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A Hybrid LCA Framework for Drug-Level Carbon Footprint Assessment under Data Constraints: Application to Narrower-Spectrum Penicillin

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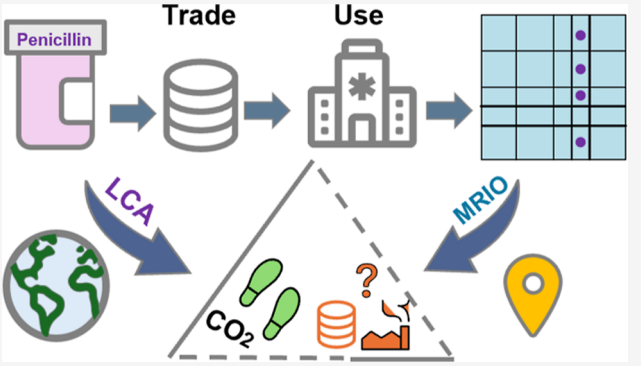
ABSTRACT: Understanding differences in drug-specific carbon footprints across countries is increasingly important as healthcare sustainability and product-level reporting gain prominence in regulatory initiatives, such as digital product passports, yet such estimates remain largely unavailable due to sparse drug-level data. Here, we develop a hybrid life cycle assessment framework that enables quantification of drug-specific carbon footprints across regions under real-world data constraints. It combines drug-level life cycle inventory with international consumption and trade statistics and embeds a structured uncertainty assessment to evaluate key data gaps and modeling choices through robustness tests. We demonstrate its application using narrower-spectrum penicillin. We estimate that its global consumption in 2019 was associated with about 90 kt CO_2e. Although modest in magnitude, the footprint's geographic distribution differs markedly from that of aggregated pharmaceuticals, showing that sector-level accounting can mask substantial cross-country heterogeneity. Across alternative assumptions, global totals vary by less than 30%, and country rankings remain largely stable, indicating that the observed patterns reflect structural differences in consumption and sourcing rather than artifacts of specific modeling choices. This framework offers a transparent pathway for drug-level carbon accounting under data scarcity and identifies data and methodological priorities to support future reporting, procurement, and decarbonization efforts in the pharmaceutical sector.



KEYWORDS: *penicillin, carbon footprint, pharmaceuticals, EE-MRIO, matrix augmentation, hybrid LCA, product environmental footprints*

1. INTRODUCTION

Pharmaceuticals are essential to modern healthcare systems, yet their production and use contribute substantially to global healthcare-related environmental impacts.[1−4] Recent research using environmentally extended multiregional input−output (EE-MRIO) models estimates that global pharmaceutical consumption generated 219.6 Mt CO_2-equivalents (CO_2e) in 2019, a 77% increase since 1995.[1] Furthermore, consistent large disparities in per-capita carbon footprint of pharmaceuticals across countries revealed inequality in the responsibility for healthcare-induced climate burdens.[1] However, these estimates treat pharmaceuticals as a single aggregated sector, masking the substantial variation in production pathways, chemical inputs, energy use, and consumption patterns across drugs. Such aggregation constrains the identification of drug-level emission hotspots and limits the development of targeted mitigation strategies across countries.

Drug-level environmental assessments remain scarce, particularly at the global scale. Most existing studies rely on process-based life cycle assessment (LCA), which provides detailed insights into production pathways, packaging, storage, and administration for specific drugs.[5] Yet, confidentiality surrounding pharmaceutical manufacturing means that many precursor chemicals and intermediates are largely absent from standard LCA databases. As such, LCAs often rely on stoichiometric modeling or laboratory-scale proxies,[6] capturing direct energy use and emissions while omitting substantial portions of upstream chemical supply chains.[7,8] More broadly, process-based LCAs are known to underestimate environmental impacts by 20−50% because upstream processes are omitted from the system boundary.[9,10] In addition, because LCAs typically employ averaged upstream data, they have limited ability to reflect the geographic sourcing of inputs within global pharmaceutical supply chains. Together, these

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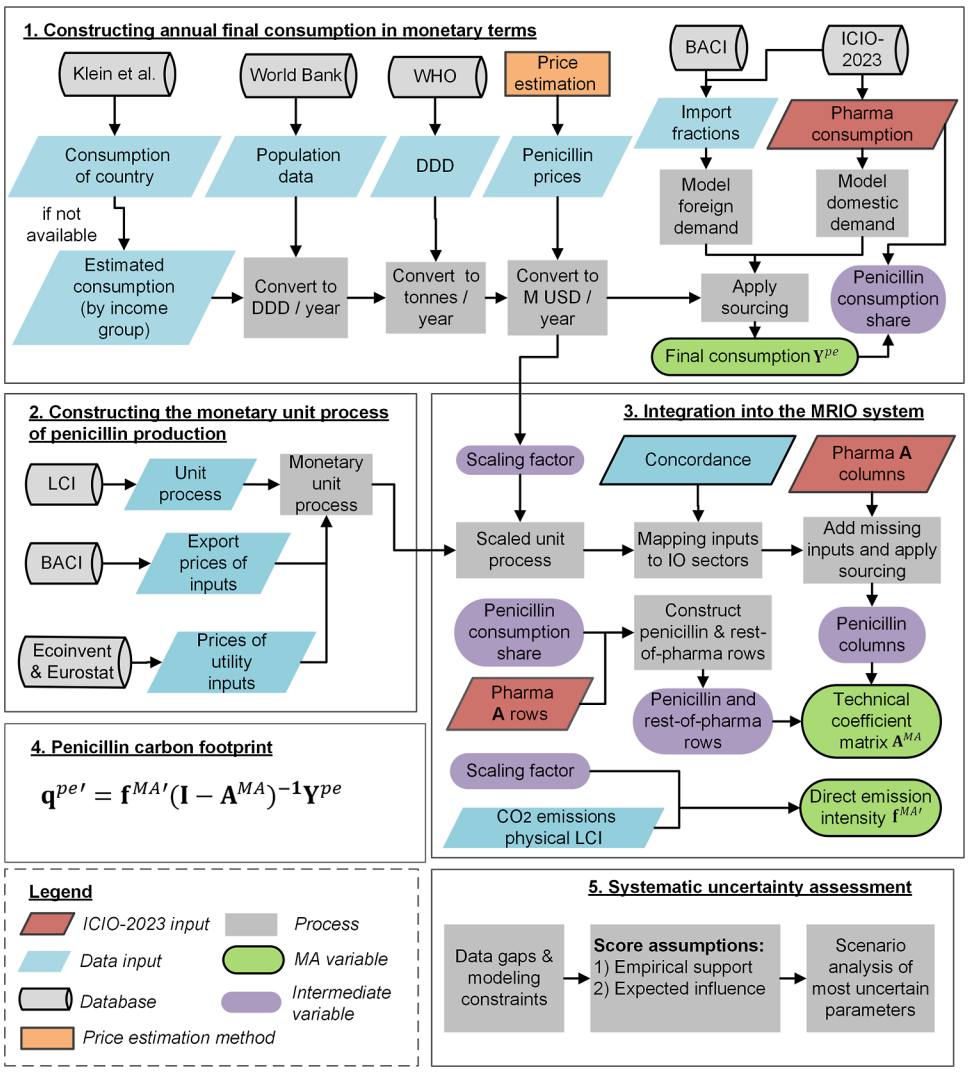

Figure 1. Analytical framework for estimating drug-level carbon footprints under data-limited conditions.

limitations underscore the need for approaches that achieve drug-level resolution while capturing full upstream and cross-country supply chain contributions.

EE-MRIO analysis complements LCAs by tracing international production networks and enabling consistent temporal and cross-country comparisons, especially as new data sets developed by international organizations such as the OECD and Eurostat become available. However, these models are constrained by sectoral aggregation: all pharmaceuticals are grouped into one sector per region, masking drug-level heterogeneity and obscuring opportunities for targeted mitigation.[11−13] Because MRIO databases are typically expressed in monetary terms, notable cross-country price variation also limits the interpretation of physical production and consumption.[14] In addition, EE-MRIO analyses predominantly capture cradle-to-gate emissions, as postconsumer processes are generally not well represented in economic accounts.

