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Environmental impacts of drug products: The effect of the selection of production sites in the supply chain

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ABSTRACT

The environmental impact of drug products is largely determined by activities beyond the direct control of pharmaceutical companies, such as outsourced production of pharmaceutical building blocks. Therefore, this study evaluates the environmental impacts of a prostate cancer drug packaged in one blister (declared unit), thereby analysing the whole value chain to gain insight into 1) the main contributors to the impact of drug product production and 2) the effect of the geographical location of production of solvents and pharmaceuticals. The carbon and resource footprints of the entire life cycle of the drug product are determined, using the IPCC GWP 100 and the Cumulative Exergy Extraction from the Natural Environment methods, respectively. Unlike many other studies, the impacts of building blocks, called intermediate pharmaceutical ingredients (IPIs), are modelled based on primary data, literature and similar processes. The carbon footprint per declared unit equals 34 kg CO_2-eq, of which IPIs and active pharmaceutical ingredient (API) production account for 96 %. The resource footprint is 647 MJ_{ex}/declared unit, with IPI and API production accounting for 93 %. The main impact contributors of these processes are solvents and electricity consumption. Four alternative scenarios for IPI and API production are developed to evaluate the geographical influence of different production locations of solvents and pharmaceuticals between Europe and China. European production of solvents and pharmaceuticals appears to have the lowest carbon and resource footprint. In contrast, Chinese production of solvents and pharmaceuticals increases the carbon footprint by 49 %, while the resource footprint increases by only 4 %, although the natural resource consumption shifts from abiotic renewable resources and nuclear energy to fossil fuels. The high contribution of IPI production and the influence of geography of the supply chain highlight the need for accurate data from external suppliers to fairly estimate the environmental footprint of drug products.

1. Introduction

For decades, the scientific literature on environmental impact has mainly focused on sectors such as mining, energy and automotive, while the healthcare sector, particularly the pharmaceutical sector, has received less attention (Belkhir and Elmeligi, 2019). In 2014, the healthcare sector contributed 4.4 % of global greenhouse gas (GHG) emissions, equating to a carbon footprint of 2.0 gigatonnes CO_2-equivalents (eq). The supply chain, including drug product (DP) manufacturing, was the largest contributor at 71 % (Karliner et al., 2019). In 2019, the Sustainable Development Commission of the United Kingdom's National Health Service (NHS) reported a carbon footprint of 25 megatonnes CO_2-eq for the health sector in England. Again, the supply chain was the largest contributor (62 %), with pharmaceutical and chemical manufacturing accounting for 32 % of supply chain emissions (Tennison et al., 2021). This is partly due to the high resource and energy intensity of DP production processes (Wernet et al., 2010). In order to reduce their environmental impact, it is important to identify the main contributing factors in the life cycle of the drug product. Therefore, this study assesses the environmental impacts of the entire life cycle of one particular drug product, considering both the carbon and resource footprint. This approach differs from other studies that examine only specific stages of the life cycle (De Soete et al., 2013; Parvatker et al., 2019). Unlike earlier studies that relied on database proxies for the building blocks (Siegert et al., 2020), this study addresses data gaps on building blocks by modelling their inventory based on primary data, data from analogous processes and literature sources. This approach allows for a more precise identification of the building blocks'

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contributions to the environmental impact of a drug product, as well as other significant contributors. In addition, the study evaluates the effect of relocating the production of solvents and pharmaceuticals from Europe to non-European countries, a trend observed in the pharmaceutical industry in recent years (Francas, 2021). Building on earlier studies that identified solvents and energy as major contributors to the environmental impact in pharmaceutical synthesis (De Soete et al., 2014), different hypothetical scenarios are developed and analysed where the production locations for solvents and pharmaceuticals shift between Europe and China. Finally, the study includes a critical review and provides recommendations for improved data collection.

2. Literature review

The life cycle of a drug product starts with the synthesis of building blocks that are used in the synthesis of the active pharmaceutical ingredient (API). This is followed by DP manufacturing, packaging, distribution, use and end-of-life (Siegert et al., 2019). API synthesis is a major contributor to the overall environmental impact of the finished product (De Soete et al., 2013), mainly due to chemical and utility consumption, contributing 80 and 20 %, respectively (De Soete et al., 2014).

Drug product manufacturing is part of the pharmaceutical supply chain (PSC). This PSC is an integrated network of suppliers, manufacturers, and logistics providers involved in sourcing raw materials such as solvents and intermediates, manufacturing drugs, and delivering them to patients (Halim et al., 2019). PSCs are often complex and inefficient, for example due to geographical dispersion of production and chemical sourcing (Halim et al., 2019). Moreover, in recent decades, pharmaceutical production has increasingly shifted to Asian countries (Francas, 2021). Within the PSC, primary and secondary manufacturers are responsible for the API and finished DP manufacturing, respectively, thereby using resources and emitting GHGs (Shah, 2004). A company's GHG emissions associated with its supply chain are included in scope 3 emissions, while scope 1 emissions cover emissions due to the company's own operations and scope 2 emissions cover those related to the purchased energy production (GHG protocol, 2015). Despite being the largest emissions category, scope 3 emissions reporting is often inconsistent (Booth et al., 2023). As scope 3 emissions are beyond the control of pharmaceutical companies, it is important for them to engage suppliers to reduce their emissions (Farsan et al., 2018). Solutions to reduce scope 3 emissions include sourcing from suppliers with lower carbon footprints, designing efficient products and integrating circular economy principles (Booth et al., 2023).

A holistic view of the product's life cycle is essential for process optimisation, hotspot identification, informed decision-making and avoiding burden shifting (De Soete et al., 2017). Life Cycle Assessment (LCA) is a widely used standardised method for quantifying the environmental impacts associated with all stages of a product's life cycle, from raw material extraction to end-of-life (ISO, 2006a). Despite its generally recognised importance, its implementation in the pharmaceutical industry has been limited. To the authors' knowledge, only a few scientific publications consider the environmental impacts throughout the whole life cycle (Siegert et al., 2020; Yang et al., 2021), while the main part focuses on API production (Parvatker et al., 2019; Van Der Vorst et al., 2013; Wernet et al., 2010) or downstream processes, including packaging, use and end-of-life (Bassani et al., 2022; Van Der Vorst et al., 2010). Upstream processes, such as precursor material production, are rarely addressed and data gaps on these materials are often filled with publicly available data, expert knowledge or generic models (Ott et al., 2014). The lack of inventory data due to intellectual property restrictions has been identified as one of the main barriers to conducting a comprehensive LCA (De Soete et al., 2017), alongside a lack of methodological harmonisation and complex supply chains (Siegert et al., 2019) . The harmonised rules developed by Siegert et al. (2019) can aid in drafting Product Category Rules (PCRs) for pharmaceutical manufacturing processes. Although specific PCRs are not yet developed, the Pharmaceutical Life-Cycle Assessment Consortium (Pharma LCA), consisting of several pharmaceutical companies, is working on their development (Pharma LCA Consortium, 2024). On that account, the European Commission's Product Environmental Footprint Category Rules (PEFCR) Guidance provides instructions for developing a PEFCR (European Commission, 2017).

All this indicates the need for insights on the influence of the complexity of the PSC on the environmental impact of a drug product. Furthermore, research on the synthesis of the building blocks for API production is scarce, potentially resulting in an underestimation of the drug product's environmental impact. Considering the full life cycle, including outsourced product synthesis is therefore necessary.

