Experts in Product Stewardship

Life Cycle Assessment of Patient Information Leaflets

A comparison of paper PILs to the digital counterpart (ePI)

Full LCA Report

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Executive Summary

Takeda, a global pharmaceutical company operating in Europe, has commissioned Long Trail Sustainability (LTS) to conduct an attributional, comparative life cycle assessment (LCA) on the patient information leaflet (PIL), to understand the difference in environmental impacts between the average European market paper PIL and the digital version, an electronic patient information (ePI) document viewed on a smartphone. The intended application and audience for the comparative study is for European Federation of Pharmaceutical Industries and Associations (EFPIA) members, the pharmaceutical companies present on the European market, that wish to understand the environmental impacts of transitioning to ePI and communicate the results externally. The functional unit, which enables comparison of two different systems, for this study is: *One patient information leaflet (PIL), provided as either a paper PIL or online as ePI, to the 2020 European market.*

Takeda and four other pharmaceutical companies (GSK, Merck, Novartis, and Sanofi) gathered primary data on the weight of the paper PIL, PIL printing facilities, packaging, the file size of the ePI, and the total sales of solid-form drugs in Europe in 2020. Secondary data was used for processes outside of their operations and where primary data was not available (e.g. raw material extraction, processing of material inputs, transportation, disposal).

Secondary data and literature values were used for energy and materials related to printing paper and the QR code for the ePI, the energy for data transfer of the ePI, the smartphone device and electricity consumption, the internet access equipment, and the end of life of the smartphone and internet equipment.

Based on the results and study assumptions, methods and data, the majority of the cradle-to-grave environmental impacts of the paper PIL come from the paper (Figure 1), whereas the majority of the impacts of the ePI come from the smartphone device (Figure 2).

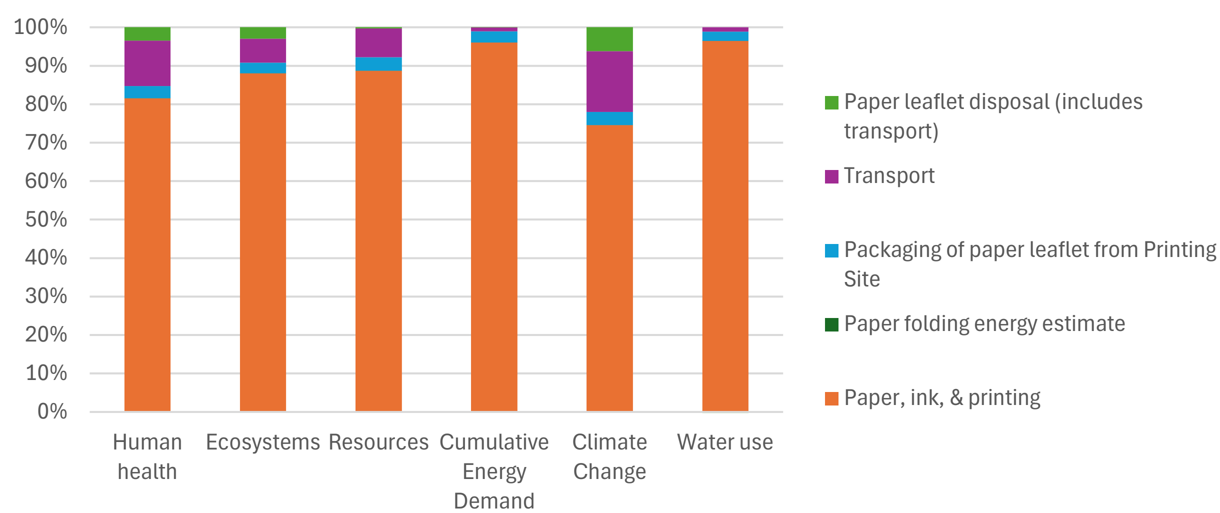

Figure 1: Contribution analysis for the lifecycle of one paper PIL, using the LTS method.

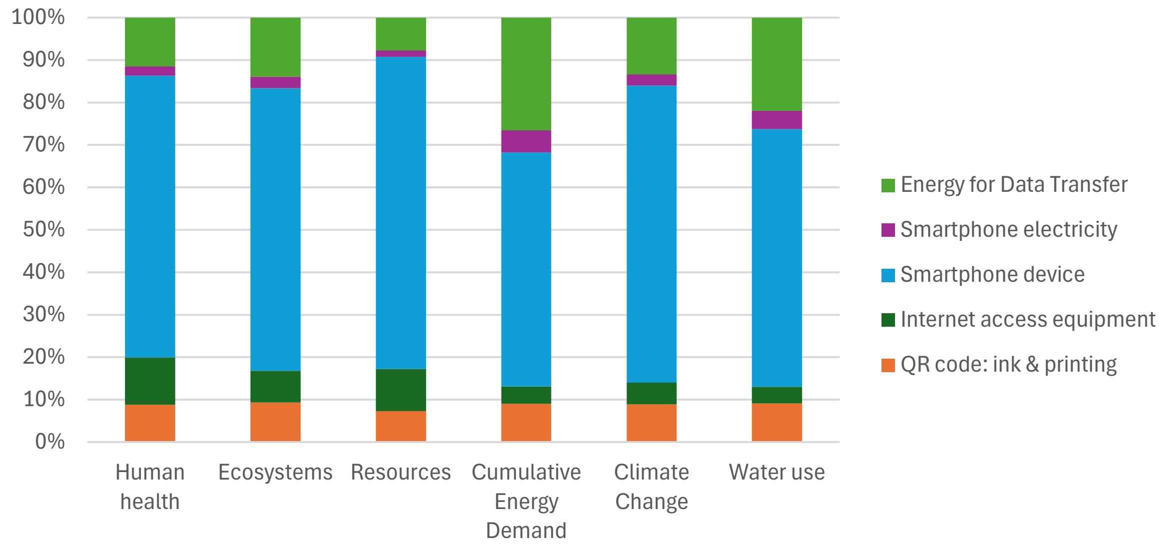

Figure 2: Contribution analysis for the lifecycle of one ePI, using the LTS method.

Compared to the paper PIL, the ePI has 89% - 98% fewer environmental impacts in all impact categories (Figure 3). Uncertainty analysis was performed to determine how data quality affects the reliability and robustness of the results. The comparative results are considered to have high certainty and to be statistically significant[1] in all impact categories, except the human health and water use categories.

[1] When paper PIL or ePI was shown to have greater impacts in 95% or more of the uncertainty analysis simulations, the comparative results are considered to be certain and statistically significant.

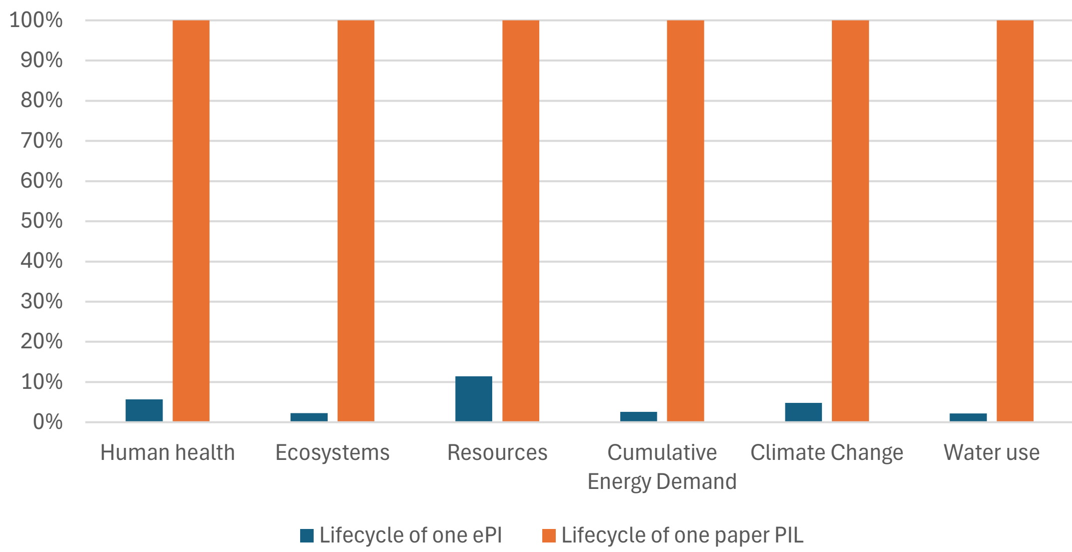

Figure 3: Comparative analysis of one paper PIL to one ePI, cradle-to-grave, using the LTS method.

The primary recommendation from this study is for pharmaceutical companies to switch from using paper PILs to ePI to reduce environmental impacts significantly. If the pharmaceutical companies continue to use some paper PILs, the size of the PIL should be reduced to reduce the weight of paper needed. Reducing the number of words in the PIL and re-structuring the content to make it easier for the patient to read would reduce the paper needed in a paper PIL, as well as reduce the reading time needed for an ePI. Both improvements would reduce the PIL environmental impacts. Regulatory requirements for the PIL would still need to be followed if it were to be redesigned for each medication. Additionally, maximizing the recycled content in the paper PIL would reduce impacts in most impact categories, as shown in a sensitivity analysis.

In future studies, the accuracy and certainty of the results could be improved with more primary data collection for both paper PILs and ePI. The study would benefit from behavioral data on the likelihood of a patient to: scan the QR code to read the ePI, not read it at all, or ask the pharmacy to print the paper PIL.

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1 Definitions / Terminology

For purposes of clarity, a brief definition of terminology used throughout the report is provided below.

Characterization: Assessment of environmental impacts associated with raw material inputs and emissions using science-based conversion factors (e.g., modeling the potential impact of carbon dioxide and methane on global warming (U.S. EPA, 2006)).

Critical review: A process intended to ensure consistency between a life cycle assessment and the principles and requirements of the International Standards on life cycle assessment (ISO 14040, 2006a).

Impact category: A class representing environmental issues of concern to which life cycle inventory analysis results may be assigned (ISO 14040, 2006a).

Impact category indicator: Quantifiable representation of an impact category. Note: The shorter expression "category indicator" is used in this report and in the International Standard (ISO 14040, 2006a).

Life Cycle Assessment (LCA): Compilation and evaluation of the inputs, outputs and the potential environmental impacts of a product system throughout its life cycle (ISO 14040, 2006a).

LCA has also been defined as a technique to assess the environmental aspects and potential impacts associated with a product, process or service, by:

- Compiling an inventory of relevant energy and raw material inputs and environmental releases.
- Evaluating the potential environmental impacts associated with the identified inputs and releases.
- Interpreting the results to help stakeholders make a more informed decision.

Life Cycle Inventory (LCI): A phase of life cycle assessment involving the compilation and quantification of inputs and outputs for a product throughout its life cycle (ISO 14040, 2006a).

Life Cycle Inventory Analysis (LCIA): A phase of life cycle assessment aimed at understanding and evaluating the magnitude and significance of the potential environmental impacts for a product system throughout the life cycle of the product (ISO 14040, 2006a).

Primary data: Data collected specifically for the study at hand. These data are based on measurements and/or estimates for a given product or process (e.g., measured electricity data for a process being studied).

Reference flow: A measure of the outputs from processes in a given product system required to fulfill the function expressed by the functional unit (ISO 14040, 2006a).

Secondary data: Industry average data that are not specific to a given process or a product. Secondary data are typically obtained from commercial data libraries.

Sensitivity analysis: A systematic procedure for estimating the effects of the choices made regarding methods and data on the outcome of a study (ISO 14040, 2006a).

System boundary: A set of criteria specifying which unit processes are part of the product system (ISO 14040, 2006a).

Uncertainty analysis: A systematic procedure to quantify the uncertainty introduced in the results of a life cycle inventory analysis due to the cumulative effects of model imprecision, input uncertainty and data variability (ISO 14040, 2006a).

2 Introduction

2.1 Introduction to the Study

When patients open their medication box, there is always a Patient Information Leaflet (PIL) inside, a bulky paper attachment with information on drug interactions, side effects, storage information, and more. This is in addition to the ‘information to use’ leaflet with step-by-step instructions on how to use the medication. The PIL is often not worded well for laymen and very long, making it not useful for most patients and often quickly discarded. All medicinal products in the European Union must include a PIL.

Many things that society formerly used paper for are becoming fully digitized, reducing the need for paper and printing, including airplane and train tickets, store receipts, and medical records. With this global march toward digital solutions, European pharmaceutical legislation is currently looking towards implementing digital patient information leaflets, known as ‘Electronic Product Information’ or ePI (AESGP, 2024). In 2021, Japan introduced the Pharmaceuticals and Medical Devices Act (PMDA), a policy requiring that all PILs be in digital rather than paper format, and the country transitioned entirely to ePI by 2023 (Matsui, 2024).

Often society views the reduction of paper as an automatic win for the environment, but it is important to conduct scientific studies to find the true environmental impact of this shift to digital. Takeda, a global pharmaceutical company operating in Europe, has commissioned Long Trail Sustainability (LTS) to conduct a full comparative life cycle assessment (LCA) on the PIL, to understand the difference in environmental impacts between the average European market paper PIL and an ePI viewed on a smartphone. The results of the LCA are intended to be communicated externally by the European Federation of Pharmaceutical Industries and Associations (EFPIA) members, the pharmaceutical companies present on the European market. This study uses primary data from four pharmaceutical companies on sales of solid-form drugs on the European market (European continent) in the year 2020, representing a total of 5.2 billion units. The scope of the assessment was limited to solid-form drugs as those constitute the majority of medication products. The four pharmaceutical companies that contributed data were Takeda, GSK, Novartis, and Sanofi. These four companies, as well as Merck, were the impetus to initiate the LCA project.

This study is based on the attributional LCA approach, which describes the physical reality of an existing supply chain by quantifying the energy and material flows to and from an existing life cycle. The attributional LCA approach is appropriate because the primary focus of the study is to inform the project team of the environmental impacts of a paper PIL and compare those impacts to an ePI.

This study is modeled using *SimaPro v9.6.0.1* LCA software (PRé Sustainability, 2024). The study conforms to the requirements outlined by the International Organization for Standardization (ISO

14040, 2006a) (ISO 14044, 2006b) for comparative assertions intended for public disclosure. There is currently no PEFCR[2] (product environmental footprint category rule) available for PIL/ePI.

2.2 Introduction to LCA

Life cycle assessment (LCA) is an analytical tool used to quantify and interpret the impacts as a result of flows to and from the environment (including emissions to air, water and land, as well as the consumption of energy and other material resources), over the entire life cycle of a product or service. By including the impacts throughout the product life cycle, LCA provides a comprehensive view of the environmental aspects of the product or process and a more accurate picture of the environmental trade-offs in comparing alternatives.

ISO 14040 and ISO 14044 (2006b) set out a four-phase methodology framework for completing an LCA, as shown in Figure 4: (1) goal and scope definition, (2) life cycle inventory, (3) impact assessment, and (4) interpretation.

Goal and scope definition: The first step of an LCA is to define the specifics of the study. To do this, one must choose and explain the goal and scope of the study, the functional unit, the system boundaries, the assumptions and limitations, the allocation methods to be used, as well as the impact categories. The goal and scope define the context of the study, which also explains to whom and how the results are to be communicated. The functional unit is the reference function, a chosen standard, to which all flows in the LCA are related. Allocation is the method used to assign portions of the environmental load of a process when several output products or functions share the same process.

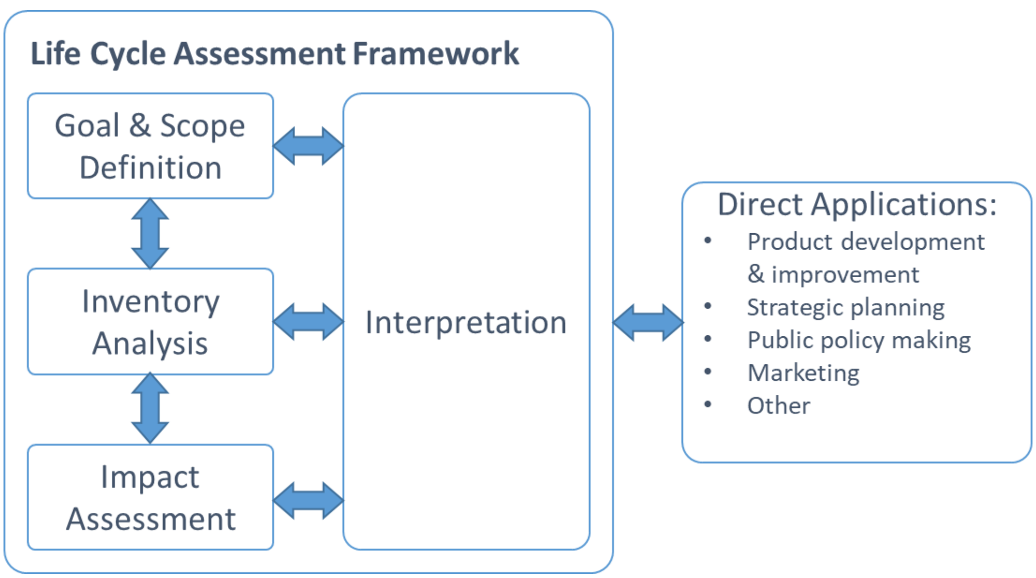

Figure 4: LCA framework (ISO 14040, 2006a)

[2] The Product Environmental Footprint (PEF) method, developed by the European Commission, provides rules to quantify and communicate environmental impacts of products, including goods and services.

Inventory analysis: After the study is defined, the raw resources, energy requirements, emissions to air and water, and waste generation that correspond to the product/process of the study are collected for an inventory analysis. In the inventory analysis, a flow model of the technical system is built using the data on inputs and outputs mentioned above. The flow model, often illustrated with a flow chart or process flow diagram, includes the activities that are going to be assessed and gives a clear picture of the technical system boundary. The inventory analysis must be directly related to the functional unit and cumulates the raw materials and emissions throughout the life cycle of the system.

Impact assessment: Following an inventory analysis, an impact assessment is conducted in which the life cycle inventory (LCI) data are interpreted in terms of their potential environmental impact (for example acidification, eutrophication and climate change). The assessment begins with the classification stage, where cumulated inventories are sorted and assigned to specific impact categories. The next step is characterization, where the cumulated inventories are multiplied by characterization factors specific to the inventory. Lastly, all characterized data included in each impact category are added to obtain the result for the impact category.

The completion of this characterization stage usually concludes the analysis in many LCAs; it is also the last compulsory stage according to ISO 14044. However, some studies involve the further step of normalization, in which the results of the impact categories are compared with the total impact in the world. In many LCAs, weighting also takes place, where the different environmental impacts are weighted against each other to attain a total environmental impact single score. This study does not use normalization or weighting.

Interpretation: Finally, the results from the inventory analysis and impact assessment are summarized and interpreted. The outcome of these interpretations is made in the form of conclusions and recommendations of the study. According to ISO 14044, the interpretation should include:

- key findings based on the results of the life cycle inventory and life cycle impact assessment (LCIA) phases of the LCA;
- evaluation of the study to consider completeness, sensitivity and consistency; and
- conclusions, limitations, and recommendations.

Although an LCA is described above in phases, the working procedure of an LCA is iterative. This means that information gathered in a later phase can affect a previous phase. When this occurs, all phases have to be reworked taking into account the new information. Therefore, it is common for an LCA practitioner to work on several phases at the same time.

3 Goal and Scope Definition

The first phase of an LCA defines the goal and scope of the study. According to ISO 14044, the goal of the study should clearly specify the intended application, reasons for carrying out the study, the intended audience, and whether the results are intended to be disclosed to the public.

The scope of the study describes the most important aspects of the study, including the functional unit, system boundaries, cut-off criterion, allocation, impact assessment method assumptions and limitations.

3.1 Objectives

The overarching goal of this study is to understand the difference in environmental impacts between the paper patient information leaflet (PIL) and the digital version, an ePI viewed on a smartphone, to the 2020 European market.

The intended application and audience for the comparative study is for European Federation of Pharmaceutical Industries and Associations (EFPIA) members, the pharmaceutical companies present on the European market, that wish to understand the environmental impacts of transitioning to ePI and communicate the results externally. Since EFPIA wishes to communicate the results of the full comparative LCA publicly, the LCA model and report follow ISO 14040 (ISO 14040, 2006a) and 14044 (ISO 14044, 2006b) requirements for comparative LCA studies intended to be disclosed publicly. The study was critically reviewed by a panel of experts. The critical review statement is provided in Appendix E: Critical Review Statement.

3.2 Function

The function of a PIL is a medium to provide information to patients regarding the safe and effective use of a drug, including information on dosage, administration, precautions, potential side effects, storage conditions, etc. (DDReg, 2025).

3.3 Functional Unit

A functional unit identifies the primary function(s) of a system based on which alternative systems are considered functionally equivalent (ISO 14040 2006). This facilitates the determination of reference flows for each system, which in turn facilitates the comparison of two or more systems. Based on the identified function, the following functional unit was used when determining the reference flows:

One patient information leaflet (PIL) provided as either a paper PIL or online as ePI, to the 2020 European market.

Reference Flows:

- **Paper PIL – 3.5 grams of printed paper**
- **ePI – 1.958 MB document viewed on a smartphone for 10.5 minutes**

In addition, we have scaled-up results for one year of PILs in Europe from four pharmaceutical companies (GSK, Novartis, Sanofi, and Takeda.) This is 5.2 billion PILs, based on sales of solid-form drugs on the European market in the year 2020 from these four companies. The purpose of the scaled-up results is to demonstrate the expected annual impacts to add context and highlight the scale of the issue, since burdens associated with just a single paper PIL or ePI will be small.

3.4 System Boundaries

System boundaries are established in LCA to include the significant life cycle stages and unit processes, as well as the associated environmental flows in the analysis. This lays the groundwork for a meaningful assessment where all important life cycle stages, and the flows associated with each alternative, are considered. The system boundary for this study is cradle-to-grave and is shown in Figure 5**.**

Further explanations on specifics of the system boundaries can be found in section 4 Life Cycle Inventory.

3.4.1 Paper PIL System Boundary

First, raw materials create paper, printer and ink, and leaflet packaging. These items are transported to the printing facility (multiple locations throughout Europe), where the paper PIL is printed. Then the paper PILs are placed in leaflet packaging and are transported to the packaging facility in Basel, Switzerland. This is where the PIL is placed in the medication carton and the leaflet packaging is discarded. Then the PIL (within carton) is transported to distribution centers across Europe and after that transported to pharmacies or hospitals and eventually to the patient. The patient reads the paper PIL, which requires no inputs or outputs and is thus excluded from the boundary. For the end of life (EOL) disposal, the paper PIL will either go to trash or recycling. The system boundary does not include distribution directly to the consumer, the carton and shipment packaging for the medication and its disposal, and storage at facilities along the supply chain.

Currently, all the PILs in softcopy are available on the European Medicines Agency (EMA) website for open access. Therefore, even though Europe is using 100% paper PILs as of early 2025, the ePI for all these medications are currently being stored on the web (https://www.ema.europa.eu/en/medicines). Therefore, energy for data storage and data center/server infrastructure is part of both the paper PIL and the ePI scenarios, and thus this has been excluded from the system boundary in both scenarios. If Europe switched from using paper PILs to ePI via QR codes on drugs, the ePI data storage would not change, but the data transfer energy would increase significantly because more patients would be accessing the stored data on their devices.

3.4.2 ePI System Boundary

First, raw materials create the printer and ink, which are transported to a facility, where the QR code is printed on the medication cartons. Unlike the paper PIL, there is negligible weight associated with the QR code on the medication carton, therefore, no additional transport is added to the lifecycle. During the use phase, the patient scans the QR code with their smartphone in order to access the

1.958 MB PDF document (ePI) from the internet (data transfer). The use phase includes the internet access equipment and the smartphone that a consumer needs to have access to in order to scan the QR code and for data transfer to occur. This phase also includes the electricity needed for data transfer, as well as the electricity to power the smartphone while the user is reading the ePI. For the EOL, the boundary includes the eventual EOL of the smartphone and internet access equipment. The system boundary does not include any potential carton waste during QR code printing, the carton and shipment packaging for the medication and its disposal, storage at facilities along the supply chain, transport of the medication carton, the infrastructure for the data center (server) and network, and energy for data storage.

