Analysis of Green Chemistry and Computational Toxicology

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Abstract

This project was sponsored by the National Center for Environmental Research of the EPA. The goal was to evaluate research in the fields of Green Chemistry (GC) and Computational Toxicology (CT) and determine how NCER should fund future research. We accomplished this through analyzing previously funded projects and interviewing CT and GC experts. We determined that NCER can develop these fields by collaborating with organizations with similar interests, publicizing developments within the fields, and centralizing chemical information in a database.

Acknowledgements

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Authorship Page

*Although some sections had a primary author, each group member reviewed and edited every part of the paper.

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Commonly Used Acronyms

ACS - American Chemical Society

ACToR - Aggregated Computational Toxicology Resource

CEINT - Center for the Environmental Implications of Nanotechnology

CO_2 - Carbon Dioxide

CPSC - Consumer Product Safety Commission

CT – Computational toxicology

DNA – Deoxyribonucleic acid

DOE - Department of Energy

DORIAN - Dose-Response Information Analysis

EDC - Endocrine Disrupting Chemical

EPA – Environmental Protection Agency

EPI - Estimational Program Interface

FDA - Food and Drug Administration

GC – Green chemistry

HTS - High Throughput Screening

MOU - Memorandum of Understanding

NCCT – National Center for Computational Toxicology

NCER – National Center for Environmental Research

NIEHS - National Institute of Environmental Health Sciences

NIH - National Institute of Health

NSF - National Science Foundation

NTP - National Toxicology Program

ORD - Office of Research and Development

P3 - People, Prosperity and the Planet

PFOA - Perfluorooctanoic acid

PI - Principle Investigator

PMN - Pre-manufacture notification

QRT-PCR - Quantitative Real Time Polymerase Chain Reaction

QSAR - Quantitative Structure Activity Relationship

REACH - Registration, Authorization and Restriction of Chemical Substances

SBIR - Small Business Innovation Research

STAR - Science to Achieve Results

TSCA - Toxic Substances Control Act

UNC - University of North Carolina

UNJ - University of New Jersey Dental

VOC - Volatile Organic Compound

Executive Summary

Manmade pollution has become one of the biggest threats to the health of the natural environment. The chemical practices used every day to generate products dump excessive amounts of dangerous chemicals into our water and air (Raven, 2008, p.2). These chemicals are often extremely toxic to humans. The Environmental Protection Agency (EPA) has sponsored research in the fields of both computational toxicology and green chemistry in order to address these problems. Computational toxicology uses new technology to assess the toxicity of chemicals, and thus can evaluate the risk of hazardous pollutants to humans (U.S Environmental Protection Agency, 2009, About Computational Toxicology and NCCT). In comparison, green chemistry focuses on changing current practices for synthesizing and producing chemicals so that they are less harmful to the environment.

Methods of pollution reduction and human health protection would be more successful if the EPA could determine where the fields of green chemistry and computational toxicology come together. This overlap would help to identify what specific chemicals are toxic, and minimize, alter, or even eliminate those chemicals from industrial practices. The goal of this project was to help the EPA identify ways of further developing the fields of green chemistry and computational toxicology both individually and in tandem. We accomplished this goal through three objectives.

- Identified past and current research and funding both by EPA's National Center for Environmental Research (NCER) and by other organizations in the fields of green chemistry and computational toxicology individually
- Identified research projects and funding both by NCER and by other organizations that combine green chemistry and computational toxicology together.

- Analyzed current research and identified gaps in research or places where the two fields could come together.

We found that NCER had funded approximately 130 projects in green chemistry through STAR, Small Business Innovations Research (SBIR) and People, Prosperity and the Planet (P3) grants. We also found that National Science Foundation (NSF) had funded research in green chemistry. NSF focused on many of the same topics as NCER, but also allocated some money for education purposes. Along with our archival research, we also interviewed several experts in the field of green chemistry. The experts provided us with information on why researchers may not be using green chemistry practices.

We found that NCER had funded seven projects through Science to Achieve Results (STAR) grants in the field of computational toxicology. The majority of their funding went to the four STAR centers, which worked to develop computational models to test toxicity. We also researched the activities of the Office of Research and Development's (ORD) National Center for Computational Toxicology (NCCT). The NCCT has created the ToxCast system to predict toxicity, and has collected current toxicology data in the Aggregated Computational Toxicology Resource (ACToR) database. The NCCT collaborated with the National Toxicology Program (NTP) and the National Institute of Health (NIH) genomics program to expand toxicity testing through the Tox21 Memorandum of Understanding (MOU.) In addition to archival research, we interviewed three NCER health scientists as well as an expert at the NCCT to determine gaps in research and collaborations with other government organizations. We found that many other government organizations were doing similar toxicity testing, but were not utilizing computational toxicology.

Through our interviews with various researchers knowledgeable in the areas of green chemistry and computational toxicology at NCER and through outside organizations, we determined where and how experts believed the fields could work together. We then combined our interviews with our archival research analysis to determine what topics both fields were studying. In particular, we looked at how computational models could predict green chemical properties, and how the twelve principles of green chemistry, the main doctrine of the field, could apply to computational toxicology.

From our results and analysis, we were able to assess the fields of green chemistry and computational toxicology separately and together to make conclusions and recommendations. Through our research, we made several conclusions about the state of green chemistry. First, we identified a general lack of knowledge about green chemistry and its practices. Second, NCER research in green chemistry has focused too much on four main areas of research. Third, there is a lack of publically available data to people who could benefit from the use of green chemical practices.

From these conclusions, we have made the following recommendations to NCER:

- **Spread out the funding within NCER.** Focus in areas such as bioengineering and alteration of starting materials will have a greater environmental impact than replacing solvents within a reaction. NCER also needs to allocate money for the purpose of education.
- **A database of GC information should be created.** Green chemistry data should be organized into a database of information, which is publicly available. The database should also make it easy to search for specific chemicals.

- **Reach out to researchers outside the field of GC in order to make them think in terms of green processes.** GC researchers need to distribute information on green chemistry out to the scientific community in order to make a greater impact on research in general. If scientists and engineers outside the field of green chemistry are actively thinking about improving how green their processes are, it will cause a greater movement toward reducing pollution.
- **Publish and educate about what makes a chemical process greener.** This could be done through altering school curriculums to include sections on green chemical practices within entry-level chemistry classes.

Computational toxicology is a newly developing field that cannot yet accurately predict toxicity. In the future, computational toxicology has the potential to greatly improve risk assessment testing and reduce or eliminate animal testing. This field has the potential for many interdisciplinary applications and many other organizations may benefit from it. We have made the following recommendations to NCER to develop the field.

- **Improve accessibility to computational information by centralizing data.** This will help eliminate data gaps and improve computational models. NCER can support this by publicizing and funding the expansion of the ACToR database, which aggregates data in one location, as well as improving publicity about this database.
- **Improve communication between agencies and increase publicity about computational research.** One way to improve communication is through expansion of an existing line of communication, like the TOX21 MOU. Through the expansion of funding, more researchers can be involved and the field will develop faster.

- **Fund projects that will make modeling systems more realistic.** NCER, as well as computational toxicologists, should work with health scientists to identify what extraneous factors affect toxicity in humans, and focus on those while models are in early stages of development. Some of these topics may include chemical mixtures and chronic exposure.
- **Gain the support of other scientists and the public sector through increased publicity.** NCER can gain the support of scientists in other fields by publicizing the interdisciplinary related results of research, and gain the support of the public by stressing the strides CT is making in reducing animal testing.

We found that computational toxicology and green chemistry have the potential to be used together to determine toxicity and reduce the use of hazardous chemicals, but only found one instance in which the two were funded in tandem, the Center for Environmental Implications of Nanotechnology. This is a partnership involving NSF, EPA and several universities to increase education in the areas of not only green chemistry, but also computational toxicology. We found that computational toxicology could benefit green chemistry research by focusing on the principles of creating less hazardous chemical synthesis, designing safer chemicals, and using safer solvents and auxiliaries. We discovered through interviews with health scientists that computational models could test the toxicity of green chemicals faster than traditional methods as well as predict other chemical properties that could be useful to green chemists. Green chemists could speed up the development and testing of new chemicals by using computational toxicology. Through these conclusions, we have made several recommendations:

- **Increase communication between the two fields.** We recommend increasing communication through a conference between green chemists and computational toxicologists, as well as the creation of a web database. This database could be an

adaptation of the ACToR database, and should contain chemical data useful to both groups.

- **Increase education in how the fields could connect.** Increasing education could be accomplished through a conference between green chemists and computational toxicologists. NCER could help increase education by encouraging other agencies that fund educational research to consider funding GC and CT projects.

- **Increase collaboration between green chemists and computational toxicologists.** NCER can help these fields grow by funding research that uses CT and GC together, such as in the CEINT. Collaboration can also be increased through workshops similar to the industrial green chemistry conference.

1. Introduction

After the onset of the industrial revolution, pollution in the environment rapidly increased. Though industrialization advanced and improved the quality of human life, it was at the cost of the well-being of the environment. Pollution in the environment is worsening and natural resources are ever diminishing; therefore, governments are funding research to achieve more sustainable practices and scientists are working toward new pollution reduction techniques. One approach to reducing pollution is through green chemistry (GC). The definition of green chemistry by the United States Environmental Protection Agency is "the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances" (EPA, 2008, Introduction to the Concept of Green Chemistry). This approach uses innovative technology and ideas to reduce pollution. Green chemistry is constantly changing, and needs tests to ensure that it is decreasing pollution. One potential method to monitor green chemistry's effectiveness is computational toxicology. Computational toxicology (CT) uses computer models to forecast possible health risks caused by chemicals on specific populations.

Ideally, chemical processes would be pollution free and perpetually sustainable, but this is not the case. Many processes do not optimize their use of raw materials to create safe and efficient chemical reactions (Hoag, 2009, p. 1). Processes to dispose of toxic waste are also insufficient or ineffective. Pollution from toxic chemicals has detrimental effects on the environment and the human population. To move closer to the ideal situation, scientists are modifying chemical processes to be safer and include fewer unwanted byproducts and waste.

Currently, the EPA has sponsored research in the areas of green chemistry and computational toxicology. Green chemistry scientists are doing research in the areas of biofuels,

catalytic reactions to replace excess reagent reactions, and more sustainable reactions, among other topics (EPA, 2009, Green Chemistry). The EPA is sponsoring research in the field of computational toxicology by starting the National Center of Computational Toxicology in 2005 (EPA, 2009, NCCT). EPA also sponsors research in the development of computer modeling systems that can predict toxicity including programs such as the ToxCast system that prioritizes the large amount of chemicals that need to be tested. Research also exists in the fields of pharmokinetics, High Throughput Screening (HTS), and genetic analysis, among many other topics that will speed up the toxicity testing and screening process.

In order for green chemistry to reach its full potential and help to reduce pollution, much more research needs to occur within the subject. Green chemistry is a new concept that could revolutionize chemical processes to be much more environmentally friendly. New methods within green chemistry are always in development, but this information is not widely publicized to the scientific community. There has also been very limited research into how researchers in green chemistry and computational toxicology can work cooperatively together.

Our goal was to aid the EPA in more efficiently advancing green chemistry research through cooperation with computational toxicology. We first identified what research the EPA has funded in the areas of green chemistry and computational toxicology. Next, we organized and analyzed that information. Through organizing this information, we identified trends within the research topics as well as the funding received. From there, we were able to make conclusions and future recommendations for the agency in their allocation of funds. We also determined logistics of integrating the two fields of green chemistry and computational toxicology. The successful integration of green chemistry and computational toxicology will lead to more effective research in both fields. We conducted archival research to review the

previous work accomplished by the EPA in the areas of green chemistry and computational toxicology and provided the EPA with information that shows what research exists, which will lead to more time and cost efficient foci for their research programs. With this information, the EPA should be able to focus more on eliminating harmful pollutants in the environment and optimizing the funds it provides to its research sectors. The integration of these two subjects could also generate growth in the production of green chemical processes.

2. Background

In order to understand the fundamentals of green chemistry and computational toxicology, we need a broader knowledge of pollution and its causes. Pollution is the main reason for research in the areas of green chemistry and computational toxicology. Scientists have gained much insight into new pollution reduction techniques with the introduction of these two initiatives. Green chemistry attempts to find more efficient methods of reducing or eliminating pollution in the environment. Computational toxicology focuses on the harmful effects of pollution and uses computer-modeling systems to map those effects as opposed to using human or animal subjects for testing. This background chapter will focus on further defining green chemistry and computational toxicology, and the connections between the two research fields.

2.1 Pollution

Pollution is a major concern in today's world. It causes harm to the earth and the various environments and ecosystems contained on it. Pollution comes in many forms, and includes but is not limited to air, noise, water, or sound pollution. The harmful effects of pollution exist throughout the world, whether aesthetically, in trash on the ground or dark billowing clouds in the sky, or through the health of the individuals, plants, and animals living in regions with such pollution. The quality of air can be directly related to the number of respiratory illnesses that are present in a region, and the water quality can be linked to other health issues (CDC, 2009, Air Quality, Fires, and Volcanic Eruption).

Each type of pollution has various sources. For instance, air pollution can be produced by motor vehicle exhaust, power plants and industry, or even the simple task of mowing a lawn (EPA, 2009, Atmospheric Science: Source Apportionment). Sources of water pollution include industries dumping chemicals directly in the water or the migration of chemicals through the soil

into the water supply. Another source of water pollution is from agriculture and household cleaning activities such as washing a car, doing laundry, or cleaning dishes. These different types of pollution are point source and non-point source pollution. Point source (PS) pollution is from a single known source such as factories' smokestacks or chemical waste from a company. Nonpoint source (NPS) pollution usually affects water and includes chemical seepage through the ground into the water, as well as storm water runoff from paved areas. Its specific origin is unknown; however, the pollution still affects the body of water (EPA, 2009, What is Nonpoint Source (NPS) Pollution? Questions and Answers). NPS pollution is not traceable to a single point, but emanates from a larger area and from various sources. Heavy rainfall exacerbates NPS pollution, which can move the pollutants into a water source more quickly and disperse them over a larger area. This type of pollution may reduce the overall pollution potency per unit of ground area because of mixing with rainwater, but it can affect a much larger area and cause more harm in the process (Raven et. al, 2008, p. 517).

2.1.1 Harmful Effects

The effects of pollution are evident in today's environment. Besides the physical appearance of trash or the unnatural color of the sky or water, there are harmful side effects seen in the various organisms living in a polluted environment. Polluted water affects the quality of drinking water. Some drinking water may appear to be clear and therefore safe to drink, however it may contain harmful chemicals and bacteria that have ended up in the water due to pollution (EPA, 2009, Water Pollution). Possible diseases that humans can get from drinking polluted water include various bacterial infections such as dysentery, salmonella, and cholera.

Any major type of pollution may cause health risks. For instance, an increase in cigarette smoke, smog, and various other air pollutants drastically increases a person's chance of having

asthma, bronchitis, or developing lung cancer (CDC, 2009, Air Quality, Fires, and Volcanic Eruption).

2.1.2 Prevention Methods

There are several methods to reduce pollution. The US Environmental Protection Agency heads several programs that help ensure proper use of resources. The EPA heads up such programs as the Reduce, Reuse, Recycle campaign, as well as the eCycle program that specifically recycles old electronic equipment. Another local initiative is the Recycle on the Go program which encourages recycling in public places (EPA, 2009, Reduce, Reuse, Recycle). These programs are in effect throughout various cities and towns across the United States.

There are ways that people can help to reduce water pollution in the environment. Many household cleaning products are very harmful to the environment, so using those products less frequently or substituting less potent chemicals for cleaning products will help to improve water quality (Raven et. al, 2008, p. 519). In addition, avoiding or reducing the use of chemical pesticides or fertilizers on farms as well as on lawns and gardens can greatly reduce the amount of water pollution in an area.

A prime example of the harmful effects of pollution in history was the Love Canal incident in Niagara Falls, NY (Anastas et. al, 1998, p.5). An old canal was a dumping ground for chemical waste from a plastics company from the 1930s to the 1950s. In the early 1970s, the chemicals began to seep through the ground, and officials declared it an official disaster area. There were numerous negative health effects linked to the exposure to chemicals from Love Canal including high birth defect and miscarriage rates, liver cancer, and seizure-inducing nervous disease. The state government spent about $10 million trying to clean this area.

2.2 Green Chemistry

"Green chemistry, also known as sustainable chemistry, is the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances. Green chemistry applies across the life cycle, including the design, manufacture, and use of a chemical product" (EPA, 2009, Green Chemistry). Unlike environmental chemistry, which is the study of chemistry in the natural environment, green chemistry strives to prevent pollution at its source.

2.2.1 History of Green Chemistry

For the past twenty years, green chemistry has been at the forefront of environmental protection methods (Hoag, 2009, p. 1). Green chemistry traces its roots back to the 1950s. Prior to 1956, the process for obtaining ethane and 1-butene was very wasteful and produced many toxic byproducts. In 1956, engineers at DuPont discovered that passing propene over a molybdenum-on-aluminum catalyst produced a mixture of propene, ethene, and 1-butene. Yves Chauvin determined that the metal carbine was jump-starting the reaction in 1971 when identifying the previously unknown mechanisms of this reaction. Twenty years later Richard Schrock and Robert Grubbs analyzed the spectrum of catalysts for this reaction. This procedure of making a product while using less material and producing less toxic waste was a novel idea. This discovery led the way in transforming processes to be less polluting and thus is a key step in initiating green chemistry.

Another example of a process that has reduced its toxic waste output is ibuprofen production. When the production of ibuprofen began, it generated more waste than drug (Hoag, 2009, p. 2). The process involved adding excessive amounts of aluminum trichloride to isobutyl-benzene along with solvents (including carbon tetrachloride) and separation agents in a six-stage

reaction. This process created 30 million pounds of product and 45 million pounds of waste annually worldwide. In 1990, however, the procedure changed to use catalytic reactions instead of excess amounts of reagents. This eliminated much of the waste created in the reaction and increased the atom economy, or the percentages of raw materials and reagents that end up in the product, to above 80%. This illustrates how waste from a process that changes from using excess reagents to catalytic reactions that will greatly reduce pollution.

2.2.2 Green chemistry is aiding in the fight against pollution

Green chemistry is important because it plays a major role in sustaining the earth's resources and is essential to the process of de-polluting the environment. Some of the goals of green chemistry according to the EPA (Anastas, 1998, p. 2) are to prevent waste, design safer chemical processes, use renewable feedstocks, use safer solvents and reaction conditions, analyze in real time to prevent pollution, and minimize the potential for accidents. For the full list of the Twelve Principles of Green Chemistry, see Appendix V.

Not only does the EPA design new and safer processes, they also encourage companies to use renewable feedstocks in their processes (Anastas, 1998, p. 2). Using renewable materials, less waste generation pollutes the environment. These materials are derived from agricultural products or waste from another manufacturing process, whereas non-renewable feedstocks are usually petroleum based, using materials such as coal or oil.

Another way that the EPA is trying to reduce waste is by insisting that companies improve the safety of the solvents and reaction conditions used in their chemical processes (Hoag, 2009, p. 2). The use of safer solvents will inherently cause less pollution since any

chemicals that do end up as waste will harm the environment less than the toxic chemicals that preceded them. Safer reaction conditions will make each reaction use less energy, thus reducing the raw materials each reaction requires to run.

The EPA strongly encourages companies running potentially harmful chemical processes to analyze their emissions and reactions in real time (Anastas, 1998, p. 2). This monitoring of systems will allow companies to minimize or eliminate harmful byproducts of reactions. Scrutinizing and filtering the emissions will also eliminate much of the pollution released to the atmosphere.

Minimizing the potential for accidents should be a goal of all major companies, but it is especially important when considering the problem from an environmental standpoint (Anastas, 1998, p. 2). Chemical spills and accidents can be devastating to the local environment. This is exemplified in the transformation of cleaning products. The majorities of older cleaning products were petroleum based, and as such, were harmful to the environment (Planet Green, 2009, Top Green Cleaning Tips). Newer versions of cleaning products are non-toxic, biodegradable, and made from renewable resources instead of petroleum. These new cleaning products are much less harmful when disposed of (i.e. poured down the drain).

2.2.3 Recent Research in Green Chemistry

Research in the field of green chemistry is constantly changing. Some of the research areas that the National Center for Environmental Research (NCER) has focused on in green chemistry are the conversion of excess reagent reactions to catalytically driven reactions and the use of water or CO_2 as a solvent. These examples show a representation of work that the EPA has funded in the last ten years, and does not cover the full spectrum of grants

The NCER has sponsored research in the area of catalytic reactions (EPA, 2009, STAR Grants). These reactions are useful to the field of green chemistry because they cause less toxic waste and use less material than the excess reagent reactions, which they replace. This is valuable in the sustainability of the world's natural resources, as well as the effort to eliminate pollution in the environment.

The NCER has also funded research to look into the use of water and CO_2 as environmentally benign solvents (EPA, 2009, STAR Grants). The use of environmentally friendly solvents would be a great advantage over current chemical processes in the area of pollution prevention. The use of CO_2 as a solvent would be especially useful since it would give a purpose to what is generally considered a waste emission. This would provide for the release of less CO_2 into the atmosphere, while also reducing toxic solvent waste output.

