmaceutical waste (Larsson, 2014).

Water pollution caused by pharmaceuticals leads to multiple problems. Besides ecotoxicological problems that occur in several species (Wöhler et al., 2020), antimicrobial resistance (AMR) is considered a global health threat (WHO, 2018a). AMR is the phenomenon that microorganisms, like bacteria, become resistant to medicines which results in those medicines becoming ineffective (WHO, 2018a). The resistance of bacteria towards antibiotics is known as antibiotic resistance (ABR), which results in challenges when curing certain bacterial infections with antibiotics (Singh et al., 2019). Research has shown that there might be a causal relation between environmental pollution from antibiotics and ABR (Huerta et al., 2013). Pollution from manufacturing sites of active pharmaceutical ingredients (APIs) sometimes reaches high numbers (Nijsingh et al., 2019). It is therefore needed to consider this wastewater streams in the protection against ABR.

Without the use of antibiotics, major surgery and other medical procedures will become risky and relatively harmless infections are less likely to be cured (WHO, 2018b). That really emphasises the need to solve the problem that has occurred due to ABR. This problem is widely known and results in 25.000 deaths a year in Europe alone due to ABR infections (CDDEP, 2015). Giubilini, 2019 describes this resistance as a collective problem known as “tragedy of the commons”. This is the problem in which individuals act to what is good for themselves, without acknowledging the overall societal problem that occurs by behaving in that way (Giubilini, 2019). For the case of ABR individuals benefit from the use of antibiotics, whereas the entire society is exposed to the risk of ABR. This becomes especially a moral issue when considering that also non-therapeutic or ineffective use of antibiotics occurs (Giubilini, 2019). Giubilini, 2019 proposes that taxing antibiotic consumption for minor infections can reduce the overall consumption. This solution raises ethical concerns in equity of health access. However, it is important to think about successful solutions to combat ABR.

The severity of this issue might become even more significant in the future. By reducing pollutant loads in waste streams, the concentrations of certain antibiotics could decrease. This is a benefit in tackling ABR, since less medicine residue is present per litre water. However, water is predicted to become scarcer in some regions due to climate change (IPCC, 2018). If pollution remains the same while there is less water available, concentrations of pollutants will rise. On the other hand the demand for antibiotics rises (CDDEP, 2015). To prevent further problems of rising concentrations in the future, pollutant loads in wastewater streams should be decreased, especially when water scarcity occurs more often (IPCC, 2018).

1.1. Research objective

The objective of this research was to assess the pollution from antibiotics manufacturing. The widely used generic[1] antibiotic amoxicillin was selected as a suitable example for this purpose. It is one of the most consumed, and therefore most produced, antibiotics worldwide (WHO, 2018b). Amoxicillin is available in two forms. One form is sterile sodium amoxicillin which is used as an injectable product. The other one is used for oral application and called amoxicillin trihydrate (ANSM, 2016). The latter is by far the most produced, thus consumed one (ANSM, 2016). Therefore, this study focused on amoxicillin for oral use. Choices of the research scope were made by setting clear boundaries to the study. Besides exclusively considering amoxicillin for oral use, the investigations focused on the Dutch market. Hence, the objective was to determine the production related pollution that occurs from the amount of amoxicillin consumed in the Netherlands.

The research used the Grey Water Footprint (GWF) as an indicator of water pollution in volumetric terms to understand the severity of this issue. The GWF describes the amount of freshwater that would be needed to lower the concentrations of the pharmaceutical waste to an extent that concentrations remain below maximum allowable concentrations and that the pollution becomes nonthreatening (Hoekstra et al., 2011). Previous research has focused on the GWF of pharmaceutical consumption (Wöhler et al., 2020). The Water Footprint (WF) concept targets to allocate footprints to products over their entire supply chain. As this research estimated a GWF of the production of a pharmaceutical, it will complete the picture of pharmaceutical pollution over a substance's entire life cycle. The research that was done is innovative, since nobody else has done this before. It was a desk-based research that has been carried out at the University of Twente in Enschede, the Netherlands.

1.2. Research Questions

To be able to achieve the research objective, a main research question was formulated as follows:

"What is the GWF of amoxicillin production for amoxicillin-based medicine sold for oral human use in the Netherlands?"

To work systematically towards an answer on the main question, sub questions were derived for this research. The first question was asked to find out which companies sell amoxicillin-based medicine in the Netherlands. Therefore the first sub question is:

1. *Which pharmaceutical companies deliver amoxicillin-based medicine for human use to the Dutch market?*

[1] A generic medicine has the same performance as brand-name medicines, but is produced by other companies after the patent of a brand-name medicine has expired (FDA, 2018).

When knowing the companies that are selling amoxicillin-based medicine, the places where the amoxicillin is manufactured had to be investigated. Therefore the following research question was posed:

2. *Where are the amoxicillin manufacturing sites for the Dutch amoxicillin market located?*

Next, the production process was investigated to get a better insight in by-products of amoxicillin production as well:

3. *What is the production process of obtaining the API amoxicillin?*

Afterwards the water pollution from amoxicillin manufacturing sites was researched. This was done by posing the following question:

4. *What are the concentrations in effluent of amoxicillin manufacturing sites?*

When this is known the environmental standards for amoxicillin manufacturing were investigated:

5. *What are the environmental standards for wastewater streams regarding amoxicillin manufacturing?*

2. Project background

2.1. Amoxicillin

Amoxicillin is a widely consumed broad-spectrum penicillin antibiotic which is used to treat bacterial infections (UNICEF Supply Division, 2018). Two groups of antibiotics exist, the small- and the broad-spectrum antibiotics. The difference is that small-spectrum antibiotics are treating a specific group of bacteria while broad-spectrum antibiotics are able to treat a wide range of bacteria. This results in affecting good bacteria as well, which can cause side effects of the treatment. Nevertheless, broad-spectrum antibiotics are a suitable choice in cases where it is not exactly known which bacteria cause the infection (van Burik, 2020). Since amoxicillin is a broad-spectrum antibiotic, it can be used to treat multiple bacterial infections. It is specifically effective against bacterial pneumonia in children, but also treating infections in blood, ears, skin, throat and urinary tract (UNICEF Supply Division, 2018).

Considering the fact that amoxicillin effectively treats bacterial infections in children, the United Nations Commission on Life-saving Commodities for Women and Children has identified the amoxicillin dispersible tablet (DT) as one of 13 life-saving commodities for child health to prevent death caused by pneumonia and other bacterial infection diseases (UNICEF Supply Division, 2018). This antibiotic replaces previous medicine, which means that demands for amoxicillin are likely to rise in developing countries. To stimulate the use of amoxicillin DT, UNICEF has supplied amoxicillin in those countries. The demand between 2011 and 2017 for those amoxicillin DT has risen from 14 to 320 million tablets in this period as seen in *Figure 1* (UNICEF Supply Division, 2018). This rise in amoxicillin DT is not comparable to the Dutch market (*Figure 2*). However, the increase of amoxicillin DT worldwide is of significant importance to the Dutch market, since more production of amoxicillin could lead to an increase of ABR. This is because more production can lead to more pollution at manufacturing sites and more consumption will lead to more environmental emissions due to an increase of human excretions.

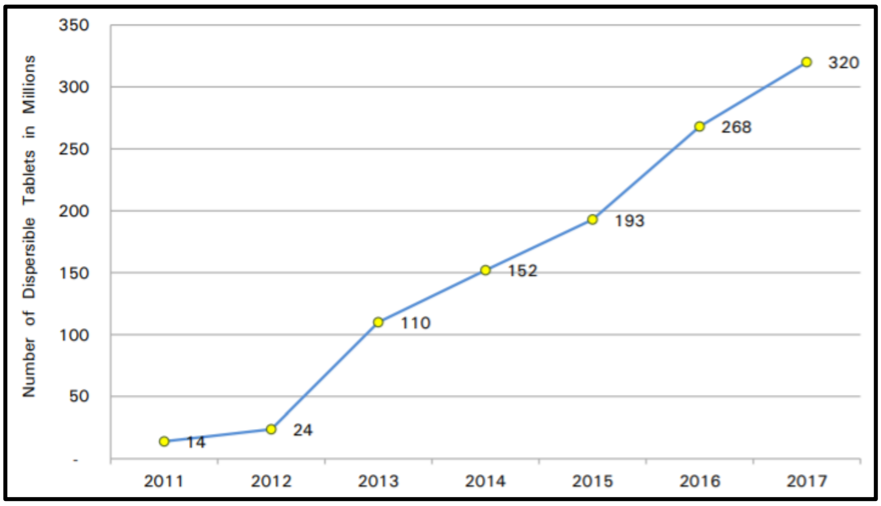

Figure 1: Demand for amoxicillin DT between 2011-2017 (UNICEF Supply Division, 2018).

Pharmaceutical doses in general are measured in Defined Daily Doses (DDD), which is the average dose of a certain medicine for an adult per day (ECDC, 2019). DDDs are medicine dependent. Throughout different European Union (EU) and EEA (European Economic Area) countries, per capita DDDs of antibiotics differ. It varies between 11.3 in the Netherlands to 31.9 DDD per 1000 inhabitants per day in Greece in 2012 (Pulcini et al., 2017). In all EU/EEA countries, except Denmark, Norway and Sweden, penicillins are the most consumed antibiotics and amoxicillin is one of the two most consumed penicillins (Pulcini et al., 2017). The DDD for amoxicillin is determined by the WHO Centre for Drug

Statistics Methodology and it changed in 2019 from 1g to 1.5g for oral use (ECDC, 2019; WHO Collaborating Centre for Drug Statistics Methodology, 2019). Since those DDD are for oral use, it refers to the amoxicillin trihydrate which is used for oral medicinal products (ANSM, 2016).

In the Netherlands the DDD per inhabitant for systematic[2] antibiotic use is the lowest of all EU/EEA countries. The DDD per 1000 Dutch inhabitants has decreased from 11.21 in 2009 to 10.05 in 2018. However, amoxicillin use has risen in those years, from a DDD per 1000 inhabitants of 1.89 in 2009 to 2.02 in 2018 (SWAB, 2019). For human use, amoxicillin is the most used antibiotic in the Netherlands (SWAB, 2019). The trend of this amoxicillin use is shown in *Figure 2*.

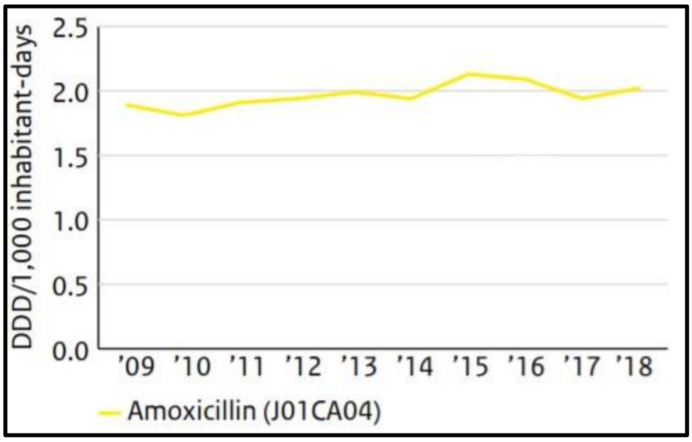

Figure 2: Use of amoxicillin for systematic use in outpatients between 2009-2018 (SWAB, 2019).

2.2. Water Footprint Concept

Water is an essential resource for producing food and goods. Large volumes of water are consumed in those productions to fulfil the needs of the (growing) world population (Hoekstra et al., 2011). To calculate the amount of water that is used, the WF concept was developed in 2002 (Hoekstra et al., 2011). This is an indicator of the direct and indirect freshwater use of consumers' products. By using the WF concept, the total WF of countries and products can be calculated (Hoekstra & Chapagain, 2007). Knowledge on products' WFs is useful to interpret products' environmental impacts and assess measures potentially decreasing WFs. The WF consists of three components: 1) the green WF which refers to water from precipitation, 2) the blue WF that inventorises water sourced from surface or groundwater and 3) the grey WF which is the amount of fresh water required to dilute polluted water enough to maintain water quality standards (Hoekstra et al., 2011). This is therefore an essential tool to measure the amount of water that is required to maintain water quality standards of the production of pharmaceuticals.

2.3. GWF of human antibiotics

As explained in the previous paragraph the GWF is the amount of fresh water required to dilute polluted water enough to maintain water quality standards and is therefore an indicator of pollution (Hoekstra et al., 2011). The GWF is expressed as a pollutant load divided by the difference of maximum allowed concentration of that pollutant and its natural background concentration (Hoekstra et al., 2011). As amoxicillin is a human induced substance, the latter is zero.

Since the WF concept was introduced, comparatively few research was conducted to assess pollution from human pharmaceutical use. Martínez-Alcalá et al., 2018 published a consumption-oriented study

[2] Systematic use emphasises an organised and detailed method of using (Cambridge Dictionary, n.d.). This means that in the case of pharmaceuticals this is related to a fixed pattern to take the medicines per day.

on the GWF of pharmaceuticals. However, this research did not include any antibiotics (Martínez-Alcalá et al., 2018). Another consumption-focussed study on the GWF of human and veterinary pharmaceuticals by Wöhler et al., 2020 does consider a selection of antibiotics. However, amoxicillin for human use was not taken into account. The highest GWF that was found for consumption of human antibiotics was 1900 m^3 yr^{-1} per capita for ciprofloxacin (Wöhler et al., 2020).

