LCA Case Studies

Cradle-to-Gate Life Cycle Inventory and Assessment of Pharmaceutical Compounds

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Abstract

Background, Goal and Scope. The research presented here represents one part of GlaxoSmithKline's (GSK) efforts to identify and improve the life cycle impact profile of pharmaceutical products. The main goal of this work was to identify and analyze the cradle-to-gate environmental impacts in the synthesis of a typical Active Pharmaceutical Ingredient (API). A cradle-to-gate life cycle assessment of a commercial pharmaceutical product is presented as a case study.

Methods. Life cycle inventory data were obtained using a modular gate-to-gate methodology developed in partnership with North Carolina State University (NCSU) while the impact assessment was performed utilizing GSK's sustainability metrics methodology.

Results and Discussion. Major contributors to the environmental footprint of a typical pharmaceutical product were identified. The results of this study indicate that solvent use accounts for a majority of the potential cradle-to-gate impacts associated with the manufacture of the commercial pharmaceutical product under study. If spent solvent is incinerated instead of recovered the life-cycle profile and impacts are considerably increased.

Conclusions. This case study provided GSK with key insights into the life-cycle impacts of pharmaceutical products. It also helped to establish a well-documented approach to using life cycle within GSK and fostered the development of a practical methodology that is applicable to strategic decision making, internal business processes and other processes and tools.

Keywords: Life cycle assessment (LCA); life cycle inventory (LCI); pharmaceutical compounds; pharmaceutical synthesis; sustainability metrics; sustainable development

Introduction

GSK has undertaken a programme of work to better understand the life-cycle impacts of pharmaceutical processes. During early phases, many attempts were made to find and collate Life Cycle Inventory (LCI) data for the types of materials used in synthetic processes that produced active pharmaceutical substances. This proved to be a difficult, if not impossible, task since very little data were available for materials routinely used in the synthesis of chemically and biologically complex pharmaceuticals. In addition, those data that did exist were merely numbers [1,2,3]; i.e., there was no transparency as to how LCI data were derived. This lack of transparency continues to be an issue for life cycle data in general.

However, at least two things were suggested by these early assessments. First, solvents and solvent use played a significant role in the overall life cycle impact of the active pharmaceutical ingredients of a drug product. Given the complexity of the materials routinely used in a typical pharmaceutical synthesis, this was a somewhat surprising result that warranted more in depth study to confirm. It became apparent that GSK could make considerable progress towards reducing environmental impacts if solvent use were optimised. The reader is referred elsewhere for a description of our development of a solvent selection guide [4]. This guide has recently been augmented with life cycle information and will be the subject of a forthcoming publication [5]. The second conclusion was that in order for us to better understand GlaxoSmithKline's overall life cycle impacts, a more detailed, transparent, rigorous and scientifically defensible methodology had to be developed. Given constraints on time and resources, GSK partnered with North Carolina State University (NCSU) in the development of a modular approach to life cycle methodology that met our criteria listed above. This publication represents the first in a series that describes our work.

1 Goal, Scope and Functional Unit

1.1 Goal

The main goal of this work was to identify and analyze the cradle-to-gate environmental impacts in the synthesis of a typical Active Pharmaceutical Ingredient (API). Another goal is to provide a comprehensive understanding of the life cycle impacts associated with complex chemical synthetic routes for API manufacture within the pharmaceutical industry. The results of this programme have also been used to develop a tool that enables process development chemists and engineers to determine and compare the life cycle impacts of processes during the early stages of process design and development.

The programme is based on a new approach for the systematic determination of cradle to gate impacts for materials.

Beyond this main aim, there are a number of additional areas of interest including:

1) The importance of solvent manufacture, use, waste recovery and disposal on overall environmental life cycle impacts;
2) An understanding of the environmental impacts associated with GSK manufacture compared to those within the external supply chain;
3) The contribution of energy usage and transportation in the pharmaceutical supply chain compared to the overall environmental impacts;
4) The identification and understanding of key factors that influence environmental impacts so they may be avoided or mitigated early in the development process.

1.2 Scope

This research estimated the life cycle emissions and potential impacts of a commercial process using a cradle-to-GSK-gate approach. Formulation, packaging, distribution and final fate of the pharmaceutical product have been excluded at this time since this case-study is intended as a comparative assessment within a manufacturing process and as a basis for comparing and benchmarking different synthetic routes to a given API. Therefore, the manufacturing impacts per kg of API will be independent of the downstream life cycle phases . The impacts of the downstream life cycle phases will be discussed in future publications.

As a consequence of the scope and boundaries chosen, the results presented here are not applicable to a comparison of two pharmaceutical products with the same function, since a full cradle-to-grave assessment would be required for this specific purpose.

1.3 Functional unit

A mass-based functional unit of 1 kg of the active pharmaceutical ingredient under study was used.

2 Methodology

A modular approach was used. This methodology, as represented in **Fig. 1**, was developed at NCSU [6] in partnership with GSK. A description of the methodology is given in the following paragraphs.

