Evaluating the environmental impact of care pathways

The environmental footprint of Chronic Kidney Disease care pathway in the Netherlands and the mitigating effect of Forxiga

Master Thesis

Giorgia Rapesta

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Abstract

In the last years, the effects of the climate crisis on the environment and living species have become increasingly tangible. Emissions and release of chemicals are damaging ecosystems and substantially increasing the rate of respiratory and infectious diseases, which have never been present previously in some of those regions. This has led to a careful reconsideration of the environmental impact of human activities which highlighted the significant footprint of the healthcare sector, arising a paradox: although it is providing cures and assistance to the population, at the same time this sector is increasing the demand for it by substantially contributing to the total environmental footprint.
Looking at the Netherlands, the healthcare sector is responsible for approximately 7 percent of the national environmental impact in terms of CO2 emission equivalent, 4 percent of the total waste, and 13 percent of the consumption of raw materials. These considerations underpin the necessity to consider this impact in evaluating new interventions in this sector. However, the lack of guidelines, agreement on methodology, and practical examples still represent a substantial barrier to the actual inclusion of sustainability criteria in the economic evaluation of healthcare interventions.
From this fragmented scenario, two research questions stem: How is it possible to evaluate the environmental footprint of care pathways? And once it has been quantified, how can it be included in the current economic evaluation of the healthcare interventions? In this thesis, answers to these research questions are provided by conducting a case study. It is centered on a chronic disease whose long-term management represents a burden for the Dutch healthcare system both in terms of natural and human resources: Chronic Kidney Disease (CKD). In fact, in the Netherlands, with a prevalence of 8.9 percent, it requires a significant number of healthcare professionals (GP, nephrologist, specialized nurse) and requires extensive natural resources (water, electricity). Therefore, the environmental impact of the care activities involved in the treatment of CKD has been evaluated. In doing so, a framework has been created to address the first research questions. Following the Sustainable Healthcare Coalition (SHC) guidelines, the entire care pathway has been disassembled into modules, tailored with experts' help on medical practices followed in the Netherlands. Therefore, next to providing relevant insights into the most environmentally impactful activities in the CKD care pathway, this work contributes to the general knowledge concerning the environmental analysis of the care pathway by providing (for the first time according to the knowledge of this author and the experts involved) a framework applicable, with the necessary modifications of the specific cases, to every chronic disease in the Netherlands. Additionally, to provide an example of how to include environmental impact in the economic evaluation of healthcare intervention, a medicine prescribed to CKD patients has been chosen: Forxiga.
So far, the few attempts to take into account the environmental footprint of treatment in their economic evaluations have been made by incorporating it as a cost. In this thesis for the first time, next to the inclusion as a cost, the environmental impact of a medicine has been translated into actual health benefits and incorporated in its economic evaluation. Additionally, an overview of the existing environmental metrics and analyses is presented to provide the reader with a full picture of the current practices.
This study is particularly relevant for several stakeholders. In the first place, its insights concerning the most polluting segments of the care pathway may be very valuable to steering policymakers' future strategies to reduce emissions and to emit guidelines in this field. Next to that, the information presented in this work may create a competitive advantage for (bio)pharmaceutical companies which can make their production and distribution processes more sustainable thereby addressing the general public's concerns about the footprint of the sector. Additional beneficiaries of this study are health insurance providers and other healthcare payers who can utilize its results in the negotiation process with (bio)pharmaceutical companies.
This study shows that carrying out an LCA (which is not a common healthcare practice yet) for care pathways is feasible and valuable. In addition, it shows the added value of including the environmental impact of medicines in their economic evaluation so to provide a more comprehensive assessment. However, despite the relevance and the added value, some limitations have been identified. Carrying out an LCA is a resource-intensive and time-consuming activity that many companies often cannot afford. It is a data-driven analysis that is severely hindered by the lack of knowledge-sharing within the healthcare sector. In the absence of data, this analysis requires several assumptions and involves many proxies that undermine the reliability of its results.

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Abbreviation	Definition
ACEi	angiotensin-converting-enzyme inhibitor
ACR	albumin-to-creatine ratio
AdViSHE	Validation-Assessment Tool of Health-Economic
AER	albumin-excretion rate
APD	autonomous peritoneal dialysis
API	active pharmaceutical ingredient
AKI	acute kidney injury
ARB	angiotensin-receptor blocker
AV	arteriovenous
BAF	bioaccumulation factor
BCF	bioconcentration factor
BMF	biomagnification factor
CAPD	continuous ambulatory peritoneal dialysis
CEM	cost-effectiveness model
CH_4	methane
CKD	chronic kidney disease
CO_2	carbon dioxide
CO_2e	carbon dioxide equivalent
CSB	central bureau voor statistiek
CNS	chronische nierschade
CUA	cost utility analysis
CVD	cardiovascular disease
DALY	disability-adjusted life-year
DAPA-CKD	dapagliflozin and prevention of adverse outcomes in chronic kidney disease
DMAIC	Define Measure Analyze Improve Control
DW	disability weights
eGFR	estimated glomerular filtration rate
ERA-EDTA	European Renal Association − European Dialysis and Transplant Association
ESRD	end-stage renal disease
FMS	Federatie Medish Specialisten
GHG	greenhouse gas
GP	general practitioner
GWP	global warming potential
HD	hemodialysis
HHF	hospitalisation for heart failure
HTA	heathcare technology assessment
HWIA	health Workforce Impact Assessment
ICU	intensive care unit
ICUR	incremental cost utility ratio
IPCC	intergovernmental panel on climate change
KDIGO	kidney disease improving global outcomes
KPI	key performance indicators
LCA	life cycle analysis
MRA	mineralcorticoid-receptor antagonist
NMB	net monetary benefit
NFN	nederlandse federatie voor nefrologie
NHG	nederlands huisarten genootschap
N_2O	nitrous oxide
PD	peritoneal dialysis
PDSA	Plan-Do-Study-Act
QALY	quality-adjusted life-year
SCC	social cost of carbon
SHC	sustainable healthcare coalition
SGLT2	sodium–glucose co-transporter 2
SoC	standard of care
SSP	shared socioeconomic pathways
WHO	World Health Organization
WWTP	wastewater treatment plant
WTP	willingness-to-pay
YLD	years lived with disability
YLL	years of life lost

1

Introduction

In this chapter the research carried out in this thesis is introduced. The emissions caused by human activities are heavily damaging the ecosystems. A substantial contribution to the total environmental footprint comes from the healthcare sector. Consequently, the environmental impact of care activities cannot be neglected anymore. This study will dive into the nascent field of sustainability in healthcare by addressing two issues: how to assess the environmental footprint of care pathways and how to include this impact in the economic evaluation of healthcare interventions.

1.1. Context

Sustainability has been defined as ”meeting the needs of the present without compromising the ability of future generations to meet their needs” [6]. However, considering the current environmental impact of human activities, society is walking in a direction that will irreversibly damage the resources available for future generations. To visualize the remaining time to act, a ”climate clock” was placed in Union Square (New York) last September 2020. The clock is currently reading slightly more than 5 years, meaning that after that, the effect of the climate crisis on the environment and living species will be irreversible. According to some other studies depicting a worse scenario, we are even closer to that point [80]. In other words, discussions need to be replaced by actions. However, taking action requires having an understanding of the most polluting activities and of the ways to alleviate their impact. Moreover, a careful evaluation of the environmental impact of human activities needs to be performed. Looking at the national environmental footprints, for several countries, the healthcare sector is responsible for more than 5 percent of total impact [61].

Specifically, the Netherlands stands out from European countries, with its healthcare sector which is responsible for approximately 7 percent of the consumption footprint in terms of CO2 emission equivalent, 4 percent of the waste, and 13 percent of the consumption of raw materials (metals and minerals) [51] [101]. These data highlight an existing paradox: although the health sector aims to make people in the Netherlands better and to prevent diseases, it simultaneously contributes to the climate crisis which, in turn, causes more infectious diseases, mental health problems, allergies, lung, cardiovascular and neurological diseases thereby increasing the demand for care and causing the opposite effect [51]. Moreover, according to recent findings, over 9 million global deaths are attributable to air pollution and over 5 million to non-optimal temperature [43]. Therefore, quantifying the environmental footprint of care activities and interventions together with incorporating it in their economic evaluation has been identified by several institutions, both at the European and national level, (European Commission, OECD, Nederlandse GGGZ, Dutch Patient Federation, KNMP, Green Care Alliance, KAMG, VIG, TNO) as a priority. For instance, the Health Systems Taskforce [44] was created, a public-private partnership that has the backing of CEOs from 7 pharma companies (AstraZeneca, GSK, Merck KGaA, Novo Nordisk, Roche, Samsung Biologics, Sanofi) who have committed to work together to deliver net-zero health care (‘Decarbonisation of Patient Care Pathways’ [3]).

1.1.1. Scientific gap

However, the lack of guidelines, agreement on methodology, and practical examples represent a substantial barrier to the actual implementation of sustainability assessment in healthcare. Specifically, two significant gaps can be currently identified in this nascent field, which can be translated into the following research questions: How can an environmental analysis be conducted to assess the footprint of care pathways[1]? How the environmental impact of new healthcare interventions can be incorporated into their economic evaluation?
This study gives its scientific contribution by addressing these two research questions. In doing so, a framework for the evaluation of the environmental footprint of chronic diseases is presented. To the knowledge of this author and of the experts involved in this study it is the first time that this type of framework is created for the Dutch healthcare system. Additionally, for the first time, the environmental impact is translated in health benefits and not only in costs. In fact, this study illustrates three different ways of taking into consideration the environmental impact of interventions in their economic evaluation and shows the pros and cons of each alternative.
However, environmental impact is not the only aspect to work on in order to make the healthcare sector more sustainable. In fact, great concerns have also arisen about the chronic shortage that affects the healthcare sector. The healthcare professional shortage has been often depicted as a vicious circle: the pressures created by the backlog, have created an increasingly difficult and demanding working environment, pushing more clinicians to leave and generating a permanent crisis in the sector, named a ”permacrisis” [9]. Looking at the Netherlands, although 1.4 million people work in the healthcare and welfare sector [79], the staff shortage is currently estimated to be 48 thousand people (32 thousand Full Time Equivalent (FTE)). The impact of interventions on the healthcare workforce and its inclusion in their economic evaluation is a crucial topic to further explore, together with the environmental footprint, to make the healthcare sector more sustainable (see section 5.6.1).

Within the healthcare sector, chronic diseases are known to be particularly resource-intensive because of their long-term management. Among them, Chronic Kidney Disease (CKD) represents a real burden for the Dutch healthcare system, with a prevalence of 8.9 percent among the population. In the last stage of the disease, dialysis, the treatment of this disease requires a large amount of resources (water, electricity) thereby producing a significant environmental footprint. For this reason, it has been selected as a case study; in the following paragraph, a brief background about Chronic Kidney Disease and its treatment is provided.

1.2. Case study background

Worldwide, there are currently more than 850 million patients with kidney disease with a 9.1 percent estimated prevalence [56] [19]. The increasing incidence of comorbidities such as diabetes and hypertension, as well as an aging population is expected to make Chronic Kidney Disease (CKD) the fifth most prevalent chronic disease by 2040 [37].
Considering these data, it appears evident that CKD poses a severe threat to human health and for this reason, it has always got quite some attention from the healthcare community. However, its environmental impact represents a burden as well. Actually, CKD treatment in later stages often involves chronic dialysis or kidney transplantation, which entails substantial costs in terms of waste, water, and energy consumption. To elucidate, hemodialysis requires an annual water use of 265 million m^3 and it creates more than one billion kilograms of medical waste [49].
Nevertheless, patients with CKD not only in the final stage but throughout all stages require a high healthcare resource use, including specialist visits, blood tests, and surgical procedures. Accordingly, at the global level, organizations such as the European Renal Association [33] have implemented green nephrology initiatives to mitigate the environmental impact of kidney care. With the Alliance for Transformative Action on Climate and Health [4], fifty countries committed to reducing the environmental burden of health care at COP26 [110] in 2021 with the aim to build more sustainable health systems. Next to that, there are the Sustainable Development Goals relevant to kidney health (improving dialysis efficiency and waste production) [62], formally adopted by all United Nations member states in 2015. Despite all these considerations, there is a paucity of research on the environmental burden of chronic kidney disease and specifically, it is the first study to present an analysis to assess the environmental impact of CKD care pathway in the Netherlands.

[1] “A care pathway is a complex intervention for the mutual decision making and organisation of care processes for a well-defined group of patients during a well-defined period.” [97]

1.2.1. Medical context

Chronic Kidney Disease (CKD) is a long-term, irreversible deterioration in kidney function. The kidneys are composed of small functional units called ”nephrons”. They contain a filtering unit called a glomerulus (fig. 1.2 [25]), consisting of a network of very small blood vessels. The glomerulus is surrounded by Bowman’s capsule (see figure 1.1 [25]), which is the initial site of blood filtration in the kidney. The filtered fluid, known as filtrate, undergoes further processing in the renal tubules to ultimately form urine.

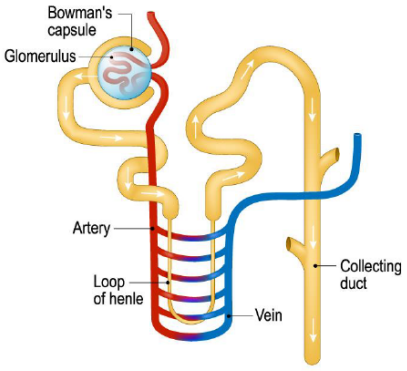


Figure 1.1: Structure of the kidney

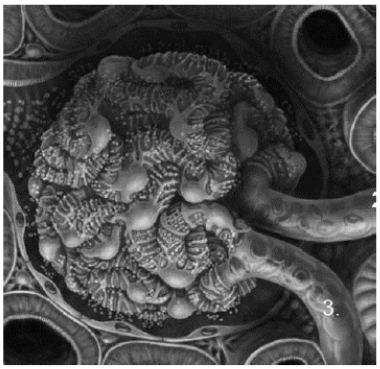


Figure 1.2: Microscopy image of a glomerulus

In CKD, progressive loss of nephrons causes harmful changes which, in turn, cause kidney function to decline over time, eventually leading to end-stage renal failure (ESRD) in some patients. The kidneys then no longer function sufficiently to maintain health and homeostasis [2]. Without treatment, CKD worsens over time, with associated declines in kidney function and increased kidney damage. One of the reasons CKD is considered a burden on the healthcare system and the environment is because of its complications (cardiovascular disease, high blood pressure, kidney failure, etc.)
CKD is diagnosed only if there is more than three months of reduced kidney function and/or elevated albumin. This can be assessed using blood and urine tests. The two most common types of tests are:

- a blood test known as the estimated glomerular filtration rate (eGFR): it is a measure of kidney function and represents the estimated volume of blood filtered through the glomeruli every minute. This is estimated based on serum creatinine and/or cystatin C (although the latter is less commonly used), along with age, gender, and ethnicity (a representation is given in figure 1.3 [42]);

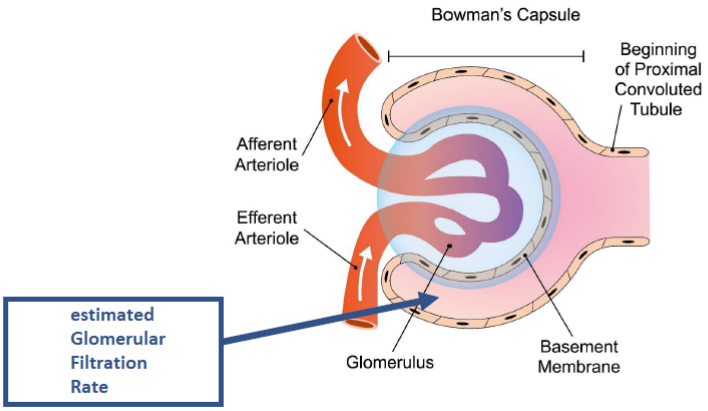


Figure 1.3: Glomerular Filtration Rate

[2] any self-regulating process by which kidneys maintain stability in the body, such as balancing electrolytes, regulating fluid levels, and removing waste products, while adjusting to conditions that are optimal for survival.

- a urine test known as the urine albumin-creatinine ratio (ACR): Albuminuria (the presence of albumin in the urine) provides an estimate of the degree of kidney damage due to structural damage to the glomerulus resulting in abnormal filtration (a representation is given in figure 1.4 [73]);.

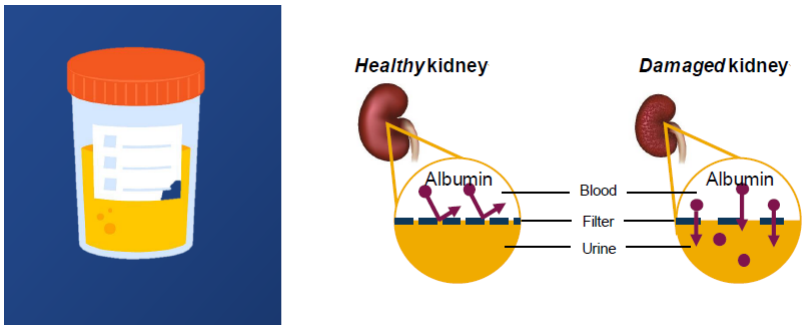


Figure 1.4: Urine albumin-creatinine ratio

However, only a combination of the two allows to get an accurate picture of the kidneys' status. Based on the results of these two tests, the KDIGO (Kidney disease: improving global outcomes association) has defined stages indicating the severity of the disease, which are shown in figure 1.5 [95].

KDIGO: Prognosis of CKD by GFR and albuminuria categories				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. GFR, glomerular filtration rate.

Figure 1.5: CKD stages

1.2.2. Current treatment: Standard of Care (SoC)

The current treatment for CKD in the Netherlands focuses on preventing cardiovascular events, slowing the progression of the disease, treating complications (e.g. anemia), and prolonging life. The treatment can be distinguished into two types:

- non-medical treatment (healthy body weight, lifestyle adjustments, exercises, etc.);
- medical treatment (established through the most relevant national/international guidelines shown in Table 1.1).

The medications typically prescribed are:

- angiotensin-converting-enzyme inhibitor (ACEi);
- angiotensin-receptor blocker (ARB);
- mineralcorticoid-receptor antagonists (MRA);
- diuretics;
- statins

Title	Issuing authority
NHG-Richtlijnen,Diabetes mellitus type 2 (2021) [28]	Dutch College of General Practitioners (NHG), Utrecht
Diabetes management in chronic kidney disease (2022) [23]	Kidney Disease:Improving Global Outcomes (KDIGO)
Guidelines for the diagnosis and treatment of acute and chronic heart failure (2021) [66]	European Society of Cardiology (ESC)
Guidelines for the management of cardiovascular disease in patients with diabetes (2023) [64]	European Society of Cardiology (ESC)
Leidraad SGLT2-remmers bij patiënten met chronische nierschade zonder diabetes mellitus type 2 (2023) [60]	Nederlandse Federatie voor Nefrologie (2023)
Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (2024) [95]	Kidney Disease:Improving Global Outcomes (KDIGO)

Table 1.1: List of Guidelines and Issuing Authorities

1.2.3. Dapagliflozin (Forxiga®)

Next to the ones in the previous list, from 2021, a new medicine has been approved in Europe for the treatment of CKD: dapagliflozin (Forxiga®). Its phase III trial demonstrated significant benefits in reducing the risk of End-Stage Renal Disease (ESRD), of worsening renal function, and death from renal or cardiovascular causes. Dapagliflozin (Forxiga®) is a selective and reversible inhibitor of sodium-glucose co-transporter-2 (SGLT2). As mechanism of action, the inhibition of SGLT2 reduces the reabsorption of glucose from the glomerular filtrate in the proximal renal tubules with a concomitant decrease in sodium reabsorption in the blood, leading to urinary glucose excretion and osmotic diuresis [3], as shown in figure 1.6. As a result, dapagliflozin increases the release of sodium to the distal tubules, which increases tubuloglomerular feedback and reduces intraglomerular pressure.

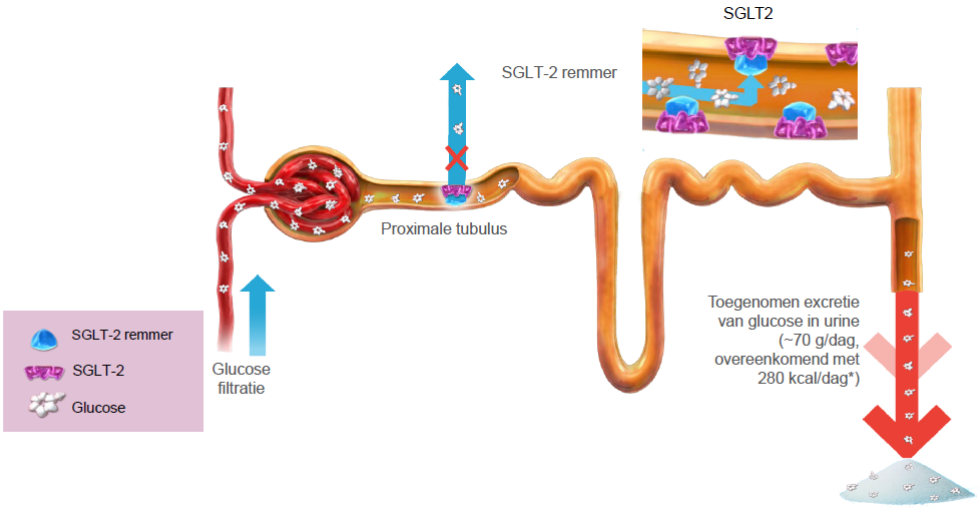


Figure 1.6: Dapagliflozin: SGLT-2 inhibition mechanism

[3] a process in which the presence of high concentrations of glucose or mannitol, in the renal tubules, draws water into the urine, thereby leading to increased urine output. This mechanism helps to reduce excess fluid in the body.

The intervention consists of administering dapagliflozin orally at a daily dose of 10 mg (showed in figure 1.7 [38]) in combination with standard of care as recommended in the relevant guidelines (described in table 1.1).

Figure 1.7: Forxiga

Forxiga has been chosen as a medicine prescribed for CKD treatment to exemplify the inclusion of environmental impact in the economic evaluation of healthcare intervention.
It is interesting to consider that in the last couple of months, new studies have been conducted to collect evidence regarding alternative mechanisms of action of Forxiga. In fact, next to the one described above, it has been hypothesized that SGLT2 inhibition has additional benefits, among them:

- Neurohormonal improvement [91];
- Inflammation/fibrosis reductions [48] [98];
- Decreased renal workload and hypoxia [48] [98].

Consequently, it may determine several clinical improvements, in terms of:

- decreasing blood pressure [48];
- decreasing glomerular injury [48] [98];
- decreasing renal ischemic injury [48].

The eventual extra benefits related to SGLT2 inhibition can have an impact on the results of the analysis conducted in this study. In fact, the care pathway was modeled by assuming that Forxiga is only prescribed in stages 1,2,3 and 4. In case evidence of the additional benefits would be found, this could be an incentive to prescribe Forxiga also in the later stages (dialysis, transplantation) thereby influencing in a positive way the environmental impact of the care pathway.

1.2.4. Relevance to stakeholders

This study is intended for several stakeholders:

- policy-makers: in the context of reimbursement decision-making, this study shows the potential of including LCA in the economic evaluation of healthcare interventions. It is a nascent field and this study discusses several options to translate and include environmental impact in the economic evaluation of healthcare interventions. Next to that, by evaluating the environmental footprint of the pathway, it allows to identify the pollution hotspots. Taking them into consideration, new policies can be steered in the direction of making production processes more sustainable. Next to that, researches of this type are necessary to help the government in developing guidelines concerning environmental analysis, in order to make them comparable and aligned;
- academia: being the bridge between environmental sciences and economics, this study is highly valuable for academia, which includes students and researchers and where awareness about sustainability is created in the first place. This study brings its scientific contribution to academia by developing a framework to assess the environmental impact of care pathways for chronic diseases in the Netherlands (environmental sciences) and by exploring several ways to include the environmental impact of new healthcare interventions in their economic evaluations (health economics);

- environmental experts in the healthcare sectors: LCA for care pathways is a practice in the infant state: the very few existing studies largely vary in terms of considered activities and methodology. Creating more studies of this type can provide a common basis for experts to build upon several new case studies. Additionally, by providing indications about challenges, opportunities, and limitations, this study paves the way for improved LCAs in healthcare;
- (bio)pharmaceutical companies: comprehensive LCAs of the care pathways, as the one performed in this study, include every stage of the life cycle of medical treatments, as medicines. Being aware of the environmental impact of the production, use, and disposal stage of their products represents an essential step for (bio)pharmaceutical companies to make them more sustainable. Next to that, currently, an increasing number of payers (from the public and private sectors) are showing interest in the environmental impact of healthcare interventions and want to take action in that direction (e.g. Green Deal Zorg 3.0 [68]). Consequently, it will become more important for companies to be able to provide insight into this type of impact of their drugs. In fact, this information will be essential for presenting their medicines (e.g. for negotiations on reimbursement);
- hospitals and healthcare centers: including environmental impact on the evaluation of new therapeutic interventions allows hospitals and healthcare centers to make more informed decisions for the well-being of their patients and of the environment;
- health-insurance providers: having LCA of medicines at their disposal allows health-insurance providers to make informed decisions by taking into consideration a broader analysis of the costs. Enlarging their understanding of the medicine impacts provides them with useful information to negotiate with pharmaceutical companies. Next to that, understanding the LCA of a medicine prepares the health-insurance providers to deal with the coming legislation concerning sustainability and to be leaders in the future market.

2

Theoretical background

In this chapter, the current practices for the economic evaluation of healthcare intervention are briefly presented. In the Netherlands, the clinical efficacy, safety, effectiveness, and cost-effectiveness of new treatments need to be shown. One way to calculate long-term cost-effectiveness is through the Markov model, which is a valuable tool to implement evidence from multiple sources and project them into the future. As an addition to the existing evaluation methods, this study is centered on an environmental analysis, an element of added value that allows a more comprehensive evaluation of the treatments. For this reason, an overview of the existing methodologies to assess the environmental impact together with a description of the chosen one (Life Cycle Analysis) is presented in this chapter.

One of the biggest problems modern society is currently facing concerns the escalating costs of care. Globally, the World Bank data [109] shows that health expenditure accounted for 9.8 percent of global GDP in 2022. Looking at the Netherlands, in 2022, the healthcare expenditure represented 13,3 percent of the Dutch GDP [14]. The increasing costs have raised significant concerns, given the government's commitment to keeping healthcare accessible and affordable for everyone and using the limited financial and natural resources in the most efficient way. Hence, in the context of governmental expenditures in the healthcare sector, policy-makers face the imperative of making judicious and fair decisions [88]. In order to do so, pharmaceutical companies need to provide them with evidence of the efficacy, safety, cost-effectiveness, budget impact, and innovativeness of their treatments through documentation (named "pharmacoeconomic dossier"). The main document of the dossier is the so-called Cost-Effectiveness Analysis (CEA) of the treatment.

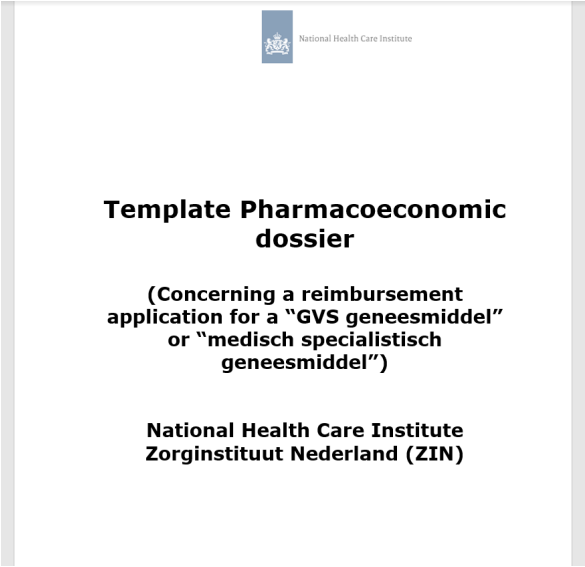
2.1. Cost-Effectiveness Analysis

Since the 1990s, an increasing number of countries have legally required an economic evaluation of healthcare interventions before their marketing [88]. The procedure is part of Health Economics, a branch of Economics that focuses on effectiveness, efficiency, and value in healthcare [59].
This sector presents several peculiarities:

- government influence: pricing and access are significantly influenced by the government, which heavily regulates the sector to ensure efficacy and safety;
- externalities: this industry can be affected by several positive externalities (for instance, the benefits of vaccinations for the society as a whole) or negative ones (antibiotics resistance due to overuse);
- inelastic demand: the purchase/use of medical interventions cannot be postponed in case of life-threatening situations. This, together with the fact that there are no substitutes leads to an inelastic demand;
- skilled workforce: both for the production and the use of health technologies, highly trained personnel are required. Indeed, one of the main challenges the sector is currently facing is a significant shortage of specialists, as discussed in section A.4;
- asymmetric information: patients often lack the medical knowledge to make informed decisions and need to rely on providers' recommendations;
- geographical accessibility: the access to healthcare facilities (and consequently technology) may significantly vary with the location and this leads to inequities in service provision;

- healthcare providers: many healthcare costs are covered by insurance companies, this means that patients do not pay directly themselves thereby generating a market distortion;
- capital intensive: producing healthcare interventions very often requires high fixed costs related to facilities and equipment;
- market control: for many healthcare technologies the market is controlled by one (monopoly) or few (oligopoly) providers thereby reducing the competition and causing market failures.

The majority of the items in this list are market failures that hinder the optimal allocation of resources. Therefore, government intervention is essential in the healthcare sector. To make resource allocation decisions, policymakers need information that is provided by economic evaluation of healthcare interventions. At the beginning, the debate arose around the different ways to perform this evaluation and operationalize costs and benefits (development and manufacturing costs, clinical trials, intellectual properties, regulatory compliance, health gains). However, Cost-Utility Analysis (CUA) brought the majority of analysts on the same page. [54].
Nowadays, CUA is still the most widely used economic evaluation method for medical treatments, and, in the Netherlands, is the core analysis in the pharmacoeconomic dossier medical companies write to the Ministry of Health for reimbursement decisions (an example of a pharmacoeconomic dossier is shown in figure 2.1).


National Health Care Institute

Template Pharmacoeconomic dossier

(Concerning a reimbursement application for a "GVS geneesmiddel" or "medisch specialistisch geneesmiddel")

National Health Care Institute
Zorginstituut Nederland (ZIN)

Figure 2.1: Example of a Dutch pharmacoeconomic dossier for reimbursement decision

The CUA included in these dossiers, provides a comparison and an estimation of costs and health benefits associated with the Standard of Care considered separately and with the addition of the new intervention thereby facilitating the evaluation of the extra benefits due to the latter. The method is grounded in Utilitarianism, meaning that the solution that holds lower costs and larger benefits to society as a whole is selected as optimal. CUA prescribes translating costs in monetary terms and benefits in Quality-Adjusted Life Years (QALYs) [54].
QALYs are defined as the number of years lived by an individual, with each year of life weighted by health utilities (between 0 and 1) assigned to the health state experienced by the individual during the years lived. [88].
To evaluate the added value of new interventions against the SoC, the Incremental Cost-Effectiveness Ratio (ICER) is calculated as the differences in costs divided by the difference in effectiveness between the two alternatives [54].
According to the national guidelines [71]), cost-effective analyses included in pharmacoeconomic dossiers, have to be undertaken with a "model-based approach". Several methods can be selected (state-transition models, partitioned survival models, discrete event simulations, dynamic transmission models, etc.). according to the research question and the clinical picture. There are several documents/tools that can be used for choosing the right type of model [13] [57] [85].
Since for the CEA describing the intervention analyzed in this study (Forxiga for CKD) the Markov model has been implemented, its core characteristics are introduced in the following paragraph.

2.1.1. Markov model

A Markov model can be defined as a mathematical framework frequently used in health economics to simulate the progression of a disease and the impact of different health interventions over time. This type of model is particularly useful since it allows to extrapolate beyond the time duration of the clinical trial, combine different information sources, and facilitate uncertainty analyses thereby handling complex clinical pathways. Together with microsimulation models, it is used for modeling chronic conditions that involve distinct health states. The model can well suit pharmacoeconomic dossiers (depending on the specific intervention/disease) because it allows to calculate long-term costs and health outcomes thereby informing cost-effectiveness analysis.