2.4. Pollution of manufacturing sites

Previous research showed concentrations of an antibiotic manufacturing site in Hyderabad where 90 manufacturers produce pharmaceuticals in a small area (Larsson et al., 2007). In Larsson et al., 2007, information from the Patancheru Wastewater Treatment Plant (WWTP) was gathered. This plant is situated in the area of Hyderabad in India. Especially the effluent concentration of ciprofloxacin - which was researched concerning the GWF of pharmaceutical consumption by Wöhler et al., 2020 - was significant and reached up to 31 mg/L (Larsson et al., 2007). Larsson et al., 2007 concluded that the ciprofloxacin concentration in the discharge of the WWTP (1.500 m^3/day) led to approximately 45 kg of this antibiotic waste per day. Thereafter it is concluded that this is approximately the same as the total amount of consumed ciprofloxacin in Sweden per 5 days (Larsson et al., 2007). This comparison really emphasises the need to look at pollution from antibiotic manufacturing sites.

The abovementioned concentrations are the pollutant concentrations of API manufacturing sites. Active Pharmaceutical Ingredients are the substances that produces the effect of the pharmaceutical. One shall not confuse the API with the medicine that is sold on the market. The medicine amoxicillin that is sold as a product on the Dutch market is therefore defined as AMOX in the next chapters. The active substance amoxicillin is called "API amoxicillin". The abovementioned concentrations are the pollutant concentrations of API manufacturing sites. APIs are the pharmacologically active substances that makes a pharmaceutical function. One shall not confuse the API with the medicinal product that is sold on the market and may contain other additives. The supply chain of the manufacturing of API amoxicillin to AMOX is discussed in "*4.1 Supply Chain*".

3. Methods and data

This chapter describes the methods that were used to answer the research questions. No research has been conducted on the GWF of production of antibiotics previously and information on the production of amoxicillin and its pollutants itself is scarce. Each research question presented in "*1.2 Research Questions*" was answered using different methods which are outlined in this chapter. The methods and data of sub questions 1 – 5 were evaluated first. Point *3.6* elaborated on the method and data of the main research question afterwards.

3.1. Pharmaceutical companies which deliver amoxicillin-based medicine for human use for the Dutch market

The medicine database of the CBG lists 50 products registered in the Netherlands that contain the API amoxicillin as single active ingredient (CBG, 2020). The CBG is the institute that judges medicine in the Netherlands on their scientific and pharmaceutical properties. Of those 50 products, 45 are for oral use and therefore contain amoxicillin trihydrate (CBG, 2020). In this research, 10 market authorisation holders for amoxicillin trihydrate were identified in the Netherlands. Those companies are able to sell amoxicillin products to Dutch pharmacies, resulting in domestic use. Sales data as a whole are not available in the Netherlands (Moermond, 2020), so the website of CBG was used to determine the pharmaceutical companies that deliver amoxicillin-based medicine in the Netherlands:

- Apotex Europe B.V.
- Astellas Pharma Europe B.V.
- Aurobindo Pharma B.V.
- Centrient Pharmaceuticals Netherlands B.V.
- Focus Care Pharmaceuticals B.V.
- Mylan B.V.
- N.V. Eurogenerics S.A.
- RIA Generics Ltd.
- Sandoz B.V.
- Teva B.V.

Those companies are not the manufacturers of the API amoxicillin. They are authorised to sell the medicine AMOX in the Netherlands. The 12 manufacturers of AMOX for the Dutch products are listed in the next paragraph. In *Table 8* in appendix *A* the different AMOX medicine for oral use are listed with its authorisation holders.

3.2. Location of amoxicillin manufacturing sites for the Dutch amoxicillin market

To determine the location of amoxicillin manufacturing sites, all package leaflets that are included with the AMOX medicine on the CBG website were researched. Most AMOX manufacturer(s) were mentioned in the package leaflets (CBG, 2020). All 12 manufacturers identified were contacted to gain insights in the manufacturing process. Two manufacturers and a researcher responded and described the supply chain of the API amoxicillin to the product AMOX.

The 10 authorisation holders of AMOX mentioned in chapter *3.1* are not essentially the manufacturers. Manufacturers of 41 amoxicillin-containing products were identified and for four products manufacturers remained unknown. *Table 1* lists the manufacturers of AMOX, their country and the number of authorisation holders (companies) they supply. The total sum of authorisation holders that are supplied is more than the available number of products. This is because certain medicines are supplied by multiple AMOX manufacturers. From the 45 AMOX products determined for the Dutch market 33 products are manufactured by multiple (2 or 3) European manufacturers, 7 products are manufactured by a European *and* a Dutch manufacturer, of 4 products the manufacturer is unknown and 1 AMOX product is manufactured by a Dutch manufacturer alone (*Figure 3*) (*Table 9* in appendix *B*).

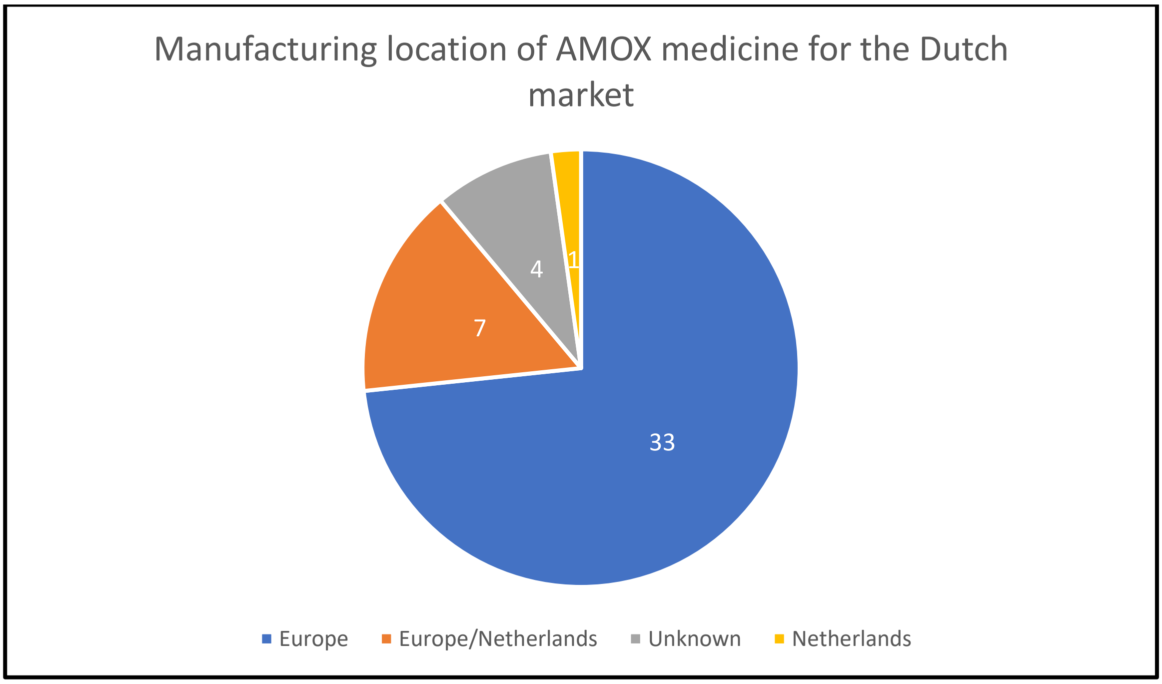

Figure 3: Manufacturing locations of AMOX medicine for the Dutch market.

Table 1: Manufacturers of AMOX products, their country and the number of authorisation holders they supply (CBG, 2020).

Country	Manufacturers	Number of products supplied to authorisation holders
Austria	**Sandoz GmbH** Biochemiestrasse 10 A-6250 Kundl	9
France	**Arrow Génériques** 26 avenue Tony Garnier Lyon, 69007	3
Germany	**PenCef Pharma GmbH** Breitenbachstrasse 13-14 13509 Berlin	18
Hungary	**Mylan Hungary Kft** H2900 Komarom Mylan utca 1	1
Italy	**HAUPT Pharma Latina S.r.L.** Strada Statale 156 Monti Lepini 04100 Borgo San Michele (Latina)	24
Malta	**APL Swift Services (Malta) Limited** HF26, Hal Far Industrial Estate, Hal Far Birzebbugia, BBG 3000	3
Netherlands	**Mylan B.V.** Dieselweg 25 3752 LB Bunschoten	1
Netherlands	**Apotex Nederland BV** Archimedesweg 2	1

	2333 CN Leiden	
Netherlands	**Astellas Pharma Europe B.V.** Sylviusweg 62 2333 BE Leiden	6
Portugal	**Generis Farmacêutica** Rua João de Deus 19 2700-487 Amadora	3
Romania	**Antibiotice S.A.** 1 Valea Lupului Iasi 707410	3
United Kingdom	**Generics [UK] Limited** Station Close, Potters Bar Hertfordshire, EN6 1TL	1

The AMOX manufacturers that deliver most products to the market authorisation holders for the Dutch market are Sandoz GmbH, PenCef Pharma GmbH and HAUPT Pharma Latina Sr.L. Those companies together account for the majority of the supply to the market authorisation holders. The three abovementioned AMOX manufacturers are responsible for 33 of the 45 amoxicillin-based medicine that are registered in the Netherlands. However, since there is no sales data available per product, it is uncertain which manufacturer is responsible for the largest amount of AMOX that is sold in the Netherlands.

Furthermore, the AMOX manufacturers APL Swift Services (Malta) Limited, Apotex, Arrow Génériques and Generis Farmacêutica are responsible for 4 other medicine as part of the bigger company Aurobindo. Antibiotice S.A. accounts for 3 AMOX medicine more and Mylan together with Generics [UK] Limited is responsible for 1 AMOX medicine. That makes a total of 41 amoxicillin-based medicine. In the following paragraphs more information of those manufacturers is given.

Sandoz GmbH

Sandoz GmbH is part of the Novartis Group, which is one of the world leaders in the manufacturing of medicine. The 28,3 hectares manufacturing site in Kundl, Austria, is the manufacturing site for 9 AMOX products for the Dutch market (Sandoz, 2020). Kundl is the central development and production location of the Novartis Group with its main focus at the production of generic medicine (Sandoz, 2020). The plant in Kundl focusses on the production and formulation of antibiotics that are ready to use.

PenCef Pharma GmbH

PenCef Pharma GmbH is part of the NextPharma group. This group operates globally with five development centres, six manufacturing plants and six storage and distribution sites throughout Europe (NextPharma, 2020). NextPharma group has one particular development & production site for penicillins. The location of this site is Berlin, Germany, and is specialised in the manufacturing, development and packaging of beta-lactam antibiotics[3] where amoxicillin is part of (NextPharma, 2020).

HAUPT Pharma Latina S.r.L.

In 2014, Haupt Pharma Latina became part of the Aenova Group and is one of the manufacturing sites of Aenova. It operates through 22 sites in eight European countries, Asia and the United States of

[3] Beta-lactam antibiotics is a class of antibiotics which is the largest in term of production volume (Gröger et al., 2017).

America (Aenova Group, 2020). According to Aenova Group, 2020), the Haupt Pharma Latina site is specialised in the production of beta-lactam pharmaceuticals. The manufacturing site for AMOX is situated in Borgo San Michele, Italy.

Aurobindo

Aurobindo Pharma is the main company of APL Swift Services (Malta) Limited, Apotex, Arrow Génériques and Generis Farmacêutica. Those four companies are all subsidiaries of Aurobindo, which has its headquarters in Hyderabad, India (Aurobindo, 2020). APL Swift Services, Arrow Génériques and Generis Farmacêutica are selling medicines and testing the products, while Apotex is still negotiating with the Dutch government about their takeover by Aurobindo, so therefore it is not sure whether Apotex becomes part of Aurobindo in the future (Leefmans, 2020). The key manufacturing sites of Aurobindo are situated in India, the USA and Brazil. For the manufacturing of antibiotics, a manufacturing site in India is used (Aurobindo, 2020). This manufacturing site is located in the region of Hyderabad. Aurobindo consists of different key facilities for the manufacturing of APIs. The unit that is used for manufacturing the API amoxicillin is called "Unit 12" and is situated in Hyderabad, India (Aurobindo, 2020). However, no information was found about this "Unit 12".

Antibiotice S.A.

Antibiotice S.A. is currently developing 157 product for human use, and in 1955 it started with penicillin products. It is nowadays one of the most important pharmaceutical manufacturers in Romania (Antibiotice, 2019). Throughout the years development took place in more pharmaceuticals. They are developing generic medicine for more than 75 countries and it focusses mostly on anti-infective medicine, which amoxicillin is part of (Antibiotice, 2019).