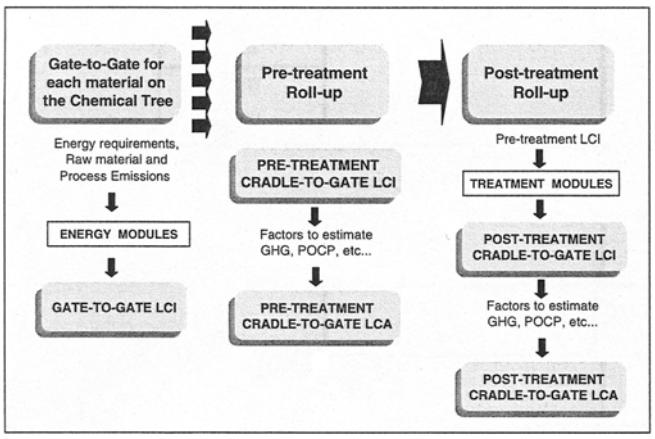

Fig. 1: Methodology

2.1 Overview

A list of the key raw materials and their masses required for the current synthesis of the active pharmaceutical ingredient under study was first established. Gate-to-gate inventories were assembled for each material using NCSU methodology and these were rolled-up to give cradle-to-gate data for the key process raw materials. The same process was used for the drug manufacturing process stages. The resultant life cycle inventory data were then rolled-up into the key GSK impact categories.

The overall approach is based upon the following fundamental building blocks:

1. An agreed set of GSK sustainability metrics [7] that defined the impact categories;
2. A transparent set of heuristics and rules of thumb for determining the gate-to-gate inventories and subsequent roll-up to give cradle-to-gate data and final impact data;
3. A modular and transparent approach that facilitates analysis of underlying data and trends.

While there was some limited use of commercial LCI/A software for the gate-to-gate development, most of the roll-up and data analysis was based on commonly used and readily available software (e.g., Microsoft EXCEL) and other approaches developed by GSK.

2.2 Definition of the system boundaries

The boundary of the life cycle assessment covers activities from the extraction of raw materials (from earth, petroleum and minerals/metals, or any material produced in agriculture, e.g., corn) to the end of the GSK manufacturing process, including waste stream treatment and all transport operations to the GSK gate. This boundary was chosen since this study compares the relative life cycle contributions of the different elements of the production process of a given API synthesis (identification of hot-spots). These relative contributions are expected to be independent of the formulation of the pharmaceutical product and other downstream life cycle phases, when accounted per unit of API. The packaging, distribution, use and disposal of the drug are beyond the scope of this assessment.

2.3 Data sourcing

2.3.1 LCI outside GSK's boundary

Technical or patent literature and/or company information was used to develop process mass balances. Energy balances were derived by applying standard thermodynamic equations and following procedures previously described in the literature [8]. Unknown heat capacities and heats of reaction were estimated using group contribution theory [9].

2.3.2 LCI within GSK's boundary

Emissions and energy usage were determined from GSK mass balance and process description information.

2.4 Development of the Chemical Tree for the Pharmaceutical Ingredient

For each material used in the synthesis of the active pharmaceutical ingredient under study, a 'chemical tree' was constructed. A chemical tree is a graphical tool GSK uses to represent and document all the raw materials required in the manufacture of a material (i.e., intermediate, reagent, product, etc.). The chemical tree identifies all other materials required for the manufacture of each material together with the mass utilized. In each case, the chemical tree went back to the extraction of materials from a natural resource (i.e., 'the cradle'). Fig. 2 illustrates the chemical tree of n-butanol.

2.5 Development of a Life Cycle Inventory (LCI) Database

2.5.1 Overview

Inventory data were generated by NCSU in partnership with GSK. After the chemical tree was developed for each of the process materials used in the manufacture of this pharmaceutical product (total 26), gate-to-gate life cycle inventory information without waste or emissions treatment was calculated for each substance in the chemical tree. The process that was used is shown in Fig. 1. The inventory data include process, energy and transportation-related life cycle parameters. Waste treatment modules were applied at the end of the inventory roll-up for each material.

Inventory data for a random selection of materials in the database were compared to external data to validate the approach. The NCSU/GSK inventory data compared favorably with the external data within the uncertainties used to develop the external data. A database of 125 materials was developed.

2.5.2 Energy modules

Energy modules were developed to determine the energy-related emissions for steam production, and cooling using refrigeration or a cooling tower. A detailed explanation of the methodology and the life cycle information for the energy modules, including electricity production, is presented elsewhere [10].

