Systems & Control Transactions

Research Article - Peer Reviewed Conference Proceeding
ESCAPE 35 - European Symposium on Computer Aided Process Engineering
Ghent, Belgium. 6-9 July 2025
Jan F.M. Van Impe, Grégoire Léonard, Satyajeet S. Bhonsale,
Monika E. Polańska, Filip Logist (Eds.)

PSE PRESS

Eco-Designing Pharmaceutical Supply Chains: A Process Engineering Approach to Life Cycle Inventory Generation

Indra CASTRO VIVAR[a]*, Catherine AZZARO-PANTEL[a], Alberto A. AGUILAR LASSERRE[b], Fernando MORALES-MENDOZA[c]

[a] Université de Toulouse, CNRS, INPT, UPS, Laboratoire de Génie Chimique, Toulouse, France
[b] Tecnológico Nacional de México, Instituto Tecnológico de Orizaba, Orizaba, Veracruz, México
[c] Universidad Autónoma de Yucatán, Facultad de Ingeniería Química, Mérida, Yucatán, México
* Corresponding Author: indra.castrovivar@toulouse-inp.fr.

ABSTRACT

The environmental impacts of pharmaceutical production underscore the need for comprehensive life cycle assessments (LCAs). Offshoring manufacturing, a common cost-saving strategy in the pharmaceutical industry, increases supply chain complexity and reliance on countries like India and China for active pharmaceutical ingredients (APIs). The COVID-19 pandemic exposed Europe's vulnerability to global crises, prompting initiatives such as the French government's re-industrialization plan to relocate the production of fifty critical drugs. Paracetamol production has been prioritized, with recent shortages highlighting the urgency to address supply chain risks while considering environmental impacts. This study uses process engineering to generate life cycle inventory (LCI) data for paracetamol production, offering an eco-design perspective. Aspen Plus was employed to model the API manufacturing process, integrating mass and energy balances to address the scarcity of LCI data. The results highlight significant differences in emissions between India and France. For 1 kg of API, India's emissions are 0.0826 kg CO_2 eq for electricity and 1.3845 kg CO_2 eq for heat from steam, compared to France's significantly lower values of 0.005228 kg CO_2 eq and 1.1828 kg CO_2 eq, respectively. These differences emphasize the environmental benefits of relocating production to regions with cleaner energy sources. The study demonstrates the value of process modeling for generating robust LCI data, enabling detailed LCAs to support eco-design in pharmaceutical manufacturing. This approach can be extended to other chemicals, facilitating sustainable decision-making in the sector's re-industrialization.

Keywords: Aspen Plus, LCA, LCI

INTRODUCTION

Sustainability in the pharmaceutical industry has become a priority as concerns grow about the environmental impact of Active Pharmaceutical Ingredients (APIs) and the increasing complexities of global supply chains. In this context, paracetamol, one of the most widely used APIs in the world, has become a relevant case study due to its current production practices, which rely almost exclusively on large-scale facilities in India and China. These facilities can produce up to 40,000 tons annually, serving as an important economic source but posing sustainability and supply security challenges. Centralized production far from major consumption centers, like Europe, creates a heavy dependence on foreign API sources.

This dependence became evident during the COVID-19 pandemic when disruptions in essential medicine supply chains were experienced due to external factors and geopolitical tensions, which underscored Europe's vulnerability to global crises and prompted policies advocating the strengthening of local production capacity. Within this framework, the European Pharmaceutical Strategy, launched in 2020, advocates the relocation of the production of essential medicines on the continent, seeking to create shorter and more sustainable value chains that are less susceptible to international disruptions. The reindustrialization of pharmaceutical production in Europe aims to ensure access to high-quality medicines, minimize the environmental impacts associated

with transportation, and promote cleaner energy sources.

