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An investigation of the potential for and application of life cycle analysis in the pharmaceutical industry

Michael Raymond

AN INVESTIGATION OF THE POTENTIAL FOR AND APPLICATION OF LIFE CYCLE ANALYSIS IN THE PHARMACEUTICAL INDUSTRY

by
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Dedication

I would like to dedicate this manuscript to the loving memory of my aunt, Catherine Raymond.

Acknowledgments

I would like to express my appreciation to Professor C. Stewart Slater, Ph.D. and Professor Mariano Savelski, Ph.D. for their guidance and help throughout this research. Partial support for this has been provided by a grant from the US Environmental Protection Agency, NP 97257006-0. I would like to acknowledge Nora Lopez of EPA Region 2 for her assistance with attaining and analyzing TRI data from the EPA. I also wish to acknowledge the following companies and personnel for their assistance: Bristol-Myers Squibb – San Kiang, Thomas LaPorte, Stephen Taylor, Lori Spangler; Novartis – Thomas Blacklock, Michael Girgis; Pfizer – Greg Hounsell, Daniel Pilipauskas, and Frank Urbanski. I would also like to express my appreciation to Timothy Moroz and Maria Nydia Ruiz-Felix for their prior efforts in the modeling of pharmaceutical life cycle analysis, as well as to Anthony Tomaino, Joseph Hankins, Christopher Mazurek, and James Peterson for their efforts in undergraduate research in pharmaceutical life cycle analysis. Finally, I would like to express my gratitude to the Royal Society of Chemistry and personnel – Sarah Ruthven and Gill Cockhead for their permission to use the article entitled "LCA approach to the analysis of solvent waste issues in the pharmaceutical industry."

Abstract

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2009/12

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Master of Science in Chemical Engineering

Life cycle assessment offers a unique opportunity to analyze emission reductions across all manufacturing sectors. However, few efforts have been made to apply this method to the pharmaceutical industry. The Toxic Release Inventory is a powerful tool to determine areas of high potential for emissions reductions in industry. When applied to the pharmaceutical industry and coupled with a life cycle assessment, areas for significant environmental improvement become apparent. By examining these trends and exploring a variety of emissions reductions techniques, life cycle emissions in these problem areas may be significantly reduced. These trends demonstrate that manufacture of virgin solvent and solvent waste management contribute significantly more life cycle emissions than comparable processes for commodity chemicals, with the majority of this waste consisting of CO_2 and other green house gas emissions. Typically, between 80 and 90% of the total mass used in the production of an active pharmaceutical ingredient (API) may be attributed to solvent use. Four case studies from Pfizer, Bristol-Myers Squibb, and Novartis are examined. In these cases, solvent recovery and reduction techniques are integrated into API syntheses. It is shown that the actual extent of the environmental footprint reduction can only be realized with a full life cycle analysis.

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Chapter 1

Introduction to Life Cycle Analysis and the TRI

1.1. The TRI and its Application

Environmental consciousness within the United States has increased significantly in the last few decades. A series of nine key environmental statutes were enacted between 1970 and 1990. Among these was the Emergency Planning and Community Right-to-Know Act of 1986. This allotted for two main provisions; states must create local emergency units that must develop plans to respond to chemical release emergencies, and the EPA must compile an inventory of toxic chemical releases from manufacturing facilities. This database of chemical releases is known as the Toxic Release Inventory (TRI).[1]

The TRI provides a means for the public to access information regarding the number of manufacturing plants in an area that release toxic chemicals, the sector of industry to which those plants belong, the types of chemicals released, and the amounts of those chemicals released. The TRI is updated annually, providing a useful tool in determining trends in the control, use, and release of toxic chemicals.

The EPA uses the TRI in a wide variety of other programs, both for government and public use. According to the EPA, the TRI:

> "help[s] the public, government officials, and industry identify potential concerns and gain a better understanding of potential risks, identify priorities and opportunities to work with industry and government to reduce toxic chemical disposal or other releases and potential risks associated with them, and establish reduction targets and measure progress towards reduction goals.[2]"

Before more detail is given on the uses and limitations of the TRI, it is important to understand how the TRI collects data. One main category exists that groups all of the data collected by the TRI, the "Total Production Related Waste." This is then split into two

categories, “On-Site Transfers” and “Off-Site Transfers.” Each of these two categories is further split into two subcategories, “Disposal or Other Releases” and “Other Waste Management.” Table 1 and Figure 1 display the different categories into which TRI data is grouped.

Table 1. Total Production Related Waste. (Note: POTW = Publicly Owned Treatment Works)[2]

	On-Site		Off-Site	
	Disposal or Other Releases	Other Waste Management	Disposal or Other Releases	Other Waste Management
Surface Water	✓			
Air	✓			
Land	✓		✓	
Underground Injection	✓		✓	
Recycling		✓		✓
Energy Recovery		✓		✓
Treatment		✓		✓
POTWs – Metals			✓	
POTWs – Non-Metals				✓

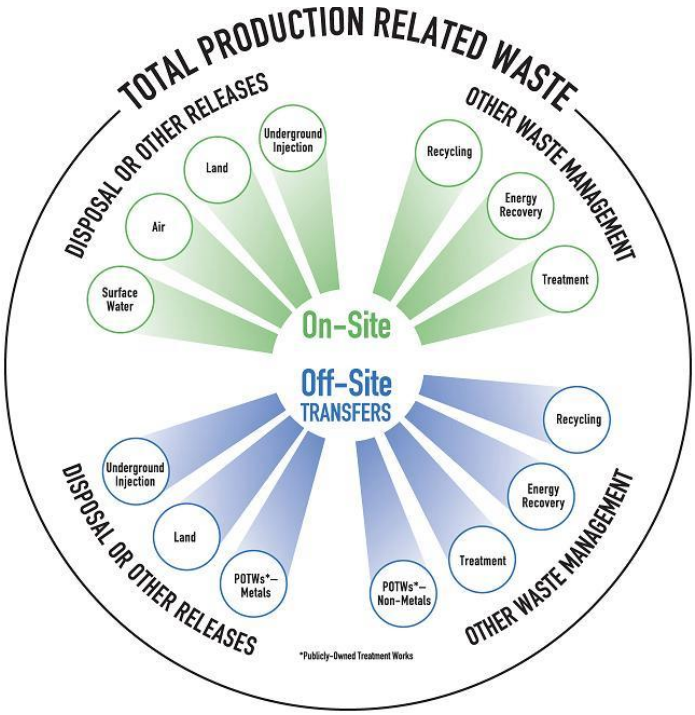


Figure 1. Diagram of the Information Collected Under the TRI.[2]

Upon understanding how the data is organized and collected, a few key points must be noted. The two foremost of which involve exposure to TRI chemicals. It is crucial to understand that the data provided by the TRI does not signify the toxicity of the chemicals listed. Each of the chemicals that are regulated under the TRI is deemed toxic to some extent; however the degree of toxicity may vary significantly between different TRI chemicals. In addition, the potential of exposure relies heavily on the persistence of the chemical being considered. Thus, the TRI does not display the harm of individual chemical releases, neither absolutely nor in relation to one another, rather it only quantifies the extent of the release.

Despite the aforementioned limitations, the TRI provides a powerful tool to identify opportunities within an industry or specific manufacturing facility to decrease

environmentally unfavorable practices. Although the TRI does not quantify waste from non-toxic sources, it highlights the waste sources that are most harmful to employees, the community, and the environment. This allows companies and private researchers to aim towards reducing the most detrimental wastes. It also aids in bringing attention to common practices that can be improved on a broader industry wide scale. The focus of this chapter will be on the use of TRI data for these means, specifically within the pharmaceutical industry. In addition, an in depth description of what defines a TRI chemical, those chemicals that are included in the TRI, and how the definition of these chemicals has developed over time is provided in the *TRI Historical Changes* section.

1.2. Introduction to TRI Use in the Pharmaceutical Industry

Small volume batches are common within the pharmaceutical industry. As a result, it is considered environmentally unfeasible to recover wastes from these batches. 80-90% of the mass that goes into producing an API is made up of solvents.[3] By implementing a small scale solvent recovery system, emissions may be reduced by over 90%. This will be discussed throughout the proceeding chapters.

To improve the environmental efficiency of a solvent recovery technique, it is important to understand both the main solvents of interest and additional opportunities for solvent recovery from other processes at the facility to maximize usage of the equipment. In addition, it is important to understand the environmental implications of recovering a TRI chemical rather than a non-toxic or environmentally benign chemical. Although there are still emissions associated with production, usage, and disposal of non-toxic and environmentally benign solvent waste, recovery and reduction of TRI solvents provides

not only a reduction in overall emissions, but the added benefit of reduction in the risks to workers, the community, and the environment associated with the process.

For this reason, the TRI provides a powerful tool for determining the most beneficial solvents to recover. Systems may be designed for recovering solvents that pose the greatest threat to the environment and community. In addition, these systems can be designed to recover a series of specific solvents that exist or are likely to exist in a pharmaceutical manufacturing facility.

Following is a tutorial for using TRI.NET. This tutorial is designed to provide an individual with no experience using the TRI or TRI.NET an introduction to the program and all of its capabilities, with a specific focus on the use of the program to determine TRI trends in the pharmaceutical industry

1.3. TRI.NET Introduction and Tutorials[4]

1.3.1. Tutorial Overview

This tutorial has been written using the TRI.NET User's Guide provided with the program and available online at http://www.epa.gov/tri/tridotnet/guide.html. The user guide provides further details of how to use the program as intended. Anyone who is considering using TRI.NET for analyzing extensive Toxic Release Inventory data should also read the user guide along with this tutorial. The majority of the pictures within this tutorial have been taken from screenshots of the program. The program is written by the United States Environmental Protection Agency. The intended use of TRI.NET is for retrieving and analyzing data from the Toxic Release Inventory for all reporting industrial sectors. It is also very useful in determining the toxic releases found in a specific area, company, or industrial sector. Data are available for 1988 through 2008 and are made up

of the reported toxic release data from all reporting industrial sectors. The tutorial case study presented is based upon the total toxic releases in the pharmaceutical sector.

1.3.2. TRI.NET Introduction

TRI.NET is a program that allows quick navigation through US EPA Toxic Release Inventory (TRI) data. The Toxic Release Inventory is a publicly available EPA database that contains information on toxic chemical releases and waste management activities reported annually by certain industries as well as federally-operated facilities. TRI.NET allows for efficient data acquisition from the TRI for years between 1988 and present. The program may be used for a variety of applications, such as waste management, public knowledge, as well as industrial and societal demographics.

1.3.2.1. Download and Installation

To access the TRI.NET program, there is a free download available at: http://www.epa.gov/tri/tridotnet/installer.msi.

1. A dialog box will open asking if you would like to open this file. Select "**Yes**."
2. Select "**Save File**" to begin downloading the install file.
3. Once the download has completed, go to **Start →My Documents→ Downloads**.
4. Double-click on the install file to launch the set-up wizard.
5. Follow the steps shown in the set-up wizard.
6. When the wizard has finished, a desktop icon and start menu entry will be created for TRI.NET.
7. To run TRI.NET, use either the desktop icon or start menu entry.

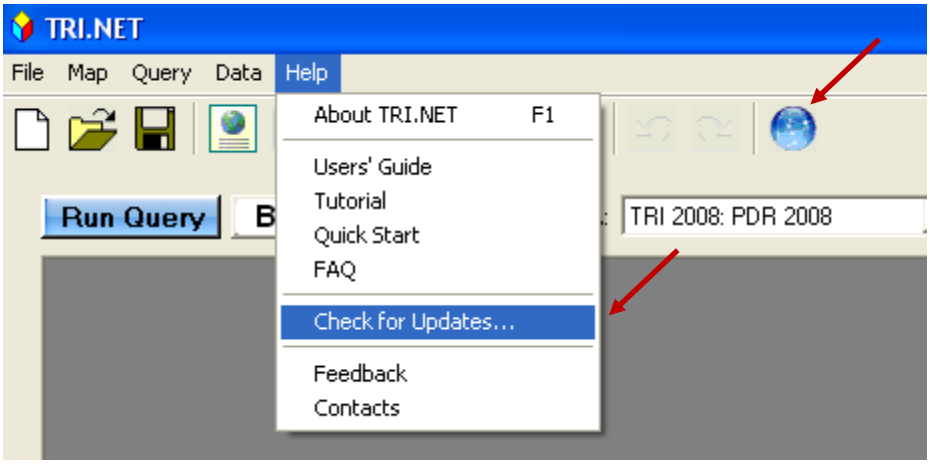
Alternatively, one may use the following link to download TRI.NET: http://www.epa.gov/tri/tridotnet/download.html. Follow the link and follow the

instructions listed for “Option 2.” This will install the program onto your computer’s hard drive. Option 1 allows for installation to a flash drive for portable use of the program and will not be included in this tutorial.

1.3.2.2. Auto-Update

Before using the TRI.NET program, ensure that all downloaded files and data are up to date. ****DO NOT UPDATE IF YOU ARE UNDER A SHORT TIME CONSTRAINT****

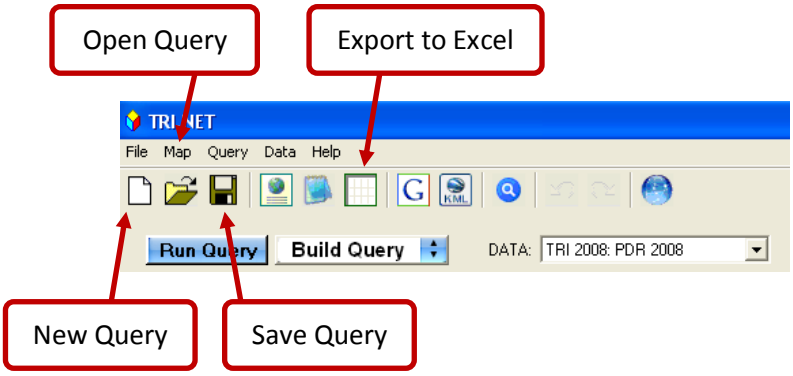
1. Run TRI.NET
2. Click on the “Check for Updates” icon or go to **Help→Check for Updates…**

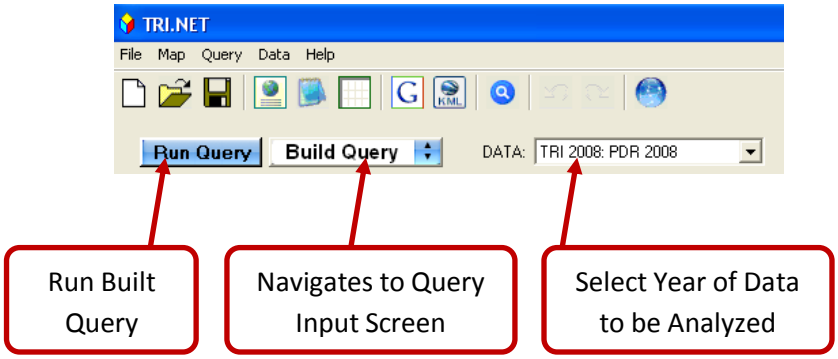


3. If data and software are current, select “**Ok**” and begin working.
4. If data and software are not current, install all updates. As the data files can be large, be patient. This may take an extensive period of time.
5. Once updates have been completed, you may begin working.

1.3.2.3. User Interface

The following figures display the options available on the TRI.NET user interface.

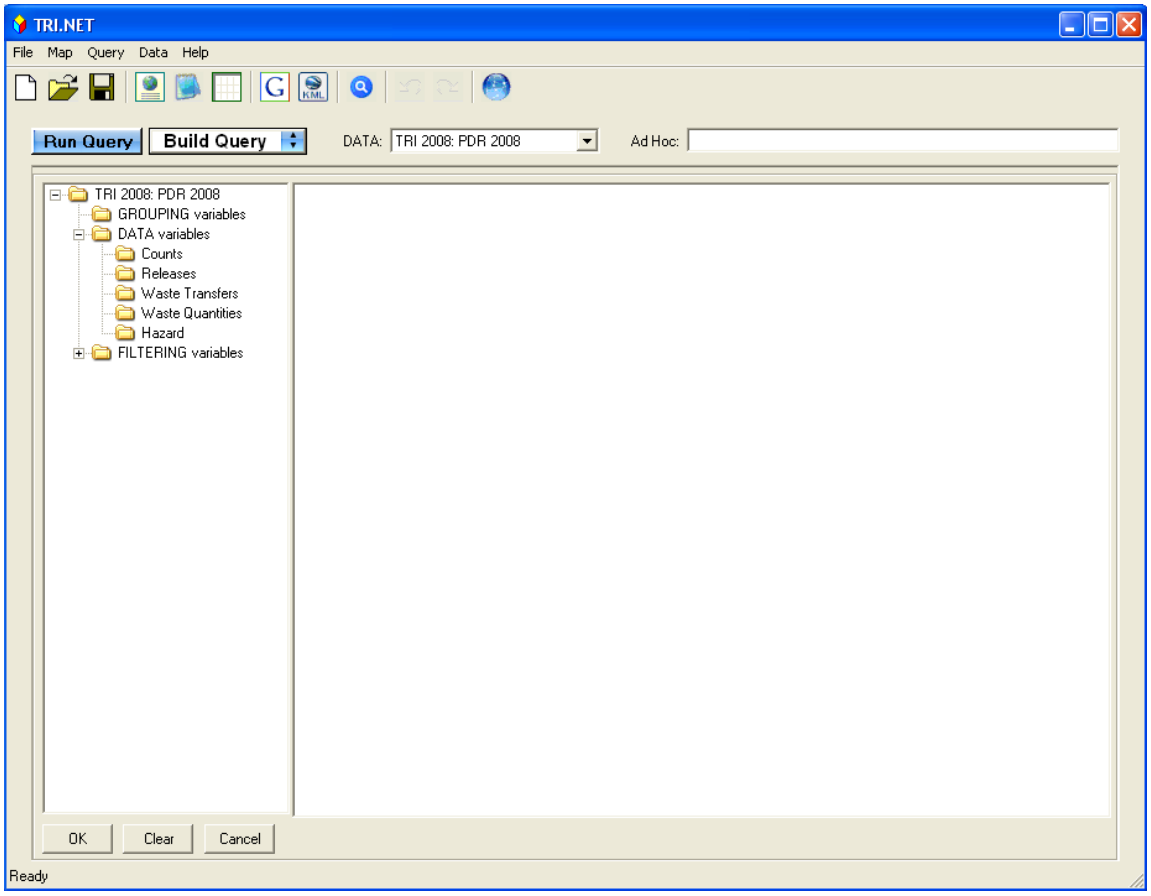




1.3.3. Introductory Tutorial

This tutorial will introduce the user to the capabilities and features of TRI.NET. Basic options and commands will be defined and demonstrated. The purpose of this tutorial is to familiarize the user with TRI.NET. It is recommended that more advanced users attempt the 1.3.4. Advanced Tutorial.

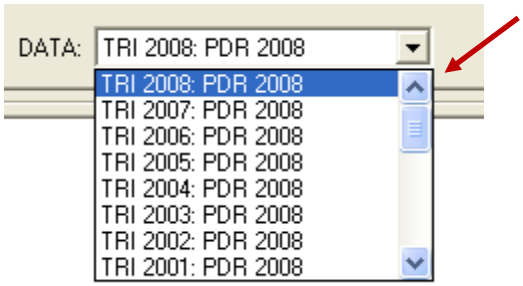
1. Open TRI.NET.
2. Click on "**Build Query**."



The screen should resemble the above image.

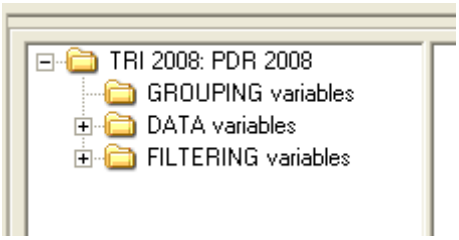
3. To save the query, click on the save icon,  , or go to **File→ Save Query As**. Save this query as "1.3.3. Introductory Tutorial."