Mylan

Generics [UK] Limited is part of Mylan. Generics [UK] is trading products as a subsidiary of Mylan, since Mylan is the main company. Mylan has several manufacturing networks in Europe. Mylan Hungary is one of the sites were oral products are produced (Mylan, 2019). This company develops the least amount of amoxicillin products for the Dutch market.

To investigate if those companies produce the API amoxicillin or that they only formulate the product AMOX, the supply chain of amoxicillin is researched.

Supply Chain

In the previous chapter the manufacturers of the different AMOX medicine is stated. Those manufacturing places are almost all in Europe. To investigate if those places produce the API amoxicillin, or that those manufacturing sites only make the final AMOX medicine, the supply chain of amoxicillin from API to AMOX has been researched. The location of the API manufacturing site is needed to estimate the GWF of amoxicillin production. Three parties were contacted about this supply chain:

Researcher

Professor Larsson from the Department of Infectious Diseases from the University of Gothenburg, Sweden, was contacted regarding information on the supply chain of amoxicillin (Larsson, 2020). After this contact it became clear that there is a difference between the production of the API and the production of the final product AMOX and that it is important to differentiate between those two processes (Larsson, 2020). China is a significant factor in the production of antibiotics, since they produce the precursors of beta-lactam antibiotics by the fermentation of fungi. A precursor is the substance before a chemical reaction, so the substance before the API amoxicillin is produced (Ren, 2016). This precursor can afterwards be modified to one of the beta-lactam antibiotics, such as amoxicillin (Larsson, 2020). The supply chain of beta-lactam antibiotics is therefore as follows:

Figure 4: Supply chain antibiotics, like amoxicillin (Larsson, 2020).

Discharges of APIs are most frequently found in the second process step, i.e. the production of the API amoxicillin. However, in the case of beta-lactam antibiotics, the raw material has pharmaceutical activity already (Larsson, 2020). In amoxicillin production this precursor is 6-APA.

Amoxicillin Manufacturer, Astellas Pharma Europe

Astellas Pharma Europe is the manufacturer of some amoxicillin-based medicine for the Dutch market (Zorginstituut Nederland, 2019). Astellas is manufacturing AMOX pills in the Netherlands, but not the active substance amoxicillin (Dijkhuis, 2020). The APIs for Astellas are not manufactured in the Netherlands and the precursors of all amoxicillin medicine that Astellas produces are from China (Dijkhuis, 2020). After the production of the precursor, there are several routes to follow for the production of the API amoxicillin, e.g. synthetical or enzymatical (Dijkhuis, 2020).

According to Astellas, many suppliers have their production sites of the API amoxicillin in China or Spain (Dijkhuis, 2020). After this, the API is distributed to sites where the AMOX medicines are formulated, packed and delivered. So in the Netherlands the companies usually are processing the API amoxicillin, which is produced in other countries, to the medicine AMOX (Dijkhuis, 2020). In the Netherlands the API amoxicillin is delivered by for example Centrient Pharmaceuticals. The supply chain according to Astellas is given in *Figure 5*.

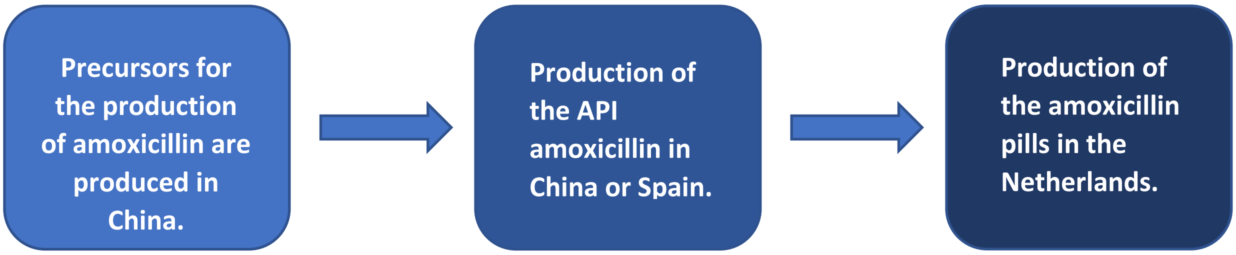

Figure 5: Supply chain of amoxicillin according to Astellas. The arrow represents transportation between the different locations of the supply chain (Dijkhuis, 2020).

Market Authorisation Holder, Centrient Pharmaceuticals

According to Centrient, which is one of the companies that are producing the API amoxicillin, the production of this API is usually outside the Netherlands (Wevers, 2020). The production in the Netherlands and other European countries is often related to the making of the AMOX medicine. In this process, besides adding the API amoxicillin, other substances are added to make the final medicine, e.g. binders and water (Wevers, 2020).

The API amoxicillin of Centrient is often produced in other regions of the world than Europe. The supply chain of amoxicillin from Centrient is as follows (Wevers, 2020):

1. Glucose is converted to 6-APA, which is the intermediate for amoxicillin. This glucose is fermented and in this process, PEN G (penicillin G) is produced. Some products are made with PEN G, however at Centrient 6-APA is used to create the API amoxicillin. This process is almost alone done in China, where Centrient has a factory as well (Wevers, 2020).
2. The 6-APA is transferred to manufacturing sites where the API amoxicillin is produced. In those factories (India, Mexico Spain) this 6-APA is converted into the API amoxicillin. However, in China there are factories as well that produce the API amoxicillin (Wevers, 2020).
3. Centrient sells this API to medicine manufacturers worldwide. Those manufacturers are making the AMOX-pill, -powder or -injection, but the manufacturing of the API amoxicillin has done already by that part (Wevers, 2020).

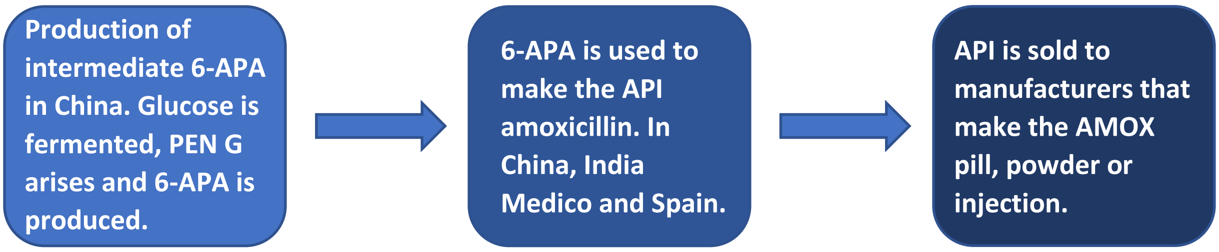

Figure 6: Supply chain of amoxicillin according to Centrient Pharmaceuticals (Wevers, 2020).

It can be concluded that the manufacturers that are described in the package leaflets given with the AMOX medicine in the Netherlands are the manufacturers of the AMOX medicine and not of the API amoxicillin. The manufacturers of AMOX medicine are almost all in Europe. However, the manufacturing locations of the API amoxicillin are in China, India, Mexico and Spain.

3.3. Production process of obtaining amoxicillin

The production process of the API amoxicillin was identified through a literature study. Several literature sources were available about the production process of amoxicillin, both chemical and enzymatic. These processes were investigated to understand production processes, including intermediate steps and by-products:

Chemical

The chemical route generates high yields and is therefore more cost-effective than the enzymatic production process. However, the chemical process is harmful to the environment since it is reported that the production of one kilogram amoxicillin will generate up to 70 kilogram non-recyclable waste (ANSM, 2016; Pereira et al., 2015). The chemical production of the API amoxicillin requires more than 10 steps (ANSM, 2016), whereby the initial substance (6-APA) is the precursor. So to conclude, the chemical process of obtaining amoxicillin is done by transforming 6-APA into amoxicillin.

Enzymatic

Semi-synthetic antibiotics are produced enzymatically as well. There are two syntheses which are suitable for these types of antibiotics. One is Thermodynamic Controlled Synthesis (TCS) and the other is Kinetically Controlled Synthesis (KCS) (Pereira et al., 2015). However, in the case of obtaining amoxicillin only the latter is suitable (Gonçalves et al., 2002; Pereira et al., 2015). The route of this synthesis is done by reacting the precursor 6-APA, catalysed by Penicillin G. During the reaction from 6-APA to amoxicillin, two side reactions take place. The by-products of this synthesis are 6-APA and *p*-hydroxyphenyl glycine (PHPG). Compared to the chemical synthesis, the steps that are taken to obtain amoxicillin in the enzymatic synthesis are less.

3.4. Concentrations in effluent of amoxicillin manufacturing sites

Through a literature study the concentrations in effluent of amoxicillin manufacturing sites were identified. The studies that were found were almost all focused on new ways of processing wastewater which contained the API amoxicillin. This resulted in multiple concentrations of the API amoxicillin and different discharges of pharmaceutical production sites. The different literature studies that were conducted are listed below:

- A study was conducted regarding an up-flow anaerobic sludge blanket to treat pharmaceutical wastewater from a pharmaceutical WWTP in Inner Mongolia, China (Chen et al., 2011). Amoxicillin concentrations were found in the range of 61-171 mg/L with an average of 92 mg/L (Chen et al., 2011). The wastewater flow of this WWTP is 1169-2805 m^3/day with an average of 2031,2 m^3/day (Chen et al., 2011). The percentage of amoxicillin that could be removed in this sludge blanket was 21,6%. This was the only research in which the amoxicillin production site was mentioned as well. The production site in this research is Zhuhai United Laboratories Co., Ltd. in Inner Mongolia, Northern China (Chen et al., 2011). However nothing was mentioned about the amounts of amoxicillin produced at this manufacturing site.
- Another test was done in a different reactor where raw antibiotic wastewater reached concentrations up to 171 mg/L and the overall removal rate in this reactor was 80% (Meng et al., 2015). No data regarding the wastewater flows was present in this research.
- A research was conducted about a production plant in Brazil as well. However Brazil was not stated in the supply chains of amoxicillin production for the Dutch market in chapter *3.2*, it was nevertheless researched. This was done since there is not much information of the manufacturing process of the API amoxicillin. This data of the manufacturing plant in Brazil is therefore used as a reference. In this research the pharmaceutical wastewater had a concentration of 120 mg/L of amoxicillin and it reached a removal rate of 80% (Marcelino et al., 2016). No data on the wastewater flow was given in this research.
- In other research a review on the anaerobic treatment of pharmaceutical wastewater was conducted. In this research a concentration of 92,2 mg/L amoxicillin was found in wastewater from production (Shi et al., 2017). No information on the wastewater flow was present in this research either.

The concentrations found were all between 61 and 171 mg/L. Wastewater flow was mentioned in one article together with removal rates. The removal percentages of amoxicillin were 21,6% and 80%. Those details are needed for the GWF calculations to determine the load of amoxicillin together with the maximum allowable concentration. Research concerning the environmental standards is done in the next chapter.

3.5. Environmental standards for wastewater streams regarding amoxicillin production

By doing a literature study the environmental standards regarding the manufacturing process of the API amoxicillin were researched. The results of this research were split into three parts. 1) The current regulations on discharges, 2) the different Predicted No-Effect Concentration (PNEC) values and 3) maximum allowable concentrations that are set by government(s).

Regulations on discharges

The Antimicrobial Resistance Benchmark provides an independent comparison between pharmaceutical companies of what they do to prevent antimicrobial resistance (Access to Medicine Foundation, 2020). Apart from attacking antimicrobial resistance, this report also strives to improve access to antimicrobials in third world countries. In this report 17 companies were researched, however none of the 17 companies published discharge levels (Access to Medicine Foundation, 2020). Some of the companies researched are not setting limits for antibacterial discharges in WWTP and none of the companies monitor discharges (Access to Medicine Foundation, 2020). This emphasises the lack of regulations in the pharmaceutical discharge industry and it could therefore be concluded that some pharmaceutical companies release pharmaceutical wastewater untreated.

The AMR Industry Alliance is a coalition of more than 100 companies in the generic, diagnostic, biotechnology and research based biopharmaceutical industry (SustainAbility, 2020). One of the largest penicillin antibiotic manufacturers is currently developing new techniques to detect antibiotic levels in wastewater up to 50 µg/L (SustainAbility, 2020). The companies that are part of the AMR Industry Alliance strive to point out the targets that are set by the AMR Industry Alliance Report in regard to environmental pollution (SustainAbility, 2020). In the next paragraph, more information with respect to those target values is given.

PNEC values

The AMR Industry Alliance has developed an approach on targeting antibiotic concentrations in discharges of the pharmaceutical industry and pharmaceutical WWTPs. These targets are based on Predicted No-Effect Concentrations (PNECs), and these PNECs can be used in environmental risk assessments (AMR Industry Alliance, 2020). The PNEC value is the value in which the concentration is not harmful to the environment, since it predicts no effects when a certain concentration is present in discharges. The PNEC values that were published in the AMR Industry Alliance report were split in two parts: 1) The PNEC-Environment (PNEC-ENV) is determined to protect ecological species (AMR Industry Alliance, 2020) and 2) the PNEC-Minimum Inhibitory Concentration (PNEC-MIC) is determined data to prevent antimicrobial resistance (AMR Industry Alliance, 2020). For amoxicillin the PNEC values according to the AMR Industry Alliance are as follows:

Table 2: PNEC values for amoxicillin (AMR Industry Alliance, 2020).