Hybrid LCA approaches that integrate LCA's product-level details with MRIO's global completeness offer a potential bridge between these limitations.[15,16] Among hybrid methods, matrix augmentation (MA) is particularly promising for pharmaceuticals because it introduces a product-specific sector into an MRIO system with relatively limited additional data requirements.[17] In practice, however, applying MA to detailing pharmaceuticals is challenging because drug-level output values, basic prices, production recipes, and sales data are rarely reported; physical life cycle inventories (LCIs) are often incomplete; and translating physical inventories into monetary MRIO values is complicated by cross-country price disparities. Despite these constraints, MA remains one of the few viable pathways for global drug-level carbon footprint quantification. It can incorporate the best available empirical information (e.g., consumption and trade statistics), reduce LCA's truncation error by integrating global supply chains depicted by EE-MRIO, and provide a consistent accounting framework even when key drug-level data are missing.

In this study, we develop and demonstrate an MA-based hybrid LCA framework to disaggregate narrow- and medium-spectrum penicillin (hereafter "penicillin") from the aggregated pharmaceutical sector in ICIO-2023, the MRIO database released by the OECD in 2023.[18] ICIO-2023 represents the global economy by 45 sectors and 76 countries, plus one "rest of the world" region (hereafter 77 countries), including CO_2e accounts from eight greenhouse gases (Supporting Information 1, p. 6). Penicillin serves as a proof-of-concept case because, unlike most pharmaceuticals, it has both a well-documented LCI[19] and internationally reported consumption data.[20]

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Combining these data with international prices and trade within ICIO-2023 allows us to estimate the carbon footprint of penicillin consumption across all countries for 2019. These estimates are complemented by a structured uncertainty assessment that documents data gaps, classifies modeling choices, and evaluates their influence through scenario-based robustness tests.

Developing consistent drug-level environmental accounting capabilities is increasingly important as emerging regulatory initiatives, such as digital product passports and corporate sustainability reporting, begin to require transparent, comparable, and verifiable product-level impact information.[21−23] This work makes three contributions. First, we develop a systematic and reproducible framework for applying MA under data-limited conditions, integrating a structured uncertainty assessment to ensure transparency of assumptions and their influence on results. Second, we demonstrate the framework using penicillin and provide, to our knowledge, the first consistent global estimate of a drug-level carbon footprint across countries. We show that drug-level disaggregation reveals substantial cross-country heterogeneity masked in aggregated pharmaceutical accounting. Finally, the framework is designed to be transferable as more drug-level LCIs and international statistics become available. Our uncertainty assessment highlights priority data and modeling gaps that, if addressed, would both improve the accuracy of product-level carbon footprints and enable coverage of a broader range of pharmaceuticals.

2. METHODS

The hybrid LCA framework for estimating drug-level carbon footprints under data constraints consists of two components: MA and a structured uncertainty assessment. The full methodological workflow is presented in five steps, including main data sources used to ensure transparency and reproducibility (Figure 1 and Sections 2.1-2.7). A structured overview of all data sources is provided in the Supporting Information 1, p.4.

MA is implemented in three steps to create an augmented version of ICIO-2023, in which the aggregated pharmaceutical sector is split to include a penicillin subsector. First, we derive annual final consumption of penicillin in monetary terms by converting physical use data[20] (daily defined doses, DDD) and estimating country-level prices that maintain the fundamental input−output monetary balances, and we allocate the resulting penicillin consumption between domestic and imported sources based on ICIO-2023. Second, we construct a monetary economic unit process for penicillin based on a detailed physical LCI,[19] applying country-specific prices for major chemical inputs based on international trade statistics,[24] uniform utility prices derived from ecoinvent[25] and Eurostat,[26] and the estimated penicillin prices; this yields monetary input coefficients that reflect cross-country price variation rather than differences in underlying physical production technology. Third, we integrate the resulting penicillin final consumption and production unit process into ICIO-2023, generating penicillin-specific production inputs, output distribution, and direct emission intensities consistent with MRIO accounting principles.

Using the augmented MRIO system, we calculated the carbon footprint associated with penicillin consumption via the standard Leontief demand-driven model, capturing both direct and upstream emissions embodied in global supply chains. We refer the reader to Supporting Information 1 (p. 10−11) and Kitzes[27] for an introduction to EE-MRIO. The structured uncertainty assessment evaluates how key assumptions required to conduct the MA affect footprint estimates. We document all data gaps and corresponding modeling choices, classify them by type and expected influence, and conduct scenario-based robustness tests targeting major sources of uncertainty.

2.1. Notation and Symbols

We use the following notation throughout the Methods section. **Bold uppercase letters** (e.g., **A**) denote matrices, **bold lowercase letters** (e.g., **x**) denote vectors, and *italic letters* denote scalars (e.g., p). The prime (′) denotes row vectors, and the symbol ":" denotes an entire row or column. Subscripts identify positions in matrices or vectors: r and c refer to countries in rows and columns, respectively, where $r, c \in C$ (the 77 ICIO countries); i refers to both sectors in rows and columns, where $I \in I$ (the 45 ICIO sectors), and "pe" and "ph" refer to the penicillin and pharmaceutical industry, respectively. Superscripts denote specific subjects: pe = penicillin, ph = pharmaceuticals; dom = domestically sourced, imp = imported; "MA" = parameters produced through MA. The symbols and their corresponding units and sizes are also summarized in Supporting Information 1, p. 5.

2.2. Constructing Annual Final Consumption in Monetary Terms

For each country c, we first calculate penicillin consumption in monetary terms (d_c^{pe} in million USD) using country-specific penicillin use in DDD reported for the year 2019[20] (d_c^{DDD}), a standard conversion factor (2×10^{-6} tonnes (t)/DDD[28]), and a country-specific estimated penicillin price (p_c^{pe} in million USD/t) (see Section 2.4.2)

$$d_c^{pe} = 2 \times 10^{-6} \cdot d_c^{DDD} \cdot p_c^{pe}, \qquad (\forall\ c) \tag{1}$$

The penicillin use dataset covered 56 of the 77 ICIO-2023 countries; consumption in the remaining 21 was estimated from population size[29] and income-group[30] average per-capita use.

We then distinguish d_c^{pe} by sourcing: domestically sourced ($d_c^{pe,dom}$) and imported ($d_c^{pe,imp}$). Because penicillin-specific sourcing data are unavailable, the domestic part is approximated using the domestic sourcing share of the pharmaceutical sector

$$d_c^{pe,dom} = d_c^{pe}\left(\frac{d_c^{ph,dom}}{d_c^{ph}}\right), \qquad (\forall\ c) \tag{2}$$

where $d_c^{ph,dom}$ denotes country c's total domestically sourced final consumption of pharmaceuticals and d_c^{ph} is c's total pharmaceutical final consumption regardless of producer; these estimates are from ICIO-2023.

Imported consumption is therefore

$$d_c^{pe,imp} = d_c^{pe} - d_c^{pe,dom}, \qquad (\forall\ c) \tag{3}$$

The imported penicillin consumption is allocated to sourcing countries using the penicillin-specific bilateral import share $m_{r,c}$ calculated from the BACI international bilateral trade data set (Supporting Information 1, p. 11). When BACI coverage is missing, we use the ICIO-2023 pharmaceutical sourcing structure as a proxy. Together, the final consumption entries for penicillin are

$$y^{pe}_{(r,pe),(c,pe)} = \begin{cases} m_{r,c} d_c^{pe,imp}, & r \neq c \\ d_c^{pe,dom}, & r = c \end{cases}, \qquad (\forall\ r, c \in C) \text{ where } \mathbf{Y}^{pe} \in \mathbb{R}^{(C\cdot(I+1))\times C} \tag{4}$$

The penicillin-augmented final consumption matrix $\mathbf{Y}^{pe}$ adds 77 new rows—one for the penicillin supplier in each country—while retaining the original 77 columns (final consumption by country). Because our analysis focuses exclusively on the carbon footprint of penicillin, all entries corresponding to nonpenicillin consumption are set to zero.