4. Select the year of interest for your study. For this tutorial, we will be analyzing data from the 2008 Toxic Release Inventory. Go to **Data:** and click on the arrow to bring down the drop down menu.



Since we will be analyzing data from 2008, click on "**TRI 2008: PDR 2008**." For data from 2007, for example, you would select "**TRI 2007: PDR 2007**."

5. On the left side of the screen, there is a directory that can now be used to specify how the data will be analyzed.



Three types of variables are listed.

   a. Grouping Variables – specify how the DATA variables are to be aggregated; specify what variables will be used to group the data in the analysis.

      i. Click on Grouping Variables. A list of options will appear to the right of the screen. By checking these boxes, you can specify how results are grouped. For example, if you checked the box next to "**State**," upon finishing the query, all of the data for releases in New Jersey will be grouped as a single data point.

   b. Data Variables – the variables to be aggregated and presented in the output; the data that will be displayed as results.

      i. Click on the "+" sign next to Data Variables to expand the list. Five types of data variables appear. If you click on any of these variables, a list of options similar to that described under Grouping Variables will appear.

1. Counts – whole number "count" of a specified metric. For example, if you choose "**Facility Count**," your results will be reported as the number of facilities in whichever grouping variables you chose.
2. Releases – amount of on-site and off-site releases, releases to air, water, and land, and releases due to fugitive emissions and other forms of release
3. Waste Transfers – amount of waste transferred to specified off-site facilities, such as recycling and energy recovery facilities
4. Waste Quantities – amount of waste managed; this includes all waste released on-site and off-site, production related waste, energy recovery, waste recycled, waste treated, and nonproduction related waste; includes all Releases (2) and Waste Transfers (3)
5. Hazard – threat posed by a specific grouping variable. Results are reported as Toxicity x Pounds; the Hazard value comes from another publically available EPA program, RSEI (Risk-Screening Environmental Indicators)

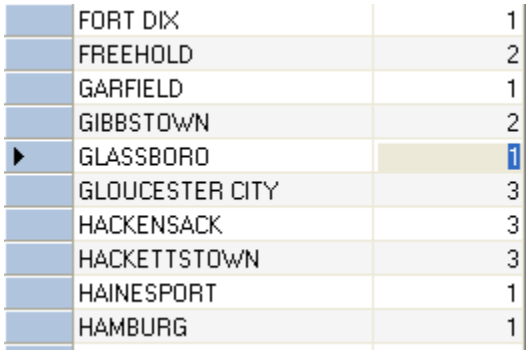
c. Filtering Variables – restrict the data that get aggregated and presented in the results; specify what data will be included in the query
    i. Click on the "+" sign next to filtering variables to expand the list. Eight types of filtering variables appear. If you click on any of

these variables, a list of options similar to that described under Grouping Variables and Data Variables will appear.

1. Chemical Group – lists types of chemicals, such as Hazardous Air Pollutants (HAPs) and OSHA carcinogens. For example, if you checked the box next to "Hazardous air pollutants," only the data for chemicals listed by the US EPA as hazardous air pollutants will be considered; if you want all TRI chemicals to be listed, do not select a chemical group
2. Chemical – lists the chemical by name, such as 2,4-dinitrotoluene
3. NAICS – lists industrial groups by their North American Industry Classification System (NAICS) classification
4. Industry – lists industries by their broader NAICS classification. For example, Medicinal and Botanical Manufacturing is NAICS 325411, however it falls into the broader industry classification of Chemicals, NAICS 325
5. EJ 3-mile – lists areas by demographics derived from the Census 2000 Block Group data
6. Tribal – lists facilities either within of within a specified distance of tribal lands
7. Facility – lists groups of facilities by a variety of factors
8. Geography – lists states and territories of the United States

9. Region – lists the ten EPA regions of the United States
10. Year – lists the years from 1988 until present, this is useful if more than one year of data is being researched, however not all of the years from 1988 until present are of interest

6. Say you are interested in the number of industrial facilities reporting to the TRI for the year 2008 that are in the city of Glassboro.
    a. Select **TRI 2008: PDR 2008** from the **DATA** drop down menu.
    b. Go to **Grouping Variables** and select **City**
    c. Go to **Data Variables→ Counts** and select **Facility Count**
    d. To speed up the search, go to **Filtering Variables→ Geography** and select **New Jersey**. This will narrow the search to only facilities in New Jersey.
    e. Select **Run Query**.
7. Results are given in alphabetical order. If you scroll down, you should see that there is one facility that reports to the TRI in Glassboro.



FORT DIX	1
FREEHOLD	2
GARFIELD	1
GIBBSTOWN	2
GLASSBORO	1
GLOUCESTER CITY	3
HACKENSACK	3
HACKETTSTOWN	3
HAINESPORT	1
HAMBURG	1

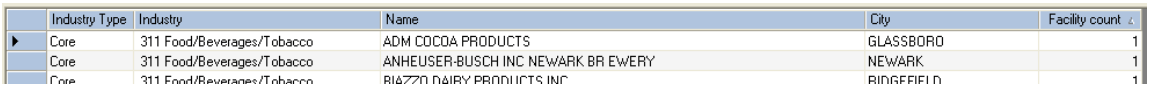
8. Say you were interested in the name of this facility, the industry to which it belongs, and what type of industry to which it belongs.

a. Click on **Build Query**. Notice that the data selections you made previously are still held in the query. If necessary, you must unclick those selections or open a new query, however, for this exercise we will leave them selected.

b. Select **Name**, **Industry**, and **Industry Type**.

c. Select **Run Query**.

9. You should find that the facility in Glassboro is a core industry in the 311 Food/Beverages/ Tobacco category and that it is called ADM Cocoa Products.



	Industry Type	Industry	Name	City	Facility count
▶	Core	311 Food/Beverages/Tobacco	ADM COCOA PRODUCTS	GLASSBORO	1
	Core	311 Food/Beverages/Tobacco	ANHEUSER-BUSCH INC NEWARK BR EWERY	NEWARK	1
	Core	311 Food/Beverages/Tobacco	BIAZZO DAIRY PRODUCTS INC	BIDGEFIELD	1

10. You may also export this data to Excel. This is useful for calculating specific data amongst industries and making comparisons between waste releases among these industries and over time. To do this, click on the Export To Excel button or go to **File→ Send To→ Spreadsheet**.

11. Say you want to visit this facility.

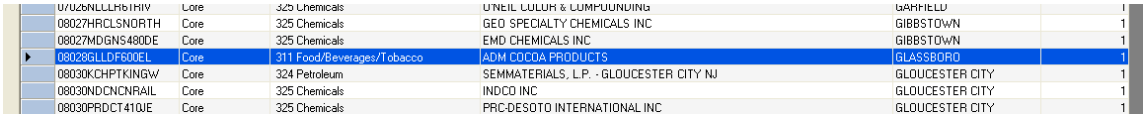
a. Click on **Build Query**.

b. Go to **Grouping Variables** and select **TRIF ID**. **This step is crucial otherwise Step F and Step H will not work.**

c. Select **Run Query**.

d. Click on **City** to alphabetize the list according to city name.

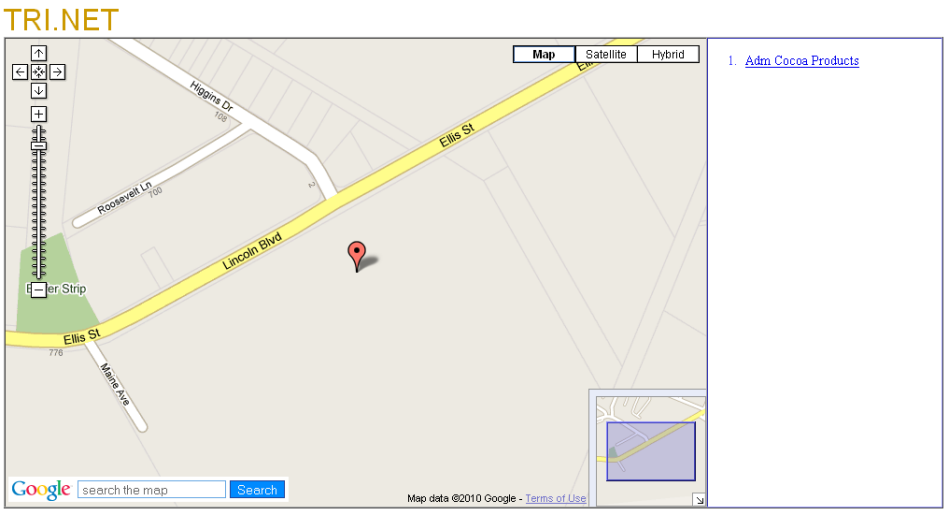
e. Go to the entry for Glassboro and click on the blue box to the far left of the entry.



	07026NLCLR6THV	Core	325 Chemicals	UNEIL COLOR & COMPOUNDING	GARFIELD	1
	08027HRCLSNORTH	Core	325 Chemicals	GEO SPECIALTY CHEMICALS INC	GIBBSTOWN	1
	08027MDGNS480DE	Core	325 Chemicals	EMD CHEMICALS INC	GIBBSTOWN	1
▶	08028GLLDF600EL	Core	311 Food/Beverages/Tobacco	ADM COCOA PRODUCTS	GLASSBORO	1
	08030KCHPTKINGW	Core	324 Petroleum	SEMMATERIALS, L.P. - GLOUCESTER CITY NJ	GLOUCESTER CITY	1
	08030NDCNCNRAIL	Core	325 Chemicals	INDCO INC	GLOUCESTER CITY	1
	08030PRDCT410JE	Core	325 Chemicals	PRC-DESOTO INTERNATIONAL INC	GLOUCESTER CITY	1

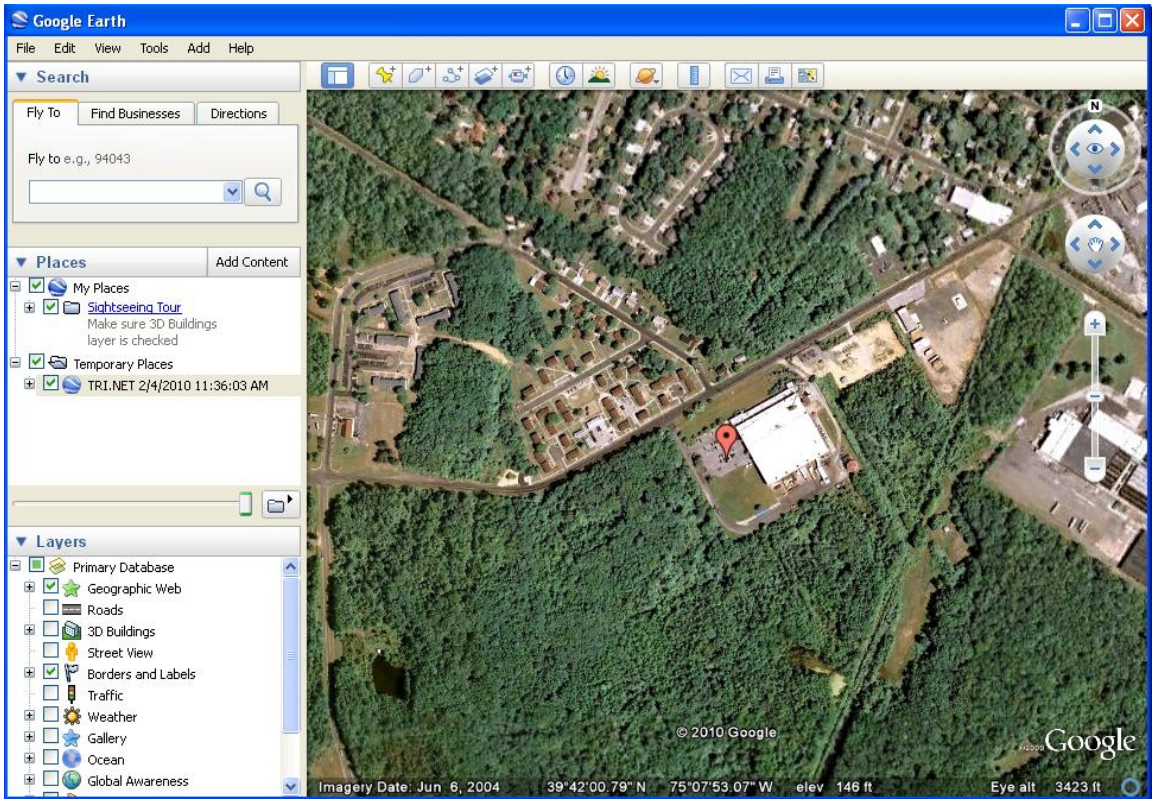
f. Click on the Export to Google Maps button.

g. This should open a browser displaying the location of ADM Cocoa Products.



h. If you have Google Earth installed, you may also search the location in Google Earth. Click on the Export to Google Earth button.

i. This should open Google Earth and display the location of ADM Cocoa Products.



This concludes the Introductory Tutorial, for a more in-depth Tutorial, see the following Advanced Tutorial.

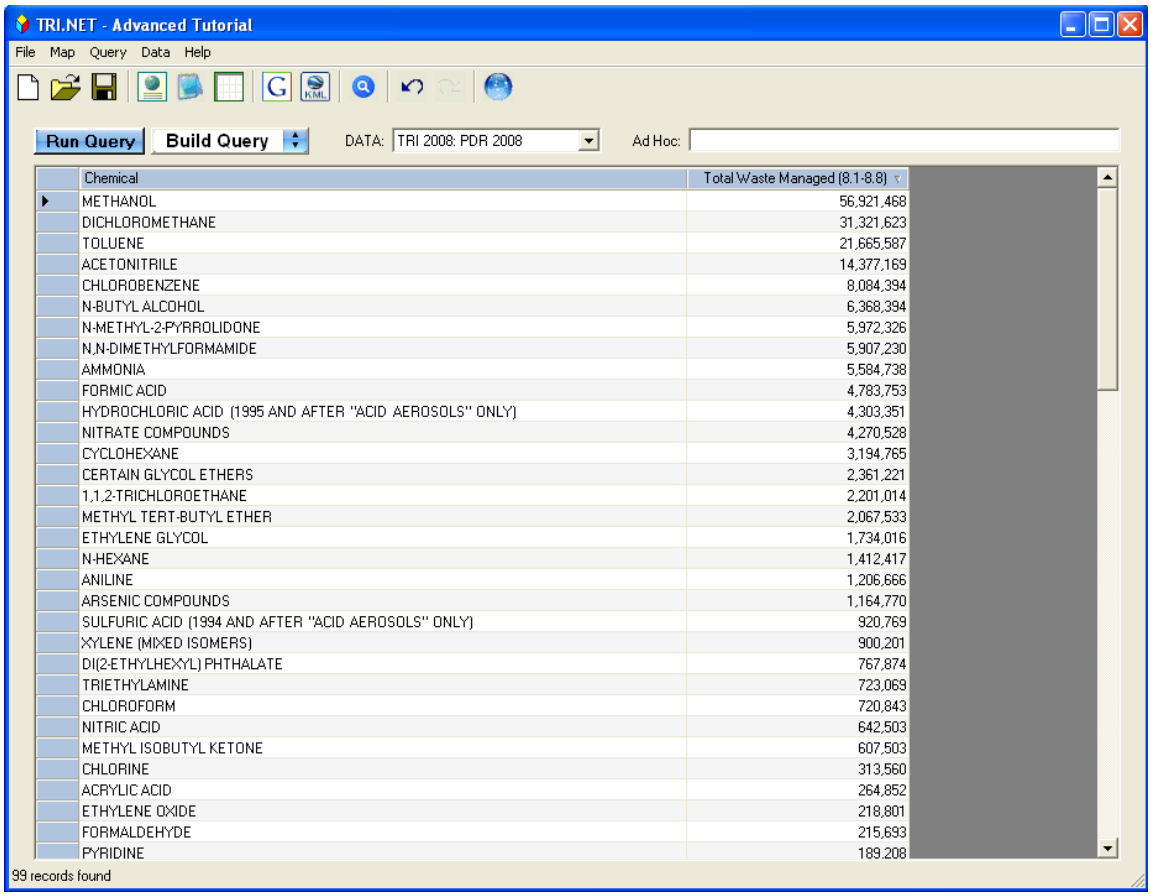
1.3.4. Advanced Tutorial

This tutorial will demonstrate how TRI.NET may be used to analyze industry data for toxic releases. The focus of the tutorial will be on the pharmaceutical sector. The top 20 chemical pollutants in the 2008 TRI for this sector will be determined, as well as the

mass of each chemical released. For those who are new to using TRI.NET, it is recommended that the 1.3.3. Introductory Tutorial be completed first.

1. Open TRI.NET.
2. Click on "**Build Query**"
3. Save the query as "1.3.4. Advanced Tutorial."
4. Go to the **DATA** drop down list and select **TRI 2008: PDR 2008**. This will ensure that only data from the 2008 TRI will be analyzed.
5. Go to "**Grouping Variables**."
6. Select "**Chemical**." This will group the data by chemical, allowing for quick selection of the top 20 TRI chemicals in the pharmaceutical sector for 2008.
7. Go to "**Data Variables**"→ **"Waste Quantities**."
8. Select "**Total Waste Managed**." Alternatively, each of the individual waste groups (8.1-8.8) may be selected.
9. Go to "**Filtering Variables**."→ "**NAICS**."
10. Select **325411 Medicinal and Botanical Manufacturing** and **325412 Pharmaceutical Preparation Manufacturing**. These NAICS codes correspond to the pharmaceutical manufacturing sector. Notice that the codes both begin with 3254. This corresponds to the broader category of Pharmaceutical and Medicine Manufacturing. If this option was selected, all four of the 3254 industrial categories will be analyzed. However, this study is not interested in 325413 In-Vitro Diagnostic Substance Manufacturing or 325414 Biological Product (except Diagnostic) Manufacturing. Thus only the first two NAICS codes under the 3254 category are selected.

11. Click on "**Run Query**."
12. Expand the columns. To do this, hover over the headings until ↔ appears, then double-click. This capability works similarly to Microsoft Excel®.
13. Put the chemicals in order of the highest mass of waste to the lowest. To do this, click on the right side of the **Total Waste Managed (8.1-8.8)** heading. This will put the chemicals in order from lowest to highest mass of waste. Click on the right side again and the chemicals will be put in order from highest to lowest mass of waste.
14. Save the query.
15. The results should resemble those below:



16. This data may then be exported to Excel®, Notepad®, or another browser for further analysis.

1.4. TRI Historical Changes

The TRI is a powerful tool for assessing the environmental impact of individual companies, corporate sectors, and American industries as a whole. However, there are a series of considerations that must be accounted for when reviewing current and historical TRI data. The most significant of these factors are the limitations on what defines a company that must report under the TRI program as well as what chemicals are defined as "toxic" by the EPA. Although TRI data provides a useful means of determining key areas for environmental improvement, it may guide the user to dismissing specific opportunities for emissions reductions. In addition, the TRI is not the best tool for reducing other specific types of emissions, such Hazardous Air Pollutants (HAPs) and Criteria Air Pollutants (CAPs). Although many TRI chemicals are also HAPs or CAPs, a chemical need not fall under these categories to be listed in the TRI. For example, an HAP is defined as an air pollutant that has an adverse human health effect, such as cancer. HAPs are one of the six CAPS defined in the Clean Air Act by the EPA, another example being particulates. Although many HAPs are defined in the TRI, particulates are not.[1] By understanding the TRI, however, one may narrow the scope for potential environmental improvement opportunities and target documented problematic areas. This allows for the design of emissions reductions systems that are guided by flexibility and a larger reduction potential.

