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LCA comparison between oral and intravenous antibiotics:

The ciprofloxacin case

Author: **Nicolas De Jaegher**
Supervisor: **Patricia Luis Alconero, Hervé Jeanmart**
Readers: **Caroline Briquet, Julien De Greef, Francesco Contino,**
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Abstract

Briefly introduce the topic and the context of your research. State the overarching research question or problem.
Objective (1-2 sentences):
Clearly state the main objective(s) of the study. Mention the specific focus, e.g., comparing the environmental impact of IV vs. PO administration of CIP.
Methodology (2-3 sentences):
Briefly describe the methods or approach used in the study. Highlight that an LCA was conducted, specifying the scope and key tools used.
Key Findings (2-3 sentences):
Summarize the main results of the study. Mention if any specific impact categories favored one method over the other.
Conclusion (1-2 sentences):
Provide a concise conclusion based on your findings. Mention the broader implications or recommendations if applicable.
Keywords (optional, depending on guidelines):
Include a few keywords that encapsulate the main topics of your thesis.

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Symbols

γ	Yield	[%]
c_p	Specific heat	[J/kgK]
E	Energy	[J]
M	Molar mass	[g/mol]
m	Mass	[kg]
n	Mole	[mol]

Abbreviations

API	Active pharmaceutical ingredient
CF	Carbon footprint
CIP	Ciprofloxacin
CIP-IV	Ciprofloxacin administered in intravenously
CIP-PO	Ciprofloxacin administered orally
CVC	Central venous catheter
DDD	Daily defined dose
EoL	End-of-life
FEP	Freshwater Eco-toxicity Potential
FTIR	Fourier-transform infrared spectroscopy
FU	Functional unit
GHG	Greenhouse gases
HDPE	High-density polyethylene
ISO	International Standard Organization
IV	Intravenous
IVOS	Intravenous to oral switch

LCA	Life cycle assessment
LCI	Life cycle inventory
LCIA	Life cycle impact assessment
LVP	Large-volume injectable
MWW	Municipal wastewater
PET	Polyethylene terephthalate
PO	Per os
PP	Polypropylene
PVC	Polyvinyl chloride
PVDC	Polyvinyl Dichloride
STP	Sewage treatment plant
WWT	Wastewater treatment
WWTP	Wastewater treatment plant

Chemical compounds

Al_2O_3	Aluminium oxide
Ar	Argon
C_2H_4O	Ethylene oxide
$C_2H_6O_2$	Ethylene glycol
$C_3H_6O_2$	1,3 dioxolane
CH_2O	Formaldehyde
CH_4	Methane
CO_2	Carbon dioxide
H_2	Hydrogen
H_2O	Water
He	Helium

KOH	Potassium hydroxide
N_2	Nitrogen
N_2O	Nitrous oxide
$NaOH$	Sodium hydroxide
O_2	Oxygen
P	Phosphorus

Key concepts in the medical field

These concise definitions may not be exhaustive but are intended to clarify terms that are not commonly used outside the medical field. Some definitions were inspired by the National Institutes of Health (USA) [1], Wikipedia [2], and ChatGPT [3].

Term	**Definition**
Active Pharmaceutical Ingredient (API)	The main substance, which is biologically active, in a drug responsible for its therapeutic effects.
Bioavailability	Proportion of a drug or other substance that enters the bloodstream when introduced into the body and is available for use or storage by the body. The bioavailability is 100% when taken in IV.
Catheter	A peripheral venous catheter is a thin, flexible tube inserted into a small vein, usually in the lower part of the arm or the back of the hand. It is used to administer intravenous fluids, blood transfusions, chemotherapy, and other medications. The second type, the central venous catheter (CVC), is connected to a central line. A CVC is a longer, flexible tube inserted into a large vein in the neck, chest, or groin, reaching close to the heart. It is used for long-term intravenous therapy, including the administration of medications, fluids, blood products, and for measuring central venous pressure.
Excipient	A component of the medication that does not provide therapeutic or preventive properties but can play a role in absorption, stability, and conditioning the drug's appearance, color, and taste.
Fluoroquinolones	A family of antibiotics to which ciprofloxacin belongs.
Galenic formulation	The process of designing and preparing medications to ensure optimal drug delivery and absorption.
Hepatic extraction	The transformation of a drug during its first passage through the liver, before it reaches systemic circulation, typically following oral administration.

Term	Definition
Intra-intestinal excrement	Also known as extrarenal excretion = feces, as opposed to renal excretion = urine.
Per os (PO) administration	Oral administration.
Physiological fluid	A solution that mimics the body's natural fluids, often used to maintain or restore fluid balance, such as saline solution.
Posology	The dosage and administration guidelines for taking a medication.
Sequential therapy	A multi-drug regimen in which two or more drugs are alternated frequently during the treatment of a patient.
Metabolites	Molecules slightly modified by metabolism; the chemical compounds that result from the biotransformation (metabolism) of a parent drug within the body.
Minimal Inhibitory Concentration (MIC)	The lowest concentration of an antimicrobial agent (e.g., antibiotic) that can effectively inhibit the growth of a specific microorganism, typically a bacterium or fungus, in a laboratory setting. It is a key measure for assessing the susceptibility of microorganisms to antimicrobial drugs and helps guide appropriate antibiotic treatment.

Table 1: Definitions of medical terms used in this document.

Introduction

With 4% of global greenhouse gases (GHG) emissions which is equivalent to 2 Gt CO_2e, the global health care sector emits almost as much as Russia, the 4th most pollutant country in the world [4] [5]. In comparison, the aviation industry accounts for the half of health care sector's emissions [6].

Based on these findings and with the introduction of the European Green Deal in 2020 and the Pharmaceutical Strategy for Europe, part of this industry is working to lower its environmental impact [7][8]. Additionally, there has been a growing interest in environmental sustainability and sustainable healthcare [9]. Indeed, the number of published articles per year in the field of green healthcare has more than doubled compared to before 2020 [10] [11]. Not only researchers and regulatory institutions are increasingly concerned about the climate crisis, but medical professionals, pharmaceutical companies, and hospitals are also making significant efforts. Companies are trying to optimize their processes and reduce the impact of their packaging. Hospitals are lowering their impact primarily through employee education and by reducing energy consumption, as seen with Massachusetts General Hospital, which cut its energy use by 36% over the past 15 years by ramping up the use of cogeneration technology, which produces electricity and usable heat simultaneously, and by installing solar panels [12]. Additionally, some physicians advocate for deprescription, as highlighted by Aaron Bernstein, pediatrician and Interim Director of The Center for Climate, Health, and the Global Environment at the Harvard T.H. Chan School of Public Health: "The best way to decarbonize healthcare is to not use healthcare" [12]. Other members of the medical profession are trying to determine the most environmentally friendly choices of drugs and medical devices.

Given the substantial amount of plastic waste generated by a single intravenous administration compared to the small quantity of waste generated by the oral administration of the same drug, Dr. Julien De Greef, an infectious diseases physician, and Ms. Caroline Briquet, a hospital pharmacist, both working at the Cliniques universitaires Saint-Luc in Brussels, sought to quantify the difference in environmental impact between the two methods of administration in order to reduce the hospital's impact in a highly emissive area. Indeed, at the beginning of this work in September 2023, there was no study in the literature comparing and involving the whole life

cycle of two paths of drug administration. However, medications and plastics account for at least half of the GHG emissions from hospitals, as noted by the CH de Niort [13]. In France, hospital waste production reaches 1.7 tonnes per bed per year [13] [14].