2.3 Life Cycle Assessment

A life cycle assessment (LCA) is "a technique to assess the environmental aspects and potential impacts associated with a product, process, or service, by compiling an inventory of relevant energy and material inputs and environmental releases, evaluating the potential environmental impacts associated with identified inputs and releases, and interpreting the results to help you make a more informed decision" (EPA, 2009, Life-Cycle Assessment). An LCA studies the entire impact a product or process will have on the environment, from the extraction process of obtaining materials to the eventual return of those products to the environment.

Specifically, the LCA will focus on the overall inputs to create a product, or run a process, and then the possible outputs from the creation of that product or process. The considerations in an LCA are below in Figure 2.1. This encompasses the "cradle to grave" idea

for a product, or more specifically, the impact the product has on the environment from its inception to its eventual return to the environment (Curran, 2006, Chapter 1 Life Cycle Assessment). It is an important method in the field of green chemistry, for it allows for a complete analysis of a product or process. This analysis allows for total assurance that the most efficient method is used. One chemical might be seen as environmentally friendly in that it does not produce much byproduct, but after doing an LCA, it is identified to not be very "green" because the process of making that chemical actually has widespread adverse affects on the environment .

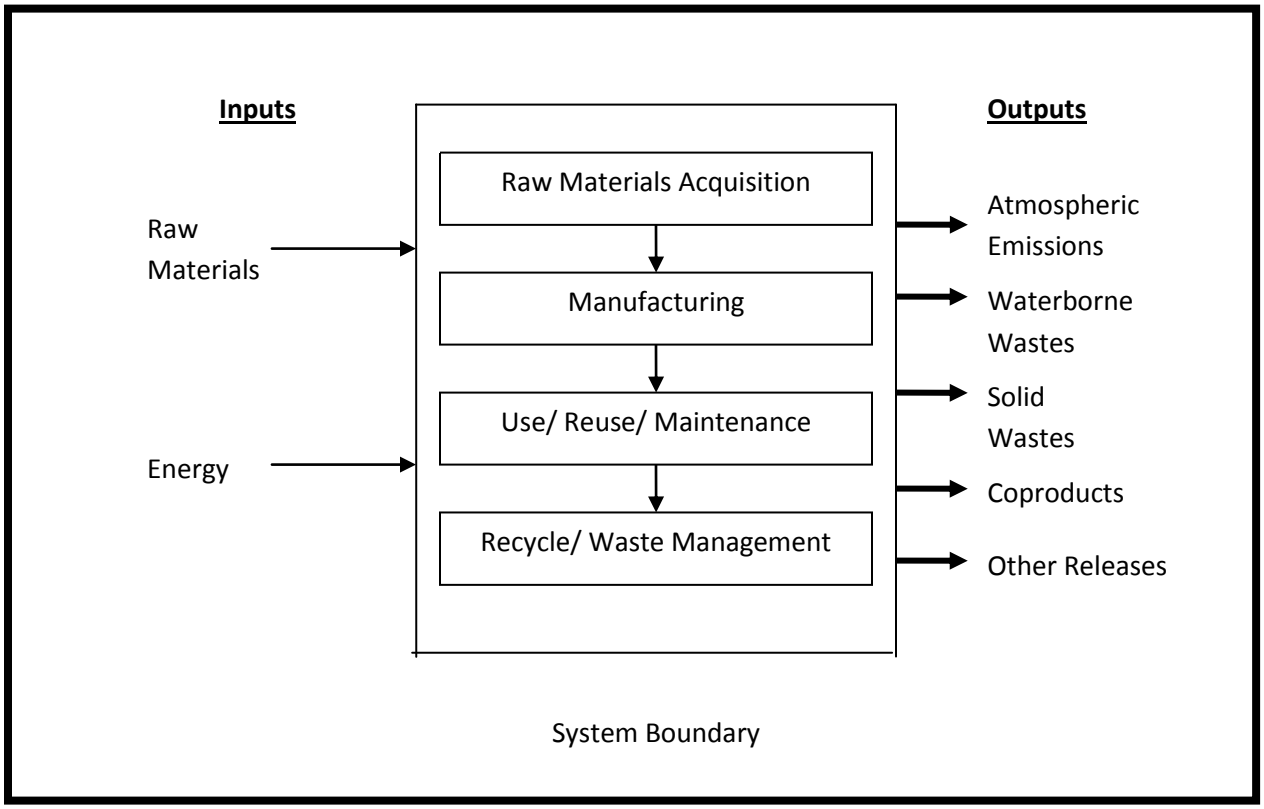

Figure 2.1: Life-Cycle Stages (Adapted from: Curran, 2006, Chapter 1 Life Cycle Assessment)

There is a process involved in conducting an LCA. First, a goal is defined, and the scope of that goal is determined. Here is where boundaries are established and environmental effects

that need to be reviewed are defined (Curran, 2006, Chapter 1 Life Cycle Assessment). Next, is an inventory analysis, which examines the energy and materials used in and produced by each process. Impact assessment analyzes the potential effects on human and ecological systems. During this assessment, scientists identify the environmental effects of the process. Finally, interpretation analyzes the data and the final product or process is chosen based on the overall impact on health and the environment.

There are some definite benefits to conducting an LCA. It helps to choose a product or process that has the least impact on the environment (Curran, 2006, Chapter 1 Life Cycle Assessment). It can help to identify the transfer of environmental impacts from one process to another, show that each phase of production is related, and that the environmental impacts can carry through those phases. This could also aid in the comparative analysis of two rival products to see which is more environmentally friendly.

There are limitations when conducting an LCA (Curran, 2006, Chapter 1 Life Cycle Assessment). Since the collection of data for the assessment can be lengthy and resource dependent, the importance of the data collected must be assessed in order to determine how worthwhile the study is. This assessment also does not decide if a product is the most cost effective, or the best in performance, so other factors may go into the decision to use a product. This obviously could lead to the implementation of a product that has a worse impact on the environment over its life cycle; however, cost and performance are necessary factors to examine when designing a product.

2.4 Toxicology and the Environment

"All substances are poison; there is none which is not a poison. The right dose differentiates a poison from a remedy" Paracelsus (Borzelleca, 2000, Profiles in Toxicology).

Toxicology is essentially the study of poisons, and it is one of the oldest sciences. Humans have a natural ability to detoxify chemicals to some extent and throughout history humans have used and abused our bodies' immune systems for various reasons (Monosson, 2007, A Brief History of Toxicology). In modern times, some of the biggest sources of toxins are manmade pollutants dumped into the environment, which is why the EPA is concerned with the field of toxicology.

2.4.1 The effect of toxins on the human body

Any foreign substance that humans are exposed to has the potential to be harmful if it can first penetrate the body's natural defenses and enter the bloodstream. There are three main ways for substances to enter the body: inhalation, absorption, and ingestion (Stelljes, 2008, p.26). When inhaled, a substance must pass through the airway, avoid being trapped in mucus, and enter the body through the alveoli in the lungs. A substance can enter the body by absorption through the epidermal layer, first passing through a thick layer of dead epidermal tissue. Ingestion is the most common way that foreign substances enter the body, but ingestion does not necessarily mean exposure. The digestive system is essentially a giant tube, and chemicals must be absorbed through the intestinal walls in order to enter the bloodstream and affect the body.

The amount of exposure time to a particular toxin is important, because the longer the chemical has the opportunity to enter the body, the more it can accumulate, and the more toxic it can become. Toxicologists traditionally divide exposure times into three categories: acute, sub-chronic and chronic exposure (Stelljes, 2008, p.30). An acute exposure is an exposure that takes place over a very short period of time, sometimes a matter of hours or even minutes, such as in a

chemical warfare situation. A sub-chronic exposure is an exposure that occurs over a period of several years, but not over an entire lifetime. Chronic exposure is usually defined as an exposure that lasts over a period of more than 7 years, and usually has occupational connotations (Stelljes, 2008, p.31). During the industrial revolution, workers often suffered chronic exposure to excessive amounts of coal tar (CDC, 2006, Advanced cases of Coal workers Pneumoconiosis). For example, coal miners have a high incidence of pneumoconiosis due to the amount of tar they breathe in that coats their lungs. In a 2006 survey, the Center for Disease Control and Prevention (CDC) found that 9% of coal workers had advanced cases of pneumoconiosis, even after safety laws had been passed to limit their exposure.

When toxins enter the body, they can wreak havoc with many of the processes and systems that keep us alive. Toxins are infamous for affecting the nervous and reproductive systems, as well as causing genetic mutations and developmental defects. Toxins can also have a huge effect on the body by inhibiting enzymes. Enzymes facilitate crucial biochemical reactions by affecting the rate of a reaction, and typically work through a "lock and key" mechanism, shown in figure 2.2. This means that the substrate (organic substance that will be affected in a reaction) fits into the enzyme in a specific, perfect way (Voet, 2008, p. 324). Toxins also have the ability to fit in the enzyme, which blocks the correct substrates from undergoing catalysis because they cannot fit in the site. This can often result in cell functions slowing down or stopping.

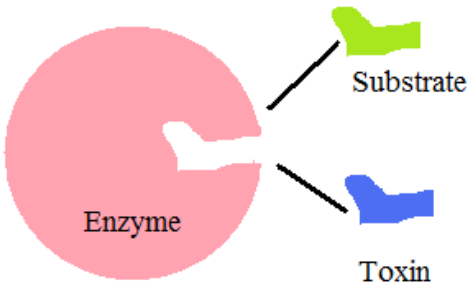

Figure 2.2-the "lock and key" mechanism of an Enzyme (adapted from Voet, 2008, p. 377)

Toxins can intercalate within the DNA to cause a variety of genetic mutations. One of the outcomes of these mutations can be uncontrolled cell growth. This uncontrolled cell growth is cancer, and many cancers are the indirect result of exposure to toxins (Stelljes, 2008, p.41). This type of mutation would most likely be caused by a chronic exposure to a chemical, since the body has repair mechanisms to fix mutations.

Toxins can affect the nervous system by penetrating the blood/brain barrier and affecting the receptors through blocking (similar to the mechanism by which they block enzymes). They can also affect the reproductive, developmental and endocrine systems of humans. These systems are extremely vulnerable because they are controlled by hormones, and many toxins can act as hormone mimics (Stelljes, 2008, p.155).

The most potent toxins are chemicals that mimic chemicals found in our own bodies, because it is far easier for them to trick the body into thinking they are not a foreign substance. However, since most biochemical reactions are extremely specific, a small change can have a huge effect on the result of a reaction. In the 1950s, a drug known as Thalidomide came on the market that illustrated this phenomenon (Stelljes, 2008, p.52). When scientists synthesized this drug, they produced two forms that differed in only one carbon group. One form helped pregnant mothers avoid morning sickness, but, unbeknownst to scientists, the chiral enantiomer (the

mirror image of the same chemical, see Figure 2.3) caused developmental birth defects to the fetus. Over the course of several years, over 5,850 babies were born with horrible defects as a result.

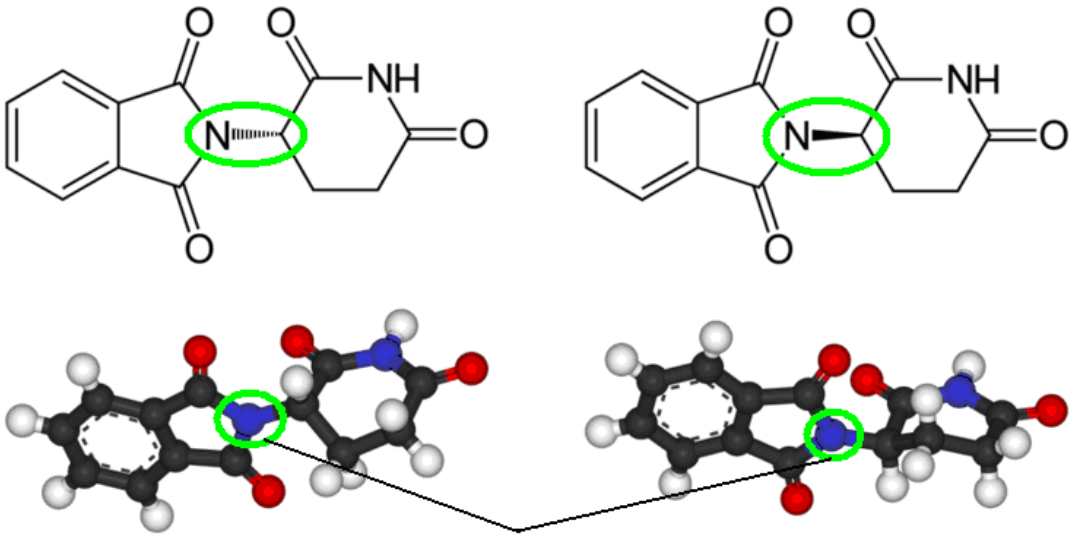

Figure 2.3-The two enantiomers of thalidomide, which differ by the position of one group (Foley S, 2009, Common Pharmaceutical names)

As noted by Paracelsus in the early 16th century, the quantity of the toxin ingested is the most important factor in determining how detrimental a toxin is to human health (Borzelleca, 2000, Profiles in Toxicology). Some chemicals can be more toxic in small doses than others. For example, 1 mg/kg concentration of dioxin (a byproduct of manufacturing processes) in the human body can be lethal, but it would take between 5,000-15,000mg/kg concentration of alcohol to have the same effect (Stelljes, 2008, p.6). A compound's chemical properties determine what concentration will have a discernable effect on the human body.

Toxicologists usually compare different dosages of toxins with respect to their lethality. A lethal dose (LD_{50}) is enough to kill 50% of a test population after an acute exposure (Stelljes, 2008, p.36). Animal modeling can easily identify the LD_{50} of a particular compound,

traditionally through a test population of mice. A sub-lethal dose is an amount that is harmful but will not cause immediate damage. Scientists usually use sub-lethal doses to look at chronic exposure experiments, and to find an acceptable amount of additives for food and drugs. Sub-lethal doses must be tested on animals over a course of 14-90 days, and the animals need to be sacrificed at the end to gather data.

2.4.2 Types of Toxicology

Toxicology is a broad field of study and is often broken down into categories that are more specific. Pharmacological toxicology is a discipline that studies how manmade products to cure a disease could cause adverse affect. These disciplines focus on a known quantity of one chemical, usually to find the amount that is safe for use as a drug. Environmental toxicology is a more imprecise form of toxicology because it is impossible for scientists to determine exactly what they are studying. Often times, scientists do not know the mixture or source of the chemicals, so it is difficult to determine specific information about them (Stelljes, 2008, p.107). Environmental toxicology often focuses on large populations rather than individuals and often studies the effects of chronic exposure to very low doses of a toxin.

2.4.3 Current Toxicological Methods

Since so many chemicals can be toxic at varying doses, it is very important for toxicologists to determine which chemicals are toxic and at what amount they are toxic. Scientists study how toxins interact with the body at different biological levels in order to understand how toxicity relates to the entire organism systematically. There are a number of unique characteristics of each biological level that toxicologists can observe to understand toxicity (See Figure 2.4).

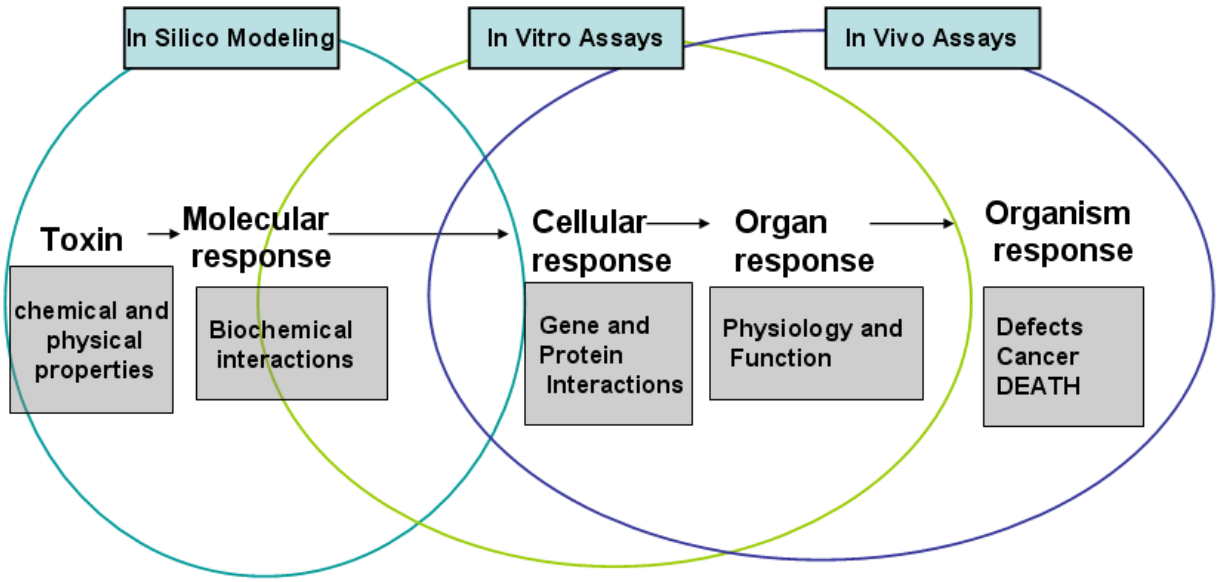

Figure 2.4-Determination of Toxicity: Modeled after Figure 2 (A model for computational Toxicology, p. 15).

In vivo experiments use laboratory animals to model how a chemical affects cells, organs, and an entire organism. Scientists can specifically research how a chemical affects signaling, tissue physiology and function, and if the compound causes cancer or death (see Figure 2.4). Mice are traditionally used for many tests because they are small and easy to house, reproduce quickly and reliably, and have many biochemical mechanisms similar to those of humans (Silver, 1994, The origin of mice in genetic research). However, animal testing with mice is not an exact science.

The biggest challenge when executing any toxicological test is to get enough valuable data to draw conclusions from. When performing an in vivo experiment, this often requires over 400 animals per experiment (Stelljes, 2008, p.65). It is expensive to house, feed, and monitor these animals, and since they must be sacrificed at the end of an experiment, there are many moral concerns. In addition, these experiments are extremely time consuming, beginning at the point of breeding the mice (which must be inbred several times to be genetically similar). It is

complicated to do long term studies in cancer or other reproductive problems with mice since setting up these experiments often takes such a long time.

In contrast to in vivo experiments, in vitro experiments take place in a test tube or petri dish as opposed to using a living sample. Scientists can test animal cells to study how the body responds to a chemical through molecular, cell, or organ response (See Figure 2.4). In vivo toxicology allows scientists to analyze biochemical reactions, protein production and signaling through cell culture experiments, as well as through mutagenicity tests. A mutagenicity test is particularly useful for screening carcinogens, because it determines if a chemical causes mutations to DNA. The most common mutagenicity test is the "Ames test," which involves a strain of salmonella to be specifically mutated so that it cannot grow unless it is on a special plate. Scientists expose these plates to the chemical in question, and if the chemicals mutate the bacterium, its DNA will have changed so that it can now grow on a normal plate. Therefore, if scientists see growth on a normal plate, they can consider the substance a mutagen (Crosby, 1998, p.151). In vitro tests are much quicker and more cost effective than in vivo experiments, but it is more difficult to predict toxicity and extrapolate the data to humans.

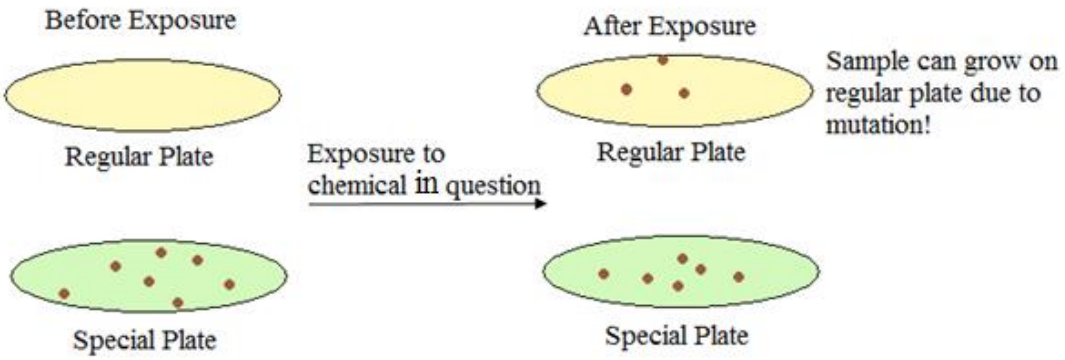

Figure 2.5-The Ames test, an example of a common in Vitro test (adapted from Crosby, 1998, p. 151)

In recent years, there have been many advances in the field of computer technology, and this can be applied to toxin testing through in silico modeling. In silico modeling uses computers to analyze the chemical and physical properties of a chemical and predict how it will react in the body at the biochemical level (see Figure 2.4). This information alone is not enough to predict toxicity, but can serve as a useful starting point to determine how different chemicals relate to each other. This serves as the basis of next generation risk assessment through the field of computational toxicology.