TRI reporting began in 1988, however, many of the chemicals and manufacturing companies that are included in the TRI database were not required to report at that time. In 1998, a large number of industries were added to the TRI. These include metal and coal mining, electrical utilities, chemical wholesale distributors, petroleum bulk terminals/bulk storage, hazardous waste treatment facilities, and solvent recovery facilities.[5] It is important here to discuss the TRI definition of a "solvent recovery facility," as it directly relates to pharmaceutical solvent recovery. According to the Standard Industrial Classification (SIC) Code for TRI Industries, a solvent recovery facility is a "facility engaged in solvent recovery, limited to facilities primarily engaged in solvents recovery services on a contract or fee basis." In addition, "refuse systems" are required to report to the TRI. This includes hazardous waste treatment and disposal facilities. As previous research has shown, common practice in the pharmaceutical industry is to send solvent waste to off-site disposal, primarily incineration, and off-site recovery. Therefore, a better evaluation of the pharmaceutical TRI could be achieved by analyzing the TRI volumes from these industrial sectors. However, no differentiation is made as to what percentage of the waste sent to solvent recovery/hazardous waste treatment/disposal facilities is allotted to the pharmaceutical sector or other industries. In addition to the aforementioned industries added to the TRI in 1998, there are conditions that require any industry to report regardless of the sector in which it operates. These conditions extend the requirement to report to the TRI to any federal facility in an SIC code, a facility that employs ten or more full-time employees, and a facility which manufactures or processes 25,000 pounds of a TRI chemical or otherwise uses over 10,000 pounds of a TRI chemical over a calendar year. In addition to this, much more

stringent rules are applied to facilities handling PBT (Persistent, Bioaccumulative, and Toxic) chemicals.[5]

In addition to changes in the facilities required to report to the TRI, the list of chemicals considered "toxic" under the TRI has expanded since its inception in 1987. These changes shall be discussed with relation to the pharmaceutical industry. Figure 2 displays the total waste managed by the pharmaceutical sector as reported to the TRI for the years of 1991 through 2008.

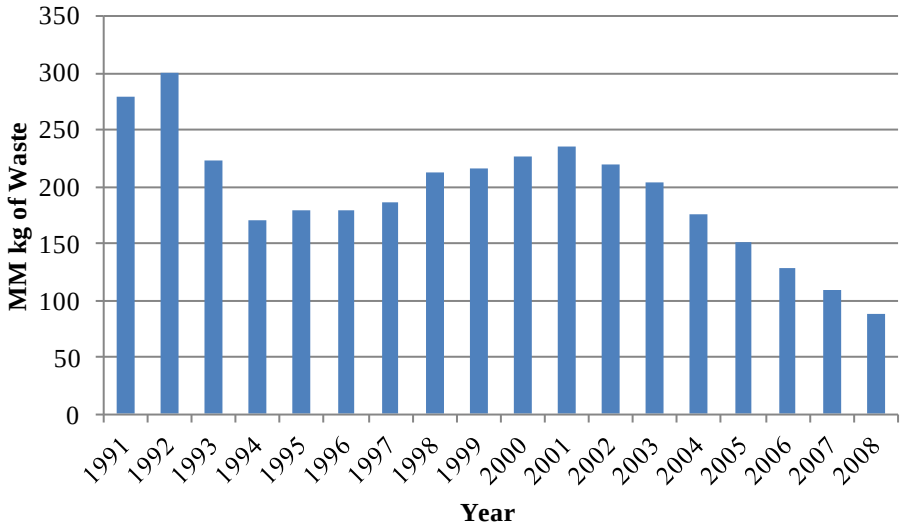


Figure 2. Total Waste Managed by the Pharmaceutical Sector (325411 and 325412) as Reported to the TRI from 1991 to 2008.

Prior to 1991, reporting to the TRI was voluntary, and as such, waste quantities attributed to the pharmaceutical sector were negligible. Thus, Figure 2 only includes TRI quantities reported after 1991. To better explain the data represented in Figure 3, the time periods presented will be separated into three distinct segments – Segment 1: 1991 through 1993, Segment 2: 1994 through 2000, and Segment 3: 2001 through 2008.

For Segment 1, 1991, 1992, and 1993 display TRI waste allocations of 280 MM kg, 300 MM kg, and 224 MM kg, respectively. These values can be attributed to an expanding U.S. pharmaceutical industry as well as government programs. The first program is the 33/50 Program, the US EPA's first initiative at reducing toxic releases. This program set goals of a 33% reduction by 1992 and a 55% reduction by 1995. This program helps to explain the emissions reductions of 300 MM kg to 224 MM kg (25%) between 1992 and 1993, as well as the reductions of 300 MM kg to 180 MM kg (38%) between 1992 and 1995. These reductions do not meet program goals, but must be taken into consideration with a second government program working simultaneously. This program was first considered in 1991 and involved a three-phase approach to broaden the TRI. The first phase of the program began in 1993, with the addition of specific Resource Conservation and Recovery Act (RCRA) chemicals as well as specific hydroflourocarbons (HCFCs). In addition, the specific requirements for reporting were changing, not solely in reference to the actual chemical, but changes were made that allowed reporting companies to omit specific TRI chemicals based upon production methods of a chemical, physical attributes, and other factors.[6] As can be seen, it is difficult to attribute trends in this segment to a single factor, as both the TRI and the pharmaceutical industry were undergoing a wide number of changes.

For Segment 2, a steadier trend begins to emerge. The increase of reported TRI waste may still be partially attributed to a growing US pharmaceutical industry. In addition, the aforementioned three-phase program completely entered into its first phase in 1994. On November 30, 1994, 286 chemicals and categories were added to the TRI. This nearly doubled the number of chemicals to be reported to the TRI from 316 in 1993 to 602 in

1994. May 1, 1997 marked implementation of the second phase of the program, with an expansion of the facilities required to report to the TRI. This included an estimated increase of 6,600 facilities reporting to the TRI. The third phase began on October 1, 1997, and was focused on chemical use reporting. The two topics most relevant to the data in Figure 2 were a further expansion on chemical use and expansion on the TRI to collect information on how chemicals are used. In addition to this program, further alterations were made to the TRI regulations between 1998 and 2000. These included the removal of "chlorosilanes", addition of dioxin and dioxin-like compounds, and addition of Persistent, Bioaccumulative, and Toxic (PBT) chemicals to the TRI.[6] The vast expansion of the TRI and the pharmaceutical industry as a whole resulted in a nearly steady increase in the amount of waste reported to the TRI by the pharmaceutical industry between 1994 (170 MM kg) and 2000 (226 MM kg).

Segment 3 of Figure 2 displays the amount of TRI waste allocated to the pharmaceutical sector for reporting years 2001 through 2008. With expansion of the facilities required to report to the TRI and the list of chemicals included in the TRI mostly complete, a picture of the waste reductions and trends is more apparent. Figure 3 displays the total waste managed by the pharmaceutical sector as reported to the TRI for the years of 2001 through 2008.

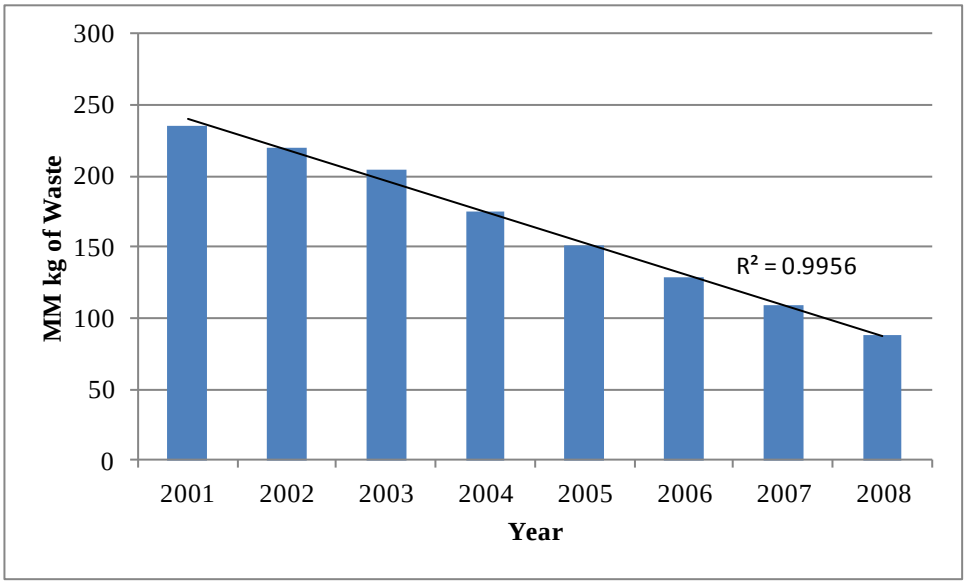


Figure 3. Total Waste Managed by the Pharmaceutical Sector (325411 and 325412) as Reported to the TRI from 2001 to 2008.

As can be seen in Figure 3, there is a linear decrease in the amount of TRI waste allocated to the pharmaceutical industry. During this time period, there was an overall reduction of 235 MM kg of waste in 2001 to 87.8 MM kg of waste in 2008. This data displays that the pharmaceutical industry has increased its focus on two areas, waste and emissions reductions, as well as reducing the amount of toxic chemicals used within its processes.

Chapter 2

Life Cycle Assessment and its Application to the Pharmaceutical Industry

Portions of this chapter are taken directly from "LCA approach to the analysis of solvent waste issues in the pharmaceutical industry" (Raymond, M.J., C.S. Slater, and M.J. Savelski. "LCA approach to the analysis of solvent waste issues in the pharmaceutical industry." *International Journal of Green Chemistry*. 12 (2010): 1826-1834) with the permission of Sarah Ruthven and Gill Cockhead.[3]

The article may be found online at the following location:

http://pubs.rsc.org/en/Content/ArticleLanding/2010/GC/c003666h

2.1. Introduction to the Use of LCA in the Pharmaceutical Industry*

Life Cycle Assessment (LCA) is a systematic method for analyzing the environmental impact of a product, process, or service through a cradle-to-grave approach. A cradle-to-grave approach assesses the environmental impact of the manufacture, use, and disposal of a material. This approach considers all effects from the point at which materials are gathered from the earth until these materials are returned to the earth.[7] This allows for a comprehensive understanding of the overall environmental effects of a process, allowing the analyst to recognize problems and solutions that a single-issue approach does not readily identify.[8] The International Standards Organization (ISO) has issued a methodology for LCA development and interpretation, including ISO documents ISO-14040 to ISO-14047.[9] Software packages with extensive process and environmental data,

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such as SimaPro 7.1® (PRé Consultants, Amersfoort, Netherlands), are also available to aid in the development and analysis of an LCA.

The methodology for developing an LCA includes the following steps: Goal Definition and Scoping, Inventory Analysis, Impact Assessment, and Interpretation. Goal Definition and Scoping involves defining the product or process to be assessed, establishing the context of the assessment, and defining the boundaries of that assessment. Inventory Analysis involves indentifying and quantifying all energy and materials used and all environmental emissions throughout the product or process's life cycle. Impact Assessment involves assessing any potential human and ecological effects from the inventory. Interpretation involves evaluating the Inventory Analysis and Impact Assessment results to make an informed decision on which process or product is environmentally superior according to the Goal Definition.[7] The development of an LCA is not linear; throughout the process it is necessary to return to previous steps and interpret the results found and the relation of these results to other steps in the LCA process. This method of evaluating processes has proven successful in a variety of industries, including electronics, production of electricity, and transportation fuels. It has been applied to pharmaceuticals, although to a smaller extent. Applications have included catalyst selection for processing an intermediate, a comprehensive study on a pharmaceutical product by GlaxoSmithKline, and an analysis of Vitamin B12 production.[10]

Life Cycle Assessment is unique in that it provides a comprehensive view of the environmental impact of a product or process. Through this comprehensive view, LCA avoids shifting environmental issues from one source to another.[7] Through life cycle

assessment of a series of case studies, it will be demonstrated that implementing a solvent recovery or reduction system into pharmaceutical manufacturing processes can significantly reduce the emissions associated with the process. The importance of solvents and solvent use in the manufacture of complex drug products often comes as a surprise to analysts, as was reported by GlaxoSmithKline (GSK).[11] Although solvents rarely enter into reaction chemistry, their use constitutes a majority of the mass and energy demand in the pharmaceutical industry. 80-90% of reaction mass and approximately 60% of energy use in the production of an active pharmaceutical ingredient (API) is attributed to solvents.[12] These solvents are used in reactions for API synthesis, providing a medium for reactions to take place, as well as separation and washing steps used to purify the API produced during the reaction. It is common practice in the pharmaceutical industry to incinerate solvent waste both on-site and off-site.[13] Two environmental incentives for life cycle analysis of pharmaceutical solvent use and recovery exist due to the current practices of solvent use and incineration. The first incentive is that by recycling an increased proportion of solvent, less solvent must be produced for use as a virgin solvent feed. The second incentive is that the inventory of solvent waste to be treated is significantly decreased. Both solvent manufacture and disposal contribute significant proportions to the life cycle emissions of an API and will be further elaborated later.

2.2. Results of Application of the TRI and LCA to the Pharmaceutical Industry

2.2.1 Current Situation

As discussed previously, the pharmaceutical industry has reduced TRI waste from 235MM kg in 2001 to 87.8 MM kg in 2008. However, the production of 1 kg of API still

results in 25 to 100 kg of waste. Before ways to reduce this waste can be discussed, one must understand how this waste is generated. Figure 4 displays a breakdown of the pharmaceutical TRI waste for reporting year 2008.

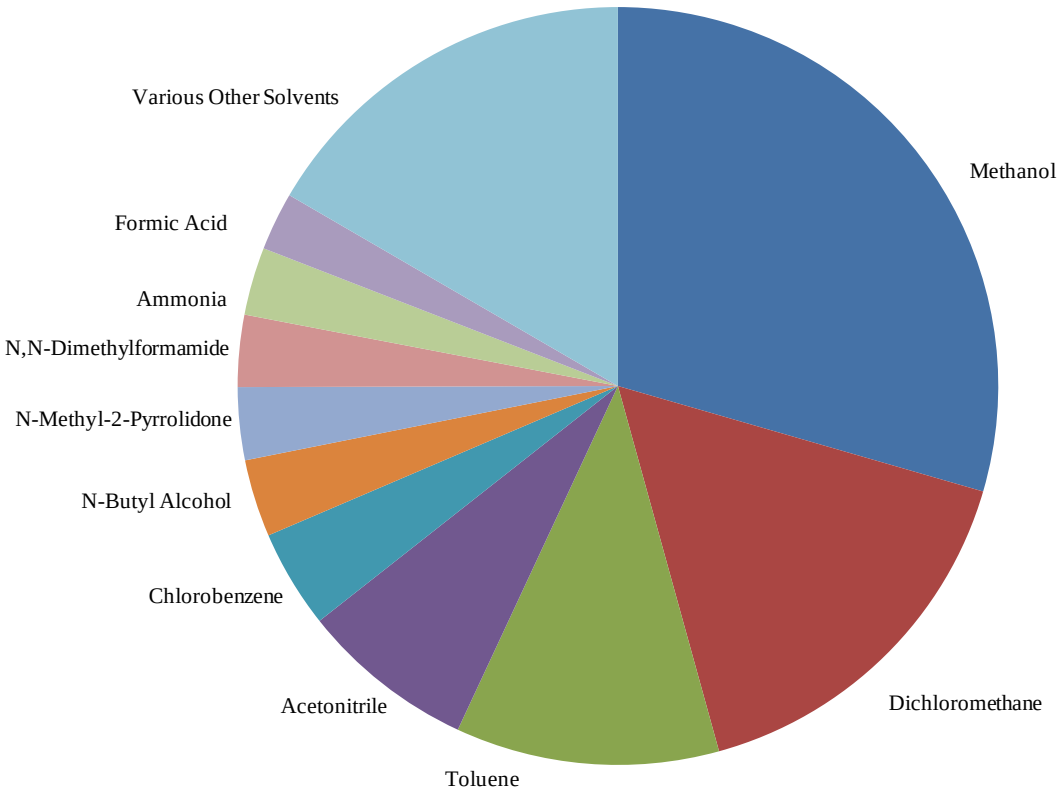

Figure 4. Breakdown of Pharmaceutical TRI Waste for Reporting Year 2008.

Displayed in Figure 4 are the top ten pharmaceutical TRI wastes. All of the top ten pharmaceutical TRI wastes are attributed to solvents. Non-solvent chemicals are included, however only appear in small quantities in the section labeled "Various Other Solvents." It should also be noted that other common pharmaceutical solvents, such as

acetone, do not appear in Figure 4 since they are not categorized as TRI wastes. These top ten solvents account for 72% of the total pharmaceutical TRI waste. It must be reiterated that of the remaining 28%, a large portion is also attributed to solvent use. As stated previously, 80-90% of the total mass that goes into making an API is attributed to solvents. Figure 4 demonstrates that although the pharmaceutical sector has greatly reduced TRI wastes, solvent waste still constitutes a large majority of the total. In addition, the top four pharmaceutical TRI chemicals – methanol, dichloromethane, toluene, and acetone – constitute 64% of the total pharmaceutical TRI waste. Furthermore, these four solvents have consistently been the top four pharmaceutical TRI wastes throughout 2001 to 2008. Figure 5 displays the amount of waste allocated to each of the top four pharmaceutical TRI chemicals for reporting years 2001 to 2008.

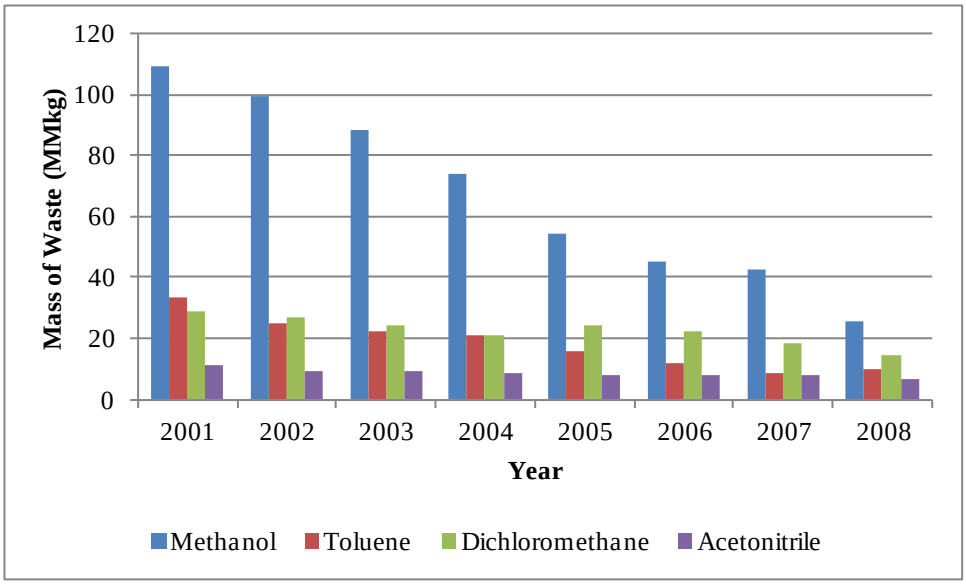

Figure 5. Amount of Waste Attributed to Each of the Top Four TRI Chemicals Reported by the Pharmaceutical Sector.

Of these four wastes, methanol consistently made up the largest portion of the TRI waste, toluene moved from the second to third largest contributor, switching positions with dichloromethane, and acetonitrile remained the fourth largest contributor. The mass of methanol waste alone was reduced by 76%, from 109 MM kg to 25.9 MM kg. By using the TRI to determine this trend, the pharmaceutical industry may focus on reducing emissions within problem areas – most notably these four recurring top TRI chemicals.