2.3. Constructing the Economic Unit Process of Penicillin Production in Monetary Terms

Based on a physical LCI for narrow-spectrum penicillin V production,[19] we first construct a 14-element economic unit process vector ($\mathbf{u}$) in physical terms that specifies 13 economic inputs (8

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chemicals, 3 utilities, 1 agricultural, and 1 pharmaceutical, in negative values), plus the economic output (i.e., one tonne of penicillin, in positive value) from the unit process (detailed in Table S3). For this, we first separate the environmental output (in kt CO_2) from the unit process, which is further discussed in Section 2.4.5. Then, we convert the remaining economic unit process into monetary terms ($\mathbf{e}_c$), using a 14-element price vector ($\mathbf{p}_c$), and conduct an element-wise multiplication

$$\mathbf{e}_c = \mathbf{p}_c \circ \mathbf{u}, \qquad (\forall\ c) \tag{5}$$

The resulting 14-element monetary vector $\mathbf{e}_c$ (million USD) expresses the value of 13 inputs ($\mathbf{e}_c^{\text{input}}$, negative value) and of the monetary value of the penicillin output ($e_c^{\text{pe,output}}$, positive value); the negative sign for inputs and positive sign for outputs reflects the LCA convention.

Since drug-level production data are limited, several assumptions are required. First, for all inputs except the utility inputs, we use country-specific FOB export prices from the BACI data set[24] as the closest observable approximation to basic prices. Although FOB prices include domestic transport and loading costs and BACI contains reexports, and therefore deviate from basic prices by incorporating additional trade-related margins, they provide the most internally consistent cross-country proxy available for this analysis. Utilities are not represented in the BACI. We hence apply uniform global prices based on ecoinvent[25] and Eurostat,[26] acknowledging that these do not fully capture cross-country variation (see Supporting Information 1, p. 9 for details on conversion to 2019 USD price levels). Finally, because no country-specific LCIs exist, all countries have the same physical-unit process. Accordingly, differences in the monetary economic unit process $\mathbf{e}_c$ arise solely from price heterogeneity rather than underlying technological differences.

2.4. Integrating Penicillin into the MRIO Production System

Augmenting ICIO-2023, that is, splitting the aggregated pharmaceutical sector into two subsectors: penicillin and "rest-of-pharmaceuticals", requires reconstructing parts of the MRIO system that describe (i) production technologies and (ii) direct emissions. In ICIO-2023, the technical coefficient matrix $\mathbf{A}$ specifies, for each country−sector pair (columns), the monetary inputs required from all country−sector pairs (rows) to produce one million USD of output. The direct emission intensity vector $\mathbf{f}$ gives the associated direct GHG emissions per million USD of output. Disaggregating pharmaceuticals into penicillin and "rest-of-pharmaceuticals", therefore, involves four steps.

2.4.1. Constructing Penicillin Input Requirements (Columns of $\mathbf{A}^{\text{MA}}$). We first scale the monetary economic unit process to ICIO-2023's unitary basis (one million USD) by calculating a country-specific scaling factor s_c.

$$s_c = \frac{1}{e_c^{\text{pe, output}}}, \qquad (\forall\ c) \tag{6}$$

We then scale the monetary inputs and map each input to the corresponding ICIO-2023 sector using a concordance matrix $\mathbf{C}$ (45 × 13: $C_{i,j} = 1$ when the LCI input j belongs to the ICIO-2023 sector I; $C_{i,j} = 0$ otherwise).

$$\mathbf{t}_c = \mathbf{C} \cdot s_c \cdot -\mathbf{e}_c^{\text{inputs}}, \qquad (\forall\ c) \tag{7}$$

The 45-element vector $\mathbf{t}_c$ shows the inputs needed from the 45 ICIO-2023 sectors to produce one million USD of penicillin in country c. The economic inputs are given a positive sign to match the positive inputs expressed in $\mathbf{A}$.

Because the penicillin LCI covers only 5 of the 45 ICIO sectors, many economic inputs must be inferred. We estimate the missing inputs for country c ($\mathbf{t}_c^{\text{est}}$) based on the total input coefficients of the pharmaceutical sector specified in $\mathbf{a}_{:,(c',\text{ph})}$ from $\mathbf{A}$ using the binary double-counting correction approach[31]

$$\mathbf{t}_c^{\text{est}} = \sum_{c' \in C} \mathbf{a}_{:,(c',\text{ph})} \circ \mathbf{k},$$
$$\text{where } \mathbf{k} = \mathbf{i} - \mathbf{C}\mathbf{i},\ (\forall\ c), \text{ and } \mathbf{A} \in \mathbb{R}^{(C\cdot I)\times(C\cdot I)} \tag{8}$$

where $\mathbf{k}$ is a 45-element filter vector (1 where LCI does not cover the sector, 0 otherwise) and $\mathbf{i}$ is a vector of ones.

The total inputs into country c's penicillin sector $\tilde{\mathbf{t}}_c$ are then

$$\tilde{\mathbf{t}}_c = \mathbf{t}_c + \mathbf{t}_c^{\text{est}},\ (\forall\ c), \qquad \tilde{\mathbf{t}}, \mathbf{t} \text{and} \mathbf{t}^{\text{est}} \in \mathbb{R}^{(I)} \tag{9}$$

Lastly, we allocate the total sectoral inputs across supplying countries, using the sourcing pattern of the country's pharmaceutical sector as the best available proxy. A country−sector pair input into country c's penicillin industry ($a^*_{(r,i),(c,\text{pe})}$) is obtained by multiplying an input i in the penicillin industry ($\tilde{t}_{c,i}$) by the share of that input sourced from the origin country r

$$a^*_{(r,i),(c,\text{pe})} = \frac{a_{(r,i)(c,\text{ph})}}{\sum_{r' \in C} a_{(r',i)(c,\text{ph})}} \tilde{t}_{c,i},$$
$$(\forall\ c, r, i) \text{ where } c, r \in C, \text{ and } i \in I \tag{10}$$

2.4.2. Re-estimating MRIO-Balance-Compatible Penicillin Prices. Country-specific penicillin prices are crucial for converting both consumption and LCI data into monetary units (see eqs 1 and 5). Using only external price data (e.g., BACI FOB prices) to convert physical inputs and outputs into monetary terms can produce an economically infeasible $\mathbf{A}$, in which total intermediate input costs exceed the value of output ($\sum \mathbf{a}_{:,(c,\text{pe})}^{\text{MA}} > 1$). We therefore re-estimate country-specific penicillin prices.

For any country c, the fundamental input−output balance requires that the value of one unit of output equals the sum of intermediate input costs and value added

$$\mathbf{t}_c^{\text{est}}\mathbf{i} + \frac{\mathbf{e}_c^{\text{inputs}}\mathbf{i}}{e_c^{\text{pe,output}}} + w_{c,\text{pe}} = 1, \qquad (\forall\ c) \tag{11}$$

where the 45-element vector $\mathbf{t}_c^{\text{est}}$ specifies the estimated intermediate inputs into country c's penicillin sector inferred from ICIO-2023, and $w_{c,\text{pe}}$ is country c's value-added coefficient for penicillin production, both in million USD/million USD. Since the value-added data for penicillin is unavailable, we use the value-added coefficients of pharmaceuticals obtained from ICIO-2023 as a proxy.

Substituting $e_c^{\text{pe,output}} = p_c^{\text{pe}} u^{\text{pe,output}}$ (based on eq 5) into eq 11, yields

$$\mathbf{t}_c^{\text{est}}\mathbf{i} + \frac{\mathbf{e}_c^{\text{inputs}}\mathbf{i}}{p_c^{\text{pe}} u^{\text{pe, output}}} + w_{c,\text{pe}} = 1, \qquad (\forall\ c) \tag{12}$$

Solving for the unknown penicillin price (in million USD/t of penicillin)

$$p_c^{\text{pe}} = \frac{\mathbf{e}_c^{\text{inputs}}\mathbf{i}}{u^{\text{pe, output}}(1 - w_{c,\text{pe}} - \mathbf{t}_c^{\text{est}}\mathbf{i})}, \qquad (\forall\ c) \tag{13}$$

These estimated country-specific penicillin prices (p_c^{pe}) are used to estimate penicillin final consumption (eq 1) and to scale the economic unit process depicting the production recipe of penicillin, which is used to construct $\mathbf{A}^{\text{MA}}$ (eqs 5−10). Note that these estimated prices are model constructs required to satisfy input−output accounting and may influence how monetary demand scales relative to upstream inputs, which we discuss further in Section 2.6.