2.4.4 Computational Toxicology

Technological advances in the field of computer modeling and the widespread use of modern biological techniques have helped spur the field of computational toxicology. The main difference between traditional toxicology and computational toxicology is the scale of the research done, and the sheer amount of data gathered, which will help scientists make much more precise and accurate predictions about the chemical nature of a substance (EPA, 2009, NCCT). Computational Toxicology uses the latest technology to gather information much more quickly than traditional methods.

Computational toxicology uses new technology to automate laboratory procedures, to eliminate tedious hours of lab work, which frees up time for scientists to focus on analyzing data, and reduces the need for lab technicians. This results in toxicity tests being cheaper and faster. Drug companies developed many of these laboratory techniques as a way to test drugs, but have been extremely versatile and can test other chemicals as well. One example of this is high throughput screening (HTS) which automatically conducts assays in a specialized plate known as a microtiter plate, so that thousands of chemicals can be scanned for characteristics in a short

amount of time (Houck, 2007, p.17). This cuts down on the time a researcher needs to spend analyzing each sample individually.

As well as utilizing new technologies, computational toxicology also uses newly discovered information from recent years to look at toxicology in a different light. The field of systems biology brings in vivo and in vitro data together to understand the structure and function of a biological system from a holistic perspective (Systems Biology, a 21st Century Science, 2008). Toxicologists can use systems biology to evaluate gene function and expression, and determine how a small chemical change affects an organism from a biochemical standpoint. Through the novel perspective of systems biology, scientists can understand how toxins affect the body at a deeper and more complex level.

The next step that the EPA and other research groups are working towards is creating in vitro organs to analyze toxins. This would have a huge advantage over traditional in vivo and in vitro tests because researchers would be able to work with a whole organ individually instead of just a part, while at the same time not sacrificing a life in the experiment (EPA, 2009, Virtual Liver). Researchers at the EPA are currently working on the development of a virtual liver, known as the Virtual Liver project, as well as a virtual embryo.

Since a chemical's toxicity is often dependent upon its chemical and physical properties, knowing these properties and understanding how they lead to a biological change is important to toxicology. In silico technology, in particular computer models can help analyze the chemical and physical properties that are important (Houck, 2007, p.15). In the past, QSAR models (Quantitative Structure Activity Relationships) have modeled these properties, but QSAR models have several disadvantages. They are very specific for different types of chemicals, so they cannot be used to screen large groups of chemicals for specific toxicity properties (Richon, 2009,

Introduction). Therefore, toxicologists are working on more developed predictive modeling systems that work better to predict properties accurately. These include the Estimational Program Interface (EPI), which predicts useful chemical information, as well as a variety of other modeling systems.

The reason that the EPA in particular is interested in funding computational toxicology is because only twenty percent of chemicals of concern have actually been tested using traditional toxicology methods (Kavlock, 2007, p. 623). There is a need to test chemicals faster and with higher accuracy, and computational toxicology appears to be the best way to fulfill this need. The EPA has given a number of grants to various companies in order to develop basic computational techniques, including new predictive modeling systems, research within the field of systems biology, and the expansion of methods like high throughput screening.

The NCER division of the EPA has provided some of the funding to four computational toxicology centers, as well as the National Center for Computational Toxicology, which started in 2005. (See Appendix C) According to the NCCT, the main goal of the center is to advance the research of computational toxicology through three primary goals (EPA, 2009, NCCT). The first goal is to improve the linkages in the source to outcome paradigm. The source to outcome paradigm is the mechanism in which an unknown chemical can produce an adverse outcome. The Center's second goal is to develop predictive hazard identification methods, which are programs that can analyze exposure and predict how hazardous a chemical is at a basic level. The third and final goal of the NCCT is to enhance quantitative risk assessment. In order to do this, they will need to develop new strategies to determine how toxic a chemical is in and at what dose.

Computational toxicology is an extremely promising technique to determine a compound's toxicity, but since it is relatively new, it is not accurate enough to determine chemicals' toxicity with complete accuracy or consistency. More research needs to be done to determine how exactly the predictive modeling systems can measure toxicity and how this data compares to classic toxicology data. Since computational toxicology is in its early stages, the actual laboratory techniques need to be well utilized and developed, so scientists understand how to use equipment. In order for computational toxicology to develop further, scientists need the money to create modeling systems and equip their labs with the latest technology. The EPA needs to give grants out to scientists, and collaborate with other funding organizations to help advance the field of computational toxicology.

2.5 Applications of Green Chemistry and Computational Toxicology

Computational toxicology can test products and evaluate processes in green chemistry. Computational models allow for testing of the toxicity of chemicals through means that do not involve human or animal subjects (EPA, 2009, National Center for Computational Toxicology). This allows for a safer method of identifying toxins that might pollute the environment. Through testing how harmful various chemicals might be in the environment, the EPA can determine which chemicals to monitor more closely.

Computational models can test these new products or developments in the areas of green chemistry. A computer program should be able effectively to show to what extent a new chemical is influencing the environment (EPA, 2009, National Center for Computational Toxicology). This information is being placed in a computer database that will allow easier

access for researchers to view how toxic or harmful a certain chemical is, or to find any patterns which have developed.

2.6 Research Gaps

Although there has been some collaboration between green chemistry and computational toxicology, the two have not been used in tandem to their full potential. One key issue is the novelty of the research being conducted. The EPA founded the National Center for Computational Toxicology in February of 2005 and it has only twenty scientists (EPA, 2009, National Center for Computational Toxicology). With such a small number of researchers, it takes quite a bit of time to reach results. Currently, the NCCT has short-term goals, which include working with various other research centers within the EPA to meet their needs, as well as improving CT processes to be more accurate, and long-term goals of helping the public by giving them a better way to analyze the chemical hazards of materials. The long-term goals include working with green chemistry to aid in pollution reduction.

The NCCT is still trying to create a legitimate system for analyzing chemicals, so the establishment of a solid network between green chemistry and computational toxicology is still unclear (EPA, 2009, National Center for Computational Toxicology). If the field of green chemistry continues to develop without the help of computational toxicology, it may not be as successful as it could be. Green chemistry has the potential of making great strides in identifying better methods to dispose of chemicals, less harmful chemicals for the environment, and methods at reducing pollution in the environment with the help of computational toxicological models (EPA, 2009, Green Chemistry). The models allow for a safer approach to the practices of green chemistry by allowing the research to be conducted with a computer as opposed to current methods, which may include animal and human test subjects.

3.0 Methodology

The goal of this project was to help the EPA make smart business decisions through determining which methods of CT/GC have been underfunded and should receive more funding through the National Center for Environmental Research. We performed preliminary background research in the fields of green chemistry and computational toxicology to identify the fundamental concepts of GC and CT as well as what scientists have researched within those fields. To help the EPA make funding decisions, we have analyzed prior research in greater depth to determine how to help GC and CT collaborate and work together more effectively. This chapter will address how we obtained this information, as well as specifically how we gathered and analyzed data.

3.1 Assessment of current GC research

Our first objective was to determine what prior research the EPA has funded in the field of green chemistry. To do this, we searched through the extensive database of Science to Achieve Results (STAR) Grants that the EPA's NCER Division funds. We also looked through other non-STAR grants given out by the EPA. In looking through this research, we determined specifically what researchers have studied, and to what extent EPA had funded those subjects. We also identified which areas have not received funding, and conducted interviews with scientists doing research in green chemistry and EPA experts who make funding decisions about GC. However, our research was primarily archival research, which we obtained by delving into the EPA's database and files, as well as information obtained from the National Science Foundation (NSF) and National Institute of Health (NIH). We created graphs and charts to show how the EPA has funded different areas of green chemistry, and organized them by the various topics funded. We then organized the funding in NSF and other organizations. For more

information on the graphs created, see the Results section of this report. From there, we determined if these agencies have been funding research in the same areas with relation to green chemistry, or if one organization has been funding more pertinent research than the other two.

3.2 Assessment of current CT research

Our second objective was to determine what prior research the EPA has funded in the field of computational toxicology. We needed to determine the state of current research, and what programs (such as the ToxCast program) have been established. We also examined which areas have not received much funding. We obtained this information through archival research in the NCER's database of STAR funded grants and STAR centers, as well as NCCT publications. We also looked into the NSF and NIH databases to see if they have funded any research in the field of computational toxicology. In addition, we conducted interviews with experts in the field of computational toxicology, both through the NCCT or through other research groups in Washington, DC. We initially focused on NCER representatives who make funding decisions, then other individuals within NCER and the NCCT in order to determine how funding is distributed. We created graphs and charts to show how the EPA has funded different computational toxicology methods, and what chemicals or classes of chemicals researchers have studied. We also organized any funded research by NSF and NIH to determine any similarities with EPA funding, and compare the agencies funding by topic and money awarded. Those graphs and other organizational tools are in the results portion of this report.

3.3 Collaboration of GC and CT research

Our third objective was to determine how researchers in GC and CT research have been or could be using the two fields in tandem to further the goals of the EPA. To do this, we needed

to find circumstances where the EPA has funded projects that used CT and GC simultaneously, as well as projects that used the two techniques, but did not necessarily identify the use of GC or CT. To accomplish this, we needed to do archival research within the EPA's library and database, and attempt to interview more experts, specifically people who would know about research completed within both fields. Through reading the research, we determined the nature of the connection between computational toxicology and green chemistry.

3.4 Determining future implications of current research

After determining the areas where researchers are currently using GC and CT research together, we also found areas where researchers might use the two fields together in the future. Through our research, we projected how the short-term goals of GC and CT relate to each other, as well as identified how the two fields could affect each other in the long term. We evaluated how the safety of newer, greener chemicals could be evaluated more quickly using CT. We have made recommendations as to where the EPA can further develop its research in GC and CT separately, which are in our Conclusions and Recommendations section. In doing our research, we found any areas in which research has not gone into enough depth on a subject, and we recommended these areas for further research.

In examining which aspects of GC and CT the EPA can best use in tandem, we were able to make recommendations to the EPA about which projects they should support in the future through grant funding. How the EPA decides to fund grants will depend on the scale of the project and the amount of money the EPA can afford to give out. Through funding these projects, the EPA will help further the efforts of GC and CT, which will help make the environment cleaner and healthier.

4. Results and Analysis

To analyze the current research in green chemistry and computational toxicology, we determined trends in current research and interviewed experts to determine the current state of the fields. We were able to determine the correlation between the fields through analysis of this research and through identification of projects where both techniques were implemented.

4.1 Assessment of current GC research

In order to analyze the past research in green chemistry, we began by looking at grants funded by NCER (EPA, 2009, Green chemistry). This research is categorized according to which program within NCER funded it. We have further categorized grants by the amount of money spent by each program as well as what topics have been investigated within each program. Through the analysis of these data, we made observations about which areas required more funding to be effectively improved.

We then made efforts to determine what research scientists were doing in other agencies within the US (NSF, 2009, Grants). This was an attempt to discover any research gaps in the work NCER and EPA were carrying out. Through the analysis of some outside agencies, we received a better understanding of what the federal government has been researching in the area of green chemistry.

4.1.1 NCER Grants

The NCER funds many different projects in the area of green chemistry. For the purposes of our analysis, we broke down the research into different areas of study (EPA, 2009, NCER). Shown in Figures 4.1 and 4.2 below are the percentages of money and projects funded in green chemistry separated by program.

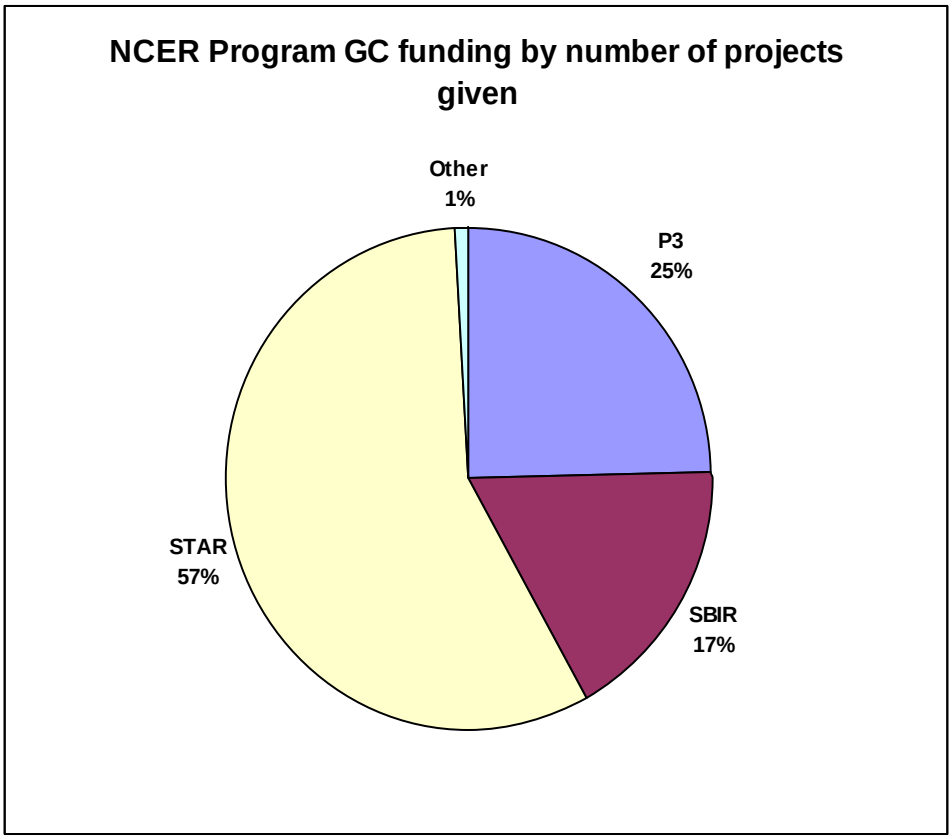

Figure 4.1: NCER green chemistry funding- number of projects by program (EPA, 2009, Grants)

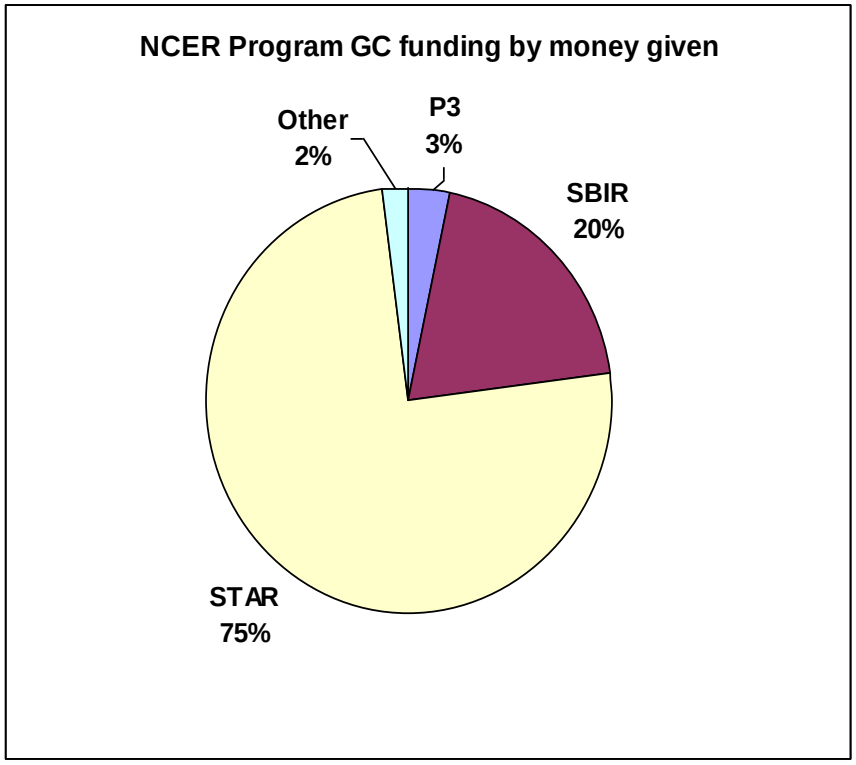

Figure 4.2 NCER green chemistry funding- amount of money by program (EPA, 2009, Grants)

4.1.1.1 STAR Grants

The majority of NCER research within the field of green chemistry comes through the distribution of Science to Achieve Results (STAR) grants (EPA, 2009, STAR Grants). There were 74 STAR grants awarded in green chemistry, which was the largest number given by any of the programs, which we studied. STAR grants make up ¾ of the total money given to green chemistry research by NCER, and make up over half of the total number of projects in green chemistry from NCER. We broke the research into categories by both purpose and materials used.

As can be seen in Figure 4.3, the majority of STAR research in the field of green chemistry has gone into the elimination of toxic solvents. (EPA, 2009, STAR Grants). This makes sense since one of the main goals of green chemistry is to create safer solvents and

auxiliaries. Many solvents used in chemical processes are toxic and greatly harmful to the environment. As such, they must be disposed of and handled carefully to prevent their release into the environment. With a change to less toxic solvents, the improved chemical processes become much less toxic and in most cases are more sustainable by virtue of being able to recover the new solvents better than their preceding chemicals.

The next biggest area of STAR research has been in the area of bioengineering. Green chemists are trying to make products more biodegradable (EPA, 2009, STAR Grants). These efforts focus on the changeover from petroleum based products to non-petroleum based products. While the petroleum-based products can remain in a landfill breaking down for many years, the new products have a much shorter lifespan and therefore are much less harmful to the environment. These new processes also have the advantage of using a renewable starting material.

Another area of research within the STAR grants is the alteration of starting materials and starting conditions (EPA, 2009, STAR Grants). In many cases, chemical processes utilize petroleum products as their starting materials. Since petroleum products are not a perpetually sustainable resource, scientists are developing ways to eliminate the use of petroleum products in starting materials. There are also efforts to alter the starting conditions of chemical processes in order for them to use less energy or materials. This provides for a reduction in consumption of resources, and is important to the sustainability of the planet.

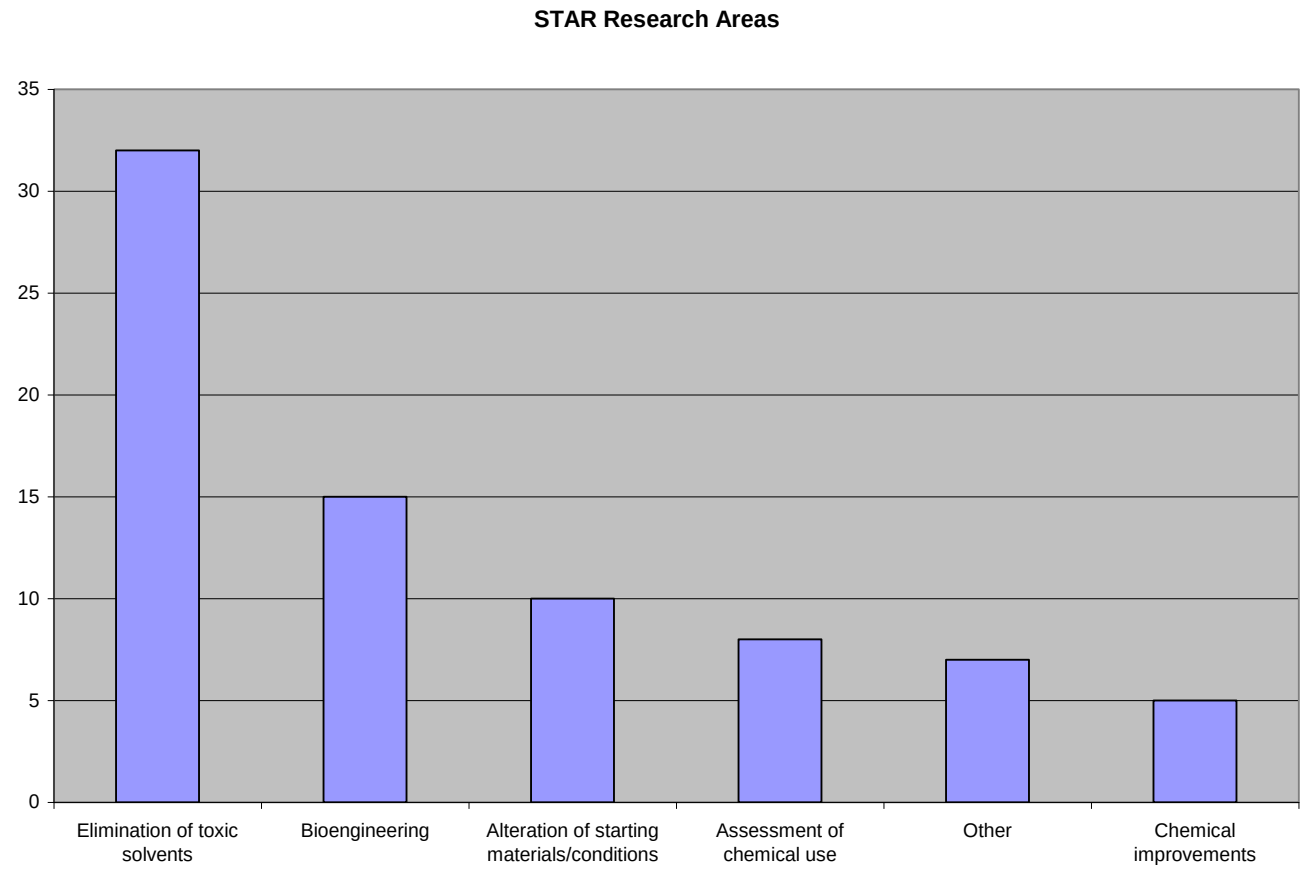

Figure 4.3: Green Chemistry Research by Purpose adapted from EPA data (EPA, 2009, STAR Grants)

Figure 4.4 shows a breakdown of the materials used and/or altered in the STAR grants funded by NCER (EPA, 2009, STAR Grants). The most funded group has been projects working toward using water or carbon dioxide as a solvent. These chemicals are plentiful and are reusable within most processes. This provides for more sustainable and less harmful chemical processes than the processes they are replacing. The use of carbon dioxide as a solvent also uses a greenhouse gas, which would otherwise be harmful to the environment.