3. Materials & methods

LCA is carried out according to ISO 14040/14044 standards to identify the main contributors to the environmental impact of Zytiga®, a metastatic prostate cancer drug product manufactured by Johnson & Johnson (J&J) (ISO, 2006a, 2006b). It is a film-coated tablet, containing 500 mg of API with a recommended daily dose of two tablets.

First, the goal and scope, data inventory and impact assessment methodology to assess the environmental impact of the supply Zytiga® packed in one blister are presented. A baseline case for manufacturing locations is introduced. Special attention is given to the modelling of the building blocks to produce the API, from now on referred to as intermediate pharmaceutical ingredients (IPIs). Second, scenarios are developed to investigate the influence of geography along the PSC on the environmental impact of the drug product. The focus is on IPI and API production, considering the current trend to move their production to Asian countries (Francas, 2021) and the fact that these steps have the highest impact in the drug product's life cycle (De Soete et al., 2013). Third, information is provided on the sensitivity analysis of the IPI modelling.

3.1. Life cycle assessment and the baseline case

3.1.1. Goal and scope

The aim of the assessment is to identify the key life cycle stages and parameters that determine the environmental impact of the supply of one blister pack containing 60 Zytiga® tablets (60 × 500 mg), which is defined as the mass-based functional unit (FU) and is further referred to as the declared unit (DU). According to Siegert et al. (2019), as the intention of this study is to analyse the production process and compare different production locations of the same process, the DU corresponds to the FU. For completeness, the effect-based functional unit is defined as the treatment of one adult in Europe with metastatic prostate cancer for 30 days. In what follows, the DU is further used. The system under study is shown in Fig. 1, which serves as the baseline case. First, two IPIs (i.e. IPI1 and IPI2) are produced and subsequently used to manufacture the API. This API is further formulated into a tablet in the DP production step, after which it is packaged into blister packs. These packs are distributed to the warehouse (distribution phase), further transported to hospitals and taken home by patients for use; this is considered the use phase and is outside the scope of this study. The end-of-life of the packaging materials is considered, assuming that all packaged drug products are consumed. The supply chain of the drug product for this baseline case is geographically dispersed, with the production of both IPIs taking place in China. The other life cycle stages take place at several European locations corresponding to the real manufacturing locations of Zytiga®. It is assumed that solvents and other chemicals are sourced from the region of production, i.e. China for the IPIs and Europe for the other stages.

3.1.2. Life cycle inventory (LCI)

Wherever possible, primary data was used to compile the data

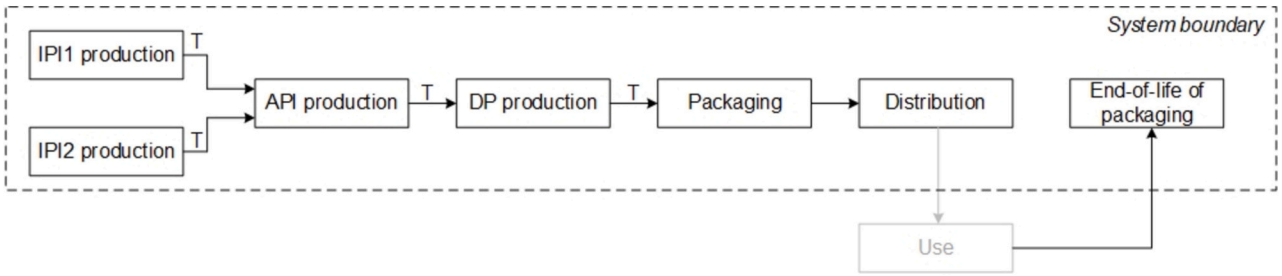

Fig. 1. Product system of the pharmaceutical under study. T: transport, IPI: intermediate pharmaceutical ingredient, API: active pharmaceutical ingredient, DP: drug product.

inventory. Where necessary, modelling was done based on literature or similar processes. For the background system, the ecoinvent v3.9 database was used, except for methanol, toluene and acetone, for which the consumption mixes of the CarbonMinds database were used. Consumption mixes consist of the country's or region's own chemical production plus imported chemicals and minus exported chemicals. Datasets were retrieved for production in Europe and China. All datasets were retrieved for Europe as a whole, as no information on specific production sites could be provided for confidentiality reasons. This is also the case for China, where datasets for the whole country were used as proxy, as no specific regions could be shared. If no information on China was available, data for the rest of the world including China were used. In some cases, the global dataset had to be used resulting in no difference between China and Europe. Detailed information on data collection can be found in Supplementary information (SI) Table S1. For utilities such as electricity and natural gas, market mixes were used for Europe and China that represent a general electricity mix for these regions. Modelling was conducted by SimaPro 9.5.

3.1.2.1. Intermediate pharmaceutical ingredient production. The two different IPIs (referred to as IPI1 and IPI2) are manufactured by two different external suppliers in China. Reaction schemes were provided by the respective companies for both IPIs. Input and output flows were established based on stoichiometric reactions and used to determine mass balances for the reagents. For IPI1, three reaction steps were considered. The final yield was available (i.e. 48 %) and the stoichiometric mass balance was adjusted to this yield. Pyridine was the solvent in which all three reaction steps took place. The mass of pyridine was modelled to be 85 % of the non-aqueous mass based on Constable et al. (2007). For IPI2, also three reaction steps were defined. Mass balances based on stoichiometry were supplemented with information obtained from wastewater composition data that was provided by the external supplier, which could not be shared because of confidentiality restrictions. The solvents used in IPI2 production were identified as tetrahydrofuran (THF), methanol and ethyl acetate. Again, an average of 85 % non-aqueous mass was used to model the solvent amounts and allocated to the solvents based on the wastewater composition. Transport of the solvents to the production facility was modelled based on an analogous process in the ecoinvent v3.9 database, and assumed to be by truck, train, barge and ship. As no information on utilities was provided for both IPIs, the utility data from API production were used, but adjusted based on the mass ratio between IPI and API production. Since the production of both IPIs is already complex and similar to API production, this is assumed to be a fair approximation. Apart from the wastewater information for IPI2 production, no information on waste treatment was available. Based on expert knowledge, it was modelled that all solvent waste was incinerated with energy recovery. Transport to the waste facilities was modelled to be by truck, using the same distance as for API production. No primary data on cleaning was available. Therefore, the same solvents that were consumed in the cleaning of the equipment used for API production were used to model the cleaning in IPI production. Important in the calculation of the impact of cleaning was the number of batches produced, and the amount of product obtained per batch. No information was available on the number of batches produced for both IPIs. For IPI2, however, the amount of IPI2 produced per batch was known. For IPI1, it was estimated that the amount produced per batch of IPI1 equals the amount needed to produce one batch of API, which was derived from primary data on API production. As from primary data it was clear that 18 batches of API were produced, it was assumed that 18 batches of IPI1 needed to be produced as well since the amount of IPI1 produced per batch equals the amount needed to produce one batch of API. For IPI2, it was known that the amount produced per batch was approximately two times lower than what was needed to produce one batch of API. So, in order to be able to produce 18 batches of API, it was calculated that 34 batches of IPI2 were needed. As the production occurs in a closed environment, no direct emissions were measured. The avoided burden approach was used for waste incineration for both IPIs. In this approach, a negative impact was attributed to the avoided burdens that come with the treatment process such as energy or solvent recovery, thereby reducing the impact of the treatment technology. The incineration process was modelled using the 'incineration of spent solvent mixture' process from the ecoinvent v3.9 database, which includes the direct emissions related to the process. More information on the solvents that were used can be found in Table S2.