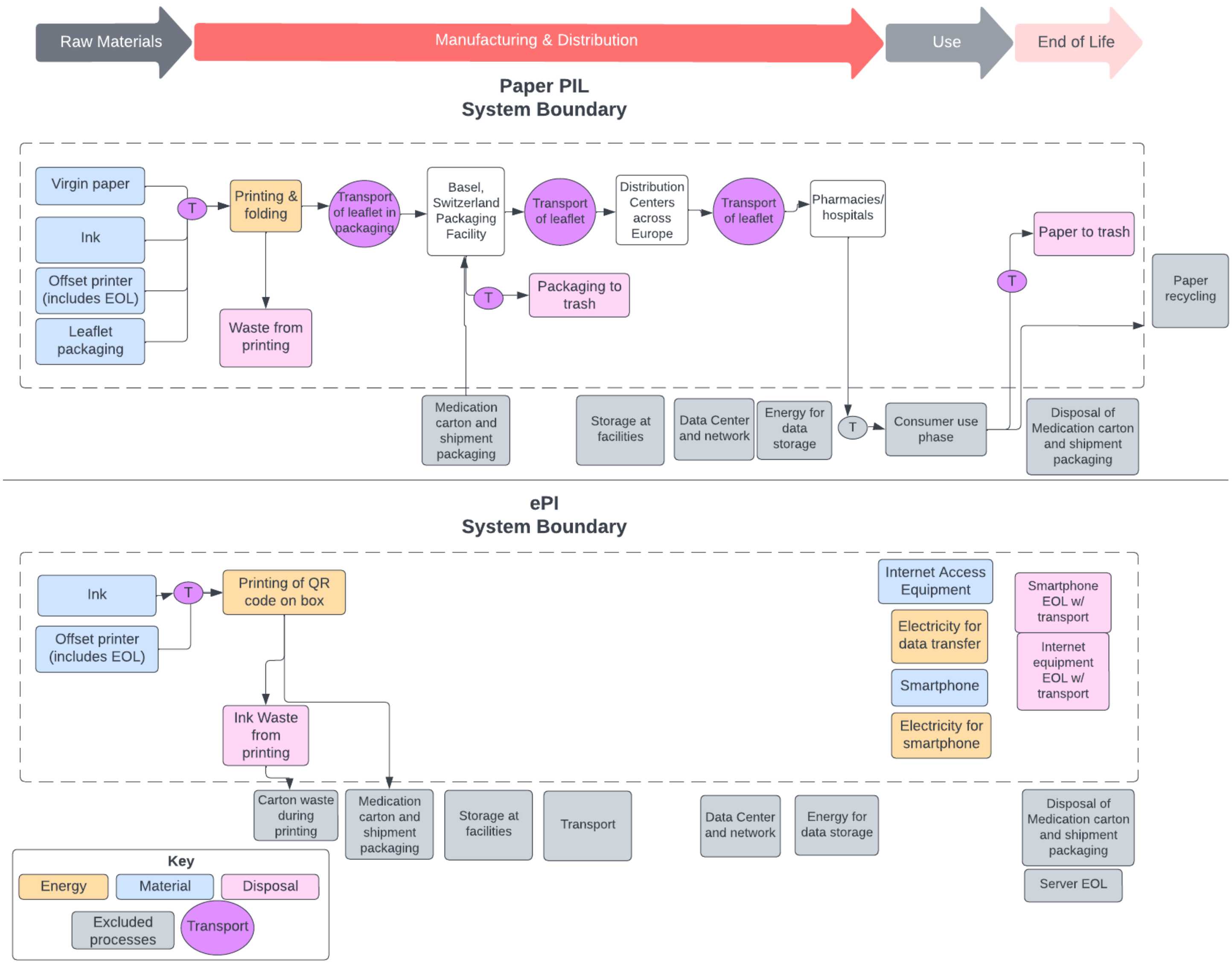

Figure 5: System boundary diagrams for both the paper PIL and the ePI.

3.5 Excluded Processes

Typically, in an LCA, some aspects within the set boundaries are excluded due to statistical insignificance or irrelevancy to the goal and scope. The following impacts were excluded from the scope and boundaries for this study:

- Entire study:
    - Human activities (e.g., employee travel to and from work);
    - R&D (i.e., the laboratory and inputs related to the development of the technologies); and
    - Services (e.g., the use of purchased marketing, consultancy services and business travel).
    - Foreground infrastructure (e.g., printing facility building, data center/server) is excluded, but background infrastructure (within secondary data) is included (e.g., printer).
    - The small carton (paperboard box) that contains the medication, the transport of that carton, the shipment packaging, and its disposal. This will be identical for the two scenarios, and thus did not need to be part of the LCA.
    - Storage of the medication at various facilities along the supply chain, because this would be identical in the two lifecycles.
    - Energy for data storage and data center/server infrastructure, because this would be identical in the two lifecycles.
- Paper PIL
    - Transport to the consumer. The added weight of the paper leaflet will not change the emissions of the consumer if walking, or biking. If driving a passenger car, the added weight would make the car use more fuel, however, the ecoinvent processes for transport by passenger car only use the unit of kilometers (km), rather than kgkm. Therefore, we were unable to represent the added weight to car transport from the paper PIL in the model. However, this is likely to be immaterial to the outcome of the study since it would be a very short transportation distance, and other transportation is not a hotspot in the results (see Figure 8).
    - Consumer use phase. There are no inputs or outputs while a person reads a paper PIL.
- ePI
    - If there is carton waste during the QR code printing due to mistakes in that printing process, carton waste is not accounted for due to lack of data.
    - Unlike the paper PIL, there is no additional weight associated with the QR code on the medication carton, therefore, no additional transport is added to the lifecycle.

3.6 Cut-Off Criteria

Cut-off criteria are often used in LCA practice for the selection of processes or flows to be included in the system boundary. The processes or flows below these cut-offs or thresholds are excluded from the study. Several criteria are used in LCA practice to decide which inputs are to be considered, including mass, energy and environmental relevance. In the current study, anything with less than 1% contribution to mass or energy is cut-off, with no more than 5% cut-off in total. Materials thought to be environmentally significant were included in the model even if they fell below this threshold.

3.7 Assumptions

Based on the data availability several assumptions were made. These assumptions included:

3.7.1 Paper PIL Assumptions

- The electricity needed for folding a paper PIL is estimated as the same electricity to produce and fold 1 envelope = 0.0034 Wh per envelope (Moberg, Borggren, Finnveden, & Tyskeng, 2008). Due to lack of data granularity, we could not separate out the energy to just fold paper, however it has a negligible impact on the paper PIL lifecycle.
- Paper was assumed to be 100% virgin based on communications with the pharmaceutical companies. This is tested in a sensitivity analysis in the Interpretation phase.
- The packaging facility was assumed to be in Basel, Switzerland, thus distances from the printing facilities to the packaging facility were calculated based on this assumption.
- The distance from the Basel packaging facility to distribution centers around Europe is estimated at 1500 km, since this would be the maximum European product transport distance. This is tested in a sensitivity analysis in the Interpretation phase.
- The distance from the distribution centers to the pharmacies/hospitals is estimated at 200 km. The Takeda Logistics team reports that one distribution center would cater to a 200 km radius of pharmacies.

3.7.2 ePI Assumptions

- The time it takes a person to read the ePI is estimated to be 10.5 minutes and there is an assumption of an additional half minute to scan the QR code and access the document. This is a conservative estimate as many people may simply skim the ePI and it is tested in a sensitivity analysis. The average reading speed of a nonfiction reader in English is 238 words per minute, which for a 2500-word PIL = 10.5 minutes total (Brysbaert, 2019).
- It is assumed that 100% of ePI views are on a smartphone as opposed to other electronic devices.
- It is assumed that 100% of people with access to an ePI will scan the QR code to view it. This is a conservative estimate since many people will not read the ePI and is tested in a sensitivity analysis. A survey of 406 people in Sweden asked how often they read the PIL. 37% of respondents said they always read it, while 52% said they occasionally read it (Hammar, Nilsson, & Hovstadius, 2016).
- It is assumed that a smartphone uses 1.83 kWh/yr and has a lifetime of 2.5 years (Marsh, 2024) (Laricchia, 2023). The smartphone lifetime is tested in a sensitivity analysis.
- It is assumed that internet access equipment has a lifetime of 6 years, based on ecoinvent documentation.

3.8 Allocation & Recycling

While conducting an LCA, if the life cycles of more than one product are connected, allocation of the process inputs should be avoided by using the system boundary expansion or the sub-division approach. If allocation cannot be avoided, an allocation method – based on physical causality (mass or energy content, for example) or any other relationship, such as economic value – should be used (ISO 14044 2006). In this study, allocation was based on time. For example, the amount of the smartphone or internet access equipment lifecycle to allocate to the ePI was based on time spent reading the ePI divided by total lifetime of the device/equipment.

This study uses the cut-off approach method for recycling, using the ecoinvent v3.10 cut-off by classification system model. According to this approach, the first life of a material bears the environmental burdens of its production (e.g., raw material extraction and processing) and the second life bears the burdens of the recycling process (e.g., transportation, collection, and refining of scrap). The burdens from waste treatment are taken by the life after which they occur (Frischknecht, et al., 2007). Because of this, for the items in this study that are recycled at end-of-life (paper and electronic scrap), no environmental burdens are applied for the recycling processes, including transportation to the recycling facility.

3.9 Impact Assessment Method

Impact assessment methods are used to convert LCI data (environmental emissions and raw material extractions) into a set of environmental impacts. ISO 14044 does not dictate which impact assessment method to use for a comparative assertion; however, the chosen method needs to be an internationally-accepted method if the results are intended to be used to support a comparative assertion disclosed to the public.

The primary impact assessment method used for this study was the ReCiPe 2016 Endpoint (H) v1.08 method (Huijbregts MAJ, 2017), which is one of the most utilized and updated methods available to LCA practitioners and thus is widely accepted. It was last updated in 2023. Using the endpoint method, the environmental impacts can be assessed for Human Health, Ecosystems and Resources. We have included the ReCiPe midpoint indicators results as well in Appendix D: Midpoint Impact Category Results.

In addition to the ReCiPe 2016 Endpoint method, two inventory indicators are used: Cumulative Energy Demand (Frischknecht, et al., 2007) and Water Use from ReCiPe 2016 Midpoint (H) v1.07 (Huijbregts MAJ, 2017). Also, one midpoint impact category is used: Climate Change (Intergovernmental Panel on Climate Change, 2021). These six categories are found to be of interest and readily understandable to readers of LCA reports. None of these impact categories are assumed to be more important than the others and they offer a range of different environmental indicators, which is important in a comparative LCA to not have burden-shifting. For purposes of simplicity, the combination of the ReCiPe Endpoint method and the selected midpoint categories is called the LTS Method (Table 1) (and summarized in

Appendix B: The LTS Method: Description of Impact Methods and Categories).

Additionally, long-term emissions were included in the LCIA.

Table 1: LTS 2023 Impact Assessment Method v1.00

Impact Category	Unit	Method	Description
Human Health	Disability Adjusted Life Years (DALY)	ReCiPe 2016 Endpoint (H) v1.08	Groups together the human health impacts from these Midpoint categories: Climate Change, Human Toxicity, Photochemical Oxidant Formation, Particulate Matter Formation, Ionizing Radiation and Ozone Depletion
Ecosystems	Species * yr	ReCiPe 2016 Endpoint (H) v1.08	Groups together the ecosystem impacts from these Midpoint categories: Climate Change, Terrestrial Acidification, Freshwater Eutrophication, Ecotoxicity, Agricultural Land Occupation, Urban Land Occupation and Natural Land Transformation
Resources	$/kg	ReCiPe 2016 Endpoint (H) v1.08	Groups together the resource impacts from these Midpoint categories: Fossil Depletion and Metal Depletion
Cumulative Energy Demand	MJ	CED V1.11	Groups together the energy demand impacts from these Midpoint categories: Non-renewable, fossil; Non-renewable, nuclear; Non-renewable, biomass; Renewable, biomass; Renewable, wind, solar, geothermal; and Renewable, water.
Climate Change	kg CO_2 eq.	IPCC 2021 GWP 100a v1.02	Combines the effect of the periods of time that the various greenhouse gases remain in the atmosphere and their relative effectiveness in absorbing outgoing infrared radiation. NOTE: This version of the method EXCLUDES CO_2 uptake and biogenic CO_2 emissions. The uptake and emissions of biogenic CO2 are part of a short cycle and has net zero impact. This version INCLUDES biogenic CH4 emissions with a characterization factor of 27 kg CO_2 eq./kg CH4.
Water Use	m^3	ReCiPe 2016 Midpoint (H) v1.08	Measures the amount of fresh water consumed

Each impact category above is characterized by a unit of measure to which the resource and emission flows are normalized. To aggregate the substances into the impact categories, substances are multiplied by their characterization factor to convert into an equivalent substance (e.g., CO_2) and then added together to create a total for each impact category (e.g., climate change).

Midpoint methods stop at the midpoints in the cause-and-effect chain. If an emission went out into the atmosphere that had the potential to destroy ozone, at the midpoint level we are measuring the stratospheric ozone depletion potential. Midpoint methods are classified as problem oriented. At the endpoint point level, less ozone allows increased UVB radiation, which leads to endpoints like skin cancer and cataracts. At the endpoint level, we are measuring the actual damage from the potential problem, such as damage to human health. Endpoint methods are classified as damage oriented. Midpoint methods have a higher degree of certainty than endpoint methods because there is just one characterization factor applied to the raw data, whereas with endpoint methods, further conversion into damage pathways is applied. Endpoints have a lower degree of certainty because they combine impact methods and are predictors for future damage if these impacts were to continue into the future. Figure 6 shows how midpoint impact categories such as global warming, water use, and human toxicity (cancer) are grouped together into damage pathways, converted from midpoint units (e.g., kgCO_2e) to endpoint units (e.g., DALY) (see Table 1) and added together to create an endpoint impact category (e.g., Human Health). Since all ReCiPe 2016 endpoint categories are utilized in the LTS Method, all the contributing midpoint impact category results for this study are shown in Appendix D: Midpoint Impact Category Results.

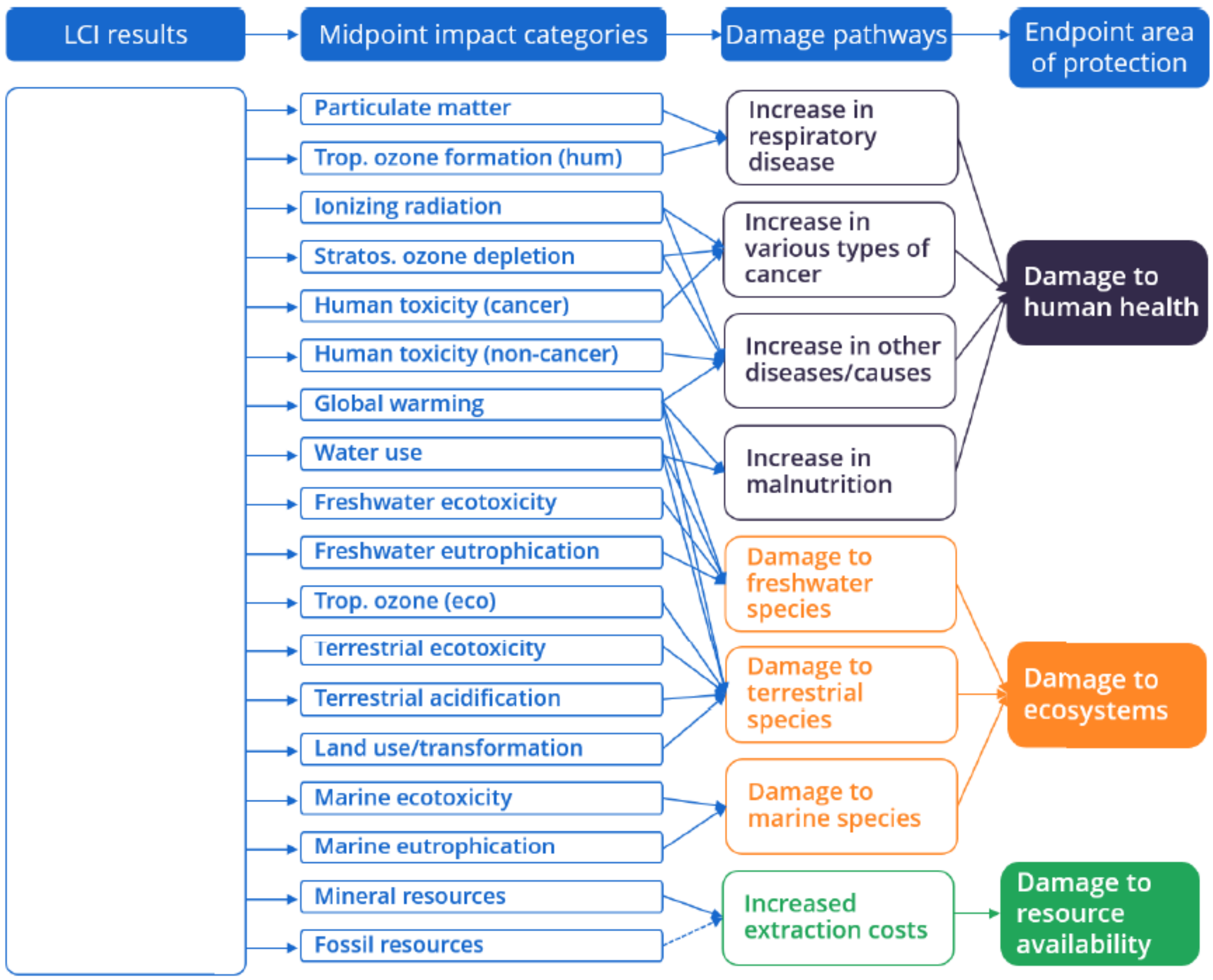

Figure 6: ReCiPe 2016 takes 18 midpoint impact categories and groups them into various damage pathways to result in 3 endpoint impact categories (Huijbregts MAJ, 2017).

3.10 Calculation Tool

Once all the required data were obtained and the associated flows were normalized to the reference flows (based on the chosen functional unit), system modeling was carried out by using the commercial *SimaPro v9.6.0.1* LCA software, developed by PRé Sustainability in the Netherlands. This software allows the calculation of life cycle inventories and impact assessment, contribution analysis, parameterization and related sensitivity and uncertainty analyses.

3.11 Critical Review

Critical review, which is required by ISO 14044 for comparative assertions intended for public dissemination, is a process that ensures consistency between an LCA and ISO requirements for carrying out the LCA. (Ultimately, the main purpose of a critical review is to ensure ISO compliance.) The critical review is carried out by an LCA expert in order to decrease the likelihood of miscommunication and negative effects on the public knowledge. As outlined by ISO 14044, the role of the critical review is to determine if:

- the methods used to carry out the LCA are consistent with this International Standard;
- the methods used to carry out the LCA are scientifically and technically valid;
- the data used are appropriate and reasonable in relation to the goal of the study;
- the interpretations reflect the identified limitations and goal of the study; and
- the study report is transparent and consistent.

The critical review panel members for the study are specified in Table 2.

Table 2: Critical Review Panel Members

Member	Affiliation
Dr. Peter Shonfield, chair	ERM
Dr. Matthew Fishwick	Fishwick Environmental
Dr. Matteo Cossutta	Aria Sustainability

The critical review does not imply that the reviewers endorse the results of the LCA study, or that they endorse the assessed products. The critical review statement is provided in Appendix E: Critical Review Statement and Record.

3.12 Limitations of the Study

The results of the study are only applicable to the defined scenarios, and any adjustment of the study boundaries, assumptions, functional unit, or processes may change the results. This study only considered the use of smartphones to view the ePI, therefore if the device were changed to tablets or computers the results would differ but would not be expected to change the overall conclusions of the study.

One limitation of this study is that it relies heavily on secondary data and estimates. There was primary data collected on the weight of the paper PIL, PIL printing facilities across Europe, paper PIL packaging, the file size of the ePI, and the total sales of solid-form drugs in Europe in 2020 by four pharmaceutical companies.

Data on the inputs and outputs associated with printing the paper PIL and the QR code for the ePI, the EOL of the paper PIL, the energy for data transfer of the ePI, the smartphone device and electricity consumption, the internet access equipment, and the EOL of the smartphone and internet equipment comes from the ecoinvent database, peer-reviewed literature, and well-respected websites. Additionally, we used estimates for all transportation distances.

Another limitation was that some of the ecoinvent background data had high uncertainty, which led to not having statistically significant results in two of the impact categories reported on: human health and water use. Additionally, some of the background data follows normal distribution leading to a higher distribution of datapoints, which could make a Monte Carlo analysis harder to interpret. Uncertainty is addressed further in 6.1 Key Observations.

3.13 Limitations of LCA Methodology

LCA's ability to consider the entire life cycle of a product makes it an attractive tool for the assessment of potential environmental impacts. Nevertheless, like other environmental management analysis tools, LCA has several limitations.

With current availability of data, it is nearly impossible to follow the entire supply chain associated with the product life in a company-specific way. Instead, almost all processes within the supply chains are modeled using average industry data with varying amounts of specificity (e.g., data on a more-or-less specific technology or region). This makes it difficult to accurately determine how well the unit process data actually represent the actual factors in the products' life cycle. It also makes it difficult to know in which region the processes are found.

Furthermore, LCA is based on a linear extrapolation of emissions with the assumption that all the emissions contribute to an environmental effect. This is contrary to threshold-driven environmental and toxicological mechanisms. Thus, while the linear extrapolation is a reasonable approach for more global and regional impact categories such as Global Warming Potential (GWP) and Acidification, it may not accurately represent the actual on-the-ground human- and ecotoxicity-related impacts.

Additionally, even if the study has been critically reviewed, it should be noted that, as for any LCA, the impact assessment results generated for this study are relative expressions and do not predict impacts on category midpoints, exceeding thresholds, or risks. It should also be noted that, even though LCA covers a wide range of environmental impact categories, some types of environmental impacts (e.g., noise, social, and economic impacts) are typically not included in LCA.

4 Life Cycle Inventory

The second phase of an LCA is to collect life cycle inventory (LCI) data. LCI data contains the details of the resources flowing into a process and the emissions flowing from a process to air, soil and water.

4.1 Choices of Background Database

All secondary data was retrieved from the ecoinvent v3.10 database, specifically the cut-off by classification system model.

4.2 LCI Data Collection

The primary data for the weight of the paper PIL, PIL printing facilities across Europe, paper PIL packaging, the file size of the ePI, and the total number of units of drugs sold in Europe in 2020 by four pharmaceutical companies was provided by Shruti Parikh, Director of Product Design, Drug Product and Device Development, and by Sriman Banerjee, Head of Diagnostics, Software Devices & Packaging, both at Takeda. The data comes from four companies: Takeda, GSK, Novartis, and Sanofi, with a fifth company, Merck, also submitting data on the location of paper PIL printing facilities in Europe. There was a data validity check for each piece of primary data to check that it met data quality requirements. Secondary/background data were retrieved from the ecoinvent v3.10 database (Wernet, et al., 2016).

The following sections describe each of the key process steps. Additional information, including the inputs and outputs for major processes, is listed in Appendix A: Additional Life Cycle Inventory Data.

4.2.1 Paper PIL

4.2.1.1 Printed Paper

The paper PIL is 100% virgin woodfree, coated paper. The weight of a PIL is 3.5 grams (g). This is an average weight from Takeda, GSK, Novartis, and Sanofi, based on total PIL weight in the sales of solid-form drugs on the European market in the year 2020, representing a total of 5.2 billion units.

Since there was no primary data collected on the printed paper for the PILs, such as paper supply chain and printer energy use, we used secondary data from the ecoinvent v3.10 database. We used the process '*Printed paper, offset {CH}| offset printing, per kg printed paper | Cut-off, U*' for 50% of the paper PILs printed in Switzerland (CH) and for the other 50%, we customized this process to be representative for 'Europe without Switzerland', by changing a few country-specific inputs and outputs. We did this since about half the printing facilities are in Switzerland and half are in other countries in the European continent.

The paper area density assumption for the ecoinvent 'printed paper' process is 80 g/meter^2. From the primary data, we know that the paper PIL is 40 g/m^2. This means that the ecoinvent process might be underestimating the amount of ink and printer use needed for a 3.5g paper PIL. The ecoinvent process was not adjusted and thus is a conservative assumption in respect to the ePI. Collecting primary data on printing ink and energy is out of scope of this project.

The process (or dataset) '*Printed paper, offset {CH}| offset printing, per kg printed paper | Cut-off, U*' has the following documentation: "The data set for offset printing is calculated from the annual material and energy consumption of three Swiss companies using modern technologies with low VOC use (solvents and cleaners). The dataset refers to 1 kg of the final product leaving the company and includes all paper loss from the preparation and further processings of print products (about 28% paper loss). A life span of 10 years was assumed for the machinery except for valves … The activity starts with the reception of materials for the printing process including paper, colors, machine and auxiliary materials as for example cleaners, printing plates and textiles. The activity offset printing ends with the packaging of final product at plant. The dataset includes the consumption of paper, printing materials and processing elements, materials of printer systems, the energy consumption of the offset printing company, the delivery of used materials from supplier, the VOC emissions from the printing process and the amount of waste, waste paper, waste packaging board, waste paints and used solvent mixtures from the printing process. The dataset does not include the delivery of the final product to the client and its final disposal."