The global paracetamol API market is projected to reach USD 13.72 billion by 2029, with a compound annual growth rate (CAGR) of 4.41% between 2024 and 2029[1]. The COVID-19 health contingency underscored the critical role of paracetamol. This surge in demand highlighted the global dependency on India and China for the medication supply. In response, initiatives like the French government's reindustrialization plan aim to localize the production of 50 essential medications, including paracetamol, addressing supply chain vulnerabilities observed during shortages in 2022 and early 2023 [2].

Despite its market significance, sustainability analysis of APIs faces challenges, mainly due to limited Life Cycle Inventory (LCI) data. To address this challenge, this study applies Life Cycle Assessment (LCA) methodology to evaluate two locations for paracetamol API production focusing on the environmental benefits of local production in France. A notable contribution is developing LCI data through chemical process modeling, addressing the data gap in LCA studies of pharmaceuticals.

By integrating process simulation with LCA methodologies, the goal is to improve the accuracy and comprehensiveness of LCI data. This approach aims to ensure a more detailed and reliable assessment of environmental impacts, thus supporting better decision-making for sustainable development within the pharmaceutical sector.

RELATED WORK

The pharmaceutical industry leverages simulation and process design to improve efficiency and sustainability, addressing the significant environmental challenges of API production. Recent advancements integrate simulation with LCA to minimize environmental impacts, focusing on generating LCI data through process modeling. This section reviews key studies in this area.

The environmental impact of excipients in the production of ibuprofen tablets is investigated in [3] through simulation at each stage of the manufacturing process. This approach helped authors collect energy consumption and emissions data for the LCI. Their findings highlight that auxiliary materials, such as excipients, significantly impact the environmental footprint of pharmaceutical products, stressing the need to optimize these materials for better sustainability.

A continuous production framework for synthesizing zuclopenthixol is proposed in [4], demonstrating simulation integration to gather process data in continuous production. This included modeling solvent use and separation operations, enabling analysis of material and energy flows in API production. Similarly, simulation is used in [5] to develop a continuous flow model in the synthesis of ibuprofen, using a series reactors to optimize solvent use and reduce the environmental impact of production. These studies highlight how continuous production can significantly reduce the environmental footprint and improve process sustainability in producing commonly used APIs.

The scope of simulation and process modeling is extended to encompass common anesthetics in [6]. Their approach included industrial-scale simulations that enabled detailed data collection for the LCI of 20 anesthetics, quantifying greenhouse gas emissions at each stage. This work provides a framework for comparing sustainability options in anesthesia.

The environmental impact of the catalytic synthesis of nopal is explored in [7]. This study used simulation to construct the LCI of two synthesis alternatives. The authors found that selecting solvents and reusing materials can significantly reduce the environmental footprint in synthesizing specialty chemicals, including those of pharmaceutical relevance.

The literature demonstrates that integrating chemical process simulation with process engineering is key to generating an accurate LCI in the pharmaceutical industry, allowing energy and materials flow to be comprehensively captured throughout production stages, facilitating more complete environmental assessments. The studies reviewed highlight that simulation can optimize the use of excipients, solvents, and continuous processes, contributing to reducing the environmental footprint of APIs and other specialty chemicals.

Despite these advances, the literature scarcely mentions the application of this approach to the environmental assessment of acetaminophen production, leaving a gap in the sustainability analysis for this medication. Implementing process modeling and simulation methodologies for acetaminophen could provide critical data for the LCI, contributing to more sustainable manufacturing practices in the future.

MATERIALS AND METHODS

Paracetamol, also known as acetaminophen, is a medication with analgesic and antipyretic effects. It is widely used for headaches, muscle aches, arthritis, backaches, toothaches, colds, and fevers due to its efficacy and low side effects. Its proven effectiveness makes it essential in over-the-counter and prescription pain management, justifying its selection for this case study developed.

This study uses LCA methodology and process modeling to assess the environmental impacts of various supply chain scenarios for active pharmaceutical ingredients, particularly evaluating the benefits of relocating production to France.