3.1.2.2. Active pharmaceutical ingredient production. The synthesis of the API takes place in successive batch processes, i.e. one chemical synthesis process and three recrystallisation processes. The chemical synthesis consists of two steps in which IPI1 and IPI2 are converted into the API. Mass balances have been prepared based on batch production reports and bills of materials and supplemented with information from disposal data sheets. The yields of the different steps were available in the batch production reports and bill of materials. The solvents used in the processes were toluene, acetone and methanol and data on their use were provided by J&J. For the utilities, i.e. electricity, natural gas and nitrogen gas, a top-down approach was used to allocate the total consumption of utilities to the API production processes. Cleaning was performed after a production campaign consisting of 18 batches of each of the four processes. Mass balances of the cleaning media (i.e. methanol, acetone, dimethylformamide (DMF) and dichloromethane (DCM)) were established based on cleaning data sheets. Due to the use of a top-down approach for utilities, no distinction could be made between utilities for production and utilities for cleaning. Therefore, no separate utilities were attributed to the cleaning process. More detailed information on the cleaning materials can be found in Table S3. As was the case in IPI production, no direct emissions were measured. All solvents and chemicals were subject to waste treatment and most waste could be assigned to the appropriate treatment technology based on disposal data sheets. Part of the toluene, methanol and DCM were distilled with a yield of 80 % for the first two (Johnson & Johnson, personal communication) and 76 % for the latter (Van der Vorst et al., 2010). Primary data on toluene distillation at J&J was used as a proxy for all three distillation processes. The remaining solvents and other chemicals were incinerated with energy recovery, discharged to wastewater treatment or sent to

other recycling processes. Incineration was modelled using the ecoinvent v3.9 database, as described for IPI production. The catalyst was recovered with an efficiency of 92 %. An avoided burden approach was used for the treatment processes. The transport of solvents to the manufacturing plant was modelled using the PEFCR guidelines (European Commission, 2017). The transport of waste to the treatment facility was modelled to be by lorry and distance data was provided by the company.

3.1.2.3. Drug product production, packaging and distribution. The tablets are manufactured by an external supplier in Europe using a batch granulation process. Primary data on excipient use was provided by the external supplier, thereby assuming a 100 % efficiency. For utilities, primary data from J&J on the DP manufacturing of another tablet was provided and used as a proxy for the manufacturing of the Zytiga® tablets. Cleaning was modelled based on primary data from another batch granulation process at J&J. The amount of API used in one batch of DP manufacturing was known and the number of batches that were needed was calculated based on the processing of the amount of API obtained from 18 batches in API production.

The tablets are packaged at another European site, using a film blister pack consisting of polyvinylchloride (PVC), polyethylene (PE) and polyvinylidene chloride (PVdC) with an aluminium lid, which was placed in a cardboard box with a leaflet and sealed with plastic tape. More detailed information on the packaging materials, based on primary information obtained from the company, can be found in Table S4. Utilities were not considered at this stage due to lack of primary data.

The packed tablets were distributed to the warehouse for further distribution to hospitals in Europe. For distribution, only the transport between the packaging site and the warehouse was considered. Utilities used for, amongst others, keeping good air quality in the warehouse, were not considered. The distance was calculated based on primary data and happened to be 1559 km. Transport was by lorry.

3.1.2.4. End-of-life of packaging. The end-of-life phase considers the disposal of post-consumer packaging in Europe. The cardboard, tape and printed paper were sent for sorting and recycling based on the Belgian situation. The blister was assumed to be incinerated. The treatment processes were retrieved from ecoinvent v3.9. Again, the avoided burden approach was used for the treatment processes.

3.1.2.5. Transport. The transport here refers to transport between life cycle stages. IPIs are transported from China to the European API production site. The transport means and distance between China and Europe have been simulated using the PEFCR guidelines (European Commission, 2017) and happened to be by truck (1000 km) and ship (18,000 km). The API is then transported to another European site to produce the DP via truck (130 km), train (240 km) and ship (270 km) according to the PEFCR guidelines (European Commission, 2017). This is followed by transport to a packaging site in Europe, again modelled according to the PEFCR guidelines (European Commission, 2017). The transport between the packaging site and the warehouse was included in the distribution phase described in section 3.1.2.3. Transport between the consumer and the waste facility was not considered.

3.1.3. Life cycle impact assessment (LCIA)

The inventory results were assigned to different impact categories in order to assess the environmental impacts (Roy et al., 2009). The environmental impacts due to emissions and to resource use were included in the study. As the impacts are discussed very extensively, one output-related and one input-related impact method was chosen. To cover the environmental impact due to emissions, the IPCC GWP 100 approach was used to determine the carbon footprint, expressed in kg CO_2-eq. The carbon footprint tackles what may be one of the most widely debated environmental issues of our time, i.e. global warming. In addition, many reports such as the sustainability reports required from companies by the European Union require carbon footprint data (European Union, 2022). To have a broader perspective on environmental impact, also the resource footprint was considered. Therefore, the Cumulative Exergy Extraction from the Natural Environment (CEENE) method was used (Dewulf et al., 2007), which is recommended as the most appropriate method characterizing resource use (Berger et al., 2020). It covers seven resource categories: abiotic renewable resources (wind, geothermal and hydropower), fossil fuels, nuclear energy, metal ores, minerals and mineral aggregates, water resources and land and biotic resources and is expressed in MJ of exergy (MJ_{ex}).

3.2. Defining scenarios to account for the influence of geography

Alternative scenarios were developed for IPI and API production to determine the influence of geographical locations along the PSC on the environmental impact of the drug product. As was the case for IPI production in the considered baseline production of Zytiga®, IPI and API production often move to China (Francas, 2021). Therefore, scenarios were developed where IPI and API production take place either in China or in Europe, as shown in Table 1. The location of solvent sourcing might differ from the location of production and is therefore considered separately. To model production, other chemicals than solvents, utilities and waste treatment processes are considered from the region where the production takes place, i.e. China or Europe. In the scenarios in Table 1, the location of IPI and API production is considered to be the same. In S1, production and solvent sourcing were assumed to be in Europe. In S2, production takes place in Europe, but Chinese solvents are used. In S3, production takes place in China but with European solvents. Finally, S4 assumed Chinese production and solvent sourcing. Other scenarios where the location of IPI production and solvent sourcing differs from this of API production were also evaluated and are presented in Table S5.

For IPI production, it was assumed that waste was always incinerated. For European API production, waste was recycled, while for Chinese API production, all waste was assumed to be incinerated. The baseline (S0) is a mix where IPI production takes place in China using Chinese solvents, while API production takes place in Europe using European solvents, representing the current situation. The datasets from the ecoinvent v3.9 and CarbonMinds databases used for the modelling of the scenarios can be found in Table S6.