Active Pharmaceutical Ingredient	PNEC-ENV (µg/L)	PNEC-MIC (µg/L)	Lowest Value (µg/L)
Amoxicillin	0,57	0,25	0,25

The Dutch Institute for Public Health and the Environment (RIVM) has conducted a research with respect to PNEC values as well. Amoxicillin was one of the 22 pharmaceuticals in this research (Aa van der et al., 2011). The RIVM has found different PNEC values for amoxicillin, based on toxicity data. Those PNEC values were split into acute toxicity and chronic toxicity (Aa van der et al., 2011). The lowest PNEC value was found for crustacea, therefore the RIVM set this PNEC value as the PNEC value for amoxicillin. The PNEC value for amoxicillin according to the RIVM is therefore 0,078 µg/L (Aa van der et al., 2011).

The Joint Research Centre is the service centre of the European Commission and they have also set regulations on antibiotic discharges. Three antibiotics are selected that are harmful to the aquatic environment and amoxicillin is one of them (Loos et al., 2018). The PNEC value for amoxicillin is set at 0,078 µg/L and the European Commission sees this PNEC as a reliable value. Therefore it is used as a standard in the EU (Loos et al., 2018).

Maximum allowable concentrations

PNEC values in the abovementioned reports are guidelines for water quality standards, however those are not regulations for pharmaceutical waste. The first country in the world to set regulations for pharmaceutical waste is India (Sinha, 2020). The Indian Ministry of Environment, Forest and Climate

Change has issued a law in which values for amoxicillin are set. It is still a draft and it should be discussed in parliament first (Ministry of Environment Forest and Climate Change, 2019). However, this has not been done by the time of writing this report. The maximum value of amoxicillin present in wastewater of the pharmaceutical industry should be less, or equal, than 0,10 µg/L (Ministry of Environment Forest and Climate Change, 2019). Even wastewater standards in countries in Europe, or the United States of America are not regulated by law (Sinha, 2020).

The following maximum concentrations found in literature are used in the GWF estimations:

- PNEC value: 0,078 µg/L (Aa van der et al., 2011; Loos et al., 2018)
- Regulation: 0,10 µg/L (Ministry of Environment Forest and Climate Change, 2019)
- PNEC value: 0,25 µg/L (AMR Industry Alliance, 2020)

3.6. Grey Water Footprint of amoxicillin production

To determine this GWF, the load of the pollutant (mass/time) is divided by the difference between the maximum concentration (mass/volume) and the natural concentration (mass/volume), see equation 1 (Hoekstra et al., 2011). The natural concentration in environmental waters in the case of human made products like pharmaceutics is zero (Hoekstra et al., 2011). First the GWF of the API amoxicillin production process was calculated. Afterwards additional GWFs were calculated. The different GWF groups are called "entities" in the next paragraphs. Those entities are:

- GWF per gram amoxicillin produced
- Average GWF of amoxicillin production per capita of the Netherlands
- Average GWF of amoxicillin production per amoxicillin user in the Netherlands
- Average GWF of amoxicillin consumption per capita and amoxicillin user in the Netherlands

$$WF_{proc,grey} = \frac{L}{c_{max} - c_{nat}} \qquad (1)$$

Due to scarce data availability, it is not possible to estimate one "true" GWF. To assess a realistic range in which the GWF is likely to be located, different scenarios were designed. This at the same time addresses uncertainty ranges. Scenarios were developed with ranges of removal rates, concentrations and wastewater flows to determine loads (L) (chapter *3.4*) and different maximum concentrations (C_{max}) that base on findings of environmental standards (chapter *3.5*). By combining those inputs, 108 scenarios regarding the GWF of amoxicillin production were designed as explained in the following sections.

Pollutant Load (L) in mass/time

Several scenarios were designed to determine the pollutant load. The removal percentages were derived by doing a literature research, which was conducted in chapter *3.4*:

- 0% removal
- 21.6% removal
- 50% removal
- 80% removal
- 100% removal (which leads to a GWF of 0, since no amoxicillin is released into the environment) is not researched.

The range of amoxicillin found in influents of WWTP of the pharmaceutical industry was between 61 – 171 mg/L with an average value of 92 mg/L (Chen et al., 2011). Therefore 3 scenarios were displayed regarding the influent concentrations:

- 61 mg/L
- 92 mg/L
- 171 mg/L

The final pollutant loads were calculated by dividing derived concentrations through the discharge of the effluent streams. For those effluent streams 3 volumes were mentioned in literature as well (Chen et al., 2011):

- 1169 m^3/day
- 2031,2 m^3/day
- 2805 m^3/day

The 3 influent concentrations combined with the 4 removal rates led to 12 different concentrations. Via the three effluent streams, 36 different pollutant loads in mass/time were calculated for the GWF calculations.

Maximum acceptable concentration C_{max} in mass/volume

As outlined in chapter *3.5*, the following 3 maximum acceptable concentrations were considered:

- 0,078 µg/L (Aa van der et al., 2011; Loos et al., 2018)
- 0,10 µg/L (Ministry of Environment Forest and Climate Change, 2019)
- 0,25 µg/L (AMR Industry Alliance, 2020)

The maximum acceptable concentrations were combined with the 36 different pollutant loads. This resulted in 108 different GWFs of amoxicillin production.

GWF per gram amoxicillin

The GWF per gram amoxicillin produced was calculated after the GWF of amoxicillin production was known. This was calculated by researching how much amoxicillin the factory produces that discharges amoxicillin wastewater to the WWTP that is used in the GWF calculation for the amoxicillin production process. There was no data present of this factory, therefore the following steps were taken to estimate the production of the factory:

1. Export data on the total amount of amoxicillin that is exported from China is known from May 2019 – April 2020, which is 19.195.619 kg (ceicdata, 2020).
2. The ratio production/export is known by using information from the China Pharmaceutical Industry Association (China Pharmaceutical Industry Association, 2018). This revealed intermediates that are used in the production process of antibiotics in general. Those intermediate products are the basis of many antibiotics. Two of the 18 intermediates are used in the production process of the API amoxicillin, i.e. 6-APA and Penicillin G. The production and export data of those intermediates are given. The average percentage of export over the years 2010 – 2018 of the intermediates used for amoxicillin production was 23%.
3. By using this percentage, the total amount of amoxicillin produced in China in the period May 2019 – April 2020 was calculated, this resulted in 83.545.865 kg.
4. The review of the China Pharmaceutical Industry Association (China Pharmaceutical Industry Association, 2018) also gave information on the amount of factories in China that are involved in antibiotic production. 17 factories are involved in China in antibiotic production, however not all are producing amoxicillin.
5. To estimate the number of amoxicillin manufacturers in China the share of amoxicillin compared to the total antibiotics consumed was researched. It turned out that approximately

25% of the antibiotics consumed worldwide is amoxicillin (WHO, 2018b). By using this data the number of amoxicillin manufacturers in China was estimated at 4.

6. By assuming that every factory produces the same amount of amoxicillin the amount of amoxicillin produced by one factory was determined. This turned out to be 20.862.716 kg annually.

Average GWF of amoxicillin production per capita in the Netherlands

To determine the GWF per capita in the Netherlands the amount of amoxicillin consumed in the Netherlands was calculated together with the population of the Netherlands. The amount of amoxicillin consumed in the Netherlands in 2018 equalled 11.866.700 DDD (Zorginstituut Nederland, 2019). The number of DDDs amoxicillin is defined by the WHO as 1,5 gram per DDD amoxicillin (WHO Collaborating Centre for Drug Statistics Methodology, 2019). With this data the amount consumed in the Netherlands per year was calculated. Afterwards the GWF of the total amoxicillin consumption in the Netherlands was calculated. Thereafter, the GWF per capita was calculated by dividing the GWF for the entire population's consumption by the number of inhabitants, which was 17.407.585 on the 1st of January 2020 (CBS, 2020).

Average GWF of amoxicillin production per amoxicillin user in the Netherlands

The GWF per amoxicillin user was determined by using data about the number of amoxicillin users in the Netherlands in 2018. This was 1.122.000 (Zorginstituut Nederland, 2019). Since the amount of grams consumed in the Netherlands was determined, the GWF per amoxicillin user was calculated by dividing the total GWF of the consumption of amoxicillin in the Netherlands by the amount of amoxicillin users.

Sort GWF data

Histograms were designed for the four GWF entities that were mentioned above. Those histograms were meant to sort the data. The GWF results per entity were divided into bins (also called intervals). The amount of intervals was determined by Sturge's Rule (equation 2), which is a rule of thumb to estimate the amount of intervals that are needed to sort the data (Statistics How To, 2018). In this equation, K is the amount of intervals and "n" are the observations, which in this study is 108.

$$K = 1 + 3{,}322\ \log n \tag{2}$$

GWF of amoxicillin consumption

To complement the total average GWF of amoxicillin per capita and per amoxicillin user in the Netherlands, the GWF of amoxicillin consumption was calculated as well. This was done by calculating the load divided by the different C_{max} (equation 1) found in chapter *3.5*. The load was calculated through equation 3, supported by data from literature (ter Laak et al., 2010). S is the amount of amoxicillin consumed in the Netherlands in kg/year, resulting from previous paragraphs. f_e is the excreted fraction of amoxicillin, which is 60% (Moffat et al., 2011). The removed fraction (f_r) is the average percentage of amoxicillin removed after wastewater treatment in Italy, which is 87,25% (Castiglioni, 2006). European information about removal rates of WWTPs with respect to amoxicillin were only available for an Italian WWTP.

$$L_h = S * f_e * (1 - f_r) \tag{3}$$

4. Results

4.1. Supply Chain

The supply chain for amoxicillin production for the Dutch market is presented in *Figure 7*. It starts at the production of the precursor and ends at the sales at pharmacies. This supply chain was created by combining the different supply chains that were discussed in chapter *3.2*.

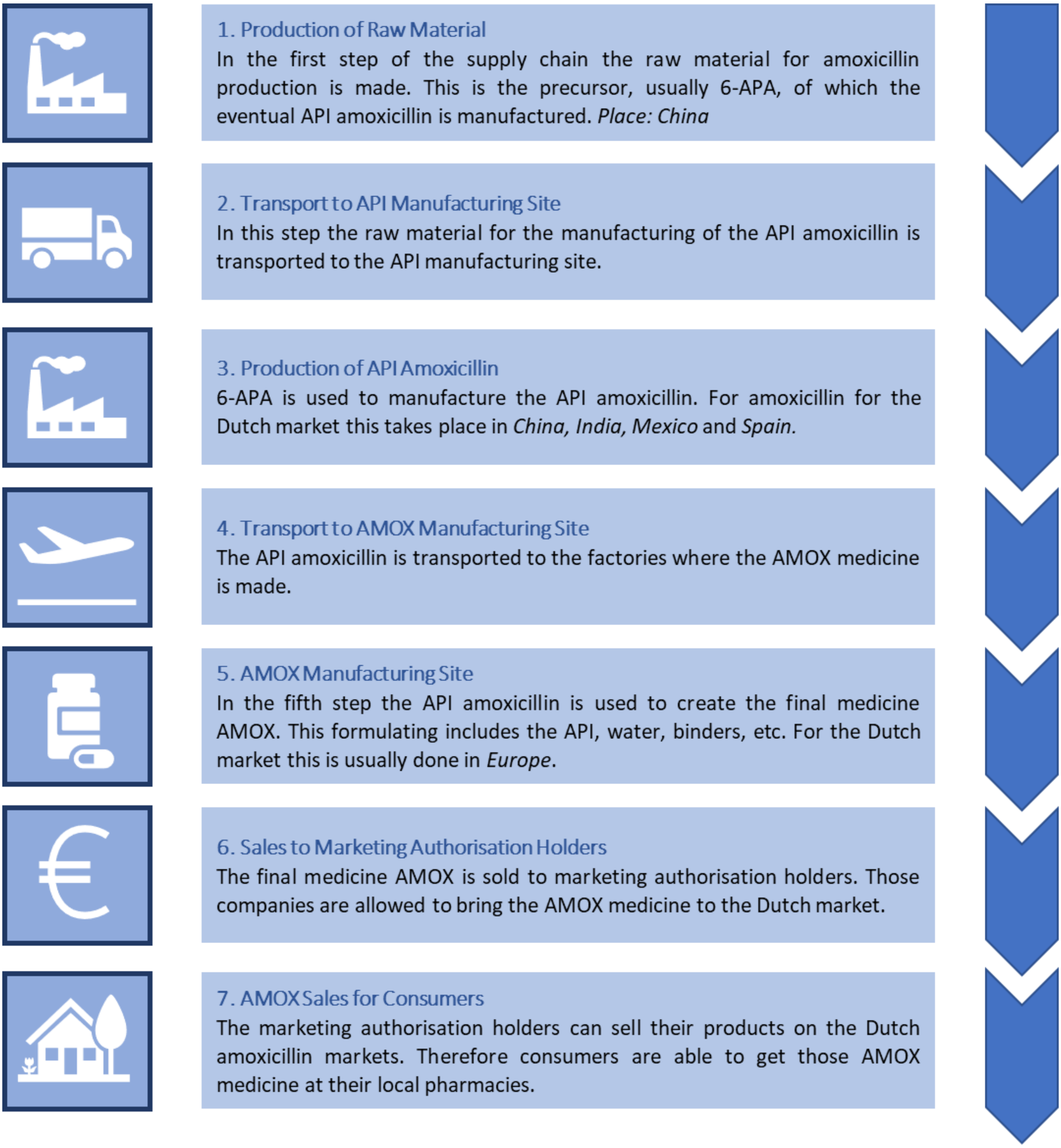

Figure 7: Supply chain of amoxicillin for the Dutch market.