Not only are GHGs involved in the environmental impact of the healthcare sector, but endocrine-disrupting chemicals also pose a significant problem. These chemicals, prevalent in plastics used widely in packaging and single-use medical devices, can interfere with hormone systems, leading to serious health issues like cancers, reproductive problems, and metabolic disorders. Their widespread use and persistent nature make them a significant threat to both human health and the environment [15].

The climate crisis is a global problem requiring action from all sectors, including healthcare. By adopting sustainable practices, healthcare professionals can play a significant role in reducing the industry's environmental impact and becoming climate activists in their daily clinical practice [16]. It is crucial to achieve strong results before initiating effective and impactful awareness-raising.

The objective of this work is to quantify the difference in environmental impact between intravenous administration and oral administration of an antibiotic to favor the method with the smallest overall impact. This study will focus on ciprofloxacin (CIP), one of the most commonly used and well-documented antibiotics. A life cycle assessment (LCA) is performed, chosen over a carbon footprint because it is essential to ensure that the difference in the antibiotic administration methods is evaluated comprehensively to avoid habit changes that could be worse rather than better. A sensitivity analysis is also conducted to determine the influence of the assumptions made for the reference LCA on its results, along with a scenario analysis of an ideal case to see the minimal environmental impacts that intravenous (IV) and per os (PO) administration of CIP could cause under ideal conditions. The study concludes with a discussion on the actions that can be taken based on the results, followed by a discussion on the limitations and weaknesses of LCA.

Chapter 1

Literature review

1.1 Context

The idea for this project originated from Ms. Caroline Briquet and Dr. Julien De Greef, members of the GGA (Groupe de Gestion de l'Antibiothérapie), a hospital committee responsible for overseeing antibiotic therapy, commonly known as "AMS" (Antimicrobial Stewardship) in the literature. The primary objective of AMS is to manage antimicrobial treatments effectively to slow the emergence of resistant organisms and prevent the rise in mortality and morbidity associated with infections caused by multi-resistant pathogens.
As part of one of their initiatives, they aimed to reduce the number of intravenous antibiotics prescribed. Promoting oral over intravenous administration offers numerous advantages, including cost reduction, increased patient comfort, and freeing up valuable time for nurses. But what about the sustainability benefits?

Since this study was initiated by a group of healthcare professionals from Cliniques universitaires Saint-Luc, it is essential to highlight some key figures concerning this hospital. With 6000 employees and nearly 950 beds, it is one of the largest healthcare centers in Belgium [17]and contributes on the 7.7% of the total national healthcare carbon footprint of Belgium [18]. The hospital has developed 30 waste management channels, including those for hazardous waste, which requires special treatment before incineration. These wastes include medical materials such as human organs, syringes, medicines, and radioactive components. They undergo specific treatments, such as chemical disinfection with chlorine or irradiative sterilization, before being incinerated, which inevitably increases both their environmental impact and their cost [19]. Indeed, with a cost of 800 €/t, it is five times more expensive to treat hazardous waste than non-hazardous waste [20]. The hospital produces 383 t of hazardous waste and 1120 t of non-hazardous waste (such as paper, cardboard, packaging, food waste, and aerosols) per year [20].

In addition, this work is directly aligned with Cliniques universitaires Saint-Luc's

strategic sustainability objectives, particularly focusing on axes 4, 6, and 8 of their sustainability framework [21]. Axe 4 targets the critical management of waste, emissions, and contamination, aiming to optimize waste sorting and reduce environmental pollution. Axe 6 emphasizes adapting medical and care practices to minimize environmental impact without compromising the quality of patient care. Finally, Axe 8 stresses the importance of effective communication, ensuring that sustainable practices and their impacts are well communicated to all stakeholders. The results of this work will be used to raise awareness through a dedicated campaign.

To further reduce GHG emissions and energy consumption, the hospital implemented a custom cogeneration solution. This project involved the installation of three 1200 kWe cogeneration units that work together to provide both heat and electricity with an overall energy efficiency of 88%, leading to a 21% reduction in CO2 emissions compared to separate heat and electricity production [22].

1.2 Intravenous and per os administration overview

Pharmaceutical administration is typically divided into two primary methods: enteral and parenteral routes. The enteral route includes oral or per os (PO), buccal, and rectal administration, while the parenteral route encompasses intravenous (IV), intramuscular, and other methods [23]. In this work, the focus will be on two of the most common routes: IV and PO. IV administration is a common method used in healthcare to deliver drugs directly into the bloodstream which allow to obtain a 100% bioavailability while PO is an easier way to take an antibiotic by ingestion. The API will be absorbed by the gastrointestinal system.[24] [25]

In this section, three different papers were selected to discuss the criteria for applying an intravenous to oral switch (IVOS), the advantages and potential drawbacks of each administration route, and the barriers to implementing the IVOS switch.

Firstly, the study by Algargoosh et al. (2022) [26] focuses on a pharmacist-led program that successfully increased the amount of IVOS's for the antibiotic metronidazole. It shows how pharmacists can help improve antimicrobial stewardship. The article by Ashiru et al. (2023) [24] focuses on the benefits of rapid switching from IV to PO, including reduced healthcare costs, reduced risk of IV complications and environmental benefits. It also discusses the difficulties encountered when implementing these changes, in particular the persistent belief among some healthcare professionals that IV antibiotics are superior. Finally, the third article by Sallach-Ruma et al. (2013) [27] assesses the criteria and outcomes of switching from IV to PO antibiotics, noting the clinical benefits while acknowledging potential barriers within healthcare teams. Together, these studies underscore the importance of well-defined protocols and interdisciplinary collaboration to optimize antibiotic use by switching from IV

to PO antibiotics.

1.2.1 Criteria for an Intravenous to oral switch (IVOS)

Switching from IV to PO administration is not a decision made lightly; certain criteria must be met to ensure patient safety and treatment efficacy. Healthcare providers consider several factors before making the switch. These include the patient's ability to swallow and absorb the medication orally, stabilization of clinical symptoms, and the proper functioning of the gastrointestinal tract [26] [24] [27]. They also includes an adequate oral bioavailability in order to achieve the target exposure at the site of infection [24].