The next largest number of grants is the catalyst group (EPA, 2009, STAR Grants). These were projects in which the main goal of researchers was to find an alternate reaction using a catalyst instead of stoichiometric reagents to achieve a product. While this category of reactions is slightly different from the others in this list, we felt that the projects were designed to accomplish similar goals with the same type of change in materials, and as such, we could group them together.

NCER has also funded a large number of projects dedicated to reformulating products using bio-based polymers (EPA, 2009, STAR Grants). This change in reactions can create more sustainable processes through the recycling of the polymers after their use. It also can cause a reduction in landfill waste, thus reducing pollution in the environment.

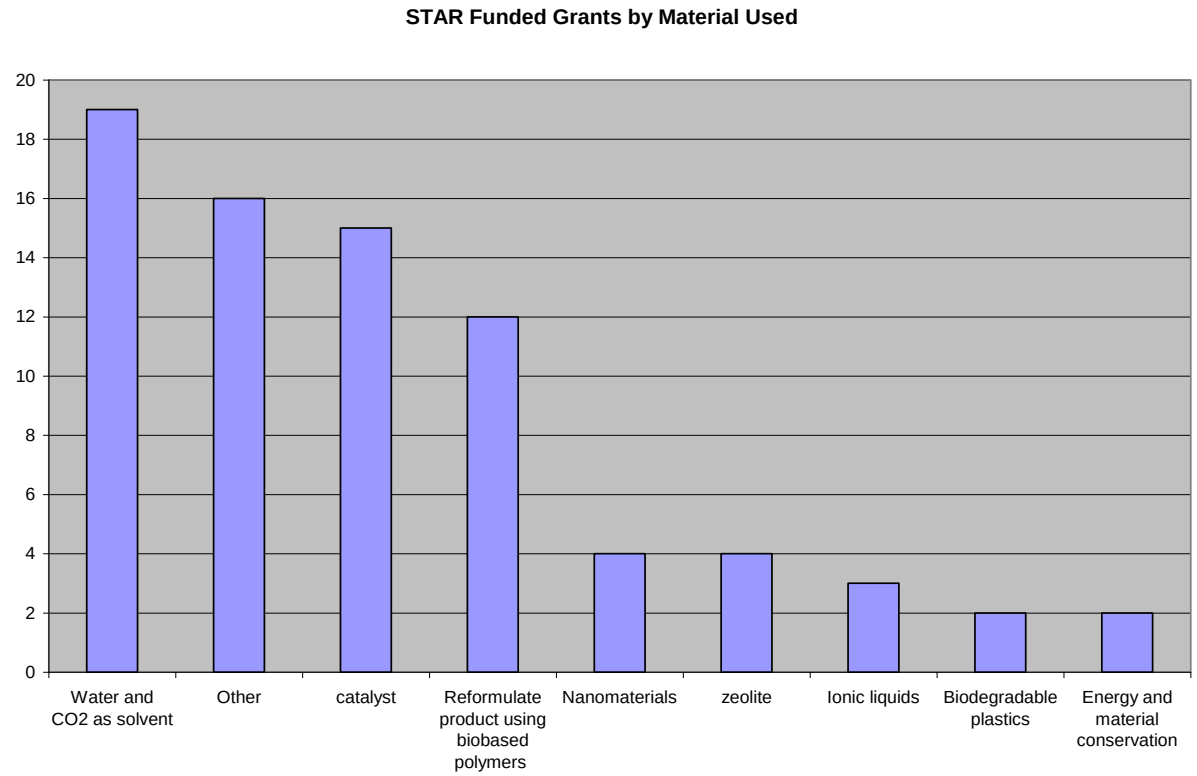

Figure 4.4: Green Chemistry Research by Materials Studied adapted from EPA data (EPA, 2009, STAR Grants)

4.1.1.2 SBIR

The Small Business Innovation Research (SBIR) program is another integral source of funding for green chemistry research (EPA, 2009, SBIR Grants). SBIR provides for about 1/5 of the money and projects designated for green chemistry by NCER. SBIR awards are different from STAR grants because they are given to small businesses instead of to universities for research. This difference in their use makes for a different approach in their analysis. Since there are not many small businesses working with the same materials, a comparison of the most often used materials would be useless. We did a comparison similar to the STAR grants by research area.

One of the large groups of projects funded through SBIR grants is similar to the STAR grants (EPA, 2009, SBIR Grants). The elimination of harmful solvents grouping mirrors the STAR grants because in both sets of funding that group has the largest number of projects. The category of solvent elimination differs in SBIR however, in that it is not the standalone leader in number of grants given.

The other subject that received the highest number of grants was benign product creation (EPA, 2009, SBIR Grants). We grouped these grants together because the goal in each of them was to replace a harmful product with one that would not be detrimental to the environment. This differs from the elimination of harmful substances category since those projects were specifically looking at some aspect of the reaction mechanism, whereas these projects were meant to correct a specific aspect of the product.

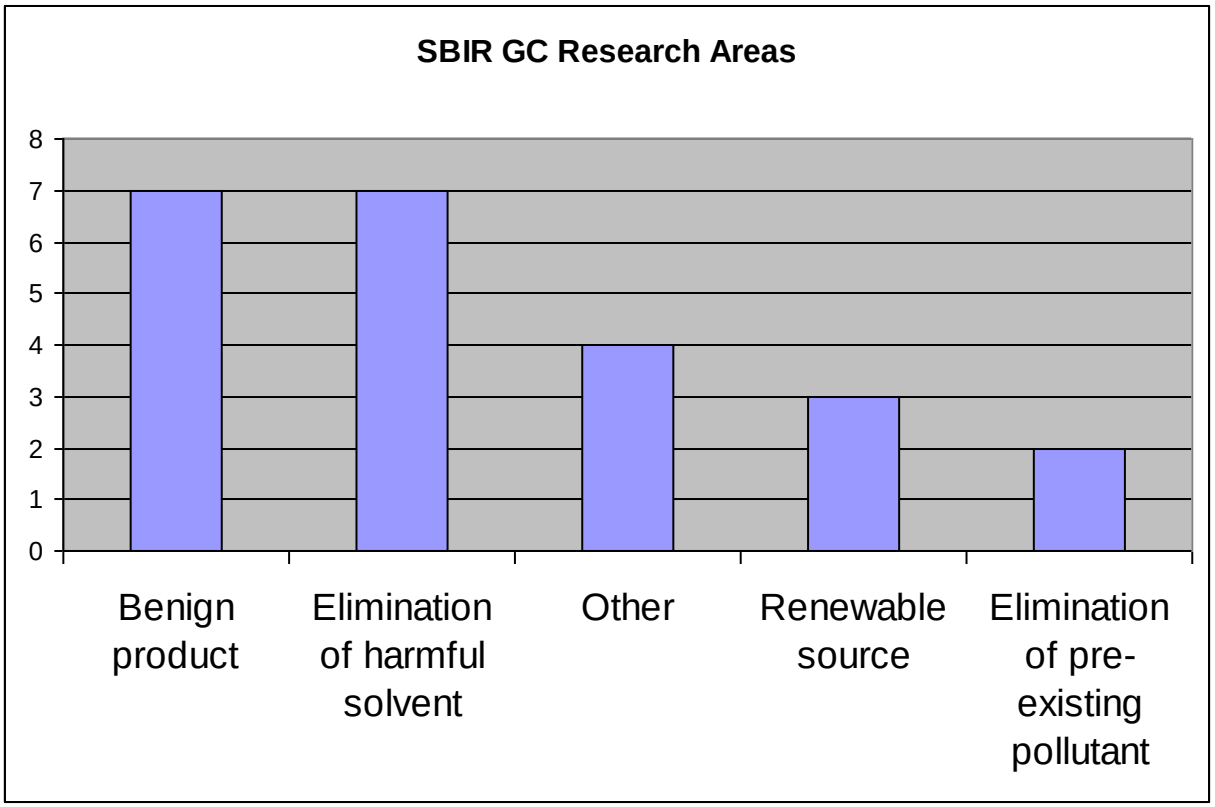

Figure 4.5: SBIR Green Chemistry Grants by Category adapted from EPA data (EPA, 2009, SBIR Grants)

4.1.1.3 P3

The People, Prosperity and the Planet (P3) program is the other main way that NCER funds research in the field of green chemistry (EPA, 2009, P3 Grants). P3 accounts for ¼ of the total number of projects sponsored by NCER in green chemistry, but have only given 3% of the total funding for research. This is because P3 is an undergraduate competition (For full descriptions of NCER programs please see Appendix B). P3 phase one grants only give $10,000 and phase two grants give $75,000 while the other programs give much larger sums of money. SBIR grants for instance give $75,000 for phase one grants and $225,000 for phase two projects.

This provides the opportunity for more varied projects in P3 but limits the amount that can be done with any singular project.

We decided to categorize the P3 grants in green chemistry according to the purpose of the projects (EPA, 2009, P3 Grants). This showed us that the P3 projects focused in different areas than either the STAR or the SBIR grants. In our analysis, we believe that these differences in funding can be correlated with the differences in who is applying for them. Undergraduate college students think up and carry out P3 projects whereas, in the other programs, experienced researchers or businesses are thinking up the project proposals. We believe that college students may often have more innovative and interesting ideas as compared to the tried and true ideas that may bog down more experienced researchers. The P3 program gives students an opportunity to show the more experienced researchers a different view or a new and innovative way of doing something that they may not have otherwise considered. P3 grants also give students with good research ideas an excellent "jumping off point" in order to receive more funding. With a P3 grant, many students go out to other organizations and show their idea and the fact that they received an EPA funded grant. This gives them a great opportunity to expand their project even if they do not receive a phase two award from P3.

The P3 grants given in green chemistry are more evenly spread out than the STAR or SBIR grants (EPA, 2009, P3 Grants). There were however two areas which received more funding than any other category. These were the categories of renewable feedstocks, and use of a novel process for treatment of a specific pollutant.

P3 grants funded the grouping of renewable feedstock use in 21% of the grants given to green chemistry (EPA, 2009, P3 Grants). Each project in this group was dedicated to finding an

alternative feedstock that was renewable in place of one that was a petroleum product. This would make the new chemical processes more sustainable, and would cut down on waste output.

The other group that received 21% of the P3 funding was projects using of a novel process for treatment of a specific pollutant (EPA, 2009, P3 Grants). This is an interesting category of project to choose to fund since each project only focused on reducing one aspect of pollution for one specific process. While the project would only help to reduce the waste output and toxicity of the waste from one particular process, the size of individual P3 grants allowed NCER to fund these projects. NCER may have tended to fund projects with more widespread goals had the size of P3 grants been larger.

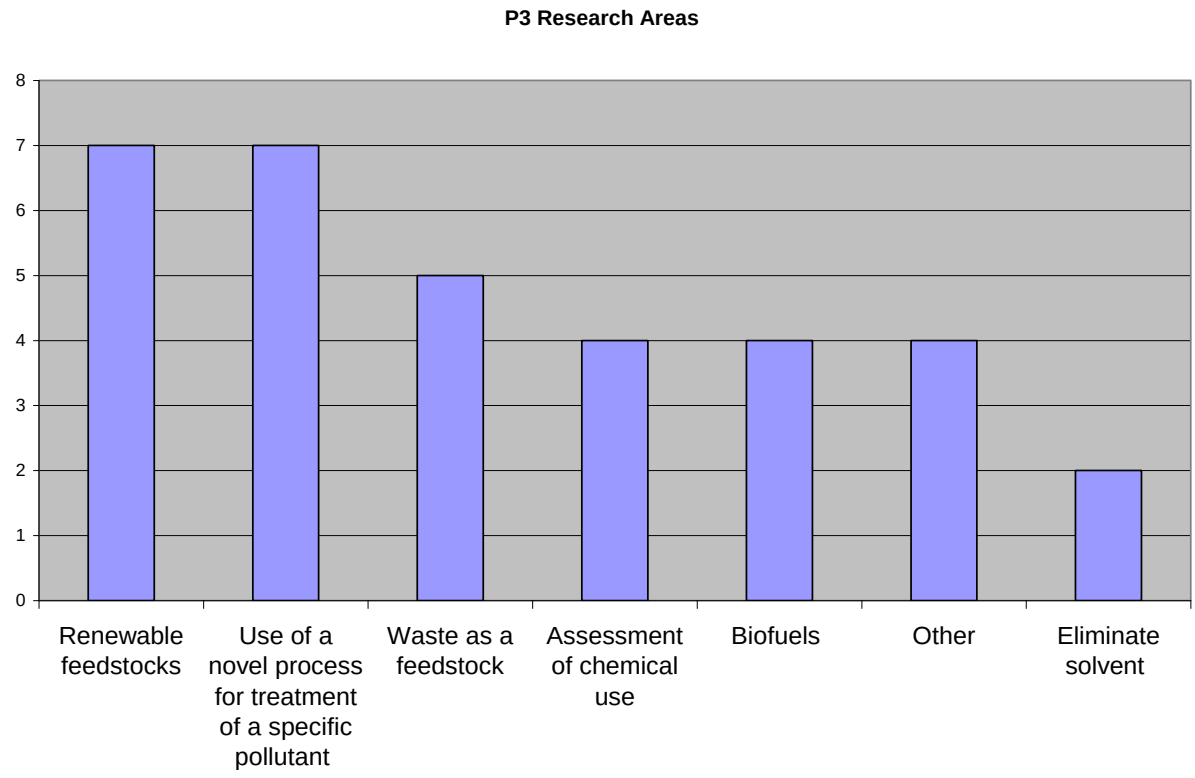

Figure 4.6: P3 Research in Green Chemistry sorted by Purpose adapted from EPA data (EPA, 2009, P3 Grants)

4.1.1.4 Overall analysis

When looking at the overall number of grants given out by NCER in the area of green chemistry, several general trends stand out (EPA, 2009, NCER). The biggest trend is that much of the research focused on eliminating specific toxic solvents in a chemical process. This category of research was the primary goal of 30% of the projects NCER funded, and accounted for almost half of the money given to green chemistry research by NCER.

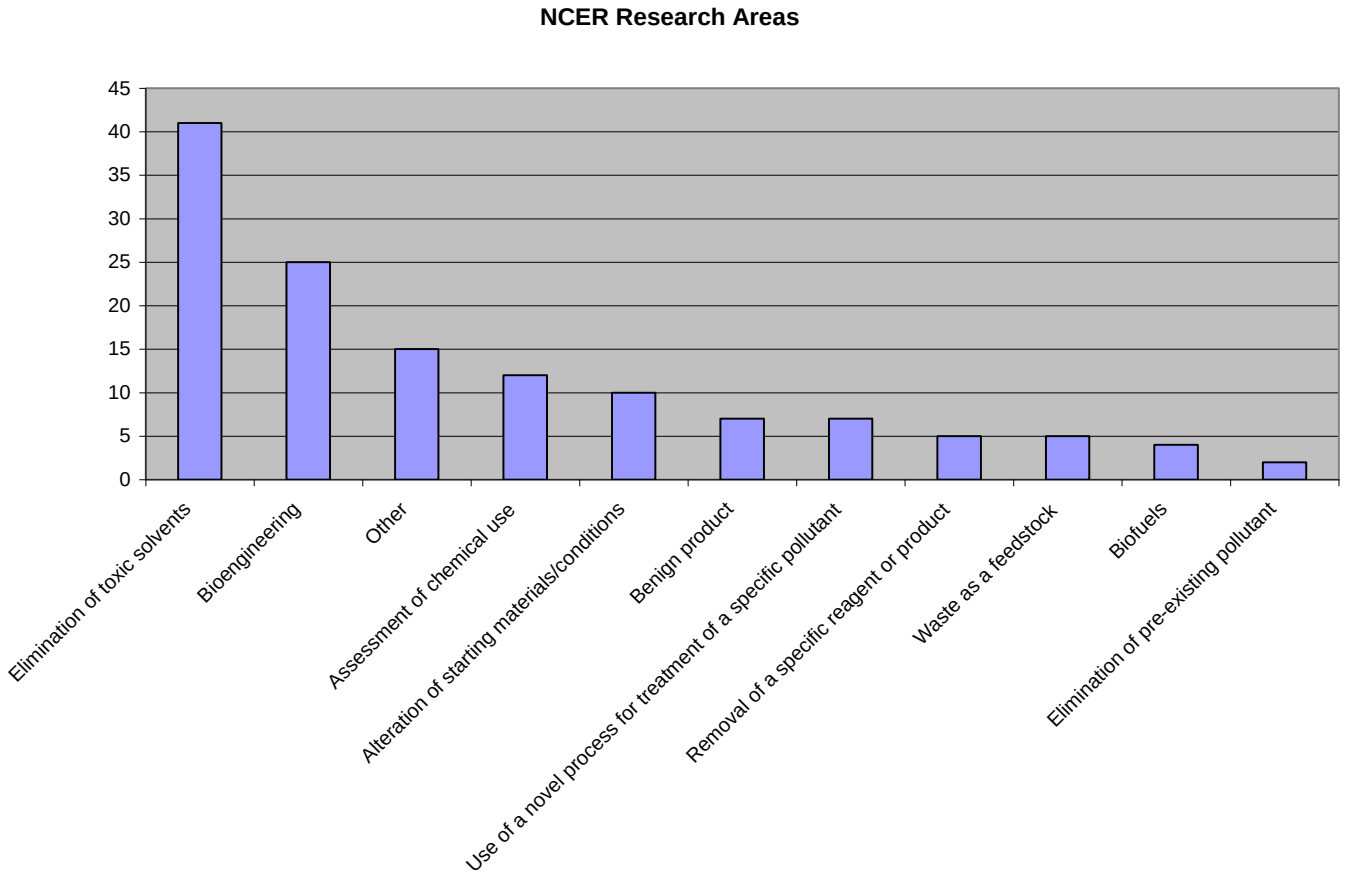

Figure 4.7: NCER Green Chemistry Grants Sorted by Purpose adapted from EPA data (EPA, 2009, NCER) (For a larger version of this graph, please see Appendix P)

4.1.2 Non-NCER Grants

NCER and the EPA are not the only organizations funding research in green chemistry. The National Science Foundation (NSF) (NSF, 2009, Grants), The Department of Energy (DOE) (DOE, 2009, Grants), and The American Chemical Society (ACS) (ACS, 2009, Grants) are funding research in the field of green chemistry. In our research, we attempted to locate grants for each of those organizations.

4.1.2.1 NSF

The National Science Foundation (NSF) has funded some projects in the field of green chemistry (NSF, 2009, Grants). Its funding has been spread over a wide variety of project types, including many of the same types of projects as the STAR grants. However, the NSF is different from the other programs we encountered. The difference is that while every other program's sole focus has been on the development of new processes or products, the NSF has spent a significant portion of their green chemistry funding (about 1/5) on education.