2.4.3. Constructing Penicillin Output Distributions (Rows $\mathbf{A}^{\text{MA}}$). Because external sales data for penicillin and total output are unknown in both economic value and mass, we assume a similar sales structure to the pharmaceutical sector, a common practice in MA.[15] Each country's penicillin row is constructed by multiplying the country's original pharmaceutical row by the ratio of total penicillin final consumption to total pharmaceutical final consumption

$$\mathbf{a}'_{(r,\text{pe}),:} = \mathbf{a}'_{(r,\text{ph}),:} \cdot \left(\frac{d_c^{\text{pe}}}{d_c^{\text{ph}}}\right), \qquad \text{with c} = r,\ (\forall\ r) \tag{14}$$

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Table 1. Overview of Key Data Gaps Encountered in the MA Workflow and the Associated Modeling Choices, Together with Their Uncertainty Levels Assessed

EE-MRIO element	data gap or modeling constraint	proxies (P), assumptions (A), modeling solutions (M)		empirical support	expected influence
final consumption	consumption data (coverage) in several countries	A	income group average per-capita consumption	medium	medium
		A	reported consumption is the national total	low	medium
	sourcing data	A	pharma industry domestic sourcing share	low	low
		P	sourcing based on BACI imports	medium	high
output distribution (**A** rows)	sales structure of penicillin	A	similar to the pharma industry	low	low
		M	reported penicillin consumption is assigned to final consumption	medium	medium
production recipe (**A** columns)	total output data	M	penicillin A based on LCI and scaling	medium	unknown
		A	pharma A columns unchanged	low	low
	multiple LCA's	M	variation in prices per country	medium	medium
	sourcing of inputs	A	pharma industry sourcing pattern	low	medium
	self-inputs	A	no self-inputs	high	low
	monetary balance	M	penicillin price estimation method	low	high
direct emissions	multiple LCA's	M	LCI variation through country-specific price data	low	high
	multiple GHGs	A	direct emissions cover CO_2 only	medium	low
price data	basic price data	P	export prices from BACI	high	low
	cross-country utility prices	A	equal across countries	low	medium
value-added	value-added of penicillin	A	pharma value-added coefficient	low	medium

2.4.4. Assembling the Augmented Technical Coefficient Matrix ($\mathbf{A}^{MA}$). After constructing penicillin production structures (Section 2.4.1), re-estimating MRIO-balanced penicillin prices (Section 2.4.2), and generating penicillin output distributions (Section 2.4.3), we assemble the augmented technical coefficient matrix $\mathbf{A}^{MA}$ in four steps.

We first insert a new penicillin production column for each country c, extending **A** by 77 columns. The pharmaceutical columns remain unchanged because penicillin's total output is unknown and cannot be subtracted without violating input−output balances (see Supporting Information 1, p. 12)

$$\mathbf{a}^{MA}_{:,(c,:)} = \left[\mathbf{a}'_{:,(c,0:11)} \quad \mathbf{a}^{*}_{:,(c,pe)} \quad \mathbf{a}'_{:,(c,12:77)}\right], (\forall\ c) \tag{15}$$

Each country r's output distribution row constructed in eq 14 gets inserted a penicillin industry, whose value is fixed at "0" to reflect zero self-inputs, across all producing countries c

$$\mathbf{a}^{*'}_{(r,pe),(c,:)} = \left[\mathbf{a}'_{(r,pe),(c,0:11)} \quad 0 \quad \mathbf{a}'_{(r,pe),(c,12:45)}\right], (\forall\ r, c), \text{ where } \mathbf{a}^{*'} \in \mathbb{R}^{C(I+1)} \tag{16}$$

Then, these penicillin output-distribution rows are inserted, thereby extending **A** by 77 rows

$$\mathbf{a}^{MA'}_{(r,:),:} = \left[\mathbf{a}'_{(r,0:11),:} \quad \mathbf{a}^{*'}_{(r,pe),:} \quad \mathbf{a}'_{(r,12:45),:}\right], (\forall\ r) \tag{17}$$

Lastly, each country's original pharmaceutical row is subtracted by the penicillin row, creating a "rest-of-pharmaceuticals" row

$$\mathbf{a}^{MA'}_{(r,ph,new),:} = \mathbf{a}^{MA'}_{(r,ph),:} - \mathbf{a}^{MA'}_{(r,pe),:}, \text{ and } \mathbf{a}^{MA'}_{(r,ph),:} = \mathbf{a}^{MA'}_{(r,ph,new),:}, (\forall\ r) \tag{18}$$

The resulting matrix $\mathbf{A}^{MA} \in \mathbb{R}^{(C\cdot(I+1))\times(C\cdot(I+1))}$ contains 77 additional rows and 77 additional columns and represents a globally consistent production system in which penicillin is explicitly modeled as a separate industry in each country.

2.4.5. Constructing the Augmented Emission Intensity Vector ($\mathbf{f}^{MA}$). The original unit process provides a single environmental output b (kt) representing the direct CO_2 emissions released during the penicillin production process. To express these emissions in monetary units consistent with the MRIO framework, we scale b using the country-specific conversion factor s_c (see eq 6) to country c's penicillin emission intensity

$$f^{MA}_{c,pe} = s_c \cdot b, \qquad (\forall\ c) \tag{19}$$

We insert $f^{MA}_{c,pe}$ into **f**, at the corresponding position for the added penicillin sector, and obtain the full augmented emission intensity vector $\mathbf{f}^{MA\prime}$. As in **f**, all elements are in kt CO_2e per million USD, except for penicillin, which accounts for CO_2 only due to the LCI's emission coverage.

$$\mathbf{f}^{MA\prime}_{c} = \left[\mathrm{f}_{c,0:11} \quad \mathrm{f}^{MA}_{c,pe} \quad \mathrm{f}_{c,12:45}\right], (\forall\ c), \text{ where } \mathbf{f}^{MA} \in \mathbb{R}^{C\cdot(I+1)} \tag{20}$$

2.5. Quantifying the Carbon Footprint of Penicillin Consumption

Using the augmented MRIO system ($\mathbf{Y}^{pe}$, $\mathbf{A}^{MA}$, $\mathbf{f}^{MA}$), we quantify the carbon footprint, i.e., the total (direct + upstream) emissions driven by the final consumption of penicillin, using the standard Leontief demand-driven model[32]

$$\mathbf{q}^{pe'} = \mathbf{f}^{MA'}(\mathbf{I} - \mathbf{A}^{MA})^{-1}\mathbf{Y}^{pe} \tag{21}$$

where **I** is the identity matrix and $(\mathbf{I} - \mathbf{A}^{MA})^{-1}$ is the Leontief inverse that captures all intermediate production requirements through global supply chains.

2.6. Note on Price-Related Modeling Artifacts

Because penicillin output values are not observed and must be estimated to maintain IO monetary balance (Section 2.4.3), the resulting penicillin prices are model-derived parameters rather than market observations. Only the LCI-based components of the penicillin production recipe scale with these estimated prices; the additional upstream inputs inherited from the pharmaceutical sector remain linked to the pharmaceutical price structures. As a result, in countries where the IO-balancing step yields higher estimated penicillin prices, monetary final consumption increases, while parts of the upstream production structure do not adjust proportionally. This structural mismatch can amplify modeled upstream emissions in high-price countries (see Supporting Information 2).