4.2.1.2 Printing Facilities

The five pharmaceutical companies submitted the locations of all their paper PIL printing facilities in Europe. There are 17 printing facilities total, nine of which are in cities in Switzerland. The other printing facilities are located in cities in Ireland, France, Italy, Belgium, and Austria. The paper PILs are printed at these facilities with offset printing. It is not known if folding of the paper PIL happens at the printing facilities or at the packaging facility, but for the purposes of this study, we assumed the former. The electricity needed for folding the paper PIL is estimated as the same electricity to produce and fold one envelope = 0.0034 Wh per envelope (Moberg, Borggren, Finnveden, & Tyskeng, 2008). Since we assume that folding happens at the printing facility, 50% of the electricity for folding is sourced from an ecoinvent process for Switzerland, while 50% of it is sourced from the same process for 'Europe without Switzerland' as can be seen in Table 9. After the paper PILs are printed and folded, they are packaged up and shipped to the drug packaging facility.

4.2.1.3 Packaging for Paper PIL

The PILs are packaged in bundles of either 3,000 pieces per shipper (carton), or 2,000 pieces. The packaging consists of banderole (plastic), bundle wrap (plastic foil), dividers (paper), and the shipper carton. This keeps the paper PIL in good condition during transit to the drug packaging facility.

Once arriving at the drug packaging facility, we assumed the packaging film is disposed of in the trash (*Waste polyethylene {CH}| market for waste polyethylene | Cut-off, U*). We assumed the paper items are recycled at a rate of 70.5% and trashed at a rate of 29.5% (see Disposal of Paper PIL section for more information).

4.2.1.4 Transportation of Paper PIL

The paper PIL travels from the printing facilities across Europe to the drug packaging facility, which was assumed to be in Basel, Switzerland for a few reasons. Most of the five pharmaceutical companies have packaging sites in Switzerland, as well as in Berlin, Germany and around Lyon, France. Basel, Switzerland is one of the most popular pharmaceutical hubs in Europe. The cities mentioned above are all within a 150 km radius of Basel.

We took an average distance from each printing facility to Basel, which was 372 miles. In one instance, GSK has a printing facility in Dublin, Ireland and the packaging facility is in Montrose, Scotland. The distance is 355 miles, and this is part of the total average of distances from printing facilities to the drug packaging facility, the one instance where Basel is not assumed. For this trip, we assumed a truck operating with diesel, with an emission standard classified as EURO6 and falling under the lorry size class of 16-32 metric tons.

The paper PIL is inserted into the drug carton for each individual medication at the packaging facility, then the medications get shipped out to distribution centers around Europe. The distribution centers are spread across Europe, including Lisbon, Madrid, Vienna, Hamburg, Frankfurt, Brussels, Amsterdam, Dublin, London, etc. We assumed a distance of 1500 km to the distribution center, as this is the radius from Basel that covers most of Europe. We tested this assumption in a sensitivity analysis. We assumed the same size truck as the one chosen from the printing facilities to Basel.

The distance from the distribution centers to the pharmacies/hospitals is estimated at 200 km. The Takeda Logistics team reports that one distribution center would cater to a 200 km radius of pharmacies. We assumed a truck operating with diesel, with an emission standard classified as EURO6 and falling under the lorry size class of 7.5-16 metric tons.

4.2.1.5 Use Phase

There are no inputs and outputs associated with the use phase of a person reading a paper PIL.

4.2.1.6 Disposal of Paper PIL

The final disposal of paper PILs is assumed to go to recycling 70.5% of the time and go to the trash for the other 29.5%. In 2022, 70.5% of paper was recycled in Europe (European Paper Recycling Council, 2022). The remainder going to the trash gets routed to this ecoinvent market waste treatment process for Europe: *Waste graphical paper {Europe without Switzerland}| market group for waste graphical paper | Cut-off, U*. The market process shows paper is mainly disposed of via incineration, but this varies by country. For example, in Germany 99% of paper that goes to the trash is incinerated, whereas in France it is 61.5% while 38% goes to sanitary landfill. The market process includes average transportation to incinerators/landfills.

4.2.2 ePI

4.2.2.1 Printing QR Code on Carton

We estimated the ink and energy to print the QR code on the medication carton. This estimate comes from the ecoinvent process '*Printed paper, offset {CH}| offset printing, per kg printed paper | Cut-off, U*'. This ecoinvent process includes 1 kilogram (kg) of paper and the associated amount of ink and printer use to print on 1 kg of paper. For the purposes of our estimation, we removed the paper input since we only needed the amount of ink and printer use.

The area of the printed QR code is one square inch (*in^2*), equal to 6.45 square centimeters, on the medication carton and calculated the weight of the paper that corresponds with that printed area, since the ecoinvent process is measured in units of kg of paper. Paper area density was assumed to be 80 g/m^2, per ecoinvent documentation. The calculation of the weight of paper was as follows:

> *area of the printed QR code * Conversion* area density of paper = Corresponding mass of paper to use for given printed area*

Where:

> *area of the printed QR code = 1 in^2*
>
> *Conversion = 0.00064516 m^2/ in^2*
>
> *area density of paper = 80 g/ m^2*

As outlined in the Printed Paper section, this ecoinvent process includes 28% waste. We do not have data for any wasted medication cartons during printing since cartons are outside the system boundary.

4.2.2.2 ePI File Size

The ePI is a 1.958 MB PDF text document, which is a weighted average from ePI at the four main pharmaceutical companies that contributed primary data.

4.2.2.3 Use Phase

We assumed each person reads the ePI for 10.5 minutes, and for a conservative estimate, assumed it takes them an additional half minute to scan the QR code and access the document. This means the person would be using their smartphone device for 11 minutes in total. The average reading speed of a nonfiction reader in English is 238 words per minute, which for a 2500-word PIL = 10.5 minutes total (Brysbaert, 2019). The Europeans will be reading the ePI in their native language (not always English), which means we can assume the same reading speed.

We assumed that 100% of ePI viewing is on a smartphone as opposed to other electronic devices since it seems likely that this is the main type of device used to scan a QR code, as opposed to laptop computers or tablets. We assumed that 100% of people with access to an ePI QR code on their prescription drug will use the QR code to view it. This assumption is tested in a sensitivity analysis.

When the patient scans the QR code, they are brought to a 1.958 MB PDF document (ePI) from the internet (data transfer). We assumed that the energy for data transfer is 0.0001 kWh/MB. See Figure 7 for a depiction of data transfer. This estimate is sourced from a study that used a top-down energy intensity estimate and publicly available data, which was employed to construct an illustrative trend (kWh/gigabyte) for the energy consumption of transmitted mobile data for the years 2010–2017 in Finland. “By combining the overall electricity consumption estimate for production networks (80% of operators’ overall consumption) with previous estimates of overall data usage, an indicative trend of electricity consumption (kWh) per transferred gigabyte for the years 2010–2017 was created, together with an estimate for the coming years… Based on the equation the 0.1 kWh/gigabyte level could be achievable by around 2020,” (Pihkola, Hongisto, Apilo, & Lasanen, 2018). This estimate is tested in a sensitivity analysis.

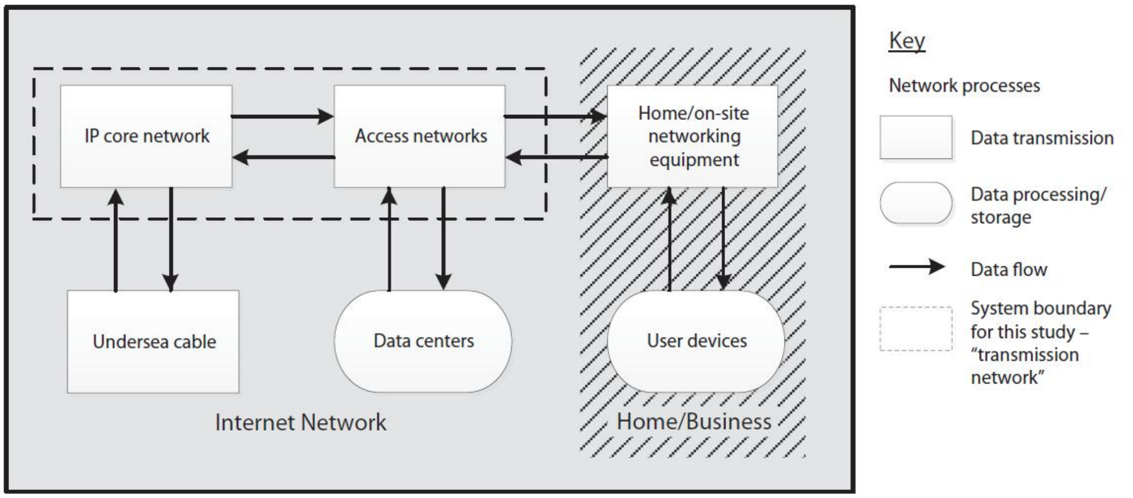

Figure 7: Simplified internet structure diagram. ‘Data transfer’ is depicted as ‘data flow’ in this diagram (Aslan, Mayers, & Koomey, 2017)

We assumed that a smartphone uses 1.83 kWh/yr and has a lifetime of 2.5 years (Marsh, 2024) (Laricchia, 2023). We assumed that internet access equipment has a lifetime of 6 years.[3] The energy for data transfer and the smartphone lifetime assumptions are each tested in a sensitivity analysis.

The infrastructure of the smartphone device and the internet access equipment, as well as their EOL, were all included in the system boundary. We used secondary data from the ecoinvent v3.10 database for these items.

We used the process ‘*Consumer electronics, mobile device, smartphone {GLO}| market for consumer electronics, mobile device, smartphone | Cut-off, U*’ to represent the smartphone and its EOL. The process has the following documentation: “This activity represents the production of one unit of a smartphone. It includes the materials for the housing, coils, simcard holder, mainboard covers various parts for assembly. The battery, display, mainboard, earpiece + speaker, internal cables, connector, an external charging device as well as a data cable (Monier, 2007) are included through separate datasets. Data on the smartphone stem from a LCA study on the Fairphone 1, a mid-range

[3] ecoinvent documentation from ‘*Chassis, internet access equipment {RER}| chassis production, internet access equipment | Cut-off, U*’

smartphone from 2014 with 4.3 inch display and a total weight of 163.45g (Güvendik, 2014) … The activity includes the materials, processes and energy use for the production of a smartphone. The dataset includes the exchange 'used smartphone' to take into account the disposal. Data on factory and packaging are not included." It can be noted that this smartphone dataset has a climate change impact of 40.3 kgCO2e using the LTS method. The iPhone 16 carbon footprint (excluding use phase) is reported as 46 kgCO2e (Apple, 2024).

We used the process '*Internet access equipment {GLO}| market for internet access equipment | Cut-off, U*' to represent the internet access equipment and its EOL. The process has the following documentation: "This is the market for 'internet access equipment', in the Global geography … This is a mobile infrastructure, representing the product of internet access equipment that is used to provide the service of internet connection. The system includes ADSL modem with router, DSLAM and connecting cables, while it is based on the factsheet of the Zyxel IES-6000 Series DSLAM, which contains ports for 768 users (ZyXel 2009). Its production represents all materials necessary to construct it and energy consumption during manufacturing." When looking at the input processes, and reading that documentation, it is clear that EOL disposal (and associated transport) is included in the dataset.

4.3 Electricity Mixes

For the paper PIL, printing processes used electricity grid mixes from either Switzerland or 'Europe without Switzerland', which is an average grid mix from the remaining countries in Europe. For the ePI, electricity for data transfer and smartphone use utilized an average grid mix for all of Europe, called 'RER' in ecoinvent. The specific processes used are detailed in Appendix A: Additional Life Cycle Inventory Data.

4.4 Data Quality

In practice, all data used in an LCA study is a mixture of measured, estimated, and calculated data. Since the quality of data is rarely homogenous, all specific data points were evaluated according to the pedigree matrix (for more details on the pedigree matrix, see Appendix C: Uncertainty Analysis). The sections below describe the data quality in this study. For a quantitative look at the data quality of each primary datapoint, see Table 16 in Appendix C: Uncertainty Analysis.

The costs of collecting primary data from all stages of the lifecycle is prohibitive to the execution of the study, and therefore we are also reliant on secondary data with less certainty.

4.4.1 Reliability

Primary data was collected from Takeda and four other pharmaceutical companies and thus has high reliability. Estimated data was based on reliable sources, such as the amount of time spent reading the ePI or the transportation distances. Reliability is considered to be adequate for all inventory data.

4.4.2 Completeness

All material flows were modeled in this study with either primary or secondary data and checked for mass and energy balance. Anything with less than 1% contribution to mass or energy was cut-off, with no more than 5% cut-off in total. Materials thought to be environmentally significant were included in the model even if they fell below this threshold. The only flow that was cut-off was the transportation of the paper PIL from pharmacy to consumer. Data completeness is considered to be adequate for this study.

4.4.3 Temporal Correlation

Primary data was collected from the pharmaceutical companies based on the total sales of solid-form drugs in Europe in 2020. Secondary data used was mainly valid through 2017 or more recent, giving it a high rating for temporal correlation.

4.4.4 Geographical Correlation

Primary data was based on the European operations of the five pharmaceutical companies to represent the paper PIL and ePI. The geographical scope of this study is Europe, and thus European secondary data was used for most processes. Global secondary data was used to represent the smartphone and the internet access equipment, which are traded on the global market. Geographic correlation is considered to be adequate for all inventory data.

4.4.5 Technological Correlation

The printing and PIL production methods used by Takeda and the other pharmaceutical companies represent current technology. Secondary data used also represents current technology, such as smartphones, mobile data transfer energy, and internet access equipment. Technological correlation is considered to be adequate for all inventory data.

4.4.6 Precision

Primary data was sourced from the five pharmaceutical companies and thus has high precision. Other data estimates have a medium level of precision, such as the amount of time spent reading the ePI or the transportation distances. Since this data was not measured, the precision and variability of these data estimates cannot be assessed.

4.4.7 Reproducibility

All primary and secondary data utilized for this study is written in this report. Where there were any changes made to ecoinvent processes, those were listed as well. Therefore, this study is reproducible.

4.4.8 Uncertainty Analysis

Uncertainty analysis is performed to determine how data quality affects the reliability and robustness of the results of the LCIA (ISO 14044, 2006). To evaluate the robustness of results in this study, uncertainty analyses were performed using the following procedure.

- Flows and parameters within the model were changed from deterministic to probabilistic values (i.e., from point estimates to probability distribution functions (PDFs)). As is common practice in LCA, lognormal distributions were used.
- Monte Carlo simulations were carried out in SimaPro (1,000 runs) to evaluate the frequency at which one system was preferable to another.

The method to change the point estimates to PDFs is based on the pedigree matrix developed by Weidema and Wesnaes (1996). Each flow type is attributed to a basic uncertainty factor, taken from Goedkoop et al. (2013), which is then combined with "additional uncertainty factors" using the following equation to calculate a squared geometric standard deviation:

$$SD_{g95} = \sqrt{exp[\ln(U_1)^2 + \ln(U_2)^2 + \ln(U_3)^2 + \ln(U_4)^2 + \ln(U_5)^2 + \ln(U_6)^2 + \ln(U_b)^2]}$$

With:

U_1: uncertainty factor of reliability,
U_2: uncertainty factor of completeness,
U_3: uncertainty factor of temporal correlation,
U_4: uncertainty factor of geographic correlation,
U_5: uncertainty of other technological correlation, and
U_6: uncertainty of sample size (as recommended by SimaPro, this was not used since this is an obsolete indicator).

When one material was shown to have greater impacts in 95% or more of the Monte Carlo simulations, we considered the comparative results to be certain and statistically significant. When the percentage was less than 95%, we considered the comparative results to be uncertain and therefore statistically significant conclusions could not be drawn.

There are some limitations of this uncertainty analysis including that it only addresses uncertainty in the background data. Additionally, the uncertainty distributions are based on high level qualitative estimates. More information about the assessment of data quality is provided in Appendix C: Uncertainty Analysis.

5 Results of Life Cycle Impact Assessment

The following sections summarize the key characterized results of the LCA, including contribution analyses of the lifecycle of one paper PIL and one ePI, the comparative analyses of the paper PIL compared to the ePI, and uncertainty analyses showing the robustness of the results. As noted, the life cycle inventory was analyzed using the LTS Method (a description is provided in Appendix B).

These results are relative expressions and do not predict impacts on category endpoints, the exceeding of thresholds, safety margins or risks. These results provide measures in which to inform the intended audience of process and material impacts, with which decisions can be made with temporally accurate data based on current methods and technologies. An LCIA shall not provide the sole basis of overall environmental superiority or equivalence in a comparative assertion, as additional information is necessary to overcome some of the inherent limitations in the LCIA.

All contribution analysis and comparative analysis results at the midpoint level can be found in Appendix D: Midpoint Impact Category Results.

5.1 Contribution Analysis

The contribution analyses identify the environmental hotspots within each system, which are the processes that contribute disproportionately to the overall life cycle impacts of the system. The identification of hotspots provides a deeper understanding of what is driving the environmental performance of the system and allows for the identification of opportunities for process improvement.

5.1.1 Lifecycle of one Paper PIL, cradle-to-grave

Figure 8 and Table 3 present the contribution analysis for the lifecycle of one paper PIL. The paper, ink, and printing accounts for between 75% and 96% of the total impact in all impact categories, making it the primary hotspot. The transport accounts for between 1% and 16% while disposal accounts for between 0% and 6% of the total impacts in each impact category. Packaging of the paper PIL accounts for 2% to 4% in each impact category. Figure 9 shows a network analysis of just the climate change impact category and Figure 10 shows the ecosystems endpoint category. The paper alone contributes 50.1% of the climate impacts and 75% of the ecosystems impacts to the entire lifecycle of the paper PIL. Other inputs are included in the analysis but contribute less than 5% to climate change, therefore are not shown on the network analysis.

Midpoint indicators are available in Appendix D: Midpoint Impact Category Results. Figure 25 and Table 17 show the midpoint results for the paper PIL. Consistent with the endpoint results, the majority of the cradle-to-grave environmental impacts of the paper PIL come from paper, ink, and printing. The paper PIL disposal has a majority of the GWP100 biogenic impacts, which is to be expected when an organic material like paper is disposed of. However, this does not have a large impact on the climate change endpoint.

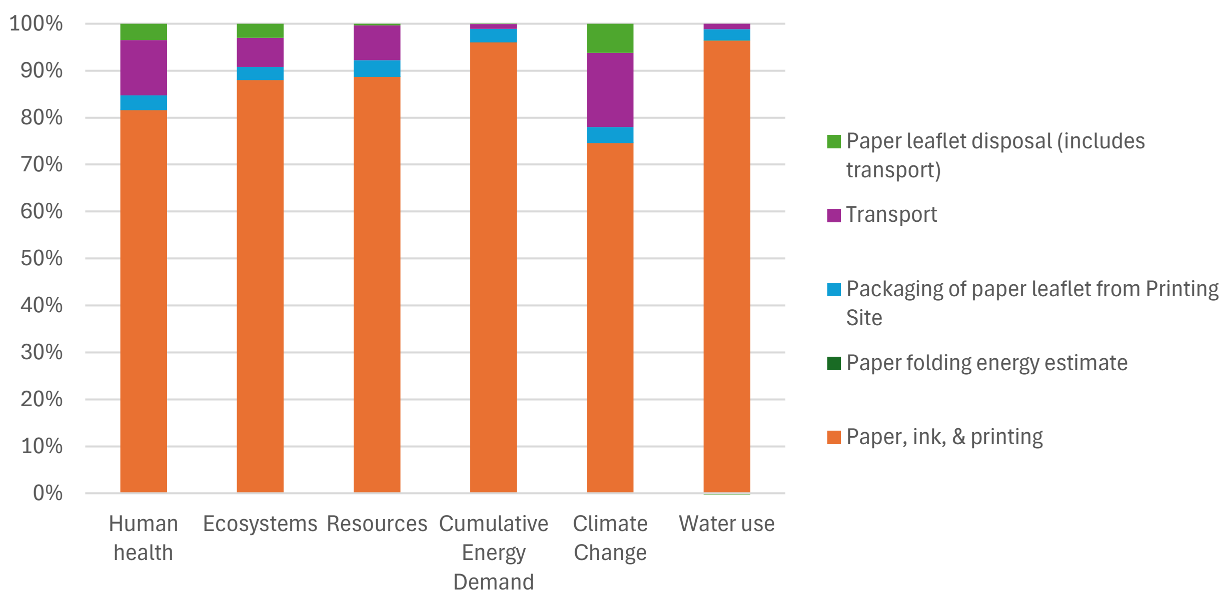

Figure 8: Contribution analysis for the lifecycle of one paper PIL, using the LTS method.

Table 3: Contribution analysis for the lifecycle of one paper PIL, using the LTS method.

Impact Category (Unit)	Paper, ink, & printing	Paper folding energy estimate	Packaging of paper leaflet from Printing Site	Transport	Paper leaflet disposal (includes transport)	TOTAL
Human Health (DALY)	2.40E-08	2.08E-12	9.25E-10	3.47E-09	1.03E-09	2.94E-08
Ecosystems (species*yr)	9.27E-11	3.55E-15	2.92E-12	6.57E-12	3.13E-12	1.05E-10
Resources ($)	3.86E-05	4.05E-09	1.52E-06	3.24E-06	1.41E-07	4.35E-05
Cumulative Energy Demand (MJ)	2.11E-01	2.35E-05	6.23E-03	2.31E-03	8.94E-05	2.19E-01
Climate Change (kg CO_2 eq)	7.48E-03	6.16E-07	3.44E-04	1.59E-03	6.21E-04	1.00E-02
Water Use (m^3)	2.62E-04	3.02E-08	6.62E-06	3.09E-06	-7.69E-07	2.71E-04

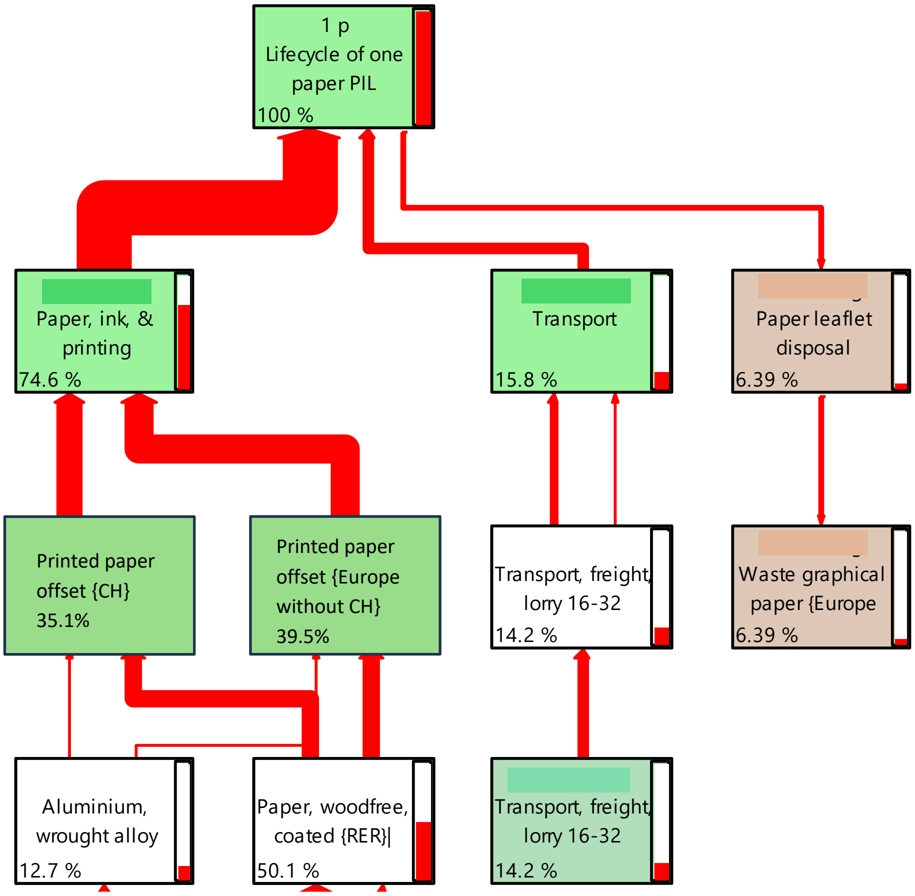

Figure 9: Climate change network analysis with 5% cut-off for the lifecycle of one paper PIL, using the LTS method.