- The flowsheet development outlines the API

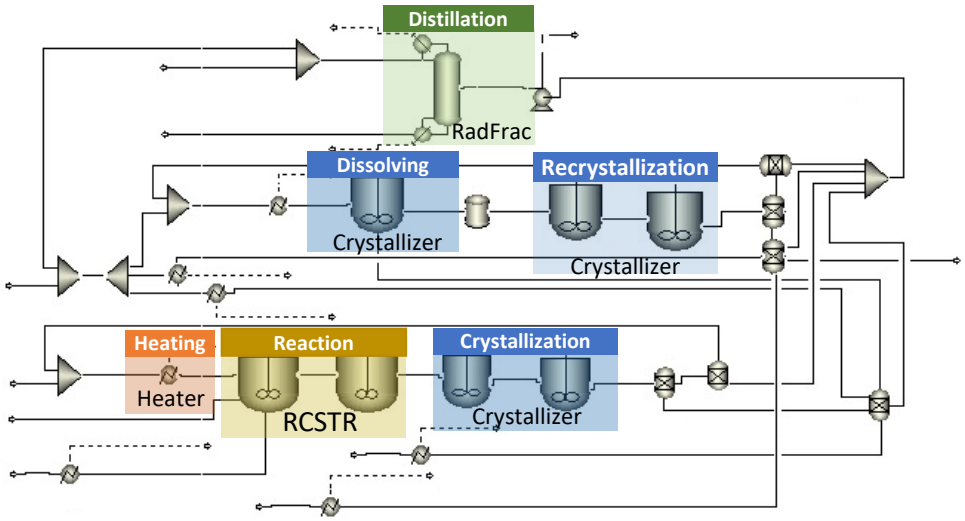

Figure 1: Simulation flowsheet and main equipment for API production

production process in Aspen Plus V14, providing energy and material balances for the LCA.

- The life cycle assessment compares the impacts of API production in France and India.

Process modeling

Simulating acetaminophen production in Aspen Plus helps analyze its environmental impact by providing data on material and energy balances. In this system, two reactions are characterized: (1) the reaction of p-aminophenol and acetic anhydride to form acetaminophen and acetic acid, and (2) the reaction of acetic anhydride and water to produce acetic acid. According to [8], (1) can be modeled as an irreversible pseudo-first order reaction when acetic anhydride is in excess relative to p-aminophenol. Regarding (2), three irreversible steps, characterized by first-order kinetics, are involved [9]. The reactions are as follows:

$$(CH_3CO)_2O + C_6H_7NO \rightarrow C_8H_9NO_2 + CH_3COOH \quad (1)$$

$$(CH_3CO)_2O + H_2O \rightarrow CH_3COOH \quad (2)$$

Both reactions must take place within a reasonable time frame; to characterize their rates, the Arrhenius equation is used:

$$k = Ae^{(-Ea/RT)} \quad (3)$$

According to [8], the activation energy for (1) is 37310 J/mol. That study compared the reaction rate as a function of temperature and used the reaction rate, activation energy, gas constant, and temperature to determine the pre-exponential Arrhenius factor over a range of 323 K to 343 K, which corresponds to the operating temperature range used in the simulation, with a value of k equal to 11,293s^{-1}.

The production process begins with water mixed with a recycle stream at 15°C, which is preheated to 53.7°C using 5 atm steam for the reaction in a Continuously Stirred Tank Reactor (CSTR). Acetic anhydride is also preheated to the same temperature, and p-aminophenol is added to the reactor. After the reaction, the fluid is cooled in a crystallizer (to 40°C and then 15°C) and sent to filtration and washing. A portion of the slurry (35%) is recycled for preheating, while the rest (65%) and wash drains go to a distillation column.