3.3. Sensitivity analysis

In order to identify the most influential parameters for IPI production, a sensitivity analysis was performed using Crystal Ball software. A triangular distribution (−10 %/+ 10 %) was chosen for each input parameter. A Monte Carlo simulation was then carried out with 10,000 iterations. This allows the parameters with the highest contribution to the variance of the output indicators to be identified (Thomassen et al., 2019). The output indicators evaluated were the carbon and resource footprint.

4. Results & discussion

4.1. Life cycle inventory (LCI)

A data inventory is made for each life cycle stage and associated transport (Table 2). For confidentiality reasons, only aggregated results can be presented.

The inputs considered in the inventory are materials, utilities and cleaning inputs. Materials are divided into two categories: solvents and other chemicals. The latter includes reagents, catalysts, excipients, packaging materials and other auxiliaries. Regarding solvents and other chemicals, the largest amount is used in API synthesis. The three solvents used are toluene, acetone and methanol, with methanol being

Table 1
Scenarios developed based on the use case with varying geographic location of production and solvent sourcing.

Name	Origin solvents IPI1	IPI1 production	Origin solvents IPI2	IPI2 production	Origin solvents API	API production
S0	China	China	China	China	Europe	Europe
S1	Europe	Europe	Europe	Europe	Europe	Europe
S2	China	Europe	China	Europe	China	Europe
S3	Europe	China	Europe	China	Europe	China
S4	China	China	China	China	China	China

Note. S0 corresponds to the baseline scenario. Drug product manufacturing and subsequent life cycle stages were not considered as they were assumed to remain unchanged and stay in Europe for every scenario. IPI: Intermediate pharmaceutical ingredient; API: Active pharmaceutical ingredient.

Table 2
Inventory of the materials and transport distances of all considered life cycle stages expressed per declared unit.

	IPI1 production	IPI2 production	API production	DP production	Packaging	Distribution	End-of-life of packaging	Transport
Input								
Materials								
Solvents (kg)	0.9	0.6	1.8					
Other chemicals (kg)	0.2	0.2	1.5	0.1	0.2			
Utilities								
Electricity (kWh)	5.4	1.7	6.2	0.3				
Natural gas (MJ)	21.8	6.7	25.0	1.7				
Nitrogen gas (kg)	1.2	0.4	1.3					
Steam (kg)				0.3				
Compressed air (m^3)				3.7				
Cleaning								
Solvents, water and detergents (kg)	0.2	0.2	0.4	1.2				
Output								
Waste								
To wastewater treatment (kg)	0.1	0.3	0.4					
To incineration (kg)	1.1	0.7	1.9				0.06	
To recycling (kg)			1.5*				0.1**	
Product								
Product output (kg)	0.05	0.02	0.03	0.07	0.3	0.3		
Transport								
Solvent transport (tkm)	0.01	0.002	1.3					
Waste transport (tkm)	0.06	0.04	0.2					
Transport between life cycle stages (tkm)						0.4		1.3

Note. IPI: Intermediate pharmaceutical ingredient; API: Active pharmaceutical ingredient; DP: drug product.
* Solvents and catalyst.
** Cardboard and paper.

predominant. The amount of solvents used in API production is high compared to the limited values found in literature (Parvatker et al., 2019). However, this study includes the solvents required for pre- and post-treatment (e.g. conditioning and intermediate rinsing) of equipment as well, corresponding to 38 % of the solvent use in the API production stage. In addition, chemical API synthesis is followed by three (re)crystallisation steps, which require significant solvent amounts.

For IPI1, no solvents other than pyridine were used. For IPI2, the estimated amount of solvents is split between THF, methanol and ethyl acetate, with the latter being the largest. The consumption of solvents is however an underestimate as no pre- or post-treatment was included. It is important to note that it is known from primary data that a three times higher mass of IPI1 than IPI2 is needed to produce the amount of API for one blister pack. So, although almost two times more solvents and almost four times more chemicals are consumed per kg IPI2 compared to IPI1, the mass per DU is lower as less IPI2 is needed. Regarding utility consumption in API and DP production, the value for electricity and heat is high compared to values found in other studies (Parvatker et al., 2019; Yang et al., 2021). This is because the top-down approach that is used in this study results in utility amounts that include not only the utilities used in the specific production processes, but also utilities that are needed for, for example, lighting of the building and process control. In addition, the utilities used for cleaning are included in the utility consumption of API production.

4.2. Environmental impact of baseline scenario

Both the carbon and resource footprint of the baseline scenario, corresponding to IPI production in China and API production and subsequent life cycle stages in Europe, were calculated. The carbon and resource footprint of the most important materials and processes that are used in the calculation of the environmental impact are shown in Table 3 for both China and Europe. It can be observed that the carbon footprint of European solvent production is lower or equal to that of Chinese production, while this is not always the case for the resource footprint. This is mostly due to the geographic location of production, and the corresponding sources of chemicals and utilities. For pyridine, for example, the difference in carbon footprint is mostly due to the lower carbon footprint of the electricity mix used for European pyridine compared to the electricity used in the production of pyridine for the rest of the world that was used as a proxy for China. For the resource footprint, the difference is less outspoken as the difference in resource footprint of the European electricity mix and the mixes for the rest of the world is less significant. The types of resources that are used are however different. In the European electricity mix, more abiotic renewable resources and nuclear energy are used, whereas in the rest of the world the electricity mixes are more fossil based. For methanol, toluene and acetone, however, the consumption mixes are retrieved from the CarbonMinds database. The differences between Europe and China are in

Table 3
Carbon and resource footprint expressed per unit of the most important solvents and utilities that are used in the production of the tablets. Data retrieved from CarbonMinds and ecoinvent v3.9.

	Carbon footprint (kg CO_2-eq/unit)		Resource footprint (MJ_{ex}/unit)	
	China	Europe	China	Europe
Solvents (kg)				
Pyridine	8.5	7.8	218.5	218.6
Tetrahydrofuran	5.7	5.7	171.7	171.5
Methanol	2.8	1.1	42.5	44.8
Ethyl acetate	3.2	2.8	93.3	88.8
Toluene	0.9	0.9	57.8	59.9
Acetone	2.7	2.3	73.3	73.4
Utilities				
Electricity (kWh)	0.9	0.3	13.8	14.3
Natural gas (MJ)	0.04	0.1	0.8	1.0
Nitrogen gas (kg)	0.4	0.2	9.0	9.2

these cases due to the different production routes used in different parts of the world. For methanol, for example, the Chinese consumption mix consists for the bigger part out of methanol made from the gasification of coal, a process that has a higher carbon footprint than gasification of heavy fuel and steam methane reforming of natural gas, the two main production routes for methanol in Europe.