1.2.2 Advantages and Potential Drawbacks of Choosing PO Over IV

There are several strong reasons to switch from IV to PO administration when appropriate. One of the main benefits is a reduction in hospital stay duration, which in turn lowers healthcare costs. It also frees up valuable time for nurses, allowing them to provide better care to other patients in need. Additionally, IV therapy carries certain risks, such as catheter-related infections, which become more likely over time. These risks can be avoided by switching to oral administration. Another key advantage is environmental: Ashiru-Oredope [24] cites research showing that IV antibiotics typically have a higher carbon footprint due to the energy and materials required for their production and disposal. Therefore, switching to PO can "contribute to a lower carbon footprint and a more sustainable" healthcare sector.
After reaching out to Dr. Sarah Walpole, the author cited by Ashiru-Oredope, it was confirmed that, as mentioned in her conference abstract [28], they applied a carbon intensity factor for pharmaceuticals developed by Tennison (2021) [29]. This factor was used alongside the cost of the medicine and the medical supplies required for a single dose. Their findings indicated that one week of ciprofloxacin 500 mg PO resulted in 1.4 kg CO2e, while one week of ciprofloxacin 400 mg IV resulted in 100.1 kg CO2e. This represents a 60-fold difference between these two administration routes. Although this study may not be highly robust, it offers a valuable initial perspective on the environmental impact. Since this small study focused on the same antibiotic as this research, it is useful to consider these results for comparison with the findings of this study.

1.2.3 Barriers to the IVOS

Despite the clear benefits of switching from IV to PO administration, some medical staff are still hesitant to adopt this practice. Ashiru-Oredope [24] mentions that one big reason is the strong belief that IV antibiotics are better than oral ones, which

makes some staff reluctant to switch, even when it's safe to do so. Also, the hierarchy in medical teams can slow down decisions, as junior doctors might feel unsure about making the switch without getting approval from senior staff.

The study by Algargoosh et al. (2022) also shows how pharmacists can help overcome these barriers. When pharmacists were given the lead in making the switch, there was a significant increase in successful switches. This suggests that empowering healthcare professionals other than doctors can help reduce resistance to change in medical teams. However, the study also found that it took time for pharmacist-led switches to become common, showing that even with clear guidelines, there are still cultural and practical challenges in changing established practices.

1.2.4 The case of Ghent University Hospital

A study conducted at Ghent University Hospital in 2010 explored the implementation of guidelines for sequential therapy, specifically the switch from IV to PO administration of fluoroquinolones [30]. The researchers introduced three key interventions: hospital-wide dissemination of guidelines, educational sessions for medical staff, and a proactive pharmacist-led conversion program. The results demonstrated a significant reduction in the duration of unnecessary IV therapy, with a decrease from 4.1 days to just 1 day post-intervention. This led to substantial cost savings, with the additional cost of prolonged IV treatment dropping from €188 to €44 per patient. Furthermore, the study found that patients spent less time in the hospital when switched to oral therapy earlier, underscoring the benefits of such a strategy in reducing both healthcare costs and patient hospitalization time.

1.3 Environmental impacts of drugs

As green health is increasing in interest [10] [11], number of studies on the topic of LCA are increasing .
A few carbon analyses or life cycle assessments on drugs have been published, including studies on the environmental impact of specific pharmaceuticals. Some tools are being created to help physicians in their decision-making. The Association of Anaesthetists promotes the "anaesthetic gases calculator," which compares inhalational anaesthetic agents, taking into account their production of CO_2e [31] and their prices. Another tool, Janusinfo, developed by Region Stockholm, provides environmental information on pharmaceuticals. It offers hazard and risk classifications for Active Pharmaceutical Ingredients (APIs), including details on persistence, bioaccumulation, and ecotoxicity. The tool supports healthcare professionals and policymakers in making environmentally informed decisions [32].
But at the beginning of the work on the master thesis, there was no researches comparing IV and PO path of antibiotics on their whole life cycle. There was just the conference paper from Walpole et al. discussed above [33] which calculated the amount of CO_2e of both path with
In view of the increasing interest in literature on pharmaceutical related LCA, Siegert et al. proposed in a set of harmonized rule for future LCAs [34]. They pointed 5 principal steps in a generic life cycle of a pharmaceutical product and processe. production of precursor chemicals, API synthesis, galenic formulation, packaging and distribution-use-EoL. From those steps were defined 4 boundaries:

- Cradle to API = Production of precursor chemicals → API synthesis
- Cradle to galenic form = Production of precursor chemicals → galenic formulation
- Cradle to preparation = Production of precursor chemicals → packaging
- Cradle to grave = Production of precursor chemicals → EoL

This section will start with a study of LCA's / carbon footprint of drugs Then, a literature review of the EoL of the CIP will be conducted.

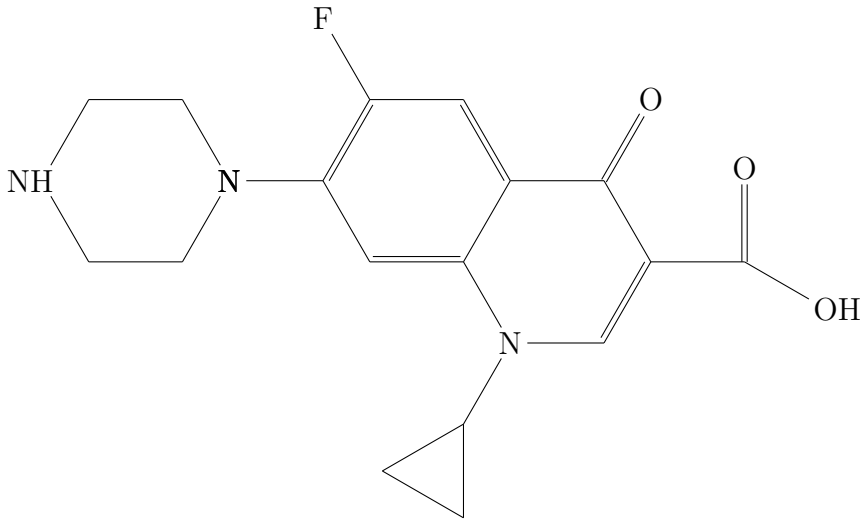
1.3.1 Ciprofloxacin

The ciprofloxacin is a widely prescribed antibiotic in the world his consumption by 2015 was 2318 t [35]. It belongs to the fluoroquinolone class used to treat bacterial infections such as urinary tract infections and pneumonia [36]

The representation of the CIP is the following,

- chemical formula: 1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid.

- molecular formula: $C_{17}H_{18}FN_3O_3$
- chemical structure: 1.1



(1.1)

- This antibiotic also has a good bioavailability of 80% [36]
- Antibiotics are metabolized by the liver and kidneys, with only a portion being absorbed to exert therapeutic effects. The unmetabolized portions, along with any metabolites, are excreted primarily through urine and feces. This excretion process helps the body eliminate excess or inactive substances, preventing toxicity and maintaining internal balance. [37] [38]
- We found many variations (of about 20%) on how and in which quantities the ciprofloxacin was rejected by feces and urine. But the notices available in the website of Federal Agency for Medicines and Health Products [39]. And it seems that there is a consensus about it between pharmaceuticals. The data are available on Table 1.2 and 1.1

500g po	**Urine**	**Selles**	**TOTAL**
Ciprofloxacine [%]	44.7	25	69.7 $\Rightarrow$ **349g**
Métabolites (M1-M4) [%]	11.3	7.5	18.8

Table 1.1: Excretion for 500g PO

400g iv	**Urine**	**Selles**	**TOTAL**
Ciprofloxacine [%]	61.5	15.2	76.7 $\Rightarrow$ **306g**
Métabolites (M1-M4) [%]	9.5	2.6	12.1