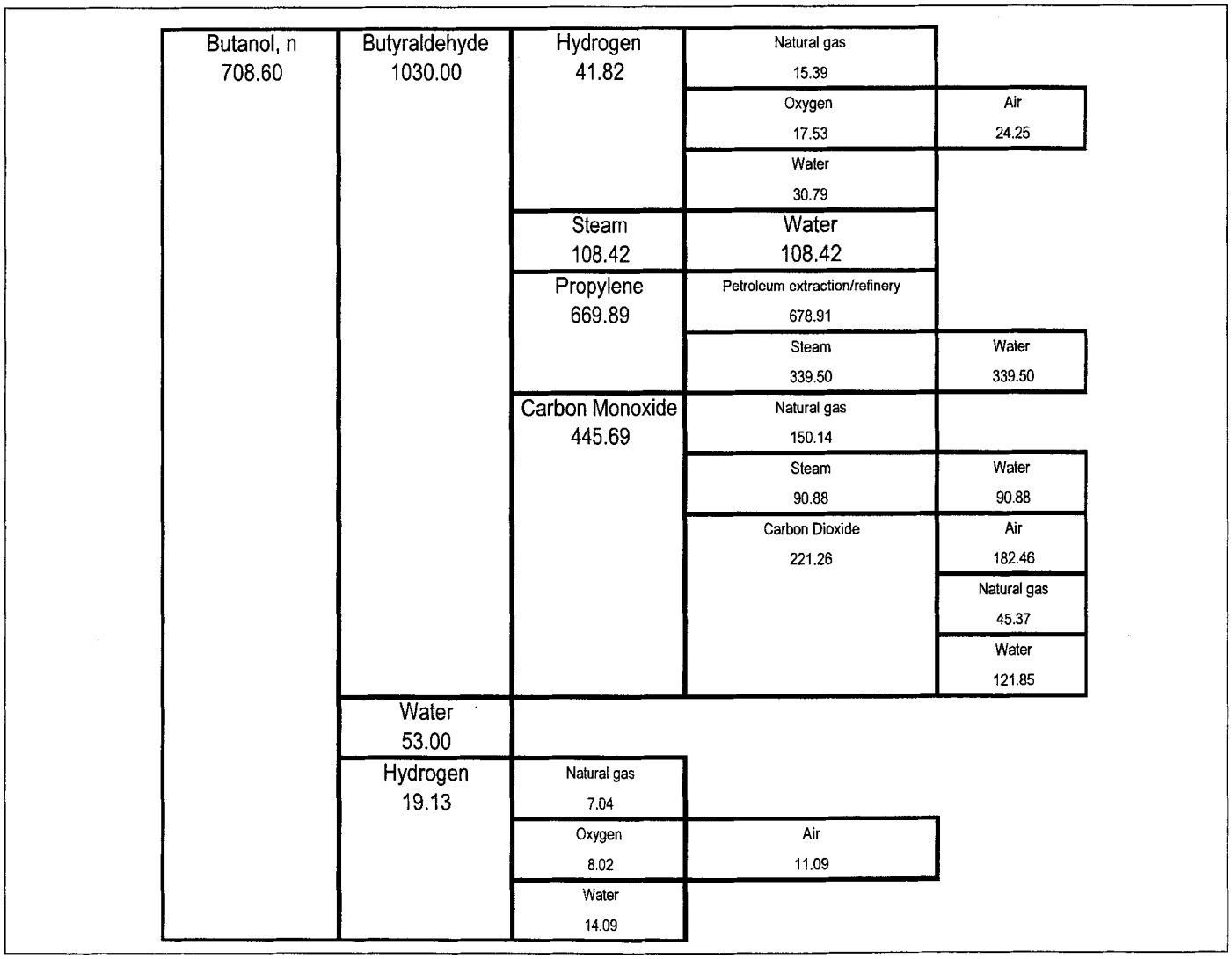

Fig. 2: Chemical tree of n-butanol

Table 1: Cradle-to-gate LCI energy-related air emissions

Air emission	Unit	Electricity [1MJ] Cradle-to-gate	Steam produced [1MJ]	Cooling water tower [1MJ of cooling water potential]	Refrigeration [1MJ of cooling potential]	Dowtherm [1MJ of heating potential]	Heating by Natural gas combustion [1MJ heat potential]	Heating by Fuel oil #2 combustion [1MJ heat potential]
CH_4	g	0.580	0.115	0.0018	0.186	0.134	0.160	0.0837
CO	g	0.045	0.0543	0.0001	0.014	0.0136	0.016	0.0121
CO_2	g	165.0	77.3	0.528	52.8	58.4	70.4	92.6
NO_x	g	0.350	0.248	0.0011	0.112	0.190	0.223	0.186
SO_x	g	0.490	0.337	0.0015	0.157	0.0226	0.0267	0.357
VOC	g	0.038	0.328	0.0001	0.012	0.326	0.392	0.234

Emissions resulting from the primary energy carriers (e.g. natural gas, fuel oil, etc.) were based on an average UK-US mix using the data reported in several commercial databases [1, 2,3,11]. A sample of energy-related air emissions is presented in Table 1.

2.5.3 Transportation-related emissions

Specific suppliers were not identified for transportation of raw materials to the production centers so transport emissions were based on an average transportation distance for chemicals of 330 miles (528 km) with an average distribution of 50% rail, 30% truck and 20% water. The emissions were based on data reported by the US Department of Commerce, Economics and Statistics Administration, US Census [12]. The percentage distribution of the various transport modes was based on average data reported for chemicals in the US by the Department of Transportation.

Table 2 shows the transportation emissions used for this study. The life cycle emissions factors were taken directly from the database of ECOPRO [1] assuming diesel trains, 40 ton diesel trucks (50% capacity), and river-sized diesel boats (70% capacity).