2.2.2. Life Cycle Inventory of the Pharmaceutical TRI

In order to fully understand the environmental impact of the TRI, a life cycle analysis must be completed. The TRI only provides data on the amount of waste produced at a facility, but does not consider the amount of emissions that are attributed to that waste. By conducting an LCA, one may determine the full impact of that waste on the environment.

A Life Cycle Inventory (LCI) is a record of the emissions attributed to a product through raw material acquisition, manufacture, use, and final disposal, and is crucial to the development of an LCA. Life cycle inventories were created for manufacture and disposal (incineration) of each of the top ten pharmaceutical TRI solvents. A life cycle inventory was made for the remaining chemicals, in which they were modeled as a "generic solvent." Table 2 displays the life cycle inventory for the manufacture of 1 kg of each of the top ten pharmaceutical TRI solvents and a "generic solvent."

Table 2. Life Cycle Inventory for the Manufacture of 1 kg of the Top 10 TRI Solvents and a "Generic Solvent."

	Raw	Air	CO_2	Water	Soil	Total
	kg	kg	kg	kg	kg	kg
Methanol	8.34E-01	6.47E-01	6.40E-01	6.39E-03	1.27E-04	6.54E-01
Dichloromethane	2.10E+00	2.36E+00	2.31E+00	3.30E-01	2.44E-06	2.69E+00
Toluene	1.36E+00	1.21E+00	1.19E+00	3.87E-03	3.46E-07	1.21E+00
Acetonitrile	1.54E+00	1.97E+00	1.95E+00	1.44E-01	6.80E-04	2.12E+00
Chlorobenzene	1.07E+01	1.04E+01	1.02E+01	1.13E+00	3.87E-04	1.16E+01
n-Butyl Alcohol	2.21E+00	1.62E+00	1.60E+00	2.54E-02	3.50E-04	1.65E+00
N-Methyl-2-Pyrrolidone	2.81E+00	3.82E+00	3.78E+00	2.82E-01	1.45E-03	4.11E+00
N,*N*-Dimethylformamide	1.78E+00	1.85E+00	1.83E+00	3.60E-01	2.11E-03	2.21E+00
Ammonia	1.02E+00	1.84E+00	1.83E+00	3.35E-02	1.21E-03	1.87E+00
Formic Acid	1.88E+00	2.40E+00	2.37E+00	9.42E-02	2.44E-03	2.50E+00
Generic Solvent	1.74E+00	1.78E+00	1.75E+00	1.22E-01	1.66E-04	1.91E+00

In Table 2, Raw refers to the mass of raw materials required to manufacture 1 kg of a solvent, Air refers to the mass of emissions to air from the manufacture of 1 kg of a solvent, CO_2 refers to the mass of CO_2 emissions from the manufacture of 1 kg of a solvent, Water refers to the mass of emissions to water from the manufacture of 1 kg of a solvent, Soil refers to the mass of emissions to soil from the manufacture of 1 kg of a solvent, and Total refers to the sum of the emissions to air, water, and soil from the manufacture of 1 kg of a solvent. Figure 6 displays the data in Table 2 in graphical form.

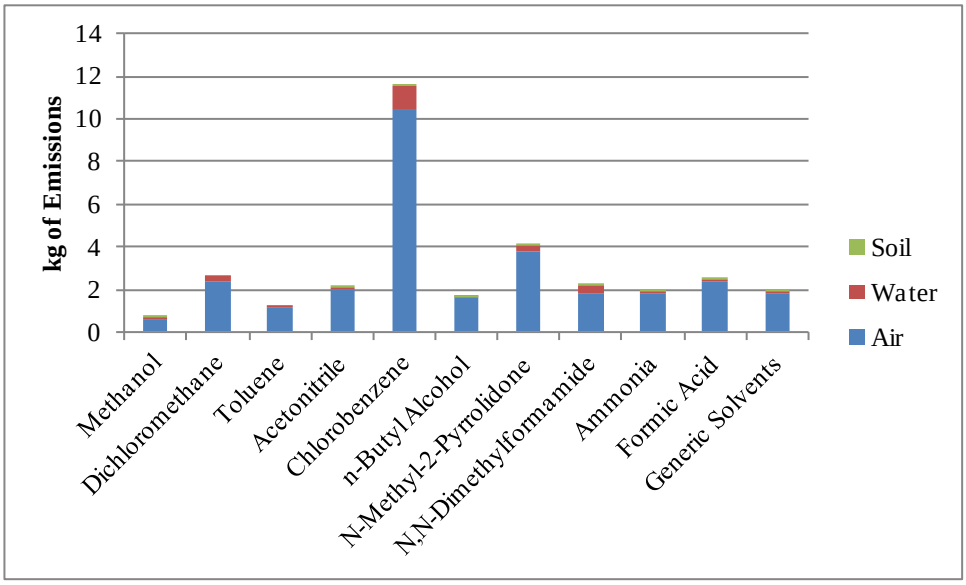

Figure 6. Life Cycle Inventory for the Manufacture of 1 kg of the Top 10 TRI Solvents and a "Generic Solvent."

As can be seen in Figure 6, chlorobenzene displays the largest mass of emissions per kg of solvent manufactured. This will be discussed in more detail in the life cycle analysis. Table 3 displays the life cycle inventory for the incineration of 1 kg of each of the top ten pharmaceutical TRI solvents and a “generic solvent.”

Table 3. Life Cycle Inventory for the Incineration of 1 kg of the Top 10 TRI Solvents and a "Generic Solvent."

	Raw	Air	CO_2	Water	Soil	Total
	kg	kg	kg	kg	kg	kg
Methanol	9.97E-02	1.93E+00	2.88E-01	0.00E+00	0.00E+00	1.93E+00
Dichloromethane	2.80E+00	2.87E+00	2.90E-01	8.32E-04	0.00E+00	2.87E+00
Toluene	1.25E-02	3.36E+00	9.18E-01	0.00E+00	0.00E+00	3.36E+00
Acetonitrile	1.78E-01	2.16E+00	5.20E-01	0.00E+00	0.00E+00	2.16E+00
Chlorobenzene	9.20E-01	2.37E+00	1.66E+00	3.12E-04	0.00E+00	2.37E+00
n-Butyl Alcohol	1.25E-02	2.39E+00	3.73E-01	0.00E+00	0.00E+00	2.39E+00
N-Methyl-2-Pyrrolidone	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
N,*N*-Dimethylformamide	1.05E-01	1.82E+00	3.75E-01	0.00E+00	0.00E+00	1.82E+00
Ammonia	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Formic Acid	4.20E-01	3.53E+00	1.03E+00	0.00E+00	0.00E+00	3.53E+00
Generic Solvent	1.20E+00	2.24E+00	1.49E+00	3.44E-04	0.00E+00	2.24E+00

In Table 3, Raw refers to the mass of raw materials required to incinerate 1 kg of a solvent, Air refers to the mass of emissions to air from the incineration of 1 kg of a solvent, CO_2 refers to the mass of CO_2 emissions from the incineration of 1 kg of a solvent, Water refers to the mass of emissions to water from the incineration of 1 kg of a solvent, Soil refers to the mass of emissions to soil from the incineration of 1 kg of a solvent, and Total refers to the sum of the emissions to air, water, and soil from the incineration of 1 kg of a solvent. Figure 7 displays the data in Table 3 in graphical form.

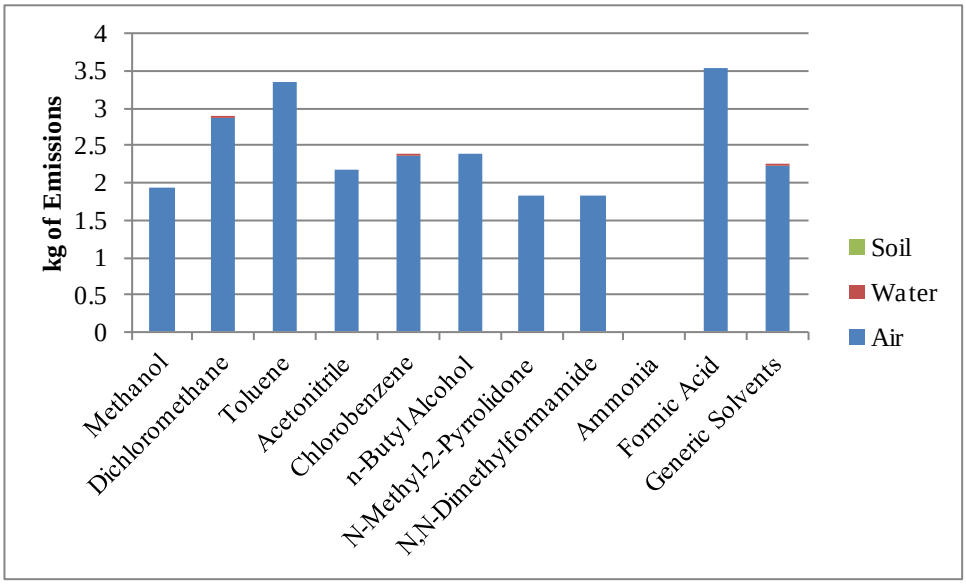

Figure 7. Life Cycle Inventory for the Incineration of 1 kg of the Top 10 TRI Solvents and a "Generic Solvent."

As can be seen, there are no emissions associated with the incineration of ammonia. EcoSolvent® was used to analyze the incineration of each of the solvents in Table 3 and Figure 7 and ammonia is not included in the EcoSolvent® database. Therefore, ammonia was excluded from the analysis. In addition, N-methyl-2-pyrrolidone is not in the EcoSolvent® database. However, it was modeled as *N*,*N*-dimethylformamide, as both belong to the same class of dipolar aprotic solvents. Table 4 displays the cradle-to-grave life cycle inventory for 1 kg of each of the top ten pharmaceutical TRI solvents and a "generic solvent."

Table 4. Cradle-to-Grave Life Cycle Inventory for 1 kg of the Top 10 TRI Solvents and a "Generic Solvent."

	Raw	Air	CO_2	Water	Soil	Total
	kg	kg	kg	kg	kg	kg
Methanol	9.33E-01	2.58E+00	9.28E-01	6.39E-03	1.27E-04	2.59E+00
Dichloromethane	4.90E+00	5.23E+00	5.21E+00	3.31E-01	2.44E-06	5.56E+00
Toluene	1.37E+00	4.56E+00	2.11E+00	3.87E-03	3.46E-07	4.57E+00
Acetonitrile	1.71E+00	4.13E+00	2.47E+00	1.44E-01	6.80E-04	4.28E+00
Chlorobenzene	1.16E+01	1.28E+01	1.19E+01	1.13E+00	3.87E-04	1.39E+01
n-Butyl Alcohol	2.22E+00	4.01E+00	1.97E+00	2.54E-02	3.50E-04	4.03E+00
N-Methyl-2-Pyrrolidone	2.81E+00	3.82E+00	3.78E+00	2.82E-01	1.45E-03	4.11E+00
N,*N*-Dimethylformamide	1.89E+00	3.67E+00	2.20E+00	3.60E-01	2.11E-03	4.03E+00
Ammonia	1.02E+00	1.84E+00	1.83E+00	3.35E-02	1.21E-03	1.87E+00
Formic Acid	2.30E+00	5.93E+00	3.40E+00	9.42E-02	2.44E-03	6.02E+00
Generic Solvent	2.94E+00	4.02E+00	3.24E+00	1.23E-01	1.66E-04	4.15E+00

In Table 4, Raw refers to the mass of raw materials required to manufacture and incinerate 1 kg of a solvent, Air refers to the mass of emissions to air from the manufacture and incineration of 1 kg of a solvent, CO_2 refers to the mass of CO_2 emissions from the manufacture and incineration of 1 kg of a solvent, Water refers to the mass of emissions to water from the manufacture and incineration of 1 kg of a solvent, Soil refers to the mass of emissions to soil from the manufacture and incineration of 1 kg of a solvent, and Total refers to the sum of the emissions to air, water, and soil from the manufacture and incineration of 1 kg of a solvent. Figure 8 displays the data in Table 4 in graphical form.

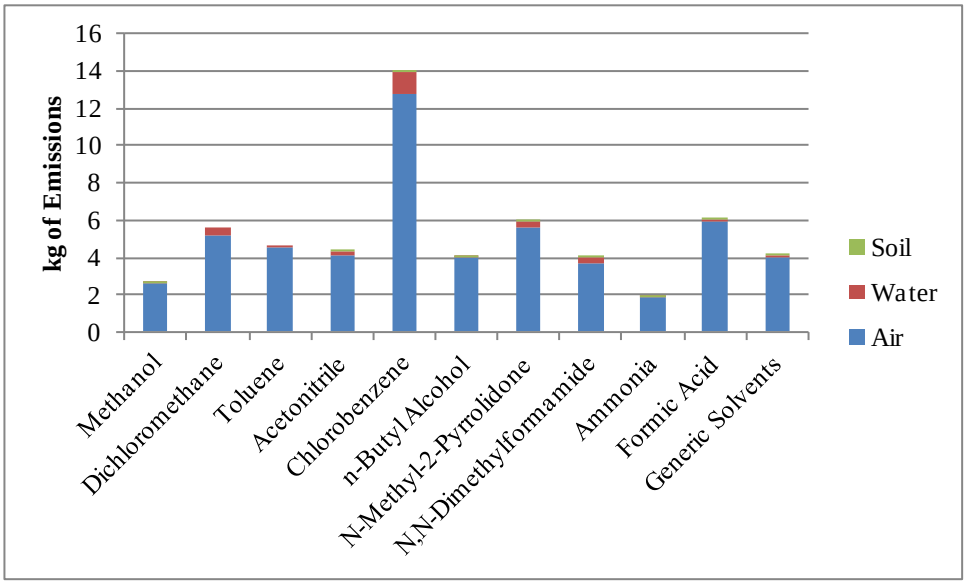

Figure 8. Cradle-to-Grave Life Cycle Inventory for 1 kg of the Top 10 TRI Solvents and a "Generic Solvent."

As can be seen in Figure 8, chlorobenzene displays the largest mass of cradle-to-grave life cycle emissions. This will be discussed in more detail in the life cycle analysis. In addition, Table 4 and Figure 8 exclude the mass of emissions for incineration of 1 kg of ammonia and model the mass of emissions for incineration of 1 kg of N-Methyl-2-pyrrolidone as that for *N*,*N*-dimethylformamide, as ammonia and N-methyl-2-pyrrolidone are not included in the EcoSolvent® database.

2.2.3. Life Cycle Analysis of the Pharmaceutical TRI

The data displayed in Figure 6, Figure 7, and Figure 8 was used to create a life cycle analysis of the pharmaceutical TRI. The life cycle analysis was completed on two bases. The first is for the total waste from the pharmaceutical TRI. For this basis, it was assumed that the total waste reported by the TRI is equivalent to the raw material amount used in the API manufacture as well as the amount disposed. In this analysis, the

emissions generated per kg of solvent from raw material manufacturing (i.e. manufacture of the actual solvent) (Figure 6), the emissions generated per kg of solvent from incineration (Figure 7), and cradle-to-grave emissions per kg of solvent (Figure 8) are multiplied by the amount of solvent used (kg/yr) (Figure 4). This yields the total life cycle emissions for that particular solvent (MMkg/yr) from manufacture and disposal. Table 5 shows the overall usage values of the individual solvents. The yearly life cycle emissions for their manufacture is shown in Figure 9. Figure 10 shows the total yearly emissions associated with incineration of the solvents as a waste. The overall cradle-to-grave life cycle emissions (MMkg/yr), which is the sum of the values represented in Figure 9 and Figure 10 is presented in Figure 11.

Table 5. Breakdown of Pharmaceutical TRI Waste for Reporting Year 2008.

Solvent	Mass MM kg
Methanol	25.9
Dichloromethane	14.2
Toluene	9.8
Acetonitrile	6.5
Chlorobenzene	3.7
n-Butyl Alcohol	2.9
N-Methyl-2-Pyrrolidone	2.7
N,*N*-Dimethylformamide	2.7
Ammonia	2.5
Formic Acid	2.2
Various Other Solvents	14.6

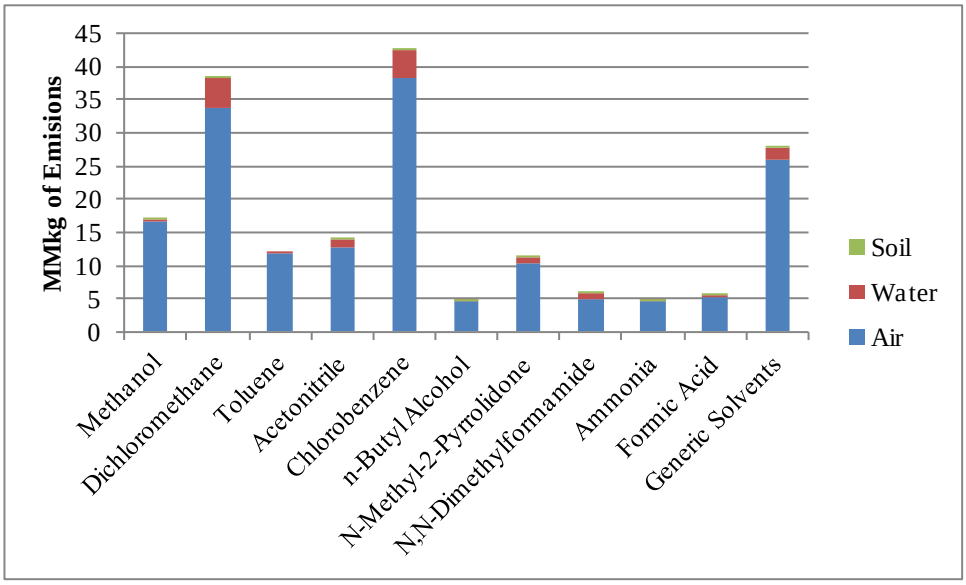

Figure 9. Emissions from Manufacture of the Pharmaceutical Industry TRI Solvents.

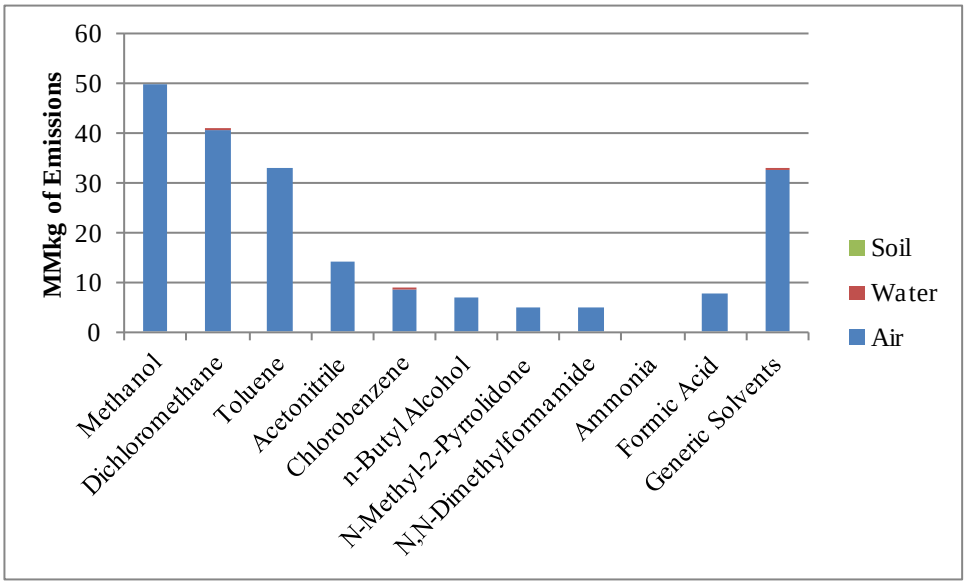

Figure 10. Emissions from Incineration of the Pharmaceutical Industry TRI Solvents.