Table 1.2: Excretion for 400g IV

Note that this study, along with subsequent ones, had the opportunity to exchange crucial information with the pharmaceutical industry regarding the industrial process of creating the medication. Obtaining robust results is indeed challenging without the cooperation of pharmaceutical companies.
The study by Yang et al. [40] on ciprofloxacin successfully implemented the industrial process of producing ciprofloxacin tablets, with the assistance of a pharmaceutical company from China. The process is divided into two main reactions, with the primary one involving the reaction of a carboxylic acid with piperazine to produce ciprofloxacin (CIP).
They implemented the 3 principal stages recommended by Siegert et Al. [34]. They results in a final the API synthesis, the galenic formulation and the packaging.
cipro (et plus globalement les autres aussi) a été analysée mais seulement pour le po.
Résultats: bcp plus d'impacts pour antibio que pour packaging. Mais quand est-il des administrations iv? Etude sur ciprofloxacine (sauf que limité à oral et prend pas en compte rejet eaux usées (=toxicité cipro dans nature))
+ expliquer pq choisi cipro (dans étape suivante: méthodologie)
In the study of Yang et al. [40], the ciprofloxacin in tablet form was analysed. They worked with GB company in China that produces more than 30% of the market of ciprofloxacin.
"they recommend optimization efforts in the two first stage since packaging counted for 15% of the overall impact

1.3.2 Paracetamol

Before January, this was the only paper comparing explicitly IV and PO administrations forms [41]. + explain the main results Those results have been
then, this arrives. Real LCA on dosage (cradle to gate or cradle to preparation according to [34]) so taking into account different forms of paracetamol including their packaging but not the distribution [42] (paracetamol)
Several papers are openly saying that IV administration emits more GHG than PO administration but this reasoning was never sourced with strong papers. It is time to prove it by applying a study.
steam sterilization of IV (see PWP)

1.3.3 Morphine environmental footprint [43]

"We were unable to estimate the environmental effects of oral morphine tablets, though this is likely to be less than intravenous preparations due to the lesser disinfection needs" main +: sterilisation of Baxter PVC plastic bags
+ g CO2 for sterilisation and packaging. (important for comparison later)

1.3.4 Ibuprofen

[44]
On this study about a cradle to grave LCA of an ibuprofen analgesic, their conclusion on the ecotoxicity is that packaging has much more impact than the API which is therefore [44]

1.3.5 End of life of ciprofloxacin

After ingestion, drugs are excreted by patients, entering the wastewater and subsequently interacting with the environment. Many studies have investigated the impact of medicines on the environment. Indeed, residues of antibiotics have been detected in water bodies. Rodríguez et al. found concentrations of around 50 ng/L of CIP in several surface waters in Spain [45]. To provide a sense of scale, this concentration is comparable to dissolving a single grain of fine table salt (approximately 0.06 g [46]) in 1 m^3 of water.
API-specific (and treatment-dependent) removal rates at WWTPs of the antibiotic ciprofloxacin reached a maximum of 30% (as reviewed in Verlicchi et al. 2012 [47])." [48]

The next study conducted by Schulte et al. in 2022 confirms the Verlicchi et al. results. It has for objective model the fate of ciprofloxacin in STPs in Germany [37]. It used SimpleTreat4.0 software [49] in which is integrated a model to predict the fate and emission of chemicals in STP. It results that approximately 50% of the ingested ciprofloxacin ends up in the environment via STP effluent, while about 25% accumulates in sewage sludge. The metabolites are not taken into account in the effluent of the STP. This means that from the affluent of the ciprofloxacin, about 70% is still rejected in freshwater. Only 30% of the effective CIP is removed from water and is accumulated in sewage sludge with STP.
The actual removal efficiency depends on the applied STP treatment technologies, the associated process parameters and the physicochemical properties of the compounds [50]. Indeed, new specific technologies have been emerged those last year. Al-Buriahi recensed some of the most efficient in 2022 [51]. Adsorption process, photocatlytic degradation and three-dimensional porous graphene has excellent results, close to 100% on removal of CIP from WWTP.

Now that quantities of CIP rejected on surface water have been discussed, it is good to discuss about the length of life of CIP in those waters. Indeed, there is a wide variety of plants and life in rivers, lakes etc... They are potential candidates to biodegraded the CIP. The question is, is there a bio accumulation of CIP in water environment.
A first study analysing the degradation of CIP in seawater in 2018 conclude that 95% of the parent compound is transformed in more than 20 by-products, which some were referenced for the first time [52]. Another work, directed by Habaki observing the elimination of CIP from water by duckweed, results in 90% removal efficiency at the end of a 7-day experiment [53].
Photo-transformation is also a crucial a key element on the lifetime of CIP in environment. Haddad and Kümmerer experienced that 98% of CIP is eliminated after being exposed to UV lamp during 2 hours [54]. They also discovered that mineralization of CIP did not occur. It means that the almost entirety of CIP turned

to transformation products.
In conclusion, approximately 50% of ingested CIP is released into water, where it degrades relatively quickly. However, the resulting by-products may persist, raising concerns about their long-term environmental impact.

Chapter 2

Objective and Research Approach

The objective of this study is to determine whether, from an environmental perspective, the IV administration of CIP is generally better, worse, or debatable compared to PO administration. It is possible that the results will favor IV administration in some impact categories and PO administration in others. To explore this, the study will conduct two LCAs, one for each administration route, aiming to potentially support the switch from IV to PO where appropriate. It is important to note that regardless of the findings, IV administration will continue to be necessary for patients who cannot take oral medications due to contraindications. Therefore, this study focuses on the environmental impact of switching from IV to PO in eligible cases, excluding certain medical disposables, such as catheters, that are already in place and thus do not need to be included in the LCA.

The rationale for selecting ciprofloxacin as the focus of this study begins with its extensive documentation in the literature. Numerous studies have examined various aspects of this antibiotic, covering almost the entire life cycle—from the production of the API to the EoL phase, including the impact of wastewater containing ciprofloxacin residues. The existing LCA data on API production is crucial. While the chemical pathway to synthesize ciprofloxacin is publicly available, accurately estimating the environmental impact of the entire industrial process would be challenging without direct input from the pharmaceutical industry, especially when it comes to determining waste output and energy consumption. Fortunately, the paper published by Yang et al. in 2021 provides a comprehensive LCA of ciprofloxacin hydrochloride, utilizing the resources available in SimaPro with the ecoinvent database [40]. LCAs of API synthesis are rarely available to the public, primarily due to the proprietary nature of drug synthesis processes [43]. Pharmaceutical companies are often reluctant to share critical data, such as process inputs and waste generation, which is why only a limited number of antibiotics have been thoroughly analyzed in LCAs in the literature.

Moreover, the objective was to select an antibiotic with a bioavailability slightly below 100% to account for the differences in API production between IV and PO

administration, making the study more representative of the typical antibiotic. The bioavailability should still be sufficiently high. A lower bioavailability necessitates a greater quantity of API for oral administration compared to its IV counterpart, thereby increasing its environmental impact. This is because API production has a significantly larger environmental footprint than the production of solvents or the processes used for galenic formulation. This observation is supported by several studies [43] [40] [55].