Table 2: Transportation-related air emissions and energy per 1000 kg of each material transported 330 miles (528 km)

Substances emitted	Kg/1000 kg of material
CH_4	0.033
CO	0.185
CO_2	33.5
NMVOC	0.216
NO_x	0.627
SO_x	0.04.3
Diesel Used [MJ]	440

2.5.4 Waste treatment modules

Waste treatment and disposal modules were developed to establish the emission profiles for wastewater treatment, spent solvent incineration and landfill. A model for landfill disposal was taken from the literature [13,14]. The solvent incineration and wastewater treatment modules were based on a mixture of GSK and available literature models and incorporated GSK commercial operational data. Table 3 summarizes the treatment modules employed.

Table 3: Air and water emissions for waste treatment modules

Pollutant	WWTP emissions, per 1000 kg of TOC treated	Landfill, per 1000 kg of inorganic solids [dry weight]	Landfill, per 1000 kg of organic solids [dry weight]	Incineration, per 1000 kg of organic carbon
Air emissions [kg]				
CH_4	8.16	0.01	152.47	6.93
CO	0.63	0.00	0.11	2.32
CO_2	4,810.38	3.07	1,019.20	6,679.86
NMVOC	0.53	0.00	0.10	17.14
NO_x	4.92	0.01	0.89	9.67
SO_x	6.89	0.01	1.24	1.16
Water emissions [kg]				
TOC	141.95[a]	0.00	0.57	0.00
BOD	211.62[a]	0.00	0.05	0.00
COD	405.98[a]	0.01	1.62	0.00
TDS	5.91	0.07	1.07	0.12

[a] Final emissions after treatment

2.5.5 Allocation rules

When a specific process produces more than one product of commercial value, the raw material and energy requirements, the form of waste treatment, and the emissions generated, need to be properly allocated to each product. Allocation is based on the mass ratio of the products and excludes water. Thus if a given process produces 25 kg of product A and 75 kg of product B, the emissions, raw materials, energy, etc., will be distributed in a proportion of 25% for product A and 75% for product B.

2.5.6 Life cycle inventory

Cradle-to-gate life cycle inventories were obtained by rolling-up gate-to-gate inventory data in agreement with accepted practices [15,16]. This was performed in a modular manner, incorporating material requirements, energy modules, waste treatment modules, transportation and gate-to-gate information for the raw materials in the chemical tree all the way back to the cradle material. The final inventory contained a summary of material consumption, energy requirements, and chemical emissions for the active pharmaceutical ingredient process. Both pre- and post-treatment scenarios were developed.

2.6 Impact Assessment using GSK sustainability metrics

The impact assessment was carried out using GSK's sustainability metrics [7,17]. The sustainability metrics include total cradle mass (the amount of materials taken directly from earth), energy requirements, greenhouse gases emissions (GHG), photochemical ozone creation (POCP), eutrophication, acidification, and total organic carbon (TOC). The methodology for the roll-up of GSK's sustainability metrics has been reported elsewhere [18].

3 Results

3.1 LCI/A without waste treatment

Fig. 3 shows the relative cradle-to-gate impact contributions from the process used to produce each material, the energy used during production of each material, and transportation. It should be noted that the term 'energy' appears both as an impact and as a process category. When 'energy' is used as an impact it denotes the total amount of energy in MJ required for production, transportation, and energy generation, as defined in GSK's sustainability metrics. When 'energy' is used as a process category, 'energy' refers to the processes that produce and deliver power or perform heat transfer functions needed in the manufacturing processes (e.g. steam, electricity). As would be expected, most of the green house gases and acidification contributions come from energy-related emissions (electricity and thermal), since energy production involves combustion processes that generate and release green house and acid-forming gases. Transport-related emissions are relatively small, and average less than 8% across all the metrics.

Fig. 4 compares the relative contributions from solvent manufacture, other process chemical manufacture, and internal GSK processes. Clearly the manufacture of solvents, when waste treatment is not included, is the main contributor to each cradle-to-gate impact category, except for total organic carbon (TOC) and eutrophication. In the case of TOC and eutrophication, internal processes produce proportionally greater impacts.