The following notions are applied in Markov models:

- health states: they represent the different stages within the disease that patients can experience. For instance,the model for CKD includes stage 1,2,3a,3b,4,5(pre-RRT), dialysis, and kidney transplant;
- cycles: time in Markov models is divided into discrete intervals named ”cycles”. Each cycle represents a fixed period. For instance, the length of the cycles used for Forxiga CKD model is 4 months. During each cycle, patients can move from one health state to another based on well-defined transition probabilities;
- transition probabilities: these are the probabilities that a patient has to move from one health state to another during a cycle. They are derived from clinical data or experts' opinions and reflect the likelihood of the disease progression;
- patient initial distribution: at the beginning, patients are distributed across the different health states according to baseline characteristics;
- patient post-cycle distribution: after each cycle, the distribution of patients across the health states is updated according to the transition probabilities. This process is repeated for each subsequent cycle so that the model is able to simulate the disease progression over time;
- transient events: they refer to states that are not absorbing, i.e. that there is a possibility of transitioning out of these states to others within the model. Transient events are temporary: the system, over time, will eventually leave these states and move towards absorbing states (if they are present). For Forxiga in CKD treatment, these events are for instance hospitalization for heart failure or acute kidney disease.

The Markov model, described in figure 2.2 from Forxiga CKD pharmacoeconomic dossier, is created by following 5 main steps:

- initialization: health states, cycle length, transition probabilities, and initial distribution of patients need to be defined;
- cycle calculation: for each cycle with a new distribution of patients (based on the transition probabilities), costs and health outcomes need to be calculated;
- iteration: to obtain the final result, it is necessary to repeat the cycle calculations for the entire time horizon and then aggregate them;
- analysis: to better quantify and present the results, they are summarised through relevant indicators such as Net Monetary Benefit (NMB).

The Markov model proves to be particularly effective in modeling chronic diseases since these types of diseases are long-lasting conditions often not curable. This model provides a structured way to simulate long-term disease progression and intervention effects. Furthermore, by simulating costs and health outcomes of different interventions over time, the Markov models allows to evaluate the cost-effectiveness of healthcare strategies. This, in turn, helps decision-makers in allocating resources and prioritizing interventions that hold the best value for money, a crucial step for optimizing healthcare spending and improving societal health outcomes.

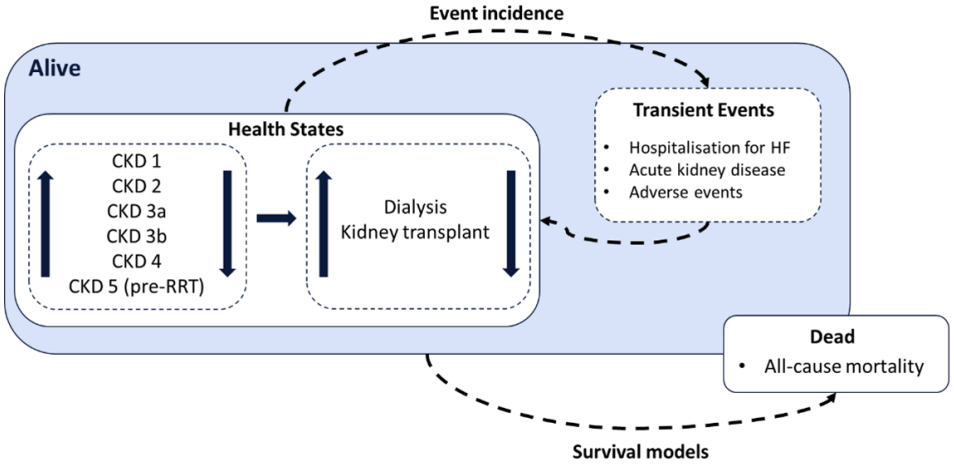


Figure 2.2: Example of Markov model for Chronic Kidney Disease (CKD)

Despite the increasing importance gained by the topic (see section 1), currently no sustainability consideration is required in these dossiers. However, numerous European and Dutch institutional reports [51] [70] [69][1], have recently emphasized the idea that circumventing non-health impacts entails ignoring real costs and this cannot be done any further. They need to be incorporated to obtain economic evaluations of medical treatments as realistic and comprehensive as possible. Since choices in patient care (design of healthcare facilities, ways in which care is delivered, innovative therapeutics interventions) can play a crucial role in reducing emissions, it is worth exploring how to assess the environmental impact of care activities and how to include sustainability criteria into medical treatment evaluation.
Since currently there are no guidelines concerning the assessment of the environmental impact of healthcare interventions, an overview of the most used approach in several fields is provided in the following paragraph.

2.2. Environmental Analysis

Currently, several methodologies are implemented in different fields for quantifying the environmental impact of products and processes. From an extensive literature review, the main ones can be summarised as follows:

- Life Cycle Analysis (LCA) is a comprehensive approach that evaluates the environmental impact during the entire life cycle of the treatment (medicines and devices), from production to disposal. This inclusive framework ensures that crucial steps, that significantly contribute to pollution, are not overlooked and, depending on the maturity and consistency of the methodology, it offers comparable results [83];
- Ecotoxicity Assessment on Ecosystem approach quantifies the impact of medical treatments on living organisms. By taking into account both terrestrial and aquatic ecosystems, it enables the implementation of the right measures for preserving biodiversity in terms of animals and plants. This approach is characterized by high specificity: it explains how chemicals present in medicines interact with ecosystems and sometimes irreversibly modify them [15] A.2;
- Pharmaceuticals in the Environment approach is focused on monitoring the actual presence of pharmaceuticals in the environment. This approach prescribes to utilize real environmental samples rather than laboratory ones, thereby ensuring an understanding as close as possible to reality. Additionally, a peculiarity of this approach is represented by the great emphasis placed on the future. It includes degradation, transformation, and chemical reactions thereby taking into account the environmental fate and persistence of pharmaceuticals [22];
- Eco-efficiency analysis is an approach with specific attention to the economic aspect, ecology aspect, and optimization. The methodology allows the identification of opportunities for employing resources and energy in the most efficient way. It involves carrying out an overall study of alternative solutions to include a total cost determination and the calculation of ecological impact [29]. One of its main strengths is ensuring an alignment of ecological and economic goals [87];

- Environmental risk assessment (ERA) is a method used to evaluate potential future impacts of an activity on the environment. It is a systematic approach that involves identifying and evaluating the potential risks to the environment in the system under consideration. It is done by considering their likelihood and severity, and elaborating measures to mitigate or avoid those risks [24]. Regulatory guidance is provided by the European Medicines Agency (EMA) on the conduct of environmental risk assessments that are legally required to be provided by applicants with any submissions for marketing authorization (and line extensions) for human medicinal products [33];
- Sustainable Pharmacy Practice Assessment is a specific approach developed for the pharmaceutical industry. Its main advantage is the focus on supply chain, manufacturing practices, and waste management. The approach extends the analysis beyond the single product thereby assessing the sustainability of practices throughout the entire pharmaceutical supply chain. Additionally, the method includes the analysis of some administrative practices, for instance, corporate practices/governance, management decisions, and policies [50];
- Circular Economy Analysis is an approach focused on environmental impacts within the context of circular economy. This methodology is used to evaluate to what extent a product aligns with circular economy principles: waste minimization, resource optimization, recycling, and repurposing of materials [31].

A more extended description of each approach with its pros and cons is provided in Table A.1 of Appendix A. Considering the above-mentioned descriptions, it can be concluded that the majority of methodologies focus on specific impact categories which may be a part of the evaluation of a care pathway, but are not comprehensive of all relevant impacts. Consequently, to evaluate the environmental impact of CKD care pathway in the Netherlands, and be consistent with the few existing examples [90], Life Cycle Analysis (LCA) is the chosen approach. The methodology together with its variants and key steps is presented in the following paragraph.

2.2.1. Life Cycle Analysis (LCA)

Although it is not the case in the healthcare context, LCA is a widely adopted approach in other sectors for its flexibility and adaptability to the different necessities, for instance:

- agriculture and food sector: in this industry, LCA is used to evaluate the impacts of the food production chain: processing, distribution, consumption, and waste, thereby helping with the identification of the most polluting activities. Furthermore, by assessing the impacts of different farming practices, this analysis is useful to foster sustainable agricultural techniques;
- manufacturing sector: in this field, LCA provides a holistic picture of manufacturing processes by resulting in a detailed analysis of environmental impacts from raw material extraction, production, and use, to disposal. Next to that, many companies use LCA to comply with sustainability reporting standards and obtain certifications;
- energy sector: in this field, LCA is mainly employed to evaluate the environmental impacts of renewable energy technologies (for instance wind, solar, and bioenergy) throughout their life cycles, including all the stages from manufacturing to decommissioning. Next to that, it allows to compare the carbon footprint of fossil fuels versus renewable energy sources, which is an essential tool for making policy and investment decisions;
- building sector: in this industry, LCA results to be particularly effective in selecting sustainable building materials since it allows to evaluate their environmental footprint across their entire life cycles. Additionally, LCA helps in understanding and alleviating the carbon footprint and energy consumption of buildings considering all their life phases from construction through demolition together with improving waste management;
- transport sector: LCAs are frequently used in the transport sector to evaluate and compare the emissions produced by different types of vehicles (electric, traditional, hybrid). Depending on the category to which the vehicle belongs, the LCA is focused on different aspects (battery production, combustion emissions, infrastructures).

Regardless of the industry, some fundamental characteristics can be identified in every LCA. In this analysis, the total life cycle of a product or activity is considered, from the extraction of resources to the waste treatment stage [107].

As pictured in figure 2.3, LCA consists of four phases [81]:

- Definition of **goal and scope**;
- **inventory** analysis;
- **impact** assessment;
- **interpretation**.

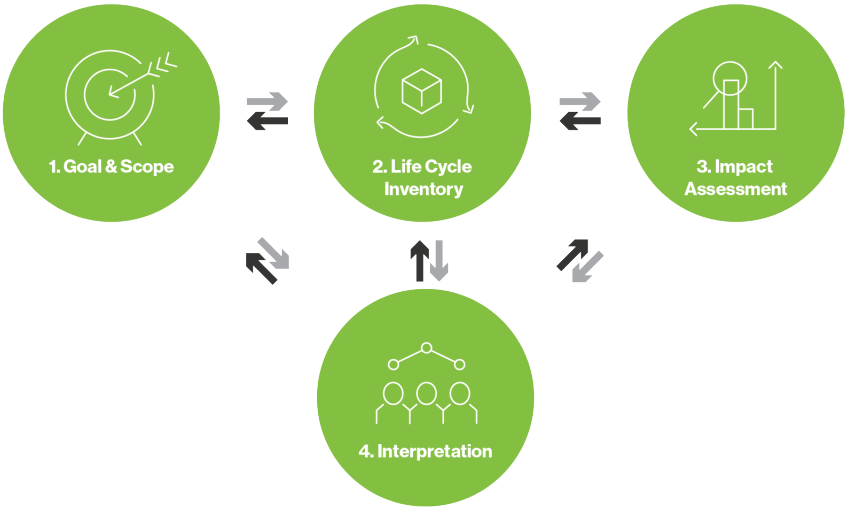


Figure 2.3: The four phases of life cycle analysis

Phase 1: Goal and scope
In this first phase of LCA boundaries are defined. Being the first part, this section is used to specify what will be analyzed and in which way. Specifically, in this phase, the analyst defines:

- the functional unit;
- the system;
- the limits of the analysis;
- impact categories.

Phase 2: Inventory analysis
This phase looks at the environmental input and output of the product/process analyzed. There are four main categories to consider when data are collected for the inventory phase:

- raw materials or resources;
- different types of energy;
- water use;
- emissions to air, land, or water from any substance.

Phase 3: Impact assessment
The impact of the product/process is evaluated according to each category defined in phase 1. Several impact categories can be selected to evaluate environmental impact, the most frequently used are:

- Global Warming Potential (GWP, carbon footprint);
- Human toxicity;
- Ecotoxicity;
- Acidification;
- Eutrophication.

Phase 4: Interpretation
The interpretation phase of LCA includes:

- to emphasize significant issues identified in inventory analysis and impact assessment phases;
- to evaluate the completeness and consistency of the analysis itself;
- to draw conclusions and to mention limitations and recommendations.

Several guidelines to conduct an LCA exist. However, the Sustainable Healthcare Coalition ones [97] (based upon ISO140 guidelines from 2006 [36]) have been chosen to define the principles and the framework for this study because they have been thought specifically to systematically evaluate the environmental footprint of care pathways. Considering a different type (for instance PAS 2050:2011 or EN 15804) would have involved more adaptation and a higher degree of subjectivity.
An LCA can be performed in different ways [92]. However, the two most comprehensive ones are:

- cradle-to-gate LCA: this LCA only covers the production part of the life cycle, from raw material extraction up to and including factory/gate;
- cradle-to-grave LCA: this LCA covers the entire life cycle by adding to the previous one the use phase and end-of-life phase.

For the case study, the cradle-to-grave LCA approach has been chosen since it allows the assessment of the impact of products and processes in a more extensive way: it includes environmentally harmful stages (e.g. end of life phase) which are usually overlooked in existing (cradle-to-gate) analyses. Therefore, if the analysis had been conducted through a cradle-to-gate LCA the environmental impact would have been assessed only partly without considering crucial steps as the disposal of products.
So far the significant potential of LCA has been discussed. However, it is important to consider that there are several criticisms concerning it. Some of the most relevant are:

- data quality and availability: one of the main challenges of conducting an LCA is obtaining reliable and accurate data for the inputs. They are very often unavailable because of confidentiality issues, not updated or ”average estimates” from similar products/processes and this can heavily influence the final results of the analysis;
- boundary definition: boundaries and impact categories of the analysis are drawn subjectively. Excluding or including a stage can lead to significantly different results and this harms the comparability of the studies;
- interpretation and presentation of the results: although indications concerning the presentation and interpretation of results exist, they only represent suggestions. This means that this phase can be conducted with a substantial degree of subjectivity thereby emphasizing some aspects rather than others;
- location: LCAs provide a snapshot of the environmental footprint of a product/process for a specific geographic area. This is unavoidable because some input data as energy mix and transportation are country-specific and cannot be generalized;
- complexity: conducting an LCA is a resource-consuming and complex task that requires experts, software, and data. These may represent barriers when there are limited resources;

In this study, an LCA will be conducted for all the care activities in the treatment of patients with CKD in the Netherlands. The impact of the same care pathway will be analyzed two times, the first considering the distribution of patients per stage due to the only SoC and the second considering the distribution of patients per stage resulting from the implementation of Forxiga in the SoC (where Forxiga slows down the progression of the disease thereby decreasing the number of patients in later stages).
Regarding LCA for medicines involved in this care pathway, production, use, and end-of-life phases will be considered. It is important to keep in mind that the end-of-life phase considered in the study only concerns the disposal of the packaging. This means that the environmental impact of medicines has been underestimated since the actual chemical compounds may have a substantial impact on the ecosystems as explained in the section A.2 in the Appendix.
In this chapter the reasons which led to the choice of the LCA have been provided. In the next chapter, the LCA will be operationalized and the methods elucidated.

3

Methodology and Operationalisation

In this chapter the methodologies adopted in this study are described. The steps to environmentally assess a care pathway according to the Sustainable Healthcare Coalition guidelines are presented together with the results of their operationalization. Additionally, the three alternatives to include environmental impact in the economic evaluation of healthcare interventions are described. The chapter ends with a description of the methodologies employed for the collection of qualitative data (interviews) and quantitative data (literature research, archive research).

The life cycle analysis has been conducted according to the Sustainable Healthcare Coalition (SHC) guidelines [97]. They are the only existing guidelines specifically designed to systematically appraise the environmental impact of care pathways. These guidelines are, in turn, built upon the ISO14040 and ISO14044 Standards for Life Cycle Assessment [36], the Greenhouse Gas Protocol Product Life Cycle Accounting and Reporting Standard (Product Standard) [93] and the Greenhouse Gas Accounting Sector Guidance for Pharmaceutical Products and Medical Devices (Sector Guidance) [78].
The SHC guidelines prescribe nine steps to conduct an LCA of a care pathway. These steps, the methods adopted to implement them, and the results of their operationalization are summarised in table 3.1 and detailed in the rest of the chapter.

Step	**Methodology**	**Operationalisation**
Defining the objective of the care pathway appraisal	Critical thinking	*Identifying the most polluting activities in the care pathway*
Defining the care pathway	Literature review	*the treatment of CKD in the Netherlands*
Defining the unit of analysis	Literature review	*the care of a patient of any age in any CKD stage in the Netherlands*
Creating a detailed map	Expert interviews, analytical thinking	*see figure 3.1*
Grouping activities into modules	Expert consultation, analytical thinking, literature review	• *screening module: blood test, urine test* • *primary care consultation: transportation, GP visit* • *secondary care consultation: transportation, specialist visit* • *standard of care module (medicines): API production, formulation, packaging phase, use phase, end-of-life phase* • *intensive care unit module: intensive-care room (heating/cooling/lighting), sanitation, medications, waste, transportation, materials* • *hospitalisation module: hospital room (heating/cooling/lighting), waste, transportation, materials and sanitation* • *palliative care module: specialist consultation, palliative medicines* • *kidney transplantation module: compatibility screenings, surgical procedure from living/deceased donor, transplantation-related medicines, transportation* • *dialysis module: arteriovenous fistula, patient training, in-center/at-home haemodialysis, CAPD, APD, transportation*
Collecting data	Literature review, Expert consultations	*Secondary data from internal documentation and scientific papers, primary data collected through interviews*
Calculating the impact of care activities	Quantitative analysis	*see Results (chapter 4)*
Calculating the impact of modules	Quantitative analysis	*see Results (chapter 4)*
Interpreting and reporting the findings	Analytical thinking	*see Results (chapter 4), Discussion (chapter 5)*

Table 3.1: Care pathways appraisal steps according to SHC guidelines

According to the SHC guidelines [97], the nine steps to conduct an environmental assessment of a care pathway are: defining the objective of the care pathway appraisal, defining the care pathway, defining the unit of analysis, creating a detailed map, grouping activities into modules, collecting data, calculating the impact of care activities, calculating the impact of modules and interpreting and reporting the findings.
In order to undertake these steps, several methodologies have been adopted. Concerning the objective of the care pathway appraisal, its definition has been derived by critically thinking about the aim of the analysis and the scientific gap this thesis was intended to fill. Regarding the definition of the care pathway, unit of analysis, and the collection of data (see section 3.4), the main methodology adopted was the literature review. Conducting the study in collaboration with a company has guaranteed access to internal reports and documentation which have been used to define the characteristics of the care pathway and derived the data concerning environmental impact. Next to that, a literature research of relevant peer-reviewed papers has been conducted to inform the operationalization. However, it has also ensured the help of experts in the environmental, medical, and economic fields, who helped with the collection of data and with the definition of modules and activities involved in the care pathway. The results concerning the environmental impact, first of the individual care activities and subsequently of the aggregated modules, have been obtained through a quantitative analysis. Finally, an analytical thinking process has guided the interpretation and report section of the environmental assessment.
In the following, a detailed description of the steps and of the results of their operationalization is presented.
The first step to ensure a well-structured environmental assessment is to specify its aim. The objective of this assessment is to provide insights into the environmental footprint of the CKD care pathway in the Netherlands in order to identify the most polluting care activities and allow policy-makers to elaborate strategies to mitigate them.
The following steps concern the definition of the care pathway and of the functional analysis. According to the SHC definition, a care pathway is ”a complex intervention for the mutual decision-making and organization of care processes for a well-defined group of patients during a well-defined period.” Consistently, the chosen care pathway for this study is the treatment of CKD in the Netherlands. Next to that, to guarantee that modules can be combined to calculate the final results, a common functional unit of analysis has to be defined: As established by SHC guidelines, a function unit of analysis describes the care pathway, its length, and the type of patient being appraised. Specifying it for this case study, what is obtained is the care of a patient of any age in any CKD stage in the Netherlands.
However, care pathways are complex and involve numerous care activities. This makes it difficult to assess them as a whole and requires them to be disassembled into several modules. A care pathway module describes one or more distinct healthcare-related activities performed for, on behalf of, or by a patient [97]. Care pathway modules are the building blocks that make up the total care pathway and within each of them, several care activities are grouped.
The modules (described in details in the section 3.1) considered for this care pathway are:

- primary care consultation;
- secondary care consultation;
- Standard of Care (medicines);
- screenings;
- dialysis;
- kidney transplantation;
- palliative care;
- intensive care unit (ICU);
- hospitalisation.

To visualize and clarify the modules and the care activities related to them, the creation of a map is essential 3.1.

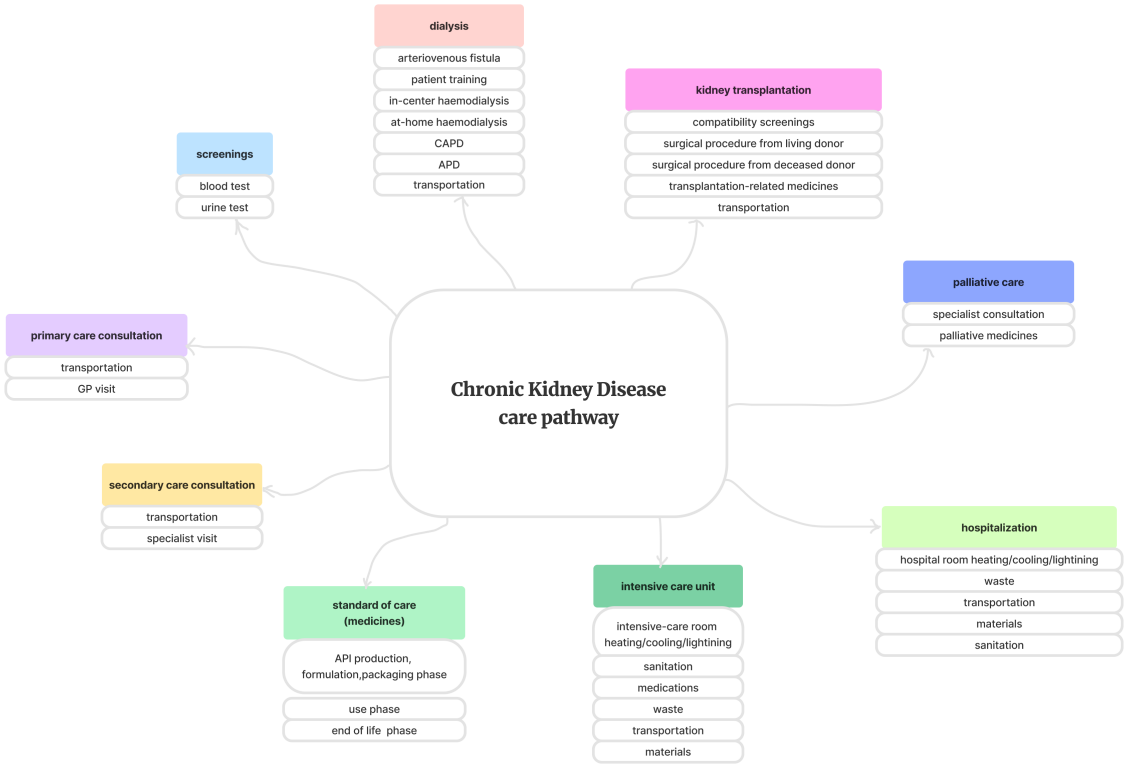


Figure 3.1: module and sub-module map

Once the objective, care pathway, functional unit, and modules have been defined, the actual evaluation of the environmental impact can be performed. For this purpose, two types of data have to be collected: activity data and emission factors. The first category refers to the resource inputs in terms of time, energy, and materials required for each care activity. Once all these data have been collected, emissions factors have been selected. An emission factor is a coefficient that allows the conversion of activity data into Green House Gas (GHG) emissions [1]. Moreover, it expresses the sum of emissions of human activity described as mass unit of CO2e [2].
Among the several existing variables (see description in section 4.46), it has been decided to evaluate the environmental impact in GHG emissions (quantified in standard kg of CO_2e) for several reasons:

- ease of comparability: this metric is globally well-established and makes it easier to compare analyses across different regions and time periods:
- inclusivity: while fine particulate matter and other pollutants affect local air quality and health, CO_2 has a more direct relation with a broader environmental impact.
- data availability: the majority of data concerning the impact of activities is available as CO_2e while it has not been quantified as Particulate fine matter yet;
- standardization: CO_2 emissions are quantified using a standard metric (tonnes of CO_2e) which simplifies the assessment and the communication of the environmental impact;

[1] GHGs are, by definition, gases that trap the heat in the atmosphere and include Carbon Dioxide (CO_2), Methane (CH_4), Nitrous Oxide (N_2O), Fluorinated gas [77].

[2] A carbon dioxide equivalent is a metric measure used to compare the emissions from various greenhouse gases on the basis of their global-warming potential (GWP), by converting amounts of other gases to the equivalent amount of carbon dioxide with the same global warming potential.

- economic integration: CO_2 is central to economic tools like carbon pricing, emissions trading systems, and carbon taxes, which are frequently used in environmental economics;
- technology compatibility: many technologies (e.g. Carbon Capture and Storage) are designed to specifically reduce the CO_2 emission impact; general understanding: among all the other environmental variables, CO_2 is widely understood by the general public thanks to awareness campaigns and educational initiatives;
- relevance: CO_2 is considered the main contributor to anthropogenic climate change. Therefore, focusing on CO_2 addresses the largest factor responsible for global warming;
- regulation: many international agreements state their objective in CO_2e terms;

The final environmental impact of each activity is then calculated by multiplying the input resource data by the specific emission factor. Successively, the total impact of the module has been obtained by summing up the impacts of all the care activities within it.
Lastly, a critical reflection on the results and the mitigating actions to improve them has been conducted.
For the analysis in this study, four different time horizons have been considered: 1 year, 5 years, 10 years, and lifetime. Among them, the 10-year horizon has been selected as the base case because it is considered a good trade-off for policy-makers to meet the current sustainability goals and still have a long-term perspective that allows them to evaluate all the benefits (holistic view) and make strategic decisions.

3.1. Modules

For transparency and replicability reasons, a detailed description of all the inputs considered in each module and their source is provided as follows (and summarised in table **??**):

- **Primary care consultation**: this module refers to a General Practitioner (GP) consultation. The module includes two sub-modules: transportation required to reach the location and GP visit itself (modeled as the CO2e emissions related to heating/cooling/lighting the GP room). Consulting the Centraal Bureau voor Statistiek (CBS), an average distance of 1 kilometer from the closest GP facility was considered for transportation. This implies a total travel distance of 2 kilometers for the round trip, which was modeled as a passenger car ride (whose emission factor is provided by CBS). As concerns the GP visit, the official report ”Zorg door de huisarts” from 2022 showed an average of 12 minutes per visit. It was selected as activity data input together with a reasonable dimension of the consultation room of 20 m^2. To obtain the corresponding emission factor for the visit, the starting point was a report about the annual CO_2 footprint of IJsselland Ziekenhuis [96]. This report considers electricity, fuel, heat, water, wastewater, and commuting of employees and visitors. By dividing the total CO_2 footprint of the hospital by its dimension, an emission factor per square meter was obtained and used for the GP room. Additional electricity usage that is not associated with heating/cooling/lighting is not included in the calculations, as it is assumed to be negligible compared to the rest of the model;
- **Specialist care consultation**: this module refers to a specialist consultation (a nephrologist or a specialized nurse). It was modeled based on the primary care consultation. In the Netherlands, consultations with specialists are performed in the hospital. This implied that, for the transportation, the distance to the closest hospital was considered (4,9 km from CBS) and modeled as a passenger car ride. For the specialist visit itself, according to the data collected by the Leids Universitair Medisch Centrum, an average time of 37 minutes was considered. Assuming a similar room as for GP consultation, the same emission factor was selected;
- **Standard of Care (medicines)**: patients with CKD in the Netherlands are currently treated according to national and international guidelines presented in the table 1.1. The two main objectives of the treatment are: preventing the progression of the disease and dealing with complications (most often represented by hypertension, CVD risks, and diabetes). A group of five nephrologists was interviewed by AstraZeneca to discuss the actual implementation of the guidelines in the Netherlands and the dosage of the medicines usually prescribed. Their answers have been used as input for this module, except for Statin dosage which was derived from the Farmacotherapeutisch Kompas [113]. This module, like the others concerning medicines, was divided into three sub-modules: 2) API production, formulation and packaging phase, 2) Use phase, and 3) End of life phase. The first submodule comprises three main blocks: *API production, formulation* and *packaging*. The API production assessment, in turn, includes chemicals (starting materials, reagents, solvents, and cleaning chemicals required), process water, electricity and heat used on-site, transport of materials, and treatment of waste generated and transport to disposal. Regarding the formulation, this block

includes excipients used, process water, electricity, and heat used on site, transport of waste to treatment, and treatment of waste generated. Concerning the last block of the submodule, packaging, its impact was assessed by including packaging materials, electricity used on-site, heat used on-site, transport of waste treatment, and treatment of waste generated. Emission factors concerning this submodule were collected from Internal LCA reports from AstraZeneca. The second submodule is represented by the use phase; it refers to the collection of medicines. The assumption made for this submodule is that medicines are collected all at once. According to the report "Farmaceutische zorg in de eerste lijn: ervaringen en meningen van burgers" [35], around 87 percent of the people in the Netherlands collect their medicines themselves at their pharmacy while 13 percent have them delivered at home. Pharmacies are assumed to deliver medicines through a light commercial vehicle comparable to a minivan. With this percentage of split and CSB data concerning the average distance to the closest pharmacy and emissions factors for both types of vehicles, the total environmental impact of this submodule was calculated. The last submodule is represented by the end-of-life phase. It includes the disposal of waste to landfill, recycling, incineration, and transportation of wastes to respective treatment destinations. Due to the impossibility of precisely quantifying the environmental impact of medicine residuals on the environment, it has been discussed qualitatively in a separate chapter A.2. Input data concerning the emission factors for this submodule were taken from internal LCA reports from AstraZeneca. Since internal LCA from AstraZeneca were only available for some medicines in the SoC, for the remaining ones, the most similar medicines produced by AstraZeneca with an available LCA were selected as proxies. Since the emission factors concern production and packaging, the two main criteria considered in the choice of proxies were chemical properties and molecular dimension. The impact of this module has been underestimated because some molecules were too different from the AstraZeneca available ones and consequently not included in the calculations. A summary of the comparison can be found in table 3.2;

Medicine	**AstraZeneca medicine used as proxy**	**Comparison**
Hydrochlorothiazide	Losec	Similar molecular weight (297.73 vs. 345.42 g/mol), both contain sulfonamide groups, and both are small molecule drugs.
Captopril	Brilinta	Similar functional groups (both contain sulfhydryl and carboxyl groups), though Brilinta is larger, both are small molecule drugs.
Losartan	Lynparza	Similar molecular weight (422.91 vs. 434.46 g/mol), both are small molecule drugs with complex ring structures.
Spironolactone	Forxiga	Similar molecular weight (416.57 vs. 408.87 g/mol), both contain steroid-like structures, and both affect electrolyte balance.