Recycled drain water and acetic acid are heated and mixed with the acetaminophen cake and purified through a column with activated carbon, then undergoes a second recrystallization, filtration, and washing process. Seventy-five percent of the drain water is recycled into the solvent, and the wash drains are sent to the distillation column. The acetaminophen cake is sent to storage. Distillate, mainly water and acetic acid, is reused in the solvent and wash processes, with the remainder stored. The bottom residues from the distillation column, considered waste, are stored separately. Figure 1 complements the description.

Life cycle assessment

The LCA evaluates a product or service's environmental impacts by examining all stages of its life cycle based on a defined functional unit. Its objective is to identify opportunities to improve its environmental performance. The LCA consists of four main stages: goal and scope definition, inventory analysis, impact assessment, and interpretation.

The goal of this LCA is to carry out a comparative analysis of the environmental impacts associated with the production of acetaminophen API in two locations: France and India. The system boundary, depicted in Figure 2, includes all material and energy inputs related to API production, following a “cradle-to-gate” approach. This approach covers resource use and emissions from raw material extraction to the final API manufacturing

stage. The functional unit is defined as 1 kg of API acetaminophen, ensuring consistency in mass and energy balance calculations in the different scenarios. Data on the API production process is taken from [8].

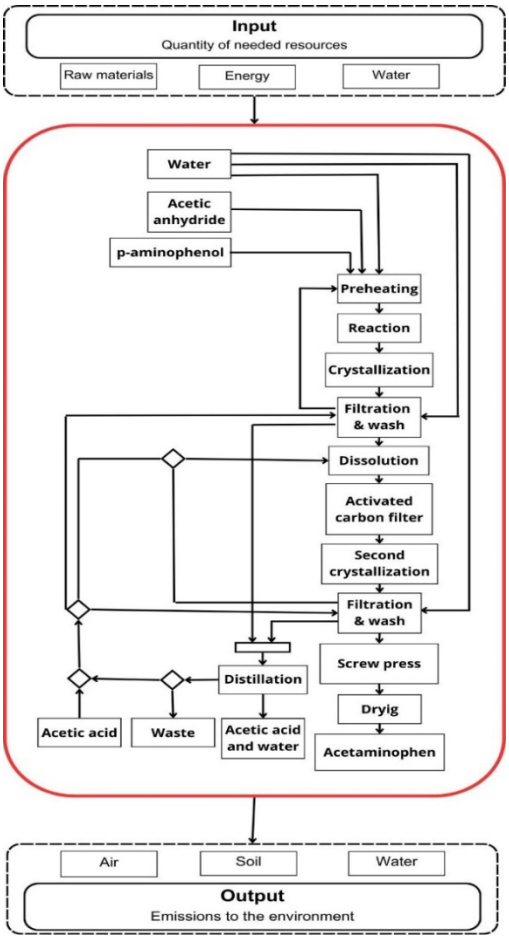

Figure 2: System boundary

The LCI phase quantifies all material and energy flows that cross the system boundary. This involves linking the units or services required to produce a functional unit with the corresponding emissions and resource extraction for each unit process. Although literature sources provide reference data on raw materials, they are often insufficient for high-quality LCA. To address this limitation, process simulation with Aspen Plus was used to generate detailed mass and energy balances of acetaminophen production. This approach allows for accurate estimation of inputs and outputs, improving the LCI accuracy and strengthening the assessment reliability of as a whole. To ensure robust and complete data collection, the LCI was developed by combining process modeling with literature-based information

For the LCIA phase, LCI data is linked to environmental impact categories. This evaluation follows the EF 3.0 (Environmental Footprint) method, implemented using the SimaPro version 9.4.0.2 software. This method aligns with European sustainability policies and industry standards, providing a comprehensive framework for assessing environmental impacts at intermediate and endpoints. In addition, the ecoinvent database complements the information on emissions, guaranteeing coherence in characterizing impacts in all the evaluated processes.

RESULTS AND DISCUSSION

This section compares the environmental impacts of acetaminophen API production in France and India to illustrate the effectiveness of the proposed methodology.