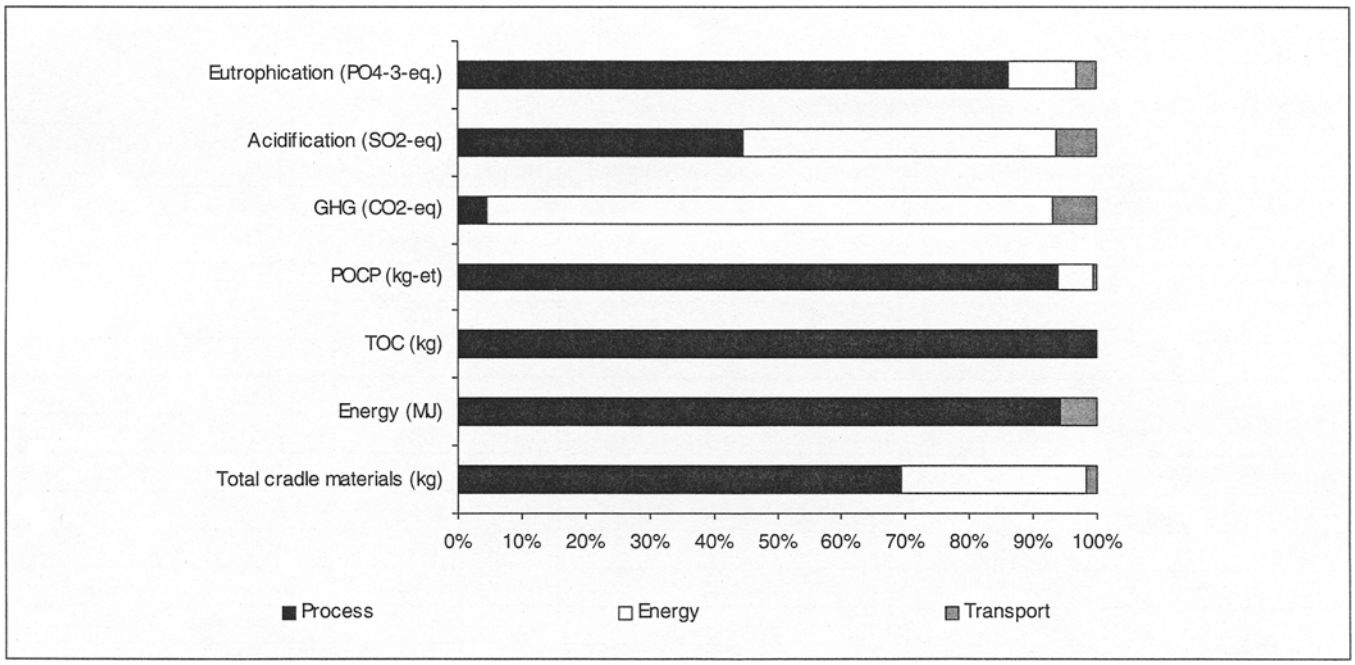

Fig. 3: Cradle-to-Gate LCA pre-treatment contributions of processes, energy and transportation

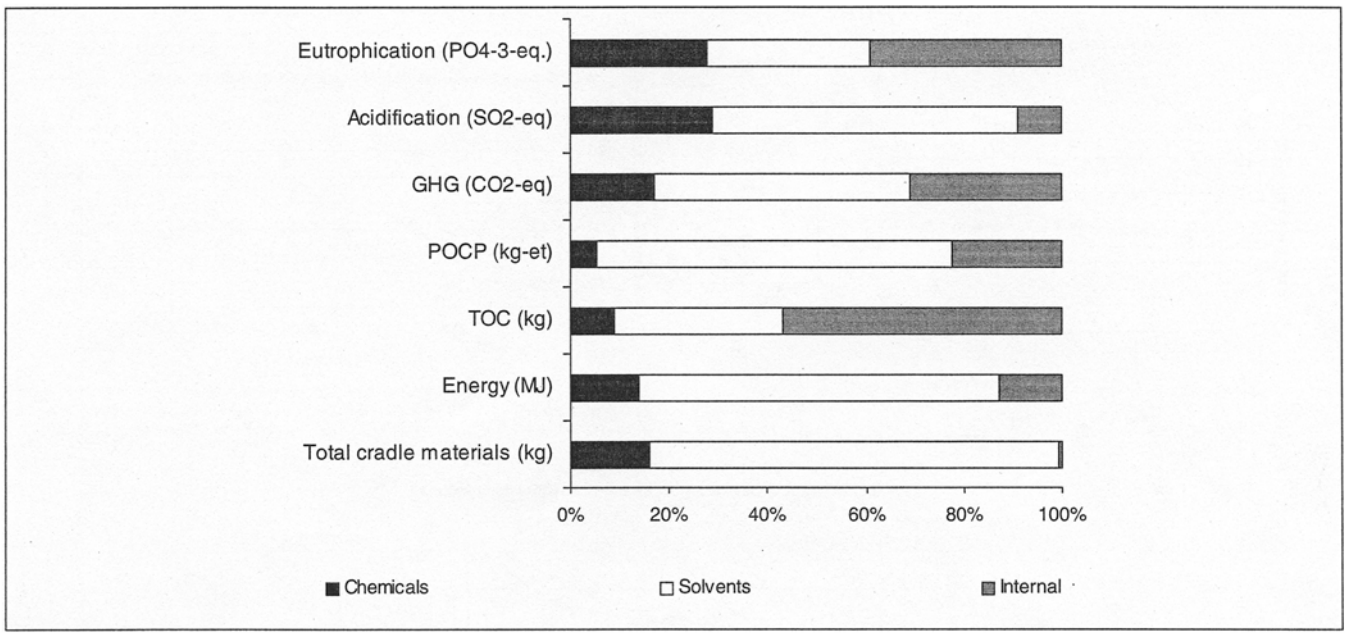

Fig. 4: Cradle-to-Gate LCA pre-treatment contributions of solvent manufacturing, production of non-solvent chemicals and internal drug manufacturing

3.2 LCI/A with waste treatment included

Fig. 5 presents the cradle-to-gate life cycle assessment results when waste treatment is included in the assessment. Fig. 5 shows the relative contributions to the life cycle impacts of process, energy, transport and treatment. For this post-treatment scenario, it was assumed that all aqueous waste streams undergo treatment in a wastewater treatment plant, non-hazardous solid waste is sent to landfill and spent solvent is incinerated. These results show that the potential for green house gas and acid gas emissions will increase after treatment.