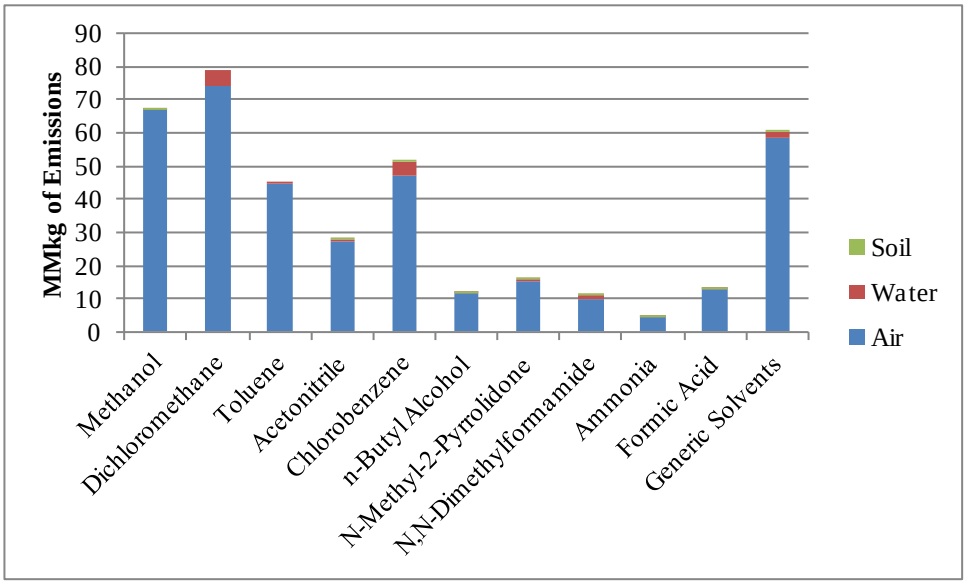

Figure 11. Cradle-to-Grave Emissions of the Pharmaceutical Industry TRI Solvents.

The effect of the life cycle inventories of each of the TRI chemicals becomes much more apparent in Figure 9 through Figure 11. For example, although chlorobenzene accounts for only 4% of the total mass of the top 10 TRI solvents, the total life cycle emissions attributed to chlorobenzene account for 13% of the total TRI cradle-to-grave emissions. Methanol, which accounts for 29% of the total mass of the top 10 TRI solvents and constitutes the largest mass of a pharmaceutical TRI chemical, contributes 17% to the total TRI cradle-to-grave-emissions. Out of the top 10 solvents, three contribute half of the total TRI life cycle emissions, methanol (17%), dichloromethane (20%), and chlorobenzene (13%). By specifically targeting chemicals such as methanol that are used in large quantities or chlorobenzene which has a disproportionately large amount of life cycle emissions when compared to other TRI solvents, one may more effectively reduce the life cycle emissions associated with a process.

2.3. Theoretical Use of the TRI to Reduce Life Cycle Emissions of a Facility

As stated, one may utilize information from the TRI and life cycle analysis software to determine what chemicals to target for "green" process improvements. To demonstrate this, a theoretical pharmaceutical facility was developed for the basis of a case study. The life cycle emissions of this facility were determined by taking the total TRI emissions in manufacture (Figure 9), incineration (Figure 10), and overall life cycle (Figure 11), and dividing by 152 – the total number of pharmaceutical facilities that reported to the TRI for reporting year 2008. This allowed for an "average" life-cycle analysis to be created for a single facility within the pharmaceutical industry. The emissions from manufacture of TRI solvents for this facility are displayed in Table 6 and Figure 12.

Table 6. Emissions from the Manufacture of TRI Solvents for an Average Pharmaceutical Facility.

	Total Waste Managed	**Raw**	**Air**	**Water**	**Soil**	**Total**
	MM kg	**MM kg**	**MM kg**	**MM kg**	**MM kg**	**MM kg**
Methanol	0.17	0.14	0.11	1.09E-03	2.17E-05	0.11
Dichloromethane	0.09	0.20	0.22	3.10E-02	2.28E-07	0.25
Toluene	0.06	0.09	0.08	2.50E-04	2.24E-08	0.08
Acetonitrile	0.04	0.07	0.08	6.21E-03	2.92E-05	0.09
Chlorobenzene	0.02	0.26	0.25	2.74E-02	9.36E-06	0.28
n -Butyl Alcohol	0.02	0.04	0.03	4.83E-04	6.67E-06	0.03
N -Methyl-2-Pyrrolidone	0.02	0.05	0.07	5.03E-03	2.59E-05	0.07
N,*N* -Dimethylformamide	0.02	0.03	0.03	6.36E-03	3.73E-05	0.04
Ammonia	0.02	0.02	0.03	5.60E-04	2.02E-05	0.03
Formic Acid	0.01	0.03	0.03	1.35E-03	3.50E-05	0.04
Generic Solvents	0.10	0.17	0.17	1.17E-02	1.60E-05	0.18
Total	**0.58**	**1.09**	**1.11**	**9.14E-02**	**2.01E-04**	**1.21**

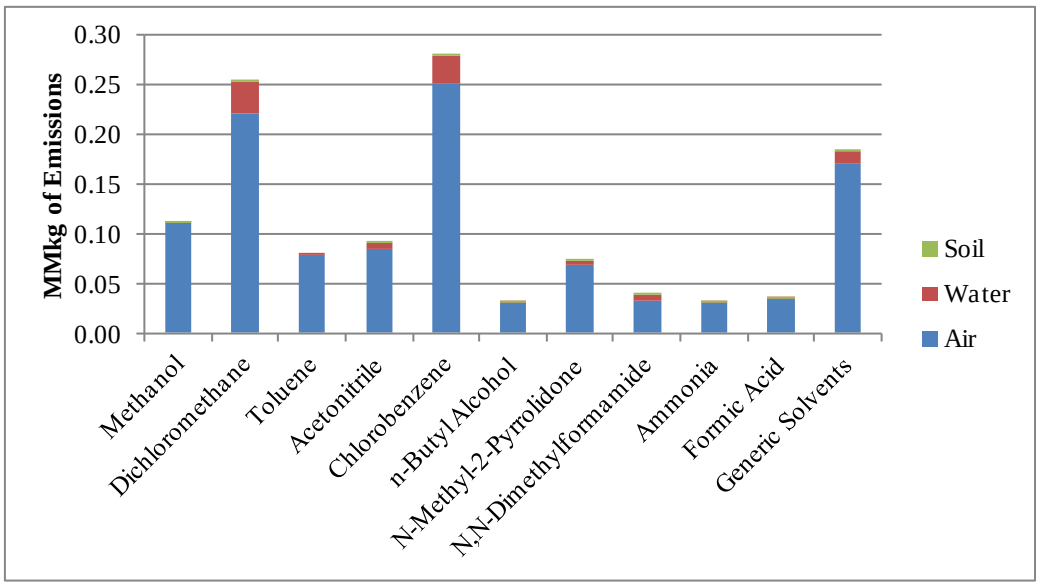

Figure 12. Emissions from the Manufacture of TRI Solvents for an Average Pharmaceutical Facility.

The emissions from incineration of TRI solvents for this facility are displayed in Table 7 and Figure 13.

Table 7. Emissions from the Incineration of TRI Solvents for an Average Pharmaceutical Facility.

	Total Waste Managed	**Raw**	**Air**	**Water**	**Soil**	**Total**
	MM kg	**MM kg**	**MM kg**	**MM kg**	**MM kg**	**MM kg**
Methanol	0.17	0.02	0.33	0.00E+00	0.00E+00	0.33
Dichloromethane	0.09	0.26	0.27	7.79E-05	0.00E+00	0.27
Toluene	0.06	0.00	0.22	0.00E+00	0.00E+00	0.22
Acetonitrile	0.04	0.01	0.09	0.00E+00	0.00E+00	0.09
Chlorobenzene	0.02	0.02	0.06	7.54E-06	0.00E+00	0.06
n-Butyl Alcohol	0.02	0.00	0.05	0.00E+00	0.00E+00	0.05
N-Methyl-2-Pyrrolidone	0.02	0.00	0.03	0.00E+00	0.00E+00	0.03
N,*N*-Dimethylformamide	0.02	0.00	0.03	0.00E+00	0.00E+00	0.03
Ammonia	0.02	0.00	0.00	0.00E+00	0.00E+00	0.00
Formic Acid	0.01	0.01	0.05	0.00E+00	0.00E+00	0.05
Generic Solvents	0.10	0.12	0.21	3.30E-05	0.00E+00	0.21
Total	**0.58**	**0.44**	**1.34**	**1.18E-04**	**0.00E+00**	**1.34**

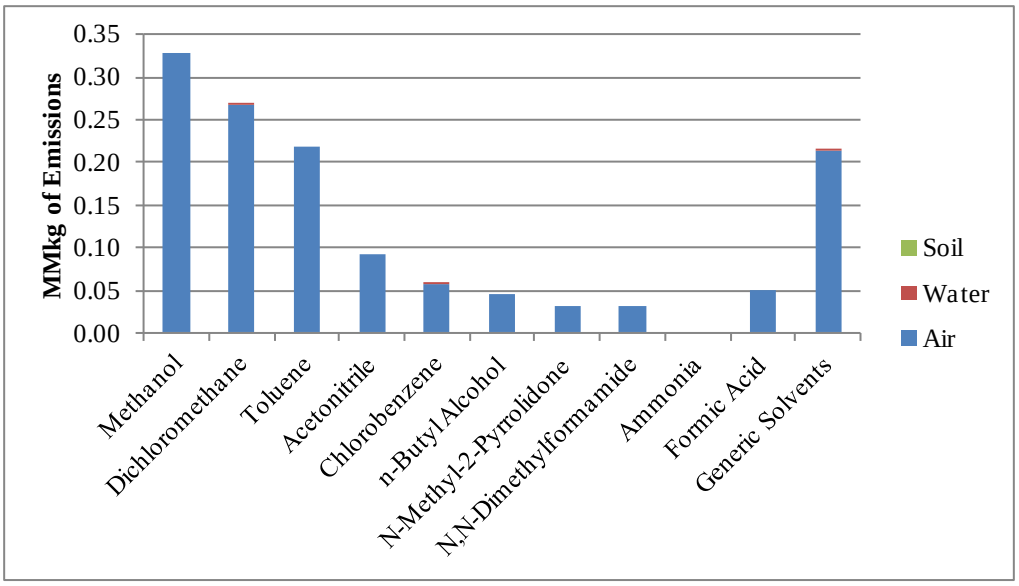

Figure 13. Emissions from the Incineration of TRI Solvents for an Average Pharmaceutical Facility.

The total life-cycle emissions for this facility are displayed in Table 8 and Figure 14.

Table 8. Total Life Cycle Emissions from the TRI Solvents for an Average Pharmaceutical Facility.

	Total Waste Managed	**Raw**	**Air**	**Water**	**Soil**	**Total**
	MM kg	**MM kg**	**MM kg**	**MM kg**	**MM kg**	**MM kg**
Methanol	0.17	0.16	0.44	1.09E-03	2.17E-05	0.44
Dichloromethane	0.09	0.46	0.49	3.10E-02	2.28E-07	0.52
Toluene	0.06	0.09	0.30	2.50E-04	2.24E-08	0.30
Acetonitrile	0.04	0.07	0.18	6.21E-03	2.92E-05	0.18
Chlorobenzene	0.02	0.28	0.31	2.74E-02	9.36E-06	0.34
n-Butyl Alcohol	0.02	0.04	0.08	4.83E-04	6.67E-06	0.08
N-Methyl-2-Pyrrolidone	0.02	0.05	0.10	5.03E-03	2.59E-05	0.11
N,N-Dimethylformamide	0.02	0.03	0.06	6.36E-03	3.73E-05	0.07
Ammonia	0.02	0.02	0.03	5.60E-04	2.02E-05	0.03
Formic Acid	0.01	0.03	0.08	1.35E-03	3.50E-05	0.09
Generic Solvents	0.10	0.28	0.39	1.18E-02	1.60E-05	0.40
Total	**0.58**	**1.52**	**2.46**	**9.16E-02**	**2.01E-04**	**2.55**

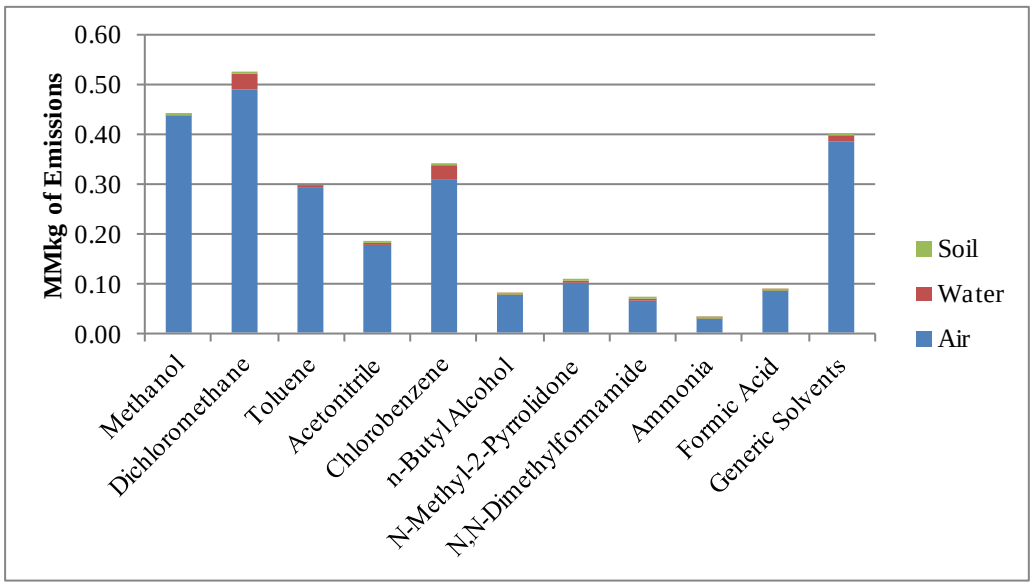

Figure 14. Total Life Cycle Emissions from the TRI Solvents for an Average Pharmaceutical Facility.

As can be seen, the total amount of waste from the average pharmaceutical plant is 580,000 kg. This equates to 2,550,000 kg of total life cycle emissions, 1,210,000 kg of emissions from solvent manufacture and 1,340,000 kg of emissions from incineration. This correlates to 75% of the total emissions, with the remainder belonging to in-process emissions.[14] When this is taken into consideration, a single pharmaceutical facility produces 3,400,000 kg of life cycle emissions. The emissions profile for a hypothetical "average" single pharmaceutical industry is displayed in Figure 15.

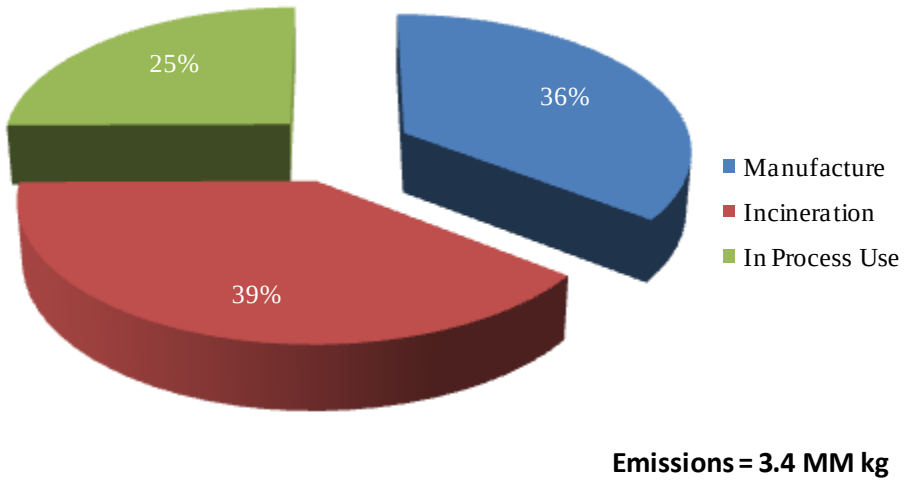

Figure 15. Emissions Profile for a Single Pharmaceutical Facility.

By using three basic green engineering techniques, solvent recovery, "green" solvent selection, and telescoping these emissions may be significantly reduced.

Solvent recovery has been thoroughly discussed in relation to the TRI. To demonstrate the potential emissions reductions of a solvent recovery system in a pharmaceutical plant, the above "average pharmaceutical facility" was considered. Assuming that 80% of solvents are recovered and recycled back into the process, an 80% reduction in the emissions from both manufacture and incineration can be expected. This results in total life cycle emissions for an average pharmaceutical facility of 1,360,000 kg of emissions – 24,200 kg of emissions from solvent manufacture, 26,800 kg of emissions from incineration, and 85,000 kg of emissions from in-process use. This is displayed in Figure 16.

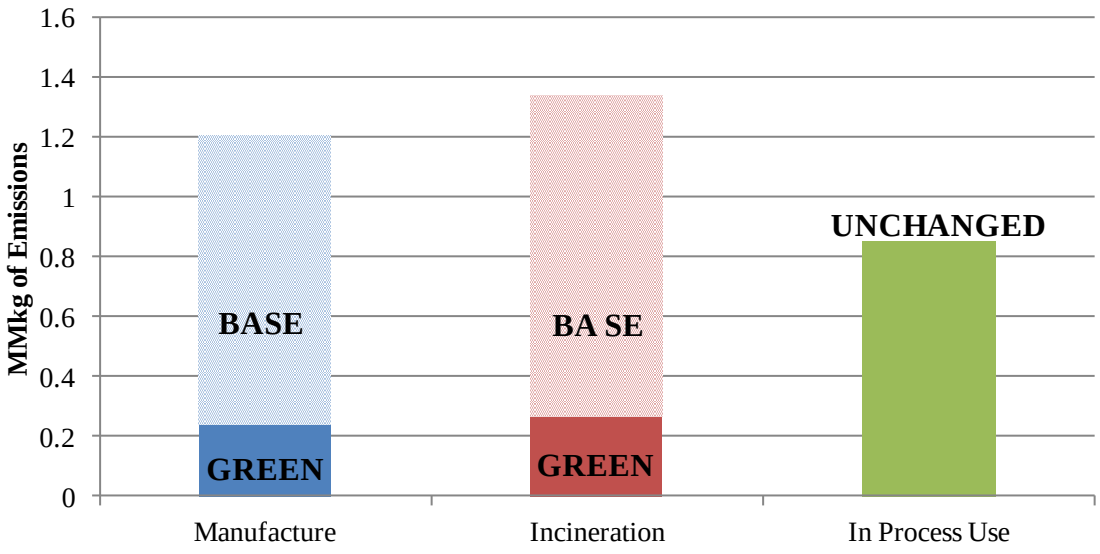

Figure 16. Solvent Recovery Scenario for an Average Pharmaceutical Facility Versus the Base Case.

In Figure 16, "Base" refers to the base case scenario for the average pharmaceutical facility and "Green" refers to the solvent recovery scenario.

A second method for reducing the emissions of an average pharmaceutical facility is by selecting a "green" solvent. This means that a solvent used in a pharmaceutical process is replaced by a solvent that has a lesser impact on the environment, i.e. it has lower emissions from manufacture, lower emissions from incineration, and/or a smaller mass of the "green" solvent is required to achieve the same effects as using the original solvent. To model a decrease in the emissions of a pharmaceutical facility be selecting "greener" solvents, a ratio of the emissions of "green" solvents to other solvents was developed. The top 10 TRI solvents, discussed previously, were split into two categories. The five "greenest" solvents – those with the lowest emissions from manufacture and incineration – were grouped together as well as the five least "green" solvents. The emissions per kg

of solvent for manufacture of the five greenest solvents was averaged. This was divided by the average of the emissions per kg of solvent for manufacture of the five least green solvents. The same process was used to determine a ratio for the kg of emissions for incineration of green solvents versus environmentally unfavorable solvents. The emissions from solvent manufacture for the average pharmaceutical facility were multiplied by the first ratio to determine the reduction of emissions from solvent manufacture if a facility replaced a solvent with a "green" solvent. The green solvents displayed a ratio of approximately 33% of the emissions from manufacture of the environmentally unfavorable solvents. The emissions from incineration were multiplied by the second ratio to determine the reduction of emissions from incineration if a facility replaced a solvent with a "green" solvent. The green solvents displayed a ratio of approximately 80% of the emissions from incineration of the environmentally unfavorable solvents. This resulted in 392,000 kg of emissions from solvent manufacture and 1,063,000 kg of emissions from incineration. The emissions from in-process use remained unchanged. The total emissions from an average pharmaceutical facility employing "green" solvents is 2,310,000 kg, a 32% reduction. This is displayed in Figure 17.