Table 3.2: comparison medicines for the choice of emission factors (standard of care)

- **Dialysis**: for this module, four different types of dialyses were taken into consideration: at-home haemodialysis, in-centre haemodialysis, Continuous Ambulatory Peritoneal Dialysis (CAPD) and Automated Peritoneal Dialysis (APD). Among them, "in-centre hemodialysis" is the only one performed at the hospital. In the Netherlands, there is a specific means of transportation that can be used by people unable to get to the hospital by themselves. It is called "Regiovervoer" and in this LCA, it was modeled as a minivan. In the absence of statistics, it seemed reasonable to assume that 50 percent of the CKD dialysis population utilizes it, while the others get to the dialysis unit by themselves or with a caregiver. For the three remaining types of dialyses, which are performed at home (at-home hemodialysis, CAPD, APD), training for the patient is required. During this training, patients learn about the equipment, how to create a hygienic environment, keep an organized log of the treatments, manage supplies, and handle needles [55]. The training sessions are provided by specialized nurses and their impact is assessed by considering the heating/cooling/lighting of the room where they are performed in the hospital. Next to that, for both types of haemodialyses, it is necessary to surgically create a shunt in the arm of the patient. The most frequent type of shunt is the Arteriovenous (AV) fistula which is, by definition, an artery directly sutured to a vein. When an artery and a vein are sewn together, the high-pressure blood does not reach the tissues anymore but is diverted

into the vein and back to the heart [7]. Time by time, the vein will dilate, carry more blood and become stronger, a process often referred to as ”maturation”. At maturation, nurses can easily access the vein with needles for dialysis therapy. According to the Beth Israel Deaconess Medical Center, the surgery for the AV fistula lasts 3 hours on average [7]. The correspondent emission factor was derived from two studies analyzing the environmental impact of surgical procedures of similar length and tools [112] [86]. In terms of resources, both types of haemodialysis require a dialysis machine (requiring in turn water, dialysate, and electricity), heating/cooling/lighting for the area in which it is performed, consumables used to set up the dialysis session (cloth, packaging, tubing, etc.) and waste disposal. Regarding peritoneal dialysis, APD modeling involves a machine, heating/cooling/lighting for the area in which the session is performed, the peritoneal fluid and drainage bags, and associated packaging/tubing. The same considerations hold for CAPD, except for the machine, which is not used for cycling dialysate. For the four types of dialysis sessions, the emission factors were selected from an AstraZeneca internal manuscript 3.4;

- **Intensive care unit visit**: the module inputs of intensive care unit (ICU) stay are based on data from a US/Australian study concerning the carbon footprint of patients being treated in an ICU for septic shock [67]. The list of inputs for the ICU is heating/cooling/lighting of the intensive care room, additional drug mix (morphine, anesthetic, iron sulfate, saline), hospital waste disposal, washing and laundry, intravenous (IV) drip, cotton, steel, plastics, oxygen, paper, rubber, and card. The emission factor was selected from an AstraZeneca internal manuscript 3.4;
- **Transplantation**: this model consists of several sub-models. The first one concerns the medicines that are usually prescribed to kidney-transplanted patients. Their main functions are immunosuppression, infection prophylaxis, managing side effects, bone health, and cardiovascular protection. This sub-module was modeled as the standard of care one, using emission factors from internal LCA reports from AstraZeneca as proxies where specific data were not available and Farmacotherapeutisch Kompas indications for the dosage. The comparison of these medicines with the AstraZeneca ones used as proxies is shown in the table 3.3. The second sub-module regards the compatibility tests performed before the surgical procedure itself: ABO compatibility test (blood test compatibility), Human Leukocyte Antigen (HLA) typing test, Crossmatch test, Panel Reactive Antibody (PRA) test, Donor-Specific Antibody (DSA) test, and Serological for infectious disease test. They are all blood tests and consequently, they are modeled as described in the ”screenings” module. For this submodule, a distinction has been made between transplantation from a living donor (10 compatibility tests) and transplantation from a deceased donor (6 compatibility tests). The last submodule consists of the surgical procedure itself. As for compatibility tests, also kidney transplantation surgery has been distinguished into two types: from living and deceased donors. They both have similar inputs but present differences in the number of hospital stay days, and transportation of the organ (deceased donor only). This sub-module includes days spent in the hospital (pre- and post-transplantation) and the transplantation surgery. For the operation, the following materials are considered: glass, steel, plastic, paper/card, and cotton. Next to that, anesthetics for undergoing surgery are included together with Marshall’s hypertonic citrate for transporting the organ. Additionally, transportation to the hospital and heating/cooling/lighting of the surgery room where the operation takes place are taken into account. Emission factors for the surgical operations were taken from the AstraZeneca Internal Manuscript;

Medicine	AstraZeneca medicine used as proxy	Comparison
Mycofenolzuur	Lynparza	Similar molecular weight (320.34 vs. 434.46 g/mol), both are small molecule drugs with complex ring structures, and used in cancer/immunosuppressive therapy.
Valganciclovir	Brilinta	Similar molecular weight (354.23 vs. 522.56 g/mol), both are antiviral/antithrombotic agents with nucleoside-like structures.
Trimethoprim	Losec	Similar molecular weight (290.32 vs. 345.42 g/mol), both are small molecule drugs with nitrogen-containing heterocycles.
Valaciclovir	Brilinta	Similar molecular weight (324.34 vs. 522.56 g/mol), both are antiviral/antithrombotic agents with nucleoside-like structures.
Amphotericin Lozenges	too different characteristics	Significantly larger molecular weight (924.1 g/mol) and more complex structure compared to the AstraZeneca drugs.
Pantoprazole	Losec	Similar molecular weight (383.37 vs. 345.42 g/mol), both are proton pump inhibitors with similar pharmacodynamics.
Aspirin	Brilinta	Similar pharmacodynamics as antiplatelet agents, though Brilinta is larger (522.56 g/mol), both inhibit platelet aggregation.
Cholecalciferol	too different characteristics	Cholecalciferol is a vitamin with a distinct steroid structure, significantly different from the AstraZeneca drugs.
Ferrous Sulphate	too different characteristics	Although there are AstraZeneca drugs which are based on inorganic compounds, they differ in function and molecular dimensions.
Risedronate	Forxiga	Similar molecular weight (283.10 vs. 408.87 g/mol), both are small molecules affecting metabolic processes (bone resorption vs. glucose reabsorption).
Furosemide	Losec	Similar molecular weight (330.74 vs. 345.42 g/mol), both are small molecule drugs with sulfonamide groups and related to renal function/metabolism.

Table 3.3: comparison medicines for the choice of emission factors (transplantation)

- **Screenings**: according to the descriptions in the previous module and in the introduction 1.2, all the main tests in the CKD care pathway are performed through urine or blood sample. For this reason, the environmental impact of these two types of tests was assessed. Specifically, it was done by considering a study conducted in Melbourne regarding prospective life cycle assessment of pathology tests [65]. In this study, all the consumables and associated waste for venepuncture and laboratory analyses, together with electricity and water were considered;
- **Palliative care**: this module includes two sub-modules: palliative care medicines and psychologist consultation. The palliative set of medicines is usually prescribed to CKD patients who refuse to undergo standard treatment in the ESRD (dialysis or transplant). They are administered in order to: alleviate the pain, control nausea and vomiting, reduce fluid retention and swelling, alleviate severe itching, treat anemia, manage imbalances in electrolytes, correct metabolic acidosis, improve sleep quality, manage high blood pressure, and address depression/anxiety. The different phases of the medicine life cycle were modeled as described in the standard of care module. The comparison of these medicines with the AstraZeneca ones used as proxies is shown in the table 3.4. Regarding psychologist consultation, this sub-module was modeled as a specialist consultation, adapted to an average duration of 1 hour per session.

Medicine	AstraZeneca medicine used as proxy	Comparison
Zolpidem	Losec	Similar molecular weight (307.39 vs. 345.42 g/mol), both are small molecules acting on the central nervous system through GABA modulation.
Paracetamol	too different characteristics	Paracetamol's low molecular weight and distinct chemical properties (analgesic/antipyretic) make it unique compared to AstraZeneca drugs.
Pregabalin	too different characteristics	Pregabalin's specific action on voltage-gated calcium channels and its small size does not match well with AstraZeneca drugs
Oxycodone	too different characteristics	Oxycodone's opioid structure and high molecular weight are not similar to any AstraZeneca drugs.
Gabapentin	too different characteristics	Gabapentin's action on voltage-gated calcium channels and small size are unique and not similar to any AstraZeneca drugs.
Ropinirole	too different characteristics	Ropinirole's dopamine agonist activity and specific use in neurological conditions don't match with AstraZeneca's current portfolio.
Lorazepam	Losec	Similar molecular weight (321.16 vs. 345.42 g/mol), both are small molecules acting on the central nervous system through GABA modulation.
Citalopram	Lynparza	Similar molecular weight (324.39 vs. 434.46 g/mol), both are small molecules affecting neurotransmitter systems (serotonin vs. DNA repair).

Table 3.4: comparison medicines for the choice of emission factors (palliative care)

- **Hospitalisation**: this module was modeled on the basis of the Intensive Care Unit one, with additional drugs and oxygen removed and the remaining inputs decreased by 25 percent to account for the less intensive nature of the hospital stay. The emission factors for hospitalization were selected from the Internal manuscript from AstraZeneca 3.4.

In order to evaluate the environmental impact of the progressive phases of the disease, modules have been successively grouped in stages (as described in the next section, 3.2).

Module	Input
Primary care consultation	transportation visit
Secondary care consultation (Both nephrologist or specialized nurse)	transportation visit
Standard of Care [API production, formulation, packaging phase] Use phase End of life phase 	 Hydrochlorothiazine Captopril Forxiga Losartan Spironolactone Crestor split: 87% pick-up, 13% delivery self-collecton(round trip) delivery (minivan)(round trip) Hydrochlorothiazine Captopril Forxiga Losartan Spironolactone Crestor
Dialysis	surgery for the shunt training at home haemodialysis in centre haemodialysis APD CAPD transport (private car\regiovervoer)
Transplantation Medicines [API production, formulation, packaging phase] Use phase End of life phase Surgical procedure	 Valganciclovir (up to 6 months after the transplant) Mycofenolzuur (lifelong) Trimethoprim (lifelong) Valaciclovir Amphotericin Lozenges Pantoprazole Aspirin Cholecalciferol Ferrous Sulphate Risedronate Furosemide split: 87% pick-up, 13% delivery self-collection(round trip) delivery (minivan)(round trip) Mycofenolzuur (lifelong) Valganciclovir (up to 6 months after the transplant) Trimethoprim (lifelong) Valaciclovir Amphotericin Lozenges Pantoprazole Aspirin Cholecalciferol Ferrous Sulphate Risedronate Furosemide transplant from living donor transplant from deceased donor
Screenings	blood test urine test
Palliative care Psychologist visit Palliative medicines [API production, formulation, packaging phase] Use phase End of life phase 	 transportation psychologist consultation Zolpidem Paracetamol Pregabalin Oxycodone Gabapentin Ropinirole Lorazepam Citalopram split: 87% pick-up, 13% delivery self-collecton(round trip) delivery (minivan)(round trip) Zolpidem Paracetamol Pregabalin Oxycodone Gabapentin Ropinirole Lorazepam Citalopram
ICU	heating/cooling /lighting of the ICU room sanitation waste trasnport materials additional medications
Hospitalization	heating/cooling /lighting of the hospital room sanitation waste transport materials

Table 3.5: Module inputs

3.2. Stages

As shown in figure 1.5, the KDIGO guidelines present different progressive stages within CKD based on the results of the eGFR and ACR tests. With the aim of evaluating the impact of each stage and identifying the most polluting ones, the modules described in 3.1 were combined together into stages. In order to allocate the modules across the stages, an interview with the medical advisor from AstraZeneca (see section A.3.2 of the Appendix for a summary of the answers), who in turn consulted a nephrologist, was conducted. Additionally, further data to inform the allocation were derived from the pharmacoeconomic dossier for Forxiga CKD. The results of this data collection are displayed in table 3.6

Stages	Care activities per year
1	1 primary care consultation,2 secondary care consultations, 2 screenings
2	1 primary care consultation, 3 specialist care consultations, 2 screenings
3a	2 primary care consultations, 3 secondary care consultations, 8 screenings, Standard of Care
3b	2 primary care consultations, 3 secondary care consultations, 12 screenings, Standard of Care
4	7 secondary care consultations, Standard of Care with Forxiga, 14 screenings
5d - in centre	9 secondary care consultations, Standard of Care without Forxiga, (haemo)dialysis treatment (81 percent), 18 screenings
5d - at home	9 secondary care consultations, Standard of Care without Forxiga, dialysis treatment (at-home haemodialysis (3.5perc), CAPD (5perc), APD (10.5perc)), 18 screenings
5t - 1 year	20 secondary care consultations, Standard of Care without Forxiga, transplantation-related medicines, 40 screenings + 6 compatibility screenings (from deceased donor) or 10 compatibility screenings (from living donor), surgical procedure (49 percent from living donor and 51 percent from deceased donor)
5t - 1+ years	4 secondary care consultations, Standard of Care without Forxiga, transplantation-related medicines, 8 screenings
5p	60 secondary care consultations (9 with the nephrologist, 51 with the psychologist), SoC with Forxiga, palliative medicines, 18 screenings

Table 3.6: Care activities per stage

It is important to note that the care activities indicated in each stage are based on the average case. Prescribed medicines, dosages, and frequency of visits can vary according to the specific needs of the patient.
Once the environmental footprint of a care pathway has been estimated, the following step concerns how to include this type of impact in the economic evaluation of the healthcare interventions. In section 3.3, for the first time to the knowledge of this author, alternative methodologies to accomplish that will be discussed and then applied to the case study.

3.3. How to include environmental impact in economic evaluation of healthcare interventions

As explained in section 2.1, in health economics, costs and benefits are summarised in the ICER. The incremental cost-effectiveness ratio allows to compare two healthcare interventions by taking into consideration their costs and QALYs. The advantage of using this ratio is that it represents a standardized measure that eases the comparison between several interventions and clearly displays their advantages compared to the costs. Regarding the methods to include environmental impact in health technology assessment, it can be essentially done using four methods [108]:

- information conduit: according to this method, environmental impacts are reported as recommendations. However, they are not considered in the deliberation process and consequently do not influence the decision made. We did not identify an application of this method.;
- integrated evaluation: this method prescribes the full inclusion of the environmental impact in the final indicator of the CEA (or CBA). The integrated evaluation can be performed in two different ways: the environmental footprint can be included on the cost side of the equation, on the health outcome one (the latter known as ”enriched analysis”) or eventually the willingness-to-pay threshold can be adjusted to include this impact;
- parallel evaluation: the method can also be applied in more than one way. In literature, this methodology exists in five different variants: the calculation of the incremental carbon footprint effectiveness ratio (ICFER), the incremental carbon footprint cost ratio (ICFCR), multi-criteria decision analysis (MCDA), existing HTA deliberation processes and alongside economic evaluations;
- environmental focused evaluation: This type of assessment solely considers the environmental impacts of the technology.

According to the results of the most recent scoping review [108], the first method has never been applied concretely in a study. Although it provides the public with information concerning the environmental impact of healthcare interventions, it is unlikely to significantly influence decision-making. For this reason, it has not been performed for this case study. The same can be said about the environmental focus evaluation method.
As concerns the integrated evaluation, it has been mainly performed by translating the environmental impact as a cost [26] [75] [76] [100], with two studies including it as DALYs [63] [102]. This approach is extremely valuable because it allows to internalize environmental impacts, in terms of negative externalities, back into the usual evaluation (e.g. CEA, CUA, and CBA) [108]. Despite this advantage in comparability, the method has not led to significant changes to the ICER in the studies conducted so far, and additionally, results heavily rely on the accuracy of conversion rates used. Furthermore, it is important to take into consideration that this method does not capture non-health impacts of environmental damage. Consequently, the integrated evaluation would not incentivize technologies with an equal health impact but a lower environmental impact.
The main discussion about including environmental impact results directly in the ICER of CEA involves ethical considerations. In fact, both for costs and health outcomes (QALYs), including the environmental impact directly in the ICER involves an implicit comparability among the three concepts. In other words, attaching a price to the environmental burden of care activities means that the environmental damage can be quantified in money as for buying a laptop. Nevertheless, the same can be said about QALYs, for which the environmental impact should be compared and converted into life years, something priceless according to some. However, this methodology has been applied to the case study (alternatively considering the environmental impact as a cost and as a health benefit) as prescribed in the following chapter. Results of the integrated evaluation method can be found in section 4.2.3.

3.3.1. Integrated evaluation: environmental Impact as a cost

One of the main barriers to the implementation of sustainability measures within companies is that the management is mainly focused on key performance indicators (KPIs). Although an increasing awareness about the importance of environmental impact is observed in the majority of the big companies, KPIs are still the driving factor in the decision-making. This consideration has led several experts to consider the idea of converting the environmental impact into monetary terms in order to include it in these financial indicators. Among the three methodologies discussed in this thesis, this is the only one that has been previously implemented. Charlotte Desterbecq et all [27] conducted a literature review of 62 existing documents analyzing environmental spillovers. Only four studies undertook a full economic evaluation of healthcare products thereby including CO2 emissions in the evaluation [26] [75] [76] [100]. In these studies, the authors calculated CO_2e emissions and then converted those into costs using specific conversion factors such as the Social Cost of Carbon (SCC) [26] [75] [76] or the carbon cost [100]. Among them, only De Preux and Rizmie [26] together with Terlinden et all [100] actually incorporated this new cost in the incremental cost-effectiveness ratio, while the others included the SCC into a budget-impact analysis over a 5-year time period perspective.
In order to align with the few existing studies and provide results as nation-specific as possible, the SCC was chosen as a conversion factor to incorporate the environmental impact as a cost in the ICER.
The Social Cost of Carbon is a metric used to estimate the economic cost of the impacts caused by emitting one additional ton of carbon dioxide into the atmosphere. It reflects the long-term damage done by CO_2 emissions in a given year by taking into account several impacts:

- agricultural productivity in terms of changes in crop yields caused by altered weather patterns, temperature changes, and the increased frequency of extreme weather events;
- infrastructure damages: increased flood risk, sea-level rise, and other climate-related damages to buildings;
- energy costs: changes concerning heating and cooling demands;
- human health: health consequences due to air quality, heat stress, and the spread of diseases;
- ecosystem losses: biodiversity and ecosystem service damages that provide economic and health benefits to humans.

It is noteworthy that the SCC incorporates a discount rate to reflect the present value of future damages. Consequently, this involves ethical considerations concerning the value that is attached to the welfare of future generations thereby leaving room for moral debate.
When discussing the inclusion of the environmental impact in the ICER, it is important to make two considerations. The first one concerns future incentives and taxes related to sustainability that could modify the costs. Governments are currently implementing several strategies to foster sustainable policies within companies. Many

of them include financial incentives and taxes, something that can influence the final costs of new healthcare interventions. Additionally, it is important to consider that in this study, environmental damage has been converted into costs and weighted in the same way as the other cost categories. However, it is an open debate whether this is the right way to proceed or whether this category should be weighted more (or less) than the others. The results of this methodology to the case study can be seen in the section 4.2.3.

3.3.2. Integrated evaluation: environmental Impact as QALYs

Another way to approach the problem is to convert the environmental impact in QALYs and then integrate it into the ICER. This method has never been explored before, the only two existing studies implementing integrated evaluation in the health outcome side of the equation, did it as DALYs. Consequently, in the following, the approach elaborated by this author is presented. This is a step-by-step process that implies the use of the health damage factor, a factor that translates the kg of CO_2e in Disability-Adjusted Life Years (DALYs).
DALYs are a metric used to quantify the burden of disease thereby including both mortality and morbidity into a single measure. Moreover, DALYs represent the total number of years lost due to ill-health, disability, or early death within a patient population. This metric is used by health organizations to assess and compare the health impact of several diseases and risk factors globally.
In order to estimate the DALYs, and subsequently the corresponding QALYs, associated with the healthcare intervention, it is essential to select the appropriate health damage factor. This choice is, in turn, dependent on the Shared Socioeconomic Pathways (SSP).
Shared Socioeconomic Pathways are scenarios developed (for the Intergovernmental Panel on Climate Change, IPCC) to explore how global socioeconomic trends might influence future climate and environmental outcomes. Each SSP outlines different trajectories for factors such as economic and population growth, urbanization, technological development, and education. There are five different SSPs:

- SSP1 - sustainability;
- SSP2 - middle of the road;
- SSP3 - regional rivalry;
- SSP4 - inequality;
- SSP5 - fossil fuel development

The choice of one pathway over another is related to the effort and the initiatives undertaken by a country to implement sustainability in its policies and objectives.
Because of the commitment shown by the Dutch government and all the climate policies recently implemented (e.g. GreenDeal), the Netherlands can be considered as part of SPP1. Consequently, a health damage factor of 1,3-E06 can be assumed [99], which, in turn, can be used to obtain the corresponding DALYs.
In order to include this impact in the ICER, it is necessary to convert the DALYs into QALYs. There is only one existing study conducted by Sassi et all [89] which suggests a way to do that. In their research, it has been shown that the ratios between QALYs gained and DALYs saved tend to stay relatively stable across different disease durations and that a conversion factor, varying by age of disease onset (a) and by disease duration (L) can be used to translate DALYs saved into QALYs gained, as shown in figure 4.41 [89]. Once the first (a) has been established, tables as the one in figure 4.44 [74] can be consulted to derive the other (L). However, this methodology is of limited applicability. In fact, the conversion factors have been calculated only for a maximum of 5 years of life expectancy which is shorter than the usual one, especially for chronic disease.

Gender	Age group (year)	Kidney function (in ml/min/1.73 m^2)			
		eGFR ≥60	eGFR 45–59	eGFR 30–44	eGFR 15–29
Male	30	39.1 (38.9–39.2)	28.4 (25.1–31.7)	20.1 (16.5–23.7)	15.3 (11.0–19.5)
	35	34.7 (34.6–34.9)	28.0 (26.3–29.8)	16.3 (13.3–19.2)	13.8 (11.0–16.7)
	40	30.5 (30.3–30.6)	24.5 (23.3–25.8)	14.5 (12.3–16.8)	10.4 (8.1–12.7)
	45	26.2 (26.1–26.4)	21.3 (20.4–22.2)	12.5 (10.9–14.2)	8.8 (7.1–10.5)
	50	22.3 (22.2–22.4)	18.3 (17.7–19.0)	10.6 (9.5–11.7)	7.4 (6.1–8.7)
	55	18.6 (18.5–18.7)	16.0 (15.5–16.5)	8.7 (7.9–9.5)	6.6 (5.6–7.6)
	60	15.1 (15.0–15.2)	13.6 (13.2–13.9)	7.8 (7.3–8.4)	5.6 (4.8–6.3)
	65	11.9 (11.8–12.0)	10.9 (10.7–11.2)	6.6 (6.2–7.0)	4.6 (4.2–5.1)
	70	9.0 (9.0–9.1)	8.4 (8.3–8.6)	5.9 (5.7–6.2)	3.9 (3.6–4.2)
	75	6.7 (6.6–6.7)	6.2 (6.0–6.3)	4.7 (4.5–4.9)	3.1 (2.9–3.3)
	80	4.6 (4.6–4.7)	4.3 (4.2–4.4)	3.4 (3.3–3.4)	2.5 (2.5–2.6)
	85	2.7 (2.5–2.8)	2.3 (2.2–2.5)	1.8 (1.6–2.0)	1.4 (1.2–1.7)
Female	30	43.8 (43.7–44.0)	33.6 (31.0–36.2)	21.4 (17.3–25.5)	12.7 (7.4–18.0)
	35	39.2 (39.0–39.3)	30.8 (28.9–32.8)	17.6 (14.0–21.2)	13.1 (10.1–16.0)
	40	34.6 (34.5–34.7)	28.7 (27.5–29.9)	16.5 (14.0–19.0)	9.1 (6.6–11.6)
	45	30.2 (30.1–30.4)	25.4 (24.5–26.3)	14.9 (13.0–16.7)	7.4 (5.6–9.3)
	50	26.0 (25.9–26.2)	22.3 (21.7–22.9)	13.2 (11.8–14.5)	7.4 (5.9–8.8)
	55	22.0 (21.9–22.1)	19.1 (18.6–19.6)	11.3 (10.3–12.3)	6.7 (5.6–7.8)
	60	18.2 (18.1–18.3)	16.5 (16.1–16.8)	10.6 (9.9–11.2)	6.2 (5.4–7.0)
	65	14.6 (14.5–14.7)	13.4 (13.1–13.6)	9.4 (8.9–9.9)	4.7 (4.2–5.2)
	70	11.3 (11.2–11.4)	10.5 (10.4–10.7)	7.9 (7.6–8.2)	4.1 (3.8–4.5)
	75	8.4 (8.3–8.5)	7.9 (7.8–8.0)	6.0 (5.9–6.2)	3.9 (3.6–4.1)
	80	5.6 (5.5–5.7)	5.3 (5.2–5.4)	4.5 (4.4–4.6)	3.1 (3.0–3.2)
	85	3.0 (2.9–3.1)	2.8 (2.7–2.9)	2.2 (2.0–2.3)	1.6 (1.4–1.8)

Figure 3.2: Chronic kidney disease and life expectancy

	a – Age of disease onset (years)							
L – Disease duration (years)	5	15	25	35	45	55	65	75
0.5	0.705	1.374	1.525	1.427	1.228	1.005	0.796	0.615
1	0.731	1.382	1.524	1.423	1.222	0.999	0.791	0.611
1.5	0.756	1.390	1.524	1.418	1.217	0.994	0.786	0.607
2	0.780	1.398	1.523	1.414	1.211	0.989	0.781	0.603
2.5	0.803	1.405	1.522	1.410	1.206	0.983	0.776	0.599
3	0.825	1.412	1.521	1.406	1.201	0.978	0.772	0.595
3.5	0.847	1.418	1.520	1.401	1.195	0.973	0.767	0.591
4	0.868	1.424	1.519	1.397	1.190	0.968	0.763	0.588
4.5	0.888	1.430	1.518	1.392	1.185	0.962	0.758	0.584
5	0.907	1.435	1.516	1.388	1.179	0.957	0.754	0.580

Figure 3.3: QALYs gained - DALYs saved conversion factors

The results of these steps implemented for the case study can be seen in the section 4.2.3

3.3.3. Parallel evaluation

Another alternative is presenting the environmental impact of a healthcare intervention in parallel with its economic evaluation without any conversion into monetary or health units. If on the one hand, it prevents facing the challenges related to converting it in costs or QALYs; on the other hand, it complicates the comparison between interventions. In fact, considering the environmental impact in absolute terms may shift focus on the environmental burden or benefit thereby neglecting the actual clinical benefits or general costs. Additionally, it is very important to take into consideration that the final recipients of the economic evaluations of healthcare interventions (healthcare professionals, insurers, policy-makers) very often lack expertise in the environmental field and may encounter difficulties in interpreting a separate indicator with which they are not familiar. On the other hand, it gives the decision-makers the opportunity to evaluate the importance of impacts on a case-by-case basis [108]. Considering the several applications of the parallel evaluation method, three (for time and complexity constraints) are applied to this case study: calculating incremental carbon footprint effectiveness ratio (ICFER), Calculate incremental carbon footprint cost ratio (ICFCR), and presenting the environmental impact without any further assessment.
As regards the first two alternatives:

- the ICFER is calculated as the difference in carbon footprint between the SoC+intervention and the SoC+placebo divided by the difference in their health benefit (reported as CO_2e per QALYs);
- the ICFCR is calculated as the difference in carbon footprint between the SoC+intervention and the SoC+placebo divided by the difference in their costs (CO_2e per euro).

The results obtained by applying this method can be found in the section 4.2.3.
The third alternative considered is presenting this impact as a single measure expressed through one of the environmental metrics, without any further assessment. The focus of this study has been an environmental assessment in CO_2e terms (for the reasons previously discussed in this chapter). However, it is important to consider that several other metrics could have been chosen. The most frequently implemented in the assessment of environmental impacts are:

- **Fine Particulate Matter Formation**: it assesses the formation of fine particulate matter (PM2.5) in the air, which can affect human health thereby causing respiratory problems;
- **Fossil Depletion**: it evaluates the depletion of fossil fuel resources, underscoring the amount of fossil fuels consumed;
- **Freshwater Consumption**: it measures the total volume of freshwater consumed during a product's life cycle;
- **Freshwater Ecotoxicity**: it assesses the potentially toxic effects of chemicals on freshwater ecosystems;
- **Human Toxicity, Cancer type**: it evaluates the potential impact of chemical substances on human health, specifically related to cancer risk;
- **Ionizing Radiation**: it indicates the potential impact of ionizing radiation on human health and the environment;
- **Land Use**: it assesses the impact of land occupation and transformation on biodiversity and ecosystem services;
- **Marine Ecotoxicity**: it evaluates the potential toxic effects of chemicals on marine ecosystems;
- **Metal Depletion**: it measures the depletion of metal resources, underscoring the amount of metal consumed;
- **Stratospheric Ozone Depletion**: it estimates the potential impact of substances on the depletion of the stratospheric ozone layer;
- **Terrestrial Acidification**: it measures the potential impact of acidifying emissions (for instance, sulfur dioxide) on terrestrial ecosystems;
- **Terrestrial Ecotoxicity**: it estimates the potential toxic effects of chemicals on terrestrial ecosystems.

With the aim of giving the reader an idea of how the environmental impact of care activities can be expressed through these metrics, the impact of dialysis (the most polluting activity of the care pathways) is expressed through several of them in section 4.2.3. These results have been obtained by implementing the DAPA-CKD Medical Care Cost Offset Model, a tool provided internally by AstraZeneca to evaluate the environmental savings 9expressed through different metrics) concerning the most polluting care activities due to Forxiga.

3.4. Data collection

Previously in this chapter, it has been explained that conducting an LCA requires both activity data and emission factors. Activity data are quantitative measures (duration of appointments, distances) used to describe activities that result in a contribution to the environmental metrics appraised, while emission factors are values that reflect the contribution made per unit of activity data against a sustainability metric [97]. In this section an overview of the data sources, collecting methods, and selection criteria is presented.
For this study, mainly secondary data have been used; the majority of them are specific to the Dutch healthcare system. Where they were not available, experts were asked to assess the chosen proxies in order to make the results of the analysis as country-specific as possible. Concerning the activity data, the most relevant national databases were consulted. Data from the Centraal Bureau voor Statistiek were used as a reference for the average distance from facilities and emission factors for vehicles, while medical center databases and national reports were consulted for the average duration of the activities [7] [35] [70]. With regard to dosages, in order to guarantee homogeneity, the Pharmacoeconomic dossier was used as a source, and where it was not possible, the national guidelines were considered [113]. Governmental reports were consulted to get data concerning the use of public services (e.g. regiovervoer) [114]. Disease-specific guidelines (multidisciplinaire richtlijn nierschade (CNS), Nederlandse Federatie voor Nefrologie (NFN) richtlijn, Federatie Medisch Specialisten (FMS) richtlijn, Kidney Disease Improving Global Outcomes (KDIGO) and Nederlands Huisartsen Genootschap (NHG)) were used to model the entire set of care pathway activities[17][18][16][58].

In regard to emission factors, an extensive literature review was conducted among internal company reports and external scientific publications. Pertaining to the emissions related to the medical room, the environmental footprint analysis of Ijsselland Ziekenhuis was used to model a generic medical consultation room (considering heating/cooling and lighting resources)[96]. Regarding medicines, AstraZeneca internal LCA reports were accurately chosen to derive emission factors concerning API production, formulation, packaging, use phase, and end-of-life phase. Because of the absence of country-specific data, an Australian publication concerning the environmental impact of blood and urine tests (which are conducted with similar procedures in the two countries) was used to obtain proxied emission factors [65].
During the literature review, the selection of relevant papers was based on the following criteria [97]:

- **Medical representativeness**: the degree to which the data reflect the actual medical procedure/activities used in the process;
- **Geographical representativeness**: the degree to which the data reflect actual locations of the processes within the Netherlands;
- **Reliability**: the degree to which the sources, data collection methods, and verification procedures used to obtain the data are dependable;
- **Temporal representativeness**: the degree to which the data reflect the current way of conducting the process;
- **Completeness**: the degree to which the data are statistically representative of the entire process.

Relevant data concerning dialyses, transplantation, and hospitalization have been derived from an AstraZeneca internal manuscript which is currently undergoing the process of review for several publications. Data for this study have been collected through a literature review and ecoinvent Life Cycle Inventory database version 3.8 [21]. The study has been conducted by a scientific steering committee (SSC) which informed the design, implementation, interpretation, and validation of the analysis. The committee had expertise in relevant fields (environmental sciences, medicine, energy) and, where country-specific data were not available, assessed the suitability of the proxies considered for the Netherlands. The LCA conducted in the manuscript has been validated using the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) best practice [30].
As regards primary data, they were collected through interviews for defining the type and the number of care activities per stage and informing the final discussions. A medical advisor from the company together with a nephrologist was consulted to derive data concerning GP visits, specialist visits, number of blood/urine tests, and assumption of medicines prescribed per stage while a nephrologist with expertise in sustainability was interviewed to discuss opportunities, barriers and next steps concerning sustainability in the nephrology, and more generally, in healthcare. A detailed description of the questions administered to the interviewees is provided in the following section 3.5 and a summary of the answer is presented in the section A.3 of the Appendix.

3.5. Interviews

Interviews have been conducted to inform and validate the results and the discussion concerning the LCA analysis. In order to do so, two medical experts specifically involved in initiatives concerning sustainability in nephrology were interviewed. According to their backgrounds, two different sets of questions were asked to the interviewees.

3.5.1. First set of questions - interviewee: Nephrologist from European Renal Association

1. Do you think assessing environmental impact is something valuable in the evaluation of a new healthcare technology or treatment?
2. Do you think the way I evaluated the environmental impact (i.e. doing an LCA of the current care pathway with and without the implementation of the intervention) is valuable or do you think that there is another way that could be better?
3. Do the results, in any way, reflect your experience as a nephrologist?
4. As a nephrologist, would you like to be informed about the environmental impacts of medicines you prescribe or use? In other words, would this piece of information be valuable for a doctor?
5. What would be an incentive for companies to share data concerning the sustainability of their products with other institutions/universities/competitors?

6. Do you think that the different stakeholders (like healthcare professionals, policymakers, and companies) should kind of collaborate?
7. Is there a way, in your vision, to implement sustainability within university curricula? If yes, should it be done by implementing some theory or quantitative analyses?
8. Are there also environmental benefits of hemofiltration compared to hemodialysis?
9. The three main domains you usually refer to in your interviews are Care, Research, and Education for Sustainability. Can you tell me one main goal for each of them?
10. Which ethical/personal motivations sparkle your interest in sustainability in nephrology? Has this interest somehow shaped you as a professional? In other words, has your acquired knowledge of sustainability shaped your practice as a doctor?
11. How should biopharmaceutical companies become more sustainable at the organizational level?