The post-treatment results also provide a compelling case for rigorous use of solvent recycling as opposed to incineration. Roughly half of the green house gas emissions and 40% of the energy requirements for the cradle-to-gate life cycle are attributable to the incineration of spent solvent in final drug manufacture, and to a lesser extent to the incineration of other organic air emissions.

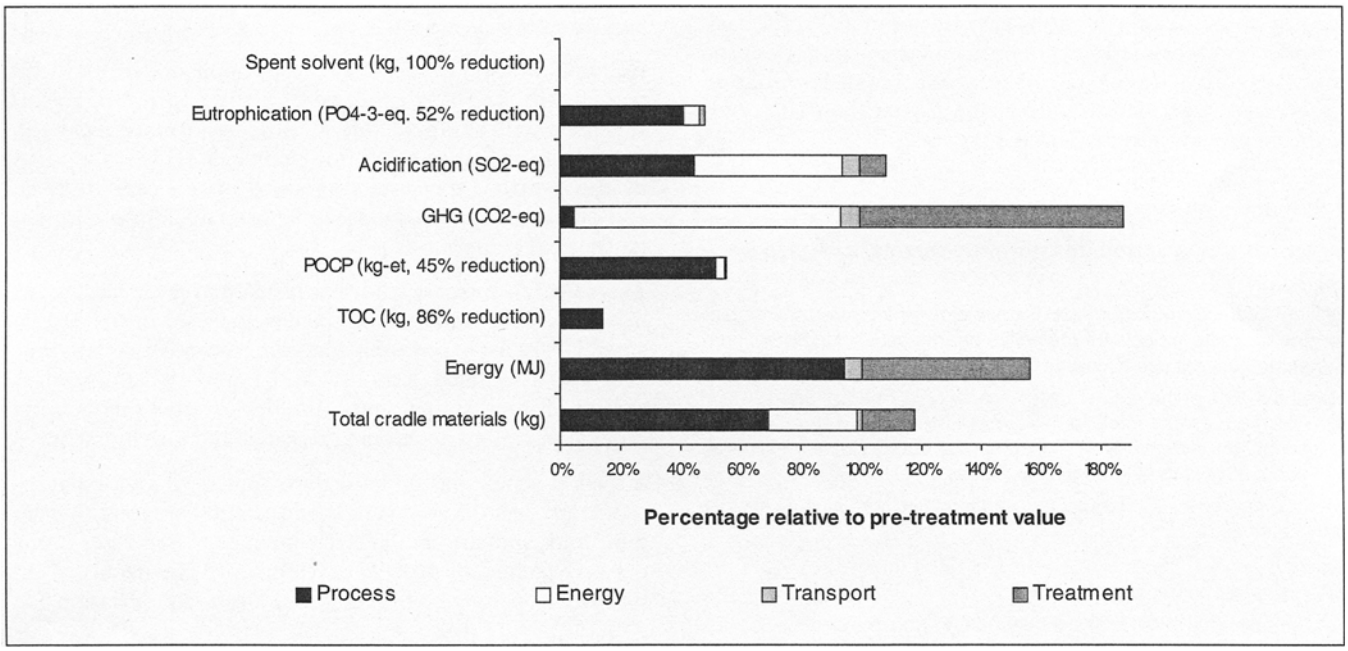

Fig. 5: Cradle-to-Gate LCA post-treatment contributions of energy, production processes, transportation and treatment systems