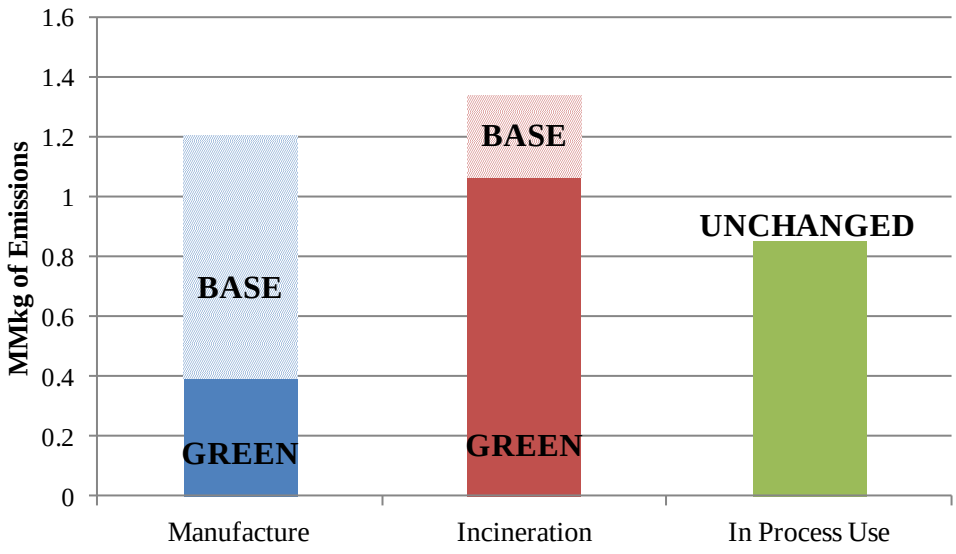

Figure 17. "Green" Solvent Scenario for an Average Pharmaceutical Facility Versus the Base Case.

In Figure 17, "Base" refers to the base case scenario for the average pharmaceutical facility and "Green" refers to the "green" solvent scenario.

A third method for reducing the emissions of a pharmaceutical facility is by "telescoping." Telescoping involves reducing the number of steps in a process. For example, a pharmaceutical production process may require a series of three separation steps, each employing a different unit operation. By reducing this to two steps, one may expect to reduce the emissions of the pharmaceutical process. In the "average pharmaceutical facility" model, telescoping was applied, assuming that the facility employed a multistep process and reduced the number of necessary unit operations by one-third. This was then assumed to correlate to a 33% reduction in emissions from solvent manufacture, incineration, and in-process use. This results in total life cycle emissions for an average pharmaceutical facility of 2,245,000 kg of emissions – 796,000

kg of emissions from solvent manufacture, 885,000 kg of emissions from incineration, and 564,000 kg of emissions from in-process use. This is displayed in Figure 18.

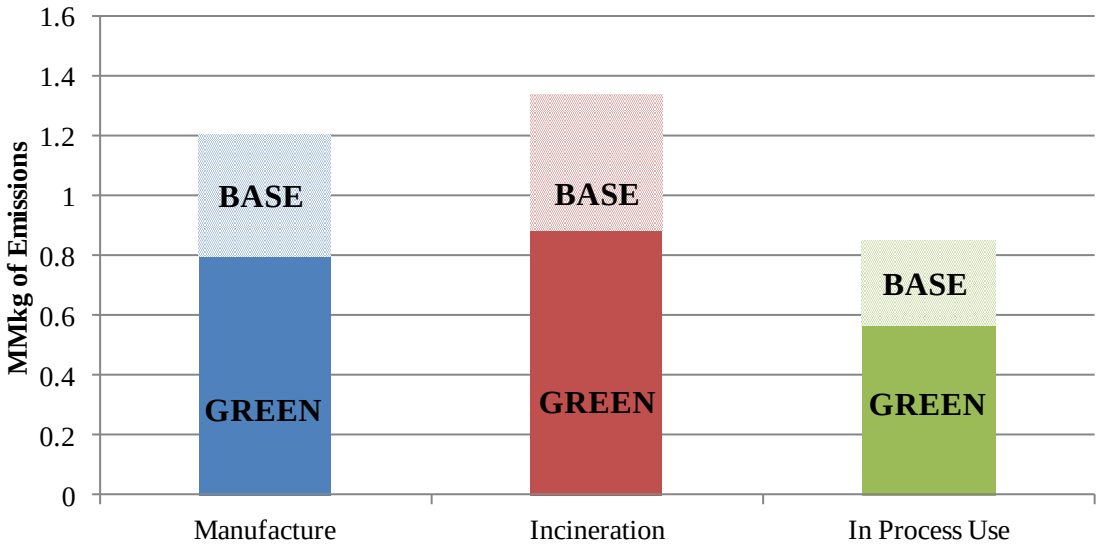

Figure 18. Telescoping Scenario for an Average Pharmaceutical Facility Versus the Base Case.

In Figure 18, “Base” refers to the base case scenario for the average pharmaceutical facility and “Green” refers to the telescoping scenario.

A final green pharmaceutical process improvement was modeled. In this process, all three previously discussed green engineering options were applied. By utilizing all three process improvements, the maximum emissions reductions may be expected. The initial emissions from manufacture and incineration of solvent waste of the average pharmaceutical facility were reduced by 80% to simulate implementation of a solvent recovery process. These emissions were then further reduced, assuming that environmentally unfriendly solvents were replaced by "greener" solvents, as described

earlier. Finally, these emissions were reduced by 33%, assuming that telescoping allowed a reduction of 33% of the total unit processes employed in the pharmaceutical production process. This resulted in a reduction of the total life cycle emissions of the pharmaceutical facility of 78%, or 2,650,000 kg of emissions, to a total of 756,000 kg of emissions per year. Emissions from solvent manufacture were reduced by 1,150,000 kg/year to a total of 51,800 kg of emissions per year. Emissions from incineration were reduced by 1,200,000 kg/year to a total of 140,000 kg of emissions per year. Emissions from in-process use were reduced by 295,000 kg/year to a total of 564,000 kg of emissions per year. This is displayed in Figure 19.

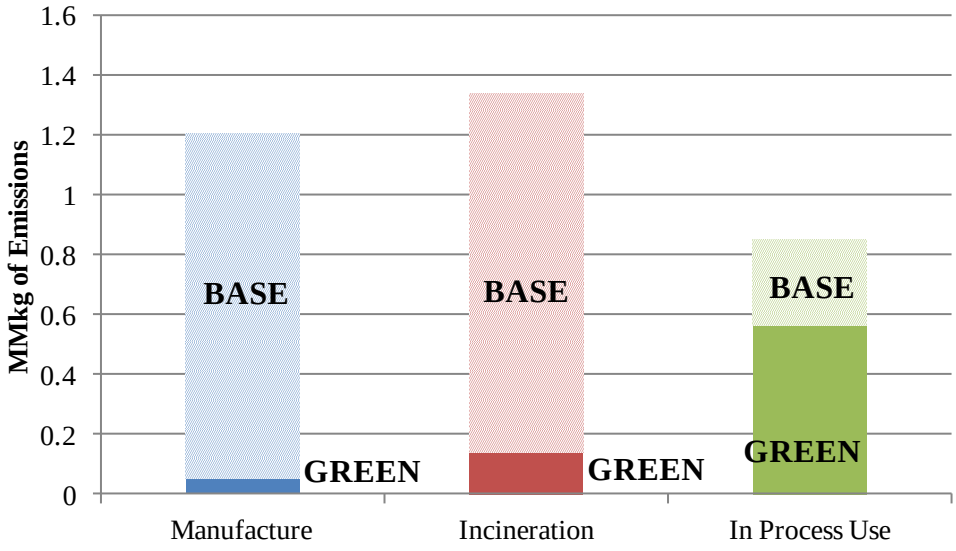

Figure 19. Scenario Using All Three Green Process Improvements for an Average Pharmaceutical Facility Versus the Base Case.

In Figure 19, "Base" refers to the base case scenario for the average pharmaceutical facility and "Green" refers to the scenario employing all three green process improvements.

2.4. Comparison of Solvent Life Cycle Emission Routes*

The general life cycle of a solvent includes its production, in-process use, and waste treatment. The environmental effects of solvent production and waste treatment are often overlooked; however, these contribute significantly to the life cycle emissions for the production of an API. A basic flow chart of the life cycle emissions of a solvent can be found in Figure 20.

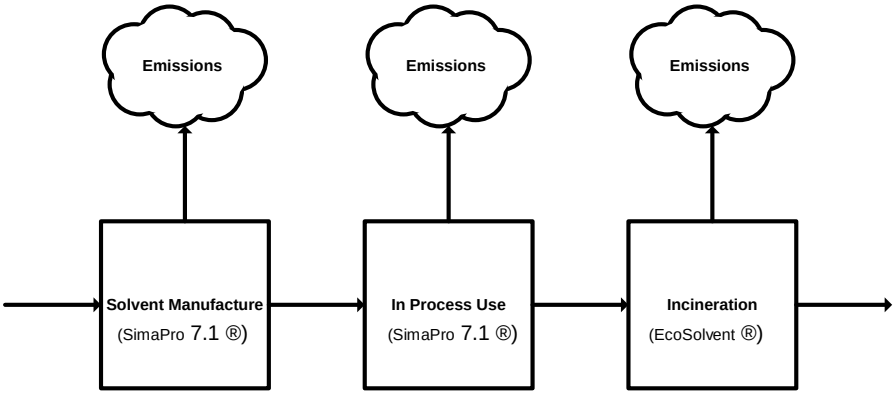

Figure 20. Basic Flow Chart of Solvent Life Cycle and Associated Emissions.

A life cycle assessment has been performed on a variety of common solvents, using EcoSolvent® (Safety and Environmental Group, Zurich, Switzerland) and SimaPro 7.1® software packages. In order to demonstrate the environmental effect of solvent use on a broader scale, in-process emissions were neglected. In the preliminary analysis, these emissions were neglected based on the assumption that no solvent was to be consumed during use and that in-process emissions, such as fugitive emissions

* Reproduced by permission of the Royal Society of Chemistry: http://pubs.rsc.org/en/Content/ArticleLanding/2010/GC/c003666h

and emissions due to pumping, mixing, and heating, are negligible in comparison to the emissions from solvent production and waste treatment. In-process emissions will be discussed in further detail in the following case studies. It was assumed that no solvent was recovered and that all solvent waste was treated by incineration. It was also assumed that energy was recovered during incineration by recovering heat generated while incinerating waste by steam production. This was used to offset CO_2 waste and energy usage by decreasing the amount of energy required to manufacture solvents and to produce steam. Incineration was assumed to be carried out in-house. Each life cycle inventory was developed on a 1 kg of solvent basis. Table 9 displays a summary of the life cycle assessment results for the production of ten commonly used organic solvents. Included in Table 9 is an analysis for a "generic solvent," which is defined in SimaPro 7.1® and is an average of the solvents in the SimaPro 7.1® database. The Cumulative Energy Demand (CED) for the production of these ten solvents was calculated using SimaPro 7.1®. The CED is the overall energy requirement for the life cycle of a component as defined by the life cycle boundaries set by the analysis. This may include the energy from production, use, and disposal.[15] In this instance, the boundaries were defined as the cradle-to-gate life cycle for the manufacture of a solvent. The air, water, and soil emissions listed in Table 9 are defined as the mass of wastes released to air, water, or soil, respectively. The mass of water in the raw materials is not included in the values listed in Table 9, as SimaPro 7.1® does not differentiate between process water and reaction water. Table 10 displays the water usage associated with the production of 1 kg of each of the solvents in Table 9. As it can be seen, the required process water, turbine water, and cooling

water are nearly tenfold higher for THF than any other solvent listed. The organic solvent data was compared to the life cycle assessment for the production of 1 kg of a variety of non-organic solvent commodity chemicals.

Table 9. Life Cycle Analysis for the Production of 1 kg of Various Organic Solvents.

		Emissions					
	Raw[a]	Air	Water	Soil	CO_2	Total	CED
	(kg)	(kg)	(kg)	(kg)	(kg)	(kg)	MJ-Eq
Acetone	1.53E+00	1.83E+00	2.56E-02	7.23E-07	1.80E+00	1.86E+00	6.73E+01
Acetonitrile	1.54E+00	1.97E+00	1.44E-01	6.80E-04	1.95E+00	2.12E+00	6.15E+01
Diethyl Ether	1.17E+00	1.09E+00	1.66E-02	1.95E-04	1.08E+00	1.11E+00	4.80E+01
Ethanol	1.17E+00	1.09E+00	1.66E-02	2.00E-04	1.08E+00	1.11E+00	4.80E+01
Hexane	1.59E+00	8.84E-01	1.75E-01	5.93E-03	8.55E-01	1.06E+00	6.17E+01
IPA	1.55E+00	1.66E+00	5.42E-01	3.18E-04	1.63E+00	2.20E+00	6.32E+01
MeOH	8.34E-01	6.47E-01	6.39E-03	1.27E-04	6.40E-01	6.54E-01	3.76E+01
THF	4.01E+00	5.52E+00	1.26E-01	2.31E-03	5.46E+00	5.65E+00	1.28E+02
Toluene	1.36E+00	1.21E+00	3.87E-03	3.46E-07	1.19E+00	1.21E+00	6.34E+01
Generic Solvent	1.74E+00	1.78E+00	1.22E-01	1.66E-04	1.75E+00	1.91E+00	6.51E+01

[a] Mass of raw materials consumed excluding water

Table 10. Water Requirements for the Production of 1 kg of Various Organic Solvents.

	Cooling	Turbine	Fresh	Saline	Unspecified[a]
	(kg)	(kg)	(kg)	(kg)	(kg)
Acetone	7.85E+01	5.57E+00	1.11E-01	3.39E-01	3.11E+00
Acetonitrile	2.41E+02	1.61E+03	5.22E+00	5.92E-01	3.45E+00
Diethyl Ether	3.16E+01	8.14E+02	1.31E+00	2.82E-01	1.46E+00
Ethanol	3.17E+01	8.15E+02	1.79E+00	2.82E-01	1.46E+00
Hexane	3.53E+01	1.68E+03	2.33E+00	1.50E+00	3.62E+00
IPA	4.91E+01	1.49E+03	4.09E+00	5.19E-01	1.35E+01
MeOH	1.03E+01	5.42E+02	1.62E+00	4.55E-01	2.34E-01
THF	7.09E+02	1.51E+04	1.67E+01	2.94E+00	4.41E+00
Toluene	8.97E+01	2.70E+00	2.05E-01	6.06E-01	8.25E-01
Generic Solvent	8.13E+01	1.41E+03	1.94E+00	5.68E-01	9.69E+00

[a] Mass of water of unspecified origin

Table 11. Life Cycle Analysis for the Production of 1 kg of Various Commodity Chemicals.

		Emissions					
	Raw[a]	Air	Water	Soil	CO_2	Total	CED
	(kg)	(kg)	(kg)	(kg)	(kg)	(kg)	MJ-Eq
Ammonia	6.24E-01	2.03E+00	4.55E-02	1.83E-03	2.02E+00	2.08E+00	4.23E+01
Sulfuric Acid	1.37E-01	1.54E-01	9.12E-03	1.54E-04	1.35E-01	1.63E-01	2.36E+00
TiO_2	5.01E+00	4.33E+00	4.33E-01	2.54E-03	4.26E+00	4.77E+00	8.86E+01
[a] Mass of raw materials consumed excluding water							

Table 12. Water Requirements for the Production of 1 kg of Various Commodity Chemicals.

	Cooling	Turbine	Fresh	Saline	Unspecified[a]
	(kg)	(kg)	(kg)	(kg)	(kg)
Ammonia	5.47E+00	1.34E+03	1.44E+00	9.70E-01	2.85E+00
Sulfuric Acid	2.26E+00	4.65E+02	5.64E-01	7.05E-02	4.92E+01
TiO_2	7.89E+01	1.15E+04	1.19E+01	2.64E+00	5.94E+01
[a] Mass of water of unspecified origin					

A statistical analysis on production emissions comparing the two sets of data was performed using StatGraphics Plus 5.1® (StatPoint Technologies, Inc, Warrenton, Virginia). A sample of the results for the commodity chemicals is displayed Table 11 and Table 12.

It was found that the only statistical difference between the production of 1 kg of an organic solvent and 1 kg of a commodity chemical was in the CED. This is supported by the notion that over half of organic chemicals require from 0 to 4 MJ of energy for manufacture as opposed to inorganic chemicals which range from -1 to 3 MJ of energy.[16] THF was also determined to have a significantly higher CED than the other organic solvents tested. This was attributed to the fact that the purification of THF poses unique difficulties, including a variety of severe azeotropes.[17] Although many of the other solvents tested also display azeotropes in a variety of mixtures, the azeotrope between THF and water is more energy intensive to overcome. This is supported by the fact that pressure swing distillation is typically employed in industry to separate THF and water mixtures.[18] The larger CED can also be associated with the smaller industrial demand and thus smaller production quantities of THF in comparison with other solvents. Considering the comparison of solvents to commodity chemicals, it may be concluded that there is no difference in the mass of waste attributed to the production of 1 kg of an organic solvent or 1 kg of commodity chemical; however, there is a significantly larger energy demand for the production of organic solvents.

The significant effect of solvent reduction is, therefore, attributed to both the larger CED and the difference in use of the chemicals. Commodity chemicals are commonly

used to adjust pH, catalyze reactions, and serve as the reactants in chemical processes. In the modern pharmaceutical industry, multiple steps are employed to produce an API. During each of these steps, large quantities of organic solvents are in use but do not enter into reaction stoichiometry. As a result, 80 to 90% of the total mass used in the production of an API may be attributed to solvents.[12] These solvents are disposed of rather than recycled, creating a massive environmental deficit from solvent production and disposal. For many commodity chemicals, the chemical inventory cannot be reduced without changing reaction pathways, stoichiometries, and catalysis. For solvents, however, implementation of a solvent recovery system can significantly decrease the chemical inventory and required raw materials thus decreasing the environmental footprint.

The life cycle inventories for the production of organic solvents display similar distributions of emissions. Since the subsequent case studies involve the solvents IPA, MeOH, and THF, the life cycle inventories of these solvents will be presented and discussed.

Figure 21 displays the distribution of emissions to air and water for the manufacture of each of these solvents. Emissions to soil are too low to be appreciated in

Figure 21 and are thus omitted. The mass of total emissions for each solvent is displayed below each graph. As it can be seen, emissions to air constitute the majority in each case. IPA is the only solvent to display a significant amount of emissions to water, approximately 25% compared to 2.2% for THF and 1.0% for MeOH. This may be attributed to the process used to produce IPA. Currently, IPA is commercially produced through the hydration of propylene in the presence of a highly concentrated

sulfuric acid solution. This requires large amounts of reaction water, often employing propylene as the limiting reagent. It is also notable that a solution of 50% sulfuric acid and water has 5.5% of total emissions to water, contributing to the elevated emissions to water for the production of IPA. Other commercial methods for the production of IPA include hydration in gas/liquid mixed phase using strongly acidic ion exchange resins, gas phase hydration using strongly acidic solid acid catalysts, and gas phase hydration by catalysts carrying hetero-poly or inorganic acids.[19] All of these methods display similar issues with elevated emissions to water. None of the solvents display an appreciable amount of emissions to soil in comparison to air and water. Figure 22 displays the composition of the air emissions stream for the production of each of these solvents, as well as the mass of CO_2 emitted during production.