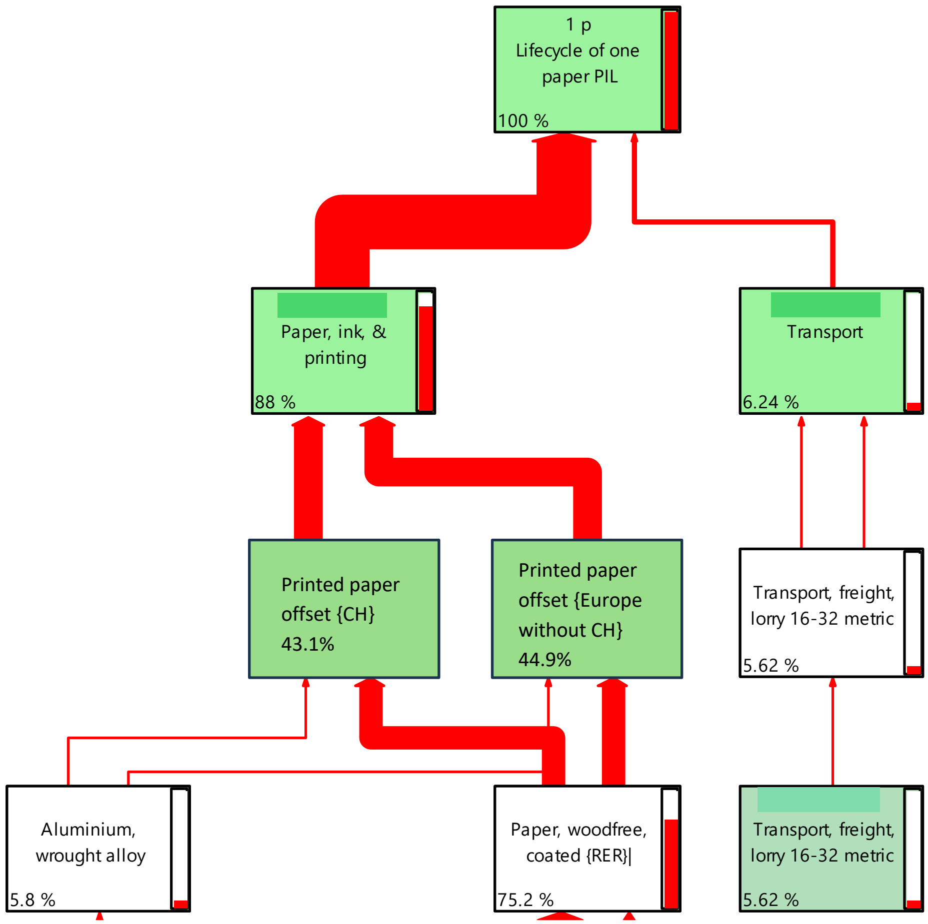

Figure 10: Ecosystems network analysis with 5% cut-off for the lifecycle of one paper PIL, using the LTS method.

The uncertainty analysis shown in Figure 11 indicates that the environmental impacts of the paper PIL could be around 80% lower and 86% higher in ecosystems, 33% lower and 68% higher in resources, and 14% lower and 25% higher in cumulative energy demand and climate change, due to variations in the data. Both human health and water use results are less certain, ranging from 671% lower to 675% higher in human health and 2289% lower to 1961% higher in water use, and shown separately in Figure 12. For human health, the paper PIL cannot have a positive effect on this endpoint, so anything lower than 100% would have zero impact on human health. However, it is possible to have negative water use if a system is releasing more water back into water bodies than it consumes. To sum it up, there is high uncertainty in the human health endpoint and water use midpoint results. This is discussed further in 6.1 Key Observations.

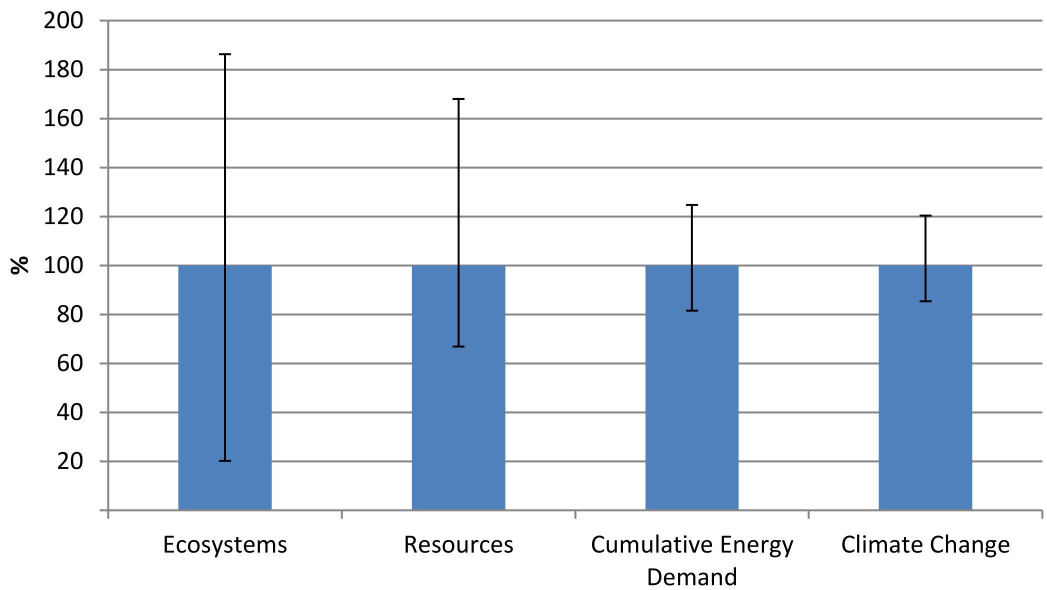

Figure 11: Uncertainty analysis of paper PIL, using the LTS Method, excluding human health and water use impact categories.

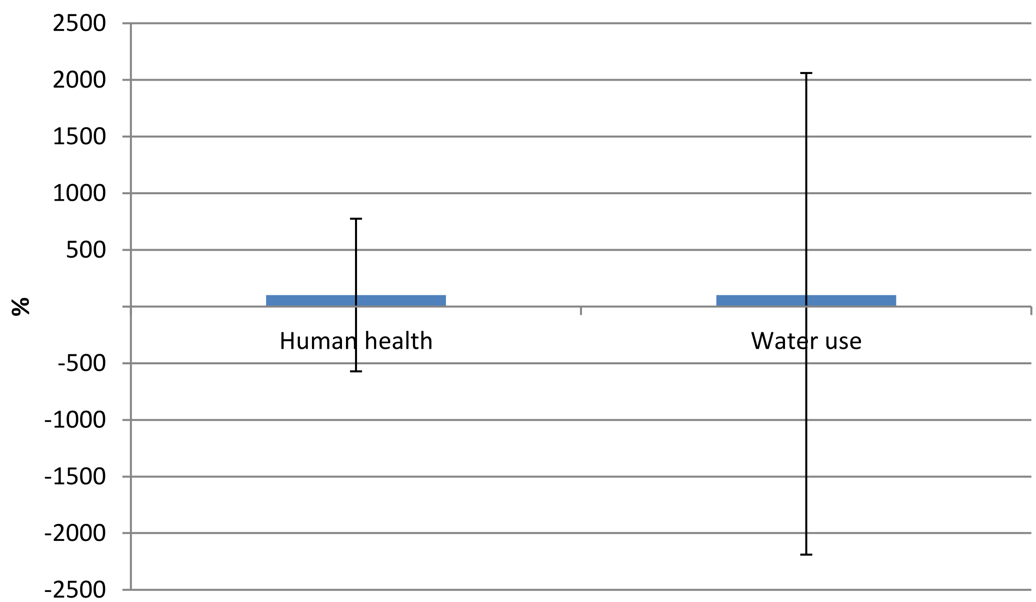

Figure 12: Uncertainty analysis of paper PIL in human health and water use, using the LTS Method.

5.1.2 Lifecycle of one ePI, cradle-to-grave

Figure 13 and Table 4 present the contribution analysis for the lifecycle of one ePI. The smartphone device accounts for between 55% and 74% of the total impact in all impact categories and is the primary hotspot. Energy for data transfer accounts for between 8% and 27% of the total impacts in each impact category, as the secondary hotspot. Internet access equipment accounts for 4% to 11% while the ink and printing of the QR code accounts for 7% to 9% in each impact category.

Midpoint indicators are available in Appendix D: Midpoint Impact Category Results. Figure 26 and Table 18 show the midpoint results for the ePI. Similar to the endpoint results, most of the ePI impacts come from the smartphone device. Energy for data transfer has a majority of the impacts in the following midpoint impact categories: ionizing radiation; non-renewable energy, nuclear; and renewable energy, wind, solar, and geothermal.

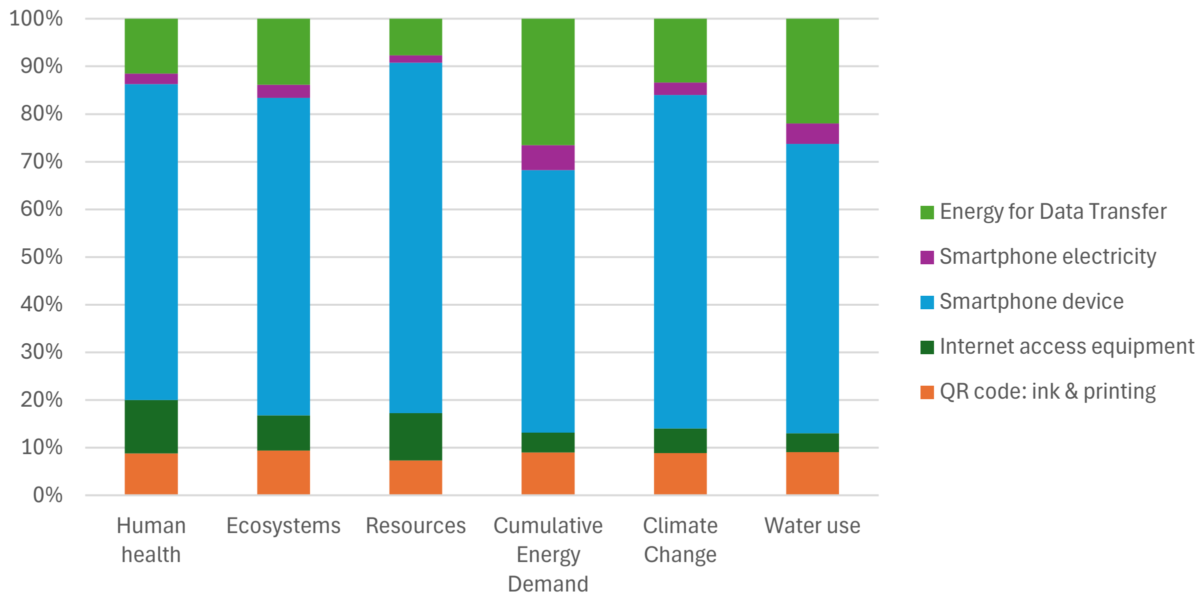

Figure 13: Contribution analysis for the lifecycle of one ePI, using the LTS method.

Table 4: Contribution analysis for the lifecycle of one ePI, using the LTS method.

Impact Category (Unit)	QR code: ink & printing	Internet access equipment	Smartphone device	Smartphone electricity	Energy for Data Transfer	TOTAL
Human Health (DALY)	1.47E-10	1.87E-10	1.11E-09	3.75E-11	1.92E-10	1.67E-09
Ecosystems (species*yr)	2.27E-13	1.80E-13	1.62E-12	6.60E-14	3.37E-13	2.43E-12
Resources ($)	3.62E-07	4.92E-07	3.65E-06	7.48E-08	3.82E-07	4.96E-06
Cumulative Energy Demand (MJ)	5.13E-04	2.34E-04	3.13E-03	2.96E-04	1.51E-03	5.69E-03
Climate Change (kg CO_2 eq)	4.28E-05	2.48E-05	3.37E-04	1.26E-05	6.45E-05	4.82E-04
Water Use (m^3)	5.33E-07	2.32E-07	3.57E-06	2.52E-07	1.29E-06	5.87E-06

The uncertainty analysis shown in Figure 14 indicates that the environmental impacts of the ePI could be around 184% lower and 205% higher in human health, 328% lower and 306% higher in ecosystems, 44% lower and 129% higher in resources, and 36% lower and 113% higher in cumulative energy demand and climate change, due to variations in the data. The water use results are again less certain, ranging from 4427% lower to 3841% higher in water use, and shown separately in Figure 15. When looking at the uncertainty analysis at the midpoint level, the water consumption (human health), water consumption (terrestrial ecosystem), and water consumption (aquatic ecosystems) midpoints have extremely high uncertainty. Again, the uncertainty is mainly driven by the data uncertainty in the underlying secondary data.

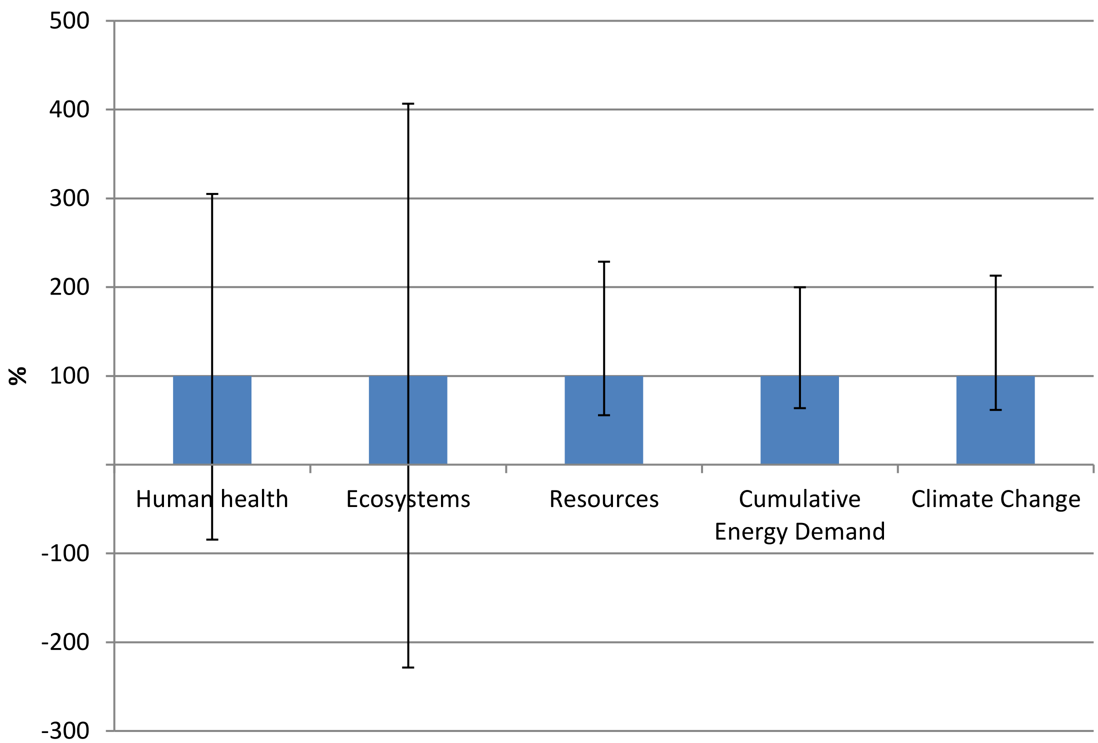

Figure 14: Uncertainty analysis of the ePI, using the LTS Method, except the water use impact category.

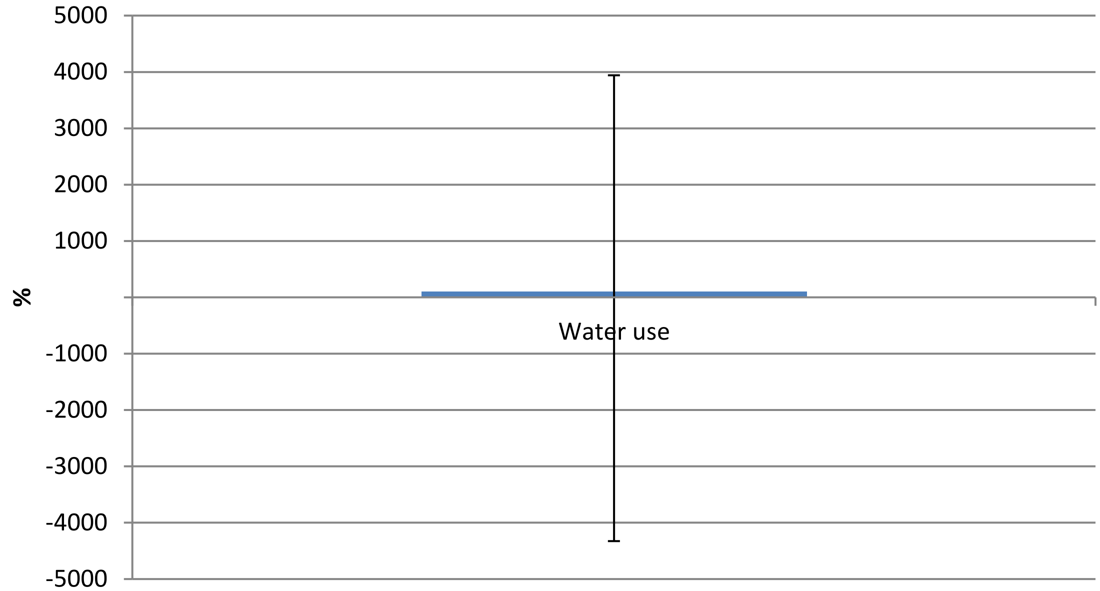

Figure 15: Uncertainty analysis of the ePI in water use, using the LTS Method.

5.2 Comparative Analysis

The following section contains the comparative analyses that show which option (paper PIL or ePI) has more or fewer environmental impacts in a given impact category.

5.2.1 Comparison of one paper PIL to one ePI, cradle-to-grave

The uncertainty analysis shown in Figure 16 indicates with a high level of certainty, within the 95% confidence interval, that one ePI has lower impacts than one paper PIL in ecosystems, resources, cumulative energy demand, and climate change. Results for human health and water use fell below the 95% confidence interval, therefore results in those two impact categories are not statistically significant.

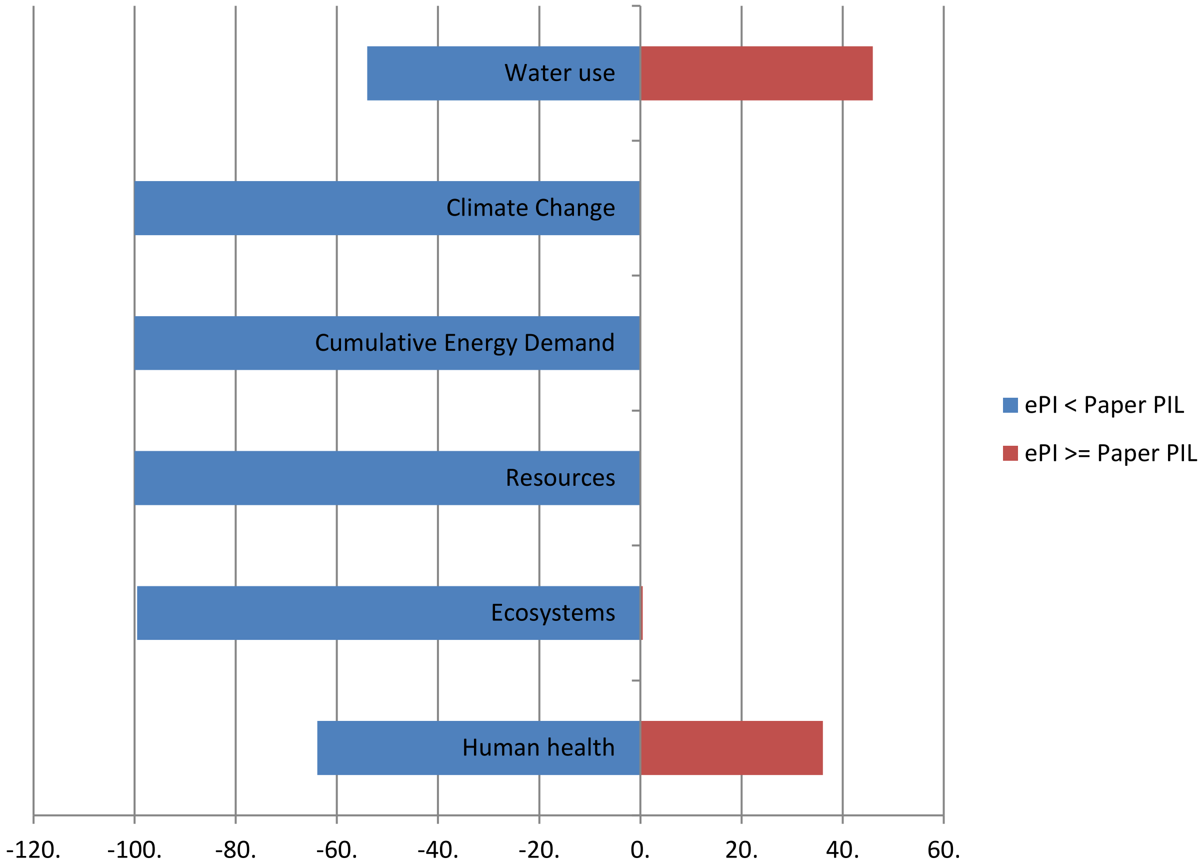

Figure 16: Uncertainty analysis of one paper PIL vs. one ePI, using the LTS Method.

Figure 17 and Table 5 shows a comparative analysis of one paper PIL to one ePI, cradle-to-grave. One ePI has between 89% and 98% lower impacts than one paper PIL in all six impact categories. This means that one ePI has 2% of the paper PIL impacts in ecosystems, 11% in resources, 3% in cumulative energy demand, and 5% in climate change. Results for human health and water use fell below the 95% confidence interval, therefore statistically significant conclusions cannot be drawn in those categories, although we still presented the results for those two impact categories in Figure 17 and Table 5. The comparison for the midpoint impact categories is shown in Figure 27 in Appendix D: Midpoint Impact Category Results. The midpoint results have the same conclusion, that one ePI has lower impacts than one paper PIL in every midpoint impact category.

A sensitivity analysis was done with the comparative data (paper PIL vs. ePI) to see how results would change if long-term emissions were excluded, and ecosystems impacts would be reduced by 11% for the ePI and 4% for the paper PIL. All other impact categories would remain the same.

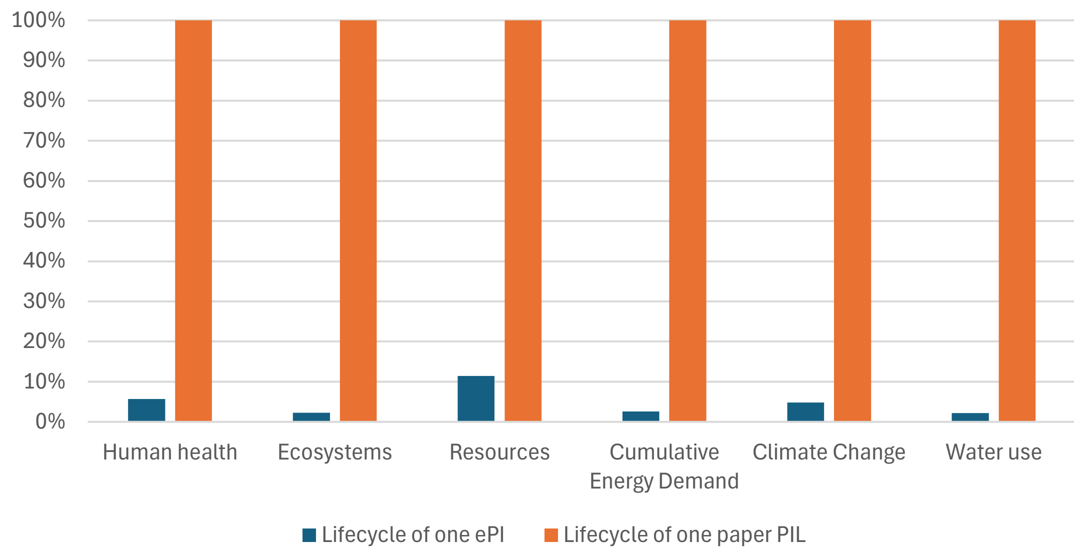

Figure 17: Comparative analysis of one paper PIL to one ePI, cradle-to-grave, using the LTS method.

Table 5: Comparative analysis of one paper PIL to one ePI, cradle-to-grave, using the LTS method.

Impact Category (Unit)	Lifecycle of one ePI	Lifecycle of one paper PIL
Human Health (DALY)	1.67E-09	2.94E-08
Ecosystems (species*yr)	2.40E-12	1.05E-10
Resources ($)	4.96E-06	4.35E-05
Cumulative Energy Demand (MJ)	5.69E-03	2.19E-01
Climate Change (kg CO2 eq)	4.82E-04	1.00E-02
Water Use (m3)	5.87E-06	2.71E-04

5.2.2 Comparison of one year of paper PILs to one year of ePI, cradle-to-grave

We have scaled up the results to show the impact of one year of PILs in Europe from four pharmaceutical companies: GSK, Novartis, Sanofi, and Takeda. This is approximately 5.2 billion PILs (5,181,729,699), based on sales of solid-form drugs on the European market (continent of Europe) in the year 2020 from these four companies.