3.5.2. Second set of questions - interviewee: Medical expert from AstraZeneca

1. Which modules should be included in the care pathway for CKD, specifically for the Netherlands?
2. Which submodules should be included in each module?
3. Which care activities should be included in each stage?
4. Where I can find data about the prevalence of the disease in the Netherlands?
5. Where I can find data concerning dialysis?
6. Can you explain to me how Forxiga operates for CKD?
7. Do these results make sense to you?
8. Do you think that LCA is important in HTA?
9. Which one do you envision as a solution?

A summary of their answers to these questions can be found in section A.3 of the Appendix.

4

Results

In this chapter, the results of the LCA of the CKD pathway for the Netherlands are presented. Starting from the environmental impact of the individual care activities, a zoom-out process guides the reader to the total footprint, by first considering the modules and then the stages. Special attention is dedicated to dialysis, which has been identified as the most polluting care activity of the pathway. Additionally, the decrease in CO_2 emissions due to Forxiga is presented and incorporated in its economic evaluation in three alternative ways. The chapter ends with the results of validation and sensitivity analyses to test the robustness of the study.

4.1. LCA results for CKD care pathway in the Netherlands

As explained in the previous chapter, because of their complexity and the numerous activities included in them, the SHC guidelines [97] prescribe evaluating the environmental impact of care pathways by breaking them down into modules, whose environmental impact is presented in the next section.

4.1.1. Environmental impact of modules

From the analysis, it can be inferred that the screening module is the least environmentally impactful with 0,215 kg of CO2e with a blood test (0,116 kg of CO2e) slightly more environmentally impactful than a urine test (0,099 kg of CO2e). This is followed by the primary consultation module with 0,753 kg of CO2e, to which the transport component contributes 40 percent and the visit itself 60 percent (figure 4.2). A similar pattern can be found in the secondary consultation module with a total impact of 2,098 kg of CO2e. The palliative care can be also considered a module with a small impact (3,4 kg of CO_2e), in which frequent consultations with the psychologist provide the biggest contribution to the environmental footprint.
Proceeding further, hospitalization and ICU fall in the middle range of the environmental impact (39,1 and 94 kg of CO2e respectively).
At the end of the spectrum, the most environmentally impactful modules are transplantation and dialysis. Within the dialysis module, surgery, transportation, and training have a negligible impact while the dialysis sessions themselves contribute the most to the final results. The dialysis sessions were distinguished (and consequently assessed) based on the four different existing types, with haemodialysis in center being the most impactful, followed by haemodialysis at home, APD, and CAPD (respectively 29,9 kg of CO_2e, 23,8 kg of CO_2e, 14,9 kg of CO_2e, and 6,1 kg of CO_2e) per session). The second most environmentally impactful module is the transplantation one. Only the surgery itself accounts for 480,4 or 552,4 kg of CO2e with a slight difference depending on whether the donor is a living or a deceased individual.
The environmental impact of medicines (Standard of Care module) deserves a separate consideration. In their environmental assessment API production, packaging, distribution, and disposal of packaging were considered. As explained in section A.2 the impact of the medicine residuals on the environment has not been taken into consideration in this module because of data unavailability issues. This implies that this module is expected to present a higher environmental impact compared with the one presented in the analysis. A summary of the environmental impacts of modules can be found in table **??**.

Module	Environmental impact (kg of CO2e)
Primary care (per consultation)	0,753
Secondary care (per consultation)	2,098
Screenings (1 set of blood test + urine test)	0,215
Palliative care (per year)	183,21
Intensive care unit (1 day)	94
Hospitalisation (8 hours)	39,1
Haemodialysis (per year)	5470,275
Transplantation (from deceased donor)	561,599
Standard of care (per year)	247,562

Table 4.1: Impact modules

Additionally, analyzing the contribution of the different activities within the modules is helpful in understanding which are the pollution hotspots and how to mitigate them (which is discussed in section 5.2).
As concerns both primary and secondary care consultation modules (figures 4.2 4.3), around one-third of the total impact is represented by the transportation while the rest is due to the GP/specialist visit itself. A similar pattern is observed for palliative care (figure 4.4), in which psychologist visits are responsible for about 83 percent of the total impact.
As concerns the screenings, figure 4.3 shows that both types have a very similar impact.
Looking at Hospitalisation and Intensive Care Unit, it can be seen that the major contribution comes from the energy required to heat, cool, and light respectively the hospital ordinary room and the intensive care room (figure 4.5 4.6). However, the two modules differ in the second bigger contribution, which is medications in the ICU module (anesthetic gases are particularly impactful) and the materials used to furnish the room in the hospitalization module. Transportation plays a considerable role in both modules (16,7 percent for hospitalization and 7,5 percent for ICU). Other submodules such as sanitation or waste are responsible for less than 5 percent of the total ICU and hospitalization impact.
Next to that, figures show the impact of the various submodules in the transplantation module, both for living and deceased donors (respectively figure 4.11 and 4.12. In both cases, it can be noticed that the biggest contribution comes from the surgery itself because of the medicines used during the operation, the tools, and the energy required for the machines. Next to that, transportation plays a key role while treatment and compatibility tests are accountable for less than 3 percent.
Figure 4.13 shows the results concerning the SOC modules. The graph presents API production, formulation, and packaging phase as the one contributing the most to the final impact (around 60 percent), followed by the use phase (delivery/collection of medicines). Despite the first stages being surely the most environmentally impactful in medicine production, it is important to take into consideration that the end-of-life stage considered in this study only includes the disposal of packaging. As discussed in section A.2, the actual impact of chemical compounds was not taken into consideration for complexity reasons. This means that the impact of the end-of-life phase of the SOC module is underestimated. The consequent uncertainty (i.e. the extent of this underestimation) is not known.
As explained in section 3.1, for the dialysis module, four different typologies of dialysis were considered: CAPD, APD, at-home haemodialysis, and in-centre haemodialysis, and for each of them a contribution analysis was made (figures 4.10 4.9 4.8 4.7). In all four kinds of dialysis, it can be observed that the prevalent impact is due to dialysis sessions themselves (always greater than 80 percent). It is relevant to consider that, for in-centre hemodialysis, transportation is accountable for 13 percent of the total impact and it is one of the factors that make this type of treatment the most environmentally impactful. For both types of hemodialysis, the surgical procedure for AV fistula represents only a negligible contribution. The same can be said for the patient training in CAPD and APD.

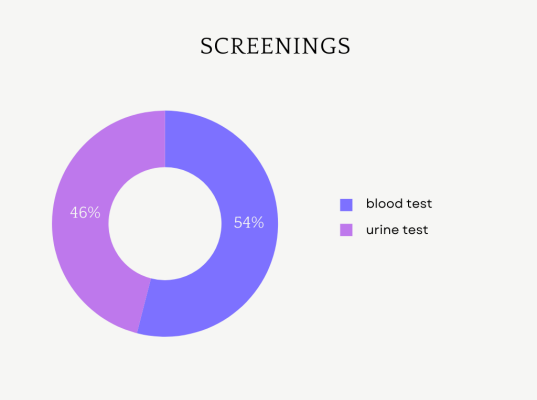


Figure 4.1: Screenings

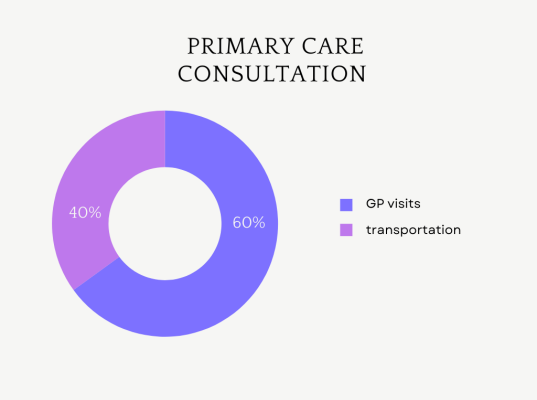


Figure 4.2: Primary care consultation

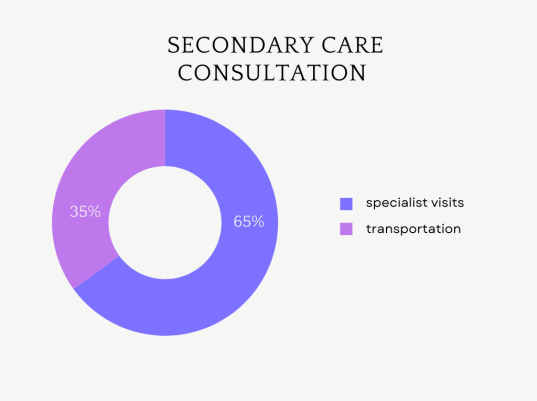


Figure 4.3: Secondary care consultation

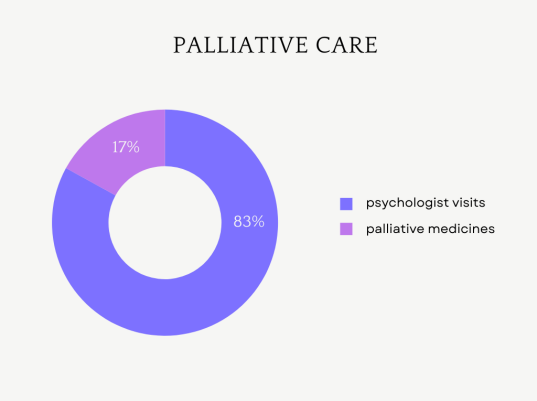


Figure 4.4: Palliative care

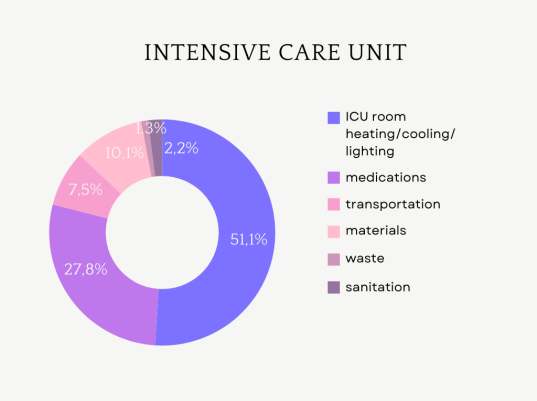


Figure 4.5: Intensive Care Unit

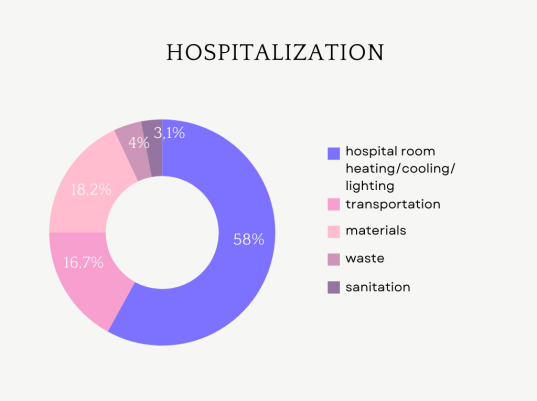


Figure 4.6: Hospitalisation

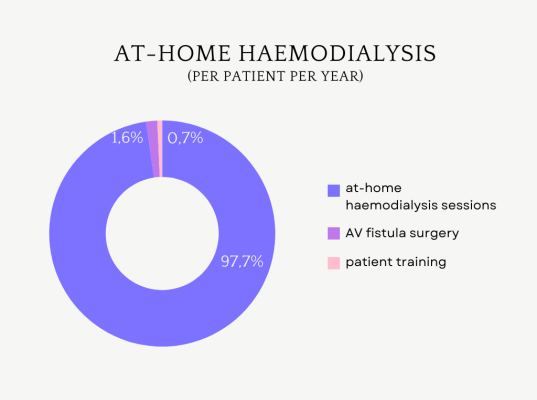


Figure 4.7: At-home haemodialysis

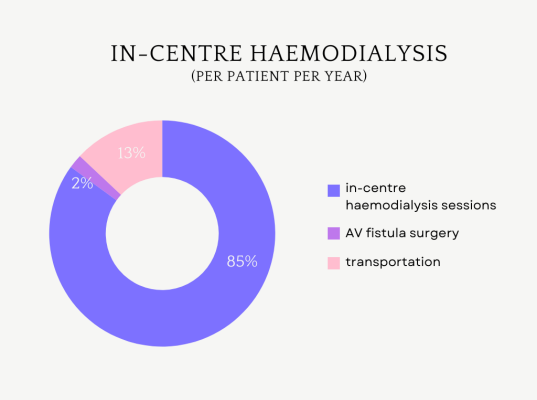


Figure 4.8: In-centre haemodialysis

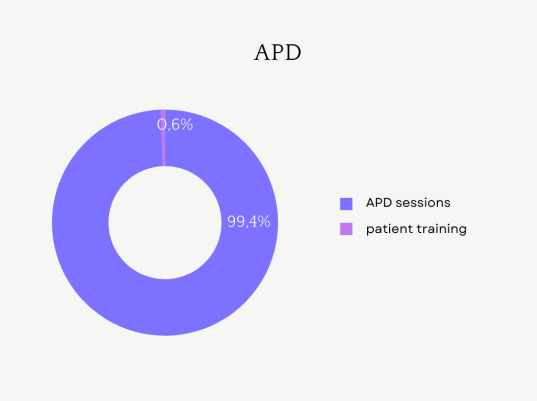


Figure 4.9: APD

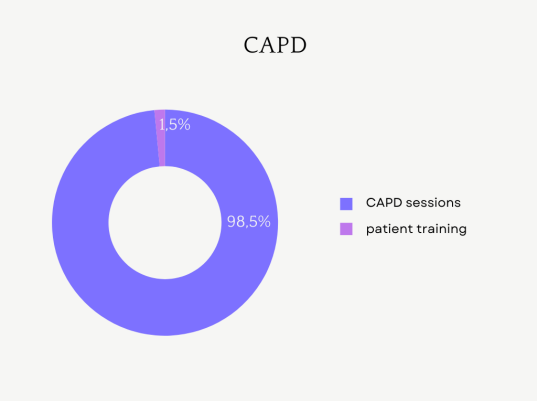


Figure 4.10: CAPD

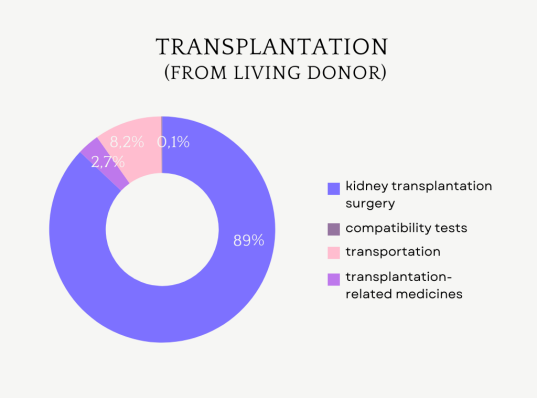


Figure 4.11: Transplantation from living donor

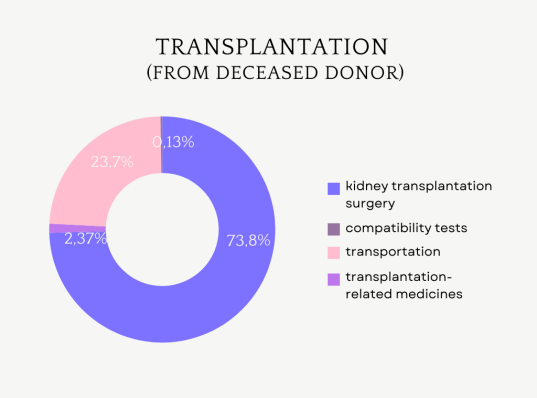


Figure 4.12: Transplantation from deceased donor

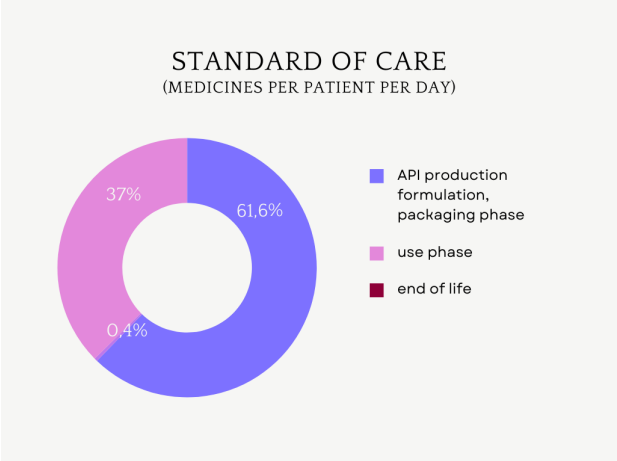


Figure 4.13: SOC

As explained in the previous chapter, interviews with the experts have been conducted to allocate the modules across the stages in order to evaluate their environmental impact. This is presented in the next section.

4.1.2. Environmental impact of stages

Interviewing medical experts (see A.3), modules have been allocated to the different stages, as shown in table 3.6. Accordingly, the environmental impact of each stage has been calculated by taking into consideration the footprint of the modules (presented in table 4.19. A summary of the environmental impact of each stage per year can be found in table 4.2.

Stage	Environmental impact (kg of CO2e)
1	5.16
2	7.26
3a	256.22
3b	256.65
4	263.75
5d	5549.44
5t	2731.76
5p	438.89

Table 4.2: Environmental impact per patient per year

As previously done for the individual care activities within each module, it is interesting to analyse the contribution of the individual modules within each stage. Concerning the first two stages (shown in figures 4.14, 4.17), it can be seen that around 80 percent of the total impact is due to specialist visits, around 10 percent is attributable to GP consultations and the remaining part is due to blood/urine tests.
Results from stages 3 (split in 3a and 3b to align with the pharmaeconomic dossier (see figures 4.16 4.17 below) and 4 (see figure 4.18) are particularly interesting. As can be seen from the pie charts, the majority of the impact is due to the medicines from the SOC. In fact, on an annual basis, the production, packaging, distribution, and disposal of medicines have a significant environmental impact.
Pertaining to the fifth stage, it is necessary to distinguish between dialysis (shown in figure 4.21), transplantation (see figure 4.25), and palliative care (see figure 4.22). Within the dialysis stage (with a slight difference between in-centre (see figure 4.20) and at-home dialysis (represented in figure 4.21) 95 percent of the environmental impact is due to the dialysis sessions themselves. This implies that all the other care activities (specialist visits, screenings, and standard of care) contribute together for less than 5 percent, which is still worthy of attention considering the significant impact of the care pathway. Concerning the transplant, it is necessary to distinguish the impact of the first year (shown in figure 4.24) from the following ones (see figure 4.25). During the first year, the major environmental contributions are the surgery and all the medicines prescribed for the treatment. On the other hand, blood/urine tests and specialist visits contribute only a small part to the total impact. From the

second year on, the majority of the environmental impact is attributable to the transplantation-related medicines (anti-rejection and management of eventual infections and symptoms) while the proportion between the impact of the remaining modules follows the pattern indicated for the first year. Pertaining to the palliative care stage, the most impactful care activities are undoubtedly SOC treatment and psychologist consultations (53,8 percent and 34,6 percent respectively). This can be explained by the fact that palliative care patients usually attend bi-weekly sessions with their psychologists thereby traveling to the hospital at least two times per week.

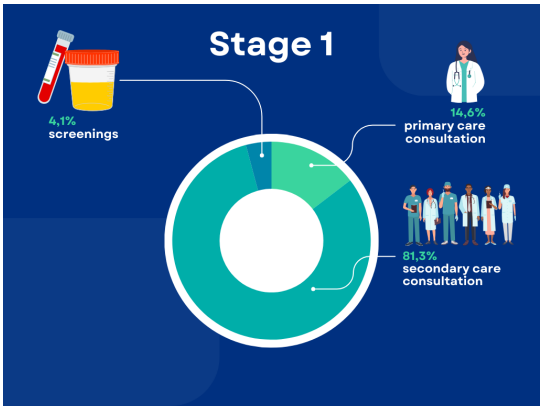


Figure 4.14: Stage 1

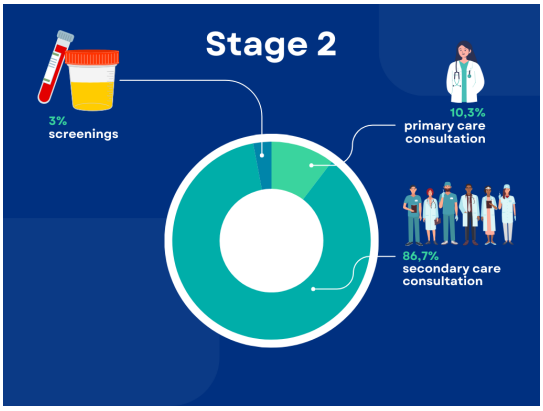


Figure 4.15: Stage 2

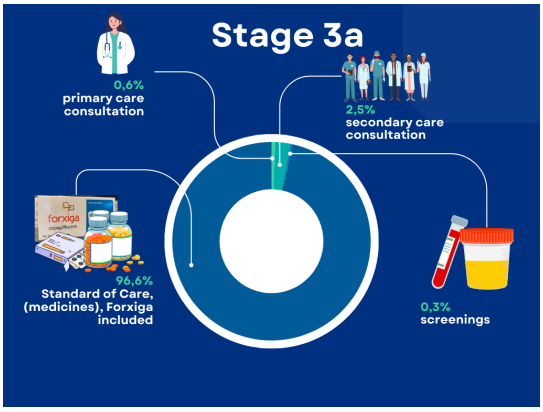


Figure 4.16: Stage 3a

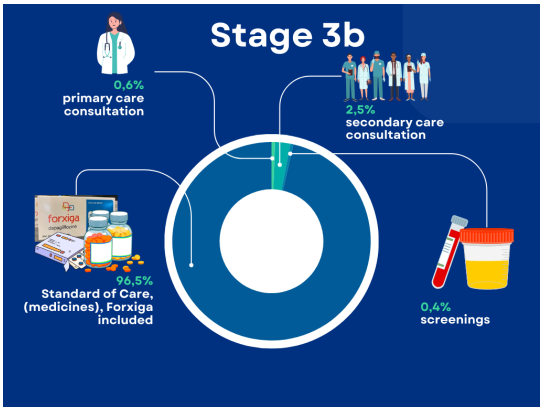


Figure 4.17: Stage 3b

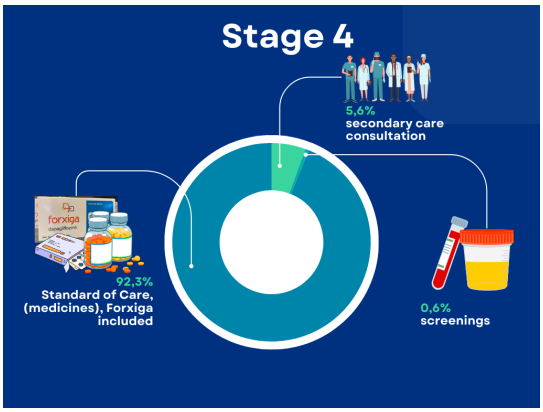


Figure 4.18: Stage 4

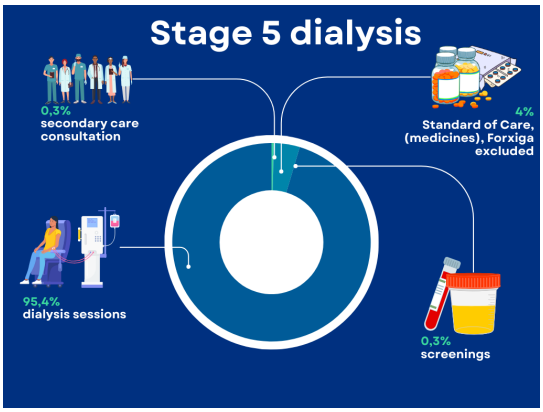


Figure 4.19: Stage 5d

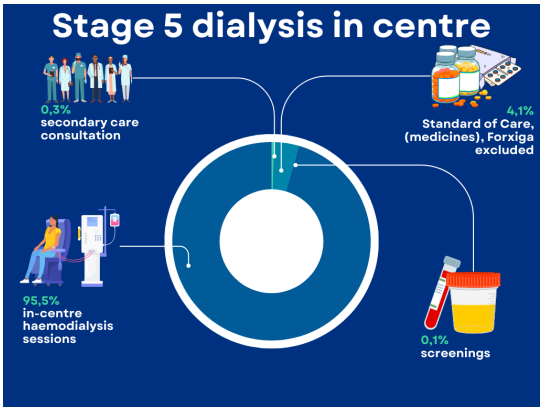


Figure 4.20: Stage 5d in centre

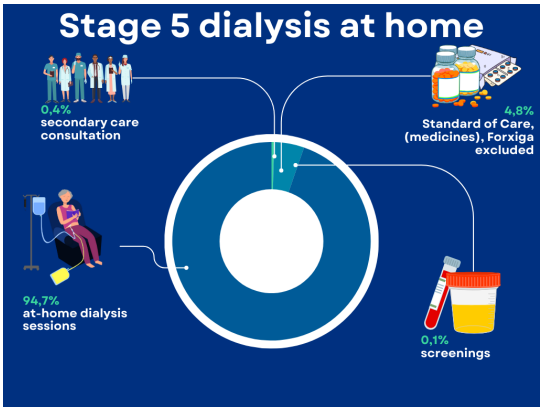


Figure 4.21: Stage 5 at home

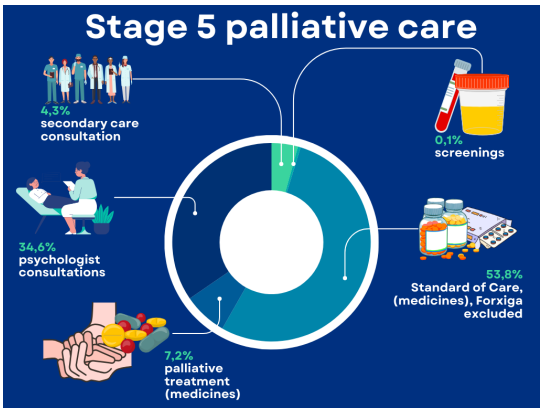


Figure 4.22: Stage 5p

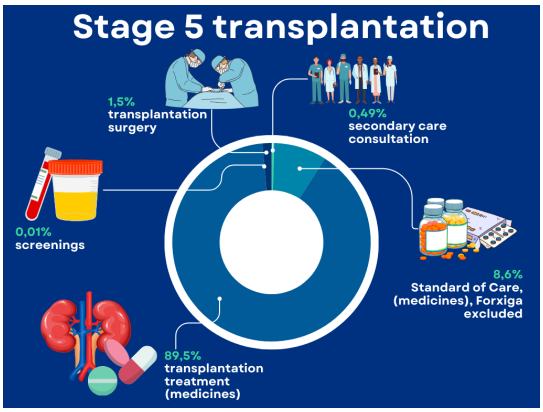


Figure 4.23: Stage 5t

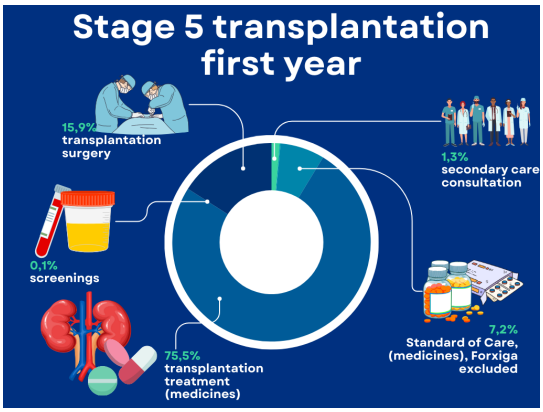


Figure 4.24: Stage 5t first year

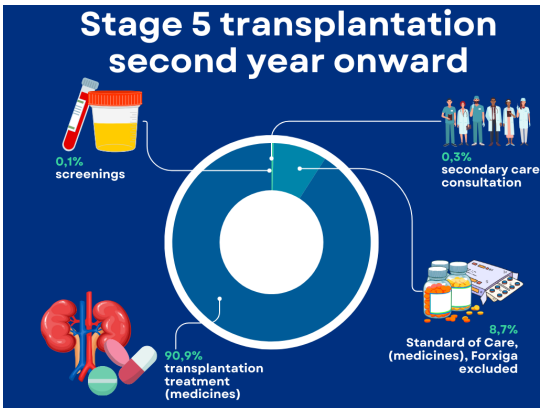


Figure 4.25: Stage 5t second year onward

4.1.3. General Results: impact of stages on the total care pathway

The pie chart in figure 4.26 shows the general results (in percentages) of the LCA for the CKD pathway and table 4.2 the CO_2 values. It can be noticed that dialysis is accountable by itself for more than half of the total impact (58 percent) thereby making stage 5d the most environmentally impactful stage of the care pathway. The second one is transplantation, which is responsible for 29 percent of the total impact of the care pathway. On the other hand, the rest of the stages only account for minor shares, as can be seen for stage 5p (5 percent), stage 4 (3 percent), and even less the first two stages (together responsible for less than 1 percent).
Consequently, looking at the aggregated results in figure 4.27, ESRD (stage 5), which brings together 5d, 5t, and 5p is the most impacting for the environment (92 percent of the total impact) due to the significant amount of resources employed. Next to that, it is interesting to observe that the environmental impact increases as the disease progresses. This makes it crucial to implement healthcare interventions (like Forxiga) to slow down the progression of the disease and consequently reduce the number of people in the late stages (which are the most harmful to the environment).
Considering the impact (presented in table 4.2) and the patient distribution per stage (presented in figure 4.28 [106]) with a 8.9 percent prevalence among the Dutch population [106], the reader can derive a general understanding of the actual impact of stage (the exact calculations have not been presented due to the lack of data concerning the distribution of patient per stage in literature: 63,5 percent of unspecified CKD patients).