Since LCA is an approach that requires a comprehensive understanding of the entire life cycle of a medication, efforts were made to consult with individuals involved in each stage to gather as much information as possible. A meeting was held with Mr Philippe De Greef to discuss the pharmaceutical industry. Additionally, a discussion with a nurse was scheduled to obtain detailed information on the materials used during the administration of the antibiotic. Another meeting was organized with Mr Patrick Pelletier, the supply chain logistics manager at Cliniques universitaires Saint-Luc, which included discussions on the hospital's waste management. Some key figures related to this have already been discussed in section 1.1. Since medicines are excreted into the wastewater by patients, it was important to investigate the wastewater treatment processes at the hospital. An exchange with Mr. Patrick Gohy and Mr. Benoît Darras revealed that the hospital currently lacks a wastewater treatment. Unfortunately, only a brief written exchange was possible with a pharmaceutical company, but it provided minimal yet valuable information, which will be discussed in more detail in Chapter 3.
The approach chosen to perform the LCA aligns with the methodology recommended by Siegert et al.in the article "Harmonized rules for future LCAs on pharmaceutical products and processes" [34], which offers valuable guidance for establishing a consistent and scientifically robust framework for conducting LCA in the pharmaceutical industry. The paper emphasizes the importance of accounting for specific factors, such as the different stages of a pharmaceutical product's life cycle. These stages include the API production, galenic formulation, packaging, distribution, use (including various administration supplies), and EoL. Siegert et al. also introduced the concepts of primary, secondary, and tertiary packaging. Primary packaging is the material that comes into direct contact with the API or the medical supply. Secondary packaging encases the primary layer, without direct contact with the API or medical supply. Finally, tertiary packaging is used primarily for transport and distribution purposes, ensuring the safe delivery of the product. This approach is crucial for producing harmonized, comparable LCA results, which can effectively guide environmental sustainability efforts within the pharmaceutical sector. Furthermore, several LCA discussed in the Chapter 1 are following and citing this methodology [40], [56], [44], [42], [55].

Chapter 3

Life cycle assessment of the ciprofloxacin

3.1 Goal and scope

The goal of this LCA is to evaluate the environmental impact of the antibiotic ciprofloxacin administered in oral and intravenous forms in order to determine which route is environmentally preferable. This study is carried out as part of a civil engineering final year thesis for a Master of Engineering in Materials and Chemical Engineering.

3.1.1 Functional unit (FU)

The functional unit defined as 1/2 (a half) DDD of ciprofloxacin. This is the typical treatment of one adult in the Cliniques universitaires Saint-Luc in Brussels with complicated urinary infection [57].
One daily defined dose corresponds, following the Belgian Centre for Pharmacotherapeutic Information (BCFI), to 1 g of CIP taken in PO which is equivalent to 0.8 g of CIP taken in IV per day. Both taken twice a day on equal quantities. [57].

3.1.2 Boundaries

This analysis assesses the environmental impact of the pharmaceutical industry from cradle to grave according to Siegert et al., as described in Section 1.3. The components included within the boundaries are illustrated in Figure 3.1. For more clarity, due to the huge amount of materials and processes involved in this LCA, the flow sheet has been simplified to keep the main outline. The materials and treatments involved in each step of the life cycle will be listed later on this work **??**. There are two main branches:

- CIP life cycle (green): production of precursor chemicals, API formulation, galenic formulation, and wastewater treatment.

- Medical administration supply (blue): includes primary, secondary, and tertiary packaging, all of which require raw materials. Waste treatment is also within these boundaries.

Note that the turquoise box labeled "Administration of 400 mg ciprofloxacin IV" represents the intersection between the two branches, but it does not mark their endpoints.

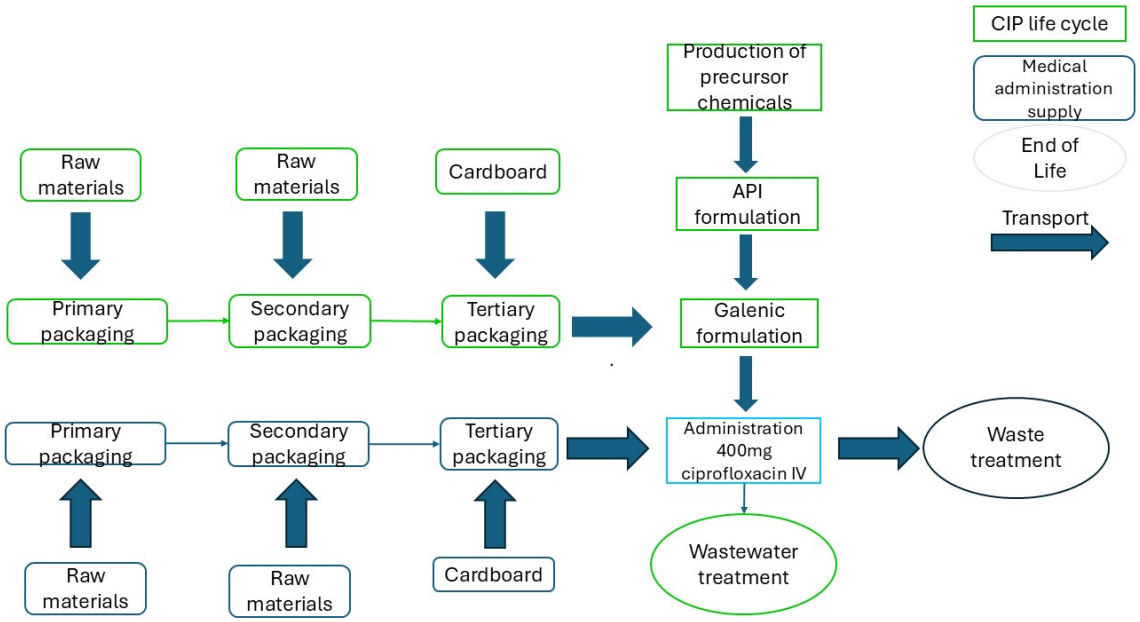


Figure 3.1: CIP-IV life cycle simplified flow sheet.

Are not included into the boundaries:

- In both IV and PO administration: the sterilisation, the
- In the CIP-IV only: the catheter and the posis of the central line/peripheral line, a dressing change once a week

3.1.3 Reference flow

3.1.3.1 Reference flow of the CIP-PO

To administer one dose of CIP-PO the following materials are required: a tablet that contains 500 mg of API ciprofloxacin and the necessary packaging. This includes primary, secondary, and tertiary packaging to transport and maintain sterility and one pouch packaging.
Please find the reference flow in the Table 3.1 bellow.
The hospital employs an automated medication flow system. This system places a pouch packaging on solid orally administered drug. It involves wrapping the medication in a layer of paper and a layer of plastic adhered together, on top of its

Category	Medical Supplies and Medications	Usable Life (Functional Unit)
antibiotic	tablet of 500 g CIP	1
	pouch packaging	1

Table 3.1: Reference flow of CIP-PO

sterile primary packaging. This additional packaging maintains sterility, allows for the medication to be labeled with a QR code, and includes other essential information, such as the expiration date, lot number, and the name of the medicine. It also enables a hole to be created in the secondary packaging for hanging the medicine in the drug dispenser.