4.2 Grey Water Footprint

In this chapter the main results about the GWF are given. This primarily concerns the minimum, maximum and median values. The MIN values are the best-case scenario values and the MAX values are the worst-case scenarios. In appendix *C* the tables with all the results are displayed.

GWF of amoxicillin production

The GWFs for the amoxicillin production process are between 5,70*10^7 and 6,15*10^9 m^3/day. The 108 GWFs are divided into 8 intervals (equation 2) and an additional rest interval to display values that are higher than the other results. The histogram to visualise this is shown in *Figure 8* together with the frequencies of values in each interval.

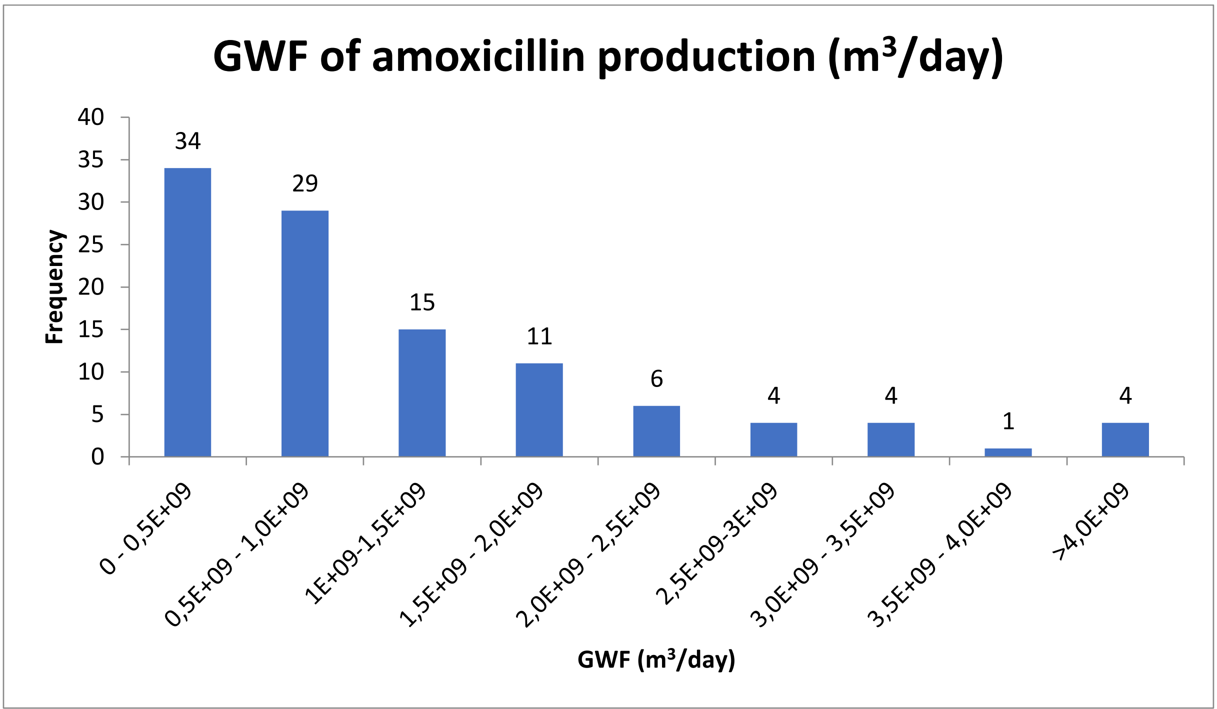

Figure 8: Histogram of the GWFs of amoxicillin production process indicating how many of the 108 values are part of a specific GWF interval.

GWF per gram amoxicillin

The GWF per gram amoxicillin produced is calculated after the GWF of the amoxicillin production process was determined. The GWF of amoxicillin production is mentioned in m^3/gram. Dividing the GWF of the amoxicillin production process by the amount of amoxicillin produced results in 108 different GWFs per gram amoxicillin produced.

The GWFs per gram amoxicillin are between 0,99 m^3/gram and 107,59 m^3/gram. The intervals of the GWF results are displayed in *Figure 9* on page 20.

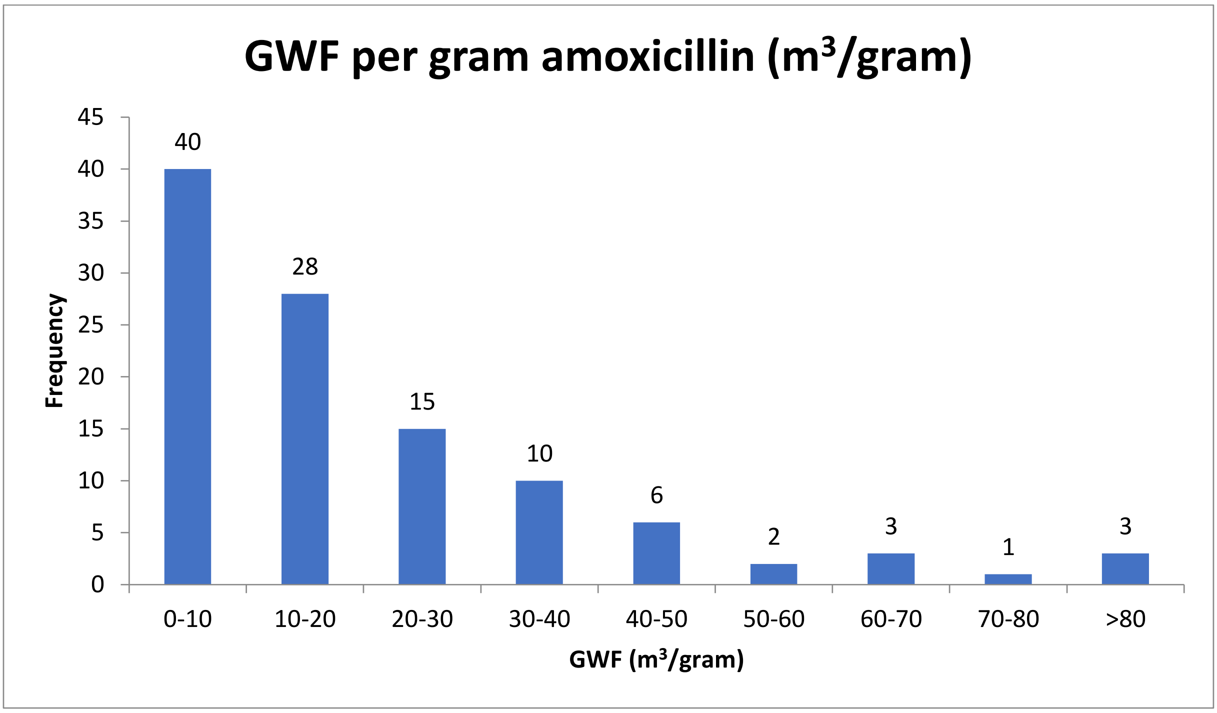

Figure 9: Histogram of the GWFs per gram amoxicillin produced indicating how many of the 108 values are part of a specific GWF interval.

Average GWF per capita in the Netherlands

The amount of grams consumed annually in the Netherlands equalled the amount of DDD's multiplied by the value of 1 DDD. This is $11.866.700\ DDD * 1{,}5\ gram = 17.800.050\ gram/year$ (WHO Collaborating Centre for Drug Statistics Methodology, 2019; Zorginstituut Nederland, 2019). This is used to calculate the average GWF per capita in the Netherlands.

The GWFs per capita in the Netherlands are between 1,02 m^3/year and 109,92 m^3/year per capita. The intervals of the GWF results are displayed in *Figure 10*.

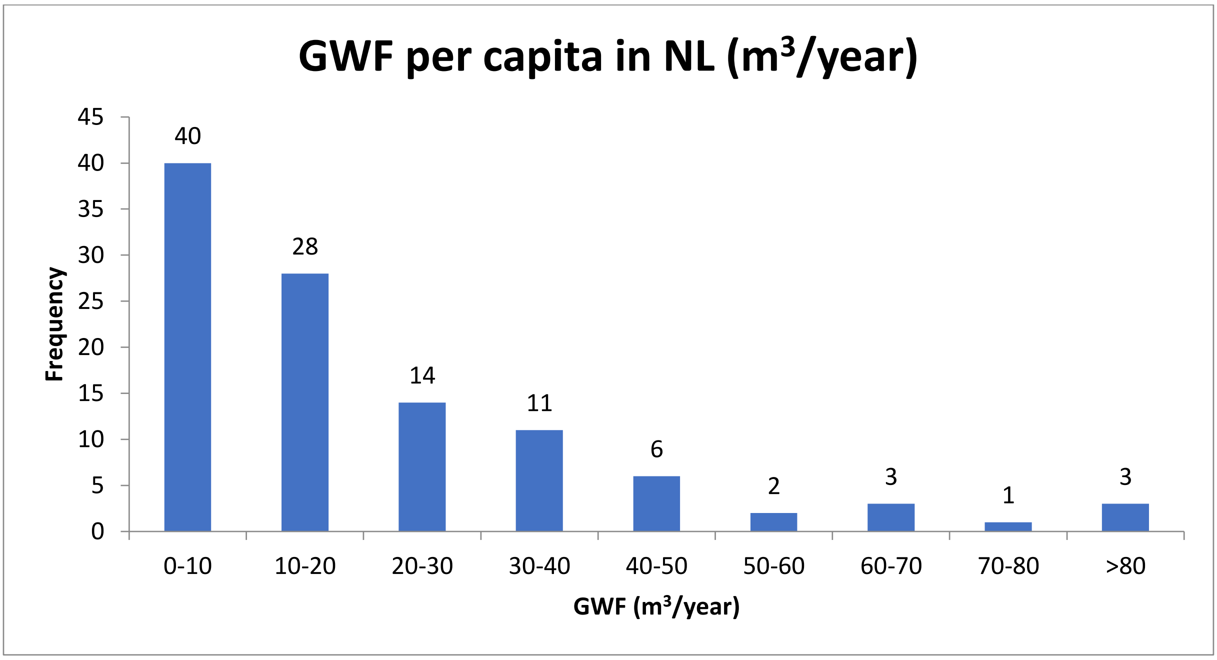

Figure 10: Histogram of the average GWFs of amoxicillin production per capita in NL indicating how many of the 108 values are part of a specific GWF interval.

Average GWF per amoxicillin user in the Netherlands

The average GWFs per amoxicillin user in the Netherlands are calculated between 15,83 m^3/year and 1.706,81 m^3/year per amoxicillin user. The intervals of the GWF results are displayed in *Figure 11*.

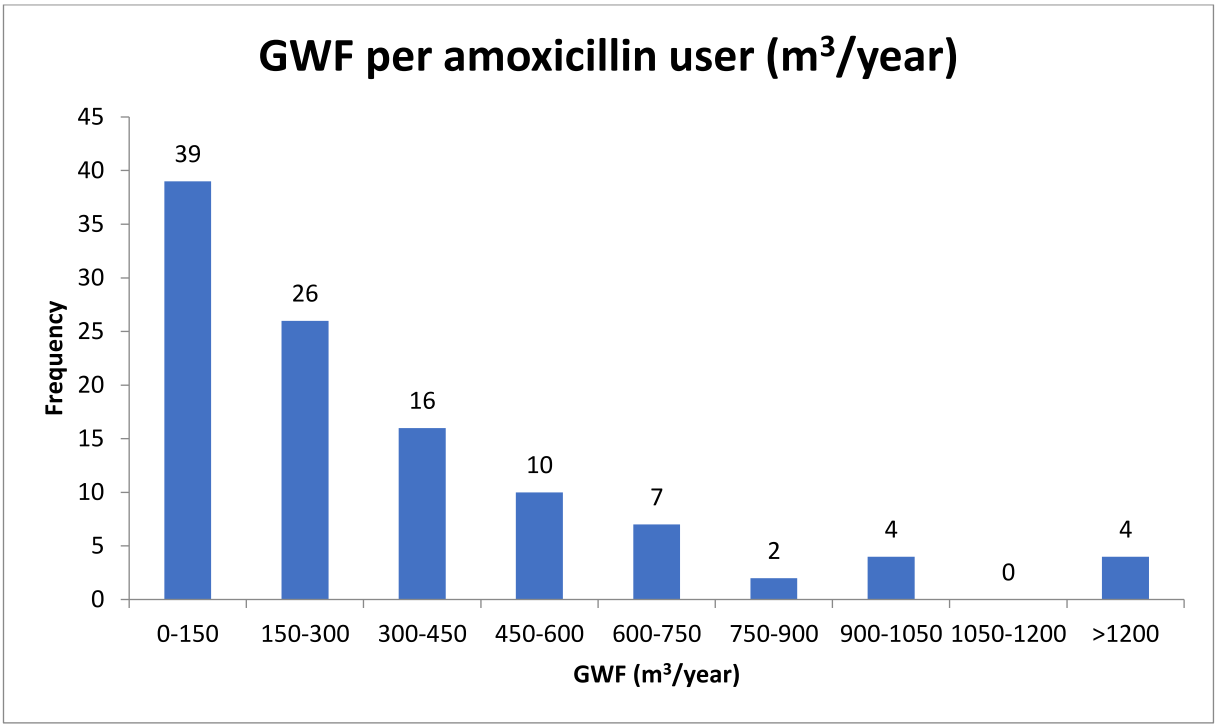

Figure 11: Histogram of average GWFs of amoxicillin production per amoxicillin user indicating how many of the 108 values are part of a specific GWF interval.