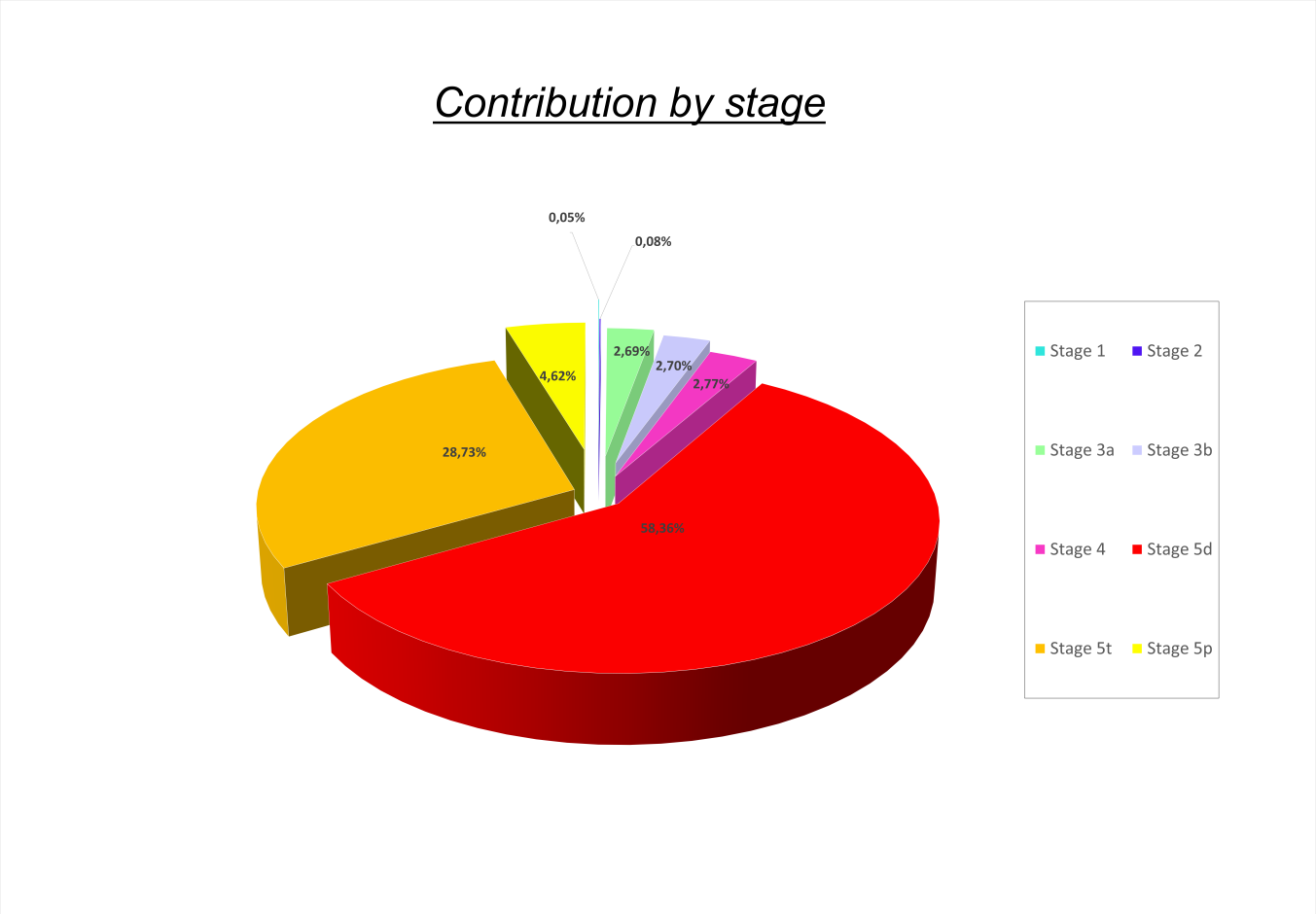


Figure 4.26: Contribution of each stage to the total care pathway footprint per patient per year

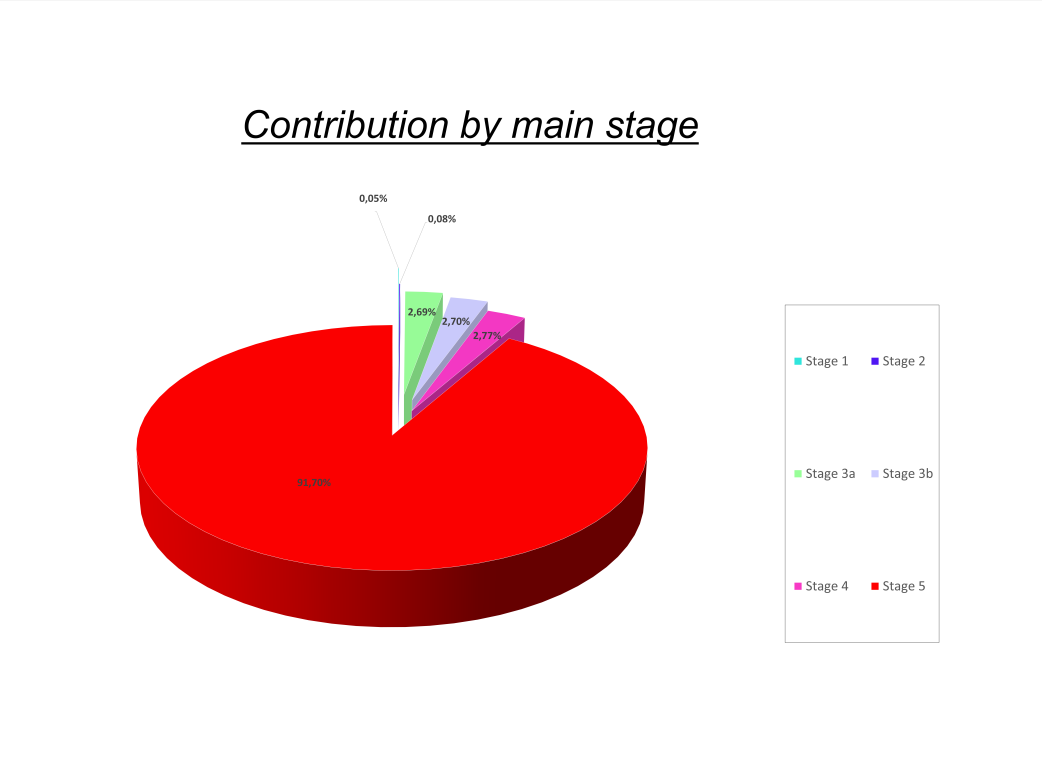


Figure 4.27: Contribution of each stage to the total care pathway footprint per patient per year

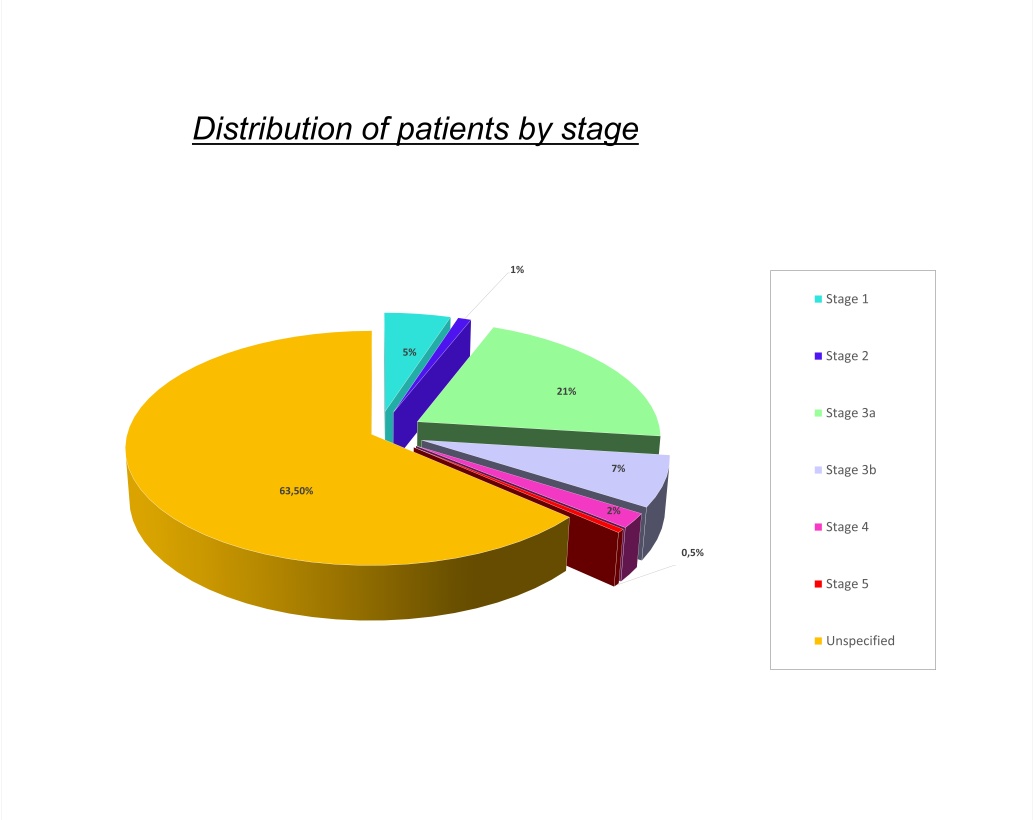


Figure 4.28: Patient distribution by stage

Since it has been found to be the most polluting care activity within the pathway due to the large amount of resources used, considerations concerning dialysis will be discussed separately in the next section.

4.1.4. Dialysis

Looking at the results of the Life Cycle Analysis for the care pathway of Chronic Kidney Disease in the Dutch context, it can be immediately derived that dialysis is the most environmentally impactful stage (more than 50 percent). Except for patients who receive kidney transplantation (successfully), this type of treatment is lifelong. In other words, the environmental impact shown on the yearly base, in the majority of the cases, needs to be extended for the duration of the life of the patient. Consequently, a closer look at the results of this stage can be interesting. The first thing which is worth noticing is that, among the four types of dialysis treatment considered (in-centre haemodialysis, at-home haemodialysis, Continuous Ambulatory Peritoneal Dialysis, and Continuous Cycler-Assisted Peritoneal Dialysis), in-centre haemodialysis results to be the most environmentally impactful (contributing for the 84 percent to the total impact of dialysis treatments, figure 4.29).
This can be explained by considering several factors:

- transportation: in-centre haemodialysis requires patients to travel to the hospital and back three times per week compared to all the other types of dialysis which are performed at home. Next to that, the traveling of the staff needs to be taken into consideration (nurses, doctors, administrative employees), which can be a substantial contribution (absent in the other types of dialysis) if the travel distance is significant;
- ultrapure water usage: to perform in-centre haemodialysis special water treatment systems are used to produce a high volume of ultrapure water. This leads to increased water consumption in the in-centre haemodialysis facilities;
- supplies: due to the centralized nature of the in-centre haemodialysis treatment, a larger stock of single-use supplies (e.g. dialyzers, needles, bloodlines) has to be transported and stored in the dialysis centers and this leads to a bigger environmental impact compared to the smaller quantities for individual use at home;
- waste: connected to the previous item there is the necessity of disposing of all these single-use supplies and their packaging. Getting rid of hospital/dialysis center waste needs to be done by following strict regulations for safety reasons. The machine and the transportation required to do it in the correct way can have a significant environmental impact;
- energy consumption: the necessary energy to run haemodialysis centers in terms of lighting, cooling, heating, and maintaining the environment perfectly sterilized has a big impact on the evaluation of the environmental footprint of the in-centre haemodialysis treatment;
- staff: compared to the other types of dialysis treatment, in-centre haemodialysis requires the presence of medical staff. They contribute to the total environmental impact with their daily activities and consumption.

Considering all the above-mentioned factors, in-centre haemodialysis is the most environmentally impactful type of dialysis. Regarding the remaining typologies analyzed, the APD is the second most impactful. Although it involves less fluids and energy use, it produces a considerable amount of waste and it is performed every day. The third most impactful stage is represented by at-home haemodialysis, followed by CAPD. The latter owes its place to the absence of any machine since it involves a manual exchange of fluids. Graph 4.29 shows how much each type contributes to the total impact of the dialysis. As discussed previously, considering their impact and their incidence (according to Dutch patient preferences), it can be seen that in-centre hemodialysis is the major contributor to the total impact (84 percent) with a big gap from the second (APD, with 11 percent). At-home haemodialysis and CAPD are the least impactful, respectively accountable for 3 and 2 percent of the total dialysis impact.

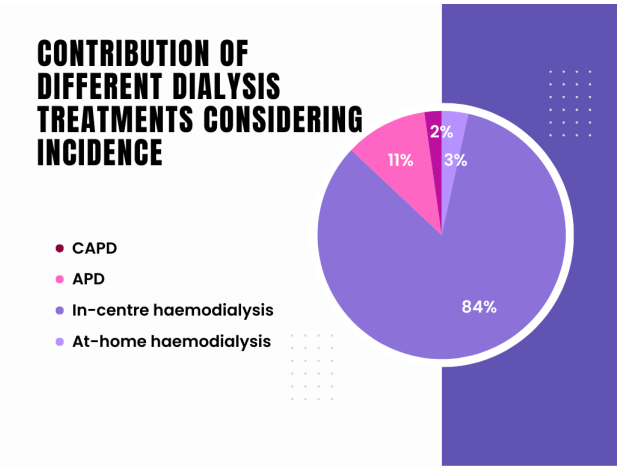


Figure 4.29: Impact of dialysis with incidence

Graph 4.30 reveals that haemodialysis is 14 percent more impactful than peritoneal dialysis and while the pie chart in figure 4.31 in-centre treatment is 8 percent more environmentally impacting than at-home ones (which highlights the impact of transportation).

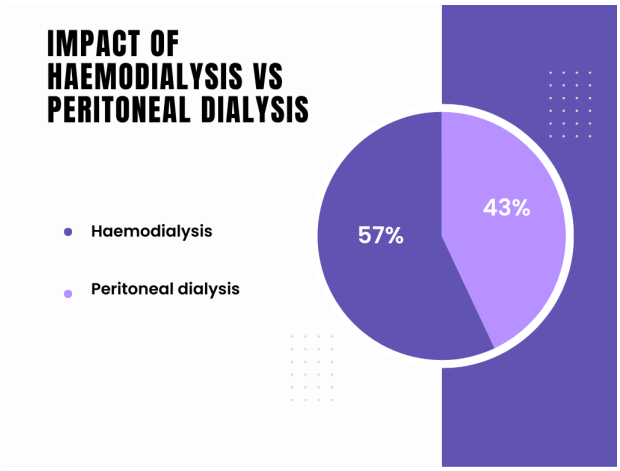


Figure 4.30: Impact of heamodialysis versus peritoneal dialysis

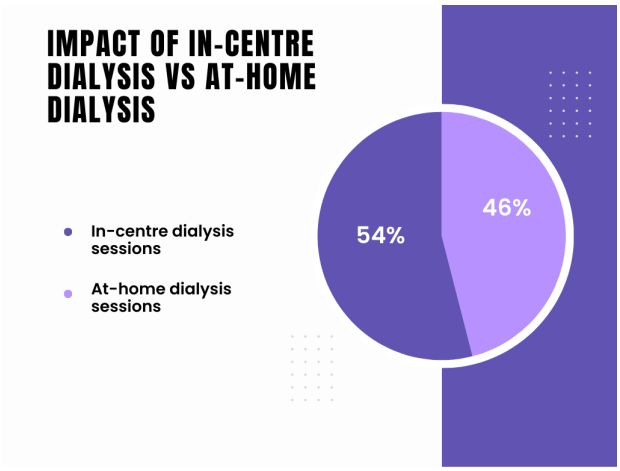


Figure 4.31: Impact of at-home vs in-centre dialysis

4.2. Impact of Forxiga on the care pathway environmental footprint

4.2.1. Modality of presentation

After conducting the LCA for the CKD care pathway in the Netherlands, the results have been used to estimate the savings in $CO2_2e$ due to the addition of Forxiga to the Standard of Care.
Forxiga has been approved for patients with CKD in any stage but it is currently prescribed to patients in stages 1,2,3a,3b, and 4. The Dapa trial conducted by AstraZeneca [47] has shown the clinical added value of Forxiga compared to the standard of care alone by demonstrating a slowdown in the progression of the disease. The longer permanence in the earlier stages of CKD implies a smaller number of patients in the late stage (ESRD, where (according to the LCA results) the most environmentally impactful activities are performed. Consequently, it is interesting to quantify the savings in CO_2 terms to show the decrease in the environmental footprint of the CKD pathway when Forxiga is included.
The analysis has been performed for four different time horizons: 1 year, 5 years, 10 years, and lifetime. In this way, environmental benefits can be compared on different time scales. A 10-year horizon has been chosen as the base case. The reason for this choice is that this time horizon represents a fair trade-off between the coming sustainability goals to meet and a long-term view that allows policymakers to strategically plan actions for reducing the environmental impact of societal activities (production processes, distribution, etc.).
For each time horizon, two tables are presented, which will be representatively discussed for the base case (the others can be found in the Appendix A.6) :

- table A (as the one in figure 4.32): this table shows Life years, QALYs, and the environmental costs (kg of CO_2) for both the standard of care with placebo, with Forxiga, and the increment;
- table B (an example of which is given in figure 4.33): as a complement to table A, this table shows a breakdown of the environmental costs. Specifically, in the first lines the environmental costs related to the life cycle of Forxiga are presented together with disease management environmental costs. These are the environmental costs associated with the treatment of the disease from stage 1 to stage 5 pre-RRT, which represents the entire care pathway for CKD excluding the ESRD (RRT). On the other hand, the second part of the table is dedicated to the ESRD and the care activities included in it. The reason for that is the fact that ESRD includes the most impactful care activities. Consequently, it is interesting to further break down the impact of its single components to deepen the understanding of the environmental footprint.

4.2.2. Description of the results for the base case

From figure 4.32 can be derived that for an average patient undergoing CKD treatment inclusive of Forxiga over 10 years, there is a decrease of 418 kg of CO_2e produced. A further understanding of this reduction is provided by the table shown in figure 4.33 and the corresponding bar charts presented in figure 4.37. Despite an increase of the CO_2 emissions due to drug acquisition environmental impact (that is logically explained by the fact that producing Forxiga increases by default the CO_2 emissions released), it is possible to note that this increase is greatly offset by the reduction in kg of CO_2e related to the ESRD. Although for the first stages (environmental impact stages 1 to 5 pre-RRT) there is no gain in CO_2e terms in including Forxiga in the standard of care (actually the emissions slightly increase), the situation drastically improves for dialysis, transplant, hospitalization, and AKI. The increase in environmental impact in the first stages can be explained by the fact that Forxiga is taken in the early stages of the disease and slows down its progression. By doing so, patients stay longer in the early stages and consequently, the total environmental impact of those stages increases. Accordingly, only looking at the first phases of the disease may give the wrong impression that the medicine is not effective in alleviating the environmental footprint of the care pathway for CKD. Actually, looking at the ESDR, over 10 years, a significant reduction of the environmental impact can be noted for the dialysis (- 654 kg of CO_2e) and the transplant (-79 kg of CO_2e). Although less notable, the addition of Forxiga to the SoC also implies a reduction of the impact of hospitalization for HF and AKI (ICU).

Average environmental impact across all the stages			
	Dapagliflozin + SoC	*Placebo + SoC*	*Incremental*
Life years	8,216	7,763	0,453
QALYs	6,223	5,868	0,355
Environmental impact (kg of CO2)	7294,151	7712,112	-417,961

Figure 4.32: Table A: Environmental impact in kg of CO_2e for an average patient over 10 years with and without Forxiga

Environmental impact breakdown (kg of CO2e)			
	Dapagliflozin + SoC	*Placebo + SoC*	*Incremental*
Drug acquisition	2004,281	1823,243	181,038
Stages 1 to 5 pre-RRT	1796,058	1658,186	137,873
Transplantation	471	550	-79
Dialysis	3006,295	3659,963	-653,668
Hospitalization	1,083	1,558	-0,475
AKI	15,708	19,019	-3,311
TOTAL IMPACT	**7294,151**	**7712,112**	**-417,961**

Figure 4.33: Table B: Breakdown environmental impact in kg of CO_2e of an average patient over 10 years with and without Forxiga

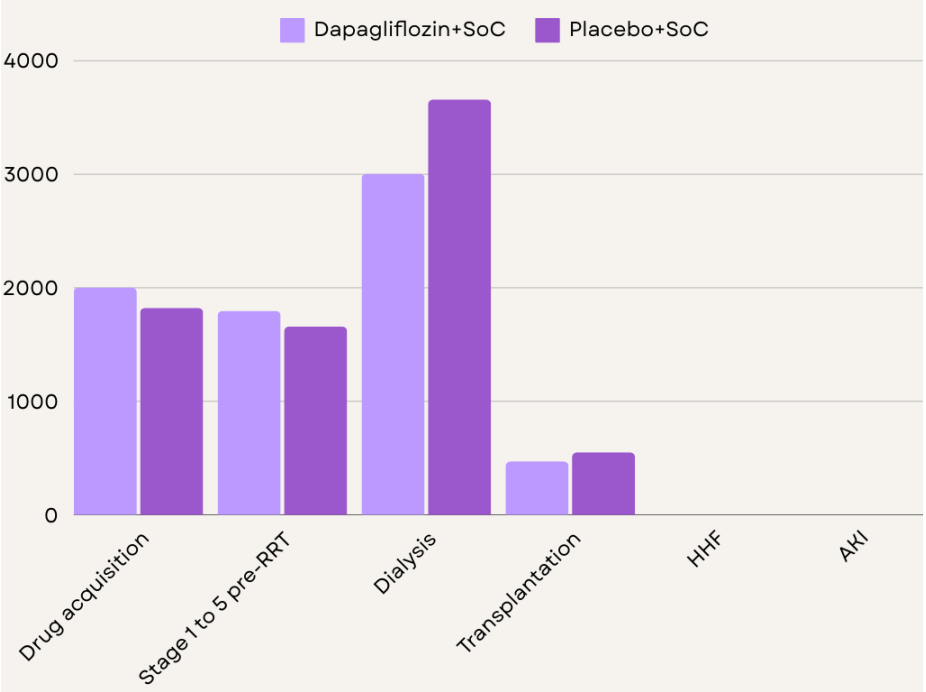


Figure 4.34: environmental impact in kg of CO_2e per patient over 10 years per category with and without Forxiga

Interesting results can be derived from figure 4.38 which presents the actual comparison between the environmental impact of the care pathway with and without Forxiga per stage over 10 years. Moreover, it can be observed that from stage 1 to 5 pre-RRT there is a growth in the environmental impact if Forxiga is included in the treatment. On the other hand, significant savings in CO_2e terms occur for Dialysis, transplant, HHF, and AKI. Consequently, considering the entire patient population over a period of 10 years, a reduction of about 6788733,96 kg of CO_2e, corresponding to 7446 flights from Amsterdam to New York City [20] or planting 271549 trees[11] (figure 4.35) or 418 kg of CO2e per patient (figure 4.36).

Figure 4.35: Net savings over 10 years

Figure 4.36: Net savings per patient over 10 years

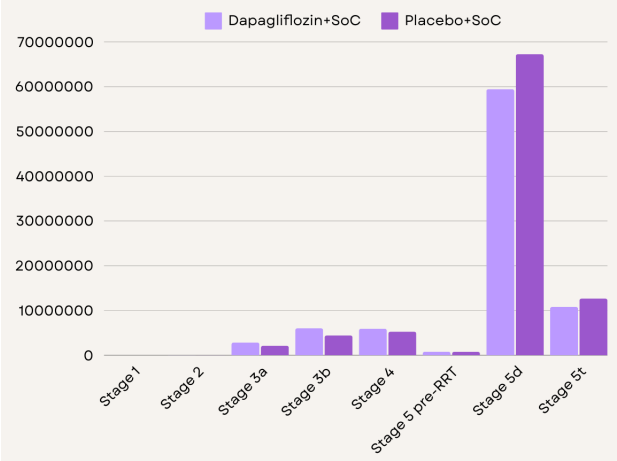


Figure 4.37: environmental impact difference in kg of CO_2e per stage over 10 years

Environmental impact difference per stage (kg of CO2e)										
	CKD 1	*CKD 2*	*CKD 3a*	*CKD 3b*	*CKD 4*	*CKD 5 pre-RRT*	*CKD 5 dialysis*	*CKD transplantation*	*HHF*	*AKI*
Dapagliflozin + SoC	1570,18	28830,70	2827164,19	5987643,66	5900411,22	778223,66	59440389,30	10792517,88	13229,04	224502,67
Placebo + SoC	959,63	22311,09	2120697,75	4428362,45	5252486,45	755639,81	67276879,66	12667172,98	15060,71	243645,92
Incremental	610,56	6519,61	706466,44	1559281,21	647924,77	22583,85	-7836490,36	-1874655,10	-1831,67	-19143,26
NET ENVIRONMENTAL IMPACT	**-6788733,96**									

Figure 4.38: environmental impact difference in kg of CO_2e per stage over 10 years and net environmental impact for the entire patient population

After having discussed the impact of Forxiga on the environmental footprint of the CKD pathway, the results of the alternative procedures (previously explained in 3.3) to include this impact in its economic evaluation are presented in the next section.

4.2.3. Results of the inclusion of environmental impact of Forxiga in its economic evaluation

As previously described in 3.3, the environmental impact of healthcare interventions can be incorporated into their economic evaluation following four different procedures. Among them, two (with their related variants) has been chosen for this case study :

- integrated evaluation;
- parallel evaluation.

Integrated evaluation: environmental impact as a cost

As previously discussed in 3.3, in order to align with the few existing studies and provide results as nation-specific as possible, the Social Cost of Carbon (SCC) was chosen as a conversion factor to incorporate the environmental impact as a cost in the ICER. This factor varies with the country, for the Netherlands a SCC of €30/kg of CO_2 emitted has been considered [94]. The SCC has been multiplied by the tonnes saved per average per patient over the lifetime due to Forxiga. In this way, it is possible to obtain "saved costs" which have successively been subtracted from Forxiga total costs in order to obtain the new ICER (presented in figure 4.40). Additionally, figure 4.42 shows the original ICER as a benchmark.

Discount rate: 1,5%			
	Dapagliflozin + SoC	Placebo + SoC	Incremental
QALYs (discounted)	8.050	7.224	**0.716**
Life years (discounted)	10.826	9.873	**0.953**
QALYs (undiscounted)	8.916	8.075	**0.841**
Life years (undiscounted)	12.028	10.905	**1**

Discount rate: 4%			
	Dapagliflozin + SoC	Placebo + SoC	Incremental
Total costs (discounted)	€103141	€108249	**-€5108**
Total costs (undiscounted)	€150169	€155794	**-€5625**

ICER		
Incremental cost/QALY (discounted)	**-€7134**	DOMINANT
Incremental cost/LYG (discounted)	**-€5359**	DOMINANT
Incremental NMB (discounted)	**€19426**	
Incremental cost/QALY (undiscounted)	**-€6688.46**	DOMINANT
Incremental cost/LYG (undiscounted)	**-€5625**	DOMINANT
Incremental NMB (undiscounted)	**€22437**	

Figure 4.39: ICER without considering environmental impact per patient over lifetime

Discount rate: 1,5%			
	Dapagliflozin + SoC	Placebo + SoC	Incremental
QALYs (discounted)	8.050	7.224	**0.716**
Life years (discounted)	10.826	9.873	**0.953**
QALYs (undiscounted)	8.916	8.075	**0.841**
Life years (undiscounted)	12.028	10.905	**1**

Discount rate: 4%			
	Dapagliflozin + SoC	Placebo + SoC	Incremental
Total costs (discounted)	€103118	€108249	**-€5130.65**
Total costs (undiscounted)	€150104.2	€155794	**-€5689.8**

ICER		
Incremental cost/QALY (discounted)	**-€7165.71**	DOMINANT
Incremental cost/LYG (discounted)	**-€5383.68**	DOMINANT
Incremental cost/QALY (undiscounted)	**-€6765.52**	DOMINANT
Incremental cost/LYG (undiscounted)	**-€5689.8**	DOMINANT

Figure 4.40: ICER per patient over lifetime considering environmental impact as a cost addition

As shown by figures 4.42 4.40, including the environmental impact implies a decrease of the ICER, which means that there are costs to face in order to gain a QALY if the savings about the environmental impact due to Forxiga are considered.

Integrated evaluation: environmental impact as QALYs

A second way to approach the problem is to convert the environmental impact in QALYs. As explained in section 3.3, this is done through two factors: the health damage factor and DALYs-QALYs conversion factor. The health damage factor selected for the Netherlands is 1,3-E06 [99] which provides a value of 0,000281 DALYs.
Successively, in order to select the conversion factor from DALYs to QALYs, an age of disease onset of 65 has been selected [82] together with a disease duration (in the paper considered as the residual life expectancy of the individual at age *a*) of 5 years [74]. As it can be seen in figure 4.44 [74], an L of 5 years is the value corresponding to a CKD patient of 65 in the ESRD stage. This means that excluding all the patients of 65 in the earlier stages (with a higher *L*), the estimation made in figure 4.43 does not reflect the real impact.

	a – Age of disease onset (years)							
L – Disease duration (years)	5	15	25	35	45	55	65	75
0.5	0.705	1.374	1.525	1.427	1.228	1.005	0.796	0.615
1	0.731	1.382	1.524	1.423	1.222	0.999	0.791	0.611
1.5	0.756	1.390	1.524	1.418	1.217	0.994	0.786	0.607
2	0.780	1.398	1.523	1.414	1.211	0.989	0.781	0.603
2.5	0.803	1.405	1.522	1.410	1.206	0.983	0.776	0.599
3	0.825	1.412	1.521	1.406	1.201	0.978	0.772	0.595
3.5	0.847	1.418	1.520	1.401	1.195	0.973	0.767	0.591
4	0.868	1.424	1.519	1.397	1.190	0.968	0.763	0.588
4.5	0.888	1.430	1.518	1.392	1.185	0.962	0.758	0.584
5	0.907	1.435	1.516	1.388	1.179	0.957	0.754	0.580

Figure 4.41: QALYs gained - DALYs saved conversion factors

Once the DALYs have been converted into QALYs, they have been added to the QALYs gained because of Forxiga, as shown in figure 4.43.

Discount rate: 1,5%			
	Dapagliflozin + SoC	*Placebo + SoC*	*Incremental*
QALYs (discounted)	8.050	7.224	**0.716**
Life years (discounted)	10.826	9.873	**0.953**
QALYs (undiscounted)	8.916	8.075	**0.841**
Life years (undiscounted)	12.028	10.905	**1**

Discount rate: 4%			
	Dapagliflozin + SoC	*Placebo + SoC*	*Incremental*
Total costs (discounted)	€103141	€108249	**-€5108**
Total costs (undiscounted)	€150169	€155794	**-€5625**

ICER		
Incremental cost/QALY (discounted)	**-€7134**	DOMINANT
Incremental cost/LYG (discounted)	**-€5359**	DOMINANT
Incremental NMB (discounted)	**€19426**	
Incremental cost/QALY (undiscounted)	**-€6688.46**	DOMINANT
Incremental cost/LYG (undiscounted)	**-€5625**	DOMINANT
Incremental NMB (undiscounted)	**€22437**	

Figure 4.42: ICER and NMB without considering environmental impact

Discount rate: 1,5%			
	Dapagliflozin + SoC	*Placebo + SoC*	*Incremental*
QALYs (undiscounted)	8.91637	8.075	**0,84137**

Discount rate: 4%			
	Dapagliflozin + SoC	*Placebo + SoC*	*Incremental*
Total costs (discounted)	€103141	€108249	**-€5108**
Total costs (undiscounted)	€150169	€155794	**-€5625**

Figure 4.43: ICER and NMB considering environmental impact as a QALYs addition

Gender	Age group (year)	Kidney function (in ml/min/1.73 m^2)			
		eGFR ≥60	eGFR 45–59	eGFR 30–44	eGFR 15–29
Male	30	39.1 (38.9–39.2)	28.4 (25.1–31.7)	20.1 (16.5–23.7)	15.3 (11.0–19.5)
	35	34.7 (34.6–34.9)	28.0 (26.3–29.8)	16.3 (13.3–19.2)	13.8 (11.0–16.7)
	40	30.5 (30.3–30.6)	24.5 (23.3–25.8)	14.5 (12.3–16.8)	10.4 (8.1–12.7)
	45	26.2 (26.1–26.4)	21.3 (20.4–22.2)	12.5 (10.9–14.2)	8.8 (7.1–10.5)
	50	22.3 (22.2–22.4)	18.3 (17.7–19.0)	10.6 (9.5–11.7)	7.4 (6.1–8.7)
	55	18.6 (18.5–18.7)	16.0 (15.5–16.5)	8.7 (7.9–9.5)	6.6 (5.6–7.6)
	60	15.1 (15.0–15.2)	13.6 (13.2–13.9)	7.8 (7.3–8.4)	5.6 (4.8–6.3)
	65	11.9 (11.8–12.0)	10.9 (10.7–11.2)	6.6 (6.2–7.0)	4.6 (4.2–5.1)
	70	9.0 (9.0–9.1)	8.4 (8.3–8.6)	5.9 (5.7–6.2)	3.9 (3.6–4.2)
	75	6.7 (6.6–6.7)	6.2 (6.0–6.3)	4.7 (4.5–4.9)	3.1 (2.9–3.3)
	80	4.6 (4.6–4.7)	4.3 (4.2–4.4)	3.4 (3.3–3.4)	2.5 (2.5–2.6)
	85	2.7 (2.5–2.8)	2.3 (2.2–2.5)	1.8 (1.6–2.0)	1.4 (1.2–1.7)
Female	30	43.8 (43.7–44.0)	33.6 (31.0–36.2)	21.4 (17.3–25.5)	12.7 (7.4–18.0)
	35	39.2 (39.0–39.3)	30.8 (28.9–32.8)	17.6 (14.0–21.2)	13.1 (10.1–16.0)
	40	34.6 (34.5–34.7)	28.7 (27.5–29.9)	16.5 (14.0–19.0)	9.1 (6.6–11.6)
	45	30.2 (30.1–30.4)	25.4 (24.5–26.3)	14.9 (13.0–16.7)	7.4 (5.6–9.3)
	50	26.0 (25.9–26.2)	22.3 (21.7–22.9)	13.2 (11.8–14.5)	7.4 (5.9–8.8)
	55	22.0 (21.9–22.1)	19.1 (18.6–19.6)	11.3 (10.3–12.3)	6.7 (5.6–7.8)
	60	18.2 (18.1–18.3)	16.5 (16.1–16.8)	10.6 (9.9–11.2)	6.2 (5.4–7.0)
	65	14.6 (14.5–14.7)	13.4 (13.1–13.6)	9.4 (8.9–9.9)	4.7 (4.2–5.2)
	70	11.3 (11.2–11.4)	10.5 (10.4–10.7)	7.9 (7.6–8.2)	4.1 (3.8–4.5)
	75	8.4 (8.3–8.5)	7.9 (7.8–8.0)	6.0 (5.9–6.2)	3.9 (3.6–4.1)
	80	5.6 (5.5–5.7)	5.3 (5.2–5.4)	4.5 (4.4–4.6)	3.1 (3.0–3.2)
	85	3.0 (2.9–3.1)	2.8 (2.7–2.9)	2.2 (2.0–2.3)	1.6 (1.4–1.8)

Figure 4.44: Chronic kidney disease and life expectancy

Parallel evaluation: environmental impact as a stand-alone metric

A third option is represented by including the environmental impact of healthcare interventions in their economic evaluation as a separate indicator, without any further assessment. If on the one hand, it excludes the difficulties related to converting it in costs or QALYs, on the other hand, it makes comparison between interventions more difficult. In fact, considering the environmental impact in absolute terms may shift the focus on the environmental burden or benefit thereby neglecting the actual clinical benefits or costs. Additionally, it is very important to take into consideration that the final recipients of the economic evaluations of healthcare interventions (healthcare professionals, insurers, policy-makers) very often lack expertise in the environmental field and may encounter difficulties in interpreting a separate indicator with which they are not familiar.

As explained in section 3.3, there are three ways to apply this methodology: calculating the ICFER, calculating the ICFCR and presenting the environmental impact in absolute terms (through environmental metrics as CO_2e, SO_2e, oil eq, etc.).