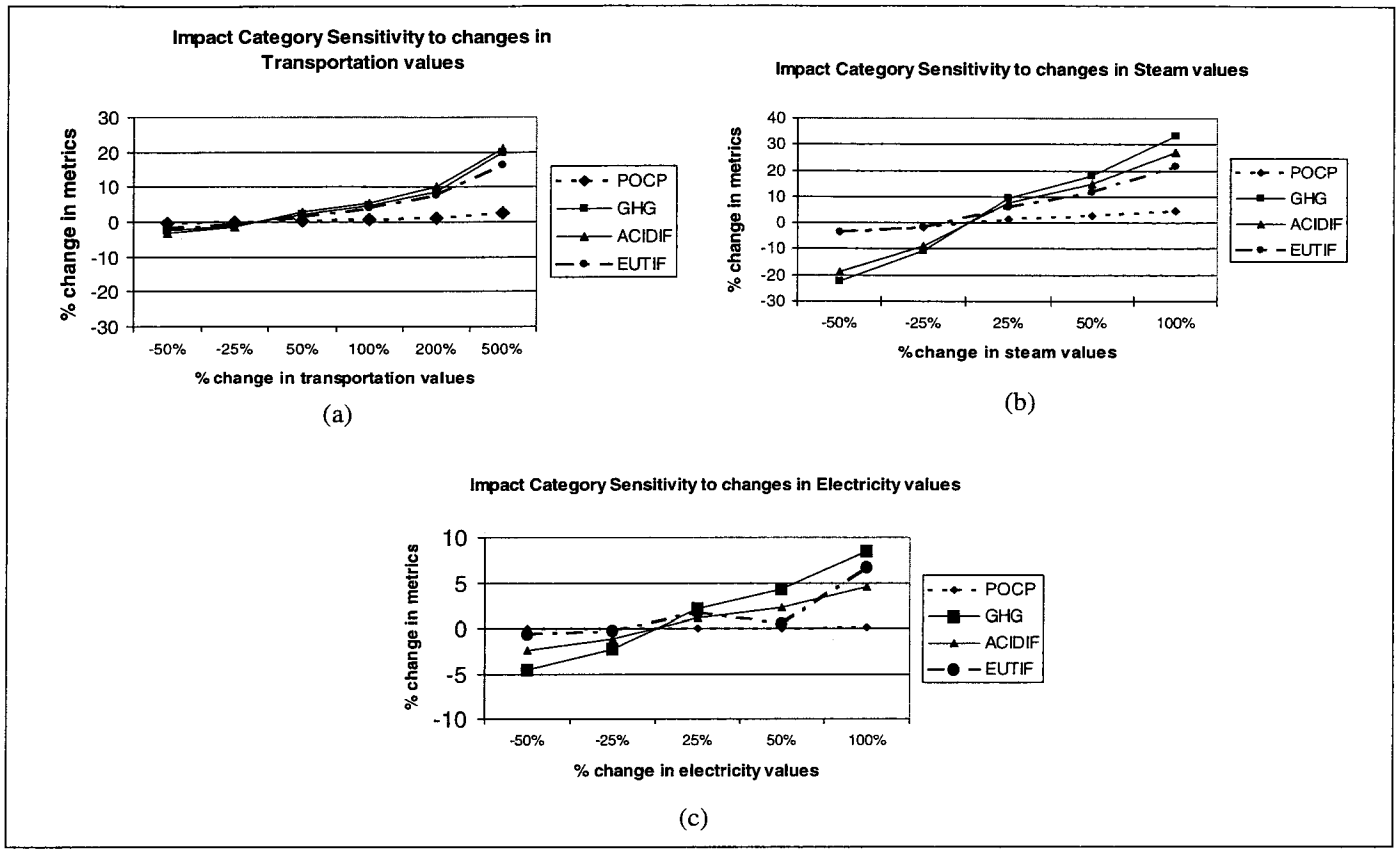

Fig. 6: Sensitivity Analysis. (a) Transportation, (b) Steam, (c) Electricity

3.3 Sensitivity analysis

A sensitivity analysis of potential variations in contributions from energy and transportation demonstrated that neither had a significant impact on the cradle-to-gate life cycle findings or conclusions. As can be seen in Fig. 6, even if the life cycle inventories for electricity generation vary by up to 100%, or the steam emissions vary by about 25%, the variation in the associated sustainability metrics categories is no more than 10%. In the case of transportation, the variation in the associated metrics will not be greater than 10% even if the transportation emissions vary by 200%.

4 Conclusions and Future Work

A few key insights from this study are summarized as follows:

Solvents:
Solvent usage (pre-incineration) is the major contributor to the cradle-to-gate life cycle impacts for the active pharmaceutical ingredient under study. Solvent use accounts for

- about 75% of the energy use,
- about 80% of the total life cycle mass, excluding water,
- about 70% of the life cycle Photochemical Ozone Creation Potential,
- about 50% of the Green House Gases,

when compared to GSK processes, transport and manufacture of other raw materials.

Energy:
Energy usage contributes

- approximately 30% of the total cradle-to-gate materials,
- approximately 70% of the resource depletion, and about 90% of the Green House Gas emissions.

Transportation makes a small contribution to the cradle-to-gate life cycle impacts with a maximum of approximately 8% for greenhouse gases.

Waste Treatment: In addition to the impacts from solvent use, solvent incineration can significantly increase the cradle-to-gate life cycle energy use, depending on the mode of operation, the efficiency of incineration, and the extent of energy recovered in the form of heat. Wastewater treatment does not significantly increase the cradle-to-gate life cycle impact profile.

General: The pharmaceutical compound under study is a typical API, and it is expected that the findings of this assessment will be applicable to other pharmaceutical substances, as well as to other fine chemicals. This is supported by the fact that the results obtained in this case study are consistent with previous research performed for other pharmaceutical compounds [6].

This research and case study has resulted in several additional benefits. While undertaking the development of the gate-to-gate LCI's, a list of screening questions representing best practices was assembled. This list can be used to help identify a variety of improvement opportunities for assessing pharmaceutical processes undergoing research and development.

A second benefit has been the development of a tool that will enable process development chemists and engineers to determine and compare the life-cycle impacts of processes during the early stages of process development. The details of this tool will hopefully be the subject of a future publication.