In all histograms it is clearly visualised that the highest 4 intervals account less then 10% to the total of 108 results. Therefore the median is used to estimate the GWF of each entity, since by using the median the extreme values are not taken into account. This results in the following GWFs of amoxicillin production per entity:

Table 3: GWFs of amoxicillin production.

Entity	GWF
GWF of amoxicillin production	$8{,}26*10^8$ m^3/day
GWF per gram amoxicillin produced	14,5 m^3/gram
Average GWF of amoxicillin production per capita in NL	14,8 m^3/year
Average GWF of amoxicillin production per amoxicillin user in NL	229,3 m^3/year

The results regarding the average GWF per capita and per amoxicillin user are compared to the total WF of a Dutch capita, which is 2300 m^3/year (Oel et al., 2008). The calculated minimum GWF, median and maximum GWF per capita and per amoxicillin user are compared to the average WF of a Dutch resident in *Figure 12* on page 22. As shown in this figure, the difference between best- (MIN) and worst-case (MAX) scenario is significant, especially compared to the total WF per capita in the Netherlands.

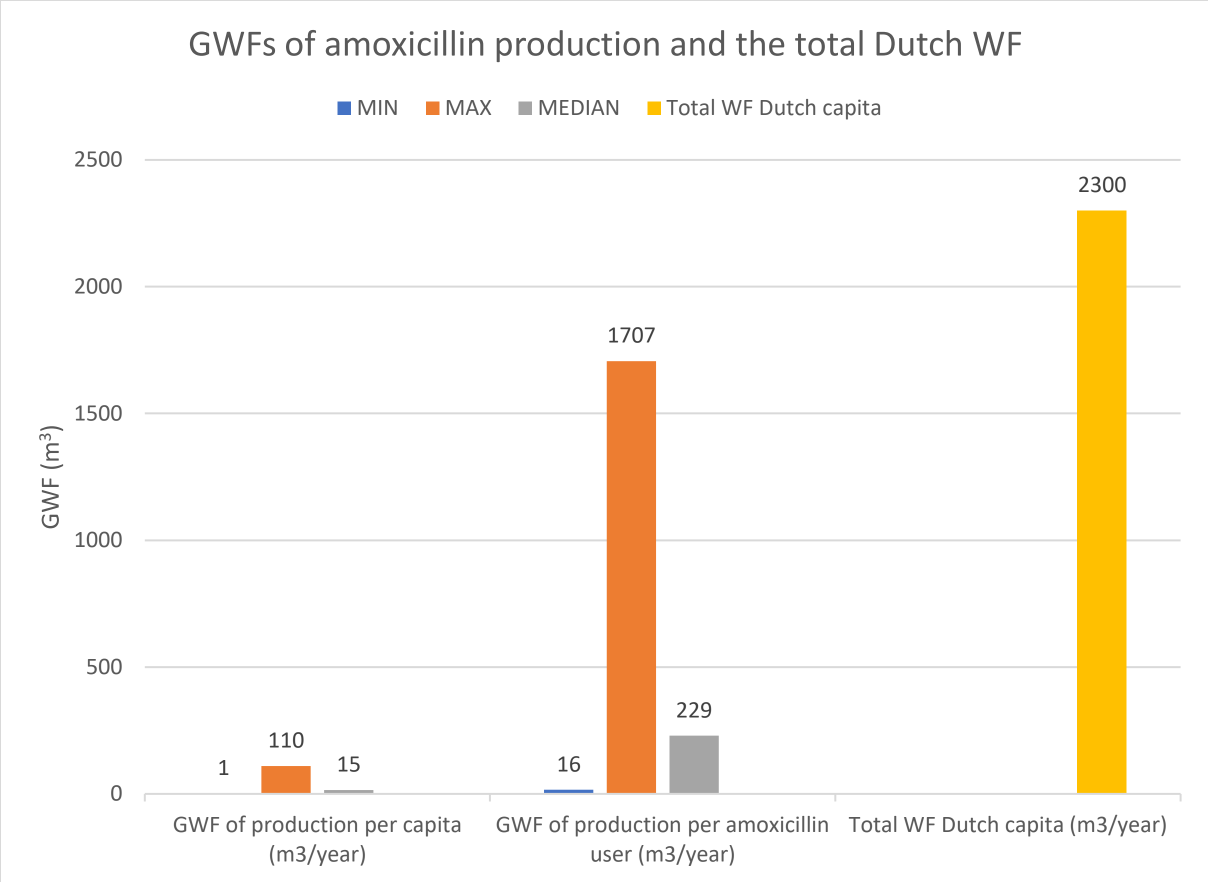

Figure 12: MIN, MAX and MEDIAN of the GWFs of amoxicillin production per capita and per amoxicillin user compared to the total WF of a Dutch resident.

GWF of amoxicillin consumption

The GWF of amoxicillin consumption equalled the load of amoxicillin that ends up in the environment through human consumption divided by the C_{max}. The load that ends up in the environment is 1361,7 kilogram per year. The GWF of amoxicillin is then for the following C_{max}:

Table 4: GWFs of amoxicillin consumption taking into account different maximum concentrations.

C_{max} (µg/L)	GWF (m^3/year)
0,078	$1{,}7*10^{10}$
0,10	$1{,}4*10^{10}$
0,25	$5{,}4*10^{9}$

The average GWF of amoxicillin consumption per capita, calculated by dividing the total GWF of amoxicillin consumption by the total Dutch inhabitants resulted in three GWFs shown in *Table 5.* The average GWF of amoxicillin consumption per amoxicillin user, calculated by dividing the total GWF of amoxicillin consumption by the total amoxicillin users in the Netherlands, is also shown in *Table 5*.

Table 5: MIN, MAX and MEDIAN of the average GWFs per capita and per amoxicillin user in the Netherlands.

	Average GWF per capita (m^3/year)	Average GWF per amoxicillin user (m^3/year)
MIN	313	4855
MAX	1002	15559
MEDIAN	782	12136

The MIN, MAX and MEDIAN GWFs of amoxicillin consumption and production, per capita and per amoxicillin user, are compared to the total WF per Dutch resident. This comparison is displayed in *Figure 13*.

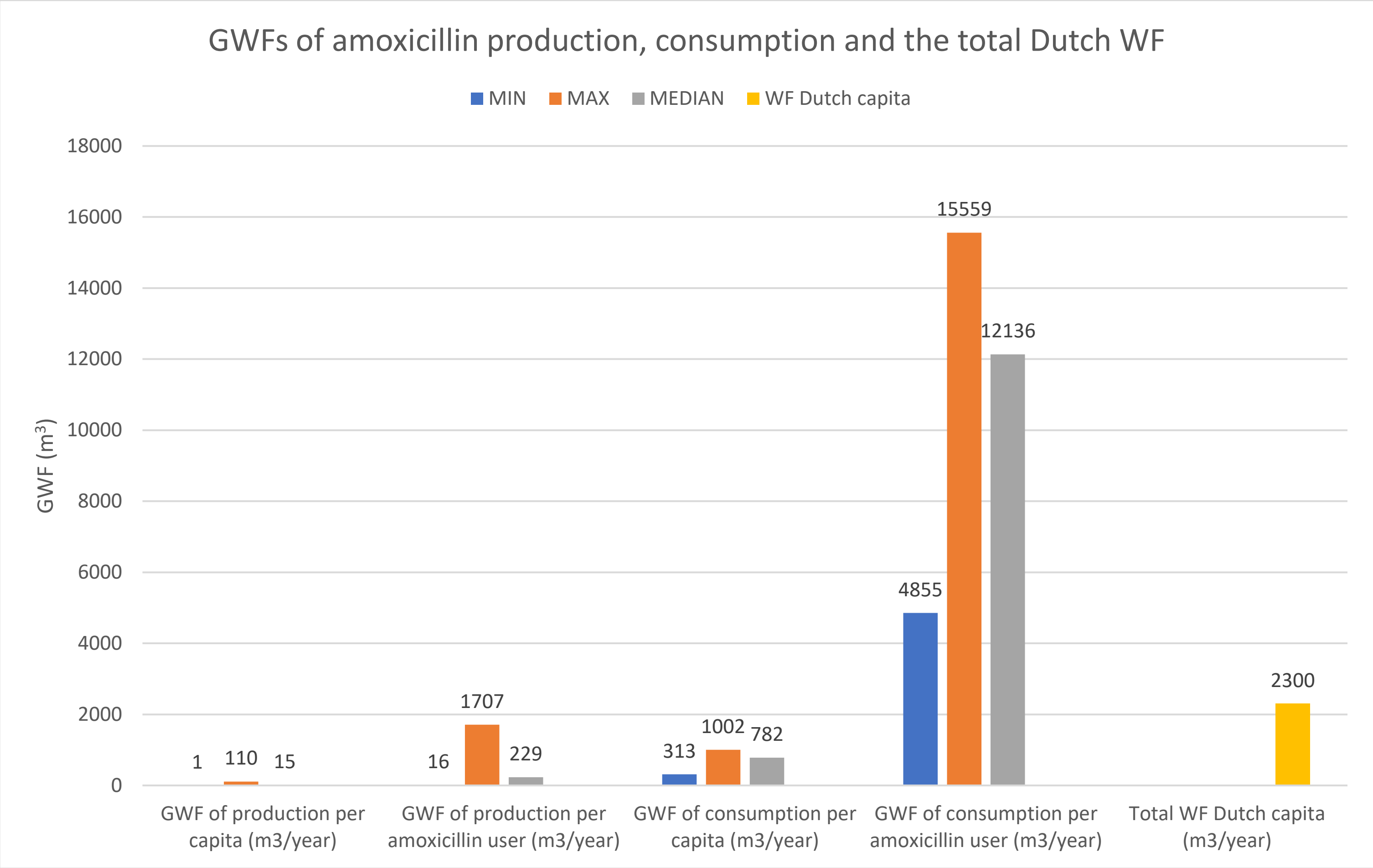

Figure 13: MIN, MAX and MEDIAN of the GWFs of amoxicillin production and consumption, per capita and per amoxicillin user, compared to the total WF of a Dutch capita.

Those results complete the GWF of amoxicillin per capita and per amoxicillin user in the Netherlands since the GWF of amoxicillin production and consumption are both calculated. The results per capita and per amoxicillin user are listed in resp. Table 6 and *Table 7*. The median value is used, since by using the median the extreme values, which do not represent the overall distribution of values, are not taken into account.

Table 6: Results GWF of amoxicillin per capita in NL

Entity	GWF
GWF of amoxicillin production per capita in NL	14,8 m^3/year
GWF of amoxicillin consumption per capita in NL	781,6 m^3/year
Total GWF of amoxicillin per capita in NL	796,3 m^3/year

Table 7: Results GWF of amoxicillin per amoxicillin user in NL

Entity	GWF
GWF of amoxicillin production per amoxicillin user in NL	229,3 m^3/year
GWF of amoxicillin consumption per amoxicillin user in NL	12136,4 m^3/year
Total GWF of amoxicillin per amoxicillin user in NL	12365,7 m^3/year

5. Discussion

Limitations and uncertainties

The several parameters used in the GWF calculations were based on data found in literature and by making assumptions. It was difficult to find data for this research since the pharmaceutical industry does not make data about supply chains publicly available. This resulted in not implementing data from the pharmaceutical industry directly, but via literature studies. The studies that were used to find data described treatment options for amoxicillin wastewater of production, but none of the studies stated the amount of amoxicillin that was produced during the production process. Therefore, the amount of amoxicillin produced was estimated. The results showed that using different parameters could affect the GWF substantially, since the maximum value is sometimes 100 times higher than the minimum value. This is due to uncertainties in the data since loads in manufacturers' discharges could not be obtained.

Further, aspects of the entire supply chain of amoxicillin are not taken into account in the GWF study. The precursors of amoxicillin already have pharmaceutical activity. This is the first step in the supply chain and the first process of obtaining the medicine AMOX. Moreover, the formulation process of AOMX medicine, is neither taken into account. So only the GWF of the manufacturing of the API amoxicillin is considered and not the entire GWF of AMOX production.