Table 6 shows a comparative analysis of 5.2 billion units of paper PILs to the same number of ePI, cradle-to-grave. The ePI scenario reduces the climate change impacts of the paper PIL by 95%. The paper PIL scenario emits 49,507 metric tonnes of CO2-equivalent (MTCO2e) units more than the ePI scenario. Over the course of one year, switching entirely from paper PIL to ePI for these 5.2 billion units would be the carbon savings of 126,072,524 miles driven by an average gasoline-powered passenger vehicle or 10,317 homes' electricity use for one year, in the United States (United States

Environmental Protection Agency, 2025). These conversions are from the U.S., which may not be as relevant for Europe.

Table 6: Comparative analysis of one year of paper PILs to one year of ePI in Europe, 5.2 billion units, cradle-to-grave, using the LTS method.

Impact Category (Unit)	5.2 billion units of ePI	5.2 billion units of paper PILs	Difference (PIL - ePI)	% Reduction
Ecosystems (species*yr)	1.26E-02	5.46E-01	5.33E-01	98%
Resources ($)	2.57E+04	2.25E+05	2.00E+05	89%
Cumulative Energy Demand (MJ)	2.95E+07	1.14E+09	1.11E+09	97%
Climate Change (kg CO_2 eq)	2.50E+06	5.20E+07	4.95E+07	95%

6 Interpretation

Interpretation is the last phase of an LCA, although it is typically done iteratively to inform and refine the goal and scope of the study as necessary. In this section, the results are examined based on data quality and consistency and key assumptions are tested to ensure that conclusions and recommendations are consistent with the goal and scope. It should be noted that the LCA results are based on a relative approach and indicate potential environmental effects and do not predict actual impacts on category impacts.

6.1 Key Observations

By analyzing paper PILs and ePI, the study provides useful insight regarding the environmental impacts of each method of patient information, as well as how an ePI compares to a paper PIL. The LCA results also identify where the largest impacts are occurring so that the project team can make further process improvements, if desired.

Based on the results and study assumptions, methods and data, the majority of the cradle-to-grave environmental impacts of the paper PIL come from the paper, whereas the majority of the impacts of the ePI come from the smartphone device and secondly the energy for data transfer.

Compared to the paper PIL, the ePI has fewer environmental impacts in all six impact categories and all midpoint impact categories. In fact, this study made some conservative estimates for the ePI, including an assumption that 100% of ePI would be viewed (QR code scanned), that each person would spend 10.5 minutes reading the ePI, and only a 2.5-year assumption for smartphone lifespan. Despite these conservative assumptions, the ePI consistently performed better than the paper PIL.

The comparative results cannot be considered statistically significant for the human health and water use impact categories. The uncertainty in the human health endpoint category was driven by two midpoint categories: 'human non-carcinogenic toxicity' and 'water consumption, human health'. All secondary (background) datasets contain uncertainty information per datapoint (pedigree matrix), and in this study the uncertainty related to these ReCiPe 2016 midpoints is largely due to the uncertainty associated with these background datasets and not the primary data reported by Takeda. The large variations in these midpoint indicators (including the water use midpoint) are most likely related to only a few data points comprising these averages for some of the background processes. Also, some elementary exchanges in background ecoinvent datasets, particularly from the agricultural sector, have normal distribution as an uncertainty type. For many of them, the variances seem overestimated in comparison to the exchange amounts. This leads to a higher distribution of datapoints, which could make a Monte Carlo analysis harder to interpret.

Uncertainty analyses are one way of indicating the statistical range of the data and how these contribute to impact indicators of interest. In this instance, the Monte Carlo analysis does not allow us to assess the data as being robust in this manner (close to the average data point used). Perhaps databases other than ecoinvent (if available) might have a narrower range of impact due to more data points collected for each process and could be better indicators of the robustness of these impacts.

Additionally, trying to collect better data would be something to increase the accuracy of this study and should be pursued in the future.

6.2 Completeness Check

Detailed information on the inputs and outputs of the paper PIL and ePI were gathered and every effort was made to perform a comprehensive analysis. An attempt was made to include as much detail as possible, even for processes that were found to be largely negligible in the environmental impact assessment. To ensure completeness, processes were mass balanced before allocation to ensure all waste and emissions were captured. Furthermore, all energy consumption that was understood as relevant for the comparison was included. Additional information is provided in Appendix A: Additional Life Cycle Inventory Data.

6.3 Consistency Check

The compared systems were modeled in a consistent manner and their boundaries were defined in a similar manner. Therefore, any differences in overall potential environmental impacts should not be due to inconsistent modeling or data. Additional information is provided in Appendix A: Additional Life Cycle Inventory Data.

6.4 Sensitivity Analysis

Sensitivity analysis was performed to understand the influence of variations in the assumptions, methods, and data on the results. In other words, sensitivity analyses were used to understand the robustness of the conclusions and identify limitations to the results. The sensitivity analyses graphs are only focusing on the four impact categories that were statistically significant.

6.4.1 Recycled content of paper PIL

The default scenario is to use 100% virgin (woodfree, coated) paper for the paper PIL. If the paper PIL were to switch to 100% recycled content, this could change the environmental impacts. To represent recycled content paper, the following ecoinvent process was substituted: *Paper, woodfree, uncoated {CA-QC}| paper production, woodfree, uncoated, 100% recycled content, at non-integrated mill | Cut-off, U*. The Quebec process was used because it was the best available LCI data for comparable recycled paper. Electricity has just 2.8% of the climate change impacts for the Quebec process. As shown in Figure 18, when the paper is switched to 100% recycled content, the ePI still has lower environmental impacts compared to the paper PIL in all scenarios and impact categories.

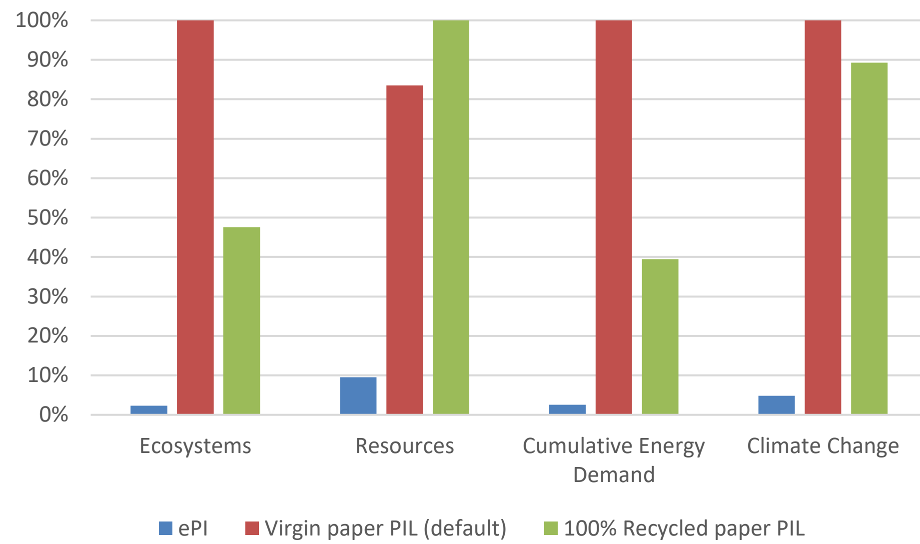

Figure 18: Sensitivity analysis of recycled content of paper PIL, per function unit, using the LTS Method.

6.4.2 Transportation distance of paper PIL to distribution centers

The default scenario is to assume the paper PIL travels a 1500 km distance from Basel, Switzerland to the distribution centers around Europe and this would be the maximum European product transport distance. We tested this assumption with 50% shorter distance (750 km) and 75% shorter distance (375 km). As shown in Figure 19, when the distance assumption is changed, the ePI still has lower environmental impacts compared to the paper PIL in all scenarios and impact categories. Changing this transportation assumption has negligible impacts on the paper PIL's environmental impacts.

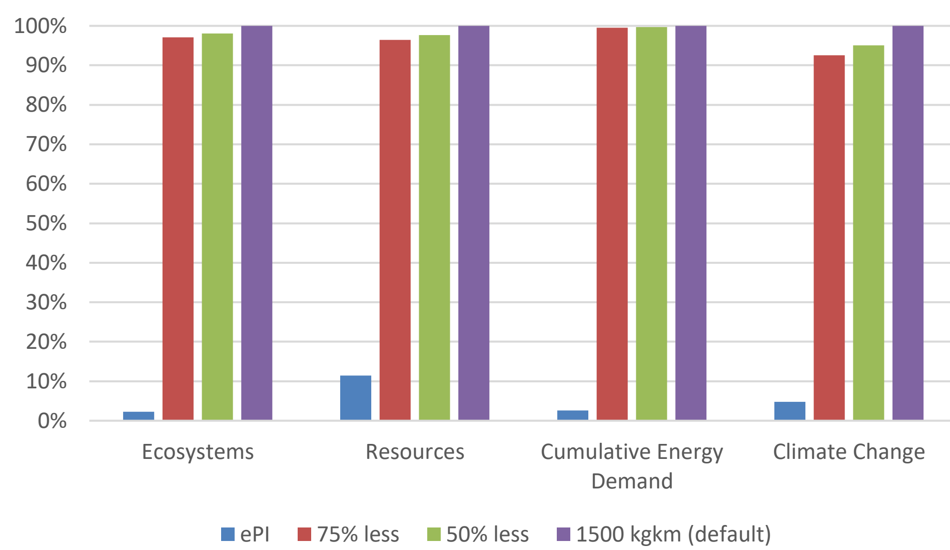

Figure 19: Sensitivity analysis of paper PIL transportation distance to distribution centers, per function unit, using the LTS Method.

6.4.3 Time spent viewing the ePI

The default scenario is to assume that the patient views the ePI on a smartphone for 10.5 minutes, with an additional 0.5 minutes to access the ePI. We tested this assumption with 12 minutes and 15 minutes of ePI view time, which would increase the impacts of the ePI. As shown in Figure 20Figure 19, when the viewing time assumption is changed, the ePI still has lower environmental impacts compared to the paper PIL in all scenarios and impact categories.

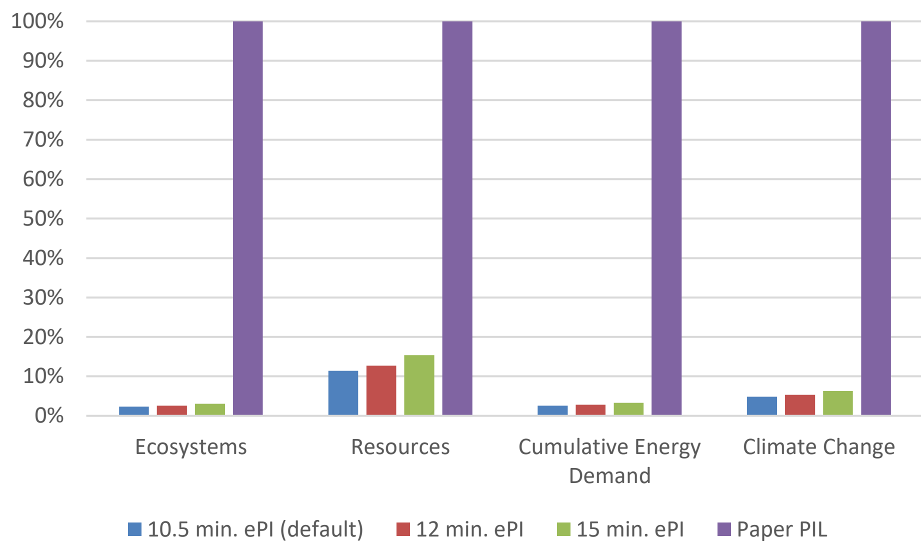

Figure 20: Sensitivity analysis of ePI viewing time, per function unit, using the LTS Method.

6.4.4 Percentage of ePI viewed

The default scenario is to assume that 100% of patients view the ePI by scanning the QR code on the drug carton. We tested this assumption with only 70% or 40% of patients scanning the QR code on the drug carton. This reduces the impacts of the ePI. As shown in Figure 21, when the viewing time assumption is changed, the ePI still has lower environmental impacts compared to the paper PIL in all scenarios and impact categories.

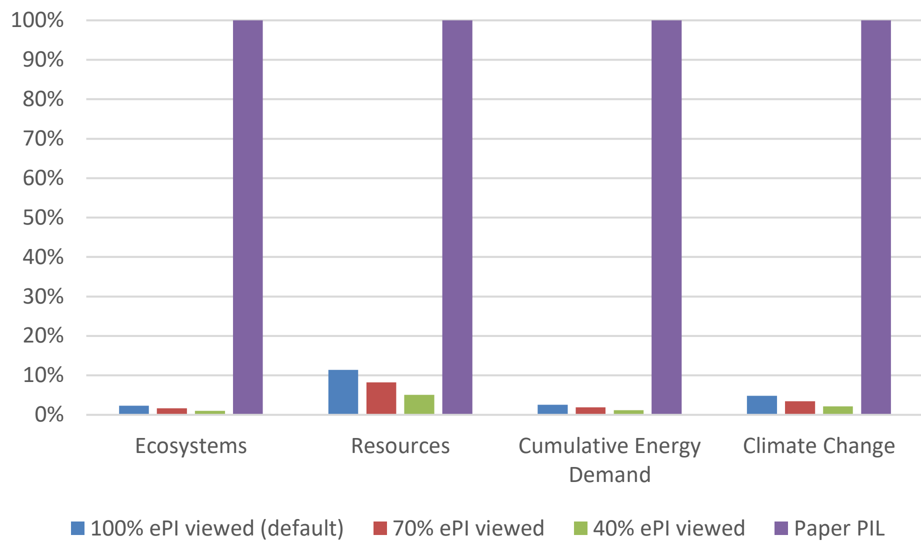

Figure 21: Sensitivity analysis of percentage of ePI viewed, per function unit, using the LTS Method.

6.4.5 Smartphone lifespan

The default scenario is to assume that the lifespan of a smartphone is 2.5 years. We tested this assumption with a reduced lifespan of 2 years and an increased lifespan of 5 years. As shown in Figure 22, when the smartphone lifespan is changed, the ePI still has lower environmental impacts compared to the paper PIL in all scenarios and impact categories.

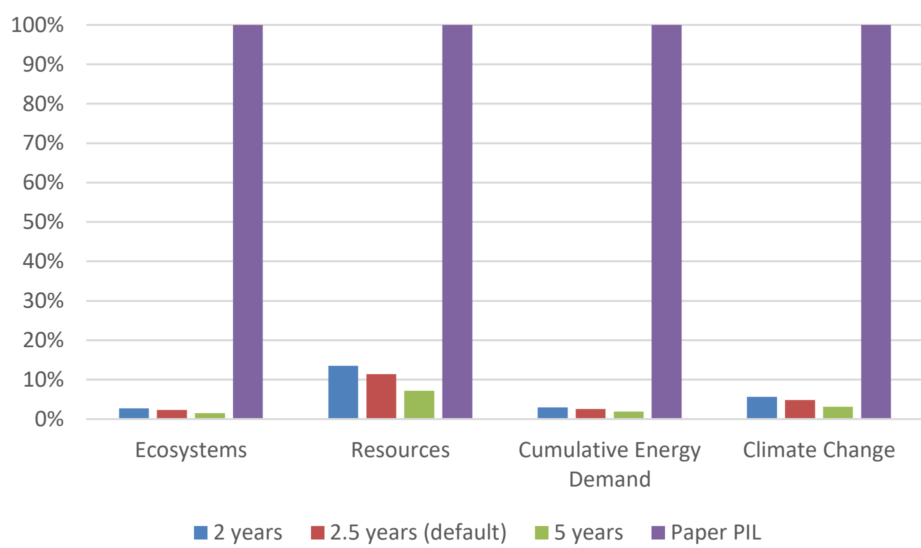

Figure 22: Sensitivity analysis of smartphone lifespan, per function unit, using the LTS Method.

6.4.6 Energy for data transfer

The default scenario is to assume that the energy for data transfer is 0.0001 kWh/MB (Pihkola, Hongisto, Apilo, & Lasanen, 2018). This estimate is sourced from a study that used a top-down energy intensity estimate and publicly available data. We tested this assumption with another estimate for energy intensity of the internet of 0.00002 kWh/MB, from a bottom-up model (Schien & Preist, 2014). This decreases the impacts of the ePI, with a reduced energy impact.

We also tested this with a third estimate for data transfer energy of 0.00042 kWh/MB. This number is originally sourced from a study that reviewed 14 estimates for the average electricity intensity of fixed-line internet transmission networks over time (Aslan, Mayers, & Koomey, 2017). As done in a previous LCA comparing paper to digital statements, we extrapolated this energy intensity to be 0.00042 kWh/MB by the year 2020. "The system boundary for the system includes data centers, Internet Protocol (IP) core network, access networks, home/on-site networking equipment, and user devices. This does not include the production of the data centers themselves or the electronic equipment," (WSP, 2018). This calculation was made by assuming that the energy intensity of data transmitted over the internet decreases by 30% per year (Coroama & Hilty, 2014). See Table 7 below.

Table 7: Energy intensity for data transfer adjustment calculations

Year	Calculation	Energy Intensity (kWh/MB)
2016	None	0.00173
2017	0.00173 * 70%	0.00121
2018	0.00121* 70%	0.00085
2019	0.00085* 70%	0.00059
2020	0.00059* 70%	0.00042

As shown in Figure 23, when the energy for data transfer assumption is increased (with the Aslan et al. 2017 scenario), the ePI still has lower environmental impacts compared to the paper PIL in all scenarios and impact categories.

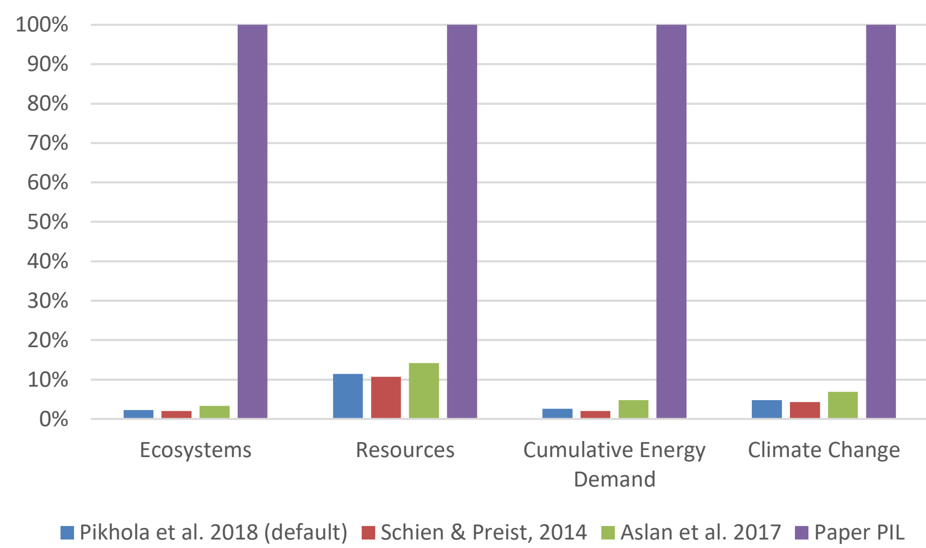

Figure 23: Sensitivity analysis of energy for data transfer, per function unit, using the LTS Method.

6.4.7 Different Impact Assessment Method Scenario

ISO 14044 requires testing the sensitivity of the results to the selected method. This approach allows for the confirmation of general patterns in the results. IMPACT World+ Midpoint[4] method was used. As shown in Figure 24, similar conclusions are reached in all midpoint impact categories, where the ePI has fewer environmental impacts in all categories than the paper PIL.

However, the following midpoint categories using IMPACT World+ are not certain when using a Monte Carlo analysis: water scarcity; land transformation, biodiversity; human toxicity non-cancer; and human toxicity cancer. Therefore, the human health endpoint category with IMPACT World+ is not within the 95% confidence interval. This is a similar result as explained in section 5.2.1, where the results for human health using the LTS Method fell below the 95% confidence interval.

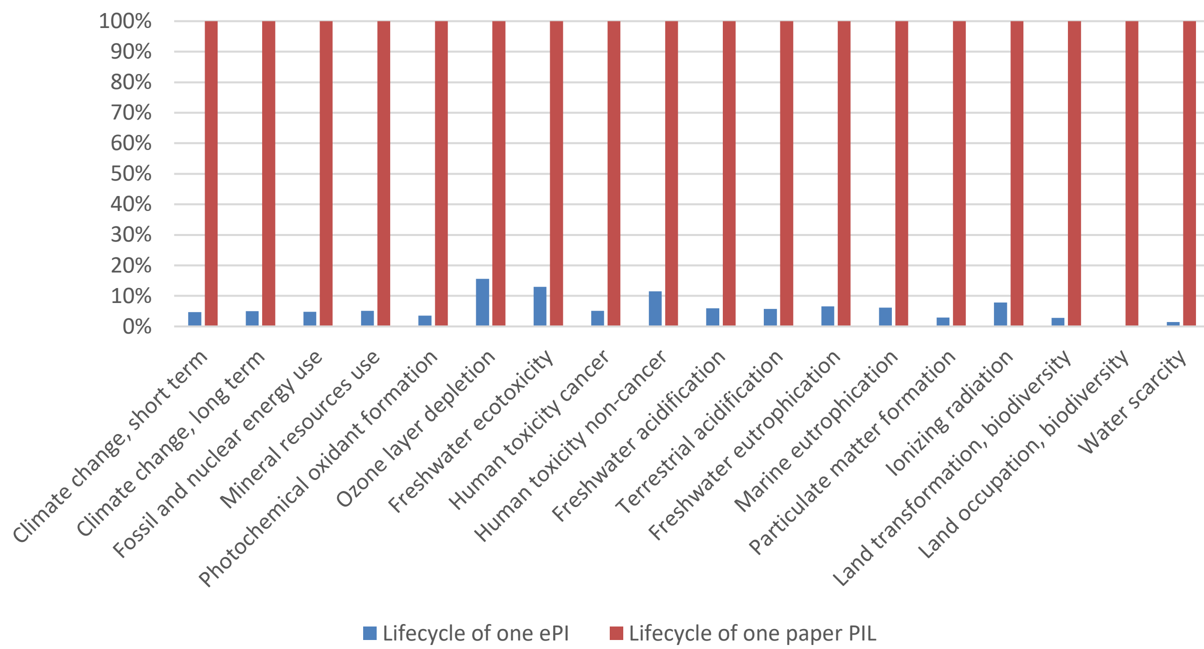

Figure 24: Scenario analysis of impact assessment method comparing one paper PIL to one ePI, cradle-to-grave, using the IMPACT World+ Midpoint method.

[4] Supporting documents for IMPACT World+ can be found at https://www.impactworldplus.org/.

7 Conclusions & Recommendations

The overarching goal of this study is to understand the difference in environmental impacts between the average European market paper patient information leaflet (PIL) and the digital version, an ePI viewed on a smartphone. Based on the results and study assumptions, methods and data, the majority of the cradle-to-grave environmental impacts of the paper PIL come from the paper, whereas the majority of the impacts of the ePI come from the smartphone device and secondly the energy for data transfer.

Compared to the paper PIL, the ePI has 89% - 98% fewer environmental impacts in all impact categories, both endpoint and midpoint. Varying the paper from virgin to recycled, the time spent viewing the ePI, the smartphone lifespan, and the energy for data transfer, the ePI still has lower impacts in all impact categories. In fact, this study made some conservative estimates for the ePI, including an assumption that 100% of ePI would be viewed (QR code scanned), that each person would spend 10.5 minutes reading the ePI, and only a 2.5-year assumption for smartphone lifespan. In one survey, 37% of patients said they always read the PIL, while 52% said they occasionally read it (Hammar, Nilsson, & Hovstadius, 2016).

Results for the human health and water use impact categories fell below the 95% confidence interval, therefore results in those two impact categories are not statistically significant.

The primary recommendation from this study is for pharmaceutical companies to switch from using paper PILs to ePI to reduce environmental impacts significantly. If the pharmaceutical companies continue to use some paper PILs, the size of the PIL should be reduced to reduce the weight of paper needed. Reducing the number of words in the PIL and re-structuring the content to make it easier for the patient to read would reduce the paper needed in a paper PIL, as well as reduce the reading time needed for an ePI. Both improvements would reduce the PIL environmental impacts. Regulatory requirements for the PIL would still need to be followed if it were to be redesigned for each medication. Additionally, maximizing the recycled content in the paper PIL would reduce impacts in most impact categories, as shown in a sensitivity analysis.

In future studies, the accuracy and certainty of the results could be improved with more primary data collection for both paper PILs and ePI. The study would benefit from behavioral data on the likelihood of a patient to: scan the QR code to read the ePI, not read it at all, or ask the pharmacy to print the paper PIL.

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Appendix A: Additional Life Cycle Inventory Data

The life cycle inventory data used in this study are listed below.