Results (see Figure 3) show that the climate change category presents higher values in India (16,35 kg CO_2 eq) compared to France (13,91 kg CO_2 eq). Similarly, non-carcinogenic human toxicity is higher in India (2.13 E-07 CTUh) compared to France (1,95 E-07 CTUh). In contrast, ozone depletion presents higher values in France (2.07 E-06 kg CFC11 eq) compared to India (1.93 E-06 kg CFC11 eq). These results highlight key areas of environmental impact in the acetaminophen production process, indicating potential opportunities for improvement of emissions related to each impact category.

Figure 4 shows the normalized energy consumption results for production in India and France. Normalization addresses unit incompatibility and compares an indicator to a reference value such as the average annual environmental load per inhabitant in a country or continent, so that the results are expressed as a "relative impact," making them easier to understand through familiar comparisons. Normalization unifies impact category indicators, aids in category comparisons, enhances the understanding of each impact's scope, and enables a more coherent analysis of results.

The results focus on energy-related processes which were explicitly selected based on the country or the corresponding geographical area and account for significant emissions and resource consumption. The impact categories with the highest environmental impacts are freshwater ecotoxicity, fossil resource use, and climate change. The freshwater ecotoxicity category shows a significantly higher impact for “heat from steam” in India compared to France. Although the values for “electricity” and “cooling energy” in both countries are similar and lower, “heat from steam” in India stands out as the major contributor to ecotoxicity, likely due to the release of specific contaminants during steam production that adversely affect aquatic ecosystems.

Regarding the use of fossil resources and climate change, both electricity and “heat from steam” in India exhibit higher values compared to the same resources in France. Electricity generation in India predominantly relies on coal-fired power plants [9]. Despite ongoing efforts to diversify the energy mix, coal remains the most cost-effective option due to India's substantial coal

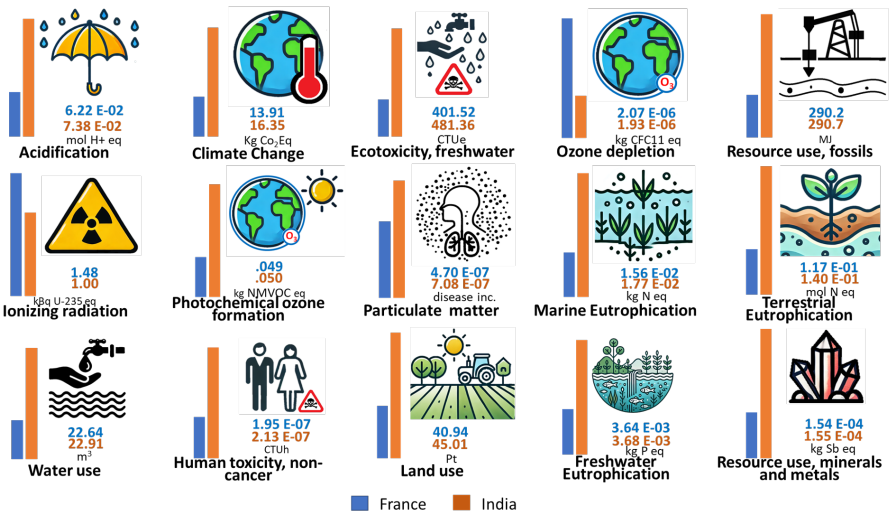

Figure 3: Characterization results per impact category for API production

reserves. In contrast, electricity production in France is predominantly nuclear-based, which plays a crucial role in reducing CO_2 emissions [10].

India and France's energy infrastructures differ significantly. India needs to enhance energy efficiency, waste treatment, and adopt renewables to mitigate environmental impacts, while France predominantly uses nuclear and renewable energy. Developing strategies to lower energy consumption and emissions is vital, focusing on energy-efficient technologies and process optimization. Transitioning to renewable energy is also crucial.