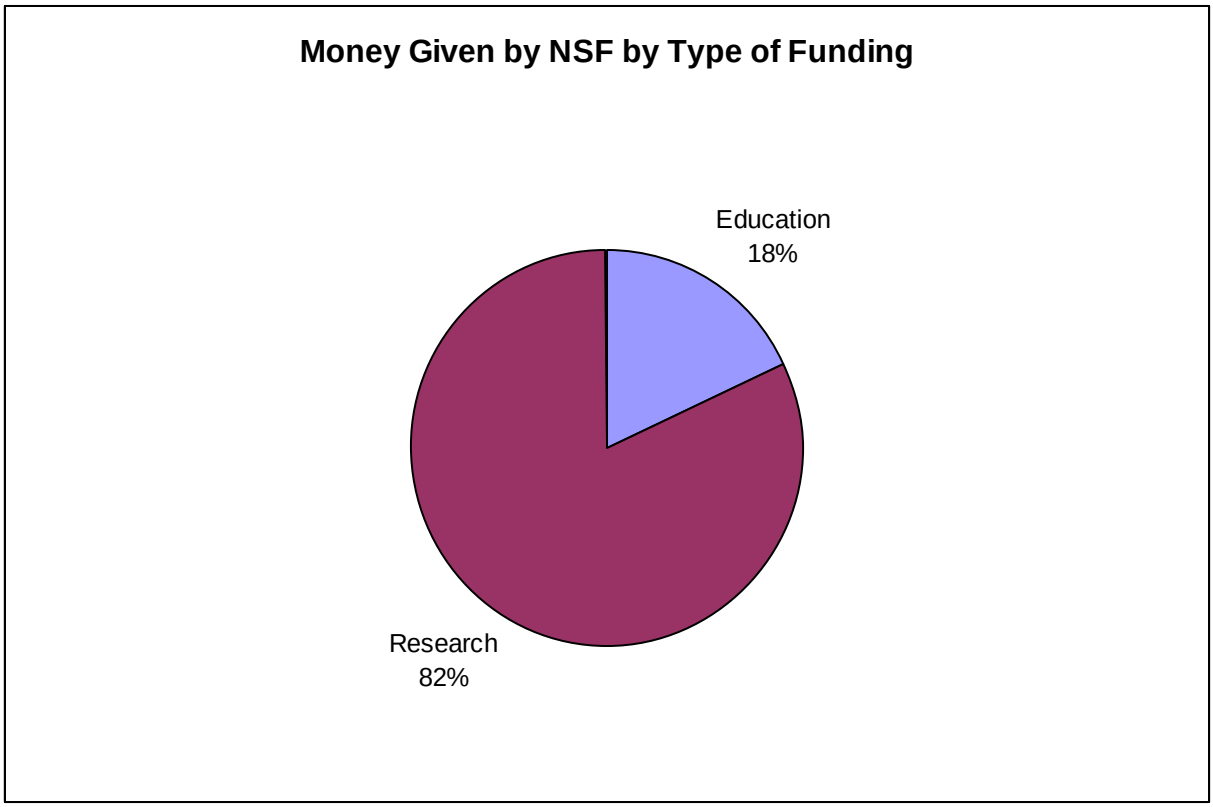

Figure 4.8: Money Given by NSF sorted by Type of Funding adapted from NSF data (NSF, 2009, Grants)

The NSF has spent over $2 million of their approximately $12 million on establishing education in the area of green chemistry (NSF, 2009, Grants). This shows that the NSF is starting to educate the general populace about the uses of green chemistry and sustainability, whereas some of the other organizations may not be thinking about educating society as of yet. The money given out to education institutions was to establish greener practices as a part of those institutions' curricula. Going forward, education will be the most important aspects of green chemistry. If up and coming scientists are aware of the concept of creating green chemical processes, then they will automatically focus more on using safer, less harmful processes.

The grants that NSF has given out for research have come in many different areas of study (NSF, 2009, Grants). These groupings closely resemble those given out by the STAR program, but do not resemble the same kinds of numbers as the STAR grants. In fact, the NSF grants focus in very different areas than do the STAR grants.

The most funded subject in NSF green chemistry research is the reformulation of products using bio-based polymers in place of petroleum-based products (NSF, 2009, Grants), Energy and material conservation, catalytic reactions, and nanomaterials closely follow that. These categories have all been funded in some way by NCER, but were not the main focus of funding efforts. This may be due to the differences in goals between the NSF and EPA.

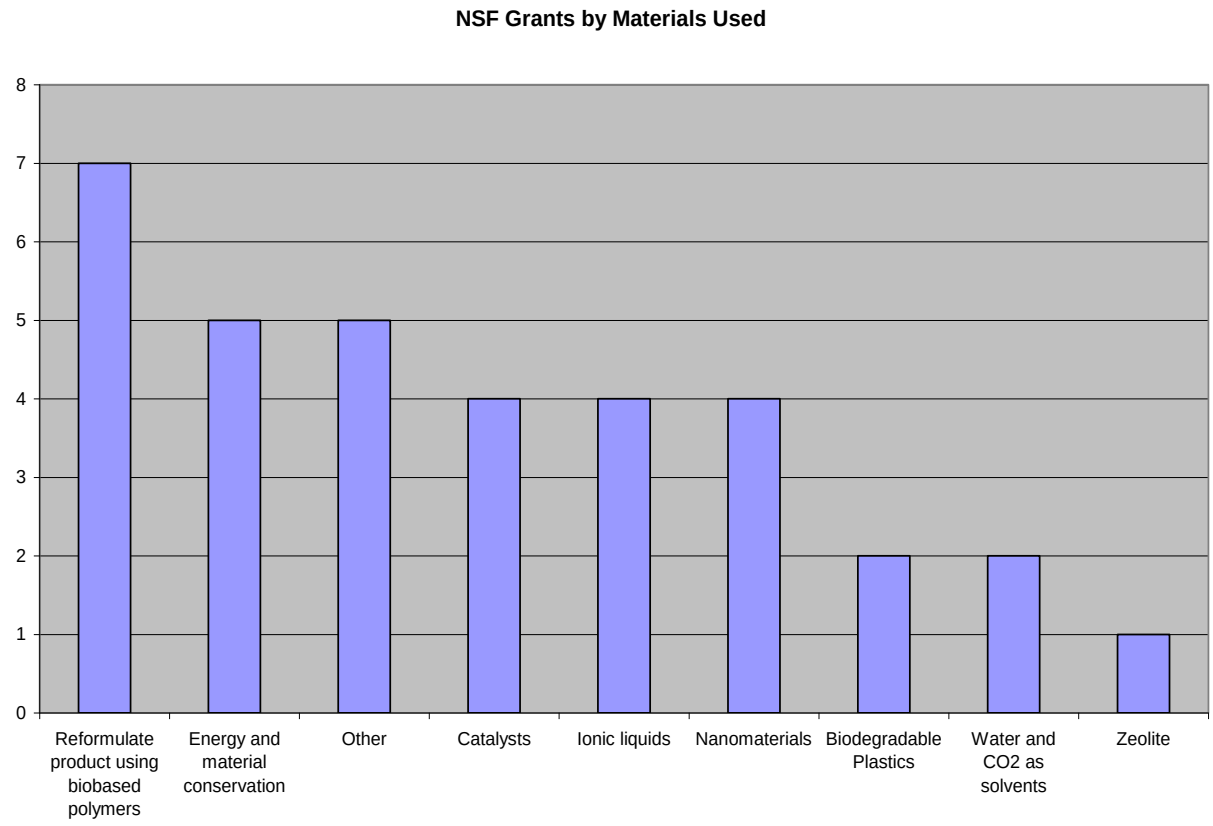

Figure 4.9: NSF Green Chemistry Research sorted by Materials Studied adapted from NSF data (NSF, 2009, Grants)

4.1.2.2 Other

We had great difficulty finding grants on other organizations' websites. We attempted a simple search feature using the phrase "green chemistry," which provided not only grant information about green chemistry but also general information. When we discovered the grants database, there was no option for a keyword search, but a drop down menu to choose from. Unfortunately, green chemistry does not fit in one specific category, so the information search was tedious. In addition, in some cases the information may be confidential, while in others the information is just very hard to find. The NIH, for example had a website where we were unable to find any information about whether or not they even give grants (NIH, 2009, Home). While several GC experts told us that National Institute of Health (NIH) was doing research in the field, we found no way for us to tell how much or in what areas they are funding research. One GC expert also referenced the ACS as having done research in the field, but we ran into the same problem of finding documentation on the subject (ACS, 2009, Grants).

One large project that we found is Emerging Frontiers in Research Innovation, and involves the Department of Energy (DOE), EPA and NSF. The project is still taking proposals and will begin in the next year. It will fund 14 different grants in green chemistry and sustainability for a total monetary value of $29 million. This is a very interesting idea since it is by far the largest single sum of money which we found in terms of grants awarded in green chemistry. Even with it being divided between 14 research projects, each grant will still be a very substantial contribution to a research project.

4.1.3 Overall GC Grants

Overall Trends

We performed an analysis and comparison between the grants given by the STAR program in NCER and the grants given by NSF (EPA, 2009, STAR Grants). While the two programs funded projects in very different areas, several trends appear when examining the data. The areas receiving the most money are still the areas with the most grants for each individual program, but there is a much wider span of categories funded.

Projects that ended up organized in the "Other" category were most interesting. This category is formed from projects which are unrelated to any of the previously established categories. This shows that between the STAR and NSF grants, scientists fund a wide array of topics within green chemistry.

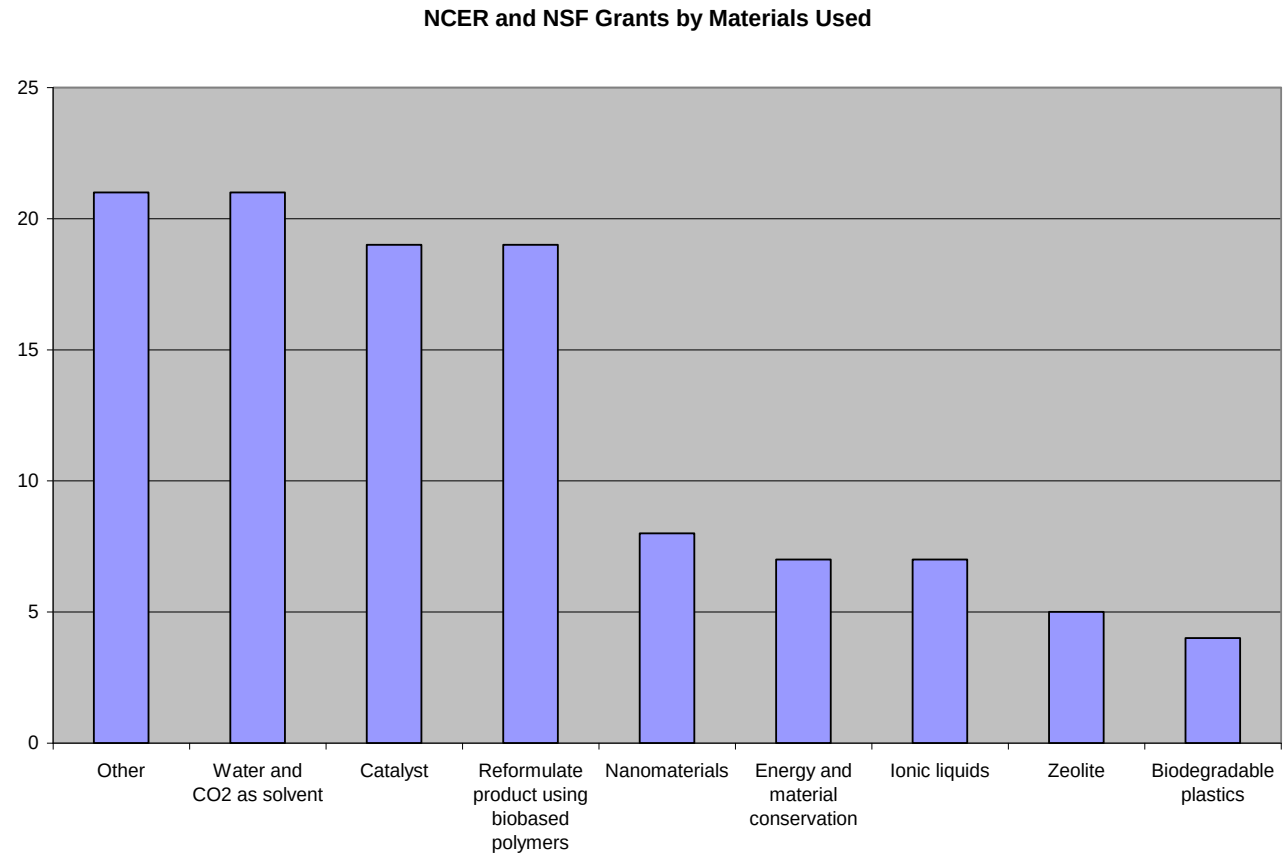

Figure 4.10: STAR and NSF Green Chemistry Grants Sorted by Materials Used adapted from both EPA and NSF Data (EPA, 2009, STAR Grants)

4.1.4 Final analysis

One of the major issues that we have run into is that scientists are simply not using green chemistry in their lab practices and chemical processes. In talking with an expert in the field of green chemistry, we discovered many different reasons why that could be (See Appendix J, Interview with Rich Engler). In many cases, scientists are unaware of green chemical processes and will therefore use a process, which is inferior in sustainability or toxicity. Without a database or central repository of information on green chemical processes, researchers and scientists have no way of determining what green chemical processes have been developed. Scientists in general also have a lack of knowledge as to how beneficial green chemical processes can be. Green chemistry is more cost effective than non-green chemistry because green chemical processes save money on waste disposal, as well as material in the overall process through the recycling of solvents.

Another major issue is the accessibility of data to the public. Much of the information involved with green chemistry research is proprietary for companies conducting the research, and is therefore confidential. This information could be very beneficial to industry and researchers, but cannot be published to the general public. Aside from the issue of confidentiality, there is also the problem of organization. Data from green chemistry research is scattered throughout many different agencies, both public and private, with no discernable way to search for specific information. This scattering of data makes finding anything specific almost impossible.

4.2 Assessment of Computational Toxicology Research

Computational toxicology is a relatively new field that has developed within the last decade. Several organizations have been involved in toxicology research, including the Environmental Protection Agency, as well as other government organizations like the National Toxicology Program. Current toxicological research involves developing accurate and reliable modeling systems to predict toxicity of chemicals.

4.2.1 NCER funded Research: STAR Grants

The National Center for Environmental Research has funded the field of computational toxicology by supporting individual PIs (Primary Investigators) through STAR grants. To date, NCER has given out a total of $3,197,519 dollars to computational toxicology grants, which represents about 1% of NCER's $444.8 million dollar budget from 2003-2008. This funding has gone to seven projects that have developed computational models or used computational models to test the toxicity of a chemical. The list of these grants are in Appendix S. None of the STAR grants have gone to education in computational toxicology, either through education initiatives or research fellowships.

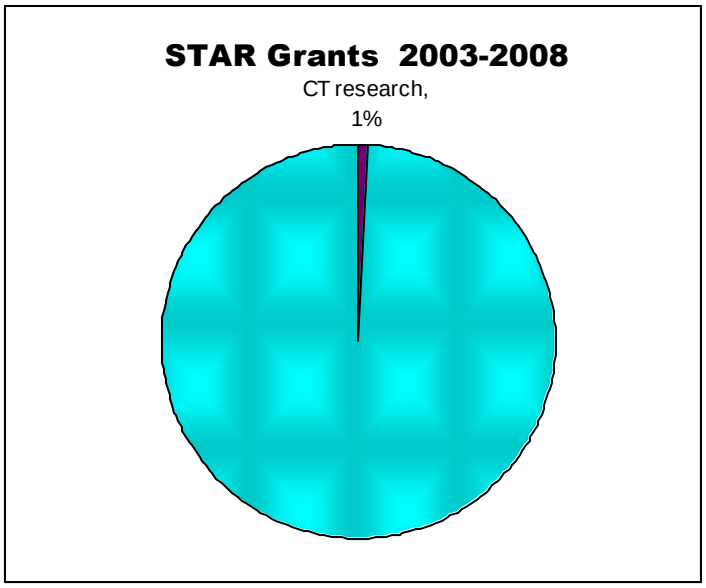

Figure 4.11: NCER Funded STAR grants (2003-2008)

These projects have used a wide variety of computational methods to test chemicals, including microarrays, high throughput screening, and reporter genes. These techniques are different ways to scan chemicals quickly for attributes using automation, and ways to study genetics. As seen in Figure 4.12, large amounts of funding went into computational studies using high throughput screening, and QRT-PCR (which measures protein function and gene expression). Less funding went into QSAR models because, according to experts, these are not as accurate at predicting toxicity, but are better at studying chemical properties. In addition, most of the projects funded used systems biology as a way to conceptualize toxicological methods, as compared to the more traditional view of biology.

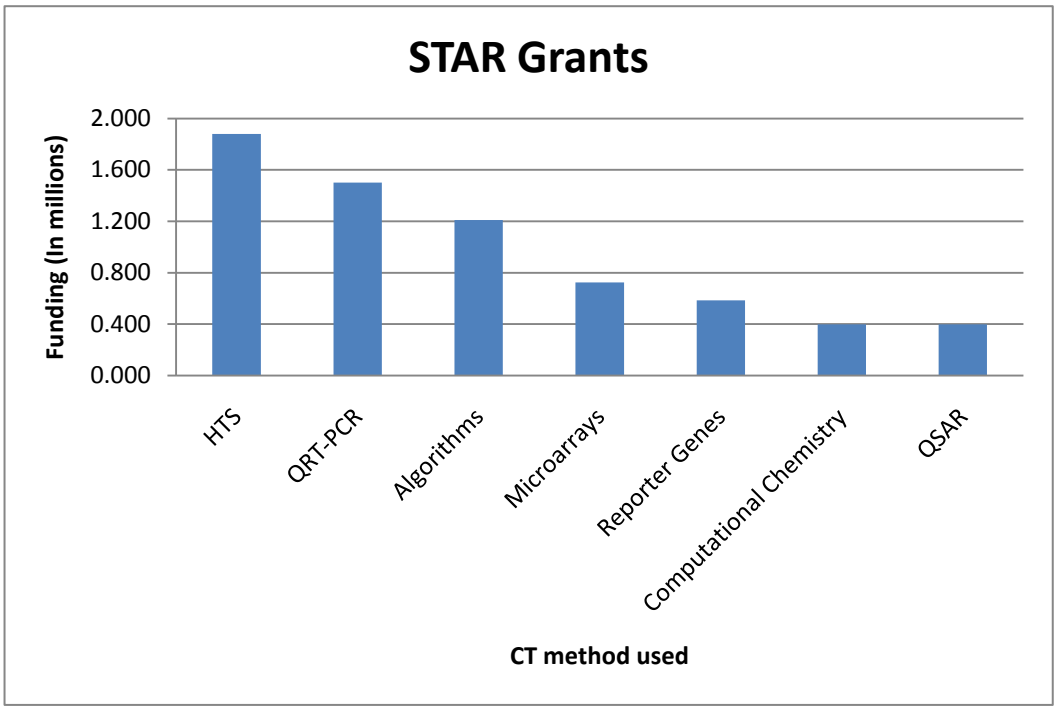

Figure 4.12: NCER funded computational Methods (adapted from Research Project Database | NCER | ORD | US EPA, Computational Toxicology)

These NCER STAR grants were used to study a variety of chemicals and their affects on living systems. Figure 4.13 shows how NCER funded different topics that were studied using computational toxicology. Five of the seven projects funded by NCER focused on the genetic affects of endocrine disrupting chemicals, which are an emerging pollutant of great concern to the EPA. Much less funding went to projects that studied chemical mixtures and nanoparticles, which indicates they are relatively new and/or underfunded areas of computational research.

In a 2007 report featured in the Reproductive Toxicity journal, Robert Kavlock (Leader of the NCCT) identified chemical mixtures as one of the areas that the EPA needed to target for improved risk assessment (Kavlock, 2007, p. 269). In addition, the Human Health Research Program (a part of the ORD) has a program involving risk assessment of chemical mixtures,

which indicates that the EPA is interested in further research involving the effect of mixtures on human health and the environment.

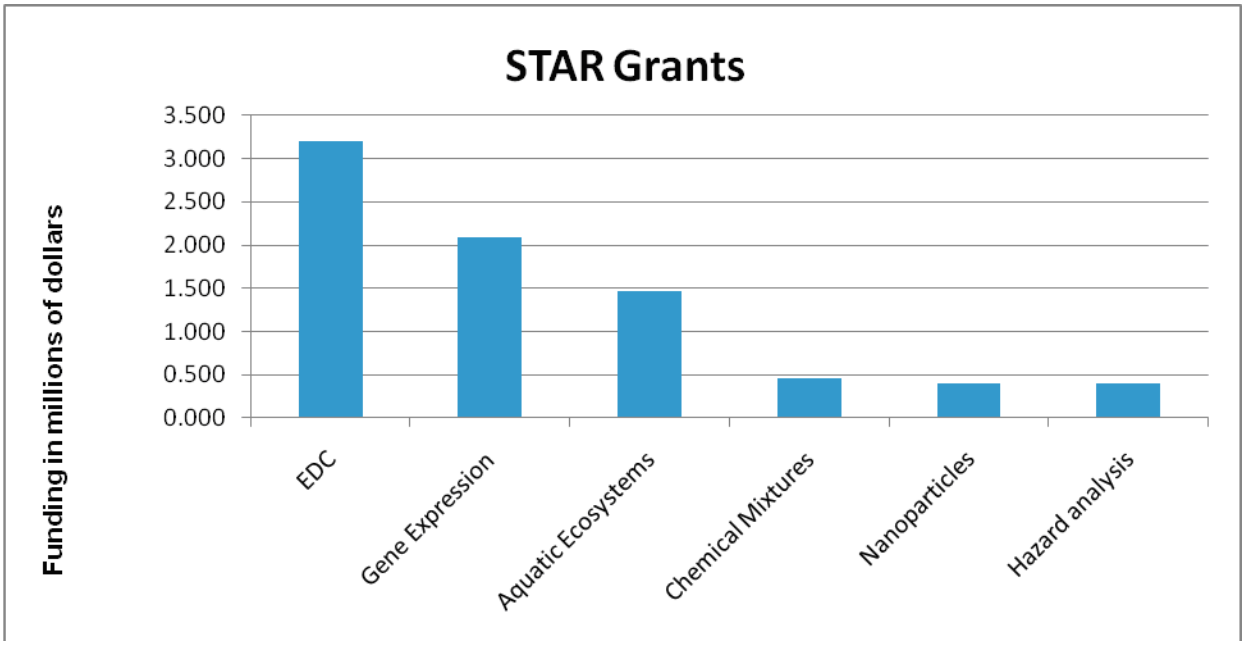

Figure 4.13: NCER Star Grants: Topics Studied in Computational Toxicology (adapted from Research Project Database | NCER | ORD | US EPA, Computational Toxicology)

In addition to the seven STAR grants, the NCER has funded one SBIR research award. The NCER SBIR grant was a phase 1 grant for $69,784. This grant was given in 2006, and as 1 of 41 grants given out that year it represents about 2.4 percent of the SBIR budget for that year. (Research Project Database | NCER | ORD | US EPA, Computational Toxicology) This grant was for a project that used high throughput screening to develop a modeling system for in vitro organs. This SBIR project was a response to a 2006 solicitation regarding computational toxicology projects funded by NCER.