Regarding the first two alternatives, the ICFER was calculated as the difference in carbon footprint between the SoC+Forxiga and the SoC+Placebo divided by the difference in their health benefit (CO_2e per QALYs), while the ICFCR was calculated as the difference in carbon footprint between the SoC+Forxiga and the SoC+Placebo divided by the difference in their costs (CO_2e per euro).

Results of the application of these two procedures are shown in figure 4.45.

Parallel Evaluation (1)		
Carbon footrpint difference (kg of CO2e)	*QALYs difference*	*ICFER (kg of CO2e per QALY)*
-216	0,841	-256,83

Parallel Evaluation (2)		
Carbon footrpint difference (kg of CO2e)	Costs difference	*ICFCR(kg of CO2e per euro)*
-216	-€5625	0,0384

Figure 4.45: Results parallel evaluation

As concerns the third alternative, in this case study, the environmental impact has been presented as a single value in CO_2e units (as can be seen in section 4.2.2). However, besides CO_2e, several other metrics can be used to express the environmental impact (as discussed in the section3.3).
To give the reader a grasp of that, the savings in the environmental impact of dialysis over 1 year due to Forxiga expressed through several environmental metrics are presented in the following figure 4.46 Results to inform these graphs have been obtained through an AstraZeneca internally-developed model.

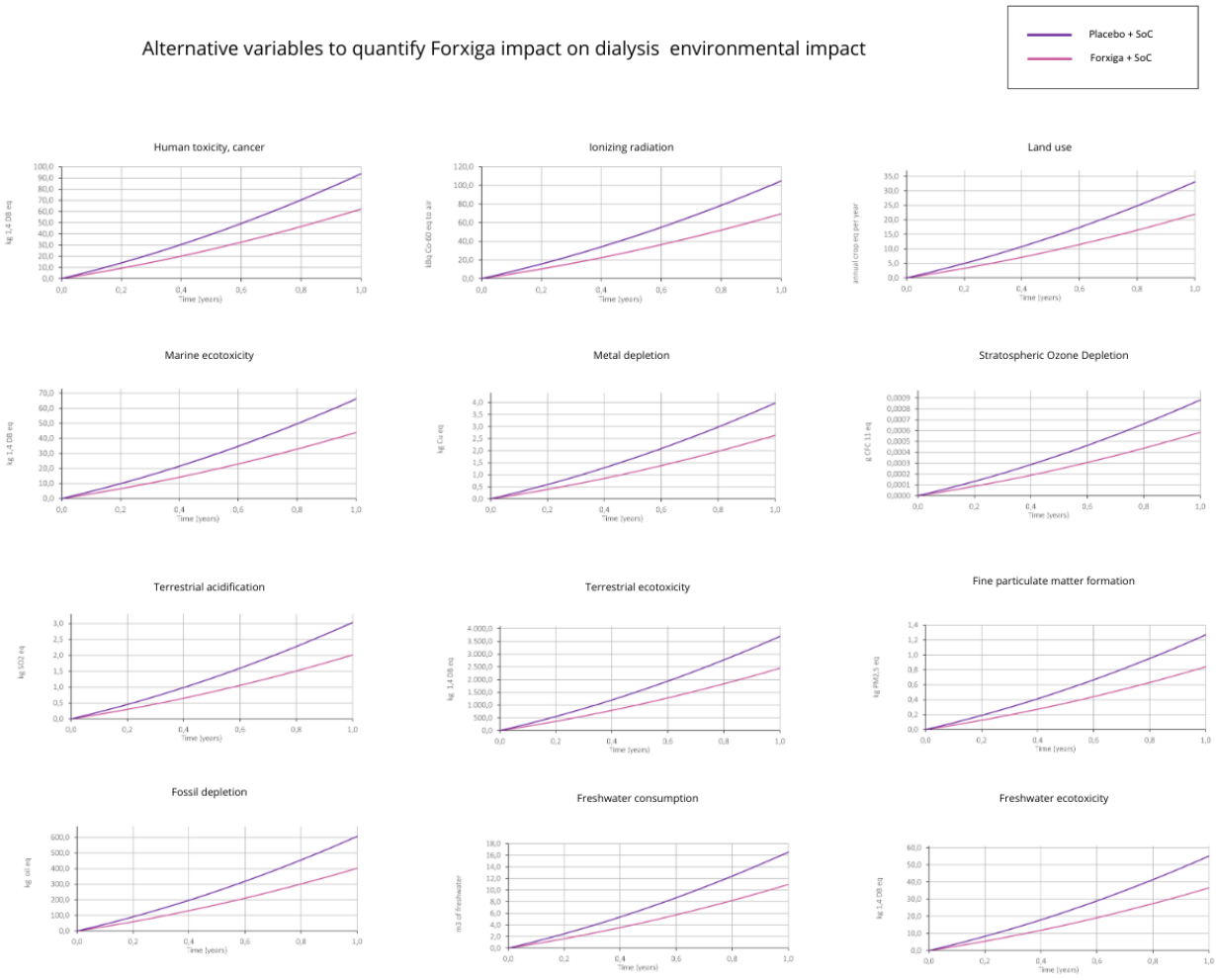


Figure 4.46: Impact on alternative metrics

Comparison between the three methodologies

The previous sections present the alternative ways to include environmental impact in the economic evaluation of healthcare interventions. As it can be seen in figure 4.43, an integrated evaluation approach where the environmental impact is included in the ICER as a health benefit involves a small increase in QALYS only of 0,00137. On the other hand, looking at figure 4.40, the same can be said about an integrated approach where the environmental impact is translated into costs. In fact in this scenario, the ICER slightly changes from -€6688,46 to -€6765,52. It can be concluded that the integrated evaluation approach does not fairly express the environmental impact of the healthcare interventions.

Concerning the parallel evaluation (discussed in the section 4.2.3), the ICFER of -256,83 kg of CO_2e per QALY and the ICFCR of 0,0384 kg of CO_2e per euro, better express the environmental impact of Forxiga. However, since it is not effectively included in the usual economic assessment economic evaluation method of healthcare intervention, it may not affect the final decision.

	Incremental costs (undiscounted)	*Incremental QALYs (undiscounted)*	*ICER (undiscounted)*
No environmental impact included	-€5625	0.841	-€6688.46
Environmental impact included as a cost	-€5689.8	0.841	-€6765.52
Enviornmental impact included as QALYs	-€5625	0,84137	-€6.685,52

Figure 4.47: Comparison between environmental impact considered as a cost or as QALYs

4.3. Sensitivity Analyses

The robustness of the results was assessed by carrying out two sensitivity analyses. The first type of analysis which is performed is a tornado analysis and the results are presented in the next section.

4.3.1. Tornado analysis

The tornado analysis is a type of sensitivity analysis that is used to assess the impact of different variables on a particular outcome. This analysis is performed by varying one key input per time while keeping the others constant in order to assess how changes in each variable affect the final result. After that, variables are ranked by their impact, with the most impactful shown at the top and the bottom (in both directions), resembling a tornado. This analysis helps in identifying which factors have the greatest effect on the outcome thereby informing decision-making and risk management.

The results of the tornado analysis for the case study are shown in figure 4.48. The analysis was performed by varying by 20 percent the input concerning the environmental impact of stage 1, stage 2, stage 3a, stage 3b, stage 4, stage 5 pre-RRT, dialysis, transplantation, SoC, and Forxiga. As can be seen in the figure, the biggest changes in the outcome are due to the input value considered for the dialysis and, in second place, for the SoC. In fact, it is possible to notice that the reduction in CO_2 because of Forxiga is considerably bigger (23 percent more) if dialysis impact is considered 20 percent higher. Furthermore, if the impact of the SoC is considered 20 percent bigger, the total savings in CO_2 result to be 8,5 percent higher. On the other hand, changing the assumptions related to the first stages does not influence the results of the analysis at all. This is in line with the fact that, as shown in figure 4.27, they have a very small impact on the environmental footprint of the total care pathways.

Starting from a value of -418 kg of CO_2 as net environmental savings due to Forxiga, figure 4.48 shows in violet the changes in input that increase the net savings and in lilac the ones which decrease them.

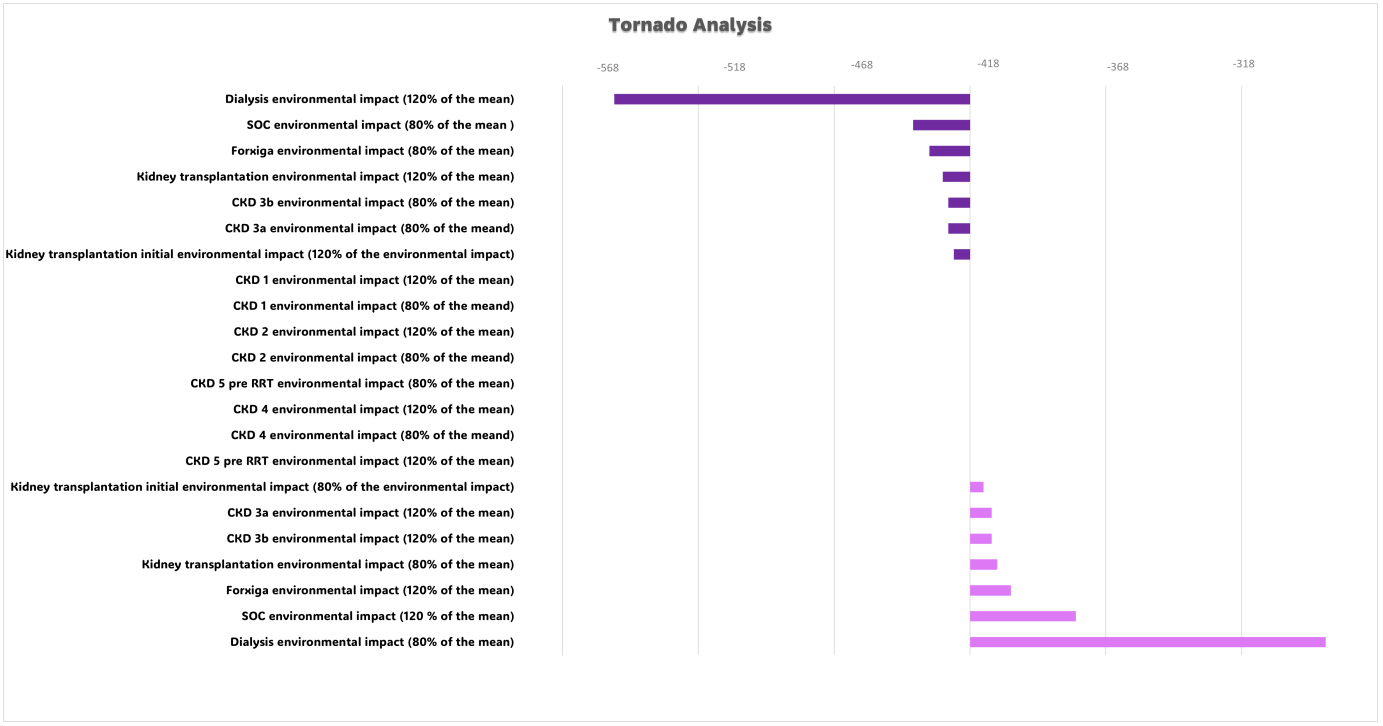


Figure 4.48: Tornado sensitivity analysis

From the results of the tornado analysis, it can be concluded that dialysis is the most impactful variable on the net savings. For this reason, a second sensitivity analysis, called threshold analysis, was performed and its results are presented in the next session.

4.3.2. Threshold analysis

Threshold analysis is a type of analysis performed to identify the point at which a certain variable will determine a significant change in outcomes or decisions. This type of analysis establishes threshold values that, once crossed, lead to a different final outcome. The threshold analysis is often used in health economics, and specifically to assess whether a healthcare intervention is still considered cost-effective compared to the existing one when varying inputs.

For this case study, the threshold analysis was used to identify the input value of the environmental impact of dialysis for which implementing Forxiga in CKD treatment does not represent a net environmental benefit anymore. As can be seen in figure 4.49, net environmental savings in CO_2 are observed due to the addition of Forxiga to the standard of care over 10 years, as long as the annual environmental impact of dialysis is estimated at least 2000 kg of CO_2e. In other words, if the emissions due to an annual treatment of dialysis are considered to be less than 2000 kg of CO_2e, then it is not environmentally convenient to implement Forxiga in the standard of care, it does not bring any environmental benefit compared to the standard treatment.

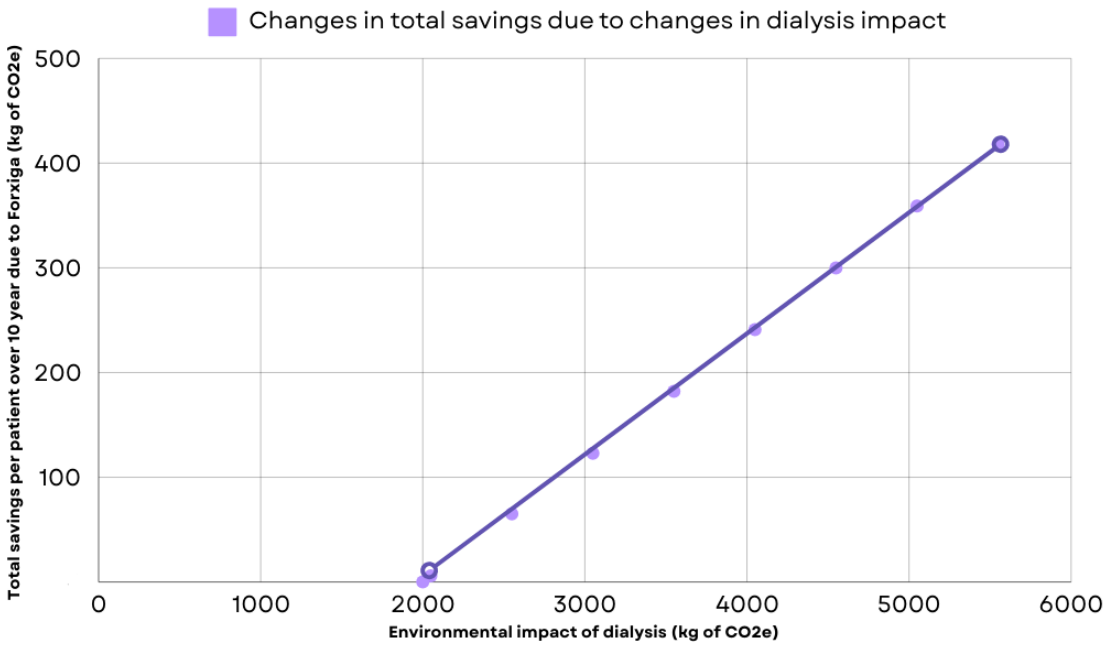


Figure 4.49: Threshold analysis for dialysis impact

After having assessed the robustness of this work through the sensitivity analyses, several strategies have been adopted to test its validity. It has been done to evaluate the accuracy, reliability, and generalizability of the study. The results of the validation are presented in the next section.

4.4. Validation

The study has been validated according to different categories of validity. Concerning the external validity of the LCA (defined as the extent to which the results could be generalized to different settings in terms of populations or time), the study was assessed by comparing its results with two similar studies. Specifically, these studies concern the environmental impact of CKD in different countries [5] (and the internal manuscript 3.4). On the other hand, face validity (defined as the extent to which the analysis appears to measure what it is supposed to, based on its contents and presentation) was ensured where data sources, assumptions and results were derived from the best available peer-reviewed papers concerning individual care activities [67] [65] [86] [112] and validated with

expert opinions (see interviews with two medical expert and sustainability expert, see Appendix A.3).
Next to the aforementioned strategies, to assess the validity of the LCA systematically, the Validation-Assessment Tool of Health-Economic Models (AdViSHE) has been used [104]. The results obtained with this tool are presented in the next section.

4.4.1. AdViSHE

AdViSHE is a validation-assessment tool for health economic models created by a large group of healthcare experts (having different backgrounds and coming from several countries) to address the trade-off between a loss of confidence resulting from lacking validation efforts, and an inefficient use of resources. The tool is designed to be filled in by modelers in order to report in a structured way on the efforts concerning the validation status of their models and the outcomes of these efforts. Next to that, AdViSHE was chosen because it presents a certain degree of consensus among model users and model developers on what is good validation in the healthcare sector. Implementing this tool, model developers comment on the validation efforts performed while building the underlying healthcare decision model.
The final version of AdViSHE consists of thirteen questions. They are grouped to cover its various aspects:

- the conceptual model;
- the input data;
- the implemented software program;
- the model outcomes.

The results obtained by implementing AdViSHE for the case study are summarised in figure 4.50.

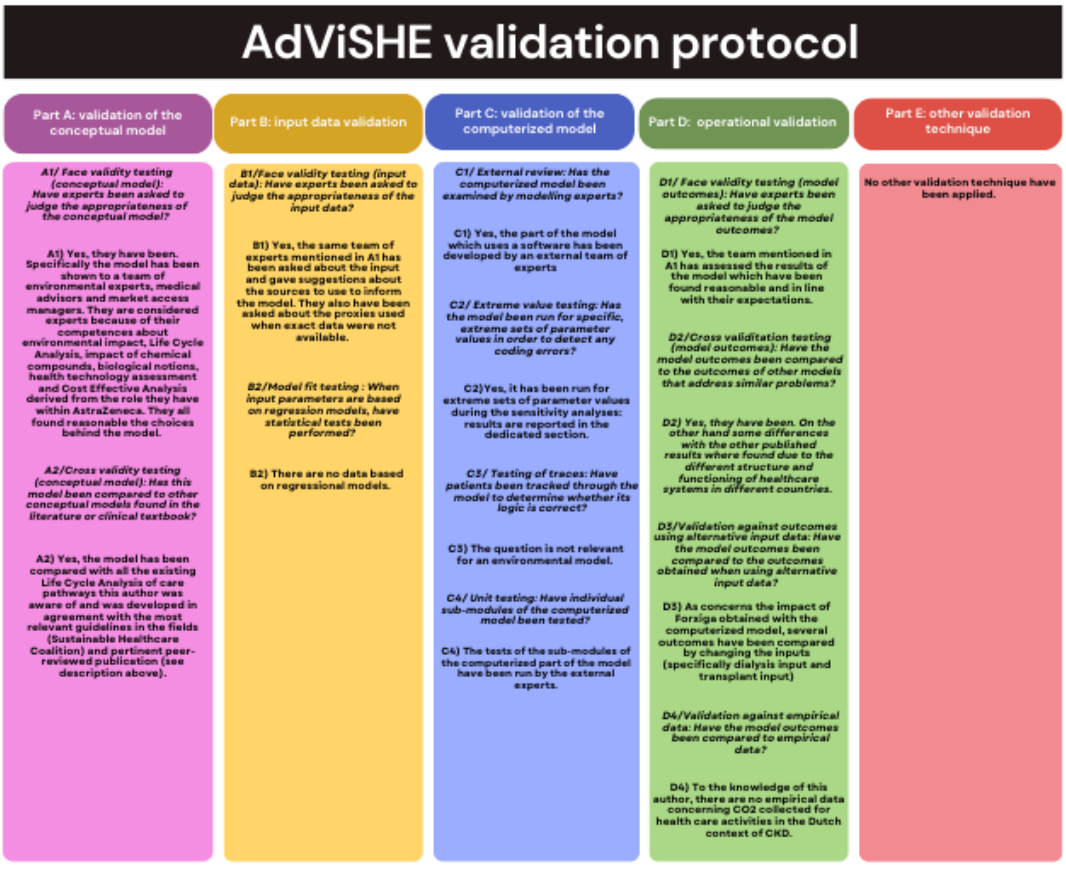


Figure 4.50: AdViSHE validation protocol

However, it is important to take into consideration that the validation performed for this study presents some limitations and can be further improved for several reasons. The first is that validation efforts were focused solely on the LCA analysis. Although the way to include its results in the Markov model and finally in the ICER were discussed with market access experts, a systematic validation has not been performed.
Concerning the validation performed through interviews, even considering the numerous consultations with AstraZeneca internal experts and academic supervisors, the number of interviewees is still very limited. Next to that, being the first LCA for CKD performed with specific Dutch data, external validity can be only partially assessed because the environmental studies considered for the comparison were based on data from other countries. Furthermore, no comparison was made with findings deriving from alternative ways to include LCA results in Markov model or from alternative ways to conduct LCA (e.g. following different guidelines).
Interesting results concerning generalizability could be derived by applying the framework created in this study for the assessment of the environmental impact of CKD in the Netherlands to other chronic diseases in order to evaluate the extent to which modules can be adapted to the specific aspects of the disease. Additionally, content validity can be improved by broadening the modules' definitions in order to check whether it actually represents a more realistic evaluation of the environmental impact.
In this chapter, the results of this work have been presented. In the next one, a discussion concerning limitations, challenges, and strengths of this type of study will be discussed together with reflections about the eventual future directions of research about sustainability in healthcare.

5

Discussion, further research and conclusions

This chapter starts with a summary of the main results of the study. Based on these findings, strategies to mitigate the impact of the CKD care pathway are introduced. In addition, considerations concerning the relevance, challenges, strengths, and limitations of this work are presented. Starting from these limitations and considering the insights from the interviews, the chapter ends with a final reflection on future research concerning sustainability in healthcare.

This study addressed two complex challenges. The first concerns the assessment of the environmental footprint of care pathways in the Netherlands and the second concerns the inclusion of the environmental impact of healthcare interventions in their economic evaluation.
To explore these two topics, the Chronic Kidney Disease (CKD) care pathway and Forxiga as a healthcare intervention have been chosen as a case study. Regarding the environmental footprint of the care pathway, it has been assessed through a Life Cycle Analysis (LCA). Concerning the inclusion of the environmental impact of healthcare interventions in their economic evaluation, three alternative ways together with their advantages and disadvantages have been presented.
A literature review has been conducted to select the best strategy to assess the environmental impact of the care pathway (see section A.1). After considering the pros and cons, LCA has been selected as the most comprehensive analysis and its several variants have been considered (see section 3). In order to perform it, a further literature review has been conducted to analyze the existing most relevant guidelines, their field of application, and their characteristic. The same considerations have been made for the environmental metric to use, after which CO_2e was chosen (see section 3). To the knowledge of this author and of the interviewees, this study includes the first attempt to evaluate the environmental impact of the CKD pathway in the Netherlands using nation-specific data. Additionally, this is the only LCA for CKD which includes the environmental impact of all the medicines of the SoC, for which production, use, and end-of-life phase has been taken into consideration for the first time.
Concerning the inclusion of the environmental impact of healthcare interventions in their economic evaluations, a literature review of the existing methodologies has been conducted. Only four studies undertook a full economic evaluation of healthcare products thereby including CO_2 emissions in the economic evaluation [26] [75] [76] [100]. In these studies, the authors calculated CO_2 emissions and then converted those into costs through the Social Cost of Carbon [26] [75] [76] or the carbon cost [100]. In line with these existing studies, this procedure has been performed for the case study and proposed as one of the three alternatives. However, to the knowledge of this author, this study represents the first attempt to translate environmental damage in QALYs and integrate it into the ICER.
In the next session, an overview of the main findings of this study is presented.

5.1. Summary of the findings

Interesting findings were obtained for both research topics. Concerning the assessment of the care pathways for Chronic Kidney Disease (CKD), consulting a Dutch medical expert (see section A.3.2, a framework to perform the LCA in the Netherlands has been created (showed in figure 3.1. The care pathway has been disassembled into several modules, which, in turn, are composed of submodules. The environmental impact of each submodule has

been calculated with activity data and emission factors. Afterward, these submodules have been grouped into modules and finally into stages, in order to obtain the total footprint of the care pathway.
This framework can be used to model other care pathways for chronic diseases in the Netherlands since they very often share similar activities (primary care consultations, secondary care consultations, SoC, hospitalization, ICU, etc.) and showed that the disease burden extends beyond the clinical, humanistic, and economic considerations. Looking at the results of the analysis, the ESRD (Stage 5) was found to be the most environmentally impactful, thereby contributing 90 percent to the total footprint of the care pathway (almost 9000 kg of CO_2e per patient per year). Within this stage, the most polluting care activities are dialysis and transplantation. Among the four existing types of dialysis, in-centre haemodialysis has been found to be the most environmentally impactful and resource-consuming, followed by Automated Peritoneal Dialysis (APD), at-home haemodialysis and Continuous Cycler-Assisted Peritoneal Dialysis (CAPD). Overall, there is an increase in carbon impact t as the patient progresses through stages. These findings underscore the carbon-saving value of halting or delaying CKD progression and keeping patients in earlier stages. It is interesting to note that the costs and the environmental impact of the care activities run parallel: mitigating the impact of the care pathway implies reducing the number of patients in the ESRD, which is also the most expensive stage. This leads to the conclusion that pursuing the environmentally best strategy very often means also implementing the cheapest one and consequently aligning with the financial goals of companies.
Regarding the second research topic, the environmental impact of Forxiga (in addition to the standard of care) has been presented in three different ways: two of them concerning the inclusion of this impact in the ICER (either as a cost or as a QALYs) while the third presenting it as a separated indicator. The first two modalities presented only slight impacts on the ICER (from -€7134 to -€7165,71 if the environmental impact was considered as a cost and with an additional 0,000037 QALYs if it was considered as health benefits). This shows that the methodologies do not take into account the environmental impact fairly. On the other hand, presenting the environmental impact of Forxiga as a separate indicator makes more explicit the substantial contribution (418 kg of CO_2e saved per average patient over 10 years). However, this option can hinder comparability between economic evaluations and the understanding of people lacking environmental expertise. The positive effect of Forxiga on the environmental footprint of CKD treatment derives from the fact that this medicine slows down the progression of the disease thereby resulting in fewer hospitalizations and fewer patients in the later stages, which are the ones having higher healthcare resource utilization and environmental impact. Based on the findings of this study, several strategies to mitigate the environmental impact of the CKD care pathway can be identified. They are presented in the next section.

5.2. Strategies to mitigate the impact of the CKD care pathway

The analysis of the impact of each care activity helps with identifying possible solutions to mitigate the impact of CKD treatment. Examples of them are:

- Optimizing treatment to reduce the progression of CKD;
- Reducing the carbon impact of dialysis treatment (e.g. power the machines with renewable energy);
- Researching interventions to reduce the frequency of CKD patient hospitalization;
- Reducing impacts associated with medicines (in terms of production, delivery, and disposal)

On the other hand, focusing on Forxiga, a reduction of its impact will also result in larger carbon savings offered by its prescription. According to the results of the internal LCA, this can be achieved by:

- Sourcing lower-impact chemicals and materials to be used in the Dapagliflozin synthetic route and Forxiga packaging stages;
- Reducing the impact of patient travel;
- Reducing the impact associated with API waste during Forxiga manufacture.

Next to these general suggestions, the environmental impact of the modules can inform the reflection on the next specific steps to take to alleviate the environmental footprint of this care pathway.
From the assessment of both primary and secondary care consultation (figures 4.2 4.3), it can be derived that around one-third of the total impact is represented by transportation. This undoubtedly suggests that all types of initiatives which prevent traveling (e.g. telemedicine) can significantly reduce the impact of these modules.
Looking at the transplantation module, both for living and deceased donors (respectively figure 4.11 and 4.12), it can be noticed that the biggest contribution comes from the surgery itself because of the medicines used during

the operation, the tools, and the energy required for the machines. This means that mitigation actions for this module (but also for ICU and hospitalisation) should be steered in the direction of renewable energy use and sustainable sources together with reusable or recyclable tools.
On the other hand, medicine impact (see Standard of Care, figure 4.13) due to APIs post-use, can be mitigated by:

- reducing medicines going to waste;
- preventing incorrect disposal of unused medicines (to landfill or down the drain);
- wastewater treatment for hospitals.

Since it has been found to be the most environmentally impactful module, special attention needs to be paid to possible ways to reduce the dialysis impact. In all four kinds of dialysis modules (heamodilaysis in-centre, hemodialysis at-home, CAPD and APD), it can be observed that the biggest impact is due to dialysis sessions themselves (always greater than 80 percent). In a recent paper, [111], some interesting solutions have been investigated to mitigate it, including:

- Recycle reverse osmosis (RO) reject water;
- Upgrade to water treatment plants that are more efficient and allow RO reject water recirculation;
- Incremental dialysis or reduction of dialysate flow rate, where appropriate, to reduce water demand;
- Renewable energy generation (e.g rooftop solar panels);
- Equip dialysis machines with heat exchangers;
- Central dialysis delivery system to reduce reliance on individually packed dialysis consumables.

Steps in this direction have been done. In fact, the medical expert during the interview A.3.2 explained that dialysis machine manufacturers have recently included a paragraph about their sustainability efforts in the dossier they present to hospitals. Although it does not represent the solution to the problem, it is a crucial step in increasing awareness and sensibility about the topic.
Being the first LCA for CKD conducted specifically for the Netherlands and the first attempt to include the environmental impact of healthcare interventions in their economic evaluations, this study presents several elements of novelties which are discussed in the next session.

5.3. Relevance

This study differs from the previous ones in several ways. In fact, studies concerning the environmental impact of CKD are usually focused solely on dialysis without taking into consideration the earlier care activities in the pathway. Next to that, there is no existing framework for the evaluation of the environmental impact of chronic diseases specific to the Netherlands. Additionally, this is the first study that takes into account the environmental impact of all the medicines in the SoC through a cradle-to-grave LCA. Another element of novelty is represented by the inclusion of the environmental impact in the economic evaluation of health intervention. So far, it has been done only by incorporating it as an additional cost [26] [75] [76] [100]. In this study, the first attempt to incorporate it as a benefit or as a separate indicator through different variables has been made together with a systematic discussion about the opportunities and limitations of each procedure 3.3.
This study is particularly relevant for several stakeholders. It is significant for Dutch policy-makers who can identify the most environmentally impactful care activities in the CKD care pathway and steer new policies accordingly (e.g. making production processes more sustainable). Additionally, together with environmental analysis conducted for other medical procedures, it can be used by policy-makers to elaborate future guidelines in the nascent field of sustainability in healthcare, which is a central topic in the current national debate [72].
This study is very relevant also per (bio)pharmaceutical companies involved in CKD treatment which can use it to improve their production processes and show their commitment to address the general public attention to the environment. Next to that, this study can be valuable for health-insurance providers and hospitals for a broader evaluation and negotiation of new healthcare interventions.
Overall this study is highly significant because it addresses the European and Dutch call for implementing sustainability in the healthcare sector [44] [3]. However, as for all the studies in nascent fields, several challenges have been encountered; they are described in the next section.

5.4. Challenges

As discussed earlier in this chapter, this study presents several elements of novelties and for this reason, many challenges have been experienced in conducting it. One of the main challenges in performing this type of study is the lack of activity data for healthcare activities. In fact, finding updated databases concerning GP and specialist visits in the Netherlands (length, facilities, duration) is a significant challenge. Next to that, in the majority of the cases, there are no specific emission factors for healthcare facilities/machines and they need to be derived from total energy consumption of facilities. Another big challenge is represented by the lack of knowledge sharing concerning the sustainability profile of drugs among pharmaceutical companies. In the SoC for a disease, it is very often the case that medicines are produced by different companies. This means, that in order to evaluate the total impact of the SoC, data about the environmental impact of each medicine need to be available. However, companies are very often reluctant to share them and this hinders the LCA thereby forcing the analyst to use proxies. Furthermore, there are no specific studies conducted for the Netherlands concerning the environmental impact of hospital stays or surgical procedures, which are crucial data to inform the LCA. As concerns the inclusion of this environmental impact in the economic evaluation of healthcare interventions, one of the main challenges has been translating DALYs (obtained from the LCA in CO_2) into QALYs. There is only one study that provides conversion factors for that but it is hardly applicable to chronic diseases because of the assumptions it was built upon.
Next to all these challenges, the study presents several strengths. However, the lack of data and knowledge sharing were translated into limitations for this work. Reflections on the topics are made in the next section.