Incorporating advanced waste treatment minimizes toxic contaminants, particularly in freshwater. Recycling solvents and by-products cuts raw material use and waste. Redesigning supply chains and relocating production to greener energy regions can lessen climate impacts and carbon footprints.

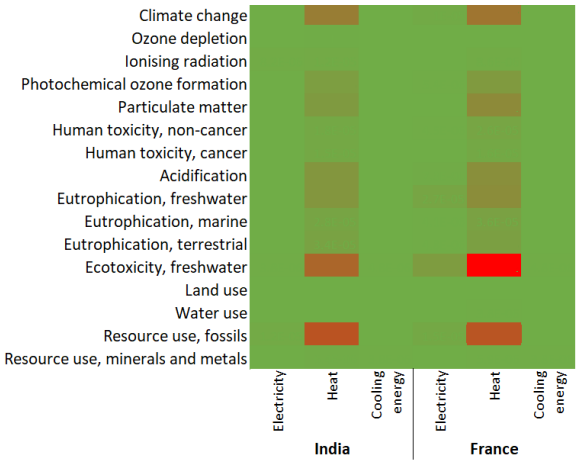

Figure 4: Normalized energy consumption results for production in India and France

It is important to highlight that France has implemented strategies to reduce the pharmaceutical industry's carbon footprint, such as government energy transition initiatives and environmental regulations. However, as some essential inputs are still imported, their impact on the overall carbon footprint must be considered [11].

Beyond domestic efforts, a key challenge is ensuring international suppliers meet sustainable standards. The French pharmaceutical industry has advanced in responsible sourcing, focusing on materials with lower environmental impact and suppliers committed to sustainability. However, the level of sustainability in supply chains outside France varies significantly, potentially affecting the $kgCO_2$/kg API value. This underscores the need for enhanced monitoring across the supply chain to maintain sustainability consistency [12].

To further reduce its environmental impact and promote sustainable production, the pharmaceutical industry must adopt a holistic approach. This includes improving energy efficiency, enhancing waste treatment, optimizing supply chains, innovating in raw materials, and integrating clean technologies. By addressing these aspects collectively, the industry can move toward a more sustainable and resilient production model.

CONCLUSIONS

The relocation of paracetamol production facilities to French territory represents a strategic response to the need for enhanced supply security and a reduced environmental impact associated with its manufacturing. This shift underscores the urgency of implementing long-term sustainable solutions that promote more resilient supply chains with a smaller ecological footprint.

This research addresses a key limitation in LCA in the pharmaceutical industry: the need for more detailed LCI data on specific processes. By using advanced process modeling tools, both LCI data collection steps and

accuracy are significantly improved. Integrating process simulation with LCA methodologies allows for an exhaustive and precise evaluation of environmental impacts. This approach not only reinforces the reliability of LCA data but also provides a solid basis for sustainability-oriented decision-making in the pharmaceutical sector.

The methodology used in this study allows the construction of a detailed and reliable LCI for the paracetamol production process, facilitating a precise quantification of the associated environmental impacts. This level of detail supports more informed sustainability decisions, allowing pharmaceutical industry players to develop production strategies with lower environmental impacts and greater alignment with sustainable development goals.

The study also highlights a gap in traditional LCA methodologies, as they lack impact factors tailored to the pharmaceutical sector. To address this, the industry relies on specific indicators to enhance sustainability like Process Mass Intensity (PMI), which measures material efficiency in API synthesis and promotes more sustainable manufacturing practices [13].

Future work will explore scenarios for producing APIs such as waste recycling, treatment, and heat recovery which can reduce environmental impact and optimize resources for a sustainable pharmaceutical production.

ACKNOWLEDGEMENTS

CONAHCYT funded this work through a scholarship.