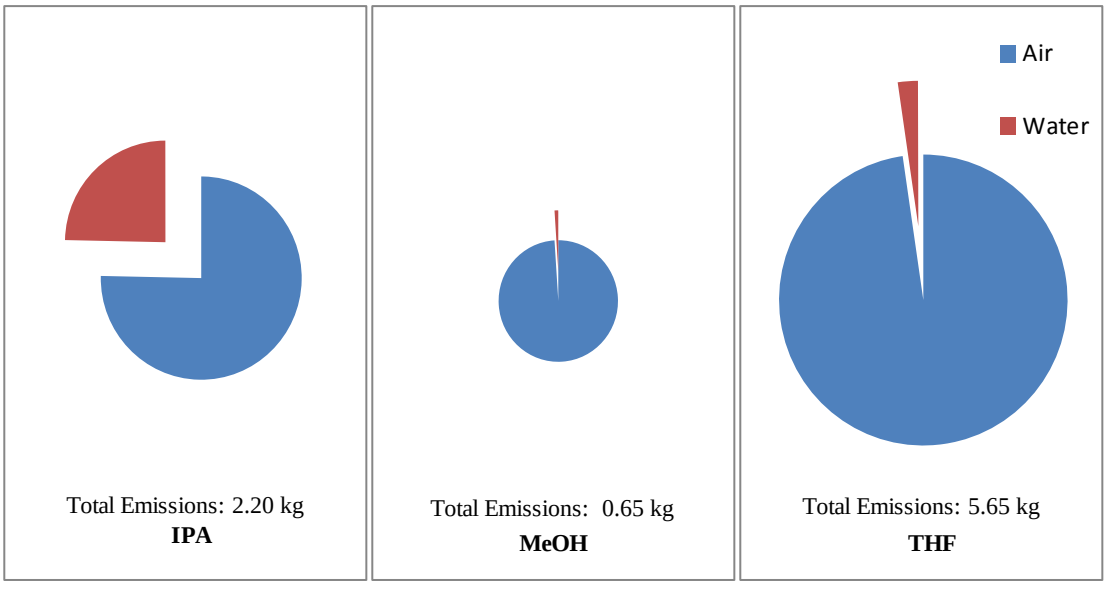

Figure 21. Waste Distribution for Production of 1 kg of IPA, MeOH, and THF.

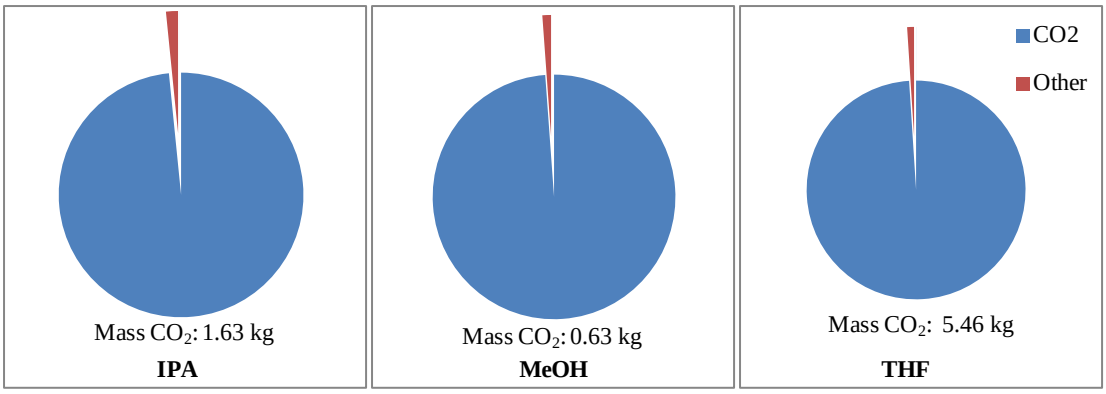

Figure 22. Distribution of Emissions to Air for Production of 1 kg of IPA, MeOH, and THF.

Figure 22 demonstrates that carbon dioxide constitutes the vast majority of emissions to air for each of these solvents, between 96 and 99%. This is attributed to combustion reactions within the production processes and transportation to and from the manufacturing plant. This is in agreement with a study done in the Netherlands that found that the majority of CO_2 emissions came from a small number of manufacturing plants. Among these plants, the refining, petrochemical production and chemical production sectors were the first, second, and third largest offenders, respectively. These emissions were directly attributed to combustion reactions.[20] A study conducted in the United States associates approximately 97% of air emissions from transportation to CO_2.[11] This exemplifies the high proportion of CO_2 emissions that occur in chemical manufacture as a direct result of combustion reactions.

Figure 22 displays that the largest portion of emissions from the production of 1 kg of solvent is attributed to carbon dioxide. This large proportion of carbon dioxide is attributed to the energy for raw material acquisition, production, and transportation of

the solvent. Therefore, reducing the amount of fresh solvent required to run a process can significantly reduce the carbon footprint of that process. It has also been determined that there are specific anomalies in the pollution profiles of particular solvents. IPA displays a significant amount of emissions to water as a result of industrial production practices specific to that solvent. Similarly, the production of THF displays a statistically larger CED than other solvents studied. THF also displays a significantly larger associated waste, resulting from the increased energy requirements. Thus, it may be concluded that the emissions from the manufacture of organic solvents is unique only in the CED, although anomalies specific to production of particular organic solvents do exist.

Table 13. CO_2 and Energy Demands/Credits Associated with the Incineration of 1 kg of Various Solvents.

	CO_2 Incin.	CO_2 Offset	CED Solvent. Prod.	Total CED Offset
	(kg CO_2)	(kg CO_2-Eq)	(MJ-Eq)	(MJ-Eq)
Acetone	2.55E+00	5.74E-01	6.73E+01	3.43E+01
Acetonitrile	3.31E+00	5.18E-01	6.15E+01	3.27E+01
Diethyl Ether	1.47E+00	3.63E-01	4.80E+01	8.56E+00
Ethanol	1.40E+00	2.90E-01	4.80E+01	1.69E+01
Hexane	1.17E+00	3.46E-01	6.17E+01	7.89E+00
IPA	2.00E+00	3.40E-01	6.32E+01	2.68E+01
MeOH	9.40E-01	3.40E-01	3.76E+01	1.57E+01
THF	8.36E+00	5.44E-01	1.28E+02	9.08E+01
Toluene	2.43E+00	9.10E-01	6.34E+01	1.50E+01

The carbon and greenhouse gas (GHG) emissions associated with incinerating each of these solvents also plays a crucial role in the life cycle emissions of these solvents. Studies have shown that roughly half of the GHG emissions and 40% of the energy

requirements of the life cycle of an API can be attributed to the incineration of solvent waste.[11] In order to demonstrate the impact on pollution from the incineration of solvent waste, two environmental metrics will be employed. These metrics are the total carbon emissions directly released from the incineration of a solvent (CO_2 Incin.) and the CED resulting from solvent production (CED Solv. Prod.). Heat energy, converted into steam and electricity, may be recovered from the incineration process. Thus, an additional two metrics will be employed, the adjusted amount of CO_2 emissions released by the incineration of a solvent (CO_2 offset) and the adjusted CED for the production of a solvent (Total CED offset). These two metrics take into consideration the CO_2 released and the energy required with recovery of all energy released during solvent incineration. These metrics are given in units of CO_2-Eq and MJ-Eq, respectively. These units represent the equivalent amount of CO_2 and the equivalent amount of energy released and required, respectively. Table 13 displays these metrics for the previously discussed solvents. Table 13 demonstrates that there is a significant amount of CO_2 released and energy consumed during the incineration of 1 kg of solvent, even when considering the use of steam generation for heating and energy production to offset life cycle CO_2 emissions. This is most notable for the life cycle of THF, displaying over double the CO_2 emissions and nearly double the energy demand of other solvents.

This analysis shows that large quantities of emissions are released during manufacture and incineration of organic solvents. Although commodity chemicals produce a similar quantity and distribution of emissions during manufacture, in process consumption of the chemical limits the quantity of the chemical that may be recycled.

The mass intensity of solvents versus that of reagents within the pharmaceutical industry also makes solvent recovery an environmentally valuable pathway. As previously stated, solvents account for approximately 80% to 90% of the total mass involved in a pharmaceutical production process.[12] It has also been determined that there is a larger CED for organic solvents than there is for commodity chemicals. Less widely used chemicals were also determined to produce a much larger amount of emissions, as in the case of THF. This may be attributed to comparatively smaller production quantities, as well as particularly problematic azeotropes in the case of THF. Although many solvents display azeotropes, the azeotrope encountered when separating THF and water is particularly energy intensive. It was also determined that the majority of emissions are released to air, mostly as CO_2. Through solvent recovery, the amount of required fresh solvent, solvent production emissions, and incineration emissions may all be significantly reduced. This in turn will decrease the environmental and economic burden of the process.[13]

Because of wide scale use in the process industry, LCA will be applied to four pharmaceutical case studies. These case studies will be used to demonstrate how solvent recovery may reduce the environmental impact of a process as well as how the use of LCA can clarify life cycle emissions for pharmaceutical solvent use. This may in turn be employed to determine greener options for solvent use involving solvent recovery or reduction.

Chapter 3

Case Studies of the Application of LCA in the Pharmaceutical Industry

Portions of this chapter are taken directly from "LCA approach to the analysis of solvent waste issues in the pharmaceutical industry" (Raymond, M.J., C.S. Slater, and M.J. Savelski. "LCA approach to the analysis of solvent waste issues in the pharmaceutical industry." *International Journal of Green Chemistry*. 12 (2010): 1826-1834) with the permission of Sarah Ruthven and Gill Cockhead.[3]

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3.1. Description of Case Studies*

Three case studies were examined in which the use of solvents in the production of an API was reduced by implementation of greener processes. Focus was directed specifically to the implications of adding solvent recovery and reduction systems to reduce the overall environmental footprint of the pharmaceutical process. A cradle-to-grave approach was used to determine the amount of waste generated by solvent production, in-process emissions, and disposal of process wastes. The first case study considers the effects of recovering solvents within a pilot scale facility for the production of a new oncology drug being developed by Bristol-Myers Squibb (BMS). The second case study considers the effects of recovering solvents within a commercial facility for the production of celecoxib, the active ingredient in Pfizer's

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Celebrex®, a non-steroidal anti-inflammatory drug (NSAID).[21] The third case study considers the effects of recovering solvents within a process for the production of a synthetic pharmaceutical intermediate. The final API is to be used for the treatment of hypertension. The fourth case study considers the effects of recovering solvents from the small volume lot production of a compound referred to here as Pfizer API "Z", the active ingredient in a Pfizer drug. Due to confidentiality, details on this drug cannot be disclosed. Following is a more detailed description of each case study. Details of the design of the greener solvent recovery and/or reduction systems are not presented in this paper and are available elsewhere.[22,23,24,25,26,27]

3.1.1. Oncology Drug in Clinical Trials – Bristol-Myers Squibb*

The process examined by this case study is for the pilot scale production of an oncology drug in clinical trials. During one step, a mixture of THF, water, and a pharmaceutical intermediate must be dehydrated. As discussed previously, THF displays an azeotrope with water at 95.7% water at standard temperature and pressure (STP). In order to dehydrate the mixture, the current process employs a constant volume distillation (CVD). CVD requires a large amount of an entrainer to be added to the separation. The entrainer used in this process is THF, resulting in an increased amount of THF waste. A proposal was made for the addition of a pervaporation (PV) system to the current CVD. The PV system would dehydrate the THF to the desired level and allow it to be recycled back into the process. The addition would decrease the amount of entrainer required thereby reducing the amount of virgin THF necessary and the amount of THF waste to be incinerated.[22,23,25,26]

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3.1.2. Celecoxib – Pfizer*

The commercial scale production of celecoxib, the API in Pfizer's arthritis drug Celecoxib™, was studied to determine a green alternative for the handling of solvent waste. During the final crystallization and production step, large quantities of IPA and water are employed and constitute the majority of the waste stream. Separation of the IPA and water mixture is complicated by a multitude of impurities in the waste stream, including dissolved solids (or Total Dissolved Solids, TDS), methanol, and ethanol. In addition, a variety of azeotropes arise between the IPA, methanol, ethanol, and water. Currently, wastes are incinerated at an off-site disposal facility. Pfizer suggested improving the process by employing existing capital assets. The goal of the case study was to configure equipment already existing at the facility to recover and recycle the IPA from the waste stream. An analysis on an array of designs demonstrated that it was necessary to employ distillation and PV to produce IPA at a high enough purity to be recycled. Based upon production flow rates and the available equipment sizes, a distillation-PV-distillation system was deemed necessary to achieve the required 99% pure IPA. Although several of the waste streams could be treated by the PV system, one waste stream containing IPA and the highest concentration of TDS was distilled once to concentrate the stream and then sold as a "generic solvent" to a third party. The remaining IPA waste mixture was sent to the distillation-PV-distillation system. This would allow an in-line recycle of the IPA at the celecoxib production facility. This recycle of IPA and sale of the "generic solvent" would reduce the total amount of virgin solvents required at the celecoxib

production facility and at the third party facility. In addition, the need to incinerate solvent waste from the crystallization and production step would be eliminated.[22,23,24]

3.1.3. Synthetic Intermediate – Novartis*

During the commercial production of a synthetic pharmaceutical intermediate, the crude reaction mixture is produced in a Heck coupling reaction. This mixture contains a significant concentration of Pd. This concentration must be reduced before the intermediate may undergo further isolation. In order to achieve this, the current process employs a batch adsorption with activated carbon as the main adsorbent. Previous research indicated that an adsorbent which is more suitable for fixed bed operation would decrease process wastes. In addition, the vessel must be thoroughly rinsed with organic solvents and aqueous detergent after each adsorption. This produces a large mass of solvent waste, containing mostly MeOH, and solid waste, activated carbon. These wastes must be treated by incineration and disposal, respectively, increasing the environmental footprint of the process. A proposal was made to replace the batch adsorption with a fixed bed adsorber (FBA), in which a synthetic resin would be used as the adsorbent. This would allow for a reduction in the mass of virgin solvent and adsorbent required as well as a reduction in the emissions from disposing of the associated wastes.[27]

3.1.4. Pfizer API "Z" – Pfizer

This case study examines the recovery of solvent waste from small scale production campaigns at a Pfizer facility. A series of potential solvent waste streams were examined and compared for the potential environmental impact of solvent recovery.

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The main stream targeted for solvent recovery was a waste stream from the production of Pfizer API "Z", the API in a Pfizer drug. The recovery process was limited to distillation designed to recover 98% pure solvent for reuse.

3.2. Analysis of Case Studies*

The four case studies were analyzed and compared using a cradle-to-grave life cycle analysis. For each case study, the current in-place process was considered the "base case" for that study. Environmental impacts were calculated considering only the differences between the base case and greener process design alternative in each case study, therefore, emissions from the manufacture of raw materials, unit processes, waste disposal, and other factors which were not affected by the green improvements were not included in the results. Results were calculated in terms of kg of waste per kg of API produced (kg of waste per kg of intermediate produced in the Novartis case study). This was done to simplify the comparison of the processes, as total production amounts varied from pilot to production scale. The total emissions and the distribution of their origins for the four base case scenarios and the four green alternatives are displayed in Figure 23 and Figure 24, respectively. These emissions take into account emissions avoided by selling waste as a generic solvent and from steam and electricity generation during incineration. These values were used to offset the emissions from incineration and disposal of solvent and solid wastes.[22,23,24,25,26,27]

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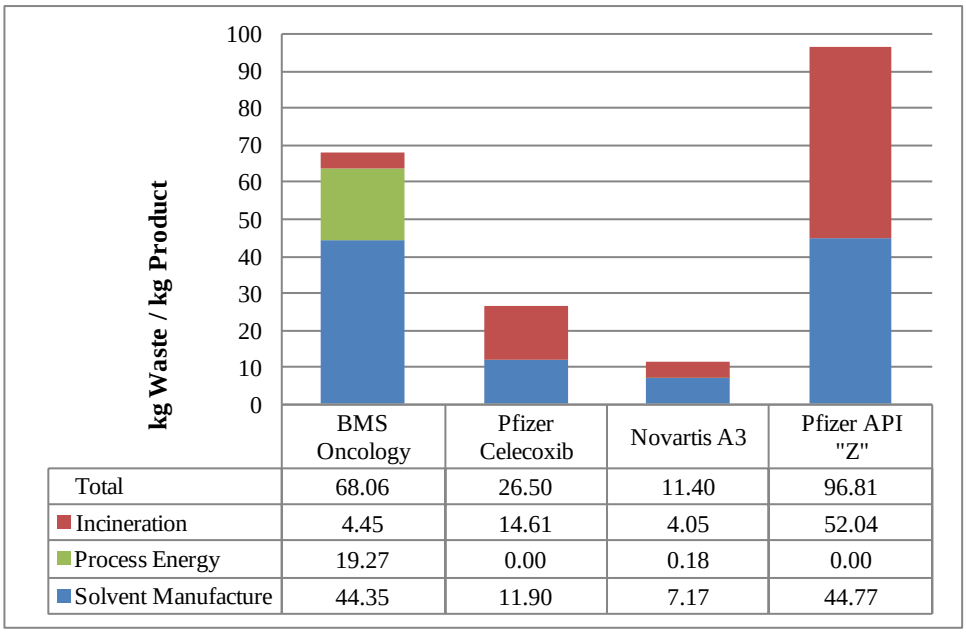
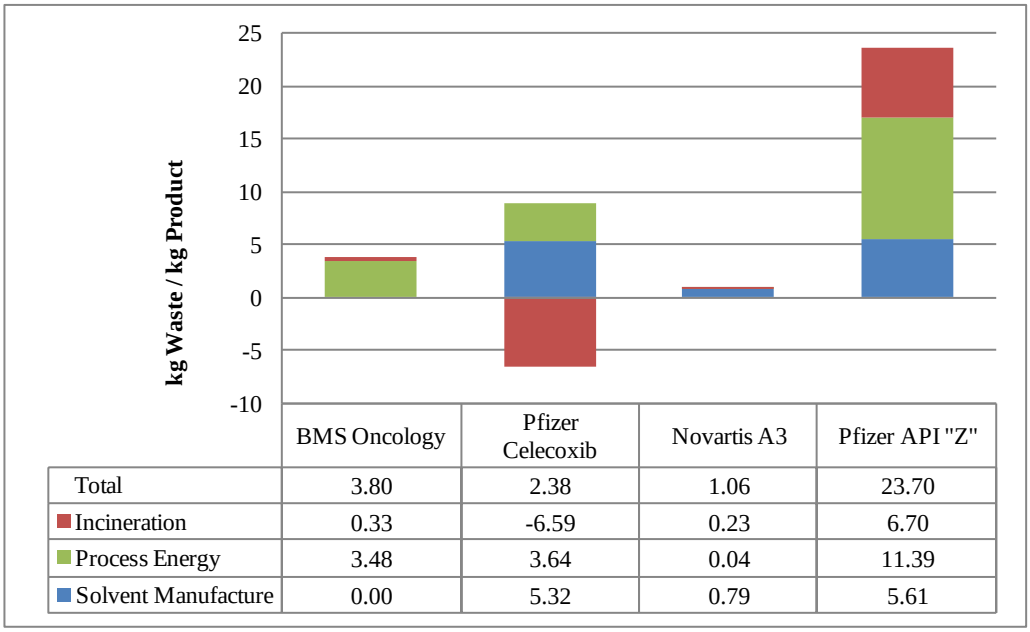


	BMS Oncology	Pfizer Celecoxib	Novartis A3	Pfizer API "Z"
Total	68.06	26.50	11.40	96.81
Incineration	4.45	14.61	4.05	52.04
Process Energy	19.27	0.00	0.18	0.00
Solvent Manufacture	44.35	11.90	7.17	44.77

Figure 23. Total Emissions for Each Base Case Scenario and the Origins of Those Emissions.