5.5. Strengths and limitations

Being the first of its type, this study allows to evaluate accurately the environmental footprint of the CKD care pathway in the Netherlands. It gives valuable insights into the environmental impact of the care activities involved in CKD treatment and provides a framework to estimate this type of impact for other chronic diseases. Additionally, a further strength of this study lies in the exploration of several methods to include environmental impact in the economic evaluation of healthcare interventions and the consequent discussion about the pros and cons related to each of them. On the other hand, the several challenges discussed in the previous section have resulted in limitations for this study. As concerns the LCA for the CKD pathway, the lack of data about competitors' medicines led to the use of proxies derived from AstraZeneca drugs which do not always perfectly suit the competitors' ones in terms of chemical properties of molecular size thereby leaving some voids in the evaluation of the SoC which has consequently been underestimated. Another significant limitation concerns the fact that the environmental footprint of the care pathway has been estimated only in CO_2 terms. This means that only part of the total environmental impact has been considered while other aspects as air pollution or ecosystem toxicity have not been included extensively. In the section 4.46, the environmental impact of dialysis has been presented by taking into consideration many other environmental metrics; ideally, it has to be done for the entire pathway but at the moment there is not enough available data to do that. As discussed in chapter **??**, dialysis has been found to be the most environmentally impactful care activity. A considerable limitation of this study is that the environmental impact of dialysis sessions has been derived only from one source (internal manuscript, described in section 3.4) since the majority of literature available for the Netherlands only includes estimates for the dialysis sessions, not actual measures. Although a sensitivity analysis has been conducted (see figure 4.49), the study would significantly improve if data from different sources were available.
As regards the inclusion of environmental impact in the economic evaluation of healthcare technologies, it has been performed with some limitations. Regarding the inclusion of environmental impact in the ICER as a cost, the SCC has been employed. This factor is mainly used in impact analysis concerning energy, transportation and infrastructure. Even if it considers the impact on human health, it is modeled on effects on crop yields, food production, damage to buildings, roads and changes in energy demand and supply. This makes the reader understand that a more health-specific factor should be considered for the conversion in the analysis of this type. Concerning the conversion of environmental damage in DALYs, it has been done considering an SP1 scenario (explained in section 3.3). This decision was based on the Dutch commitment and initiatives to reduce the environmental impact of healthcare activities in the next years. However, it cannot be considered certain and the conversion should be performed also considering other scenarios in order to get a complete picture of the possible outcomes. Additionally, the further conversion from DALYs to QALYs has been performed through the only available factors. These were derived considering diseases of very different natures (tuberculosis vs CKD) and only include a maximum of 5 years of life from the disease onset (which is usually longer for CKD in the majority of the cases). Ideally, *ad hoc* conversion factors should be calculated by collecting real-life data.

It is important to consider that currently there is no comprehensive monetary equivalent estimate of environmental damage. Consequently,
For this reason, further research is required in this field to explore the most effective way to include environmental impact in the economic evaluation of healthcare interventions. For instance, it would be interesting to consider the alternative to consider it by introducing a ”correction factor” for the ICER. This factor could be calculated as a function of the CO_2e emission of the intervention. Next to that, there is also the option to inflate the costs in order to take into account the environmental damage. However, these possible procedures are not straightforward and univocal and they involve consideration about the weight to assign to environmental damages.More generally, including environmental costs in the economic evaluation of healthcare technologies will involve several implications. For instance, the environmental costs are not directly and immediately experienced. In order to properly take into consideration these costs some other mechanisms should be implemented, such as additional taxes. This idea is based on the consideration that externalities should be internalized at the initial source of the emissions [26].
However, the inclusion of sustainability in the evaluation of healthcare interventions goes beyond the environmental impact. In fact, great concerns have arisen about the chronic shortage that affects the healthcare sector and the consequent necessity to take into consideration the impact of new healthcare intervention on workforce in their future evaluations. In order to make these economic evaluations as comprehensive as possible, this topic should be explored in future research (see section 5.6).

5.6. Future research

5.6.1. Future research: assessing the workforce impact of healthcare interventions

Next to its environmental footprints, great concerns have arisen about the chronic shortage that affects the healthcare sector. It is well recognized as one of the biggest obstacles to achieving accessible and fair healthcare. In fact, the overwhelming workload of healthcare professionals leads to a lack of motivation, fatigue, absenteeism, and even career change. [46].
The majority of the problems causing healthcare professional shortage and burden have been exacerbated by the COVID-19 pandemic and by increased levels of influenza and respiratory syncytial virus, thereby getting rising attention. Overcrowded and under-resourced hospitals have placed even more pressure on an already overburdened healthcare workforce [9]. This represents a constraint that can influence the estimation of costs and effects of therapeutic interventions and consequently decisions based on them. Moreover, the limited availability of healthcare professionals inspires some reflections about the higher value that may be attached to their deployment as a resource. It sustains the debate about whether to include the impact of medical treatments on the healthcare workforce in the criteria for their economic evaluation and how to value it. [103]
The healthcare professional shortage has been often depicted as a vicious circle: the pressures created by the backlog, have created an increasingly difficult and demanding working environment, pushing more clinicians to leave and generating a permanent crisis in the sector, named a ”permacrisis” [9].
Looking at the Netherlands, although 1.4 million people work in the healthcare and welfare sector [79], the staff shortage is currently estimated to be 48 thousand people (32 thousand Full Time Equivalent (FTE)). At the moment, the Dutch healthcare system is facing the largest shortage in specialist medical care (MSZ) and nursing and home care (VVT). The illness rate is more than 7.5 percent. This shortage in the Dutch context is mainly due to a growing personnel outflow, part-time contracts of few hours, and time wasted on ”unnecessary administrative burdens” (e.g. the manual five-minute registration in community nursing). One of the suggestions from Stichting Volksgezondheidszorg Zuid Nederland (VGZ) is an efficient deployment of the working time of the healthcare professionals together with the implementation of sustainable care measures [79]. The shortage is expected to increase to 140 thousand by 2031 (93 thousand FTE). In other words, everything staying unchanged, the only way to meet the future demand for care will be that one person out of five will work in the healthcare sector [105] and even one out of three by 2060 [79]. These scenarios are impossible and also undesirable: the healthcare sector is not the only one suffering from staff shortage. This means that it is crucial to look for solutions that allow us to solve the problem within the sector and one of the most promising is the implementation of interventions that reduce the deployment of healthcare professional staff. Implementing less labor-intensive treatments is essential to guarantee the availability of care.

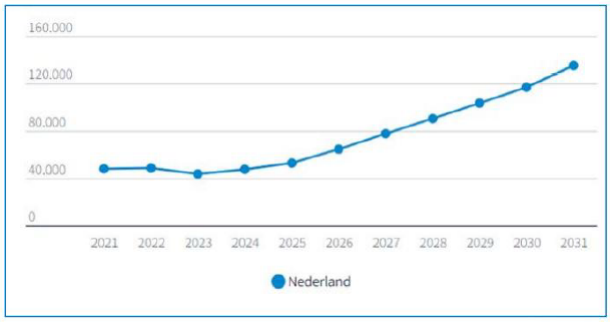


Figure 5.1: Labor market shortage in the healthcare and welfare sector in persons

Looking at CKD, it represents also a substantial burden in terms of healthcare workforce resources. In fact, the Dutch capacity plan 2022-2025 [12] shows the critical situation concerning dialysis nurses, who represent the category of healthcare professionals involved in the most resource-consuming stage of CKD (figures 5.2 [12]).

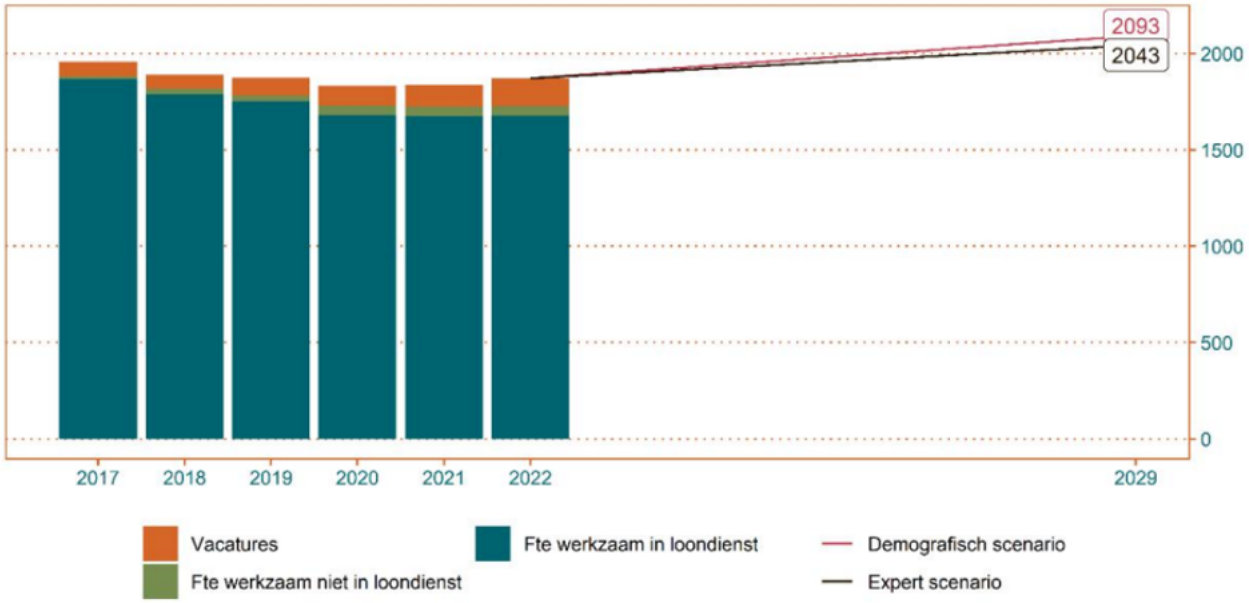


Figure 5.2: Dialysis nurses, historical and required FTE

In recent years, the number of dialysis nurses employed by hospitals has fallen thereby causing a worrying shortage that is expected to increase in the coming years (between 1.3 and 1.7 percent per year over the next seven years) [12]. Next to that, experts predict an increase in the demand for dialysis nurses because of the projected number of diabetic patients who will require dialysis in the future.
Despite the situation shown by these data, to date, there have been only a very limited number of attempts to incorporate environmental and workload capacity impact in the economic evaluation of medical treatment [92] [103]. In fact, a literature review performed by van Baal et al. [103] shows that the majority of the studies ignore workforce capacity considerations resulting in biased cost-effectiveness studies, thereby highlighting the existing gap and the necessity to include these considerations in the future medical treatment evaluations. This leads to the conclusion that the impact of therapeutic interventions on staff shortages is still largely unexplored territory and hardly any scientific research has been conducted on the topic [105] and that is an important topic for future research.
A literature review of the existing method to evaluate the impact of interventions on the workforce and a discussion about the most suitable ones for the healthcare industry can be found in Appendix A.4.

5.6.2. Future direction of sustainability in neprhology

In the previous section, further research topics in the economic evaluation of healthcare technologies have been discussed. However, from the interview with the Dutch nephrologist expert in sustainability and member of the European Renal Association − European Dialysis and Transplant Association (ERA-EDTA) A.3.1, several points of reflection concerning the future research in sustainable nephrology emerged. The expert confirmed the necessity to quantify the environmental impact as well as the uncertainty concerning methodology and variables to take into consideration. According to the doctor, it is a necessary step in creating awareness. Only after that, it would be possible to focus on the influence of this type of information on healthcare professionals' choices. However, one of the main barriers concerns knowledge sharing. Disadvantages, in terms of intellectual properties and trade secrets, seem to outweigh the advantages as concerns sharing information about the sustainability impact of medicines. The expert identifies social responsibility as the incentive and driver for the collaboration between several stakeholders (healthcare professionals, companies, and policymakers), a duty from which nobody can subtract themselves anymore. Making it specific to the new healthcare intervention, responsibility can be distributed along the redesigned blockchain (API production, packaging, transportation, delivery, prescription, etc) between the stakeholders. To significantly increase the awareness of future professionals it is important, according to the nephrologist, that the change is made in a step earlier: education. The real mitigation action, in fact, is to implement sustainability in the university curricula. This is an ongoing process in North Europe and the United States which will allow the next generation of professionals to be already aware of the importance of sustainability in healthcare.

The expert outlined the great value of this study as a crucial step to mitigate the impact of the healthcare sector in the Netherlands and confirmed that it is the first of its type to his/her knowledge. Very often, in fact, goals and objectives are clear but only approximate and generic evaluations of environmental impacts are available. This makes it essential that environmental experts work on producing LCAs for care pathways.

Next to that, during the interview, it was recognized an important responsibility in the leadership styleof the companies. In fact, according to the doctor, the big transition to a more sustainable society requires creative thinking and innovation. He/She believes that thinking outside of the box is essential and that managers need to have a long-term vision. Moreover, the journey towards sustainability is long and does not involve easy wins and the effective benefits can only seen in the long run.

5.7. Conclusion

To summarise the aim of this study was to evaluate the environmental footprint of the CKD care pathway in the Netherlands. Next to that the environmental impact of Forxiga (as a medicine added to the SoC) was assessed and incorporated in its economic evaluation. Alternatives and discussions about the inclusion of environmental sustainability were performed. The environmental footprint was evaluated through an LCA for which a framework composed of modules and submodules for chronic disease was created. The study shows the environmental burden of the CKD care pathway thereby identifying dialysis and transplantation as the most impactful care activities. The environmental impact of the various stages of the disease was quantified and Forxiga was found to save 6 percent of CO_2e per average patient over 10 years.

Next to that, in this and other existing studies [108], translating the environmental impact of new healthcare interventions into costs or QALYs was found to have a small impact on the final ICER. Consequently, presenting it as a separate indicator or as a corrective factor to apply to the ICER to modify it in a more significant way should be considered as an option. However, before weighting the environmental impact in a more significant way, the general willingness to pay and consequently the importance attached by the general public to environmental damages caused by healthcare interventions should be further investigated.

This study shows that conducting LCA in healthcare is feasible. Although it is a time and resource-consuming practice, the type of analysis fits the sector. Performing LCAs for care pathways has been found to be a very valuable way to provide insights about the most polluting activities of treatments. Nevertheless, when considering an extensive application of this methodology in healthcare, it is important to take into consideration the disadvantages. Next to the large amount of resources necessary (both in terms of time and costs), it is essential to consider that LCA is a data-driven method. Considering the knowledge-sharing barrier (previously discussed in section A.3.1) and the lack of updated data available, this severely hinders LCAs in healthcare which tend to be built upon numerous assumptions and proxies. They, in turn, harm the reliability of the studies and restrict their applications. Consequently, if this methodology is envisioned as the future of sustainability in the healthcare sector, it is crucial to work on removing these barriers by fostering knowledge-sharing through common databases. In this study, one way to account for carbon emissions was presented, but beyond quantifying and addressing environmental

damages, achieving sustainability in healthcare requires more systematic transformations and holistic integration of sustainability goals into the overarching healthcare assessment. However, the barrier does not seem to be a lack of interest in sustainable development by healthcare leaders. The real obstacle seems to be the lack of means and metrics available to support sustainability goals. Such objectives can only be achieved with both a change in leadership style from policy-makers and stakeholders and engagement of the general public [26]. However, for future researchers, is important to explore the evaluation of the environmental footprint of care pathways and its inclusion in economic evaluation further, considering the limitations of this study. Additionally, it is essential to broaden the idea of sustainability by considering the impact of these interventions on the healthcare workforce.

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A

Appendix

A.1. Strengths and weaknesses of environmental impact assessment approaches

Method	Focus	Strenght(s)	Weakness(es)
Life Cycle Analysis (LCA)	Entire life cycle of the drug, from the production to the disposal	This inclusive framework ensures that crucial steps which significantly contribute to pollution are not overlooked. LCA is performed by dividing the life cycle into steps. Doing so enables to pinpoint the most impactful activities for the environment and consequently to prioritize them for mitigative action. Another strength of the method is the fact that it provides the analyst with quantitative results that can be compared and that can facilitate the decision-making process.	Analysing each step of the life cycle of the medical treatment requires an extensive dataset. Confidentiality, competition and absence of shared standards make the collection of necessary data very difficult. Additionally, indices and results of the LCA are not always intuitive, this requires interpretation from the experts which inevitably involves a certain degree of subjectivity.
Ecotoxicity Assessment on Ecosystem	Consequences of the environmental impact of medicines on living organisms	By taking into account both terrestrial and aquatic ecosystems, the the method allows to implement the right measures to preserve biodiversity. One of the strengths of this approach is represented by its high specificity: it explains how the chemicals in medicines interact with ecosystems and sometimes modify it in a significant way.	If on one hand this specificity is a strength because it makes the mechanisms of the impact on the ecosystems very clear; on the other hand, some experts recognize in this aspect also a limitation. The per capita use of APIs varies over many orders of magnitude leading the an extremely wide range in the levels of environmental exposures. That being so, the comparatively high ecotoxicological potential of a compound that is used in very small amounts (very few patients and/or very low prescribed dose) will pose a LOWER risk to the environment compared to a high-use volume API (prescribed for a high prevalence indication and/or at high dose) with comparatively low ecotoxicity. Because of its limited scope, some important potential environmental impacts, which do not concern ecosystems directly, are not taken into account thereby giving an incomplete picture of the general situation.

Pharmaceuticals In the Environment (PIE)	Monitoring of the actual presence of effects of pharmaceuticals in the environment	The method presents several strengths. Unlike the rest of the methods, the approach makes use of real-world samples (to understand exposure) as well as data from laboratory studies (to understand the breakdown and environmental fate of APIs as well as the ecotoxicological effects thresholds). Thanks to that, it is possible to obtain an understanding as close as possible to the real situation. Alongside that, the analysis is also focused on the future. This is a crucial step in the long-term impact evaluation. Although looking at the future is necessary for prioritisation of mitigation measures with long-term goals, it is sometimes overlooked in other frameworks.	Studies of this type [39] [40] are clearly limited to compounds for which environmental risk assessments have been conducted (according to regulatory requirements in connection with marketing approvals granted by the European Medicines Agency). This means that other potentially harmful compounds used in the manufacturing process or present in the medicinal product are not included and could alter the results. Regulatory requirement to conduct ecopharmacovigilance (EPV) or standard EPV methodology prescribed is currently preventing the widespread application of this approach.
Environmental Risk Assessment (ERA)	Risk identification	One of the main strengths of this method is that foreseeing environmental impacts can inform the effective deployment of mitigation measures to prevent environmental harm. Next to that, clear guidance is provided to the pharmaceutical industry on the data requirements (environmental fate and effects studies) and risk assessment methodology ([52]). As such, the risks resulting from the patient use of medicines first registered since 2006 are well understood. A legal requirement has been in place since 2005 to conduct ERAs for medicinal products when applying for EMA approval of marketing and line extensions.	Data gaps exist for APIs that were first registered before 2005 (so-called legacy APIs) and, while the conclusions on any existing ERAs are accessible in the EPARs (European Public Assessments reports) on the EMA website [52], there is limited transparency of the environmental fate and effects study data that underpin these ERAs.
Eco-efficiency analysis	Relation between environment and economy	Among its strengths, it is possible to find the focus on the optimisation. Moreover, the methodology allows to identify opportunities for employing resources and energy in the most efficient way. Alongside this, the methodology guarantees an alignment of sustainability and economic goals.	Its specificity represents a limitation. Furthermore, the focus on optimisation of resources may sometimes lead to an oversimplification of the environmental impact without capturing the overall environmental footprint.
Circular Economy Analysis	Circular economy	One of the strengths of this method is represented by its long-term outlook and the resulting suggestions about utilization of resources.	On the other hand, the model has been criticised because some of the results and suggestions have been considered unrealistic and very difficult to apply concretely
Sustainable Pharmacy Practice Assessment	Pharmaceutical supply chain	The approach extends beyond the single product thereby assessing sustainable practices in the entire pharmaceutical supply chain. Next to the environmental impact, the method includes the analysis of some administrative practices, for instance, corporate practices/-governance, management decisions and policies.	Among the negatives, it is possible to cite the subjectivity required in the estimation of some parameters included in the analysis and the lack of agreement concerning social aspects.

Table A.1: Strengths and weaknesses of environmental impact assessment approaches

A.2. The environmental impact of medicine residues

As described in the section 3.1, the term ”end-of-life phase” has been used in this LCA to refer to the disposal of medicine packages. The reason for that is the current limitations to precisely quantifying the environmental impact of medicine residuals on the environment. There are three main routes through which residues of active pharmaceutical ingredients (APIs). In proportional order of their contribution to the total environmental load these are; patient use (excretion of drug residues not broken down by patient metabolism), incorrect disposal of unused medicines (into landfill or down the drain), effluents from manufacture. However, in order to give the reader an idea of how this may be done, a qualitative description will be presented in this section. This reflection appears to be very valuable and in line with institutional agendas. In fact, concerns over potential long-term human and environmental health impacts from environmental pollution have been the input for the Zero pollution ambition under the European Green Deal. Another example is the EU strategic approach to pharmaceuticals in the environment [2], which is focused on identifying ”the pharmaceuticals that pose a risk through their individual presence in the environment so that risk management efforts can be targeted”. Looking ahead, regulatory changes are also expected in the near future, such as the recently proposed incorporation of Extended Producer Responsibility into the EU Urban Wastewater Treatment Directive [34], which could require pharmaceutical manufacturers to mitigate potential environmental impacts of their products through advanced wastewater treatment. As such, incorporating environmental parameters into the R and D and evaluation process may well be aligned with corporate foresight and ongoing and the revision of the European pharmaceutical legislation which refers to a future inclusion of environmental risk assessment outcomes in medicine approval decisions. [84]. This undoubtedly requires knowledge sharing among environmental experts and a general agreement about integrating environmental safety criteria into the framework that currently selects compounds on the basis of efficacy and human safety criteria.
When the impact of pharmaceuticals is discussed, four main environmental hazards need to be taken into consideration [10]:

- **ecotoxicity**: pharmaceuticals are designed to interact with specific molecular targets in human beings, but these targets often have closely related counterparts in other environmental species due to evolutionary conservation. As a result, drugs may have biological mechanisms of action on these other species as well to cause ecotoxicological effects. Correspondingly, off-target effects (observed in humans) might lead to ecotoxicological impacts if the same off-target molecules are conserved. Additionally, ecotoxicological effects may arise through mechanisms that are not related to the intended human pharmacological target or any off-target interactions [41];
- **persistence and degradation in the environment**: environmental persistence is defined as the characteristic of some compounds that do not degrade efficiently and consequently have long residence times in the environment. Specifically, compounds with slow degradation rate (laboratory half-lives of 40 to 180 days), are considered persistent or very persistent according to the guidelines. Another way to take into consideration this characteristic of chemical compounds is through environmental degradation. It can be defined as the process through which compounds become transformation products (TPs) via abiotic or biotic processes in wastewater treatment plants or the natural environment. Despite the fact that in wastewater treatment plants (WWTPs), compounds can be removed through adsorption to sludge, degradation to TPs, or full mineralization, it is often the case that remaining pharmaceutical residues still enter the environment, as figure A.1 shows [10]. It happens via treated effluent or sludge used as fertilizer from where they enter the surface water or soil compartments, respectively, leading to the potential exposure of environmental organisms in water, sediment, soil, and groundwater. Concerning the degradation rate, it depends on environmental conditions such as pH, light intensity, temperature, water and oxygen levels, redox potential, nutrient status, and the metabolic capabilities of microbial communities present. With the aim to obtain better predictions, several features that can influence biodegradation have been identified [8]: structures with oxygen degrade faster, while those with multiple halogens or extensive branching are less susceptible to enzymatic degradation.

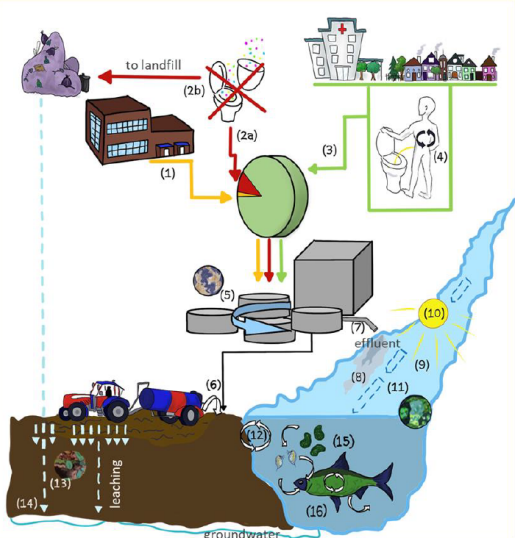


Figure A.1: Approximate proportion of inputs of API residues into wastewater from (1) manufacturing emissions, (2a) incorrect disposal (into wastewater), (3) patient use (hospital and domestic) including (4) (partial) biotransformation by patient metabolism. Inputs due to (2b) incorrect disposal into household waste. WWTP processes; (5) microbial breakdown or elimination and/or subsequent exposure of agricultural soils via (6) sewage sludge application and irrigation with WWTP effluent. Release of (7) WWTP effluent into surface water. Environmental distribution, dissipation and (a)biotic degradation processes include; (8) dilution by receiving waters/transport with flowing waters (surface water mobility), (9) hydrolysis, (10) photolysis, (11) microbial degradation in water-sediment systems, (12) partitioning (adsorption/desorption) in aquatic sediments, (13) soil microbial degradation, (14) sorption to soil and/or transport through the soil profile with potential for leaching to groundwater (and resulting groundwater mobility). Impacts on biota via (13) exposure of soil organisms, (15) exposure of freshwater (algae, invertebrates, fish) and sediment communities, with (16) potential bioaccumulation, depending on pharmaco-kinetics in aquatic organisms.

- **mobility**: the environmental mobility of a compound defines its potential distribution within the environment beyond the point of release and indicates in what compartment(s) of the environment a compound may be predominantly detected. In combination with persistence, a compound's mobility determines the concentrations it might reach in the environment. In combination with persistence, mobility affects how far a compound can spread and its concentration at various distances from the source. A key factor in determining a compound's mobility is represented by adsorption to environmental solids. In fact, in WWTPs, the extent of adsorption influences a compound's partitioning from wastewater into sludge, thereby reducing its concentration in surface water. Consequently, if sludge is used as fertilizer, this also affects soil exposure. Regarding the soil, adsorption determines whether a compound is retained or leaches into groundwater, impacting soil-dwelling organisms, and potential degradation by soil microbes or soil accumulation. On the other hand, in aquatic environments, adsorption onto suspended particles can transport residues over long distances, determining their geographic distribution (e.g. oceans). The type of compounds that do not significantly adsorb to environmental solids, remain in the 'free water phase'. It means that they stay in wastewater instead of sludge, surface water instead of sediments, and soil pore water potentially leaching into groundwater A.1. Highly mobile compounds pose a significant concern as they can move between environmental compartments and into drinking water sources.
- **bioaccumulation**: this term refers to the process by which a compound is transferred from the environment to an organism where it accumulates [32]. In the field of environmental risk assessment, bioaccumulation is quantified through several factors: the bioconcentration factor (BCF), which measures the ratio of compound concentration in an organism to that in water when exposed only to water; the bioaccumulation factor (BAF), which includes exposure through ingestion of food, sediment, or soil; and the biomagnification factor (BMF), which measures the concentration ratio between predator and prey organisms. Depending on their habitat and their diet, organisms absorb compounds from water, food, sediment, and soil. Due to their physiological similarities to mammals and conservation of human drug targets [41], fish is the primary model (shown in figure A.2 [10]) used in ecotoxicological bioaccumulation studies. Compounds that bioaccumulate significantly in fish or other aquatic organisms pose risks of ecotoxicological and secondary poisoning effects to predators and humans. The bioaccumulation potential of active pharmaceutical ingredients (APIs) is linked to three main factors: their lipophilicity (absorption and distribution), affinity for transport proteins, and elimination (metabolism and excretion).

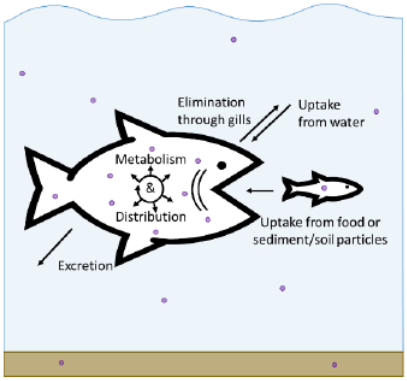


Figure A.2: bioaccumulation in a fish

The compound characteristics of pharmaceuticals that determine their environmental impact are interrelated with each other and with the characteristics that determine the required drug profile, as figure A.3 [10] shows.

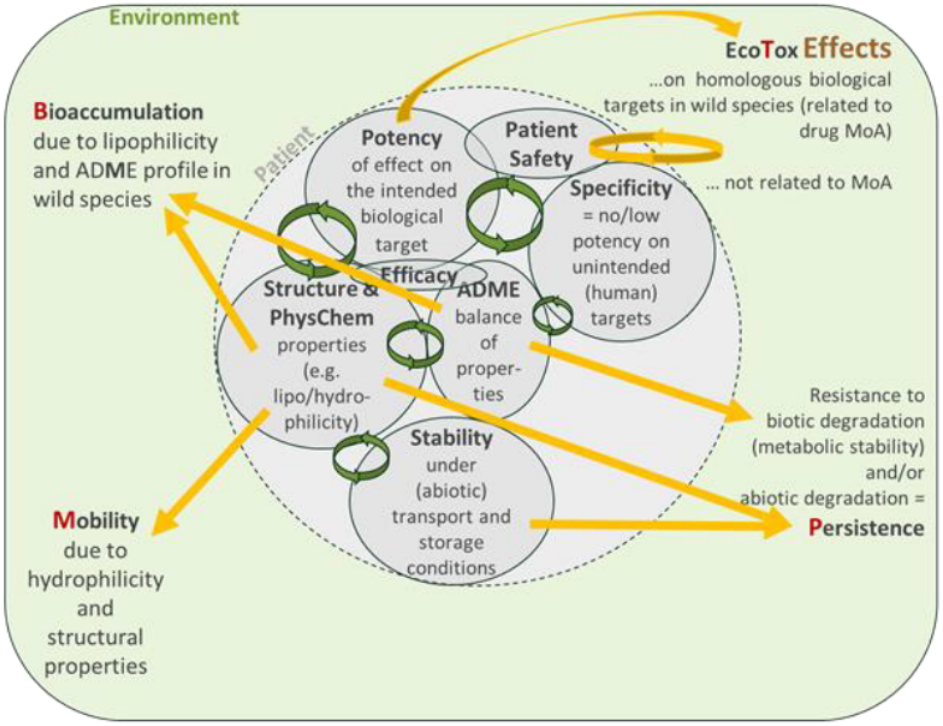


Figure A.3: Schematic illustration of the inter-relatedness of compound properties determined in drug design and development - and their (unintended) environmental characteristics.

For instance, persistent compounds that are also bioaccumulative and toxic (so-called ”PBT compound”) are of heightened environmental concern because they can reach ecological species before degrading and becoming bioavailable, thereby causing adverse effects. Next to them, persistent, mobile, and toxic compounds (so-called ”PMT compound”) are also of concern due to their potential for widespread distribution and groundwater contamination, including drinking water sources. Consequently, this interrelatedness between the compound properties pursued in drug design and development and their consequent environmental characteristics (and risk potential) is very interesting to be looked into and poses a challenge in balancing these properties.
In light of all these considerations, determining how medicine residuals interact with the environment appears to be a complex task but essential to move towards a more sustainable biopharmaceutical industry.

A.3. Interviews

A.3.1. Interview with Dutch nephrologist, involved in sustainability initiatives at the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA)

The nephrologist from ERA-EDTA was asked the following questions:

1. Do you think assessing environmental impact is something valuable in the evaluation of a new healthcare technology or treatment?
2. Do you think the way I evaluated the environmental impact (i.e. doing an LCA of the current care pathway with and without the implementation of the intervention) is valuable or do you think that there is another way that could be better?
3. Do the results, in any way, reflect your experience as a nephrologist?
4. As a nephrologist, would you like to be informed about the environmental impacts of medicines you prescribe or use? In other words, would this piece of information be valuable for a doctor?
5. What would be an incentive for companies to share data concerning sustainability of their products with other institutions/universities/competitors?
6. Do you think that the different stakeholders (like healthcare professionals, policymakers, and companies) should kind of collaborate?
7. Is there a way, in your vision, to implement sustainability within university curricula? If yes, should it be done by implementing some theory or quantitative analyses?
8. Are there also environmental benefits of hemofiltration compared to hemodialysis?
9. The three main domains you usually refer to in your interviews are Care, Research, and Education for Sustainability. Can you tell me one main goal for each of them?
10. Which ethical/personal motivations sparkle your interest in sustainability in nephrology? Has this interest somehow shaped you as a professional? In other words, has your acquired knowledge in sustainability shaped your practice as a doctor?
11. How should biopharmaceutical companies become more sustainable at the organizational level?