4.2.2 NCER funded Research: STAR Centers

The majority of NCER's funding towards the field of computational toxicology has been invested in four computational toxicology centers, which perform cutting edge research in the field of computational modeling systems as well as conduct a wide variety of toxicology research. To date, NCER has given the four centers a total of $16,507,240 (See Figure 4.14). The funding is split unevenly among the centers, with the earlier centers receiving more money than the newer centers.

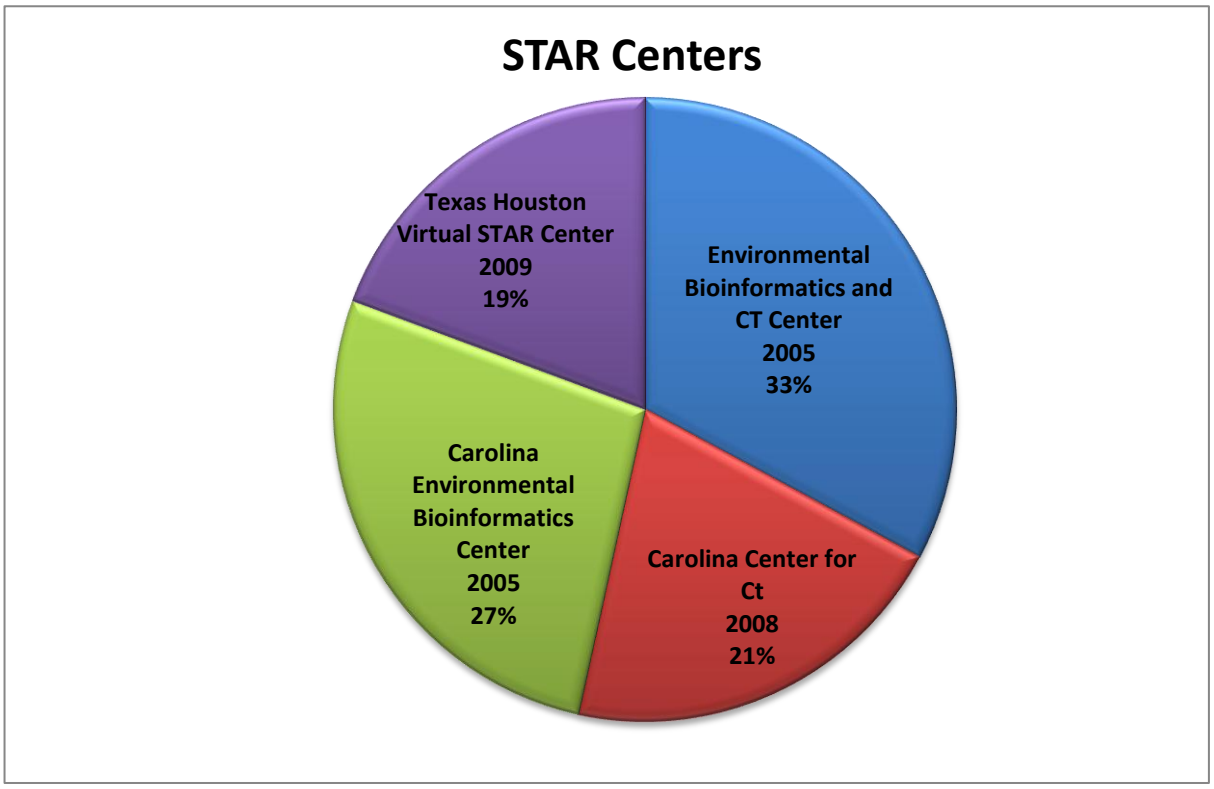

Figure 4.14: STAR Center Funding

4.2.2.1: Center 1: Environmental Bioinformatics and Computational Toxicology Center

The Environmental Bioinformatics and Computational Toxicology center received $5,422,135 dollars in 2005, making it the first STAR center funded. (Environmental

Bioinformatics and Computational Toxicology Center| Research Project Database, October 24, 2005) Its main objectives are to investigate the source to outcome paradigm, and to develop a variety of chem-informatic tools that will help predict toxicity. In the past five years, this STAR center has taken part in five research projects, which are in Table 4.1. These research projects have helped develop accurate predictive modeling systems.

Table 4.1: Environmental Bioinformatics Center Research Projects (adapted from Environmental Bioinformatics and Computational Toxicology Center| Research Project Database, Approach, October 24, 2005)

Project Title	**Goal**	**keywords**
Development and Application of a Dose-Response Information Analysis [DORIAN] System	Provide framework for other projects creating a web knowledge base Use Bayesian modeling to edit computational toxicology pathways Enhanced tools for risk assessment	Statistical modeling and risk assessment
Hepatocyte Metabolism Model for Xenobiotics	Creating analysis tools to identify toxicologically relevant genes and networks, and transcriptional regulation, and an expanded hepatocyte metabolism model	Hepatocytes, xenobiotics, gene function and expression
Tools for Optimal Identification of Biological Networks	Develop tools to analyze biological network structure and extract quantitative data Develop tools to identify biochemical pathways	Biological networks, molecular targets, feedback loops

Chem-informatic tools for Toxicant characterization	Create decision forest framework for toxicant characterization, including shape signatures tool polynomial neural network, and virtual HTS screening methods	Toxicant characterization, vHTS, chem-informatic tools
Optimization tools for In silico proteomics	Create computational models for protein structure prediction, and peptide and protein identification	Mass spec, proteomics, signal transduction networks

4.2.2.1-The Carolina Environmental Bio informatics Center

The Carolina Environmental Bioinformatics Center received funding through a grant of $4,494,117 at the same time as the Environmental Bioinformatics and Computational Toxicology STAR center. This center employs multiple investigators within the field of biostatistics, computational biology, chem-informatics, and computer science. (Carolina Environmental Bioinformatics Center| Research Project Database, objectives, 24 Oct. 2005) The center has published 81 papers to date, and has divided its work into 3 major project areas, which can be seen in table 4.2.

Table 4.2: Carolina Environmental Bioinformatics Center Project Areas (adapted from (Carolina Environmental Bioinformatics Center| Research Project Database, approach, 24 Oct. 2005)

Project Areas	**Goal**	**keywords**
Biostatistics in Computational Biology	Perform analysis and develop new methods	biostatistics
Chem-informatics	Coordinate data mining and perform	QSAR data,

	analysis of QSAR data	computational models
Programming support	Computer programming support to develop projects 1 and 2	

4.2.2.3 The Carolina Center for Computational Toxicology

The Carolina Center for computational toxicology started in 2008 with a $3,400,000 STAR grant. The center plans to develop complex predictive modeling systems from a mechanistic perspective, where researchers try to understand underlying biochemical mechanisms of toxicity. (Carolina Center for Computational Toxicology| Research Project Database, Objectives, May 29, 2008). The PIs who work at the center have expertise in three sub-disciplines: biomedical modeling of how chemicals affect different biological networks, toxico-genetic modeling, and chem-informatics. This center is focusing on risk assessment usability, and plans to make its computer models available to the public.

4.2.2.4 The Texas Houston Virtual STAR Center

The Texas Houston Virtual STAR center is the newest STAR center, which started in November 2009 with a $3,190,993 STAR grant. This center focuses on risk assessment through in vitro and in silico screening of chemicals for developmental defects (The Texas-Indiana Virtual STAR Center, 2009, Objectives). The center plans to approach their goal through three objectives, which are in Table 4.3. Researchers will make this data available to the public as it is published and verified, to help understand at a deeper level the developmental defects caused by a wide variety of toxins.

Table 4.3-Texas Houston STAR Center Goals (adapted from The Texas-Indiana Virtual STAR Center; Data-Generating in vitro and in silico Models of Developmental Toxicity in Embryonic Stem Cells and Zebrafish| Research Project Database, Approaches, August 10, 2009).

Goal	**Keywords**
Generate developmental models suitable for high throughput screening using zebrafish and embryonic stem cell models.	HTS, developmental models, morphology features, signaling pathways, environmental pollutants
Generate models that recreate morphological features of zebrafish development and compare with in vivo data to test the validity of model and determine how defects occur	Vascular and neural development, developmental defects
Perform proof of concept experiments	Chemical testing, computer modeling

4.2.3 The National Center for Computational Toxicology

The National Center for Computational Toxicology is a part of the EPA's Office of Research and Development. The goals of this center are to advance the field of computational toxicology through developing computational modeling systems and to develop a better understanding of chemical risk assessment (Appendix B for more information about the structure and goals of the NCCT). Since 2005, the NCCT has been involved in several long-term projects, including the ToxCast program and the v-liver program (Research Activities |NCCT, Research Activities, September 15, 2009). In addition to these projects, the NCCT has published fifty-three papers regarding different aspects of computational toxicology. Some of these papers are analyses of projects, and some of them are new discoveries.

The NCCT uses a variety of computational methods to determine toxicity, including studying both the molecular reactions of a compound and how they affect how compounds interact with the body at a genetic level. Over the past five years, most of their publications have involved pharmo-kinetic modeling, which is the process of how compounds move throughout the body (See Figure 4.15: NCCT Publications and Toxin Analysis Methods). There are no clear

trends as far as funding from year to year, so it appears that the NCCT is focusing on different aspects of CT as they become more relevant.

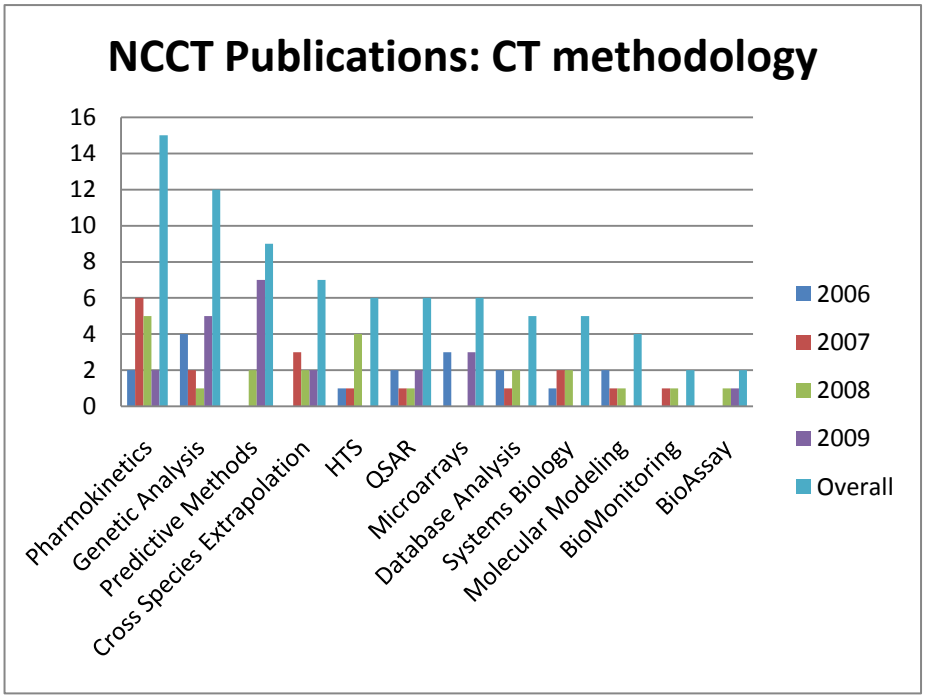

Figure 4.15: NCCT Publications and Toxin Analysis Methods (adapted from National Center for Computational Toxicology | US EPA, 2009, Journal Articles).

The NCCT studies the effects of both chronic and acute exposures to toxins, as well as determining routes of exposure and performing risk assessment. In the past four years, the NCCT has focused most of its research in the field of risk assessment, to determine what compounds are toxic and at what doses (See Figure 4.16: NCCT Publications: Aspects of CT Studied). Scientists have studied in depth the effects of chronic and acute chemical exposures, which makes sense because chronic toxicity is very hard to study since it takes place over such a long period, and the correct predictive models have yet to be built to study this.

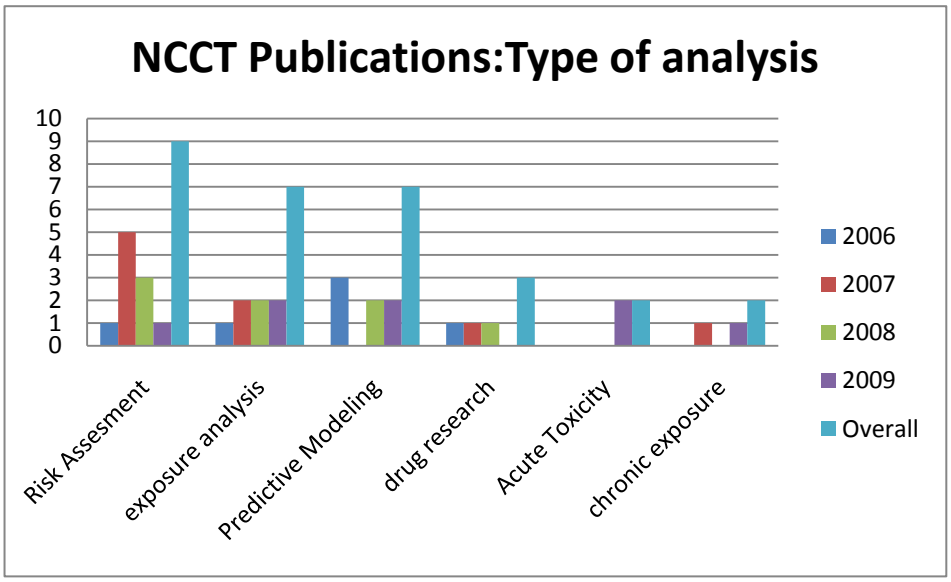

Figure 4.16: NCCT Publications: Aspects of CT studied (adapted from National Center for Computational Toxicology, US EPA, 2009, Journal Articles).

In addition to studying different types of toxicity, the NCCT has studied how different toxins affect the body. They have done research within the field of developmental defects, carcinogens, and reproductive defects equally (see Figure 4.17: NCCT Publications: Toxic effects). There has also been some scattered funding within the field of hepatocytes, and the majority of the funding has gone into genetic research.

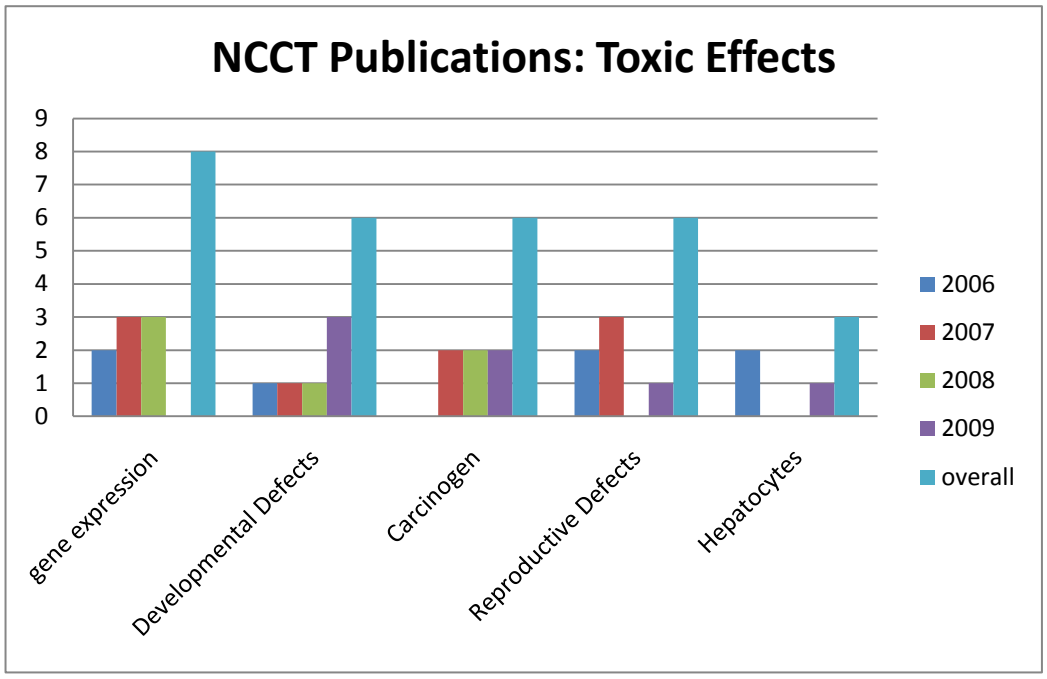

Figure 4.17- NCCT Publications: Toxic effects

The NCCT studies a variety of chemicals through computational toxicology. Most of the compounds studied have received only one or two grants, but PFOA and Triazole antifungals have both received six grants over several years (see Figure 4.18-NCCT Publications: Compounds studied). This indicates that these two compounds are serious problems that the EPA feels need further analysis. Pesticides have known toxicities, but the NCCT is studying them because of their part in the ToxCast program.

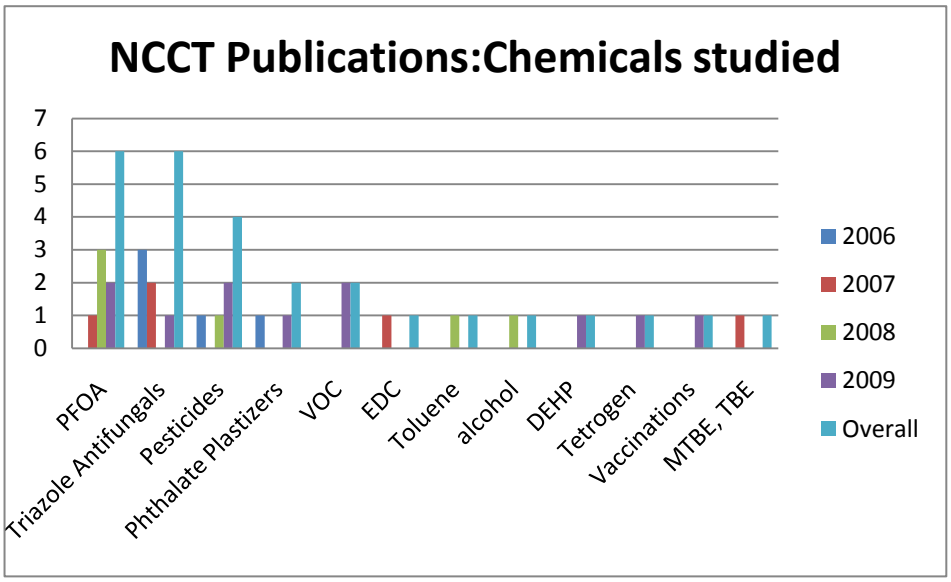

Figure 4.18: NCCT Publications-Compounds Studied (adapted from National Center for Computational Toxicology, US EPA, 2009, Journal Articles).

4.2.4 The ToxCast Program

The National Center for Computational Toxicology runs the EPA's primary chemical prioritization program, which is the ToxCast system. This program uses hundreds of high throughput screens to analyze the toxicity endpoints of thousands of different chemicals. It started in 2007, and at the current time, phase one of this project is complete (See Figure 4.19). Phase one of this project was the proof of concept phase, when scientists tested 300 chemicals with 235 chemical bioassays using high throughput screening. Most of the chemicals tested during this phase were pesticides with known toxicities, including tumorigens, as well as developmental and reproductive toxins. (November 20, 2009, US EPA,) The results of these screens were compared with the previously known in vivo data through a relational database known as Toxref. This helped determine how well the program could predict toxicity.

Table 4.4: The Phased Approach to Development of Bioactivity Signatures (Kavlock, Page 626, 2007).

Phase	Number of Chemicals	Chemical Criteria	Purpose	Est. Cost per Chemical	Target Date
I	>300	Data Rich (pesticides)	Signature Development	$20k	FY07-08
II	>1000	Expanded Structure and Use Diversity	Evaluation and Extension	$15-20k	FY08-09
III	Thousands	Data poor	Prediction and Prioritization	$10-15k	FY10-12

According to NCCT scientist Tom Knudsen, the ToxCast system is currently in its second phase of testing, where NCCT researchers have expanded the assays to include 228 cell based assays (See Appendix L: Interview with Tom Knudsen). Researchers are testing 1000 additional chemicals that have known toxicology in order to expand the diversity of the ToxCast database. Once this phase is complete, which should happen around 2010, scientists will be able to expand the ToxCast database to include thousands of environmental chemicals. This presents an inexpensive way to perform toxicological tests. The NCCT also plans to use information from this database when designing their virtual organs.