4.2.1. Carbon footprint of the baseline case

The carbon footprint over the life cycle is 32 kg CO_2-eq/DU. Fig. 2a shows the contribution of each life cycle stage. IPI1, IPI2 and API production have the highest contribution to the carbon footprint with a share of 51, 17 and 28 %, respectively. Smaller contributions are made by DP manufacturing (2 %) and packaging (1 %), while distribution, end-of-life of packaging and transport together contribute for 1 %. The carbon footprint of IPI and API production together is 31 kg CO_2-eq/DU, which is in the range of the values found by Parvatker et al. (2019). However, the relative contribution of 95 % for these first life cycle stages is high compared to previous findings (Siegert et al., 2020; Yang et al., 2021). On the one hand, this can be due to the high impact of the IPIs, which are extensively modelled in this study. The model in this study includes not only the chemical conversions that occur but utilities,

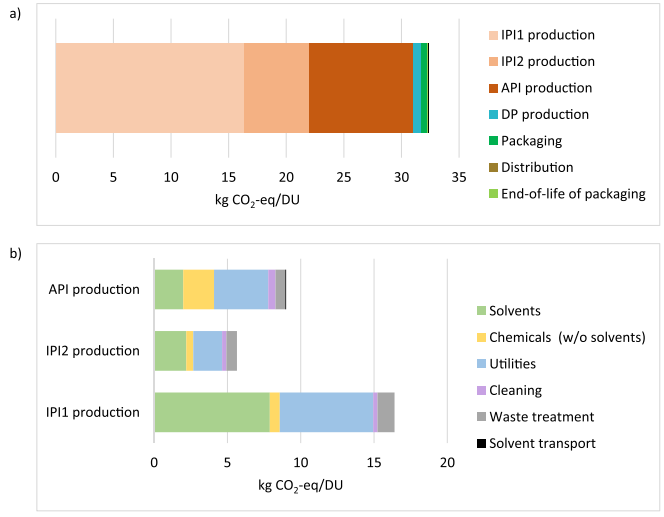

Fig. 2. a) Contribution of all life cycle stages to the total carbon footprint per declared unit, i.e. one blister pack of Zytiga (R) for the baseline scenario. b) Carbon footprint of IPI1, IPI2 and API production according to contributing categories. IPI: intermediate pharmaceutical ingredient; API: active pharmaceutical ingredient; DP: drug product.

cleaning and transport as well. In the previously mentioned studies, input materials are modelled based on stoichiometric reactions or approximated as organic chemicals or other chemicals retrieved from LCI databases. If organic chemicals from the ecoinvent v3.9 database were used as a proxy for both IPIs in this study, the carbon footprint of IPI and API production would be 9 kg CO_2-eq/DU, i.e. a decrease of 71 %. On the other hand, the use stage was excluded in this study and assumptions had to be made in other latter life cycle stages (packaging, distribution) which might result in possible underestimations of the other life cycle stages.

Fig. 2b zooms in on the different contributions to the carbon footprint of IPI and API production, the key contributors to the impact. The higher impact of IPI1 compared to IPI2 is twofold. Firstly, the carbon footprint per kilogram of intermediate product is slightly higher for IPI1 than for IPI2, i.e. 359 compared to 327 kg CO_2-eq/kg, respectively. Secondly, as already indicated in section 4.1., three times more IPI1 than IPI2 is needed to produce one blister pack of the drug product, thereby reinforcing the difference in impact between IPI1 and IPI2 per DU. In IPI1 production, solvents have the highest impact resulting in a high contribution of this category of 48 % to the total carbon footprint of IPI1 production. This is due to the use of pyridine as solvent, which has a high carbon footprint of 8.5 kg CO_2-eq/kg (Table 3) in combination with the high estimated amount of 0.9 kg/DU (Table 2) that is used. Utilities have the second largest impact in IPI1 production, resulting in a contribution of 39 %. In this category, electricity accounts for 80 %, due to the coal used in the Chinese electricity mix. In IPI2 production, solvents have again the highest impact, followed by utilities with a respective contribution of 39 and 35 % to the total carbon footprint of IPI2 production. The impact of solvents in IPI2 production is significantly lower than in IPI1 production, which is due to the fact that less IPI2 and therefore less solvents are needed per DU (0.6 kg of THF, methanol and ethyl acetate together) and the solvents have a lower carbon footprint per kg, as shown in Table 3. Electricity is again the highest contributor to the utilities category (80 %) due to the Chinese electricity mix. All in all, the high impact of IPI production, which are obtained from external suppliers, indicates the importance of (external) suppliers in the assessment of the environmental impact of a drug product. In addition, the high impact of solvents adds to the importance of (external) suppliers, in this case referring to solvent suppliers.

In contrast to the IPI manufacturing stages, the impact of solvents in API production is lower, contributing for 22 % to the total impact of this stage. Although the amount of solvents used per DU is higher in API production compared to IPI production (Table 2), the carbon footprint of the used solvents, i.e. toluene, acetone and methanol, is lower (Table 3). Utilities have the largest impact in API production, resulting in a share of 41 %, of which electricity consumption accounts for 57 %. Although the amount of electricity used per DU is higher for API production than for IPI1 production (Table 2), the absolute impact is significantly lower due to API production taking place in Europe and thereby using the European electricity market mix. As shown in Table 3, the carbon footprint of the European mix is lower than this of the Chinese mix, resulting in the lower impact of utilities in API production. Chemicals other than solvents (e.g. reagents, catalysts, …) have the second highest impact and a contribution of 23 %, due to the higher consumption of these chemicals in API compared to IPI production per DU (Table 2) and the use of a high impact palladium catalyst in API production (22,811 kg CO_2-eq/kg). As mentioned by McCarthy et al. (2021) the use of palladium can be made more sustainable by catalyst recovery. Here, the palladium is recovered with an efficiency of 92 % (section 3.1.2.2.), resulting in a reduction of the carbon footprint of the catalyst with 92 %. This significantly limits the ultimate contribution of the palladium catalyst to the carbon footprint of API production.

Other contributing categories that are shown in Fig. 2b are cleaning, waste treatment and solvent transport. The absolute impact of cleaning is low for all three productions, resulting in low contributions to the total impact from 2 % (IPI1 production) to 6 % (API production). For waste

treatment, the avoided burden approach was used, where a negative impact is attributed to the avoided purchase of virgin materials and energy. As the production of IPI1 and IPI2 takes place in China, the assumed waste treatment technology was solvent incineration with energy recovery. Energy in the form of heat and electricity is generated as a by-product and replaces the generation of heat and electricity. In API production, some of the solvents are distilled with a yield of maximum 80 %. This avoids the need to purchase maximum 80 % virgin solvent in a subsequent process, resulting in the low impact of waste treatment for API production. The contribution of solvent transport is very low for all three steps and is at most 1 % for API production.

4.2.2. *Resource footprint of the baseline case*

The resource footprint over the life cycle of the drug product is 647 MJ_{ex}/DU, as shown in Fig. 3a. The largest contributors are IPI1 (48 %), API (29 %) and IPI2 (16 %) production. DP production and packaging have a much smaller impact with contributions of 4 and 3 %, respectively. The resource footprint of end-of-life of packaging is, with a resource footprint of −2 MJ_{ex}/DU, slightly negative due to the recycling of the cardboard and paper. The impact of other life cycle stages is negligible. The resource footprint up to and including API production is 605 MJ_{ex}/DU, representing 93 % of the total resource footprint. Compared to the values found by De Soete et al. (2014), this value is rather high, but still in line with their findings. However, in De Soete et al. (2014), chemical building blocks such as IPIs have a lower contribution to API production, due to the use of proxies from databases. If the proxy 'organic chemical' from the ecoinvent v3.9 database was used for both IPIs instead of modelling, the resource footprint of API production would decrease by 68 % to a value of 195 MJ_{ex}/DU.