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Table 2. Overview of Robustness Scenarios: Parameters Varied, Modifications Applied, and Their Expected Influence on the Magnitude and Distribution of Carbon Footprints of Penicillin

scenario	tested parameter (from Table 1)	empirical support	change applied	expected influence
S1	consumption data coverage	low	+25%/+50% for countries with partial coverage	increased carbon footprint of LMICs and UMICs
S2	energy prices	low	−10% to −30% (UMICs) −30% to −50% (LMICs)	decreased global carbon footprint of penicillin
S3	sourcing of final consumption	low−medium	BACI import shares replaced by ICIO pharma sourcing	decreased/increased global carbon footprint shifts in country ranking
S4	value-added coefficients	low	−20% across countries	decreased global carbon footprint
S5	combined	mixed	all parameter changes at the extreme setting	compound effects on totals and rankings

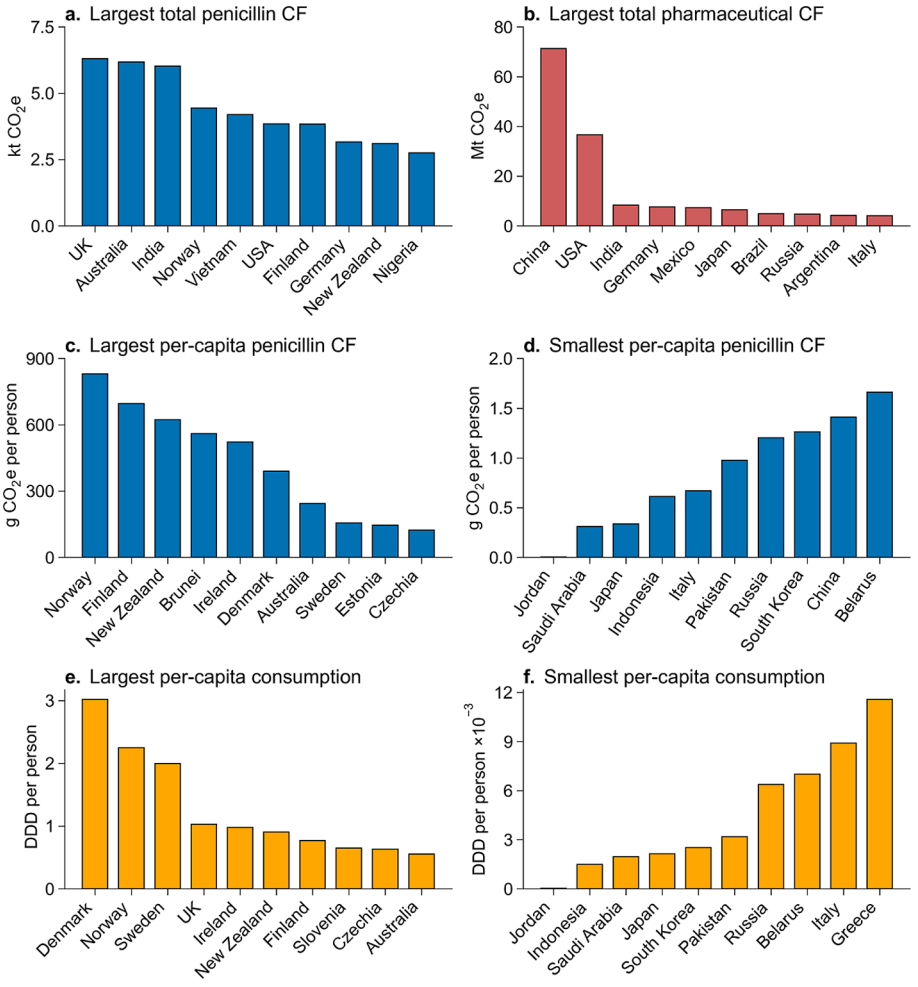

Figure 2. Comparative analysis of the largest and smallest carbon footprints of penicillin. (A) Largest national carbon footprints of penicillin, driven by population size and per-capita consumption levels. (B) Largest national carbon footprints of pharmaceuticals driven by population size and economic scale. (C) Largest per-capita carbon footprints of penicillin driven by physical consumption levels and influenced by price artifacts and sourcing patterns. (D) Smallest per-capita carbon footprints of penicillin. (E) Largest per-capita consumption in daily defined doses (physical units). (F) Smallest per-capita consumption of penicillin in daily defined doses. CF = carbon footprint.

2.7. Structural Uncertainty Assessment

Because several key data inputs required for MA are incomplete or unavailable for most countries, the resulting carbon footprint assessments of penicillin necessarily rely on controlled assumptions. To ensure transparency and evaluate the robustness of the key findings, we embedded a structured uncertainty assessment with three components.

2.7.1. Systematic Documentation of Data Gaps and Modeling Choices. We document data gaps across all MA steps that necessitate modeling choices (Table 1). In addition, we use a proxy-assumption-modeling solution (P/A/M) scheme to classify each modeling choice, making clear where empirical grounding exists and where the approach depends on necessary approximations driven by data scarcity.

- Proxy (P): an empirical substitution using the closest available observable data set when drug-level data are unavailable (e.g., BACI export prices as the best available approximation to basic prices for tradable chemical inputs).
- Assumption (A): a modeling choice required when no empirical data exist, relying on a reasonable but untested approximation (e.g., adopting the pharmaceutical sector's value-added share for penicillin in the absence of drug-level data).

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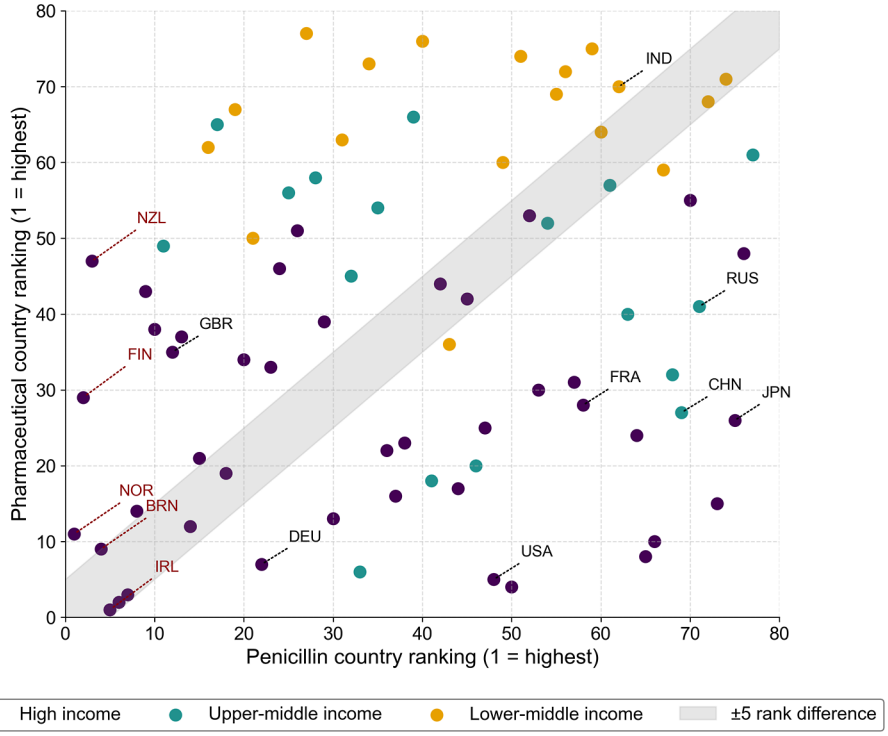

Figure 3. Comparison in ranking of countries' per-capita carbon footprints of penicillin and aggregate pharmaceuticals. The shaded zone shows the countries that have only a 5-position difference in ranking between the two carbon footprints. Red country labels refer to the top 5 per-capita carbon footprints of penicillin, and the black country labels refer to the G7 countries plus India, China, and Russia.

- Modeling solution (M): a procedural step required to maintain input−output accounting consistency (e.g., MRIO-balanced price estimation).

2.7.2. Uncertainty Level Assessment of Each Modeling Choice. To identify which uncertainty warrants explicit stress-testing, we rate each modeling choice along two dimensions: "empirical support" (high/medium/low), indicating the strength of underlying evidence (Supporting Information 1, p. 13−15), and "expected influence" reflecting the anticipated impact on national or global carbon footprint of penicillin estimates.