8.1 Paper PIL

8.1.1 Paper, ink, & printing

Table 8: Paper, ink, & printing: Inputs per 1 kg of printed paper

Description	LCI Data Source	Quantity	Unit	Notes
Virgin printed paper {CH}	Printed paper, offset {CH}| offset printing, per kg printed paper | Cut-off, U	0.5	kg	
Virgin printed paper {Europe}	Takeda_Printed paper, offset {Europe without Switzerland}| offset printing, per kg printed paper | Cut-off, U	0.5	kg	This is a custom process using the {CH} ecoinvent process, changing any {CH} LCI to {Europe without Switzerland} LCI.

8.1.2 Paper folding energy estimate

Table 9: Inputs per 1 kWh of electricity to fold paper PIL

Description	LCI Data Source	Quantity	Unit	
Electricity {CH}	Electricity, low voltage {CH}| market for electricity, low voltage | Cut-off, U	0.5	kWh	Assume 50% of folding happens in Swiss printing facilities.
Electricity {Europe}	Electricity, low voltage {Europe without Switzerland}| market group for electricity, low voltage | Cut-off, U	0.5	kWh	Assume 50% of folding happens in broader Europe printing facilities.

8.1.3 Packaging of paper PIL from printing site

Table 10: Packaging inputs and outputs per 1 kg of printed PIL ready to be transported to Basel, Switzerland

Description	LCI Data Source	Quantity	Unit	Notes
Inputs				
Banderole (Plastic)	Packaging film, low density polyethylene {GLO}| market for packaging film, low density polyethylene | Cut-off, U	0.00104	kg	
Bundle wrap (Plastic foil)	Packaging film, low density polyethylene {GLO}| market for packaging film, low density polyethylene | Cut-off, U	0.00173	kg	
Dividers (Paper)	Paper, newsprint {RER}| market for paper, newsprint | Cut-off, U *and*	0.03264	kg	
Shipper (Carton)	Folding boxboard carton {RER}| market for folding boxboard carton | Cut-off, U	0.02250	kg	
Outputs				
Waste plastic	Waste polyethylene {CH}| market for waste polyethylene | Cut-off, U	0.00277	kg	Includes transport
Waste paper (trash)	Waste graphical paper {Europe without Switzerland}| market group for waste graphical paper | Cut-off, U	0.03364*0.295	kg	Includes transport
Waste paper (recycling)	Paper (waste treatment) {GLO}| recycling of paper | Cut-off, U	0.03364*0.705	kg	
Waste paperboard (trash)	Waste paperboard {CH}| market for waste paperboard | Cut-off, U	0.02250*0.295	kg	Includes transport
Waste paperboard (recycling)	Paper (waste treatment) {GLO}| recycling of paper | Cut-off, U	0.02250*0.705	kg	

8.1.4 Transport of Paper PIL

Table 11: Transportation inputs per 1 kg of paper PIL

Description	LCI Data Source	Quantity	Unit
Transport from printing facility to packaging facility in Basel	Transport, freight, lorry 16-32 metric ton, EURO6 {RER}| market for transport, freight, lorry 16-32 metric ton, EURO6 | Cut-off, U	633.4976	kgkm
Transport from packaging facility to distribution centers	Transport, freight, lorry 16-32 metric ton, EURO6 {RER}| market for transport, freight, lorry 16-32 metric ton, EURO6 | Cut-off, U	1500	kgkm
Transport from distribution centers to pharmacies/hospitals	Transport, freight, lorry 7.5-16 metric ton, EURO6 {RER}| market for transport, freight, lorry 7.5-16 metric ton, EURO6 | Cut-off, U	200	kgkm

8.1.5 Lifecycle of one paper PIL

Table 12: Inputs and outputs in the Lifecycle of one paper PIL, cradle-to-grave

Description	LCI Data Source	Quantity	Unit	Notes
Inputs				
Paper, ink, & printing	LCA model	0.0035	kg	
Paper folding energy estimate	LCA model	0.0000034	kWh	
Packaging of paper PIL from printing site	LCA model	0.0035	kg	
Transport of paper PIL	LCA model	0.0035	kg	
Outputs				
Paper PIL disposal (trash)	Waste graphical paper {Europe without Switzerland}| market group for waste graphical paper | Cut-off, U	0.0035*0.295	kg	Includes transport
Paper PIL disposal (recycling)	Paper (waste treatment) {GLO}| recycling of paper | Cut-off, U	0.0035*0.705	kg	

8.2 ePI

8.2.1 Lifecycle of one ePI

Table 13: Inputs in the Lifecycle of one paper ePI, cradle-to-grave

Description	LCI Data Source	Quantity	Unit	Notes
QR code: ink & printing	Takeda without paper_Printed paper, offset {Europe without Switzerland}| offset printing, per kg printed paper | Cut-off, U	0.0516	g	This is a custom process using the ecoinvent process but removing paper, to get the rest of the printing inputs/outputs.
Internet access equipment	Internet access equipment {GLO}| market for internet access equipment | Cut-off, U	11	minutes	Equipment lifetime is 6 years. Includes EOL.
Smartphone device	Consumer electronics, mobile device, smartphone {GLO}| market for consumer electronics, mobile device, smartphone | Cut-off, U	11	minutes	Smartphone lifetime 2.5 years. Includes EOL.

Smartphone electricity	Electricity, low voltage {RER}| market group for electricity, low voltage | Cut-off, U	11	minutes	Smartphone uses 1.83 kWh/yr
Energy for data transfer	Electricity, low voltage {RER}| market group for electricity, medium voltage | Cut-off, U	0.000196	kWh	1.95 MB file at 0.0001 kWh/MB

Appendix B: The LTS Method: Description of Impact Methods and Categories

Impact assessment methods are used to convert life cycle inventory (LCI) data (environmental emissions and raw material extractions) into a set of environmental impacts. The LTS 2023 Method v1.00, created by Long Trail Sustainability, covers a range of midpoint and endpoint impacts. The method combines ReCiPe 2016 Endpoint (H) v1.08 with Climate Change and Water Use.

Table 14: LTS 2023 Method v1.00.

Impact Category	Unit	Method	Description
Human Health	Disability Adjusted Life Years (DALY)	ReCiPe 2016 Endpoint (H) v1.08	Includes human health impacts from Climate Change, Human Toxicity, Photochemical Oxidant Formation, Particulate Matter Formation, Ionizing Radiation and Ozone Depletion
Ecosystems	Species * yr	ReCiPe 2016 Endpoint (H) v1.08	Includes ecosystem impacts from Climate Change, Terrestrial Acidification, Freshwater Eutrophication, Ecotoxicity, Agricultural Land Occupation, Urban Land Occupation and Natural Land Transformation
Resources	$/kg	ReCiPe 2016 Endpoint (H) v1.08	Includes resource impacts from Fossil Depletion and Metal Depletion
Cumulative Energy Demand	MJ	CED V1.11	Includes both renewable and non-renewable energy types
Climate Change	kg CO_2 eq.	IPCC 2021 GWP 100a v1.02	Combines the effect of the periods of time that the various greenhouse gases remain in the atmosphere and their relative effectiveness in absorbing outgoing infrared radiation
Water Use	m^3	ReCiPe 2016 Midpoint (H) v1.08	Measures the amount of fresh water consumed

Each impact category is characterized by a unit of measure to which the resource and emission flows have been normalized. To aggregate the substances into the impact categories, substances are multiplied by their characterization factor to convert into an equivalent substance (e.g. CO_2) and then added together to create a total for each impact category (e.g., climate change). The life cycle impact assessment (LCIA) results are relative expressions and do not predict impacts on category endpoints, the exceeding of thresholds, safety margins or risks.

ReCiPe 2016, one of the most recent and updated impact assessment methods available to LCA practitioners, addresses a number of environmental concerns at the midpoint level and then aggregates the midpoints into a set of three endpoint impact categories. Endpoint characterization models the impact on Areas of Protection (i.e., on human health, ecosystems, and resources). In other words, endpoint is a measure of the damage – at the end of the cause-effect chain – caused by a stressor in terms of human life-years lost and the years lived disabled (human health), species disappeared (ecosystems), and resources lost (resources).

The Cumulative Energy Demand (CED) of a product is the direct and indirect energy use throughout the life cycle, including the energy consumed during the extraction, manufacturing and disposal. The CED method considers both renewable and non-renewable energy and the direct and indirect energy consumption. For its implementation in SimaPro, the method published by Ecoinvent (Frischknecht *et al*. 2007) is used. The method is expanded further by PRé Consultants to include the energy resources available in SimaPro.

The IPCC 2021 method for assessing Global Warming Potential (i.e., Climate Change) was developed by the International Panel on Climate Change (IPCC) and is one of the most widely used methods to estimate the climate change potential of global warming gases in LCA studies. The global warming factors have been developed for 20- and 100-year time horizons to address the global warming potential of emissions in both the short and long term. This study uses the climate change factors for the 100-year time horizon.

8.3 Endpoint Categories

Human Health: In this category, the damage analysis links the six midpoint categories (Climate Change, Human Toxicity, Photochemical Oxidant Formation, Particulate Matter Formation, Ionizing Radiation, and Ozone Depletion) to the Disability Adjusted Life Years (DALYs). The DALY tool is primarily a disability weighting scale of 0 – 1, where 0 represents perfect health and 1 represents death.

Ecosystems: The damage to ecosystems is measured by calculating the species that disappear in a given time period and area. The unit of damage assessment is species*yr. The midpoint impact potentials that apply to ecosystem quality are: Climate Change, Terrestrial Acidification, Freshwater Eutrophication, Ecotoxicity, Agricultural Land Occupation, Urban Land Occupation and Natural Land Transformation.

Resources: The two midpoint categories contributing to the resources category are Fossil Depletion and Metal Depletion. The quantification of the damage is based on the marginal increase of cost due to the extraction of resources, measured as U.S. dollars per kilogram ($/kg).

8.4 Midpoint Categories

Climate Change: There are several gaseous emissions that cause global warming, including carbon dioxide (CO_2), methane, nitrous oxides and fluorinated gases. This category combines the effect of the periods of time that the various greenhouse gases remain in the atmosphere and their relative effectiveness in absorbing outgoing infrared radiation. The global warming potential is measured as kg equivalents of CO_2 (i.e., the relative global warming potential of a gas as compared to CO_2). The IPCC model with a 100-year time horizon is used for characterization. The uptake of CO_2 from the air (i.e., sequestration of CO_2 by plants) and the subsequent emission of biogenic CO_2 (from the burning of biomass) is not included.

Water Use: This category measures the amount of fresh water consumed. This does not include regionalized characterization factors, nor the impact that water draw has on humans or the environment. The unit is m^3 of water consumed.

Appendix C: Uncertainty Analysis

8.5 Pedigree Matrix

In practice, all data used in an LCA study is a mixture of measured, estimated, and calculated data and its quality is rarely homogenous. In this study, some data is very reliable while some has been estimated. To evaluate the quality of data used for modeling the three siding product systems, Data Quality Indicators (DQI) have been assigned to each flow using the data quality matrix approach. These scores have also been used to assess uncertainties on the data and to subsequently assess the uncertainty of the model and the results.

Six types of DQI are evaluated by the Pedigree matrix (Weidema & Wesnaes, 1996) by using scores from 1 to 5:

1. Reliability (related to the reliability of the collected *primary* data);
2. Completeness (related to the completeness of the *primary* data);
3. Temporal correlation (related to the temporal correlation of the *primary* data);
4. Geographical correlation (related to the geographical correlation of the *secondary* data used);
5. Further technological correlation (related to the technological correlation of the *secondary* data used); and
6. Sample size (Considered obsolete, therefore N/A was used).

In addition, a score is given to the basic uncertainty of the measured input or output. Inputs to a manufacturing process are given a low uncertainty, for example, since these quantities are well known and often metered. Higher uncertainties are given to transportation, for example, since transportation routes may change based on weather, construction, accidents, etc., and to emissions such as carbon monoxide, which may vary from engine to engine and even from week to week using the same engine. Scores are assigned to the data based on the criteria presented in the Pedigree matrix and a Monte Carlo uncertainty analysis is conducted to determine the influence of data quality on the significance of the study results.

Scores have been assigned to the data in the SimaPro model based on the criteria presented in the Pedigree matrix. Table 15 presents the Pedigree matrix which was used to assign uncertainty to the modeled data. Table 16 shows the scores assigned to each piece of primary data or estimate in the model (foreground data).

Table 15: Pedigree matrix

DQI	1	2	3	4	5
Reliability	Verified data based on measurements	Verified data partly based on measurements OR non-verified data based on measurements	Non-verified data partly based on qualified estimates	Qualified estimates (e.g., by industrial experts), data derived from theoretical information	Non-qualified estimate
Completeness	Representative data from all sites relevant for the market considered over an adequate period to even out normal fluctuations	Representative data from >50% of the sites for the market considered over an adequate period to even out normal fluctuations	Representative data from only some sites (<50%) relevant for the market considered OR >50% of the sites but from shorter periods	Representative data from only one site for the market considered OR some sites but from shorter periods	Representativeness unknown or data from a small number of sites AND from short periods
Temporal correlation	Less than 3 yrs of difference to reference year	Less than 6 yrs of difference to reference year	Less than 10 yrs of difference to reference year	Less than 15 yrs of difference to reference year	Age of data unknown OR more than 15 yrs difference from reference year
Geographical correlation	Data from area under study	Average data from smaller area than area under study or from similar area	Data from smaller area than area under study, or from similar area	Data from area with slightly similar production conditions	Data from unknown or distinctly different area
Further technological correlation	Data from enterprises, processes and materials under study (i.e., identical technology)	Data from processes or materials under study (i.e. identical technology) but from different enterprises	Data from related processes or materials but same technology, OR data from processes and materials under study but from different technology OR process partially represented	Data from related processes or materials but different technology, OR data on laboratory scale processes and same technology	Data on related processes or materials but on laboratory scale of different technology

Table 16: Data quality ratings for all primary data points in the model

Datapoint in model	Reliability	Completeness	Temporal correlation	Geographical correlation	Technological correlation
Packaging of paper leaflet from Printing Site	1	3	2	1	1
Paper folding energy estimate	1	1	4	1	4
Distribution average: transport from printing facility to pharmaceutical packaging facility	3	1	1	1	1
Distribution average: transport from pharmaceutical packaging facility to distribution centers	4	1	1	1	1
Distribution average: transport from distribution centers to pharmacies/hospitals	2	1	1	1	1
Weight of paper PIL	2	1	1	1	1
Total number of PILs in one year	1	1	1	1	1
File Size of ePI	2	1	1	1	1
Energy for data transfer	2	1	1	2	2
Amt. of time to view ePI	3	1	1	1	1
ePI QR code: ink & printing	4	1	1	1	3
Smartphone electricity usage	2	1	1	1	1
Lifespan of smartphone	2	1	1	2	1
Internet Access Equipment	1	1	1	2	2
Percentage of the time people view ePI	4	1	2	1	2

Appendix D: Midpoint Impact Category Results

The LTS Method is comprised of a range of midpoint and endpoint impact categories. The three ReCiPe endpoints (human health, ecosystems and resources) are reported in 18 midpoint categories. Cumulative Energy Demand is further detailed into six inventory categories, separating non-renewable and renewable energy types. Climate Change is further detailed in GWP 100 fossil, biogenic, and land transformation. The midpoint results for the endpoints included are provided below.

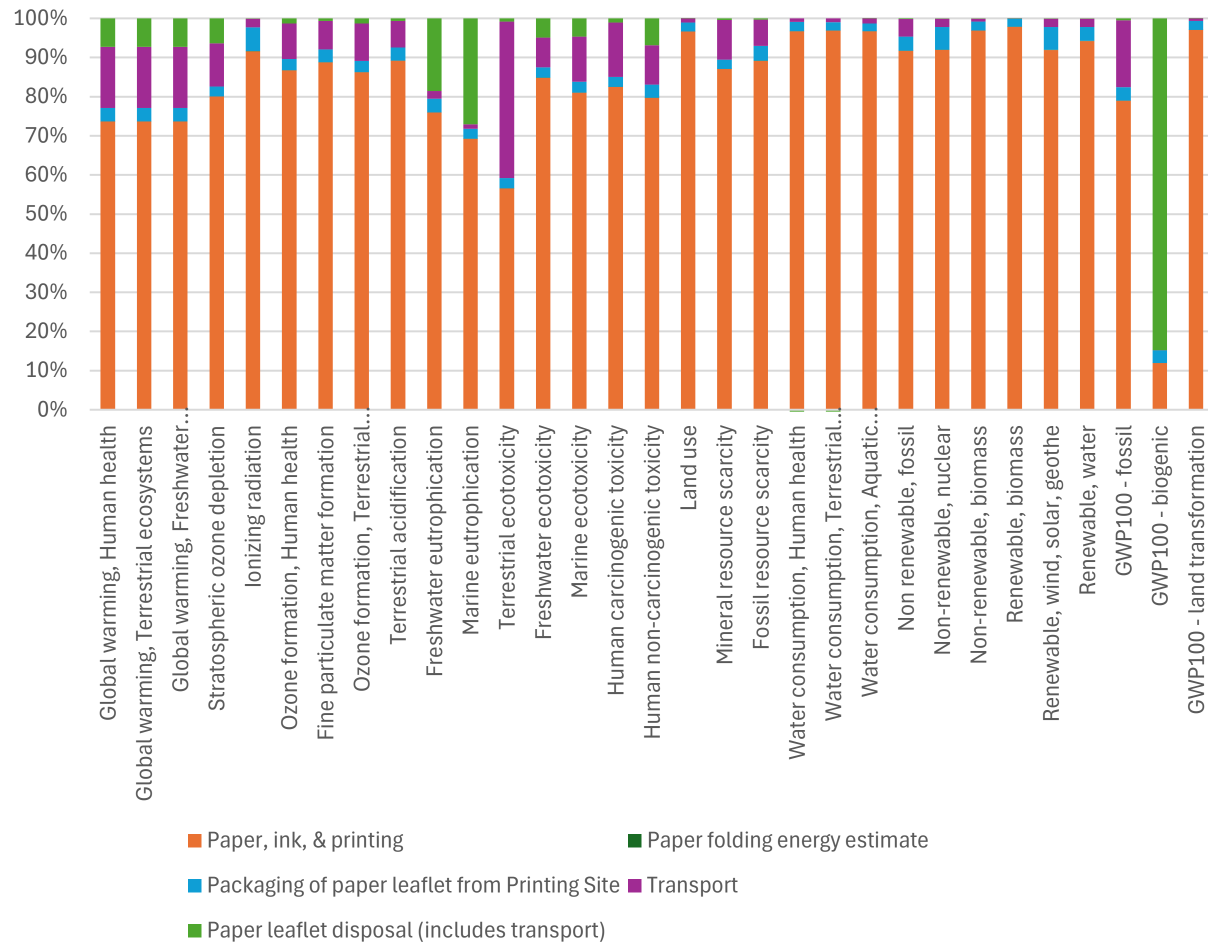

Figure 25: Contribution analysis for the lifecycle of one paper PIL, using the LTS method, midpoint category results.

Table 17: Contribution analysis for the lifecycle of one paper PIL, using the LTS method, midpoint category results.

Impact Category (Unit)	Paper, ink, & printing	Paper folding energy estimate	Packaging of paper leaflet from Printing Site	Transport	Paper leaflet disposal (includes transport)	TOTAL
Global warming, Human health	7.11E-09	5.82E-13	3.30E-10	1.51E-09	7.02E-10	9.65E-09
Global warming,	2.14E-11	1.76E-15	9.95E-13	4.55E-12	2.12E-12	2.91E-11

Terrestrial ecosystems						
Global warming, Freshwater ecosystems	5.86E-16	4.79E-20	2.72E-17	1.24E-16	5.78E-17	7.95E-16
Stratospheric ozone depletion	2.80E-12	2.14E-16	9.13E-14	3.84E-13	2.25E-13	3.50E-12
Ionizing radiation	9.04E-12	4.90E-15	5.97E-13	2.22E-13	5.82E-15	9.87E-12
Ozone formation, Human health	2.20E-11	1.13E-15	7.25E-13	2.29E-12	3.38E-13	2.54E-11
Fine particulate matter formation	8.37E-09	6.89E-13	3.05E-10	6.88E-10	5.89E-11	9.43E-09
Ozone formation, Terrestrial ecosystems	3.33E-12	1.65E-16	1.08E-13	3.71E-13	4.91E-14	3.86E-12
Terrestrial acidification	5.93E-12	5.87E-16	2.23E-13	4.46E-13	4.52E-14	6.64E-12
Freshwater eutrophication	3.62E-12	4.02E-16	1.65E-13	9.35E-14	8.83E-13	4.76E-12
Marine eutrophication	1.69E-15	7.45E-20	6.24E-17	2.72E-17	6.62E-16	2.45E-15
Terrestrial ecotoxicity	2.69E-13	2.92E-17	1.08E-14	2.76E-13	3.04E-15	5.59E-13
Freshwater ecotoxicity	3.30E-13	9.80E-17	1.03E-14	2.91E-14	1.92E-14	3.89E-13
Marine ecotoxicity	6.43E-14	1.85E-17	2.10E-15	7.27E-15	3.91E-15	7.76E-14
Human carcinogenic toxicity	5.83E-09	3.98E-13	1.84E-10	9.77E-10	7.73E-11	7.06E-09
Human non-carcinogenic toxicity	2.26E-09	3.96E-13	9.49E-11	2.86E-10	1.93E-10	2.83E-09
Land use	5.46E-11	3.93E-16	1.32E-12	5.70E-13	1.34E-14	5.65E-11
Mineral resource scarcity	8.36E-06	1.05E-09	2.29E-07	9.74E-07	3.60E-08	9.60E-06
Fossil resource scarcity	3.02E-05	3.00E-09	1.30E-06	2.27E-06	1.05E-07	3.39E-05
Water consumption, Human health	4.25E-10	1.06E-14	1.03E-11	4.10E-12	-2.17E-12	4.37E-10
Water consumption, Terrestrial ecosystem	2.67E-12	6.50E-17	6.07E-14	2.60E-14	-1.31E-14	2.75E-12
Water consumption, Aquatic ecosystems	1.83E-16	2.89E-21	3.79E-18	2.44E-18	2.35E-20	1.89E-16

Non renewable, fossil	2.96E-02	3.44E-06	1.15E-03	1.44E-03	6.49E-05	3.23E-02
Non-renewable, nuclear	2.11E-02	1.08E-05	1.33E-03	4.90E-04	1.28E-05	2.29E-02
Non-renewable, biomass	1.24E-04	1.50E-10	2.90E-06	9.76E-07	5.29E-08	1.28E-04
Renewable, biomass	1.47E-01	6.14E-07	3.15E-03	8.71E-05	2.78E-06	1.50E-01
Renewable, wind, solar, geothermal	4.32E-03	2.31E-06	2.72E-04	1.02E-04	2.98E-06	4.70E-03
Renewable, water	8.63E-03	6.32E-06	3.21E-04	1.98E-04	5.92E-06	9.16E-03
GWP100 - fossil	7.32E-03	6.12E-07	3.20E-04	1.59E-03	4.29E-05	9.27E-03
GWP100 - biogenic	8.16E-05	2.63E-09	2.18E-05	2.61E-07	5.78E-04	6.81E-04
GWP100 - land transformation	8.26E-05	1.75E-09	1.98E-06	5.24E-07	1.69E-08	8.52E-05

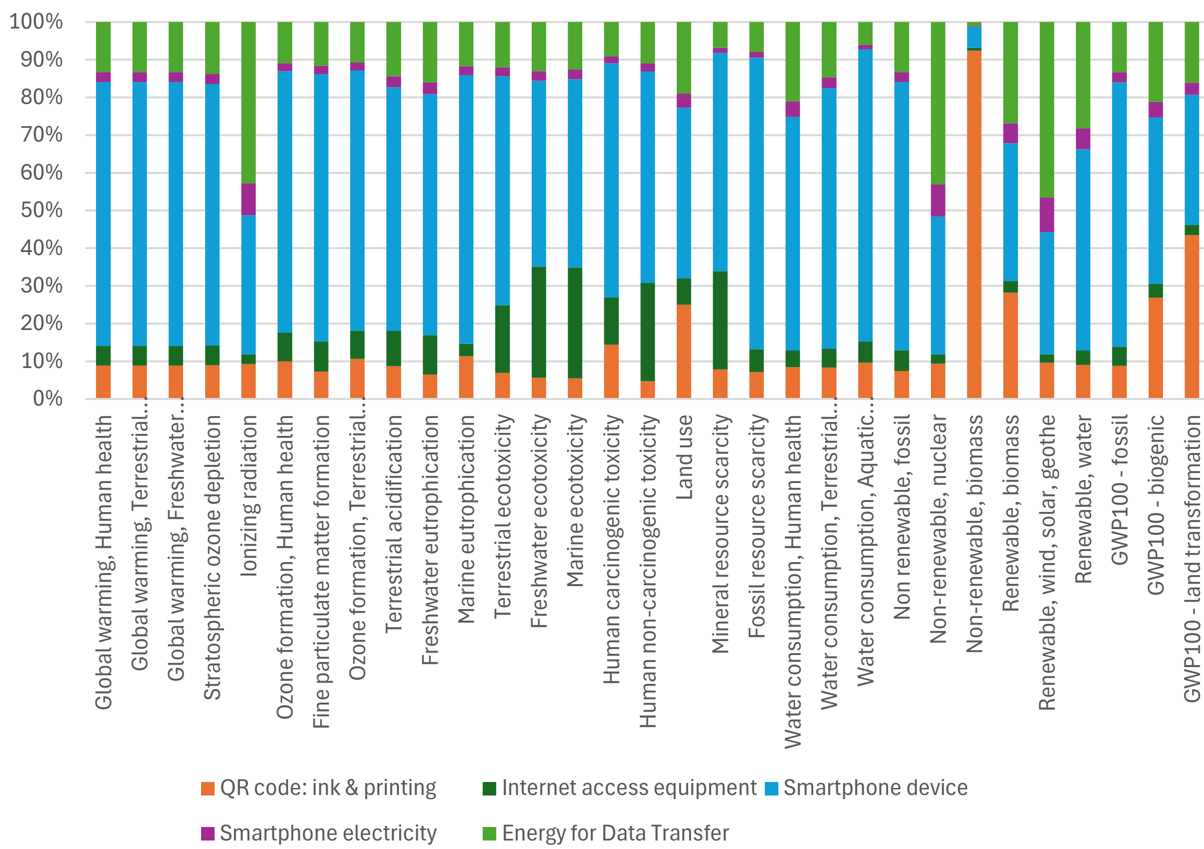

Figure 26: Contribution analysis for the lifecycle of one ePI, using the LTS method, midpoint category results.