An anonymized summary of the answers is provided as follows:

1. Yes, it is a considerable topic.
2. It can be undoubtedly a powerful instrument by it is also quite new and it is important to define and understand what is meant by ”life cycle analysis” of medications and which parameters are used.
3. The results make sense, they do not surprise me.
4. Yes, but the first step is creating awareness. After that, we can think about how to modify this environmental impact by talking to prescribers and physicians (organizations).
5. I can see that there may be many hesitations but they should do that because big companies have social responsibility toward the population.
6. Yes, they should. Responsibilities of various stakeholders should be designed and defined throughout the different parts of the long chain of medication use (fabrication, transport, etc.)
7. It is an ongoing process and steps have been made in the last two years in North Europe. The idea that it is necessary to implement sustainability in curricula is there, but there are still some barriers (e.g. curricula already full). However, how to add sustainability to the curricula, the modality, is not clear yet.
8. That was not the focus of the study, we did not collect real measures about the environmental impact of hemofiltration.
9. The first step in Care is indeed creating awareness. This goal goes in parallel with quantifying impact, so producing numbers in Research. After that, it will be possible to try to identify ways to modify the current practice and make it more sustainable.
10. Everything started 6 years ago with a Lancet publication which made me realize that sustainability in nephrology was a big subject. Then I started working on that for the ERA-EDTA and a Dutch governmental committee and the interest started spreading more and more among nephrologists in the Netherlands and in Europe. Healthcare professionals need to have their role in the big sustainable transition in Europe.
11. It requires creative thinking, innovations, leadership, and new developments. Smart people have to think out of the box because sustainability can distinguish your company from competitors. The essential part at the organisational level is a long-term view because the benefits of sustainable initiatives can only be seen in the long run, not focusing on ”short-termism”. Bottom line: ”Think big but act small”.

A.3.2. Interview with the medical expert from AstraZeneca

The medical expert from AstraZeneca was asked the following questions:

1. Which modules should be included in the care pathway for CKD, specifically for the Netherlands?
2. Which submodules should be included in each module?
3. Which care activities should be included in each stage?
4. Where I can find data about the prevalence of the disease in the Netherlands?
5. Where I can find data concerning dialysis?
6. Can you explain to me how Forxiga operates for CKD?
7. Do these results make sense to you?
8. Do you think that LCA is important in HTA?
9. Which one do you envision as a solution?

An anonymized summary of the answers is provided as follows:

1. The main modules that should be taken into consideration are: Primary care consultation, Secondary care consultation, Standard of Care (medicines), Intensive Care Unit, Hospitalisation, Palliative care, Kidney transplantation, Dialysis and Screenings.
2. For primary and secondary care, transportation and visits should be considered. For the Standard of Care, the most comprehensive life cycle analysis of medicines should be done. For intensive care unit, heating/cooling/lighting of the room, sanitation, medications, waste, transportation, and materials should be considered. For hospitalisation lighting/-cooling/heating of the room, waste, transportation, materials and sanitation should be considered. For palliative care: psychologist consultations and palliative medicines should be considered. For kidney transplantation, a difference should be made between living and deceased donor and compatibility screenings, surgical procedure, transplantation-related medicines and transportation should be considered. For dialysis, the four different types of dialysis should be taken into consideration and arteriovenous fistula, patient training, dialysis sessions and transportation should be considered. For screenings, blood and urine tests should be considered.
3. I spoke with a nephrologist and these are plausible numbers for activities per stage (see table 3.6).
4. The paper ”Prevalence of chronic kidney disease in the Netherlands and its cardiovascular and renal complications” from Vervloet et all, 2023 is the most recent and reliable [106].
5. You can find data concerning dialysis on this website https://www.nefrovisie.nl/
6. The inhibition of SGLT2 reduces the reabsorption of glucose from the glomerular filtrate in the proximal renal tubules with a concomitant decrease in sodium reabsorption in the blood, leading to urinary glucose excretion and osmotic diuresis.
7. Yes, these results make sense to me. They seem logical considering the modules and the impact taken into consideration.
8. Yes, I think that evaluating the environmental impact of care pathways and new healthcare interventions is crucial in making the healthcare sector and biopharmaceutical companies more sustainable.
9. I don’t really have an answer, but for sure the first step is creating awareness and this can only be done by quantifying the environmental impact of care activities.

A.4. Further research: assessing the workforce impact of healthcare interventions

Analysing the existing literature on the topic, several frameworks that can be used to assess the impact of new healthcare interventions on the workforce are found. Some relevant ones are:

- Kirkpatrick's Four-Level Training Evaluation Model: This model evaluates interventions by measuring four levels: Reaction (how the workforce feels about the intervention in terms of satisfaction and engagement), Learning (the increase in knowledge and abilities resulting from the intervention), Behavior (changes in the workforce's practices after the introduction of the intervention), and Results (the overall impact on productivity, efficiency, and other outcomes);
- Donabedian Model: the model is focused on healthcare quality and assesses three components: Structure (the setup and resources, e.g. facilities, equipment, and staffing), Process (in terms of methods and procedures used in delivering care), and Outcomes (the effects on health outcomes and workforce metrics, e.g. job satisfaction and productivity);
- Balanced Scorecard: this tool, typically used in business, assesses interventions through four perspectives: Financial (return on investment, cost savings and financial performance), Customer (patient and staff satisfaction and retention), Internal Process (efficiency and effectiveness), and Learning and Growth (in terms of staff development, learning opportunities, and innovation);
- Institute for Healthcare Improvement (IHI) "Model for Improvement": this model uses rapid-cycle testing to improve healthcare processes. The first step is defining an Aim, specifically, what the intervention seeks to accomplish. Next, other elements are defined: Measures (how success will be quantified), Changes (strategies for achieving improvement), and the Plan-Do-Study-Act (PDSA) cycle to test these changes in real settings;
- RE-AIM Framework: it evaluates the impact of interventions through five dimensions: Reach (the extent of the intervention's coverage among the target population), Effectiveness (the impact on key outcomes), Adoption (the uptake of the intervention by staff), Implementation (consistency of the new intervention delivery), and Maintenance (the long-term sustainability of the effects);
- Health Workforce Impact Assessment (HWIA) Framework: it was designed specifically to assess the impact of health policies and interventions on the workforce and it involves understanding the Policy Context, describing the Intervention Characteristics, mapping out Impact Pathways (describing how the intervention affects the workforce), and conducting an Impact Analysis (considering direct and indirect effects on workforce metrics);
- Lean Six Sigma: this methodology, very common in the agile approach, is aimed at performance enhancement by systematically removing waste and reducing variation. It follows the Define-Measure-Analyze-Improve-Control (DMAIC) process, which involves identifying the problem, quantifying the current performance, analyzing causes, implementing solutions, and monitoring the effects.

Among them, there are two that are particularly interesting in the Biopharmaceutical field.

A.4.1. The model for improvement

The Model for Improvement has been developed by Associates in Process Improvement and it is a simple and powerful framework for accelerating improvement, compatible with many interventions companies are implementing currently. The Model for Improvement is divided into two parts [53]:

- a group of three questions;
- the Plan-Do-Study-Act (PDSA) cycle, used to test and adapt changes to achieve the desired improvement.

The model is usually implemented by starting with the question "What are we trying to accomplish?" which facilitates the aim setting. However, answering the three fundamental questions is an iterative process through which the team moves back and forth, informing their answer with PDSA cycle results. This model has been successfully implemented in many industries, including thousands of healthcare organizations in several countries. If an equity lens is taken into consideration, this model can also be used to ensure that improvements are effective in closing equity gaps rather than maintaining them. A schematic representation is presented in figure A.4 [53].

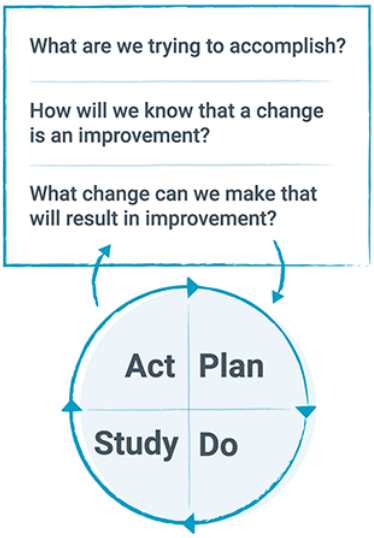


Figure A.4: Plan-Do-Study-Act cycle

A.4.2. Health workforce impact assessment from WHO

Another interesting framework to model the impact of new interventions on the healthcare workforce has been developed by the World Health Organization (WHO). This model provides a structured framework to analyze factors such as workforce availability, capacity, and the total well-being of healthcare personnel. It takes into consideration various stressors, for instance, workload, resource allocation, and psychosocial factors in order to guarantee a comprehensive understanding of how health policies affect the essential workforce. This framework is essential for policymakers to make informed decisions that support and sustain the healthcare workforce in an effective way. The model is summarised in figure 5.3 [45]

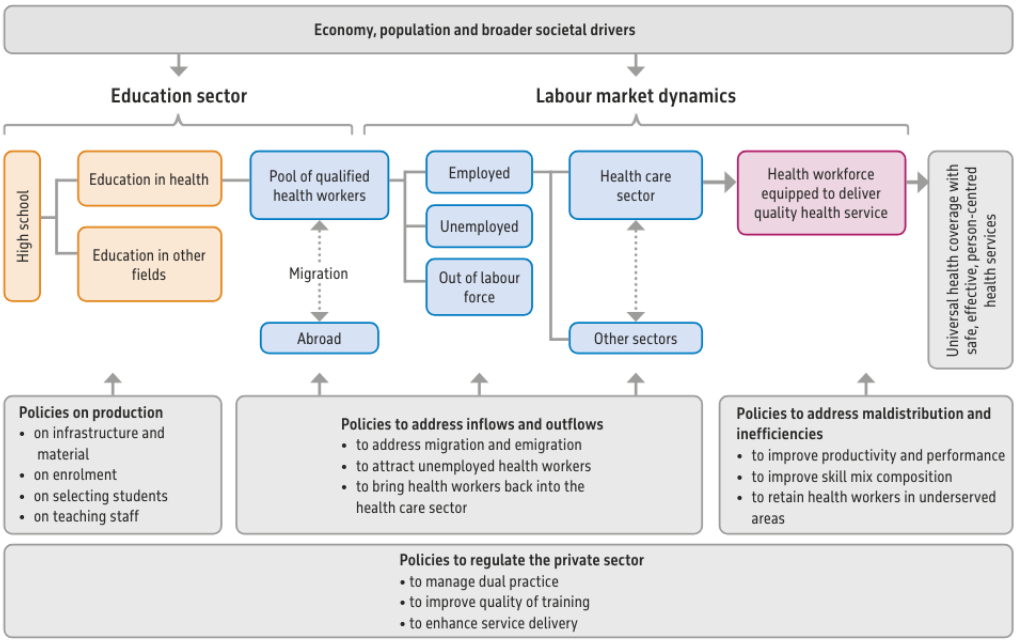


Figure A.5: Health workforce impact assessment framework from WHO

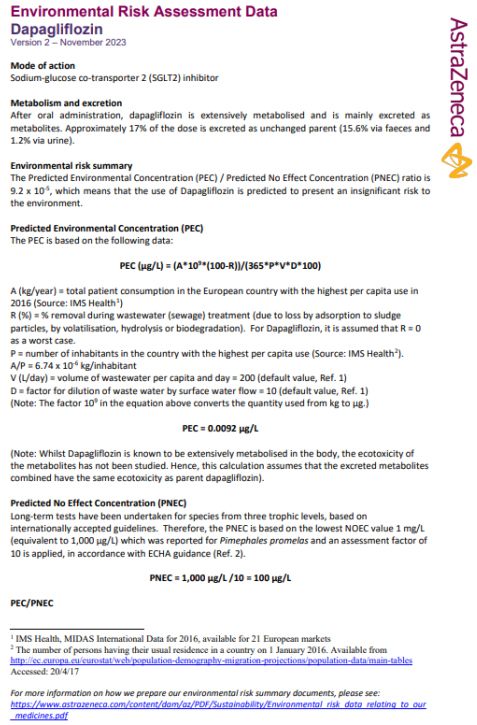
The choice of the methodology is closely related to one of the metrics. There are several relevant metrics used in the healthcare workforce assessment, among them:

- Operational Metrics (e.g. average length of stay, patient wait times, bed occupancy rates, and appointment no-show rates);
- Clinical Outcomes (e.g. patient morbidity and mortality rates, together with complication rates, infection rates, or readmission rates)
- Workforce specific Metrics (e.g. Full-Time Equivalents (FTEs) [1], absenteeism rates, overtime hours, staff turnover rates, employee engagement and job satisfaction);
- Patient Experience (e.g. Patient satisfaction scores, feedback from patient surveys, or patient retention rates);
- Financial Metrics (e.g. Cost per patient, total healthcare expenditure, return on investment (ROI));
- Quality and Safety Metrics (e.g. Adherence to clinical guidelines, adverse event rates, compliance with safety protocols and error rates);
- Productivity Metrics (e.g.Number of patients seen per hour, utilization rates of medical equipment and facilities, and procedures performed per day).

For future research a mixed approach between the two (with a focus on the context and particularly on the interventions) needs to be undertaken with an attentive choice of the metrics to consider.

[1] An FTE is the unit of measurement that represents the number of hours a full-time employee works for an organization. The concept has been introduced to conduct analyses with a standard version of the working hours which allows to evaluate workload and labor costs by comparing them across different industries. This unit of measurement is often used to give indications concerning the workload capacity.

A.5. Dapagliflozin - Environmental Risk Assessment Data



Environmental Risk Assessment Data
Dapagliflozin
Version 2 – November 2023

AstraZeneca

Mode of action
Sodium-glucose co-transporter 2 (SGLT2) inhibitor

Metabolism and excretion
After oral administration, dapagliflozin is extensively metabolised and is mainly excreted as metabolites. Approximately 17% of the dose is excreted as unchanged parent (15.6% via faeces and 1.2% via urine).

Environmental risk summary
The Predicted Environmental Concentration (PEC) / Predicted No Effect Concentration (PNEC) ratio is 9.2×10^{-5}, which means that the use of Dapagliflozin is predicted to present an insignificant risk to the environment.

Predicted Environmental Concentration (PEC)
The PEC is based on the following data:

PEC (µg/L) = (A*10^3*(100-R))/(365*P*V*D*100)

A (kg/year) = total patient consumption in the European country with the highest per capita use in 2016 (Source: IMS Health[1])
R (%) = % removal during wastewater (sewage) treatment (due to loss by adsorption to sludge particles, by volatilisation, hydrolysis or biodegradation). For Dapagliflozin, it is assumed that R = 0 as a worst case.
P = number of inhabitants in the country with the highest per capita use (Source: IMS Health[2]).
A/P = 6.74×10^{-6} kg/inhabitant
V (L/day) = volume of wastewater per capita and day = 200 (default value, Ref. 1)
D = factor for dilution of waste water by surface water flow = 10 (default value, Ref. 1)
(Note: The factor 10^3 in the equation above converts the quantity used from kg to µg.)

PEC = 0.0092 µg/L

(Note: Whilst Dapagliflozin is known to be extensively metabolised in the body, the ecotoxicity of the metabolites has not been studied. Hence, this calculation assumes that the excreted metabolites combined have the same ecotoxicity as parent dapagliflozin).

Predicted No Effect Concentration (PNEC)
Long-term tests have been undertaken for species from three trophic levels, based on internationally accepted guidelines. Therefore, the PNEC is based on the lowest NOEC value 1 mg/L (equivalent to 1,000 µg/L) which was reported for *Pimephales promelas* and an assessment factor of 10 is applied, in accordance with ECHA guidance (Ref. 2).

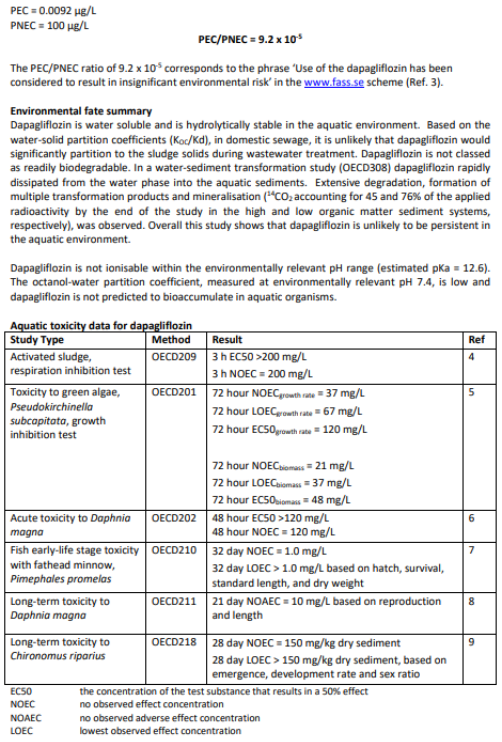
PNEC = 1,000 µg/L / 10 = 100 µg/L

PEC/PNEC

[1] IMS Health, MIDAS International Data for 2016, available for 21 European markets
[2] The number of persons having their usual residence in a country on 1 January 2016. Available from http://ec.europa.eu/eurostat/web/population-demography-migration-projections/population-data/main-tables Accessed: 20/4/17

For more information on how we prepare our environmental risk summary documents, please see: https://www.astrazeneca.com/content/dam/az/PDF/Sustainability/Environmental_risk_data_relating_to_our_medicines.pdf

Figure A.6: Dapagliflozin - Environmental Risk Assessment Data, page 1



PEC = 0.0092 µg/L
PNEC = 100 µg/L

PEC/PNEC = 9.2×10^{-5}

The PEC/PNEC ratio of 9.2×10^{-5} corresponds to the phrase 'Use of the dapagliflozin has been considered to result in insignificant environmental risk' in the www.fass.se scheme (Ref. 3).

Environmental fate summary
Dapagliflozin is water soluble and is hydrolytically stable in the aquatic environment. Based on the water-solid partition coefficients (K_{OC}/Kd), in domestic sewage, it is unlikely that dapagliflozin would significantly partition to the sludge solids during wastewater treatment. Dapagliflozin is not classed as readily biodegradable. In a water-sediment transformation study (OECD308) dapagliflozin rapidly dissipated from the water phase into the aquatic sediments. Extensive degradation, formation of multiple transformation products and mineralisation ($^{14}CO_2$ accounting for 45 and 76% of the applied radioactivity by the end of the study in the high and low organic matter sediment systems, respectively), was observed. Overall this study shows that dapagliflozin is unlikely to be persistent in the aquatic environment.

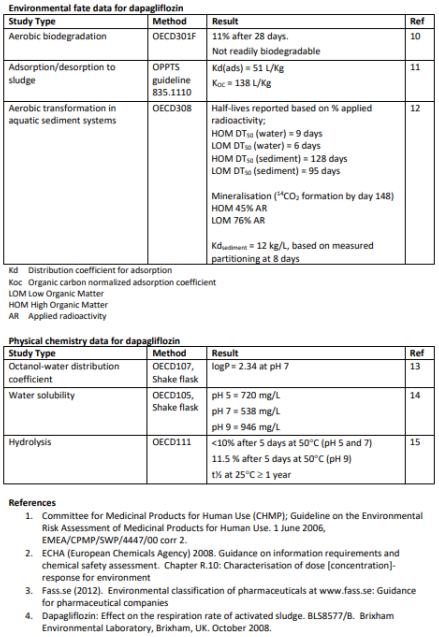
Dapagliflozin is not ionisable within the environmentally relevant pH range (estimated pKa = 12.6). The octanol-water partition coefficient, measured at environmentally relevant pH 7.4, is low and dapagliflozin is not predicted to bioaccumulate in aquatic organisms.

Aquatic toxicity data for dapagliflozin

Study Type	Method	Result	Ref
Activated sludge, respiration inhibition test	OECD209	3 h EC50 >200 mg/L 3 h NOEC = 200 mg/L	4
Toxicity to green algae, *Pseudokirchinella subcapitata*, growth inhibition test	OECD201	72 hour $NOEC_{growth\ rate}$ = 37 mg/L 72 hour $LOEC_{growth\ rate}$ = 67 mg/L 72 hour $EC50_{growth\ rate}$ = 120 mg/L 72 hour $NOEC_{biomass}$ = 21 mg/L 72 hour $LOEC_{biomass}$ = 37 mg/L 72 hour $EC50_{biomass}$ = 48 mg/L	5
Acute toxicity to *Daphnia magna*	OECD202	48 hour EC50 >120 mg/L 48 hour NOEC = 120 mg/L	6
Fish early-life stage toxicity with fathead minnow, *Pimephales promelas*	OECD210	32 day NOEC = 1.0 mg/L 32 day LOEC > 1.0 mg/L based on hatch, survival, standard length, and dry weight	7
Long-term toxicity to *Daphnia magna*	OECD211	21 day NOAEC = 10 mg/L based on reproduction and length	8
Long-term toxicity to *Chironomus riparius*	OECD218	28 day NOEC = 150 mg/kg dry sediment 28 day LOEC > 150 mg/kg dry sediment, based on emergence, development rate and sex ratio	9

EC50 the concentration of the test substance that results in a 50% effect
NOEC no observed effect concentration
NOAEC no observed adverse effect concentration
LOEC lowest observed effect concentration

Figure A.7: Dapagliflozin - Environmental Risk Assessment Data, page 2



Environmental fate data for dapagliflozin

Study Type	Method	Result	Ref
Aerobic biodegradation	OECD301F	11% after 28 days. Not readily biodegradable	10
Adsorption/desorption to sludge	OPPTS guideline 835.1110	Kd(ads) = 51 L/Kg K_{OC} = 138 L/Kg	11
Aerobic transformation in aquatic sediment systems	OECD308	Half-lives reported based on % applied radioactivity; HOM DT_{50} (water) = 9 days LOM DT_{50} (water) = 6 days HOM DT_{50} (sediment) = 128 days LOM DT_{50} (sediment) = 95 days Mineralisation ($^{14}CO_2$ formation by day 148) HOM 45% AR LOM 76% AR $Kd_{sediment}$ = 12 kg/L, based on measured partitioning at 8 days	12

Kd Distribution coefficient for adsorption
Koc Organic carbon normalized adsorption coefficient
LOM Low Organic Matter
HOM High Organic Matter
AR Applied radioactivity

Physical chemistry data for dapagliflozin

Study Type	Method	Result	Ref
Octanol-water distribution coefficient	OECD107, Shake flask	logP = 2.34 at pH 7	13
Water solubility	OECD105, Shake flask	pH 5 = 720 mg/L pH 7 = 538 mg/L pH 9 = 946 mg/L	14
Hydrolysis	OECD111	<10% after 5 days at 50°C (pH 5 and 7) 11.5 % after 5 days at 50°C (pH 9) t½ at 25°C ≥ 1 year	15

References

1. Committee for Medicinal Products for Human Use (CHMP); Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use. 1 June 2006, EMEA/CPMP/SWP/4447/00 corr 2.
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Figure A.8: Dapagliflozin - Environmental Risk Assessment Data, page 3

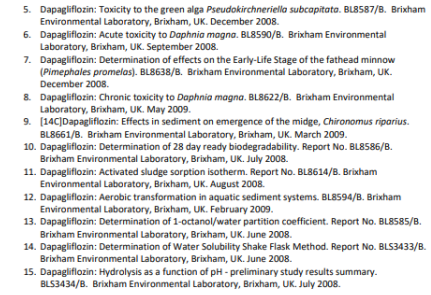

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Figure A.9: Dapagliflozin - Environmental Risk Assessment Data, page 4

Table 3. Summary of main study results

Substance (INN/Invented Name): dapagliflozin					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	2.34 at pH 7			Potential PBT: NO
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.05 (default) 0.00915 (refined)	µg/L			> 0.01 threshold YES Refined PEC accepted for Phase II
Other concerns (e.g. chemical class)					No
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OPPTS 835.1110	K_{oc} =138 K_d = 51			
Ready Biodegradability Test	OECD 301	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 13.5 d (12°C) $DT_{50, sediment}$ = 240 d (12°C) Mineralisation: 37.5 and 67.5% on d 99 40.7 and 75.7% on d 148 Bound residues: 44 % on d 99 49.3 % on d 148			Dapagliflozin is persistent in sediments.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/	OECD 201	NOEC	37,000	µg/L	***Pseudokirchnella subcapitata***
Daphnia sp. Reproduction Test	OECD 211	NOEC	10,000	µg/L	
Fish, Early Life Stage Toxicity	OECD 210	NOEC	1,000	µg/L	***Pimephales promelas***
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	107,600	µg/L	
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	150	mg/kg	***Chironomus sp.***

Considering the above data, dapagliflozin is not expected to pose a risk to the environment.

Figure A.10: Dapagliflozin - main results 1

2.3.5. Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) for dapagliflozin was provided in accordance with the CHMP guideline EMEA/CHMP/SWP/4447/00. A Phase I environmental risk assessment was performed to evaluate potential environmental risks of dapagliflozin. The log K_{ow} was determined according to study OECD 107 with a value of 2.34 at ph /7. Based on the log K_{ow} value being below 4.5, dapagliflozin is not expected to be a bio-accumulative substance. The refined $PEC_{surfacewater}$ of 9.15 ng/L did not exceed the action limit of 0.01 µg/L. However the use of market forecasts for Fpen refinement is not allowed in Phase I of the ERA. The applicant performed nevertheless a phase II – Tier A assessment. Based on the calculated PEC/PNEC ratios, it is predicted that dapagliflozin will not significantly partition into the solid phase waste water treatment in domestic sewage, which means that an ERA in the terrestrial compartment is needed. Based on the results of the water/sediment study (OECD study 308), a phase II - Tier B assessment was triggered for dapagliflozin.

Dapagliflozin – PEC/PNEC assessments			
	PEC (µg/L)	**PNEC (µg/L)**	**PEC/PNEC**
Microorganisms	0.00915	20000	4.58×10^{-6}
Surface water	0.00915	100	9.15×10^{-5}
Groundwater	0.00229	1000	2.29×10^{-6}

Based on the $PEC_{sediment}/PNEC_{sediment}$, dapagliflozin is considered unlikely to present a risk to sediment dwelling species and therefore no further testing is required. Dapagliflozin is not a PBT substance.

Figure A.11: Dapagliflozin - main results 2

A.6. Different time horizon results

Table A.2: average savings in Kg of CO2 per patient over 1 year

	Dapagliflozin + Soc	Placebo + SoC	Incremental
Life years	0,990	0,986	0,004
QALYs	0,771	0,768	0,003
Environmental costs	524,937	519,676	5,262

Table A.3: breakdown savings in Kg of CO2 per patient over 1 year

	Dapagliflozin + Soc	Placebo + SoC	Incremental
Management costs			
Drug acquisition costs	244,593	231,582	13,011
Disease management costs (exc. RRT)	227,936	227,344	0,592
Clinical event costs			
Dialysis	34,646	42,905	-8,259
Transplant	16,744	16,454	0,290
Hospitalisation for HF	0,086	0,156	-0,071
AKI	0,933	1,234	-0,301
Adverse events	0,000	0,000	0,000
Total cost	524,937	519,676	5,262

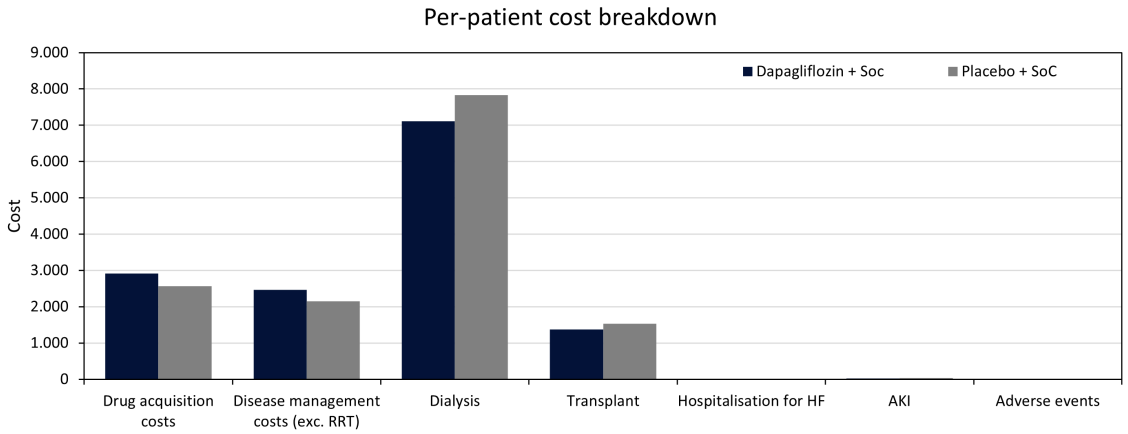

Figure A.12: breakdown savings in kg of CO2e per patient over 1 year

Table A.5: breakdown savings in Kg of CO2 per patient over 5 years

	Dapagliflozin + Soc	Placebo + SoC	Incremental
Management costs			
Drug acquisition costs	1139,517	1062,760	76,758
Disease management costs (exc. RRT)	1051,141	1014,093	37,048
Clinical event costs			
Dialysis	894,157	1139,667	-245,510
Transplant	141,986	157,552	-15,566
Hospitalisation for HF	0,531	0,860	-0,329
AKI	6,911	8,881	-1,970
Adverse events	0,000	0,000	0,000
Total cost	3234,244	3383,813	-149,569

Table A.4: average savings in Kg of CO2 per patient over 5 years

	Dapagliflozin + Soc	Placebo + SoC	Incremental
Life years	4,644	4,525	0,119
QALYs	3,568	3,472	0,096
Environmental costs	3234,244	3383,813	-149,569

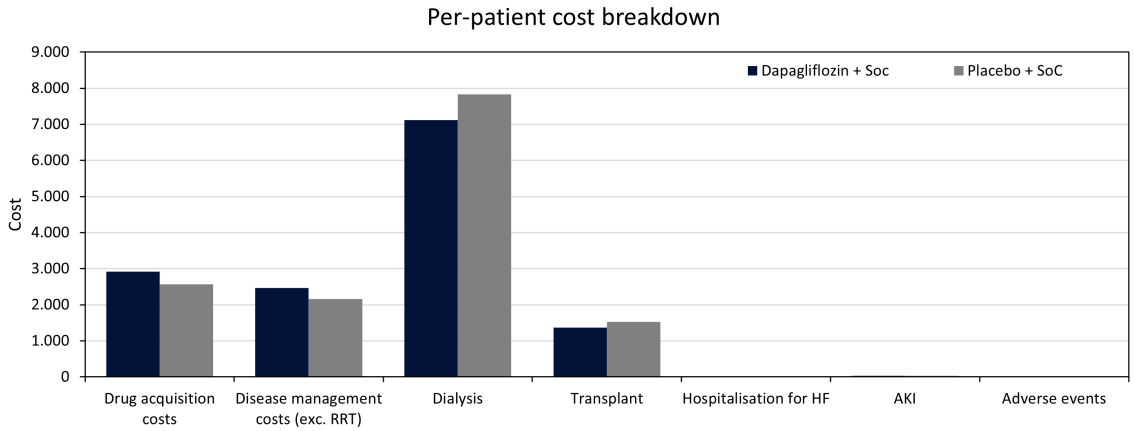

Figure A.13: breakdown savings in kg of CO2e per patient over 5 year

Table A.6: average savings in Kg of CO2 per patient over lifetime

	Dapagliflozin + Soc	Placebo + SoC	Incremental
Life years	12,028	10,905	1,124
QALYs	8,916	8,075	0,841
Environmental costs	13895,134	14111,229	-216,095

Table A.7: breakdown savings in Kg of CO2 per patient over lifetime

	Dapagliflozin + Soc	Placebo + SoC	Incremental
Management costs			
Drug acquisition costs	2916,098	2561,084	355,014
Disease management costs (exc. RRT)	2463,476	2154,868	308,608
Clinical event costs			
Dialysis	7112,940	7833,119	-720,178
Transplant	1371,362	1527,244	-155,882
Hospitalisation for HF	1,802	2,277	-0,475
AKI	29,455	32,637	-3,182
Adverse events	0,000	0,000	0,000
Total cost	13895,134	14111,229	-216,095

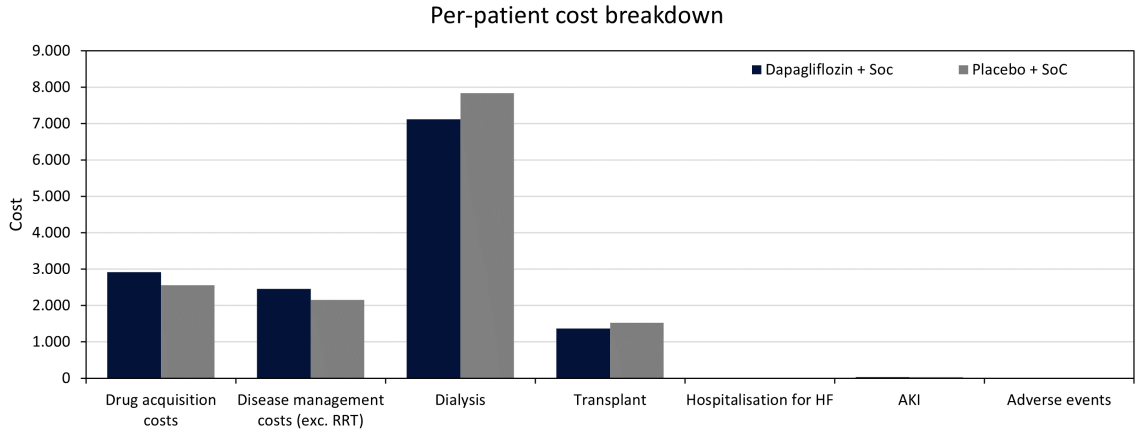

Figure A.14: breakdown savings in kg of CO2e per patient over lifetime