3.1.3.2 Reference flow of the CIP IV

In the case of ciprofloxacin administrated in IV, giving one dose to a patient will requires 400 mg of ciprofloxacin in solution. What is also needed but in a fraction lower of 1 unit [1] is maintenance IV infusion, an antibiotic IV line and the disinfectant supply. The detailed reference flow and the fraction of each medical supply is precised in the Table 3.2

Category	Medical Supplies and Medications	Usable Life (Functional Unit)
antibiotic	400 g of CIP in injectable form	1
maintenance IV infusion	maintenance infusion bag	2
	IV infusion set	8
	flow rate controller	8
antibiotic IV infusion	IV infusion set	2
shared	manifold (3 port)	8
	extension line	8
	disinfectant	1.6
	sterile compress	1.6

Table 3.2: Reference flow of CIP-IV

A picture showing the material is presented in Figure 3.2. The fluid line represented in the center of the figure with black lines starts with two branches. The left one represents the IV infusion set. It starts with the maintenance infusion bag. It delivers a continuous supply of fluids and electrolytes, a physiologic liquid, to a patient helping to maintain hydration and electrolyte balance, particularly when oral intake is insufficient or not possible [58]. The physiologic liquid passes trough an IV infusion set and a flow rate controller just before arriving at the connection with the

[1] The reason is because, those IV sets will stay for longer than 1 FU.

other line, that is connected to the CIP-IV. The connection occurs at the manifold which regroups at this point the different fluid lines. Other lines could be added and merge on the manifold. For instance, it would be the case if another medicine has to be taken intravenously. Finally, an extension line connects the manifold to the catheter inserted in the patient.
The reference flow also contains a disinfectant and a sterile compress, used when the components of the IV infusion are changed. As explained previously, the totality of the IV set is not changed everyday. It is important to keep in mind that the IV line photographed is not corresponding to one single dose (FU).
To finish, on the bottom right is the CIP-PO. Containing the tablet, the blister and the pouch.

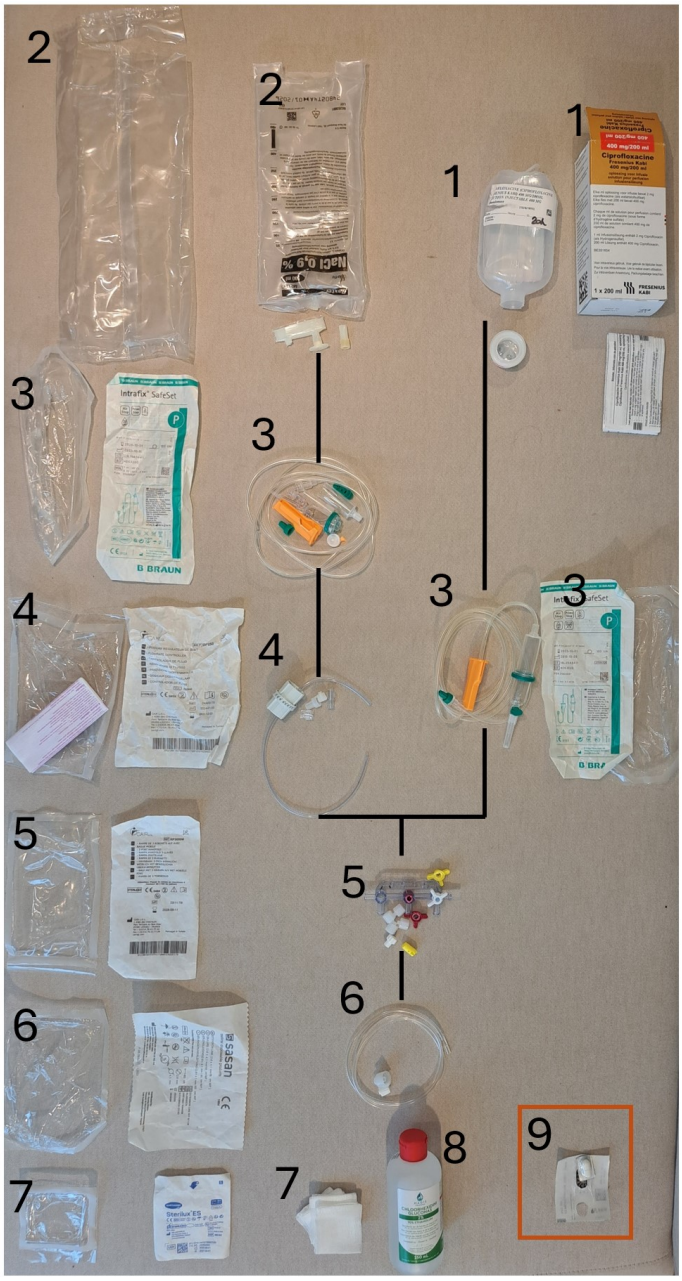


Figure 3.2: 1 to 8: Reference flow of the CIP-IV.
1. 400 mg of CIP in injectable form and its primary packaging (left), secondary packaging and notice (right).
2. Maintenance infusion bag: secondary packaging (left), physiologic liquid and primary packaging (right).
3. IV infusion set: primary packaging (left and right), IV infusion set (middle).
4. Flow rate controller: primary packaging and notice (left), flow rate controller (right).
5. Manifold (3-port): primary packaging (left), manifold (3-port) (right).
6. Extension line: primary packaging (left), extension line (right).
7. Sterile compress: primary packaging (left), sterile compress (right).
8. Disinfectant and primary packaging.
9. Reference flow of the CIP-PO. In the orange rectangle: a tablet, a blister, and a pouch.

3.2 Life Cycle Inventory Analysis of the reference scenario

Impact assessment was performed using the ReCiPe LCIA (Life Cycle Impact Assessment) method. The following impact categories (and their units) were calculated: climate change (g CO2 e); ozone depletion (kg trichlorofluoromethane (CFC-11) equivalents); photochemical oxidant (smog) formation (kg non-methane volatile organic compound equivalents); and human, terrestrial and marine ecotoxicity (kg 1,4-dichlorobenzene equivalents).

Medical Supplies and Medications	**Name of Medical Supply**	**Bra**
400 g of CIP in injectable form	Ciprofloxacine	Freseniu
Maintenance infusion bag	Viaflo NaCl 500 ml	Bax
IV infusion set	Intrafix SafeSet	B.BR
Flow rate controller	Dosicair DF050	Cair
Manifold (3 port)	Manifold RP3000M	Cair
Extension line	Extension line M/F 85cm	Sas
Disinfectant	Chloorhexidini Gluconas 2% - 70% Ethanolum	Magis
Sterile compress	Sterilux ES	Hartn

Table 3.3: Brand and name of medical supply

In the literature [34] there has been said that primary, secondary, tertiary on literature for medicines. It has been decided to secondary and tertiary packaging should be assumed to be recycled while primary packaging should be incinerated due to the contamination with the API. Therefore, the composition and manufacturing [34];

3.2.1 Active Pharmaceutical Ingredient (API)

As obtaining accurate data from production of pharmaceuticals is very important to start a solid LCA, pharmaceuticals companies who provide CIP to the Cliniques universitaires Saint-Luc were contacted but not with the positive responses it was hoped for. It was process o pharmac
The difference is explained Including purification and extraction

3.2.1.1 CIP-PO

As seen in the literature review , Yang et al. studied the production of the ciprofloxacin [40]. They did not involved the production of tablets with the , they considered their tablets as made of 98% of CIP. While the CIP
Could not find piperazine so used piperine instead, because the molecule is very similar
please find in Appendice **??** a detailed process on how work the process of tablets

3.2.2 Administration packaging

3.2.2.1 per os

The water drinked to swallow the medicine is not included in this LCA, as it is considered a fundamental need that would have been consumed regardless of the medication intake.