2.7.3. Scenario-Based Robustness Testing. For items in Table 1 that exhibit low empirical support and high expected influence, we design five scenarios for robustness testing (Table 2).

- S1: consumption data coverage—increasing reported values for countries with partial hospital or retail data;
- S2: energy prices—reducing electricity and heat prices for lower- and upper-middle-income countries;[33]
- S3: sourcing of final consumption—replacing BACI-based import shares with ICIO pharmaceutical sourcing structure;
- S4: value-added margins—decreasing penicillin's value-added coefficients by 20% to reflect lower profit margins of generic drugs;[34]
- S5: a combined scenario applying all changes from S1−S4 simultaneously, providing an upper-bound stress test of the framework.

For each scenario, we re-estimate national and global carbon footprints (Table 2). Instead of deriving probabilistic uncertainty bounds, here we assess the direction, magnitude, and stability of the footprint estimates under the alternative modeling conditions.

Although two additional sources of uncertainty, the sourcing pattern of penicillin's production inputs and potential variation in countries' physical production recipes, are likely to influence results, we do not include them as formal scenarios. There was no empirically grounded way to specify consistent alternatives; multiple equally plausible modifications exist, and selecting any single perturbation would be arbitrary. Further details on the empirical support scoring and the construction of uncertainty scenarios underlying Figure 4 are provided in the Supporting Information 1 (pp. 13−14).

In addition to the formal scenario analyses, we conducted two supplementary diagnostic checks. One assesses the influence of supplementing missing LCI inputs with IO-derived inputs by comparing the baseline carbon footprints to footprints calculated using LCI inputs only. The second evaluates the plausibility of the IO-balanced penicillin price estimates by comparing them to BACI export prices for penicillin, ensuring that the price estimation method yields values consistent with international market ranges.

3. RESULTS

3.1. Global and National Carbon Footprint of Narrower-Spectrum Penicillin

The global carbon footprint of narrow- and medium-spectrum penicillin in 2019 is approximately 90 kt CO_2e, with nearly half (43%) attributable to ten countries. This concentration largely follows consumption values: high-income countries (HICs) and upper-middle-income countries (UMICs) with large populations, such as the United States, Germany, and the United Kingdom, are among the top contributors (Figure 2a). China is notably absent despite its population size, reflecting its comparatively low per-capita penicillin consumption (Supporting Information 2).

Conversely, small-population HICs, including Norway, New Zealand, and Finland, show disproportionately large carbon footprints because of very high per-capita penicillin consumption (Figure 2c,e). The elevated consumption levels, especially in the Scandinavian countries, align with national prescribing guidelines that favor narrower-spectrum agents to reduce antibiotic resistance.[35] Although lower-middle-income countries (LMICs) typically have much lower per-capita carbon footprints of pharmaceuticals,[1] their per-capita carbon footprints of penicillin are similar to those of UMICs.

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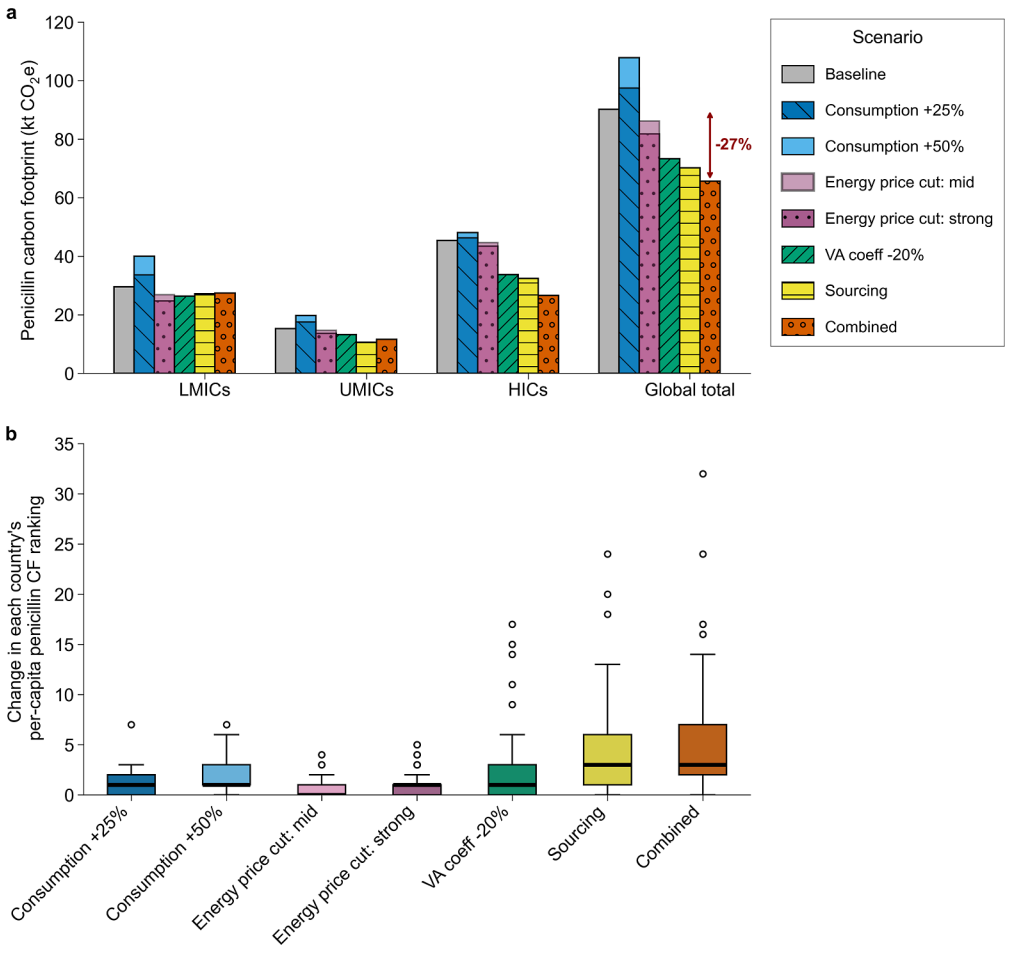

Figure 4. Change in the carbon footprint of penicillin across scenarios that focus on the uncertain parameters in the MA model. (A) Change in the total carbon footprint of penicillin by income groups and globally. (B) Change in country ranking of the per-capita carbon footprint of penicillin in each scenario compared to the baseline. VA coeff = value-added coefficient, CF = Carbon footprint. See Section 2.7 for the selection of uncertain parameters and scenario design.

Documented challenges in antibiotic stewardship and inappropriate use in several LMICs[36−38] likely contribute to this pattern. Combined with large populations, this helps explain why India, Vietnam, and Nigeria have some of the largest total carbon footprints of penicillin (Figure 2a).

Per-capita carbon footprints of penicillin vary widely—on an average six times higher in HICs than in UMICs and LMICs—producing substantial gaps between the highest and lowest per-capita footprints (Figure 2c,d). The largest per-capita carbon footprints of penicillin occur exclusively in HICs, predominantly in Europe (Figure 2), although variation within HICs is also considerable. For instance, Korea, Italy, and Japan are estimated to have some of the lowest per-capita carbon footprints of penicillin despite being HICs (Figure 2d). Physical consumption level is the primary driver of the cross-country variation (Figure 2c−f).

Two additional factors contribute to cross-country variation in the modeled per-capita carbon footprints of penicillin. First, sourcing patterns matter because countries differ in the emission intensities of their suppliers. For example, Finland's per-capita carbon footprint exceeds Ireland's despite similar consumption levels: Finland sources a large share of penicillin from China, a high-intensity producer in our model, whereas Ireland sources mainly from lower-intensity suppliers such as the UK, India, and Spain (Supporting Information 2). Second, estimated penicillin prices also influence per-capita footprints because they convert physical consumption into monetary final consumption in the MA framework. Higher estimated prices increase monetary consumption and thus scale total emissions. As detailed in Methods (Section 2.5), the price-related effects can partly reflect structural artifacts of the data-limited MA procedure rather than true production or supply chain differences. Hence, Norway's higher per-capita footprint is partly a modeling consequence of its estimated price, not evidence that its penicillin is produced more emission-intensively than Denmark's.