At the current time, scientists at the NCCT as well as NCER scientists have estimated ToxCast's predictive capability to be about 60-70% (see Appendix L). Tom Knudsen explained that the newer biological assays are less accurate than the chemical assays originally used in phase one of testing. The scientists at the NCCT have had a difficult time performing some of the tests due to the chemical properties of the pesticides they are testing. In spite of this, the ToxCast system is very effective at predicting the chemical and physical properties of other compounds, and represents a promising way of determining toxicity.

4.2.5 The ACToR (Aggregated Computational Toxicology Resource) Database

The NCCT has developed a database known as the Aggregated Computational Toxicology Resource (ACToR) in order to organize and analyze computational toxicology data. This database was compiled by Richard Judson of the NCCT, and is a large collection of the toxicity data from over two hundred different databases of environmental chemicals (Home | ACToR | US EPA, November 20, 2009). In addition to the data compiled by the NCCT from the ToxCast program and Tox21 MOU, this database contains information from other computational toxicology groups, as well as information from chemical companies and universities. It includes information from other organizations that conduct toxicological tests, including the FDA (Food and Drug administration), WHO (World Health organization), USDA (US Department of Agriculture), DEA (Drug Enforcement agency), OSHA (Occupational Safety and Health Administration) and the DOE (Department of Energy). Finally, it includes public information about the chemicals that are tested by outside companies in the United States and Europe through the TSCA and REACH databases respectively. (For more Information, see section 4.3.1)

The ACToR database contains search options based both by name and synonym, but also by chemical structure. In addition, this database creates results of chemicals with related properties. It gives information that includes not only different types of toxicities (developmental, reproductive, etcetera) but also chemical, biological, and manufacturing data, in addition to regulations regarding the chemical.

The ACToR database is well organized with an easy user interface, and has large amounts of toxicology information and other chemical information that could be useful to other scientists outside of the NCCT. However, some of the green chemists we interviewed used other

chemical databases, which are not available to the public (See Appendix J: Interview with Rich Engler). The ACToR database has not been not widely used because green chemists simply are not aware of the uses of the ACToR database, or have found more relevant information within the databases they currently use.

4.2.6 The Tox 21 Memorandum of Understanding (MOU)

The National Center for Computational Toxicology does not act alone to develop computational techniques, but collaborates with other government organizations who are interested in computational toxicological testing through the TOX 21 initiative. This five-year Memorandum of Understanding (MOU), triggered by the national research council's report *"*Toxicity Testing in the 21st Century: A Vision and a Strategy*."* (Schmidt, Charles, the Tox21 Partnership, 2009). This partnership utilizes the strengths of the National Center for Computational Toxicology, the NIEHS National Toxicology Program, and the NIH national human genomics project.

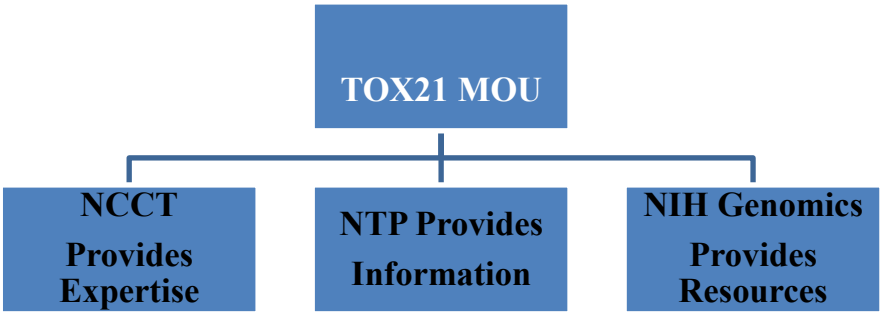

Figure 4.19-Tox 21 Organization Chart

Each of the three organizations has different strengths and focuses, but they work together to further the field of computational toxicology (See Figure 4.19). The National Center

for Computational Toxicology has the most expertise and experience with computational methods (See Appendix L: Interview with Tom Knudsen). The NCCT has fewer resources than the other two organizations because it is a new organization.

The National Institute of Environmental Health Sciences runs the National Toxicology Program, which is a part of the NIH. The NTP focuses on industrial chemicals, and mainly performs testing through in-vivo animal tests (Testing Information -National Toxicology Program, 14 July 2005). According to experts at the NCCT, the NTP supplies the organization with information about all the industrial chemicals they have tested (See Appendix L). This information is invaluable to systems biologists when they begin to build computer-modeling systems, because it helps fill in data gaps so that fewer chemicals need to be tested.

The NIH national genomics center recently received a grant of 3.5 million dollars to develop their high throughput screens, which can be useful for genetic analysis and for computational toxicology. These HTS are extremely powerful; "In a week, depending on the nature of the assay, it can yield up to 2.2 million molecular data points derived from thousands of chemicals tested at 15 concentrations each" (Schmidt, Charles, Introduction, 2009). The NIH genomics center provides these resources to the NCCT to scan thousands of chemicals quickly to determine toxicity.

Since each organization has its own goals and focus for toxicology research, their scientists test different chemicals and use slightly different techniques. In order to collaborate, these organizations share all published data and meet four times per year to discuss the data they have produced and strategies to advance the field (See Appendix L: Interview with Tom

Knudsen). Through this MOU, each organization can focus on its individual goals but continue to assist each other and advance the field of computational toxicology.

4.2.7 Computational Toxicology in other Government Organizations

Many other organizations test chemicals for toxicity and could benefit greatly from computational toxicology. The NIH has sponsored three projects in the field of computational toxicology for a total amount of $4,160,114 (NIH, 2009, NIH Search Page). Information about these projects is in Table 4.3. This funding represents a very small amount of the NIH's 163 billion dollar funding to grants over the past eight years (see Appendix C: Other Funding Agencies and their Budgets). The NIH has sponsored toxicity testing mainly through the National Institute of Environmental Health Sciences, as part of the TOX 21 initiative. This money went towards the high throughput assays used to test chemicals.

The main initiative of the NSF involves research in the areas of high throughput analysis. The NSF has not directly sponsored any grants involving computational toxicology methods, but has used the technique of high throughput technology to synthesize some chemicals. We found four projects funded in the area of high throughput technology that amounted to a total of $1,122,272. This funding is split between SBIR grants and research grants given to universities. Due to the way that the NSF grant process is set up, it is difficult to apply for projects involving multidisciplinary fields, including CT. According to Dr. Paul Anastas, this is a major impediment to computational toxicologists applying for funding.

The FDA and the CPSC also do a limited amount of toxicity testing. They have considered the field of computational toxicology to gather information. The National Center for Toxicological Research, an FDA program, has sponsored research involving QSAR modeling to predict toxicity of dioxins (National Center for Toxicological Research, 2009, Research at

NCTR). The FDA is trying to focus on how QSAR models can be of use to the food industry to test food for salmonella or other biological agents. The FDA and CPSC have considered computational toxicology testing, but do not use it to make any regulatory decisions at the current time (Rizzuto, 2009, The Carolina Center for Computational Toxicology).

Although all these government organizations use toxicology for risk assessment, they have not fully developed communication methods to share toxicology information. According to Dr. Pasqual, this is because many of these organizations are testing completely different types of compounds for different properties (See Appendix N: Interview with Pasky Pasqual). However, since there is limited communication between agencies, they may be testing the same chemical or very similar chemicals and never know it. The TOX 21 MOU and the ACToR database are the main organizational methods that different groups are using to share computational information. Increased collaboration with regard to chemical information, and supplementing the ACToR database with more information would help develop more data that would be useful for developing models.

4.2.8 Pharmaceutical Companies and Computational Toxicology

Pharmaceutical companies and the EPA cannot collaborate on systems modeling or any computational analysis projects financially, because it would represent a conflict of interest (See Appendix N: Interview with Pasky Pasqual). Alternative collaborations with pharmaceutical companies are important because the technological discoveries made by pharmaceutical companies have indirectly helped the field of computational toxicology, specifically within the field of high throughput screening. Drug companies use HTS to analyze new drugs for a desired property, in contrast to toxicologists, who use HTS to screen chemicals for undesired properties.

The techniques used in both methods are extremely similar, and the development of HTS was one of the most important advances of the field of computational toxicology.

In addition to developing technology, pharmaceutical companies also share information. According to NCCT scientist Tom Knudsen, Pfizer has given the NCCT about 120 chemicals that they developed but could not use due to toxicity, which scientists discovered in testing or through clinical trials (See Appendix L: Interview with Tom Knudsen). This information is useful to computational toxicologists because it can help them develop modeling systems, and if other chemicals with properties similar to those Pfizer tested come up, they can extrapolate that those chemicals are unsafe too.

4.2.9 The Public Sector and Computational Toxicology

Through traditional toxicology methods, thousands of animals are sacrificed every year to identify compounds that are toxic, so that human lives are protected. There are many animal rights groups that oppose this testing, but the unpleasant reality has been that animal testing is necessary for risk analysis. The demand to reduce chemical testing caused the European Union to outlaw animal testing of cosmetics in 2003 (Franks, 2003, EU bans animal testing). Computational toxicology represents an accurate way to determine toxicity that will reduce or even eliminate animal testing, and animal rights groups like the humane society, PETA, and the animal liberation front focus on computational toxicology as the answer to the animal testing debate. Martin Stephens, The director of the humane society called the Tox21 agreement a "milestone," and said, "We believe this is the beginning of the end for animal testing. We think the [conversion] process will take about 10 years" (Weise, 2008, Three U.S. agencies aim to end animal testing). Animal rights groups have given a lot of coverage within their websites to computational toxicology, calling this testing "alternatives to animal testing."

4.3 Green Chemistry and Computational Toxicology Results and Analysis

Our goal was to find instances in which green chemistry and computational toxicology could work together to improve a scientific methods and help protect the environment and human health. Through our search through not only the EPA's database of grants but also the NSF and NIH databases, we were able to discover few grants that funded research in the areas of both green chemistry and computational toxicology. We also posed the question to people we interviewed within the EPA to see if they found any instances in which the two fields would fit together.

4.3.1 Research funded in Green Chemistry and Computational Toxicology

The best example of EPA and NSF funded research within green chemistry and computational toxicology is the Center for Environmental Implications of Nanotechnology (CEINT). An award created the CEINT in 2008 and received $1,000,000 from the EPA and $14,000,000 from the NSF (EPA, 2009, The Center for Environmental Implications of Nanotechnology). The center was created at Duke University and partnered with several other universities to educate students in the areas of environmental toxicology and ecosystem biology, nanomaterial transport, transformation, and fate in the environment, biogeochemistry of nanomaterials and incidental airborne particulates, nanomaterial chemistry and fabrication, and environmental risk assessment, modeling, and decision sciences. The study of environmental toxicology and the novel systems biology approach are fundamental concepts of computational toxicology, and nanomaterial chemistry and fabrication are topics of great interest to green chemists. Specifically, this center hopes to create discovery-based lab classes at the undergraduate level; interdisciplinary courses between scientists and engineers that show the connections between these various areas. This center could be a significant step towards bridging the fields of green chemistry and computational toxicology.

4.3.2 Chemical Databases in Green Chemistry and Computational Toxicology

The Environmental Protection Agency's Office of Prevention, Pesticides and Toxic Substances (OPPTS) controls all new and previously produced chemicals in the United States through the Toxic Substances Control Act. This act provides the EPA "with authority to require reporting, record-keeping and testing requirements, and restrictions relating to chemical substances and/or mixtures" (EPA, 2009, Summary of TSCA). All new and previously produced chemicals are required to go through some amount of chemical testing. Many chemicals fall under the jurisdiction of other agencies, including food, drugs, cosmetics and pesticides, so TSCA is responsible for the regulation of about 83 thousand chemicals.

TSCA requires information about a new chemical before it is manufactured (pre-manufacturing notification, or PMN).TSCA does not determine the toxicity of a substance itself, but analyzes the toxicity data provided by companies to determine if the compound is toxic, needs to be controlled, or needs to be further tested. TSCA can use these data to determine if a chemical needs regulations, by making specific requirements during use, use of hazard labels, or an outright ban (The Toxic Substances Control Act of 1976, 2005, an introduction to TSCA). According to green chemistry expert Rich Engler who works for EPA's OPPTS, it is very rare for a hazardous chemical to get an outright ban, but chemicals are usually subject to some type of regulation.

TSCA maintains all of the information provided by chemical companies in a permanent database known as the TSCA database. At the current time, the TSCA database contains information for over 83,000 chemicals (EPA, 2009, Summary of TSCA). Since this database is compiled with information produced by private companies, it is highly confidential and not

available to the public. The EPA verifies the chemical information given to them by companies and places new information into the database.

Green chemists use chemical databases to find chemical properties of new compounds, specifically toxicological data. According to green chemistry expert Rich Engler, the TSCA database, along with other books and websites that contain information about chemicals, are frequently useful for risk assessment of hazardous chemicals (See Appendix J: Interview with Rich Engler). These databases often lack vital data regarding mammalian toxicology, so there is no way for green chemists to have toxicity information when creating a new chemical.

In the future, computational toxicologists will be able to forecast toxicity using predictive modeling systems. These predictive modeling systems would easily be able to fill in the data gaps that are missing from databases that green chemists are currently using. In order for this to happen, computational toxicology data will need incorporation into chemistry databases used by green chemists in order for the predictive modeling systems to be used by both fields.

Since the TSCA database is confidential, incorporating these data will be extremely difficult. Most computational toxicologists do not have access to the database, and it is hard to find out any specifics about what chemicals are contained in the database, or how they were tested. In a phone call with the TSCA hotline, an EPA representative could not give any information about how private businesses tested their chemicals or even how or where TSCA gathered toxicity data.

4.3.3 Interviews to discover connections in green chemistry and computational toxicology

Responses to our questions varied between each person we interviewed, as not all were experts in both green chemistry and computational toxicology. Green chemistry experts said they

were not knowledgeable in computational toxicology, while toxicologists and health scientists said they were unaware of green chemistry. We then provided more background information on the field the person knew less about, and found they actually knew more about it then they previously thought. We showed the twelve principles of green chemistry (EPA, 2009, Twelve Principles of Green Chemistry) to each person we interviewed, and asked them to pick out what principles computational toxicology follows. The three principles that always ended up on their list were numbers three, four, and five.

- Principle Three is **"less hazardous chemical synthesis,"** which is an obvious choice as computational toxicology will help determine which chemicals are toxic and eliminate their use.

- Principle Four is **"designing safer chemicals,"** which also is an outcome of computational toxicology.

- Principle Five is **"safer solvents and auxiliaries,"** and in computational toxicology, those solvents are being tested for toxicity and, if toxic, should not be used in chemistry practices. In using fewer chemicals in testing, computational toxicology is already a greener process.

Computational toxicology can be viewed as a "greener" method of performing traditional toxicity testing by altering testing at a fundamental level. Using solely in vivo methods, millions of animals are sacrificed per year. These animals produce large amounts of waste, and testing for toxicity uses medical supplies that are all discarded as "biological waste". According to a scientist at the NCCT, computational toxicology produces less chemical waste and uses fewer animals, which makes it intrinsically greener (see appendix L: Phone Interview with Tom

Knudsen). By funding research in computational toxicology, NCER is indirectly promoting green chemistry because it is funding a process that reduces hazardous waste production at a basic level.

We next asked experts what the two fields could accomplish if scientists became more aware of the usefulness of both fields. From interviews with computational toxicology experts, we found out that they believe that computational toxicology could test green chemicals and identify any toxic properties of those substances. In addition, computational models could help to determine how the structure of a green chemical would behave in a reaction by comparing it to similar structures. This information is produced from predictive modeling systems and can be found in the ACToR database; however, most green chemists are unaware that this information is available. Green chemistry experts also feel that the use of computational toxicology databases would be helpful in the testing and creation of green chemicals. Computational toxicology could predict the toxicity of a chemical without actually running a laboratory test, saving time and money. Computational toxicology can scan chemicals while they are in the development stage so that green chemists could eliminate potentially hazardous chemicals sooner in the design process, before these chemicals go into further production and testing.

Green chemistry experts also noted that there have been instances where green chemistry and computational toxicology relate in research; however, people do not recognize them as related fields. The chemical company CEM did a project involving sprint protein analysis using fluorescent markers, and that method is common in computational toxicology. The project may not relate to computational toxicology, but it used some of the methods that are developing in the field of CT. Experts from NCER also pointed out that not all green chemists design their chemicals from a holistic perspective and may not choose the process or the reagents that are

least harmful to the environment. Ideally, a chemist would begin to plan a process by focusing on molecular interactions of chemicals. This is where the predictive models used in computational toxicology, including developed QSAR models, could play a role in chemical development. (Kavlock, 2009, p.268).

Through an interview with green chemistry expert Paul Anastas, we discovered that there are efforts currently going on to discuss computational toxicology within green chemistry (see Appendix O: Phone Interview with Paul Anastas). When we interviewed Dr. Anastas, he had recently left the Industrial Green Chemistry Workshop 2009 in Mumbai, India (Industrial Green Chemistry, 2009, Industrial Green Chemistry Conference 2009). He pointed out to us that topics included in this conference discussed computational toxicology. One speech was titled "A revolution in the environmental health sciences: New challenges to the safety of common chemicals in commerce." This shows that green chemists are recognizing the importance of creating green chemicals that are also not going to be toxic to consumers. This conference, however, was geared towards workers in industry, and not the entire green chemistry community, which is made up of academics and researchers.

Upon further research based on suggestions from Dr. Anastas, we discovered that the American Chemical Society (ACS) Green Chemistry Institute has information about several upcoming conferences in green chemistry including one to implement Greener Chemicals Product and Process Standards (American Chemical Society, 2009, Green Chemistry Conferences).

Green chemistry and computational toxicology experts both believe that a combined database could help link the fields because much of the information is useful to both fields.

Currently, each field has its own independent database to look up the properties and structures of chemicals. Neither database individually is developed enough to stand alone for sharing information with experts in both fields, but through the combination of information between the various databases, a more complete knowledge of certain chemicals will be present in one location for scientists to research. Experts also discussed the REACH system in Europe, which involves the collaboration of a large database for use in chemical research, and they believe that the United States should move towards a similar system. Gathering data for this database from private companies may be difficult due to intellectual property laws. Due to these existing laws, companies may already have available information regarding the toxicity of a chemical, but are unwilling to share with competitors to give them a head start in the research of a product or chemical process. Experts from both fields believe that the unavailability of research information is stifling the growth of both the fields of green chemistry and computational toxicology.

We also found that the twelve principles of green chemistry were not highly publicized. Some health scientists and toxicology experts had never even seen the Twelve Principles of Green Chemistry before, but once seen, they noticed that computational toxicology does effectively carry out some of the Principles of Green Chemistry. In providing this information to them, we were able to give these experts insight into green chemistry and something to consider with future work in the field of computational toxicology.

Another recommendation made by experts to help advance the fields of green chemistry and computational toxicology was to raise awareness about their fields. Some scientists are already participating in greener practices and are leaning towards computational models, but do not necessarily call their work “green chemistry,” or “computational toxicology.” Through raising awareness of the fields, both fields can grow and become a more mainstream scientific

practice. These experts also believe increased awareness could help other scientists who are reluctant to make their practices greener because they will feel the pressures of the entire scientific community, and not just a small group of green chemists and computational toxicologists that are currently interested in the widespread implementation of greener lab practices. They noted that the greener practices are usually more cost effective for businesses, however, many companies are against changing what is already working for them and having to spend the up-front money to train workers how to work the newer processes.

5. Conclusions and Recommendations

After conducting extensive research in the fields of green chemistry and computational toxicology individually, as well as inclusively, we were able to draw conclusions and make some recommendations not only on how to increase awareness of each field in the scientific community, but also to provide easier access to the information that is available in both fields. If these changes are made, there will be a significant growth within the individual fields of green chemistry and computational toxicology, as well as the connections between the two fields.

5.1 Conclusions and Recommendations for Green Chemistry

Through our research in the field of green chemistry, we made conclusions about the current state of the research. The research that NCER has funded in the past has led to useful advances in the field of green chemistry, however, there needs to be more innovation and fresh ideas in the research. The information on previously completed research needs to be easier to access in order to allow continuation of research as well as to use that information to help implement practices of green chemistry in a smaller lab setting.

5.1.1. Conclusions for Green Chemistry

- **The research that NCER has funded is too narrowly focused**

NCER has given too much funding in the area of using water and CO_2 as solvents, and not enough in the area of sustainability. This has limited the growth of the field. The research needs to spread out more amongst various areas of green chemistry in order to help advance all facets of the field. NCER currently has no budget for STAR grants in green chemistry, which has been the primary source of green chemistry funding from NCER in the past. This will further limit the

growth of the field. There has also been little funding into educating the public on the idea of green chemistry, an important area.