Zooming in on the environmental impact of IPI and API production, solvents and utilities account for of the highest proportion of the resource footprint of these three stages (Fig. 3b), as observed in previous studies (De Soete et al., 2014; Van Der Vorst et al., 2011). In IPI1 production, the solvents category has the highest impact with a share of 62 % to the total resource footprint. As for the carbon footprint, this is due to the high impact of pyridine (Table 3). Utilities have the second highest impact, with electricity being the main contributor (76 %). Analogous for IPI2 production, where solvents have the highest impact with a contribution of 56 %. In this category, ethyl acetate is responsible for the highest contribution due to the high quantity that is used compared to tetrahydrofuran and methanol. The solvent category is followed by the utilities category, with electricity being again the main contributor (74 %).

For API production, the impact of utilities is the highest, with a contribution of 46 %, as was the case for the carbon footprint. However, in contrast with the carbon footprint, the absolute resource footprint of utilities of API production is higher than that of IPI1 production. This is not only because more electricity is used, but also because of the origin

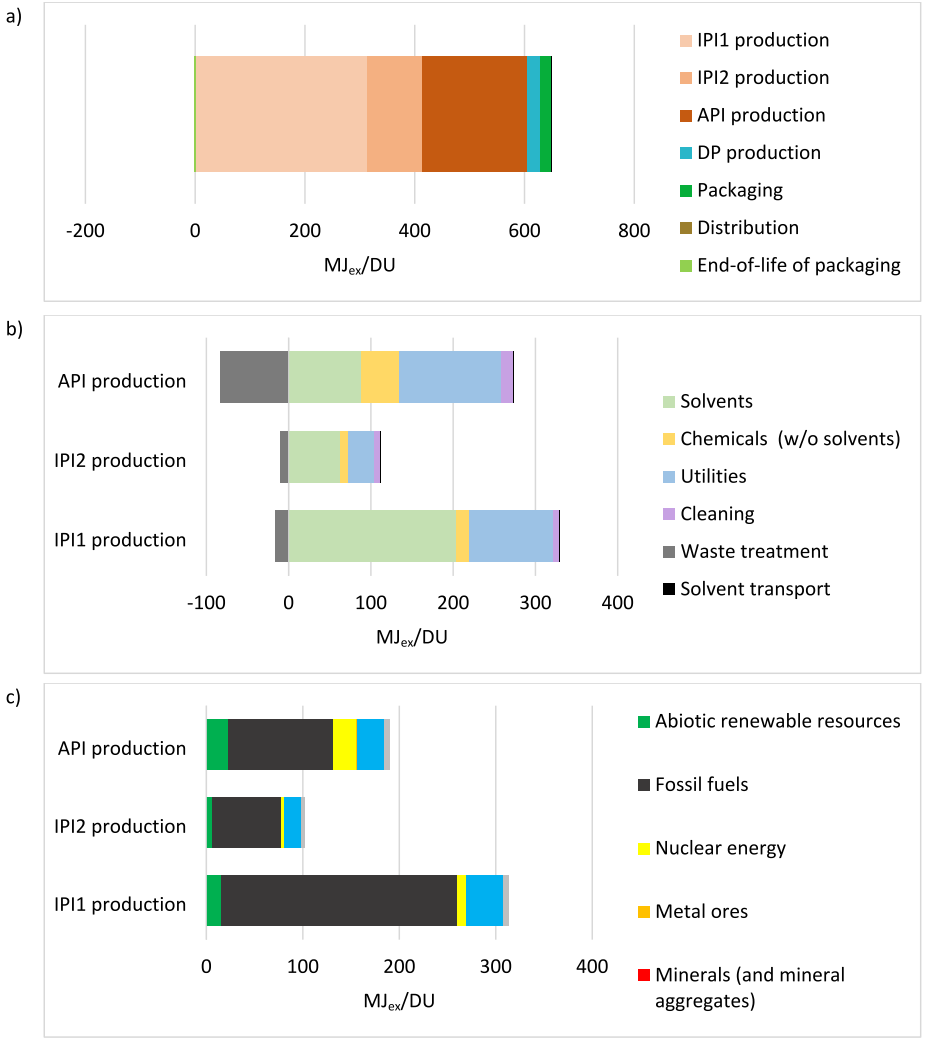

Fig. 3. a) Resource footprint per life cycle stage of the drug. b) Resource footprint of IPI1, IPI2 and API production per contributing category. c) Resource footprint of IPI1, IPI2 and API production per natural resource category. IPI: intermediate pharmaceutical ingredient; API: active pharmaceutical ingredient; DP: drug product.

of the electricity mix. Indeed, the resource footprint per kWh of the European mix is higher than that of the Chinese mix, which contrasts with the carbon footprint (Table 3). This pinpoints the importance of studying both carbon and resource footprint. The impact of solvents is lower, due to the lower resource footprint of the solvents that are used (Table 3). The impact of other chemicals in API production is higher compared to IPI production, due to the higher consumption of chemicals (Table 2) and the nature of these chemicals.

Other contributing categories are again cleaning, solvent transport and waste treatment. The contribution of cleaning varies between 2 % and 7 % between IPI and API production, while the contribution of solvent transport is negligible. For the latter category, however, a negative resource footprint is obtained for IPI and API production due to the use of the avoided burden approach. This leads to a reduction of the total resource footprint of 5, 9 and 30 % for IPI1, IPI2 and API production, respectively. The high reduction in resource footprint in API production is due to the solvent recycling that is implemented, by which at maximum 80 % of virgin solvent acquisition can be avoided, together with energy from incineration of the residual solvent. For the incineration of solvent waste, only energy in the form of heat and electricity is avoided which has a lower impact.

Fig. 3c shows the resource footprint of IPI1, IPI2 and API production per resource category. Due to solvent and electricity production, fossil fuels are the main contributors for all three compounds. However, due to the difference in electricity mix for IPI and API production, there is a shift from fossil fuels to abiotic renewable resources and nuclear energy for API production. In fact, the European electricity mix consists of more renewable electricity sources and more nuclear energy. Solvents and electricity are also responsible for the contribution of water and land and biotic resources. The contribution of minerals and mineral aggregates is negligible.

4.3. Geographical influence on environmental impact

To discuss the influence of the geographical location of solvent, IPI and API production on the carbon and resource footprint, several scenarios were developed. The location of the other life cycle stages remains unchanged and is therefore not further discussed. Four scenarios are presented here, while the full range of considered scenarios are shown in Fig. S1 and Figure S2**Error! Reference source not found.**. The environmental impacts of all scenarios are compared to S1 (i.e. full European production), as this allows for a straightforward identification of the influence of changing the geography on the environmental impact.

4.3.1. Comparison of the carbon footprint of the different scenarios

As shown in Fig. 4, the carbon footprint of European production and solvent sourcing (S1) is 26 kg CO_2-eq/FU, which is the lowest of the four scenarios. If solvents are sourced from China for European production (S2), the carbon footprint increases by 14 %. The carbon footprint of the solvents produced for API production increases the most (98 %) due to the two times higher carbon footprint of Chinese methanol (Table 3). As mentioned in section 4.2., this is due to Chinese methanol being produced from coal whereas the European methanol mostly comes from heavy fuel and natural gas. If IPI and API production are moved to China, but solvents are sourced from Europe (S3), the carbon footprint increases by 40 % compared to a full European supply chain (S1). This implies that moving pharmaceutical production to China results in a higher increase in carbon footprint than changing the production location of the solvents. This is because the carbon footprint of utilities significantly increases by moving to China, caused by the almost three times higher carbon footprint of the Chinese coal-based electricity mix compared to the European mix (Table 3). Additionally shifting to using solvents produced in China increases the carbon footprint further with 9 % (S4). This results in a total increase of the carbon footprint with 49 % comparing S4 to S1. In case only IPI production and IPI solvent sourcing would be shifted to China while API production and API solvent sourcing still take place in Europe (S0), a 21 % increase in the carbon footprint compared to S1 would be obtained. The other 28 % difference between S0 and S4 is due to the Chinese API production and API solvent sourcing. Therefore, in this case, it is less harmful to shift IPI production and solvent sourcing to China than to shift API production.