3.2. Drug-Level Disaggregation Reveals Substantial Cross-Country Differences Hidden in Aggregated Pharmaceutical Accounting

The geographic distribution of the carbon footprint of penicillin varies markedly from that of the aggregated pharmaceutical sector (Figure 2a,b). Whereas China and the United States dominate the global carbon footprint of pharmaceuticals (together 49% of the global total), the United Kingdom and Australia dominate the carbon footprints of penicillin (together 12% of the global total). Similarly, although China and India have similar population sizes, India's carbon footprint of penicillin is three times larger than China's, whereas the opposite pattern holds for pharmaceuticals. Moreover, the largest carbon footprints of pharmaceuticals

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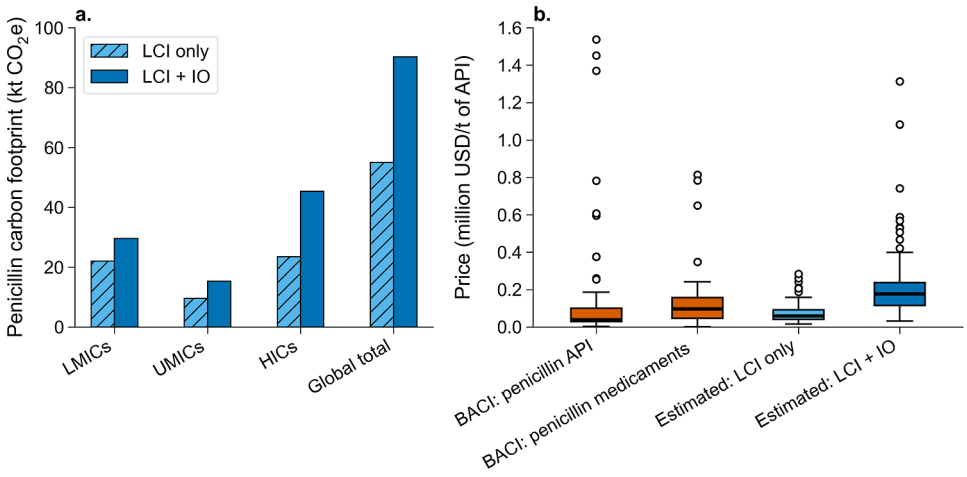

Figure 5. Robustness check of two uncertain parameters. (A) Comparison of the carbon footprint of penicillin based on LCI inputs only and with additional IO inputs. (B) The variation of the estimated penicillin price compared to penicillin export prices in BACI. Hungary is excluded from the BACI penicillin API boxplot for better visualization (price of 5.5 million USD/t).

are dominated by large economies (with high global GDP share) and large populations, but these are not good indicators of the large carbon footprints of penicillin, which are more strongly driven by per-capita consumption levels.

Drug-level disaggregation also reveals large shifts in country rankings of per-capita carbon footprints (Figure 3). On average, countries move 23 positions when comparing their carbon footprint of penicillin to that of pharmaceuticals, and only a small subset lies within a ± 5-position band. Several HICs with modest per-capita carbon footprints of pharmaceuticals (e.g., Finland and New Zealand) rank among the highest for penicillin, whereas other countries show a large shift in the opposite direction. The cross-country variation in per-capita carbon footprints is also substantially greater for penicillin (coefficient of variation, CV, 2.2) than for pharmaceuticals (CV = 1). Together, these results show that carbon footprint assessments of aggregated pharmaceuticals are a poor proxy for drug-level patterns, masking substantial heterogeneity and limiting the ability to identify true emission hotspots or target mitigation efforts effectively.

We further examined the sources of the discrepancies. The dominant driver is cross-country variation in per-capita penicillin consumption, which varies far more than for pharmaceuticals (CV = 2.7 vs 1.5). In contrast, modeled emission intensities vary similarly between penicillin and pharmaceuticals and contribute far less to ranking differences. This is reflected in the average ranking shifts: 21 positions for per capita consumption versus only 8 for emission intensities. Sourcing differences also play a modest role: when penicillin is forced to follow the same sourcing structure as pharmaceuticals, the average per capita ranking changes by only four positions.

In 70% of the countries, the penicillin sector's total (direct + indirect) emission intensity exceeds that of the pharmaceutical sector, mainly due to higher modeled supply chain emissions. Although penicillin's direct emission intensity is 38% lower, partly because only CO_2 is covered and partly reflecting process differences, the indirect emission component is larger. This arises because missing LCI inputs are approximated using inputs into the pharmaceutical sectors, so only the five LCI-covered sectors differ between the two sectors. As such, higher agricultural, chemical, and energy inputs drive penicillin's higher total intensity. As more complete LCIs become available, these indirect contributions may change, and additional sectoral hotspots may emerge.

3.3. Footprint Estimates Remain Robust under Alternative Assumptions for Final Consumption, Energy Prices, Value Added, and Sourcing

Across all robustness scenarios, the global penicillin carbon footprint changes by less than 30% (Figure 4a), indicating that the main results of the data-limited MA framework are not overly sensitive to plausible alternative assumptions. The largest deviation occurs in the combined scenario S5 (−27%), where multiple parameter adjustments compound. At the income-group level, the greatest changes in carbon footprint estimates occur for HICs, primarily under the sourcing scenario (S3) and value-added scenario (S4). In contrast, the value-added scenario has limited impact in LMICs and UMICs, and the sourcing scenario affects LMICs only marginally—largely because many LMICs already relied on ICIO-based sourcing patterns in the baseline due to limited BACI coverage, not because sourcing is inherently unimportant in those economies. Applying unequal energy prices across income groups produces only a modest change (−9% globally), reflecting the relatively small weight of energy expenditures in the modeled penicillin production structure.

The cross-country distribution of the carbon footprint of penicillin is also robust across alternative assumptions. Rankings of the countries' per-capita carbon footprint shift only slightly across scenarios; even the largest observed median change of three positions in the sourcing and combined scenarios is small (Figure 4b). Under the combined scenario, larger shifts of up to 15 positions occur for a small subset of countries whose baseline sourcing is concentrated in suppliers with particularly high or low emission intensities. For example, Lithuania, Costa Rica, Latvia, and Bulgaria rank lower in the combined scenario because their sourcing becomes more diversified compared to the baseline scenario, which had 90−94% of penicillin imports from high-intensity producers such as China. Conversely, Malta moves substantially upward because its baseline sourcing relied almost exclusively on the low-intensity United Kingdom producers, and its low value-added coefficient makes its estimated price, thus its modeled

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carbon footprint, relatively insensitive to value-added adjustments.

Overall, the scenario analysis demonstrates that both aggregate totals and cross-country patterns remain stable across a wide range of plausible parameter values, underscoring the internal consistency of the MA framework under data-limited conditions. The observed robustness, however, does not eliminate the need for improved empirical data, which we further describe in the discussion. Most assumptions incorporated into the MA model are either empirically grounded or explicitly stress-tested. We also note that parameters such as emission multipliers and estimated penicillin prices are model artifacts rather than true values; however, they serve as constructs to enable the estimation of the global carbon footprint of penicillin.

3.4. Additional IO Inputs Substantially Increase the Estimated Carbon Footprint and Price of Penicillin, Consistent with Expectations

Incorporating IO-derived inputs for sectors not covered in the penicillin LCI increases the global carbon footprint of penicillinby 64% (Figure 5a). This uplift is somewhat higher than typical LCA underestimation ranges reported for incomplete LCIs (20−50%),[9,10] but it is reasonable given the limited scope of the available penicillin LCI, which covers mainly mass and energy balances and omits many upstream inputs captured economically. Because the true magnitudes of the missing inputs are unknown, the 'LCI inputs only footprint' should be interpreted as a lower bound, while the LCI + IO result provides a more complete but still approximate estimate.