3.2.2.2 intravenous

Ms Caroline Briquet and Dr Julien De Greef gave me the necessary material needed for the intravenous line. to , we found an agreement on what will be decided
Some compositions were easily available either on the packaging (primary packaging CIP injectable, primary packaging disinfectant). Others were described on public online notice (maintenance infusion bag 500 ml by Baxter). But most of the compositions were unavailable. To compensate this lack of information and to avoid making too much assumptions, a laboratory of Fourrier Transform Infrared Spectrum has been conducted to determine the composition of some of the compositions unknown. 5 different samples were chosen. The criteria was to select the most frequent material. The report of this laboratory is can be find in Appendix A.2.

3.2.2.3 transport

In terms of transport, the origin of the product is always written in the packaging. The ecoinvent data base counts the transport with the unit tkm.

"Transport, freight, lorry 16-32 metric ton, euro6 RER| market for transport, freight, lorry 16-32 metric ton, EURO6 | APOS, S"

3.2.3 End of life

Pharmaceutical residues can enter the environment during production, consumption, and disposal. We need to achieve zero discharge from the manufacturing plants.
Dr Magasich in Cliniques universitaires Saint-Luc presented in a conference on how reduce the amount of waste in the hospital, that some IV fluid lines are disposed in the hazardous waste garbage can [20]. Since the nurse confirmed us that it is not the most frequent comportment, it has been decided to count as if the IV fluid line was put in the correct garbage. Moreover, an intern campaign advocate that this kind of waste should be putted in the PMC bin.

3.2.3.1 Incineration

in [34], "or instance, secondary and tertiary packaging should be assumed to be recycled while primary packaging should be incinerated due to the contamination

with the API." but here not the case!

3.2.3.2 Wastewater

The discussion with Mr Patrick Gohy and Mr Benoît Darras revealed that the hospital has no wastewater treatment. The totality of those water are treated in the public WWTP. The sewage of Cliniques universitaires Saint-Luc is in consequence connected to civil and other industries sewage. The drains are connected to the WWTP of Brussels-North which is exploited by Aquiris [59].
The study from Schulte et al. introduced in the literature section in Chapter 1 did not take into account the impact pathwasy of subtances contained in the sewage sludge for example for the entry into soils by application of sewage sludge as a fertilizer as it is mostly the case in Germany [37].
In contrary, in Brussels, the WWTP exploited by Aquiris has another sludge treatment that reduces by more than 99% the volume of sludge. They pass throughout several processes that will not be discussed in this work, for further information, they are quickly presented in their website [60]. The principal technology behind this treatment is wet oxidation. There are 3 main output of this treatment, filtered water that returns to the wastewater plant, a "clean gas"[61] rejected to the atmosphere and a inert residual sludge (called technosable in French). The residual sludge is used in trench backfill and cerarmic industry [61]. Due to the complexity of the different output and the lack of studies on this specific compounds, sludge will not be taken into account in the LCA.
Decided to not take into account the energy used on the epuration of water in WWTP since the the water is treated anyways. But the impact of the ciprofloxacin in the environment after the passage in the WWTP will be taken into account.

3.3 Impact assessment of the 2 references scenarios

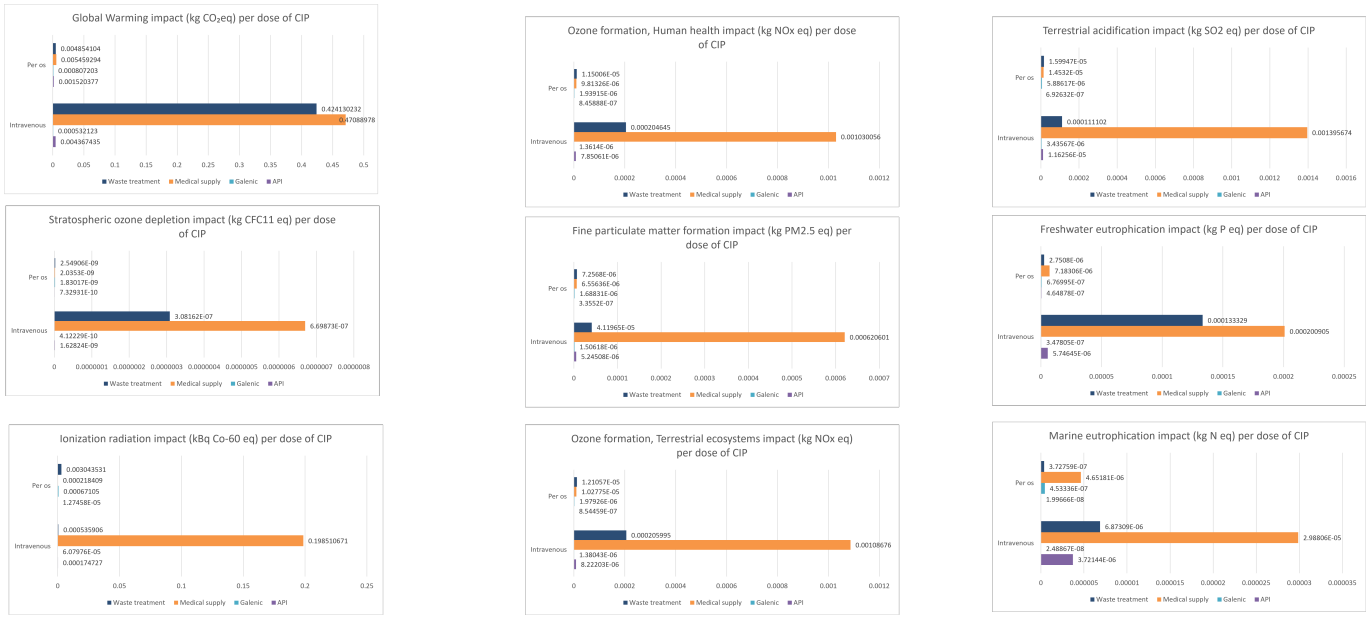


Figure 3.3: Characterised midpoint impact categories from Recipe methodology to

3.3.1 Discussion

3.3.1.1 improvements/weaknesses

The sterilization is a possible improvement[62]
I don't take into account the fact that one day in hospital creates a lot of impact (visitors, heating, ...). It gives even more difference of impact on switch EoL parle des micropolluants? pas sûr. The metabolites not taken into account. There is not enough literature on this. Decomposition of dozens of different metabolites in the environment but barely know a small portion of them.
EoL API not that important, seems coherent with other LCA reviewed on Chapter 1 Literature. But keep in mind that some categories of impacts covered by Ecotox are not covered by the impacts taken into account in our LCA.