The variable C_{max} which was used in the GWF calculations is represented by three different values, resp. 0,078, 0,10 and 0,25 µg/L. As stated in chapter *3.6*, the highest 4 intervals used in the histogram visualisation account to less than 10% of the total 108 results. Of those 10% (11 values), the 0,078 µg/L PNEC value is responsible for 7 values. On the other hand, the highest PNEC value of 0,25 µg/L is responsible for 8 of the 11 lowest values. This emphasises the importance and sensitivity of the variable C_{max} and the different PNEC values that are used in GWF calculations.

GWFs of pharmaceuticals

The median and maximum of the GWFs of amoxicillin production per capita calculated in this study are 14,8 and 109,9 m^3/year. Since the total Dutch WF per capita is 2300 m^3/year (Oel et al., 2008), this GWF of amoxicillin is significant. This is the case since amoxicillin is only a small part of the pharmaceutical spectrum. It is interesting to see that the GWF of only one pharmaceutical accounts to such significant percentages to the entire WF per capita. When looking at the GWF per amoxicillin user in the Netherlands the part in the total Dutch WF per person is even higher. This median GWF of 229,3 m^3/year is more than 16% of the total WF per person. The maximum GWF per amoxicillin user of 1706,8 m^3/year accounts to 74% of the total WF per person in the Netherlands.

The novel part of this study is related to the GWF of pharmaceutical production. This has never been done before, and it is therefore not comparable to other literature on GWF of pharmaceutical production. However when comparing the GWF per gram amoxicillin to for example the WF of beef, the results are significant. The average WF of beef, which is the biggest of all animal meat, is 0,0154 m^3/gram (Mekonnen & Hoekstra, 2012). Comparing this to the median GWF per gram amoxicillin, which is 14,5 m^3/gram mentions the importance of researching GWF of pharmaceutical production.

The GWFs of amoxicillin consumption were calculated as well. This led to mean values of 781,6 m^3/year for amoxicillin consumption per capita and to 12136,4 m^3/year for amoxicillin consumption per amoxicillin user. The maximum values were even higher. Those values are extremely high compared to the GWF of production and to the Dutch WF per capita. This is partly due to average removal rate of the WWTP (87,25%). This was the only WWTP in Europe that had data on amoxicillin removal rates, therefore more research on this should be done to increase the reliability of these calculations.

However, the values of GWF of amoxicillin consumption could be overestimated since normal working WWTPs that are treating human excrements should be able to break down amoxicillin in wastewater easily (Derksen & ter Laak, 2013). This could mean that the WWTP investigated in Italy is not working properly, or that Dutch WWTP are more efficient in treating amoxicillin in domestic wastewater. Since this removal rate is a variable of such significance, more research on those removal rates of domestic WWTPs should be conducted for more accurate results.

6. Conclusion

Water pollution of amoxicillin production is displayed in this research by calculating GWFs in four entities. The GWF of amoxicillin production accounts for a significant fraction in relation to the total WF per capita and the WF of animal products. It is therefore needed to regulate environmental standards and wastewater pollution of pharmaceutical manufacturing sites. The pollution indicator that is used in this researched emphasises the need to attack pharmaceutical pollution. By not taking actions, too many pollutants will be part of wastewater streams of pharmaceutical manufacturing sites. Besides pharmaceutical pollution, pollution from human antibiotic consumption should be taken into account as well. Without well functioning domestic WWTPs, environmental pollution through excreted pharmaceutical fractions by humans will also increase water pollution. Furthermore the world population is likely to rise which increases the demand for antibiotics like amoxicillin. Due to climate change water scarcity will occur more often. Those aspects will eventually result in more ABR and even more freshwater pollution. This is a great threat to human health, and the pharmaceutical industry should therefore act responsibly to prevent further damage to the environment.

6.1. Recommendations for further research

Since this research is the first that has been done about the GWF of pharmaceutical manufacturing, more research needs to be done. In following research concerning the GWF of pharmaceutical manufacturing, this study can be used. To complete the GWF calculations of amoxicillin manufacturing there are more aspects that need to be taken into account. The by-products that occur during the process of obtaining amoxicillin should be investigated regarding their pharmaceutical activity and their pollutant loads in wastewater. This is the same for the precursors of amoxicillin production. Those have pharmaceutical activity already, but this GWF should be calculated to complement the GWF calculations of amoxicillin production. To increase uncertainties in further research, more accurate data is needed. Preferably data that is delivered by the pharmaceutical industry directly. This will lead to more accurate results, since less data is estimated in that case. Further research regarding removal rates of domestic WWTP should be conducted as well, since this variable is of great importance in the GWF of amoxicillin consumption. More and better founded data will improve the results for both the GWF of amoxicillin production and consumption, which together complete the entire GWF of amoxicillin.

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Appendices

A. Market authorisation holders

Table 8: List of authorisation holders of registered amoxicillin trihydrate medicine in the Netherlands (CBG, 2020).

Market Authorisation Holder	Proprietary amoxicillin trihydrate products
Apotex Europe B.V.	- Amoxicillin Apotex 500 mg, capsules
Astellas Pharma Europe B.V.	- Flemoxin Solutab 1000 mg, dispersible tablets - Flemoxin Solutab 125 mg, dispersible tablets - Flemoxin Solutab 250 mg, dispersible tablets - Flemoxin Solutab 375 mg, dispersible tablets - Flemoxin Solutab 500 mg, dispersible tablets - Flemoxin Solutab 750 mg, dispersible tablets
Aurobindo Pharma B.V.	- Amoxicillin Aurobindo Disper 375 mg, dispersible tablets - Amoxicillin Aurobindo Disper 500 mg, dispersible tablets - Amoxicillin Aurobindo Disper 750 mg, dispersible tablets
Centrient Pharmaceuticals Netherlands B.V.	- Amoxicillin Centrient 1000 mg, dispersible tablets - Amoxicillin Centrient 1000 mg, dispersible tablets - Amoxicillin Centrient 125 mg/5 ml, powder for oral suspension - Amoxicillin Centrient 250 mg capsules, hard - Amoxicillin Centrient 250 mg/5 ml, powder for oral suspension - Amoxicillin Centrient 250 mg/5 ml, powder for oral suspension - Amoxicillin Centrient 500 mg capsules, hard - Amoxicillin Centrient 500 mg, dispersible tablets - Amoxicillin Centrient 500 mg/5 ml, powder for oral suspension - Amoxicillin Centrient 750 mg, dispersible tablets
Focus Care Pharmaceuticals B.V.	- Amoxicillin forte sugar free 250 mg/5 ml Focus Care, powder for oral suspension - Amoxicillin 500 mg Focus, capsules, hard
Mylan B.V.	- Amoxicillin capsules Mylan 500 mg, capsules
N.V. Eurogenerics S.A.	- Amoxicillin Eurogenerics 125 mg/5 ml, powder for oral suspension - Amoxicillin Eurogenerics 250 mg/5 ml, powder for oral suspension - Amoxicillin Eurogenerics 500 mg/5 ml, powder for oral suspension - Amoxicillin Eurogenerics 500 mg/5 ml, powder for oral suspension
RIA Generics Ltd	- Amoxicillin dispers RIA 500 mg, dispersible tablets - Amoxicillin dispers RIA 750 mg, dispersible tablets - Amoxicillin RIA 500 mg, capsules
Sandoz B.V.	- Amoxicillin disper 1000, dispersible tablets - Amoxicillin disper 500, dispersible tablets - Amoxicillin disper 750, dispersible tablets - Amoxicillin Sandoz disper 1000 mg, dispersible tablets - Amoxicillin Sandoz disper 500 mg, dispersible tablets - Amoxicillin Sandoz disper 750 mg, dispersible tablets - Amoxicillin Sandoz Forte 250 mg/5 ml, powder for oral suspension - Amoxicillin Sandoz 125 mg/5 ml, powder for oral suspension - Amoxicillin Sandoz 500 mg, hard capsules
Teva B.V.	- Amoxicillin Disp Teva 1000 mg, dispersible tablets

	- Amoxicillin Disp Teva 500 mg, dispersible tablets - Amoxicillin Disp Teva 750 mg, dispersible tablets - Amoxicillin Teva 125 mg/5 ml powder for oral suspension - Amoxicillin Teva 250 mg/5 ml powder for oral suspension - Amoxicillin Teva 500 mg, capsules

B. AMOX manufacturers

Table 9: Information of registered amoxicillin-based medicine for human use in the Netherlands (CBG, 2020).

Product Name	Market Authorisation Holder	Pharmaceutical Form	Manufacturer
Amoxicilline Apotex 500 mg, capsules	Apotex Europe BV	Capsule, hard	Apotex Nederland BV
Amoxicilline Aurobindo Disper 375 mg, dispergeerbare tabletten	Aurobindo Pharma B.V.	DT	- APL Swift Services (Malta) Limited - Arrow Génériques - Generis Farmacêutica
Amoxicilline Aurobindo Disper 500 mg, dispergeerbare tabletten	Aurobindo Pharma B.V.	DT	- APL Swift Services (Malta) Limited - Arrow Génériques - Generis Farmacêutica
Amoxicilline Aurobindo Disper 750 mg, dispergeerbare tabletten	Aurobindo Pharma B.V.	DT	- APL Swift Services (Malta) Limited - Arrow Génériques - Generis Farmacêutica
Amoxicilline capsules Mylan 500 mg, capsules	Mylan B.V.	Capsule, hard	- Mylan B.V. - Generics [UK] Limited - Mylan Hungary Kft
Amoxicilline Centrient 1000 mg, dispergeerbare tabletten	Centrient Pharmaceuticals Netherlands B.V.	DT	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.
Amoxicilline Centrient 1000 mg, dispergeerbare tabletten	Centrient Pharmaceuticals Netherlands B.V.	DT	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.
Amoxicilline Centrient 125 mg/5 ml, poeder voor orale suspensie	Centrient Pharmaceuticals Netherlands B.V.	Powder for oral suspension	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.
Amoxicilline Centrient 250 mg capsules, hard	Centrient Pharmaceuticals Netherlands B.V.	Capsule, hard	Antibiotice S.A.
Amoxicilline Centrient 250 mg/5 ml, poeder voor orale suspensie	Centrient Pharmaceuticals Netherlands B.V.	Powder for oral suspension	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.
Amoxicilline Centrient 250 mg/5 ml, poeder voor orale suspensie	Centrient Pharmaceuticals Netherlands B.V.	Powder for oral suspension	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.
Amoxicilline Centrient 500 mg capsules, hard	Centrient Pharmaceuticals Netherlands B.V.	Capsule, hard	Antibiotice S.A.
Amoxicilline Centrient 500 mg, dispergeerbare tabletten	Centrient Pharmaceuticals Netherlands B.V.	DT	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.
Amoxicilline Centrient 500 mg/5 ml, poeder voor orale suspensie	Centrient Pharmaceuticals Netherlands B.V.	Powder for oral suspension	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.

Amoxicilline Centrient 750 mg, dispergeerbare tabletten	Centrient Pharmaceuticals Netherlands B.V.	DT	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.
Amoxicilline Disp Teva 1000 mg, dispergeerbare tabletten	Teva BV	DT	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.
Amoxicilline Disp Teva 500 mg, dispergeerbare tabletten	Teva BV	DT	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.
Amoxicilline Disp Teva 750 mg, dispergeerbare tabletten	Teva BV	DT	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.
Amoxicilline disper 1000, dispergeerbare tabletten	Sandoz B.V.	DT	Sandoz GmbH
Amoxicilline disper 500, dispergeerbare tabletten	Sandoz B.V.	DT	Sandoz GmbH
Amoxicilline disper 750, dispergeerbare tabletten	Sandoz B.V.	DT	Sandoz GmbH
Amoxicilline dispers RIA 500 mg, dispergeerbare tabletten	RIA Generics Ltd	DT	
Amoxicilline dispers RIA 750 mg, dispergeerbare tabletten	RIA Generics Ltd	DT	
Amoxicilline Eurogenerics 125 mg/5 ml, poeder voor orale suspensie	N.V. Eurogenerics S.A.	Powder for oral suspension	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.
Amoxicilline Eurogenerics 250 mg/5 ml, poeder voor orale suspensie	N.V. Eurogenerics S.A	Powder for oral suspension	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.
Amoxicilline Eurogenerics 500 mg/5 ml, poeder voor orale suspensie	N.V. Eurogenerics S.A	Powder for oral suspension	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.
Amoxicilline Eurogenerics 500 mg/5 ml, poeder voor orale suspensie	N.V. Eurogenerics S.A	Powder for oral suspension	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.
Amoxicilline forte suikervrij 250 mg/5 ml Focus Care, poeder voor orale suspensie	Focus Care Pharmaceuticals B.V.	Powder for oral suspension	
Amoxicilline RIA 500 mg, capsules	RIA Generics Ltd	Capsule, hard	
Amoxicilline Sandoz disper 1000 mg, dispergeerbare tabletten	Sandoz B.V.	DT	Sandoz GmbH
Amoxicilline Sandoz disper 500 mg, dispergeerbare tabletten	Sandoz B.V.	DT	Sandoz GmbH
Amoxicilline Sandoz disper 750 mg, dispergeerbare tabletten	Sandoz B.V.	DT	Sandoz GmbH
Amoxicilline Sandoz Forte 250 mg/5 ml, poeder voor orale suspensie	Sandoz B.V.	Powder for oral suspension	Sandoz GmbH
Amoxicilline Sandoz 125 mg/5 ml, poeder voor orale suspensie	Sandoz B.V.	Powder for oral suspension	Sandoz GmbH
Amoxicilline Sandoz 500 mg, harde capsules	Sandoz B.V.	Capsule, hard	Sandoz GmbH
Amoxicilline Teva 125 mg/5 ml poeder voor orale suspensie	Teva BV	Powder for oral suspension	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.