Table 18: Contribution analysis for the lifecycle of one ePI, using the LTS method, midpoint category results.

Impact Category (Unit)	QR code: ink & printing	Internet access equipment	Smartphone device	Smartphone electricity	Energy for Data Transfer	TOTAL
Global warming, Human health	4.05E-11	2.35E-11	3.20E-10	1.19E-11	6.07E-11	4.56E-10
Global warming, Terrestrial ecosystems	1.22E-13	7.08E-14	9.65E-13	3.59E-14	1.83E-13	1.38E-12
Global warming, Freshwater ecosystems	3.34E-18	1.93E-18	2.63E-17	9.79E-19	5.01E-18	3.76E-17
Stratospheric ozone depletion	1.05E-14	6.18E-15	8.12E-14	3.16E-15	1.61E-14	1.17E-13
Ionizing radiation	7.06E-14	1.92E-14	2.81E-13	6.37E-14	3.25E-13	7.60E-13
Ozone formation, Human health	1.01E-13	7.76E-14	7.05E-13	2.17E-14	1.11E-13	1.02E-12
Fine particulate matter formation	4.15E-11	4.57E-11	4.06E-10	1.30E-11	6.65E-11	5.73E-10
Ozone formation, Terrestrial ecosystems	1.60E-14	1.13E-14	1.04E-13	3.18E-15	1.62E-14	1.51E-13
Terrestrial acidification	3.35E-14	3.62E-14	2.50E-13	1.09E-14	5.58E-14	3.87E-13
Freshwater eutrophication	1.71E-14	2.75E-14	1.69E-13	8.27E-15	4.23E-14	2.64E-13
Marine eutrophication	7.18E-18	2.08E-18	4.53E-17	1.45E-18	7.43E-18	6.34E-17
Terrestrial ecotoxicity	8.58E-16	3.34E-15	9.86E-15	3.80E-16	1.94E-15	1.64E-14
Freshwater ecotoxicity	2.66E-15	1.40E-14	2.34E-14	1.21E-15	6.19E-15	4.75E-14
Marine ecotoxicity	5.07E-16	2.77E-15	4.64E-15	2.31E-16	1.18E-15	9.33E-15
Human carcinogenic toxicity	5.14E-11	4.50E-11	2.23E-10	6.38E-12	3.26E-11	3.58E-10
Human non-carcinogenic toxicity	1.30E-11	7.22E-11	1.55E-10	5.96E-12	3.05E-11	2.77E-10
Land use	2.94E-14	8.16E-15	5.33E-14	4.36E-15	2.23E-14	1.17E-13
Mineral resource scarcity	7.51E-08	2.50E-07	5.55E-07	1.28E-08	6.53E-08	9.58E-07
Fossil resource scarcity	2.87E-07	2.42E-07	3.09E-06	6.20E-08	3.17E-07	4.00E-06

Water consumption, Human health	4.51E-13	2.35E-13	3.30E-12	2.19E-13	1.12E-12	5.33E-12
Water consumption, Terrestrial ecosystem	2.86E-15	1.71E-15	2.36E-14	9.76E-16	4.99E-15	3.41E-14
Water consumption, Aquatic ecosystems	4.08E-19	2.41E-19	3.29E-18	5.03E-20	2.57E-19	4.25E-18
Non renewable, fossil	2.11E-04	1.56E-04	2.02E-03	7.40E-05	3.78E-04	2.84E-03
Non-renewable, nuclear	1.57E-04	4.21E-05	6.15E-04	1.42E-04	7.24E-04	1.68E-03
Non-renewable, biomass	1.06E-06	8.74E-09	6.48E-08	2.23E-09	1.14E-08	1.14E-06
Renewable, biomass	5.23E-05	5.75E-06	6.78E-05	9.74E-06	4.98E-05	1.85E-04
Renewable, wind, solar, geothermal	4.30E-05	9.96E-06	1.45E-04	4.07E-05	2.08E-04	4.46E-04
Renewable, water	4.83E-05	2.05E-05	2.86E-04	2.96E-05	1.51E-04	5.36E-04
GWP100 - fossil	4.20E-05	2.47E-05	3.36E-04	1.25E-05	6.41E-05	4.80E-04
GWP100 - biogenic	1.80E-07	2.49E-08	2.95E-07	2.78E-08	1.42E-07	6.71E-07
GWP100 - land transformation	5.27E-07	3.23E-08	4.18E-07	3.82E-08	1.95E-07	1.21E-06

Figure 27 shows the midpoint comparative results for the paper PIL vs. the ePI. Similar to the endpoint results, the ePI has lower impacts than the paper PIL in all impact categories.

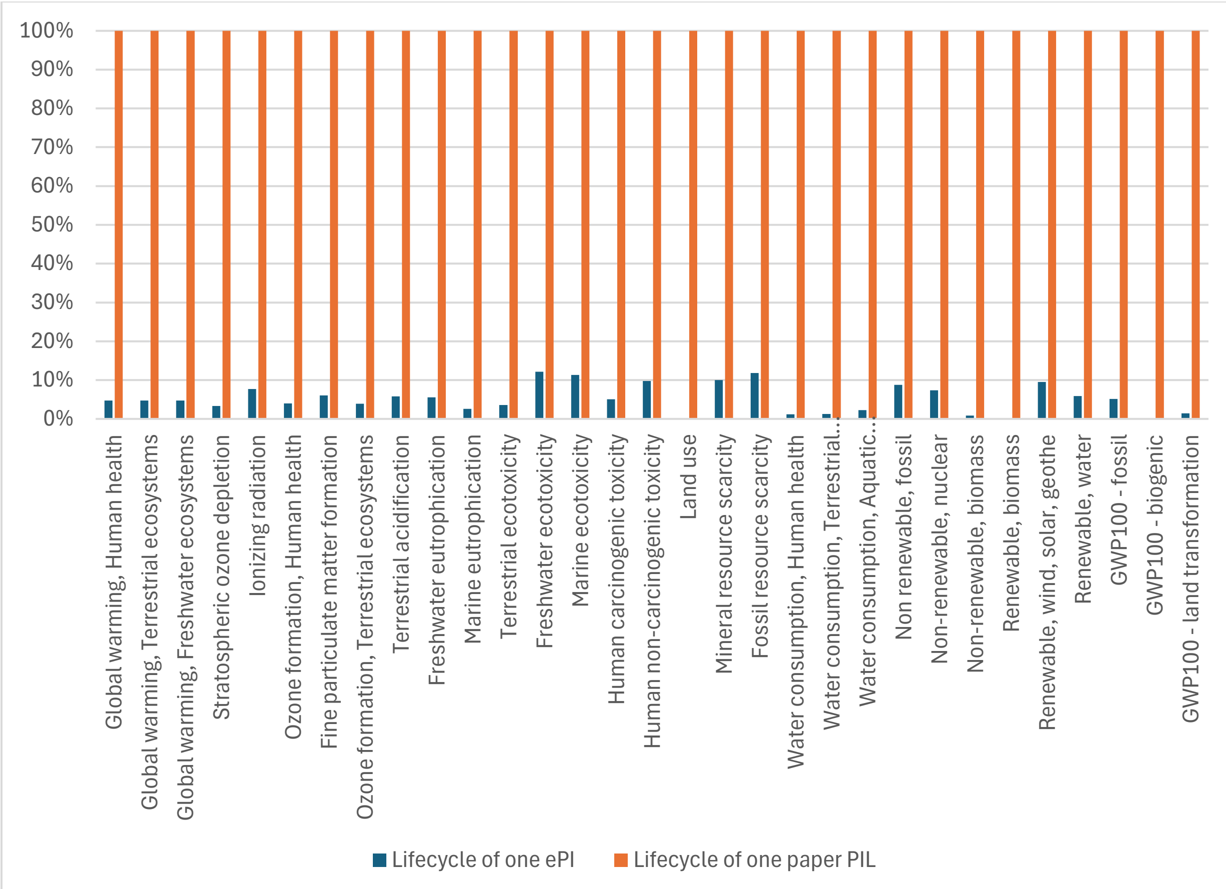

Figure 27: Comparative analysis of one paper PIL to one ePI, cradle-to-grave, using the LTS method, midpoint category results.

Figure 28 shows the uncertainty analysis at the midpoint indicator level, comparing the paper PIL vs. the ePl. Similar to the endpoint results, this indicates with a high level of certainty, within the 95% confidence interval, that one ePI has lower impacts than one paper PIL in most midpoint impact categories, with the exception of water use, water consumption categories, and human non-carcinogenic toxicity. The uncertainty in the human health endpoint category was driven by two midpoint categories: Human non-carcinogenic toxicity and Water consumption, Human health. All other human health midpoints were within the 95% confidence interval: Global warming, Human health; Stratospheric ozone depletion; Ionizing radiation; Ozone formation, Human health; Fine particulate matter formation; and Human carcinogenic toxicity.

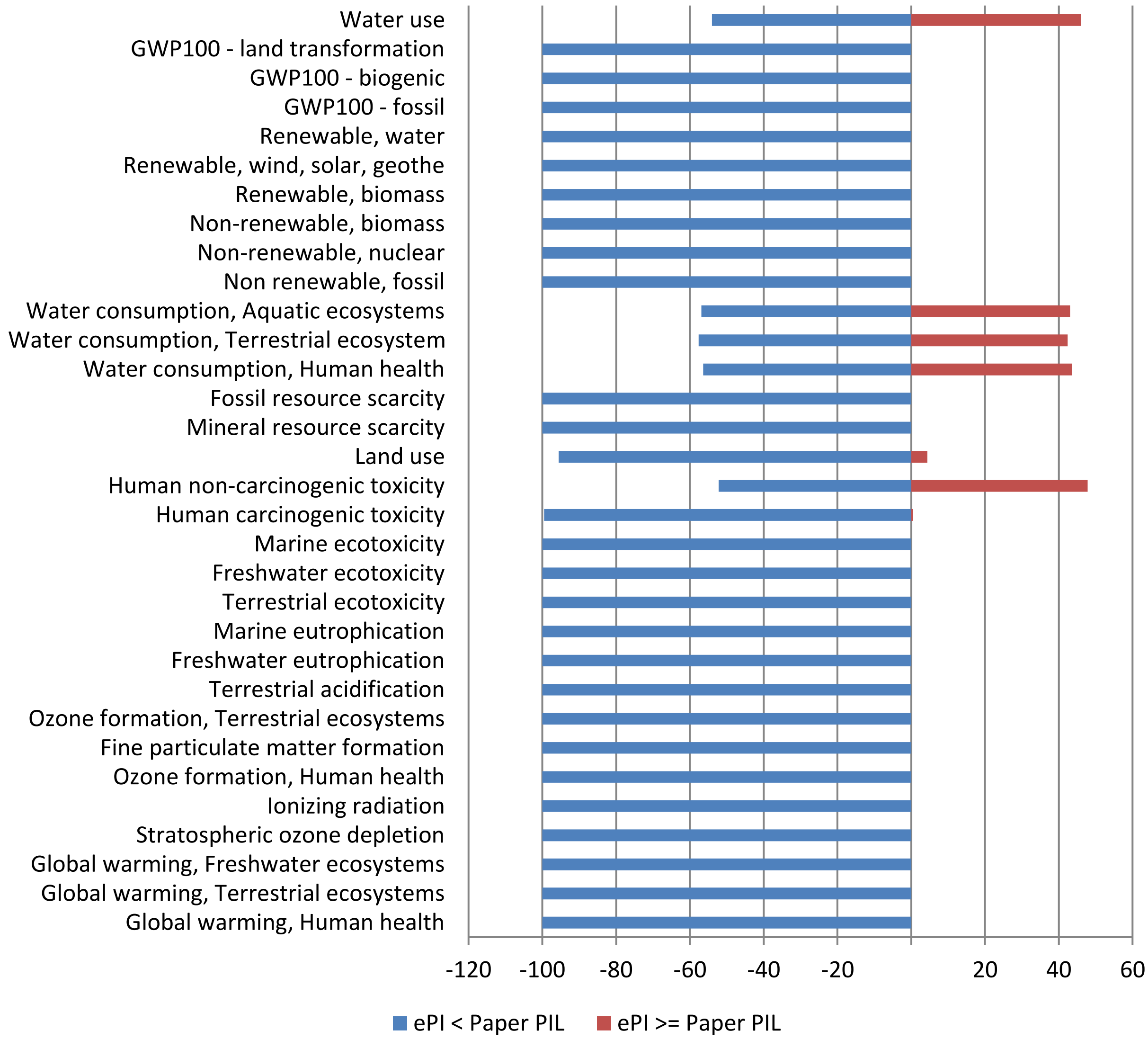

Figure 28: Uncertainty analysis of one paper PIL vs. one ePI, using the LTS Method, midpoint category results.

Appendix E: Critical Review Statement and Record

CRITICAL REVIEW STATEMENT

LIFE CYCLE ASSESSMENT OF PATIENT INFORMATION LEAFLETS

BACKGROUND

The life cycle assessment (LCA) study 'Life Cycle Assessment of Patient Information Leaflets' was undertaken by LCA practitioners from the consultancy Long Trail Sustainability (LTS) on behalf of Takeda. The goal of the study was to conduct an attributional, life cycle assessment (LCA) comparing the environmental performance of an average paper patient information leaflet (PIL) against an alternative digital version, an electronic patient information (ePI) document, as viewed on a smartphone. The study was undertaken for the European market.

The audience for the study includes the following:

- Takeda and other members of the European Federation of Pharmaceutical Industries and Associations (EFPIA), which represents innovative pharmaceutical companies present in the European market; and
- Customers of drug products (e.g. healthcare providers), patients/consumers, and other external stakeholders.

The intended use of the study is to:

- Inform EFPIA members on the environmental costs and benefits associated with moving to ePI from paper PIL; and to
- Communicate these findings to external stakeholders.

CRITICAL REVIEW PROCESS

The study was critically reviewed by a panel of three independent experts:

- Dr Peter Shonfield, ERM (panel chair);
- Dr Matt Fishwick, Fishwick Environmental; and
- Dr Matteo Cossutta, Aria Sustainability.

The reviewers are independent of any party with a commercial or any other interest in the study.

The aims of the critical review process were to ensure that:

- The methods used are consistent with ISO 14040 and ISO 14044;
- The methods used are scientifically and technically valid;
- The data used are appropriate and reasonable in relation to the goal of the study;
- The interpretations reflect the limitations identified and the goal of the study; and
- The study report is transparent and consistent.

The critical review process involved the following:

• Review of the initial LCA study report prepared by EFPIA members titled "Life-Cycle Assessment of E-leaflet vs Paper leaflet" dated 15 January 2024.

• Following feedback on the initial report Takeda engaged LTS to update the study. Two versions of the draft Goal and Scope Definition document (10 January 2025 and 6 February 2025) and two draft versions of the LCA Study Report (1 April 2025 and 14 May 2025) were reviewed by the panel according to the criteria listed above and recommendations for improvement were provided to LTS, who then provided their responses.

• A review of the third and final version of the report (29 May 2025), in which the authors of the study addressed all the reviewers' comments.

The critical review did not involve a review of the LCA models developed by LTS, so all the findings of the critical review are based solely on the LCA study report provided to the review panel during the review process.

CONCLUSION OF THE CRITICAL REVIEW

The reviewers confirm that this LCA study follows the guidance of, and is consistent with, the international standards for life cycle assessment (ISO 14040:2006 and ISO 14044:2006) as follows:

• The methods used are scientifically and technically valid given the goal of the study;

• The data used are appropriate and reasonable in relation to the goal of the study;

• The interpretation of the results and the conclusions of the study reflect the goal and findings of the study; and

• The study report is transparent and consistent.

This critical review statement is only valid for the final LCA study report as presented to the reviewers, dated 29 May 2025.

Dr Peter Shonfield | Dr Matt Fishwick | Dr Matteo Cossutta

02 June 2025

Goal and Scope comments (round 1)

Comment numb	Section	Line/Paragraph/ figure/tabl	Reviewer comment	Reviewer recommendation	Practitioner response Please state wl exactly has be	Reviewer response	Practitioner response
1	Goal and scope	General	The report is written very much in the style of bullet-point notes rather than a technical report. It requires much more detail and restructuring to meet the minimum ISO requirements and what is expected for an LCA report.	See ISO comments for requirements of content. As a general rule, an LCA report should have sufficient detail to allow the reader to understand exactly how the products were assessed, gain a detailed understanding of the environmental profile and conclusions, and be able to recreate results. Typically a comparative LCA report is in the order of 80-150 pages, with the goal and scope section being around 20 pages. Missing elements from the goal and scope: – the reasons for carrying out the study; – interpretation to be used; – data requirements; – value choices and optional elements; – data quality requirements; – type of critical review, if any; – type and format of the report required for the study. – Data quality requirements shall be specified to enable the goal and scope of LCA to be met and shall be characterized by both quantitative and qualitative aspects. Where a study is intended to be used in comparative assertions intended to be disclosed to the public, the data quality requirements stated in a) to j) in 4.2.3.6.2 shall be addressed. – Cumulative cut-off criteria.	This has all been added to the report.	Comment closed.	
2	Goal and scope	General	How is biogenic carbon treated? This is relevant for the paper PIL.	Provide section on how removals and emissions of biogenic carbon are dealt with.	Please see Table 1 in the report	Can an explanation of how biogenic carbon released as methane is considered in the method. Comment closed.	Please see Table 1 in the report. I have added in the methane explanation.
3	Goal and scope	General	It would be good to reference ISO 16759, as this standard deals specifically with carbon footprinting of printed paper.	Just a suggestion to read this standard and see if any recommendations can be used for this study.	I did not purchase this ISO standard.	Comment closed.	
4	Goal and scope	General	It is not clear whether conformance to ISO 14044 is being claimed by the way this text is framed.	It should be explicitly stated that the study conforms with these standards, as determined by a critical review by a panel of experts.	See section 3.11 'Critical Review', also this quote on pg. 11 "This study is modeled using SimaPro v9.6.0.1 LCA software (PRé Sustainability, 2024) and follows International Organization for Standardization (ISO) 14044 guidelines (ISO 14044, 2006b)." and the 3.1 Objectives on page 14.	"Following guidelines" should be changed to "confirms to the requirements of" on Pg 11. Comment closed.	Done.
5	Goal and scope	General	Leaflets are referred to with varying terminology throughout the report.	Use the standard terms that have already been introduced (PIL and ePIL) consistently through out the report. E.g. '...the use of paper patient information leaflets (PIL) and electronic patient information leaflets (ePIL) for ......'	Done. We are saying paper PIL and ePI throughout.	Comment closed.	
6	Goal and scope	General	It would be beneficial to add some details about the critical review.	Add to the report details such as the type of review, who reviewed the study and what the critical review entails. In addition, to confirm that publicly disclosed comparative assertions will be made.	See section 3.11 'Critical Review'. And section 3.1 'Objectives'. And Appendix E.	Comment closed.	
7	Goal and scope	General	Section, table and figure numbering would be usedul for cross-referencing. Currently there is no numbering of sections, tables or figures at all.		Done	Comment closed.	
8	Goal and scope	Pg 1	Function description should state that the PIL provides information for patients, not for prescribers and pharmacists (it is literally a "patient information leaflet").	Adapt text	Done	Comment closed.	
9	Goal and scope	Pg 1	No mention of intention to be used as comparative assention to be disclosed to the public. It mentions in the target audience that it'll have an "external use" but it is not clear what this means.		This has been edited accordingly in section 3.1 Objectives	Comment closed.	
10	Goal and scope	Pg 1	Product systems not described (there are system boundary diagrams but no written explanation). It can be deduced from the goal but there is no description of the systems. What is a Paper Information Leaflet? Where is it found (I guess inside medication carton)? How is the e-leaflet accessed, etc..		This is all now included in section 3.4 System Boundaries	Comment closed.	

11	Goal and scope	Pg 1	FU description is a bit bloated and contains more information than is needed specifically for the FU definition. The statement that the study is cradle-to-grave relates to the scope not the FU and should be removed as it is repeated in the section directly below.	Suggest that FU should be something like: One average 2020 European market patient information leaflet (PIL) provided as either paper leaflet or online. The other aspects mentioned here relate to assumptions for each leaflet and would need to be stated but do not form part of the FU. Should comment that that the online PIL being available in more languages could be regarded as functional difference between it and the paper PIL. However, this would not likely have relevance for the comparison since users would only	The functional unit has been changed.	Comment closed.	
12	Goal and scope	Pg 1	It is assumed that the ePIL will be accessed via a smart phone. Should other devices also be considered for the base case?	Consider adding other devices within the model e.g. ipad, PC. I do see that this is intended to be assessed in a sensitivity analysis (pg 6) which may resolve this issue	I wrote this is 4.2.2.3 Use Phase "We assumed that 100% of ePI viewing is on a smartphone as opposed to other electronic devices since it seems likely that this is the main type of device used to scan a QR code, as opposed to laptop	Comment closed.	
13	Goal and scope	Pg 1	No reference flows are specified.	Add to report	Added in 3.3 Functional	Comment closed.	
14	Goal and scope	Pg 2	System boundary makes it seem like emissions associated with recycling are		I have fixed this.	Comment closed.	
15	Goal and scope	Pg 3	Transport to customer is excluded for the paper leaflet. The statement that *"The added weight of the leaflet will not change the emissions of the consumer, whether driving a car, walking, or biking."* is not true for a car (more mass = more fuel needed to move). This is also inconsistent since transport has been included for other life cycle stages as shown in the system boundary.		I have changed the reasoning for this exclusion in the report. "The added weight of the leaflet will not change the emissions of the consumer if walking, or biking. If driving a passenger car, the added weight would make the car use more fuel, however, the ecoinvent processes for transport by passenger car only use the unit of km, rather than kgkm. Therefore, we were unable to represent the added weight to car transport from the paper PIL in the model."	Comment closed.	
16			"The data is written by a laser on a hard disk but does not use energy when it is sitting idle"		I have changed this to say magnetic in the study.	Comment closed.	
17	Goal and scope	Pg 3	Cut off criteria only refers to 1% environmental impact cut off. How will you establish whether this threshhold has been met (there is no way to determine this without undertaking the full study including the items you wish to cut off). There is no mention of mass or energy cut		We have removed this cut-off criteria from the study. "In the current study, every effort is made to include all the flows associated with the processes studied."	Comment closed.	
18	Goal and scope	Pg 3	Energy for data storage has been omitted, but are there no overheads that require active electronics that must also be considered? The sensitivity analysis on this point is welcome.		Energy for data storage is outside the scope of the study now. See explanation on page 17. Energy for data storage was also left out of the Bank of America comparative LCA (paper statements vs. digital) conducted by WSP in 2018. Even if I wanted to conduct a sensitivity analysis, I was unable to find an estimate for energy for data storage after looking through the literature.	Comment closed.	
19	Goal and scope	Pg 3	The electricity needed for folding paper leaflets is estimated as 50% of the amount of energy used to print on paper (by weight). What is the basis for this assertion?		This estimation has changed and now has a source. "The electricity needed for folding paper PIL is estimated as the same electricity to produce and fold 1 envelope = 0.0034 Wh per envelope (Moberg, Borggren, Finnveden, & Tyskeng, 2008)"	Comment closed.	
20	Goal and scope	Pg 4	"We extrapolated it by customizing this ecoinvent process", Do you mean you just adjusted to fit the smaller area/mass?		I am now showing the calculation in the report, and provided a more thorough description. Please see section 4.2.2.1 Printing QR Code on Carton	Comment closed.	
21	Goal and scope	Pg 5	The 15 minute duration for reading the e-leaflet is repeated twice in the bullet list.	Adapt text	The text has been changed accordingly.	Comment closed.	