4.3.2. Comparison of the resource footprint of the different scenarios

The resource footprint of full European production (S1) is with 606 MJ_{ex}/FU the lowest of the four scenarios (Fig. 5a). Sourcing solvents from China for European production (S2) increases the resource footprint with only 1 %. A decrease in resource footprint of the solvents of IPI1 and API production is observed, due to the lower resource footprint for Chinese pyridine, toluene and methanol than the European ones (Table 3). However, this decrease is counteracted by a higher resource footprint for transport, as the solvents must be shipped from China to Europe. If solvents are sourced from Europe but used in Chinese production (S3), the resource footprint increases with 6 % compared to S1. This is mostly due to the increase in the impact of API production. In general, moving production to China results in a decrease of the resource footprint of the chemicals and utilities as the Chinese resource footprint of most chemicals and utilities is lower than the European one (Table 3). This decrease is counteracted by an increase of the impact of the waste treatment, due to the incineration of all waste in case of Chinese API production. The resource footprint of incineration is higher than this of

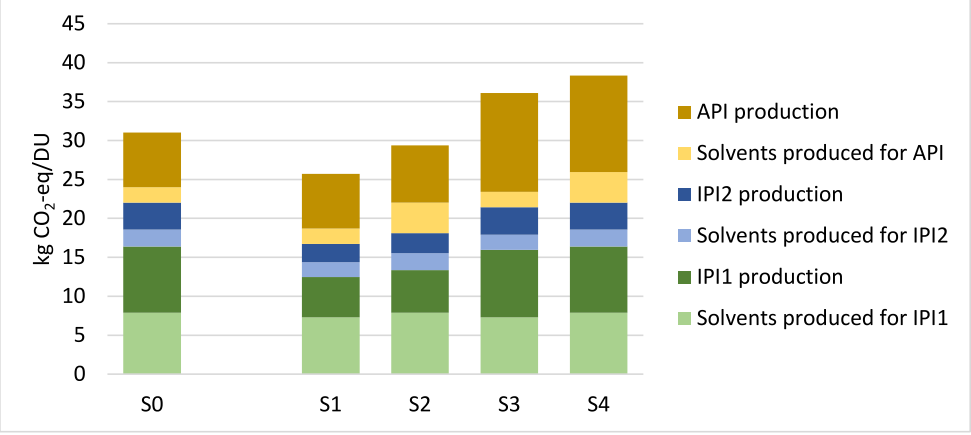

Fig. 4. Carbon footprint of the baseline case S0 and the four considered scenarios S1, S2, S3, S4. Solvents are considered separately, while API, IPI1 and IPI2 production refers to the impact of production excluding solvent use. API: active pharmaceutical ingredient.

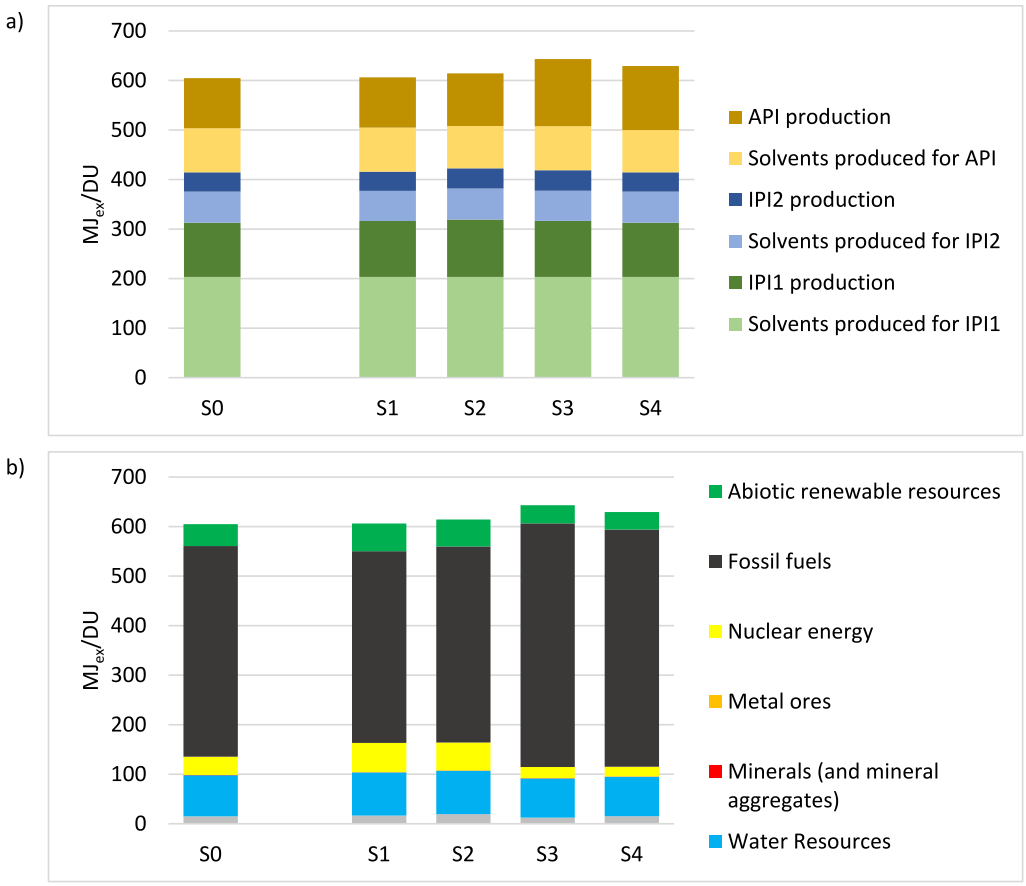

Fig. 5. a) Resource footprint of the current situation S0 and the four scenarios divided in solvents produced for IPI or API production and the actual production of the compound (w/o solvents). b) Resource footprint of the current situation S0 and the four scenarios (S1 – S4) per natural resource category. IPI: intermediate pharmaceutical ingredient; API: active pharmaceutical ingredient.

recycling technologies, due to a smaller avoided burden in case of incineration. In addition, as for S2, the solvents must be transported from Europe to China. Sourcing solvents from China for Chinese production (S4) results in an increase of only 4 % compared to S1. As for S2, the lower resource footprint of Chinese pyridine, toluene and methanol causes a decrease in the total footprint (Table 3). In contrast with S2, the solvents are shipped within China, thereby limiting the impact of transport. The total resource footprint is further decreased by the lower impact of other chemicals and utilities but increased by the shift from waste recycling to incineration, as was the case in S3. Those two aspects result in the small rise of only 4 %, which is lower than for S3 (6%). As opposed to the carbon footprint, sourcing solvents from Europe for Chinese production results in a higher resource footprint than sourcing Chinese solvents for Chinese production. Thereby the importance of considering both emission-based and resource-based indicators is proven again.