Estimated penicillin prices fall within the broad range of BACI export prices (Figure 5b), supporting the validity of the IO-balanced price estimation method used to maintain monetary consistency after disaggregation (Table 1). Adding IO-derived inputs triples the average estimated penicillin price, consistent with the inclusion of additional production inputs. As expected from the structure of the price estimation equations, estimated prices are more sensitive to value-added adjustments when both LCI and IO inputs are included (−32%) than under the LCI-only configuration (−14%). This behavior further confirms that the price estimation mechanism responds coherently to changes in underlying cost components and operates as intended.

4. DISCUSSION

4.1. New Insights into the Country Drivers of Pharmaceutical Emissions

Disaggregating the pharmaceutical sector to isolate penicillin reveals distinct carbon footprint patterns that are different from those observed for pharmaceuticals. Whereas China and the United States together account for nearly half of the global pharmaceutical footprint, the same share of the global penicillin footprint is distributed across ten countries. These alternative geographic hotspots arise because penicillin use does not align with overall pharmaceutical spending, which is dominated by large economies and populous countries. Instead, for penicillin, the carbon footprints are driven more substantially by per-capita consumption levels and population size: HICs with small populations (e.g., New Zealand) and populous lower-income countries (e.g., India, Vietnam, and Nigeria) emerge as major contributors.

High penicillin per-capita carbon footprints are primarily driven by elevated per-capita consumption and to a smaller extent by sourcing patterns and price-related modeling artifacts. Moreover, similar to the total cross-country carbon footprints, the patterns of per-capita carbon footprints of penicillin differ markedly from those of pharmaceuticals. For example, Finland has a small per-capita carbon footprint of pharmaceuticals yet ranks among the highest for penicillin. Overall, the per-capita carbon footprint patterns of penicillin versus pharmaceuticals reflect the differences in countries' per-capita consumption rankings between the two, as well as the greater cross-country variability in per-capita penicillin consumption compared with pharmaceuticals. In contrast, differences in sourcing structure and modeled emission intensities between penicillin and pharmaceuticals only marginally contribute to these distinct patterns.

The scenario-based robustness analysis shows that these patterns are not artifacts of specific parameter choices. Across all scenarios, global totals vary by less than 30%, and the relative ranking of countries is largely preserved. The MA-based framework thus captures stable structural features of global consumption and trade rather than being driven by uncertain assumptions, increasing confidence in its applicability to other drug classes, where production, sales, or sourcing data are similarly incomplete.

4.2. Data and Process Representation Limitations in Drug-Level Footprint Estimation

Despite the robustness of the qualitative patterns, several data and methodology constraints limit the accuracy of the carbon footprint of penicillin estimates. We selected the MA hybridization method for two main reasons: (1) it reduces the need for detailed LCI data, which is often limited for pharmaceuticals, and (2) the country heterogeneity captured in the EE-MRIO enables cross-country comparisons. However, this approach also affects accuracy due to sectoral aggregation and larger reliance on price data compared to other hybridization methods. Furthermore, the disaggregation relies on a single detailed LCI—currently, the only transparent, mass- and energy-balanced LCI we can find for penicillin. In the absence of country-specific LCIs, we model geographic variation through country-specific prices. However, LCIs describing alternative fermentation or purification routes would better represent technological diversity in global penicillin production and allow testing whether the modest role of emission intensities and sourcing differences reflects real-world dynamics or limitations of the current model.

The existing LCI includes only CO_2 emissions, whereas the pharmaceutical-sector emission factors cover eight greenhouse gases. This narrower GHG coverage reduces penicillin's modeled direct intensity but does not explain its small share of the global carbon footprint of pharmaceuticals (0.04%), which is primarily due to its small market volume: antibiotics represent roughly 2.6% of global pharmaceutical sales,[39] and narrower-spectrum penicillin accounts for ∼4.5% of these antibiotics.[20]

Beyond penicillin, the analysis reveals systemic data gaps, limiting drug-level footprint assessments. Production volumes, prices, and sales structures are rarely publicly available. Final consumption statistics are sparse: the only open-source OECD database[40] includes primarily HICs and reports drug use by the anatomical therapeutic chemical category, which groups together substances with divergent chemical and production characteristics. Our review of 36 pharmaceutical LCAs shows only 43% document inventory data and only 16% document

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environmental flows (Supporting Information 1, pp. 16−17). Moreover, most studies lack alternative synthesis routes or scaled-up laboratory[6] conditions, making it difficult to generalize production characteristics across countries.

4.3. Mitigation and Regulatory Implications for Pharmaceuticals and Beyond

Because consumption levels dominate footprint variation, cleaner production alone cannot realign global emission responsibilities. In HICs, reducing narrower-spectrum penicillin use is constrained by clinical needs and stewardship policies[35] that prioritize narrow-spectrum antibiotics to limit resistance. Mitigation efforts should therefore focus on formulation efficiency, waste reduction, supply chain optimization, and minimizing losses across distribution systems. Although LMICs' and UMICs per-capita consumption of narrower-spectrum penicillin is six times lower than that of HICs, antibiotic consumption in LMICs, it is expected to keep rising.[20] Reducing misuse and overuse of antibiotics through improved access and prescription regulation and improving sanitation infrastructure in LMICs[36] are critical for limiting future emissions.

The hybrid LCA framework developed here addresses the growing demand for product-level carbon footprint assessment under data scarcity. While demonstrated for pharmaceuticals, the framework is applicable to other sectors characterized by limited process-level data, such as fine chemicals and electronics. Under the EU Corporate Sustainability Reporting Directive, pharmaceutical companies must disclose their sustainability performance,[22] yet drug-level upstream emissions are difficult to quantify with LCA alone. Hybrid EE-MRIO modeling can complement corporate reporting by capturing indirect emissions in supply, services, and R&D. The approach also aligns with the EU's Ecodesign for Sustainable Products Regulation, which introduces digital product passports.[21] Pharmaceutical products face challenges similar to those in battery carbon footprint estimation, that is, incomplete LCIs and the need to integrate economic system data to capture upstream impacts in data-poor countries. A hybrid LCA−MRIO structure can therefore serve as a foundation for future pharmaceutical DPPs, balancing transparency with confidentiality.

More broadly, drug-level emission factors can inform procurement, guideline development, and clinical decision making. For this, sector-average intensities are currently used that systematically overattribute emissions to high-cost drugs;[41] providing empirically grounded, product-level metrics supports more evidence-based environmental stewardship in healthcare systems.

4.4. Research Priorities from Identified Data Limitations

Without publicly available output and sales data for most drugs, further disaggregation of the pharmaceutical sector entails an improved data infrastructure. Future research can explore alternative means of deriving drug-level output, e.g., data mining regulatory filings, using customs and trade databases, or developing statistical inference models based on reported shipment and procurement data. High-quality LCIs covering multiple production pathways, environmental impacts, and regions can enhance representativeness and avoid burden shifting. Furthermore, it facilitates using alternative hybrid LCA methods (i.e., tiered approach), which model the foreground processes directly using LCI data, reducing aggregation errors and reliance on price data.

As highlighted in Table 1, parameters with medium empirical support but high leverage, such as consumption coverage, sourcing structure, value-added coefficients, and the assumption of one global production process, should be prioritized for improvement. International organizations could facilitate systematic tracking of drug consumption and price data using classifications that reflect both the therapeutic function and chemical composition. Improving these foundational data would reduce structural uncertainty in drug-level accounting and strengthen product-level environmental assessments across sectors where production and sales data remain scarce, but regulatory demands for transparency continue to grow.

■ ASSOCIATED CONTENT

Data Availability Statement

All data and code used in this work are available on Zenodo: https://doi.org/10.5281/zenodo.18034091.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.6c00661.

LCI, additional data and classifications, additional methods, assumptions used, scenarios in more detail, and review of pharmaceutical LCA studies (PDF)

Additional results for all countries and the concordance (XLSX)

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Author Contributions

Conceptualization: RHH, RW, and AdK; methodology: RHH, AdK, RH, and RW; software: RHH; validation: RHH; formal

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analysis: RHH; investigation: RHH; writing—original draft: RHH; writing—review and editing: AdK, RH, AT, and RW; visualization: RHH; and supervision: AdK, RH, AT, and RW.

Notes

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