Finally, the development of this case study has provided GSK with a well-documented life cycle methodology that may be

used for strategic decision making, business processes and other processes and tools.

Future plans include completion of a cradle-to-grave assessment that incorporates distribution, packaging, consumer transport and final disposal.

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References

[1] EMPA (1996): ECOPRO Life Cycle Assessment software. St. Gallen, Switzerland, EMPA (Swiss Federal Laboratories for Material Testing and Research)
[2] PIRA (1998): PEMS Life Cycle Assessment software. Surrey, UK, Pira International
[3] Pré Consultants (1998): SIMAPRO Life Cycle Assessment software. Amesfoort, The Netherlands. Pré Consultants BV
[4] Curzons AD, Constable DJC, Cunningham VL (1999): Solvent Selection Guide: A Guide to the Integration of Environmental, Health and Safety Criteria into the Selection of Solvents. Clean Products and Processes 1, 82–90
[5] Jiménez-González C, Curzons AD, Constable DJC, Cunningham VL (2003): Expanding GSK's Solvent Selection Guide – Application of Life Cycle Assessment to Enhance Solvent Selections. Manuscript submitted to the Journal of Clean Technologies and Environmental Policy
[6] Jiménez-González C (2000): Life Cycle Assessment in Pharmaceutical Applications. Ph.D. Thesis, North Carolina State University, 257 pp
[7] Constable DJC, Curzons AD, Cunningham VL (2002): Metrics to 'green' chemistry – Which are the best? Green Chemistry 4, 521–527
[8] Jiménez-González C, Kim S, Overcash MR (2000): Methodology of Developing Gate-to-Gate Life Cycle Analysis Information. Int JLCA 5 (3) 153–159
[9] Reid RC, Prausnitz JM, Poling BE (1987): The Properties of Gases and Liquids, 4th Ed., McGraw Hill, New York, 741 pp
[10] Jiménez-González C, Overcash MR (2000): Energy sub-modules applied in life cycle inventory of processes. J Clean Products and Processes 2, 57–66
[11] Dumas RD (1997): Energy usage and emissions associated with electric energy consumption as part of a solid waste management life cycle inventory model. Department of Civil Engineering, North Carolina State University, Raleigh NC
[12] US Department of Commerce, Economics and Statistics Administration, US Census Bureau, US Department of Transportation, Bureau of Transportation Statistics (1999): 1997 Economic Census, Transportation. 1997 Commodity Flow Survey (Issued in 1999), EC97TFC-US
[13] Jiménez-González C, Overcash MR, Curzons AD (2001): Treatment Modules – A partial Life Cycle Inventory. J Chemical Technology and Biotechnology 76, 707–716
[14] Camobreco V, Ham R, Barlaz, M, Repa E, Felker M, Rousseau C, Rathle J (1999): Life-cycle inventory of a modern municipal solid waste landfill. Waste Manage Res 17, 394–408
[15] International Organization of Standardization (1997): ISO 14040 – Environmental management – Life cycle assessment – Principles and framework, Geneva, Switzerland, 12 pp
[16] International Organization of Standardization (1998): ISO 14041 – Environmental management – Life cycle assessment – Goal and scope definition and inventory analysis. Geneva, Switzerland, 22 pp
[17] Constable DJC, Curzons AD, Freitas Dos Santos LM, Green GR, Hannah RE, Hayler JD, Kitteringham J, McGuire MA, Richardson JE, Smith P, Webb L, Yu M (2001): Green Chemistry Measures for process research and development. Green Chemistry 3, 7–9
[18] Curzons AD, Constable DJC, Mortimer DN, Cunningham VL (2001): So you think your process is green, how do you know? Green Chemistry 3, 1–6

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Methodology for Developing Gate-to-Gate Life Cycle Inventory Information

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Life Cycle Assessment (LCA) methodology evaluates holistically the environmental consequences of a product system or activity, by quantifying the energy and materials used, the wastes released to the environment, and assessing the environmental impacts of those energy, materials and wastes. Despite the international focus on environmental impact and LCA, the quality of the underlying life cycle inventory data is at least as, if not more, important than the more qualitative LCA process.

This work presents an option to generate gate-to-gate life cycle information of chemical substances, based on a transparent methodology of chemical engineering process design (an ab initio approach). In the broader concept of a Life Cycle Inventory (LCI), the information of each gate-to-gate module can be linked accordingly in a production chain, including the extraction of raw materials, transportation, disposal, reuse, etc. to provide a full cradle to gate evaluation. The goal of this article is to explain the methodology rather than to provide a tutorial on the techniques used.

This methodology aims to help the LCA practitioner to obtain a fair and transparent estimate of LCI data when the information is not readily available from industry or literature. Results of gate-to-gate life cycle information generated using the cited methodology are presented as a case study.

It has been our experience that both LCI and LCA information provide valuable means of understanding the net environmental consequence of any technology. The LCI information from this methodology can be used more directly in exploring engineering and chemistry changes to improve manufacturing processes. The LCA information can be used to set broader policy and to look at more macro improvements for the environment.