22	Goal and scope	Pg 5	Reference for smartphone energy consumption is very old (2013)	Is a more recent reference available?	Now using a reference from 2024.	Comment closed.	
23	Goal and scope	Pg 5	Multiple product allocation for background data not described and end-of-life allocation for foreground data not described (but can be assumed to follow cut-off approach used for ecoinvent data).	Expand allocation section.	I believe section 3.8 Allocation & Recycling is sufficient now.	Comment closed.	
24	Goal and scope	Pg 5	No transport to end of life for the paper PIL? This should be included if applying the cut-off approach (thisb activity is still part of the current product system, only the recycling itself is cut off).		I have now included transport in the System boundary diagram, in both the paper and ePI. The transport is within ecoinvent market waste treatment processes, and that will be shown in Appendix A.	Suggest that there should also be transport associated with taking scrap paper to recycling. These burdens should be linked to the producer of the scrap. This is how the cut off approach to recycling is described in the GHG Protocol Product Standard and is also consistent with the 'Producer Pays' principle where the generator of the waste is responsible for burdens up to the point of recycling. However, I acknowledge that there are differing views on this topic and it is a minor point that will not influence the results. OK to leave as is but please include a note in the text that the end of waste point has been set to the gate of the generator of the scrap.	That is not how the cut-off approach to recycling works. The burden of transportation and re-furbishing for life 2 falls to the company that purchases the recycled material. https://pre-sustainability.com/articles/finding-your-way-in-allocation-methods-multifunctional-processes-recycling/. We are not following 15804 methodology where the producer takes the burdens. ***I have written the note in the last paragraph of section '3.8 Allocation and Recycling'.***
25	Goal and scope	Pg 6	What is the justification for the choice of impact categories and selected methods?	Clarify in text	See section 3.9 and Appe	We have some further comments on this in the Round 2 feedback (see below)	
26	Goal and scope	Pg 6	Several end point methods are reported. A more comprehensive set of mid-point indicators would be beneficial. Will the mid point methods that these are based on also be reported separately?	Consider including all ReCiPe mid-point indicators.	Yes, see Appendix D	Please can the mid-point results be discussed in the main body of the report? In particular, an ISO requirement for comparative LCAs is that comparison should be on a category indicator by category indicator basis.	
27	Goal and scope	Pg 6	Will CED be reported separately for fossil and renewable sources?	Clarify in text	Yes, see Appendix D	We have some further comments on this in the Round 2 feedback (see below)	
28	Goal and scope	Pg 6	The data transfer energy seems quite high, however I know there are large ranges of published values. The reference is quite old and perhaps this is the reason the value is quite high.	Please find a more up to date source for the energy requirements to transfer data. Ideally a range of values that could be tests in a sensitivity analysis. A good source (although also old now) gives a value of 0.02 kWh / GB. Schien, D ., & Preist, C. (2014). Approaches to energy intensity of the internet. IEEE Communications Magazine, 52(11), 130-137. https://doi.org/10.1109/MCOM.2014.6957153	I will continue to use the number from Pihkola et al, 2018, as I have found numerous papers to cite it. This will be tested in a sensitivity analysis with the Schien and Preist source. From Carbon Trust 2021: "The mobile network energy intensity used in the conventional approach is 0.1kWh/GB and is representative of mobile network energy intensity in Finland in 2020. This figure is sourced from academic literature (Pihkola et al., 2018), where mobile network energy intensity was estimated using publicly reported energy consumption figures from mobile network operators and data traffic figures from the Finnish Communications Regulatory Agency (FICORA)." I was not able to find other studies with energy for data transfer that had the same system boundaries and were also for a mobile network. For example, the Bank of America	Comment closed.	
29	Goal and scope	Pg 6	Reference for energy associated with data storage is very old. However, this may be justified as probably being an overestimate as efficiency has presumably improved over time. Would be helpful to state this.	Adapt text	Have decided to exclude data storage from the boundary. See the 'ePI' bullet point in 3.5 Excluded Processes.	Comment closed.	
30	Goal and scope	Pg 6	*Sensitivity:* *o Energy for data storage and data transfer assumptions* *o Energy for data storage. This is tested in a sensitivity analysis to show it is also below the 1% environmental impact cut-off. Use an estimate of 0.006 kWh/MB/day*		See 3.4.2 ePI system boundary and ePI bullet point in 3.5 Excluded Processes. Additionally see 4.2.2.3 Use Phase. See Figure 7. Does all of this suffice?	Comment closed.	

Study Report comments (round 2)							
31	Executive summary	Pg 2	"Takeda and four other pharmaceutical companies..." - can the other four be named			Comment closed.	Done.
32	Executive summary	Pg 3	"The comparative results are considered to have high certainty and to be statistically significant in all impact categories, except human health and water use, which therefore were removed from the comparative analysis as statistically significant conclusions cannot be made in those categories." This may bias the reader as they only see results where there is a large difference. Categories where the difference is smaller are omitted so this context is lost. Please include all impact categories in the comparison. Should also be discussion about robustness of impact categories (eg larger uncertainty in end point indicators than mid point).			OK to limit the sensitivity analyses to fewer impact categories but please include an explanatory sentence that these are only focusing selected impact categories with lower uncertainty.	I have now included all impact categories in the comparative graph figure 3, figure 17 and table 5. There is still a BIG difference between paper PIL and ePI in the Human Health and Water Use categories, however the results are not statistically significant according to the MC analysis. I have edited the paragraph before figure 3 and figure 17 accordingly. Do you also want me to include all 6 impact categories in all the sensitivity analyses as well? This would require quite a bit more work. ***I placed this sentence in section 6.4 "The sensitivity analyses graphs are only focusing on the four impact categories that were statistically significant."***
33	Executive summary and 7	Pg 4 and Pg 51	"Reducing the number of words in the PIL and re-structuring the content to make it easier to read for the patient, would reduce the paper needed in a paper PIL, as well as reduce the reading time needed for an ePI" Is this feasible in practice? Are there regulatory requirements on what needs to go into a PIL?			Comment closed.	This is beyond the scope of this LCA. I have read other papers that discuss making the PIL easier for patients to read, reducing content. I have added this sentence in the LCA report "Regulatory requirements for the PIL would still need to be followed if it were to be redesigned for each medication."
34	Executive summary and 7	Pg 4 and pg 51	In the recommendations section, add maximising recycled content, as the sensitivity analysis showed this to reduce the impact of the paper PIL.			Comment closed.	Done.
35	2.2	Pg 13	"Although an LCA is described above in stages..." Suggest to use "phases" for consistency with ISO terminology, and also later in this para.			Comment closed.	Done.
36	3.3	Pg 15	"In addition, there is a declared unit of one year of PILs in Europe from four pharmaceutical companies (GSK, Novartis, Sanofi, and Takeda.) This is 5.2 billion PILs, based on sales of solid-form drugs on the European market in the year 2020 from these four companies." Declared unit is not the correct term for this. "Scaled-up results" or similar might be better. Also add explanation that the purpose of this is to demonstrate the expected annual impacts to add context and highlight the scale of the issue, since burdens associated with just a single PIL will be small whether in paper or electronic form.			Comment closed.	Done.
37	3.4.1	Pg 15	Is transport to recycling included in scope (does not appear to be based on Figure 5, but would be expected when using cut-off approach.)			Comment closed.	I already addressed this in comment 24.
38	3.4.1	Pg 15	Data storage is common between the 2 systems (as reported in the exclusions section). Please, either remove the exclusions from 3.4.2 or include discussion of energy storage consideration in 3.4.1 for consistency. Exclusions are reported in a different section, so removing the redundancy might be the best option. In general, all assumptions should go in the assumption section.			Comment closed.	Yes, I have moved this to 3.4.1 and have also included it in the excluded process for the Entire Study in 3.5. I have added Data Center and network as well as Energy for Data Storage into figure 5 for the paper PIL.
39	3.5	Pg 17	Transport to the consumer is excluded due to lack to data. Please comment on whether or not you consider this to be material to the outcome of the study. (presumably not since other transport that is included only has a moderate to negligible contribution to burdens).			Comment closed.	I have added that comment.
40	3.6	Pg 17	Are all known exclusions documented in section 3.5?			Comment closed.	Yes, it matches the system boundary diagram.

41	3.6	Pg 17	The sentence: "In the current study, every effort is made to include all the flows associated with the processes studied." seems vague. Are they all included or not? The transport of the physical leaflet with a passenger car was excluded, hence there should be a cut-off rule. Recommend to still include cut off criteria but limit to mass and energy (eg anything less than 1% contribution can be excluded with no more than 5% in total) and then state that any materials thought be environmentally significant were modelled even if they fell below this threshold.			Comment closed.	Done.
42	3.7.1	Pg 18	"•The distance from the Basel packaging facility to distribution centers around Europe is estimated at 1500 km, since this would be the maximum European product transport distance and therefore is a conservative assumption. " Whether this is conservative depends on perspective. If trying to show superiority of ePI it is not conservative since it raises burdens of paper leaflet.			Comment closed.	I took out the words about conservative estimate. I changed the sensitivity analysis for this in 6.4.2. Now I am only testing with shorter distances to show how insignificant this is.
43	3.7.2	Pg 18	Add smart phone lifetime to ePI assumptions list and that a sensitivity analysis was carried out on this.			Comment closed.	Done. Also added the smartphone energy use and internet access equipment lifetime to the list of assumptions.
44	3.7.2	Pg 18	Mention on pg 18 that 10.5 mins read time is a conservative assumption as many will not read the full PIL and there is a sensitivity on read time.			Comment closed.	I added this. I also added the following "A survey of 406 people in Sweden asked how often they read the PIL. 37% of respondents said they always read it, while 52% said they occasionally read it"
45	3.7.2	Pg 18	Add that paper is assumed 100% virgin to paper PIL assumptions list and that a sensitivity analysis was carried out on this.			Comment closed.	I added this. "Paper was assumed to be 100% virgin based on communications with the pharmaceutical companies. This is tested in a sensitivity analysis in the Interpretation phase."
46	3.7.2	Pg 18	"•It is assumed that 100% of ePI views are on a smartphone as opposed to other electronic devices." Test with sensitivity analysis. How much more energy does a tablet or PC use? Although results show energy consumption is minor and main burden is from device manufacture. But even with this the ePI far outperforms the paper PIL.			OK. Then please just note in 3.12 Limitations that the study only considered phones, as these are the most likely device for accessing the ePIL. Results using other devices such as tablets or PCs will differ, but are not expected to change the overall conclusions of the study.	I don't think this will bring anything extremely valuable to the LCA. We know that the main burden is device manufacture. We also know that most people will use their smartphones to scan the QR code. This is out of scope for the project. At this point, the project is out of budget. ***I have added this in the first paragraph of section 3.12 Limitations.***
47	3.8	Pg 18	"process inputs should be avoided by using the system boundary expansion approach"			Comment closed.	Included sub-division in the sentence.
48	3.8	Pg 18	"Allocation was not needed in this study since none of the processes produced multiple products." While there are no co-products allocation is still used in the assessment (eg to determine what fraction of the burden of manufacturing a phone is assigned to looking at the ePIL).			Comment closed.	I have changed this sentence to "In this study, allocation was based on time. For example, the amount of the smartphone or internet access equipment lifecycle to allocate to the ePI was based on time spent reading the ePI divided by total lifetime of the device/equipment."
49	3.8	Pg 18	"the second life bears the burdens of refurbishment (e.g., collection and refining of scrap)." Should refer to recycling, not refurbishment. These have different meanings.			Comment closed.	This has been changed, now top of pg. 19.
50	3.9	Pg 19	"The primary impact assessment method used for this study was the ReCiPe 2016 Endpoint (H) v1.08 method (Huijbregts MAJ, 2017), which is one of the most robust and updated methods available to LCA practitioners." The robustness of end point methods is debatable and 2016 is not particularly recent.			Comment closed.	I have changed the wording here "The primary impact assessment method used for this study was the ReCiPe 2016 Endpoint (H) v1.08 method (Huijbregts MAJ, 2017), which is one of the most utilized and updated methods available to LCA practitioners and thus is widely accepted. It was last updated in 2023."

51	3.9	Pg 19	Cumulative Energy Demand is an inventory indicator rather than an impact category. "Energy use" is not an environmental impact. If you just focused on non-renewable energy sources then you could argue it is a resource depletion measure, and also a reasonable proxy for other impacts. But CED includes all energy types. As such this does not provide much insight into environmental performance (100 kWh wind power probably has lower impacts than 10 kWh power from coal).			Comment closed.	I have changed the wording here "In addition to the ReCiPe 2016 Endpoint method, two inventory indicators are used"
52	3.9	Pg 19	Water use in ReCiPe is also effectively an inventory metric as it does not account for scarcity.			Comment closed.	I have changed the wording here "In addition to the ReCiPe 2016 Endpoint method, two inventory indicators are used"
53	3.9	Pg 19	"Other midpoint categories (e.g., freshwater ecotoxicity) are more difficult for a general audience to understand" While the general public is one audience for the study does it make sense to select impact categories based just on what the public can understand? If experts consider less well known impacts to be relevant then these should be selected and it is the duty of the author to explain the significance of the results to the audience.			Comment closed.	Changed text to "We have included the ReCiPe midpoint indicators results as well in Appendix D: Midpoint Impact Category Results" "None of these impact categories are assumed to be more important than the others and they offer a range of different environmental indicators, which is important in a comparative LCA to not have burden-shifting."
54	3.9	Pg 20	When discussing mid point and end point methods please also discuss uncertainty, and that this is significantly higher for end point methods.			Comment closed.	I added this on the top of page 21 now "Midpoint methods have a higher degree of certainty than endpoint methods because there is just one characterization factor applied to the raw data, whereas with endpoint methods, further conversion into damage pathways is applied. Endpoints have a lower degree of certainty because they combine impact methods and are predictors for future damage if these impacts were to continue into the future. "
55	3.11	Pg 22	Add other panel members and affiliations			Comment closed.	Done.
56	4.2	Pg 24	Note in the report that a validity check shall be performed during collection to check it meets data quality requirements.			Comment closed.	Included.
57	4.2.1.1	Pg 24	In reference to "This means that the ecoinvent process is underestimating the amount of ink and printer use needed for a 3.5g paper PIL" - confirm if this was adjusted in the dataset or left as it is conservative assumption in respect of the ePI.			Comment closed.	No I didn't modify the ecoinvent process and I am not sure I could do it accurately. I am okay with having an underestimate of impacts associated with the paper PIL since it is clearly the loser in the comparison. I have placed this in the text "The ecoinvent process was not adjusted and thus is a conservative assumption in respect to the ePI."
58	4.2.1.1	Pg 24	"This means that the ecoinvent process is underestimating the amount of ink and printer use needed for a 3.5g paper PIL." Did you modify the dataset to correct this? Eg by doubling the burdens.			Comment closed.	Same as comment 57 above.
59	4.2.2.1	Pg 27	"The area of the printed QR code is one square inch (in2)" Please also include cm2 equivalent since other units in the report use metric.			Comment closed.	Done.
60	4.2.2.1	Pg 27	"area density of paper = 80 g/ m2" Cartonboard used for the carton, is typically 160 g/m2. Should adjust the dataset accordingly.			Comment closed.	Cartonboard density is irrelevant here. We just needed to find the Corresponding mass of paper to use for given printed area from the ecoinvent process. This was just so we could allocate the correct amount of burdens from the printer and ink for printing a one square inch QR code. The cartonboard is not in the system boundary.
61	4.2.2.3	Pg 27	"2 MB PDF " Was it modelled as being 2 MB or 1.958 MB as listed in 4.2.2.2?			Comment closed.	It's 1.958 MB. I have changed this here as well as in 3.4.2. for clarity
62	4.2.2.3	Pg 28	"Data on the smartphone stem from a LCA study on the Fairphone 1, a mid-range smartphone from 2014" iPhone 16 series carbon footprint is about 60 kg CO2e https://www.apple.com/ca/environment/pdf/products/iphone/iPhone_16_and_iPhone_16_Plus_PER_Sept2024.pdf. The modelled dataset has a burden of 38 kg. Would be worth adding some commentary on this in the report.			Comment closed.	I have added a sentence about this in this section. The numbers were a little different: "It can be noted that this smartphone dataset has a climate change impact of 40.3 kgCO2e using the LTS method. The iPhone 16 carbon footprint (excluding use phase) is reported as 46 kgCO2e"

63	4.2.2.3	Pg 27	Lifetime of equipment seems to be allocated in the use phase, but in section 3.8 there is this sentence "Allocation was not needed in this study since none of the processes produced multiple products."			Comment closed.	I have changed this sentence in 3.8 to "In this study, allocation was based on time. For example, the amount of the smartphone or internet access equipment lifecycle to allocate to the ePI was based on time spent reading the ePI divided by total lifetime of the device/equipment."
64	4.4	Pg 29	Data quality is not reported - there is no scoring			Comment closed.	This section has been expanded to include qualitiative data quality ratings and the quantitative ratings are in table 16 in the Appendix.
65	4.4	Pg 29	Need more comprehensive reporting of foreground and background data quality - discussion of temporal, geographical and technological representiveness. Goegraphic is currently commented on but only at very high level. Others are not mentioned. A pedigree matrix can be useful for doing this but alternatively discussion within the text is also adequate. Should also comment on precision and reproducibility.			Comment closed.	This section has been expanded to include qualitiative data quality ratings and the quantitative ratings are in table 16 in the Appendix.
66	4.4.2	Pg 30	As documented here, the uncertainty distributions reported in Ecoinvent are not very robust (based on high level qualitative estimate using pedigree matrix). Also these do not account for uncertainty in foreground data. The meaningfulness of the results of Monte Carlo assessment are questionable			Please include some additional commentary on the limitations of the uncertaintly analysis - it only addresses uncertainty in the background data - the uncertainty distributions are based on high level qualitative estimates.	I am now presenting a qualitative description of data quality in section 4.4. Additionally, I have added a table in the Appendix C that shows you the data quality scores for all primary data. I also added a sentence to section 4.4: "The costs of collecting primary data from all stages of the lifecycle is prohibitive to the execution of the study, and therefore we are also reliant on secondary data with less certainty." ***I have now added that in the last paragraph in section 4.4.8.***
67	5	Pg 31	"These results are relative expressions and do not predict impacts on category endpoints" Not quite the exact text required by ISO... should state "LCIA results are relative expressions and do not predict impacts on category endpoints, the exceeding of thresholds, safety margins or risks."			Comment closed.	I have changed this accordingly.
68	5	Pg 31	Note in the report that the LCIA shall not provide the sole basis of comparative assertion (as per ISO 14044 section 4.4.5)			Comment closed.	Included.
69	5	Pg 31	It would be useful and informative to the reader to include some commentary on the mid-point indicators that contribute to each of the end point categories in this section. I know that these are described in Appendix D but it would be good to show them in the main report. Even if just to present Figure 28 as very clearly showing that when considering mid point categories, it is clear that ePI outperforms paper PIL in every case. This is a very strong message.			Comment closed.	I now have additional tables in Appendix D as well. I have also described the midpoint results in the Results section 5 as well, including talking about the comparative midpoint graph Figure 28 in the Comparison section.
70	5.1.1	Pg 35	"Both human health and water use results are more uncertain, ranging from 671% lower to 675% higher in human health and 2289% lower to 1961% higher in water use" Isn't anything more than 100% lower less than zero? Is this suggesting negative impacts (ie benefits)? I do not know how to interpret this.			Comment closed.	I added the following to the paragraph "For human health, the paper PIL cannot have a positive effect on this endpoint, so anything lower than 100% would have zero impact on human health. However, it is possible to have negative water use if a system is releasing more water back into water bodies than it consumes. To sum it up, there is high uncertainty in the human health endpoint and water use results."

71	5.1.1	Pg 36 Figure 12	I would expect that inventory metrics such as water use (which is something that usually recorded quite well) will be more accurate than mid-point indicators, which in turn will be more accurate than end point indicators. It is very surprising to me that water use has the greatest uncertainty of all the indicators, significantly worse than human health which comprises mid point indicators known to be very uncertain (eg human toxicity). I would expect water to be among the most accurate. This analysis does not make sense to me. It seems that this analysis is not accounting for this difference in robustness of methods and also seems to omit consideration of uncertainty in foreground data. I am not convinced that Monte Carlo analysis based on ecoinvent's high level qualitative pedigree matrix approach is robust enough to say anything useful about the uncertainty in the assessment. Please add more commentary on the limitations of the Monte Carlo analysis if you wish to keep this in the study.			Comment closed.	Please see the expanded section 6.1 Key Observations for more of an explanation about the Monte Carlo analysis and uncertainy. I wrote this in the Limitations section as well.
72	5.1.1	Pg 35	The uncertainty analysis is usually discussed in the interpretation section, so it is a bit odd to see it in the results.			Comment closed.	I discuss the uncertainty in detail in the Interpretation section now in 6.1 "Key Observations". I will be leaving the uncertainty graphs in the results section, as they fit nicely there.
73	5.2.2	Pg 42	"European market " is this the EU or broader Europe (if not just EU, what countries are covered)?			This could be clearer, eg (continent of Europe, not just EU)	Broader Europe and I have written this now in the report's Introduction in section 2.1
74	6.1	Pg 44	Text on Key Observations is very bland and high level, does not provide any useful information. A bullet point summary of key findings would be useful.			Comment closed.	I have expanded this section and included discussion about the uncertainty.
75	6.4.3	Pg 46	Would be good to see the effects if reading time is reduced as well as increased. 10.5 minutes seems like a long time. It might be required to read the whole thing in detail but many people may skim it or only read certain sections.			Comment closed.	I now address in the conclusions that indeed 10.5 minutes is a conservative assumption. There is no need to do a sensitivity analysis for a shorter reading time as the ePI will continue to perform better than the paper PIL. I also suggest ideas for future research in the conclusions, which includes expanding realistic scenarios.
76	6.4.7	Pg 49	You are not looking at comparable indicators to those used in the base case, so, while interesting, this is not really a sensitivity, but just additional impact assessment results.			Figure 24 caption refers to "IMPACT World+ Endpoint method" but mid-point categories are reported.	I have renamed this to "scenario analysis" ***Thanks, I have fixed this.***
77	6.4.8	Pg 50	Would be nice to see how the values change compared to cut off approach... this would really highlight the sensitivity of results to choice of method.			Comment closed.	I'm getting rid of this sensitivity analysis. I don't think this study should use the avoided burden method, which is best for studies on recycling items that are in high demand for reuse (like steel). The study does not use any recycled raw materials. Additionally, I do not have an estimate for the energy use of recycling electronics or paper, and would need that input for the avoided burden method. The cut-off recycling method is the best approach and doing this sensitivity would take more time and budget and would very likely not change the results of ePI outperforming paper.
78	7	Pg 51	A couple of points I would emphasise more in the conclusions that provide even more evidence that ePI have better performance than PIL are: - relating to 6.4.4 - many people never look at the PIL. When using ePI this means greatly reduced burdens but with PIL there are still full burdens. - relating to 6.4.3 - assumed reading time of 10.5 minutes. This is the baseline assumption but seems very conservative to me. I would expect that most people would not spend this long.			Comment closed.	I put this in the conclusion.
79	8.1.3	Pg 55, Table 10	Waste paper recycling. Some transport should be modelled to get to the recycling site. Since these burdens are associated with waste disposal to get to end of waste state.			Comment closed.	Same as comment 24 and 37.
80	Full report	General	A small issue, but there are a few small typos and unusual phrasing that could do with checking and revising. E.g. "fewer impacts" rather than "lower impact", "high certainty" rather than "low uncertainty".			Comment closed.	These examples have been fixed.

81	Third party report	Is it the intention to make this report in its entirety publicly available? If not, please can you also share with us the third party report that will be developed to provide to external stakeholders should they want to understand the study in detail.			The critical review does not need to cover all communications but it does cover the development of a third party report that external stakeholders can access to obtain a thorough description of the study. If you can confirm that either the full report will be made available or a third-party report will be prepared that will cover the LCA study report in its entirity, with any confidential data removed, this point can be closed.	I do not know what Takeda will do with this report, but I will also be writing a 2 page white paper that will be a condensed version of this report. ISO standards do not require that all the communications that get made based on this report also be approved by the critical review panel. I promise that the white paper will simply contain the comparison graph and briefly explain this paper, similar to an Executive Summary. ***Yes, I can confirm that.*** ***If it is a third party report that is shared publically, it will be a condensed version of what is presented within the full LCA document, with all appropriate detail and description so as to not change the content or context.***