REFERENCES

1. Mordor Intelligence, “Ibuprofen API Market - Manufacturers, Size & Share.” Accessed: Jul. 15, 2024.[Online].Available:https://www.mordorintelligence.com/industry-reports/ibuprofen-api-market
2. Medscape, “E. Macron announces that the production of about fifty medicines will be ‘relocated’ to France,” 2023. Accessed: Jun. 29, 2023. [Online]. Available:https://francais.medscape.com/voirarticle/3610180?ecd=WNL_mdplsfeat_230617_mscpedit_fr&uac=298107MV&impID=5535696&faf=1
3. D. Wang, W. S. Cheow, N. Amalina, M. Faiezin, and K. Hadinoto, “Selecting optimal pharmaceuti-cal excipient formulation from life cycle assess-ment perspectives: A case study on ibuprofen tablet formulations,” J Clean Prod, vol. 292, Apr. 2021, doi: 10.1016/j.jclepro.2021.126074.
4. A. E. Cervera-Padrell, T. Skovby, S. Kiil, R. Gani, and K. V. Gernaey, “Active pharmaceutical ingre-dient (API) production involving continuous pro-cesses - A process system engineering (PSE)-assisted design framework,” European Journal of Pharmaceutics and Biopharmaceutics, vol. 82, no. 2, pp. 437–456, Oct. 2012, doi: 10.1016/j.ejpb.2012.07.001.
5. H. G. Jolliffe and D. I. Gerogiorgis, “Process modelling and simulation for continuous pharmaceutical manufacturing of ibuprofen,” Chemical Engineering Research and Design, vol. 97, pp. 175–191, May 2015, doi: 10.1016/j.cherd.2014.12.005.
6. A. G. Parvatker et al., “Cradle-to-Gate Green-house Gas Emissions for Twenty Anesthetic Ac-tive Pharmaceutical Ingredients Based on Pro-cess Scale-Up and Process Design Calcula-tions,” ACS Sustain Chem Eng, vol. 7, no. 7, pp. 6580–6591, Apr. 2019, doi: 10.1021/acssuschemeng.8b05473.
7. L. A. Gallego-Villada, C. Hasenstab, E. A. Alarcón, and A. L. Villa, “Identification by Life Cycle Assessment of the critical stage in the catalytic synthesis of nopol using heterogeneous cataly-sis,” Sustain Prod Consum, vol. 27, pp. 23–34, Jul. 2021, doi: 10.1016/j.spc.2020.10.017.
8. S. Scholarlycommons, S. Riksen, N. Chau, and S. Byabato, “Batch Versus Continuous Acetamino-phen Production,”2022.[Online].Available:https://repository.upenn.edu/cbe_sdrhttps://repository.upenn.edu/cbe_sdr/137
9. L. S. Tiewsoh, J. Jirásek, and M. Sivek, “Electrici-ty generation in India: Present state, future out-look and policy implications,” Energies (Basel), vol. 12, no. 7, 2019, doi: 10.3390/en12071361.
10. U. K. Pata and A. Samour, “Do renewable and nuclear energy enhance environmental quality in France? A new EKC approach with the load ca-pacity factor,” Progress in Nuclear Energy, vol. 149, Jul. 2022, doi: 10.1016/j.pnucene.2022.104249.
11. “France - Countries & Regions - IEA.” Accessed: Mar. 10,2025.[Online].Available:https://www.iea.org/countries/france
12. “The challenges of sustainable pharmaceutical sourcing - Lactalis Ingredients Pharma.” Ac-cessed: Mar.10,2025.[Online].Available:https://pharma.lactalisingredients.com/2024/05/31/the-challenges-of-sustainable-pharmaceutical-sourcing/
13. C. Jimenez-Gonzalez, C. S. Ponder, Q. B. Broxterman, and J. B. Manley, “Using the right green yardstick: Why process mass intensity is used in the pharmaceutical industry to drive more sus-tainable processes,” Org Process Res Dev, vol. 15, no. 4, pp. 912–917, Jul. 2011, doi: 10.1021/op200097d.