Amoxicilline Teva 250 mg/5 ml poeder voor orale suspensie	Teva BV	Powder for oral suspension	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.
Amoxicilline Teva 500 mg, capsules	Teva BV	Capsule, hard	- PenCef Pharma GmbH - HAUPT Pharma Latina S.r.L.
Amoxicilline 500 mg Focus, capsules, hard	Focus Care Pharmaceuticals B.V.	Capsule, hard	Antibiotice S.A.
Flemoxin Solutab 1000 mg, dispergeerbare tabletten	Astellas Pharma Europe B.V.	DT	- Astellas Pharma Europe B.V. - HAUPT Pharma Latina S.r.L.
Flemoxin Solutab 125 mg, dispergeerbare tabletten	Astellas Pharma Europe B.V.	DT	- Astellas Pharma Europe B.V. - HAUPT Pharma Latina S.r.L.
Flemoxin Solutab 250 mg, dispergeerbare tabletten	Astellas Pharma Europe B.V.	DT	- Astellas Pharma Europe B.V. - HAUPT Pharma Latina S.r.L.
Flemoxin Solutab 375 mg, dispergeerbare tabletten	Astellas Pharma Europe B.V.	DT	- Astellas Pharma Europe B.V. - HAUPT Pharma Latina S.r.L.
Flemoxin Solutab 500 mg, dispergeerbare tabletten	Astellas Pharma Europe B.V.	DT	- Astellas Pharma Europe B.V. - HAUPT Pharma Latina S.r.L.
Flemoxin Solutab 750 mg, dispergeerbare tabletten	Astellas Pharma Europe B.V.	DT	- Astellas Pharma Europe B.V. - HAUPT Pharma Latina S.r.L.

C. GWF results

The parameters and GWF results are mentioned in this appendix.

Parameters calculation of GWFs

Load:	The load depends on the volume of the effluent and the concentration of the effluent). Effluent concentration depends on the removal rate of the WWTP and the concentration of the influent of the WWTP.
C_*max*	The maximum concentration issued by PNEC values and Indian governmental figures.
C_*nat*	The natural concentration is 0 when it comes to products that are entirely made my humans and do not occur in the environment usually.
GWF	The GWF of the process is calculated by using the loads and the three different maximum concentrations.
GWF per gram amoxicillin	When one knows the amount of amoxicillin produced in the factory, the GWF per gram produced amoxicillin can be estimated by dividing the GWF of the process (m^3/day) by the amount amoxicillin produced (g/day).
GWF per capita in NL	This can be estimated when the total amount of amoxicillin consumed in NL is known. The total GWF of this consumption in a year is divided by the amount of inhabitants of NL (m^3/year). Total amount consumed is total DDD multiplied by the amount of grams 1 DDD represents. For amoxicillin for oral use this is 1,5 g.
GWF per amoxicillin user	Same method as per capita, but then divided by the total amount of amoxicillin users instead of dividing by the total population of NL.

Load calculations

Table 10: Calculations of the load and C_{max} regarding the GWF calculations.

Load (gram/day) calculations:							C_*max* (gram/L)
Removal rate	**Concentration influent (g/L)**	**Option**	**Concentration effluent (g/L)**	**Volume L/day**	**Option**	**Load (g/day)**	C_*max* (g/L)
0	0,061	1	0,061	1169000	1	71309	0,000000078 (*1*)
0,216	0,092	2	0,047824	2031200	2	55906	0,0000001 (*2*)
0,5	0,171	3	0,0305	2805000	3	35655	0,00000025 (*3*)
0,8		4	0,0122		4	14262	
		5	0,092		5	107548	
		6	0,072128		6	84318	
		7	0,046		7	53774	
		8	0,0184		8	21510	
		9	0,171		9	199899	
		10	0,134064		10	156721	
		11	0,0855		11	99950	
		12	0,0342		12	39980	
					13	123903	
					14	97140	
					15	61952	
					16	24781	
					17	186870	
					18	146506	
					19	93435	
					20	37374	
					21	347335	
					22	272311	
					23	173668	
					24	69467	
					25	171105	
					26	134146	
					27	85553	
					28	34221	
					29	258060	
					30	202319	
					31	129030	
					32	51612	
					33	479655	
					34	376050	
					35	239828	
					36	95931	

GWF amoxicillin production result tables

Table 11: GWF of the production process of amoxicillin production.

	GWF Process 0,078 microgram/L	0,1 microgram/L	0,25 microgram/L
Option	**GWF_*process* (m³/day) (1)**	**GWF_*process* (m³/day) (2)**	**GWF_*process* (m³/day) (3)**
1	9,14E+08	7,13E+08	2,85E+08
2	7,17E+08	5,59E+08	2,24E+08
3	4,57E+08	3,57E+08	1,43E+08
4	1,83E+08	1,43E+08	5,70E+07
5	1,38E+09	1,08E+09	4,30E+08
6	1,08E+09	8,43E+08	3,37E+08
7	6,89E+08	5,38E+08	2,15E+08
8	2,76E+08	2,15E+08	8,60E+07
9	2,56E+09	2,00E+09	8,00E+08
10	2,01E+09	1,57E+09	6,27E+08
11	1,28E+09	9,99E+08	4,00E+08
12	5,13E+08	4,00E+08	1,60E+08
13	1,59E+09	1,24E+09	4,96E+08
14	1,25E+09	9,71E+08	3,89E+08
15	7,94E+08	6,20E+08	2,48E+08
16	3,18E+08	2,48E+08	9,91E+07
17	2,40E+09	1,87E+09	7,47E+08
18	1,88E+09	1,47E+09	5,86E+08
19	1,20E+09	9,34E+08	3,74E+08
20	4,79E+08	3,74E+08	1,49E+08
21	4,45E+09	3,47E+09	1,39E+09
22	3,49E+09	2,72E+09	1,09E+09
23	2,23E+09	1,74E+09	6,95E+08
24	8,91E+08	6,95E+08	2,78E+08
25	2,19E+09	1,71E+09	6,84E+08
26	1,72E+09	1,34E+09	5,37E+08
27	1,10E+09	8,56E+08	3,42E+08
28	4,39E+08	3,42E+08	1,37E+08
29	3,31E+09	2,58E+09	1,03E+09
30	2,59E+09	2,02E+09	8,09E+08
31	1,65E+09	1,29E+09	5,16E+08
32	6,62E+08	5,16E+08	2,06E+08
33	6,15E+09	4,80E+09	1,92E+09
34	4,82E+09	3,76E+09	1,50E+09
35	3,07E+09	2,40E+09	9,59E+08
36	1,23E+09	9,59E+08	3,84E+08

Table 12: GWF per gram amoxicillin produced

Gram amoxicillin produced/day		**GWF per gram amoxicillin**		
amoxicillin produced (gram/day)	*Option*	*m^3/gram amoxicillin (1)*	*m^3/gram amoxicillin (2)*	*m^3/gram amoxicillin (3)*
57158126,03	1	16,0	12,5	5,0
	2	12,5	9,8	3,9
amoxicillin produced (gram/year)	3	8,0	6,2	2,5
20862716000	4	3,2	2,5	1,0
	5	24,1	18,8	7,5
	6	18,9	14,8	5,9
	7	12,1	9,4	3,8
	8	4,8	3,8	1,5
	9	44,8	35,0	14,0
	10	35,2	27,4	11,0
	11	22,4	17,5	7,0
	12	9,0	7,0	2,8
	13	27,8	21,7	8,7
	14	21,8	17,0	6,8
	15	13,9	10,8	4,3
	16	5,6	4,3	1,7
	17	41,9	32,7	13,1
	18	32,9	25,6	10,3
	19	21,0	16,3	6,5
	20	8,4	6,5	2,6
	21	77,9	60,8	24,3
	22	61,1	47,6	19,1
	23	39,0	30,4	12,2
	24	15,6	12,2	4,9
	25	38,4	29,9	12,0
	26	30,1	23,5	9,4
	27	19,2	15,0	6,0
	28	7,7	6,0	2,4
	29	57,9	45,1	18,1
	30	45,4	35,4	14,2
	31	28,9	22,6	9,0
	32	11,6	9,0	3,6
	33	107,6	83,9	33,6
	34	84,3	65,8	26,3
	35	53,8	42,0	16,8
	36	21,5	16,8	6,7

Table 13: Average GWF of amoxicillin production per capita in NL

Gram amoxicillin consumed/year		0	GWF per capita		
amoxicillin consumed (g/year)		Option	m^3/year (1)	m^3/year (2)	m^3/year (3)
	17800050	1	16,3	12,7	5,1
		2	12,8	10,0	4,0
Dutch inhabitants		3	8,2	6,4	2,5
	17422947	4	3,3	2,5	1,0
		5	24,6	19,2	7,7
Dutch amoxicillin users		6	19,3	15,1	6,0
	1122000	7	12,3	9,6	3,8
		8	4,9	3,8	1,5
		9	45,8	35,7	14,3
		10	35,9	28,0	11,2
		11	22,9	17,9	7,1
		12	9,2	7,1	2,9
		13	28,4	22,1	8,9
		14	22,3	17,4	6,9
		15	14,2	11,1	4,4
		16	5,7	4,4	1,8
		17	42,8	33,4	13,4
		18	33,6	26,2	10,5
		19	21,4	16,7	6,7
		20	8,6	6,7	2,7
		21	79,6	62,1	24,8
		22	62,4	48,7	19,5
		23	39,8	31,0	12,4
		24	15,9	12,4	5,0
		25	39,2	30,6	12,2
		26	30,7	24,0	9,6
		27	19,6	15,3	6,1
		28	7,8	6,1	2,4
		29	59,1	46,1	18,5
		30	46,4	36,2	14,5
		31	29,6	23,1	9,2
		32	11,8	9,2	3,7
		33	109,9	85,7	34,3
		34	86,2	67,2	26,9
		35	55,0	42,9	17,1
		36	22,0	17,1	6,9

Table 14: Average GWF of amoxicillin production per amoxicillin user

Gram amoxicillin consumed/year	0	GWF per amoxicillin user		
amoxicillin consumed (g/year)	Option	m^3/year (1)	m^3/year (1)	m^3/year (1)
17800050	1	253747	197922	79169
	2	198937	155171	62068
Dutch inhabitants	3	126873	98961	39584
17422947	4	50749	39584	15834
	5	382700	298506	119402
Dutch amoxicillin users	6	300037	234029	93611
1122000	7	191350	149253	59701
	8	76540	59701	23880
	9	711322	554831	221933
	10	557677	434988	173995
	11	355661	277416	110966
	12	142264	110966	44387
	13	440898	343901	137560
	14	345664	269618	107847
	15	220449	171950	68780
	16	88180	68780	27512
	17	664961	518670	207468
	18	521330	406637	162655
	19	332481	259335	103734
	20	132992	103734	41494
	21	1235960	964049	385620
	22	968993	755815	302326
	23	617980	482025	192810
	24	247192	192810	77124
	25	608861	474912	189965
	26	477347	372331	148932
	27	304431	237456	94982
	28	121772	94982	37993
	29	918283	716261	286504
	30	719934	561548	224619
	31	459141	358130	143252
	32	183657	143252	57301
	33	1706808	1331311	532524
	34	1338138	1043747	417499
	35	853404	665655	266262
	36	341362	266262	106505

GWF amoxicillin consumption results

$$WF_{grey} = \frac{L}{c_{max} - c_{nat}}$$

$$L_h = S * f_e * (1 - f_r)$$

S (g/year)	17800050	C_*max* (gram/L)	
F_e	0,6		
F_r	0,8725	C_*max* (g/L)	
L (g/year)	1361704	0,000000078 (1)	
		0,0000001 (2)	
		0,00000025 (3)	
Total GWF consumption			
GWF (1) (m3/year)	1,75E+10		
GWF (2)	1,36E+10		
GWF (3)	5,45E+09		
Per capita	17422947		
avg. GWF consumption per cap			
GWF per capita (1) (m3/year)	1001,997	MIN	312,6231
GWF per capita (2) (m3/year)	781,5577	MAX	1001,997
GWF per capita (3) (m3/year)	312,6231	MEDIAN	781,5577
Per amox user	1122000		
avg. GWF consumption per user			
GWF per user (1) (m3/year)	15559,48	MIN	4854,559
GWF per user (2) (m3/year)	12136,4	MAX	15559,48
GWF per user (3) (m3/year)	4854,559	MEDIAN	12136,4