Moving IPI production to China and keeping API production in Europe (S0), results in a decrease of the RF of 6 % compared to S1. However, one should keep in mind that with respect to resource footprint, it is important to consider the shift in natural resource use. As shown in Fig. 5b, no significant shift in resources is observed when shifting from solvents produced in Europe to solvents produced in China (S2). However, shifting production from Europe (S1 and S2) to China (S3 and S4) results in a significant shift of the resources from abiotic renewable resources and nuclear energy to fossil fuels, due to the beforementioned difference in electricity mixes. So, while the differences in total resource footprint are small, the nature of the resources changes.

4.4. Considerations and recommendations

4.4.1. Sensitivity analysis on modelling of IPI production

Since the production of IPIs, and IPI1 in particular, was found to be of great importance for the environmental impact of the drug, a sensitivity analysis was performed on the modelling of both IPIs for both carbon and resource footprint. The contribution to the variance of the environmental footprints is shown in Fig. S3. The assumed solvent amount of 85 % of the non-aqueous mass is shown to be the parameter with the highest contribution to this variance (up to 96 %). Other main contributors to the variance are, amongst others, the environmental footprints of pyridine and ethyl acetate and the factors that were used to calculate electricity consumption (i.e. electricity consumption in API production and the mass ratio). This confirms the importance of solvents and utilities, particularly electricity, to the environmental impact of IPI production as was shown in Fig. 2b and Fig. 3b.

4.4.2. Critical look at the data inventory and limitations of the study

To the authors' knowledge, this is one of the few LCA studies of a drug that includes the modelling of the intermediate building blocks. However, validation of this modelling of the IPI would be of added value. For instance, the solvent amount being 85 % of the non-aqueous mass used in API production is used as a proxy for IPI production in this study. This could lead to overestimates of the solvent use in IPI production and corresponding environmental footprints, which is important as it is the most sensitive parameter. In addition, API cleaning was used as a proxy for IPI cleaning, but with solvents and chemicals amounts adjusted to the number of batches of IPI that are produced. To check this proxy, primary data on cleaning in IPI production is

necessary. At last, the utilities used in API production were also assigned to IPI production based on the mass ratio between IPI and API production, which is only a proxy. However, utility consumption for API production was calculated using a top-down approach. Consequently, the consumption of utilities in the production plant over one year is allocated to the tablet production based on production mass and time. In this way, all electricity used in the plant is included, such as the utilities used for cleaning, general lighting and power consumption of process control. This leads to high amounts of, for example, electricity consumption compared to other studies that use a bottom-up approach. Considering a bottom-up approach next to the top-down approach might be interesting to check for the origin of the utilities that are allocated to API production.

Apart from IPI modelling, the assumption of a 100 % yield in DP production may result in an underestimation of the environmental impact. Therefore, the contribution of DP production in the environmental footprints of the drug product may be underestimated as well. In addition, excluding the use phase in the baseline scenario affects the environmental footprint. What could be considered in the use phase is the transport of products from the warehouse to hospitals, followed by the transport of the patients to the hospital and back home together with the water consumption and intake of another drug that must be combined with Zytiga®. Also, the distribution phase could be extended by including e.g. the utilities needed for heating, ventilation and air conditioning of the warehouse. Furthermore, it was assumed that all tablets are consumed, while in reality losses occur that could end up in the environment when not properly handled. On that account, the products excreted from the body could be considered as well.

The biggest limitation in this study is the limited availability of accurate primary data regarding the IPI modelling due confidentiality constraints. This modelling occurred based on high level stoichiometric data received from the company, completed with information from literature and previous processes. In addition, the absence of complex chemicals, such as excipients, in databases poses another limitation, as proxies for these chemicals are used. On top of that, the geographical location of the datasets is often limited to general regions such as Europe, Rest of the world or even only global data is available. At last, considering only two impact categories limits the application of the results of this study. In future studies, other input and output-related impact categories such as ecotoxicity, human toxicity and land use can be considered, as recommended by Van Wilder et al. (2024) which would result in a broader picture of the environmental footprint of pharmaceutical products.

4.4.3. Recommendations towards data collection

Fig. 2a and Fig. 3a show the high contribution of IPI and API production to the environmental impact of the drug. As these steps have a high impact, it is important to know what the losses are in subsequent production steps such as DP production. Therefore, a first important parameter to collect or consider is the yield of the processes. Zooming in on IPI and API production learns that solvents and utilities, especially electricity, are the highest contributors to their environmental impacts, which is confirmed by the sensitivity analysis. Important data to collect from external suppliers are therefore solvent and electricity consumption data and, if possible, the origin thereof. By collecting electricity data it is important to be aware of the differences between a top-down and bottom-up approach.

5. Conclusions

In this study, the carbon and resource footprint of the entire life cycle of a particular drug were assessed using the LCA methodology. The modelling of the IPIs based on stoichiometric reactions and literature instead of using database proxies resulted in a high contribution of IPI production in the carbon and resource footprint. Apart from IPI production, API production also appeared to have a high contribution in the environmental footprint, together contributing for 96 % to the carbon footprint and 93 % to the resource footprint. Zooming in on IPI and API production learned that solvents and electricity contribute significantly to the carbon and resource footprint of these processes. For IPI production, the importance of especially solvent consumption was confirmed by a sensitivity analysis. As IPI and solvent production are, in this case, part of the (external) supply chain of the pharmaceutical company, they are responsible for part of the scope 3 emissions of this company. Therefore, correct information and modelling of these compounds is important to correctly assess and possibly reduce these emissions. However, in future research, it would be relevant to validate the results with primary data to proof the modelling approach. In addition, the importance of the geographical location of solvent sourcing and production of IPIs and API is shown in this study. Several scenarios were identified in which solvents were sourced from Europe or China and combined with IPI and API production in Europe or China. The carbon footprint was lowest for European production with European solvents, whereas Chinese production with Chinese solvents increased the carbon footprint with 49 %. For the resource footprint, the most optimal production route was the scenario with IPI production and solvent sourcing in China and API production and solvent sourcing in Europe, which is the current production situation. It has a 6 % lower resource footprint than European production with European solvents. The geographical location of the processes in the pharmaceutical supply chain can thus have an effect on the environmental impact of the delivered products and is therefore important for the producing companies. Hence, it is recommended that data collection by a pharmaceutical company from external suppliers focuses not only on process yield and solvent and electricity consumption, but also on the origin of the compounds. In this study, the importance of considering both emission-based and resource-based indicators was proven several times as the results differ for carbon and resource footprint. This is mainly due to the use of non-fossil fuel-based energy sources, which results in an absolute decrease of the carbon footprint, but only results in a shift in resources for the resource footprint without decreasing its absolute value. At last, switching production to Asian countries might imply social issues such as e.g. poor working conditions. A social LCA might bring additional insights to this geographical shift.

CRediT authorship contribution statement

Amelie Verlinden: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Lieselot Boone:** Writing – review & editing, Validation, Supervision. **Wouter De Soete:** Writing – review & editing, Validation, Supervision. **Jo Dewulf:** Writing – review & editing, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.spc.2024.10.016.

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