	BMS Oncology	Pfizer Celecoxib	Novartis A3	Pfizer API "Z"
Total	3.80	2.38	1.06	23.70
Incineration	0.33	-6.59	0.23	6.70
Process Energy	3.48	3.64	0.04	11.39
Solvent Manufacture	0.00	5.32	0.79	5.61

Figure 24. Total Emissions for Each Green Alternative and the Origins of Those Emissions.

The energy used to operate the solvent recovery and reduction systems was analyzed and the resultant life cycle emissions for its generation were determined. The difference in emissions for the energy of the processes is listed as an emissions source in Figure 23 and Figure 24 and includes the difference in energy requirements for steam and electricity within the API/intermediate production processes with incorporation of the solvent recovery or reduction system. Figure 23 and Figure 24 display the effect of solvent use on emissions within the pharmaceutical manufacturing processes. Emissions are associated with heating, pumping, and recovering solvents and entrainers used in the process. In some instances, the implementation of a solvent recovery system will not affect other process emissions. However, it may actually reduce emissions within the manufacturing process as there is less solvent to be heated and pumped. As stated, all values are calculated comparing the greener alternative process with the base case. For this reason, the Pfizer Celcoxib and Pfizer API "Z" base case scenarios display no emissions from the energy of the process as there was no change in the Celecoxib or Pfizer API "Z" process, only in adding the solvent recovery system, which is shown in Figure 24.[22,23,24] For the BMS case study, the allocation of wastes from the energy of the process was altered significantly. The heat duty required to run the CVD was decreased with the addition of the PV system, reducing the amount of steam required. This was because the need to add and heat an entrainer was avoided. However, the PV system has an associated electrical requirement so there is an increase in the emissions from electricity usage. In essence, the PV system reduces the amount of steam required for the CVD but increases the total amount of electricity

required.[22,23,25,26] Similar differences are observed in the energy of the process for the Novartis case study, resulting from allocation of process electricity. The replacement of batch adsorption with an FBA system actually decreases the amount of energy required as less adsorbent may be used and fewer vessel rinses are required. This difference in energy, however, is insignificant as it represents only 1.34% of the total life cycle emission reduction for the Novartis case study.[27]

Pollution credits are given to the Pfizer Celecoxib proposal for sale of the mother liquor waste. This is displayed as a negative value in Figure 24 and is used to offset the total pollution attributed with the Pfizer Celecoxib case study.[22,23,24]

For these case studies, it is apparent that the reduction in emissions due to solvent manufacture is the most significant source of emission reductions, as can be seen in Figure 23 and Figure 24. It represents 69% of the emission reductions for the BMS case study - 49.4 kg of waste per kg of API produced, 62% of the emission reductions for the Novartis case study - 6.38 kg of waste per kg API, and 54% of the emissions reductions for the Pfizer API "Z" case study - 39.2 kg of waste per kg API. Excluding the emissions avoided by sale of IPA, solvent recovery accounts for 37% of the emission reductions, 6.58 kg of waste per kg API for the Pfizer Celecoxib case study.[22,23,24,25,26,27]

When these emission reductions are coupled with the reduction in emissions due to avoidance of excess solvent waste that must be incinerated, the effect is comparatively more significant. Figure 23 and Figure 24 demonstrate that a considerable proportion of the life cycle emissions for an API are attributed to solvent manufacture and incineration. This accounts for 88%, 75%, and 97% of the emission

reductions in the BMS, Pfizer Celecoxib, and Novartis case studies, respectively. This is attributed to the large amount of emissions resulting from solvent manufacture and incineration, as opposed to the energy of the process. This accounts for 100% of the emissions reductions in the Pfizer API "Z" case study, as the only source of reductions is through solvent recovery and incineration. These proportions are displayed in Figure 25.[22,23,24,25,26,27]

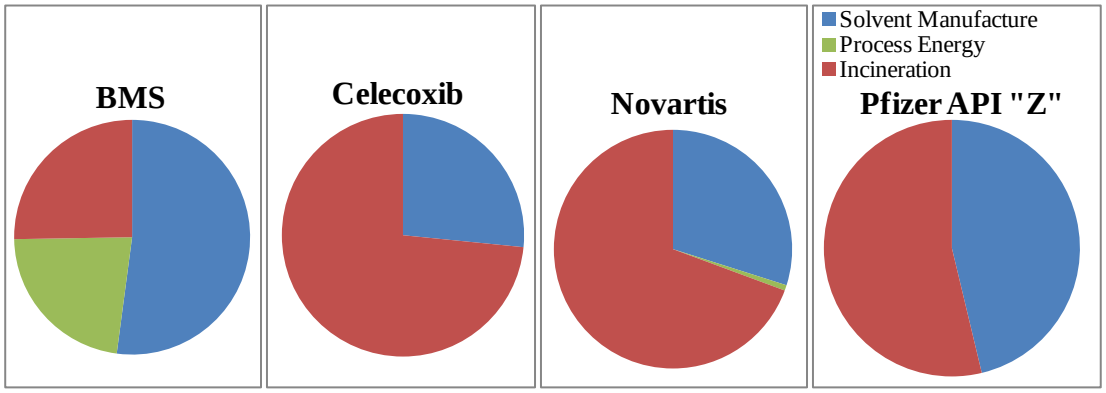
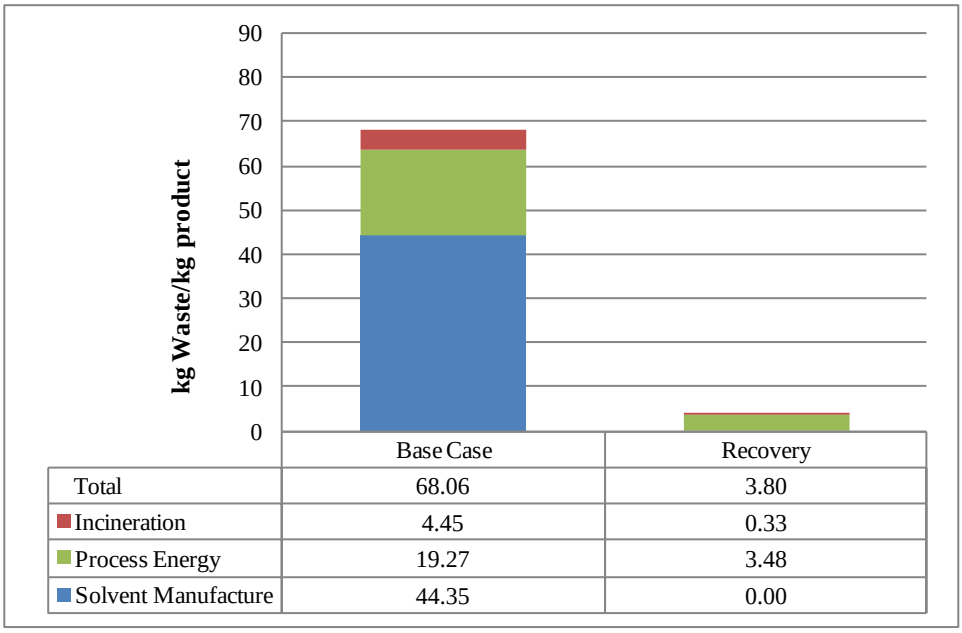


Figure 25. Proportion of Wastes Attributed to Solvent Manufacture, Process Energy, and Waste Incineration for Each Base Case Scenario.

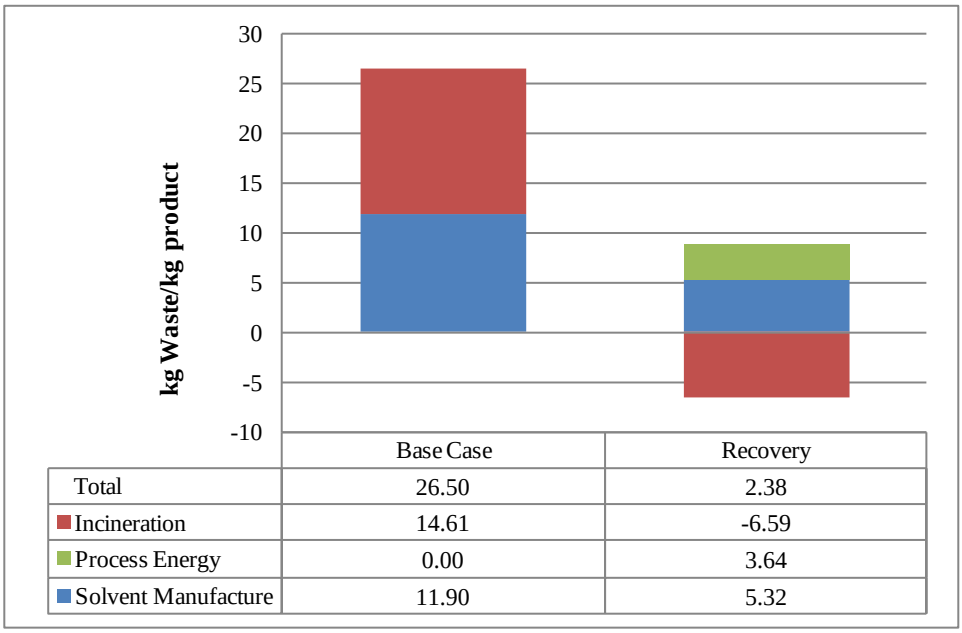
By implementing a solvent recovery or reduction system, over 90% of life cycle emissions from solvent use may be avoided. When considered with the mass intensity of solvents within the pharmaceutical industry, as discussed previously, this is a significant reduction in overall process emissions for the production of an API. Generally, greater than 80% of the raw materials that are employed in the production of an API are solvents. If 90% of the associated emissions may be avoided, an overall reduction of over 70% of the total emissions for the production of an API may be expected.

The overall reduction in emissions for each case study may best be displayed by a direct comparison of each base case with the associated greener process case. This comparison is displayed in Figure 26, Figure 27, Figure 28, and Figure 29.[22,23,24,25,26,27]



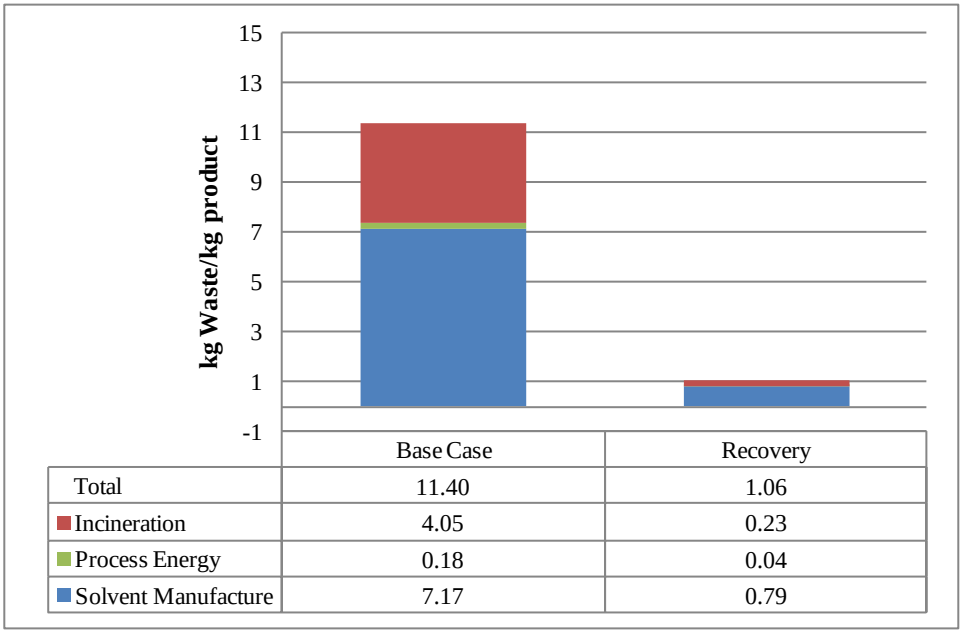
	Base Case	Recovery
Total	68.06	3.80
Incineration	4.45	0.33
Process Energy	19.27	3.48
Solvent Manufacture	44.35	0.00

Figure 26. Comparison of the Base Case and Green Process for the BMS Case Study.



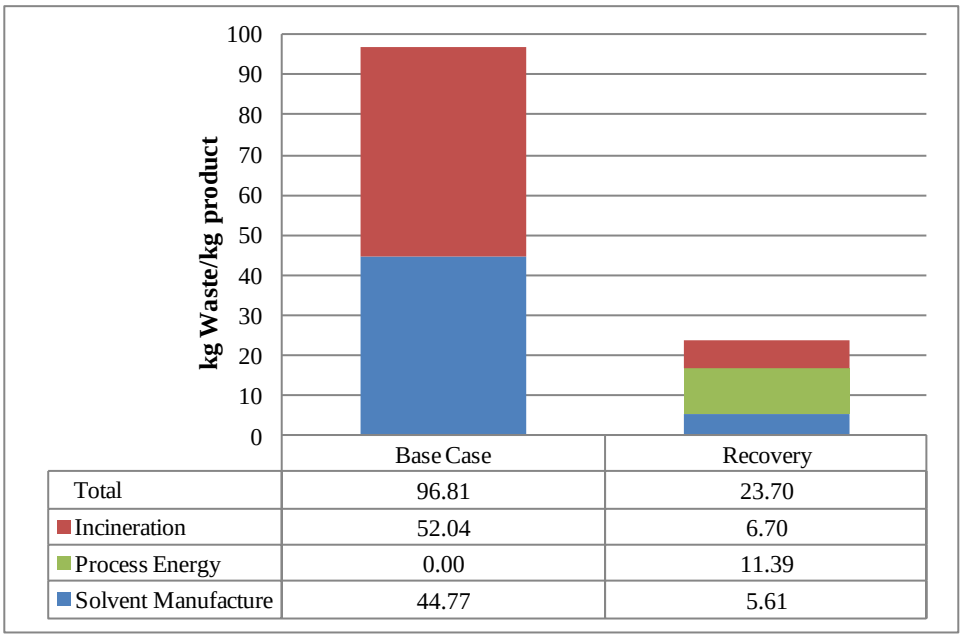
	Base Case	Recovery
Total	26.50	2.38
Incineration	14.61	-6.59
Process Energy	0.00	3.64
Solvent Manufacture	11.90	5.32

Figure 27. Comparison of the Base Case and Green Process for the Pfizer Celecoxib Case Study.



	Base Case	Recovery
Total	11.40	1.06
Incineration	4.05	0.23
Process Energy	0.18	0.04
Solvent Manufacture	7.17	0.79

Figure 28. Comparison of the Base Case and Green Process for the Novartis Case Study.



	Base Case	Recovery
Total	96.81	23.70
Incineration	52.04	6.70
Process Energy	0.00	11.39
Solvent Manufacture	44.77	5.61

Figure 29. Comparison of the Base Case and Green Process for the Pfizer API "Z" Case Study.

Figure 26, Figure 27, Figure 28, and Figure 29 display that there is a large reduction in emissions with the addition of a solvent recovery or reduction system. The BMS case study displays a 94% reduction in overall emissions, equating to a reduction of 64.3 kg of waste per kg of API. Similarly, there is a 91% reduction in overall emissions for both the Pfizer celecoxib and Novartis case studies. This equates to a 24.1 and 10.34 kg of waste per kg of API reduction for the Pfizer and Novartis case studies, respectively.[22,23,24,25,26,27] The Pfizer API "Z" case study displays a 76% reduction in overall emissions, equating to a reduction of 73.11 kg of waste per kg of API.

As it can be seen, the majority of the total emissions are attributed to processes outside of the battery limits of a pharmaceutical production facility. Solvent

manufacture and disposal account for the majority of emissions in all four base case scenarios. If one were to view the environmental implications of solvent recovery within the gate-to-gate perspective, restricting emissions to those within the battery limits of the pharmaceutical manufacturing facility, there is little environmental incentive to implementing a solvent recovery system. However, when the entire life cycle analysis is taken into account, the environmental implications become much more significant.

Chapter 4

Conclusions

Portions of this chapter are taken directly from "LCA approach to the analysis of solvent waste issues in the pharmaceutical industry" (Raymond, M.J., C.S. Slater, and M.J. Savelski. "LCA approach to the analysis of solvent waste issues in the pharmaceutical industry." *International Journal of Green Chemistry*. 12 (2010): 1826-1834) with the permission of Sarah Ruthven and Gill Cockhead.[3]

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The TRI is a powerful tool for reducing the emissions for pharmaceutical facilities. The TRI displays that the pharmaceutical industry has reduced its total emissions from 235 MM kg in 2001 to 85 MM kg in 2008. A closer look at the TRI displays that during this eight year period, the same four chemicals - methanol, toluene, dichloromethane and acetonitrile - have consistently ranked the top four most common pharmaceutical solvents. It also displays that specific solvents attribute a proportionately much larger amount of emissions per kg of solvent. By targeting these common solvents and environmentally unfriendly solvents specifically, one may expect to maximize the emissions reductions within a pharmaceutical production facility. The effect of targeting a pharmaceutical facility was modeled and demonstrates this fact. By applying three of the most common green engineering practices to a pharmaceutical production facility, one may expect a 78% decrease in the overall emissions of the facility. By properly

employing the information available in the TRI, green engineering practices may be applied more precisely, targeting the largest environmental issues at hand, thus resulting in a maximal reduction in facility emissions.

In 2008, the Toxic Release Inventory cited that the United States pharmaceutical industry generated 88 million kg of waste (categorized by the US EPA as either priority pollutants or hazardous air pollutants). 83% of this waste was attributed to the top ten solvents in use in the pharmaceutical sector.[4] By implementing an on-site solvent recovery system, this waste may be significantly decreased. A multitude of separation processes may be used to these ends, including traditional distillation and more novel approaches such as pervaporation and nanofiltration, along with shifting towards a continuous rather than batch process.[12]

Through the use of Life Cycle Assessment in a series of case studies, it has been shown that solvent recovery in the pharmaceutical industry has a significant and universal effect on the environmental impact of API manufacture. First, the necessity of performing an LCA on pharmaceutical solvent use was demonstrated by displaying the large quantity of emissions produced outside of the battery limits of a pharmaceutical plant due to solvent production and waste treatment.

Three aspects of solvent recovery and reduction are made apparent by these case studies. The first is that solvent manufacture and incineration play a significant role in the life cycle emissions of a pharmaceutical API. By implementing a solvent recovery or reduction system, these emissions can be considerably decreased. The second is that the energy of the process and the associated emissions are trivial compared to the emissions due to manufacture and incineration of solvents. From this it is apparent

that the increased energy and associated emissions resulting from the addition of a solvent recovery or reduction system are minor in comparison to the emission reductions resulting from the reduced amount of virgin solvent and solvent waste. In some instances, the addition of a solvent recovery system may actually decrease overall energy requirements of a process, as seen in the BMS case study. The final and most significant aspect of solvent recovery and reduction is that the resultant process emission reductions become apparent only when viewing the process from the perspective of the entire life cycle. The gate-to-gate approach associated with the emissions within an API manufacturing facility overlooks the global implications of solvent recovery and reduction. When a life cycle analysis at a cradle-to-grave perspective is considered, these emission reductions become evident. From such an analysis, one may make a more complete decision on the greenest process for the manufacture of an API.

Appendices

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