Talk about regional aspects from [34]

3.4 Sensitivity analysis

3.4.1 Tyvek medical paper

The medical paper, which is the paper-based part of the secondary packaging for the medical administration supply, has been defined as basic wood-based paper in

SimaPro. This likely underestimates the actual environmental impact of medical paper. On the other hand, Tyvek is a widely used material that, depending on the brand, replaces standard wood-based medical paper [63].
Tyvek is made from polyethylene (PE). The process begins with the production of PE granules. These granules are then spun into very small polyethylene fibers. The fibers are arranged on a mat and compressed under heat and pressure, forming the dense Tyvek material [64]. Due to its composition, Tyvek is likely to have a greater environmental impact.
The objective of this sensitivity analysis is to determine if the underestimated environmental impact of the medical paper significantly affects the overall comparison between CIP-IV and CIP-PO.

Category	Wood-based Medical Paper	Tyvek
Material/Assembly	Paper, wood-containing, lightweight coated RER| market for | APOS, S	Polyethylene, high density, granulate, recycled RoW| market for polyethylene, high density, granulate, recycled | APOS, S
Process		Polar fleece production, energy use only GLO| market for | APOS, S

Table 3.4: Comparison of Wood-based Medical Paper and Tyvek

3.4.2 Other formulations (glas bottles)

3.5 Scenario analysis

3.5.1 Tri

Even thought medical packaging is made of multi layer or multi components that are too costly to be valourized during their end of life, it is still interesting to check if this could cause a significant change.

3.5.2 change of parenteral bottle

3.5.3 IV line shared with someone else

3.6

Chapter 4

Further discussion

4.1 EoL antibiotics

lower impact of antibiotics in wastewater? Until now, the wastewater treatment has not been discussed. As seen in the literature review 1,
micropollutant not stopped when wwtp classic epuration clinique saint pierre ottignies "abattement jusqu'à 90% d'exénobiotique: 1) favorize niches (bacterienne?) écologique to have more bacteries and more epuration 2) filter bacteries that could be antibio resistants 3) epuration with ecological niches with active carcoal [**<empty citation>**]
Also, technologies as eXeno by Veolia provide additional installations for WWTP that remove even more fractions of compounds. It removes 70% of the residual ciprofloxacin contained in the effluent of the WWTP [65]. As far as we know, this is not used in the WWTP of Brussels-North . The eXeno process is using 3 Moving Bed Biofilm Reactor (MBBR) in series. MBBR is a biological wastewater treatment process where biofilm (communities of microorganisms, such as bacteria [66]) grows on suspended carriers to beak down pollutants[67].
Lack of information on metabolites. Could be less or more toxic than parent compound [68]
Other factors are not taken into account in Usetox and ReCiPe. For instance, antibimicrobial resistance is a preoccupation in the field of healthcare. Indeed, it has been estimated that in 2019, 4.95 million of dearths were associated with antimicrobial resistance [69]. and bioresistance! [**emara**] ATTENTION regarder à quel point cipro est biodégradable!!

4.2 PICC line

Possibility to add Picc line, mid line and ... . It will even increase the impact of IV. It was chosen to not include this line in the LCA because when there is a switch from oral to intravenous path of administration, this medical device is already in place. And is generally not changed during the the treatment of CIP-IV

4.3 changing packaging of PO

Plastic botles

4.4 Intravenous to oral switch on other antibiotics

4.5 Economy behing IVOS

Conclusion

In conclusion, ciprofloxacin administered orally has a significantly lower environmental impact than ciprofloxacin administered intravenously. The findings of this study consistently show that oral administration (CIP-PO) is less impactful across all environmental impact categories assessed. Even when varying the criteria parameters, the overall trend remains unchanged. The difference in environmental impact ranges from 7 times greater in marine eutrophication (4.05E-02 g Neq for CIP-IV compared to 5.49787E-03 g Neq for CIP-PO) to over 233 times greater in marine ecotoxicity (207.104497 g 1,4-DCB eq for CIP-IV compared to 0.886177 g 1,4-DCBeq for CIP-PO).

In terms of global warming potential, CIP-IV generates 899.92 g CO_2eq, while CIP-PO produces 12.640978 g CO_2eq.

The significant difference in environmental impact primarily stems from the extensive use of medical supplies for IV infusion. Specifically, the maintenance infusion bag accounts for nearly half of the impact in several categories. Reducing the environmental impact of this infusion bag could lead to a substantial decrease in the overall environmental footprint. Some patients receive IV maintenance infusion bags containing 250 mL, which warrants further investigation.

Despite these results demonstrating a substantial disparity between CIP-IV and CIP-PO, it is not possible to generalize this conclusion to other antimicrobials. Instead, other available LCAs that cover the cradle-to-preparation phase [34] for IV and PO formulations of an antimicrobial could use these findings to inform a comprehensive cradle-to-grave life cycle assessment.

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Appendices

A Life Cycle Assessment

A.1 Hypothesis and detailled collected data's

while in the text, will be very brief on each data collected. will juste explain the approach

A.2 FTIR spectrum analysis

A.2.1 Theory

The equipment utilized in this laboratory was the *Nicolet™ iN10 Infrared Microscope*, produced by *Thermo Fisher Scientific™* [70]. This device combines a traditional microscope with an FTIR (Fourier-Transform Infrared Spectroscopy) system. The instrument is equipped with two detectors: a Mercury-Cadmium-Telluride (MCT) detector and a deuterated triglycine sulfate (DTGS) detector. The MCT detector is advantageous due to its superior signal-to-noise ratio, though it has a higher cutoff at 700 cm^{-1}, which limits analysis below this threshold. On the other hand, the DTGS detector offers a lower cutoff but at the expense of a lower signal-to-noise ratio. Consequently, the choice between these detectors depends on the specific requirements of the analysis, as each has its strengths depending on the situation.[71]

For this experiment, the MCT detector was selected to avoid potential issues with resolution that might cause peak merging and subsequent loss of information within the analyzed range. If initial results with the MCT detector proved inconclusive, the option remained to supplement the data with an FTIR DTGS analysis. The machine's source is a black body, and it features a Michelson interferometer configuration. The system allows for different modes of sample analysis, including reflection, transmission, and ATR (Attenuated Total Reflectance).

ATR was chosen for this analysis, as it is a widely utilized technique for examining polymer samples with low transmission [71]. This has for consequence that only the surface up to a few µm could be analysed. This method involves direct contact with a high refractive index crystal that exhibits low IR absorption within the relevant

IR region. During this experiment, a germanium crystal with a refractive index of 4 was used as the internal reflection element in the ATR technique.

A.2.2 Results

The parameters selected in OMNIC PICTA are a time collection of 220 and a high spectral resolution.
The first medical supply analysed was the IV infusion set.
Due to the choose of transmission FTIR:

A.3 Detailed results

Here are the normalization results

B Impact assessment of the 2 references scenarios

Figure 4.1: Normalized midpoint impact categories from Recipe methodology to

UNIVERSITÉ CATHOLIQUE DE LOUVAIN
École polytechnique de Louvain
Rue Archimède, 1 bte L6.11.01, 1348 Louvain-la-Neuve, Belgique | **www.uclouvain.be/epl**