- **Scientists do not utilize green chemical practices due to a lack of publicly available data**.

Government agencies provide the information on grants they have funded in the area of green chemistry; however, finding that information on their websites is no small feat. Within the private sector, the information remains private, due to intellectual property laws. Without the availability of this information, researchers use old chemical practices because the old processes are more convenient or more familiar to them. This in turn slows the implementation of green chemical processes.

- **Researchers don't use green chemical practices because they feel that it isn't in their area of expertise**

It appears that scientists do not consider life cycle approach and the implications of a chemical before it is created. Scientists right now are still focusing on creating a chemical to perform a specified task, and may not consider the fact that this chemical can also cause adverse health effects. This focus could be due to a lack of knowledge in green chemistry. This causes some researchers to continue using more toxic and wasteful processes instead of looking into greener avenues to accomplish the same processes.

- **Green chemistry is not well known outside the field**

In talking with some environmental health scientists, we discovered that they knew very little about the 12 Principles of Green Chemistry. This led us to believe that researchers outside the field of green chemistry may be confused about its uses. This has a stifling effect on the

expansion of green chemistry principles. Another instance, noted in an interview with John Warner, was that people may already be using green chemistry, but they do not call it "green chemistry." This again, plays into a lack of awareness even within the field of green chemistry.

- **Many different agencies do the same testing and risk assessment for different results**.

Several different agencies could be testing the same chemical and looking for different results. One way to lessen waste and increase communication between different institutions that are doing green chemistry research is to integrate these risk assessment tests. If there were communication between the agencies, not only would they know what the other agencies were researching, but the different agencies could all use one test to determine many different risk factors of a chemical or process.

- **There is a general lack of knowledge about how to implement green chemistry practices**

In talking with some researchers who were familiar with the 12 Principles of Green Chemistry, we found that they sometimes were unsure about how they could apply the 12 Principles to their research. This shows a failure to inform researchers within the field of chemistry about the application and implementation of green chemistry.

5.1.2 Recommendations for Green Chemistry

- **There needs to be more breadth to the research NCER is doing in green chemistry**.

NCER must put more money into areas other than that of water and CO_2 for use as solvents. NCER must allocate more money to places like biodegradability and alteration of starting materials. The focus of funding thus far has been to improve one aspect of a process, but that only reduces the problem rather than eliminate it. More focus on starting from the beginning of a

process and making it fully green would greatly improve the field. One way for NCER to get many different applications for funding in green chemistry would be to have green chemistry as the "featured topic" in the 2010 SBIR solicitation. This will bring green chemistry to the forefront of the minds of anyone applying for an SBIR grant at that time. NCER should devote some of its funding back into STAR grants as well. These grants have been the main source of green chemistry funding through NCER over the years. If money cannot be focused back into STAR grants, then the P3 and SBIR programs should be more focused on the area of green chemistry to somewhat supplement the loss of the STAR grants. Money also needs to go into the education of the general populace. Education is an important tool for getting a concept accepted into common knowledge.

- **A database of green chemistry information should be created**

One of the main reasons that scientists do not utilize green chemical practices is a lack of publically available data. Therefore, in order for green chemistry to grow as a field there needs to be an increase in the amount of data that is available to researchers. In addition, scientists must organize these data in such a way that finding individual processes within a database is easy. The chemical database could include data about reactivity such as entropy and/or enthalpy of reaction for chemicals. This database should also be accessible online without any difficulty.

- **NCER should encourage more researchers to do work in green chemistry through education and funding**

Another reason why researchers might not use green chemical practices is that they think green chemistry research does not fall under their field of research, when in fact it can. The implementation of green chemistry is simple in virtually any process involving a chemical reaction and decreases the amount of harm on the environment, while saving money at the same

time. NCER should encourage more researchers to do work in the field of green chemistry through education and funding for research. With more funding available, more work can occur in the field, and green chemistry will expand at an accelerated rate.

- **Green chemistry should make itself better known outside the field**

In talking with some experts in the field of computational toxicology, we discovered that they knew nothing of the 12 Principles of Green Chemistry. These principles could be very useful in making their laboratory practices and chemical processes greener. Green chemistry should make an effort to distribute the 12 Principles out into the realm of common knowledge within the scientific community. One way to distribute information about green chemistry would be through the creation of a pamphlet. This pamphlet could include the 12 principles of green chemistry along with some simple examples of green chemical practices being utilized to exemplify to the reader how green chemistry can be applied.

- **Different agencies should communicate about what research they are doing in order to avoid repeat work**

Many different agencies do the same testing and risk assessment for different results. There needs to be integration in some work between agencies to reduce waste and increase communication. This is especially true if the research is conducted in-vivo, since there is much animal and material waste involved with in vivo testing. If even two of the same tests are integrated, that is a 50% reduction in waste.

- **More money needs to be put into educating the industry and the public about green chemistry**

NCER should put some money into education so that researchers will know more about how to apply the 12 principles instead of just knowing that they exist. Education will be the most important tool for making green chemistry acceptable in the realm of common knowledge, and thus NCER must begin to focus on the educational aspects of funding. One place that NCER could focus money in order to fund education is the STAR fellowships. Education will help to spread the word of green chemistry to the seasoned scientists working in industry, and to the up-and-coming students who will be looking for jobs in that industry in the near future. New workers could possibly provide some insight to a company on using green chemistry in their research. One way to educate students would be to incorporate green chemical practices into entry-level chemistry courses in universities. This would give students in many differing fields some idea of how to improve chemical processes.

5.2 Computational Toxicology Conclusions and Recommendations

The Environmental Protection Agency is one of the leaders in the novel field of CT research, with many different parts of the agency sponsoring different types of research. As computational models develop that can scan chemicals and accurately determine toxicity more quickly, the field will become more popular and widely developed.

5.2.1. Conclusions for Computational Toxicology

- **Computational Toxicology is not developed enough for accurate toxicity predictions**

From interviews with experts and analysis of current research, we determined that computational toxicology is not developed enough to accurately predict the toxicity of a compound. This is simply the result of computational toxicology being such a new field, so more scientists conducting CT research and more funding to this research will help these models

develop. NCER has funded computational toxicology in a variety of ways, with the majority of NCER funding going to four STAR research centers, which are developing and refining modeling systems. In order to develop accurate models to predict toxicity, it is important to have many data points. Many of the computational systems like the ToxCast system simply need more time devoted to this research so that they can get the data they need and be wholly developed. Other organizations, specifically external PIs, need more funding to continue their toxicological research.

It is important for computational models to develop fully before widespread use so that they are accurate, and gain the trust of the scientific community. Statisticians could manipulate data in such a way that computational models could easily be invalid if they are not backed up with lots of data. If scientists implement these models too early and they appear to be wrong about predicting toxicity, this will make people more hesitant to use the models and could stifle the growth of computational toxicology.

Although computational toxicology is not accurate enough to determine the toxicity of in vivo and in vitro systems for most chemicals, it is still able to predict limited toxicity information, as well as the chemical properties of compounds. Scientists currently use the ToxCast system to prioritize what chemicals need further testing. Using the ToxCast system to do limited toxicity testing, scientists are producing more endpoints and further refining the computational models. In using computational toxicology to do testing while in the developmental stages of ToxCast, and making this information publicly known through the ACToR Database, researchers are helping to expand the role of computational toxicology.

- **Computational Toxicology has the potential to greatly impact human life**

Computational toxicology has the potential to revolutionize testing by making it accurate in ways that traditional toxicology could not match. Since traditional toxicology is expensive and time consuming, extenuating factors are often not considered when producing toxicity information, which saves time but makes testing less accurate. One of the biggest opportunities for computational toxicology to become more accurate than traditional testing is considering multiple variables, including chemical mixtures, because in reality we are exposed to a wide variety of different chemicals that may impact our health when compounded together. Leading toxicological experts have identified chemical mixtures as an important subject needing more computational research. In addition, factors like stress may affect how our body reacts to toxins by altering our immune system. Computational toxicologists have the opportunity to account for these problems when developing computational models.

In addition, computational toxicology presents a realistic alternative to the controversial issue of animal testing. Scientists believe that the future of computational toxicology will significantly reduce and eventually eliminate the need to use animals to test chemical toxicity. This interests animal rights groups, and the public sector that frowns upon the ethical implications of sacrificing animals to scientific tests.

- **Computational Toxicology has many interdisciplinary applications**

Many other agencies or organizations that perform risk assessment through toxicological testing have a stake in the fate of computational toxicology. These organizations include the TOX21 MOU, which has created a direct collaboration between agencies in order to further

computational toxicology research. The Tox21 initiative shows how different agencies with different agendas can collaborate to work towards a common objective.

Other organizations, including the NIH, NSF, CPCS and external pharmaceutical companies, could benefit from computational toxicology, but have had limited interaction or experience with it. At the current time, computational systems are developed enough to predict reactions at the biochemical level, which could not only be useful to toxicologists, but other chemists and biologists. For example, computational models could make compounds that target specific cells or cell receptors. There has been little computational toxicology funding from these organizations compared to NCER, even though these organizations have much bigger budgets.

5.2.2 Computational Toxicology Recommendations

In order to advance the field of computational modeling, more models need to be developed, which will require more researchers and more funding. In addition to simply funding more research, NCER can help the field of computational toxicology grow by working with other agencies that have larger budgets and have more power than NCER.

- **Improve accessibility to toxicological information focusing on data centralization**

Since so many organizations test chemicals for toxicity, universal access to published computational data would help further the field of computational toxicology by providing researchers with more information and filling in data gaps. Since chemicals that have similar properties have similar toxicities, researchers could extrapolate many toxicity data and reduce testing by comparing toxicological results of different chemicals. The ACToR database includes a wide variety of toxicity data, as well as other chemical data, in one centralized location. The widespread use of this database could help centralize data and give researchers easier access to

similar information. In order for the ACToR database to develop, the NCCT will need to reach out to more organizations to put information into the database, as well as publicize what information is available. NCER can help aid the effort of centralizing data by funding projects that would contribute information to the ACToR database, as well as improving the publicity of this database by encouraging different organizations to look into its uses.

- **Improve communication between agencies**

Research funding could be increased and the money could go much further if different agencies could work together to distribute their funding. The TOX 21 MOU shows how companies can maintain their own goals while supporting computational studies in a way that is mutually beneficial. Other organizations that do toxicological testing could participate in the TOX21 MOU or collaborate with computational labs individually. Some of these organizations include the FDA, CPSC or any other organization that does toxicity testing. High throughput screening is so widely utilized that other organizations benefit from its advancement, including pharmaceutical companies. Even though pharmaceutical companies cannot collaborate financially, they could continue to supply information to the NCCT and other organizations that would be useful.

NCER can help organize this collaboration by increasing external and internal communication about the advancements and applications of computational toxicology that they have funded, and encourage companies who apply for NCER funded grants to apply for grants within other organizations. Since the grant process is difficult for interdisciplinary fields like computational toxicology, NCER might need to help different scientists with recommendations of what organizations would be interested in their research.

- **Work to make modeling systems more realistic**

In addition to considering the potential of computational toxicology to improve other fields, the EPA needs to consider how to improve the accuracy of computational toxicology by considering "real life circumstances." Computational models need to mimic real life circumstances by considering extraneous factors besides simple chemical testing. Some of these factors include environmental factors, such as mixtures of different chemicals, as well as human factors, such as how stress on the body affects toxicity. NCER can help improve the legitimacy of these models by funding research in topics like chemical mixtures, as well as consulting with health scientists when making funding decisions to determine what factors to consider.

- **Work to gain the support of other scientists and the public sector.**

Computational Toxicology is an interdisciplinary field, and many of the discoveries made within this field could be beneficial to other fields. Through increasing the publicity about the research toxicologists do and considering its broader implications, other organizations might be interested in funding or collaborating with toxicologists to further the cause. NCER can help promote interdisciplinary communication by increasing publicity of their research to other interested agencies, as well as sponsoring computational toxicology research projects with widespread applications. Small funding with these projects could "plant seeds," and encourage other agencies to also fund the project.

Computational Toxicology has the potential to affect not only human life, but the lives of animals sacrificed each year through traditional testing. Animal rights groups, as well as the media, have focused on the animal testing alternative aspect of computational testing, which has helped the NCCT and the Tox21 MOU gain a lot of publicity. The EPA and NCER should

encourage this publicity, and consider sending animal rights group's information about new discoveries and developments that would further reduce animal testing.

5.3 Conclusions for Green Chemistry and Computational Toxicology

Through our research in each individual field of green chemistry and computational toxicology, we were able to discover some areas in which the two fields were connected. From our interviews with experts, we determined that CT could test green chemicals faster than current methods, and provide useful information about chemical properties. Although CT is not developed enough to test toxicity, its methods could be useful for other aspects of green chemical analysis. We were able to make the following conclusions after analyzing our research.

- **There is a lack of communication between the two fields.**

The fields of green chemistry and computational toxicology are intrinsically related, but currently that relationship is not evident. From interviews, we discovered that computational toxicologists were unaware of how their research could benefit green chemistry, so much so that they were unaware of the twelve principles of green chemistry. Green chemists were also unaware as to how they could use computational models to predict chemical properties. This is mainly due to a lack of communication between experts within each individual field.

There have been some efforts towards advancing both fields simultaneously, as seen in the recent Industrial Green Chemistry Workshop 2009.The topics included in this conference geared towards green chemists to consider the environmental and human health impacts in the green chemicals they are creating. This is a step in the right direction of connecting green chemistry and computational toxicology, however, this conference was only for industry. Green chemistry not only includes industry, but also academia, and government agencies that provide

funding for this research. In order to bring about change in the entire field of green chemistry, all parties involved should be considered.

- **There is a lack of education in both fields**

Another area in which the two fields need work is improvements in education of scientists and researchers about interdisciplinary fields. P3 grants have gotten students interested in green chemistry, as have STAR fellowships from the EPA and NSF grants. Computational toxicology may still be in its early developmental stages, but the techniques that are being used now could be applied in various scientific applications, and therefore should be taught sooner than later, once the field is strong enough to stand on its own in the scientific community. P3 grants will have more difficulty including both green chemistry and computational toxicology because student teams decide what project they are interested in working on, and then apply for funding from the EPA. The NSF could however, fund either research or education. Through funding more grants that will help to create education curriculums, students who are up and coming in the fields of chemistry, biology, and engineering will be more aware of the practices of green chemistry and computational toxicology, and could help to implement them in the workplace in the future.

- **The information on the two fields is not easily accessible**

Each individual government agency has a different system of organizing their information on grants they have sponsored. Some are easier to use than others are and provide a search bar option, whereas other agencies have a drop down categorical list to choose from. The NSF and NIH websites are difficult to navigate and make it hard to find information about the

research conducted in the fields of green chemistry and computational toxicology, let alone to find any connections between the two fields

5.4 Recommendations for Green Chemistry and Computational Toxicology

Due to the lack of communication and education in the fields of green chemistry and computational toxicology, have several recommendations that would help NCER further both fields. We believe a public semantic web database could serve both fields as a means to share information on various chemicals. In addition, a conference or seminar, which includes workers from both fields, could help to bring scientific minds together to provide innovative solutions to the various problems within each field separately as well as the combination of the two fields.

- **Increase communication between the two fields**

Through increased communication, green chemistry and computational toxicology technology and information could develop simultaneously. Each field has individually conducted quite a bit of research on various chemicals and chemical processes. All of this information is scattered throughout various online and paper sources. Unfortunately, not all of this information is available to the public, because some research conducted by individual companies is protected for copyright reasons. Since this information is not public, scientists from different fields do not have access to each other's work.

If communication increased between the various government agencies that are currently funding green chemistry and computational toxicology research, they might see some overlap, and potentially could spend their research dollars in a more efficient manner with that communication. The research could spread between various topics within green chemistry and computational toxicology, and could integrate the two fields to accomplish even greater research goals.

- **Green Chemistry and Computational Toxicology conference**

Another way to increase communication would be a conference or seminar that would cater to experts and educators in the fields of green chemistry and computational toxicology. There, those experts could share ideas and insights into the state of both fields, and use a collaborative effort from a large group to work to fit the two fields together.

Scientists in the fields of green chemistry and computational toxicology should work together to advance both fields. Through this seminar, green chemists could suggest chemicals that computational toxicologists should be looking at in terms of their toxicity. Once green chemists know whether a chemical is toxic through the testing performed by computational toxicologists, they can use that information in their efforts to reduce harmful chemical emissions in the environment.

- **Supplement existing chemical databases**

Currently, the ACToR database includes chemical information from a multitude of public sources that we have previously mentioned. Through our interviews, we have discovered that many green chemists use private chemical databases instead of toxicology databases like ACToR. We recommend that ACToR include more information about green chemicals that are publically available. This would help to transform the database to be useful to green chemists, and green new green chemistry data could help computational toxicologists further develop their models. By centralizing computational toxicology data about green chemicals in one location, it would remove the need to search multiple websites and learn the specific procedures of finding desired information on all those sites, and could show where there are gaps in all of the government research.

We would recommend an increase in publicity about the ACToR database. Currently, there is a large amount of information organized in this database, but from our interviews with experts; we discovered it was not widely used, especially by green chemists. Once scientists update ACToR to include more publically available green chemistry data, we would recommend that scientists share this information with various green chemists. One way to share this information could be through informing grantees that NCER is funding about this database that could be useful in their research.

The organization of this information could help to highlight areas in which the fields need improvement. From there, organizations such as the EPA, NSF, and NIH can gear their grant proposals towards helping to fill those gaps in the research, and continue the growth of both fields individually and collectively.

In addition to the modification of the ACToR database, we would recommend a larger meeting or conference with both green chemists and computational toxicologists. This would include both government scientist and those funding research in the two fields, as well as the scientists actually performing the research. This would help increase communication between the two fields by allowing both green chemists and computational toxicologists a voice in this organizational system. Both groups could also learn the best way to use the ACToR database to their advantage during this meeting.

- **Increase collaboration with green chemists and computational toxicologists**

Through increasing collaborative efforts between green chemists and computational toxicologists, both fields can benefit. Computational testing methods can be implemented in green chemistry, which could in turn make the testing of those chemicals faster and cheaper.

Green chemicals could possibly be implemented in the chemicals that are used in testing using computational toxicology.

We believe that currently NCER could not sponsor a project using computational toxicology to perform toxicological tests on green chemicals, since computational toxicology is still in its preliminary developmental stages. NCER however, could sponsor a project using current computational methods, such as QSAR models, to predict other chemical properties about green chemicals. Once computational toxicology is developed enough, it could be used in risk analysis of green chemicals, and NCER could fund grants that specifically target the use of those methods.

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Appendix A: The United States Environmental Protection Agency

The United States felt a need for a government environmental agency in the late 1960s. Pollution had begun to build up over time due to the onset of the Industrial Revolution in the mid 1800s. During that timeframe, people were utilizing natural resources in a new way; however, the disposal of those used resources was not in an environmentally friendly manner. Pollution then built up over time until the United States government realized that it needed to take action. In April of 1969, Secretary of the Interior Russell Train stated, "If environmental deterioration is permitted to continue and increase at present rates, [man] wouldn't stand a snowball's chance in hell [of surviving]"(EPA, 2009, The Birth of the EPA).

President Richard Nixon proposed the EPA in July of 1970. He intended to establish an independent government agency that would deal with the environment. On December 2, 1970, the EPA became an officially recognized organization by the government when US Congress passed the proposal (EPA, 2009, The Birth of the EPA). The EPA is now part of the Executive Branch of the US Government, and any activities need to be voted on by Congress to maintain the checks and balances system present in the United States government. The organization has changed a bit since its inception in 1970; however, its main mission of protecting human health and the environment remains. The specific mission of the EPA can be broken down into five main goals. These goals are below in Table A.1.

Table A.1: Outline of EPA's main goals (EPA, 2009, EPA's Goals).

Goal	Overview
Clean Air and Global Climate Change	Improve air quality so it is healthy to breathe; reduce greenhouse gas emissions
Clean and Safe Water	Maintain safety of water for drinking purposes as well as oceans, rivers, and watersheds to ensure healthy environments for humans and animals and to promote economic and recreational use of water
Land Preservation and Restoration	Use new waste management and contamination techniques to preserve and restore land areas
Healthy Communities and Ecosystems	Use many partnerships and cooperative efforts to maintain and support the health of people, communities and ecosystems
Compliance and Environmental Stewardship	Ensure observance of environmental policies and rules to prevent pollution, and encourage new ideas to help the environment

The US government provides for funding for the EPA. The proposed budget for the fiscal year 2010 is around $10.5 billion (EPA, 2009, Budget). The head of the EPA proposes the budget based on the needs to accomplish each specific goal of the agency. As seen in Figure A.1, the EPA divides the budget to accomplish their specific goals. The head of the EPA proposes the budget each February for the upcoming fiscal year, which runs from July 1 to June 30. It will then be combined with the budgets of other organizations mandated by the Executive Branch of the government and will be sent by the President to Congress. Congress will then deliberate over the proposed budgets and make any amendments that they see fit. Congress passes the budget through bills, which will become law and act as the framework of the agency's activities for the following fiscal year.

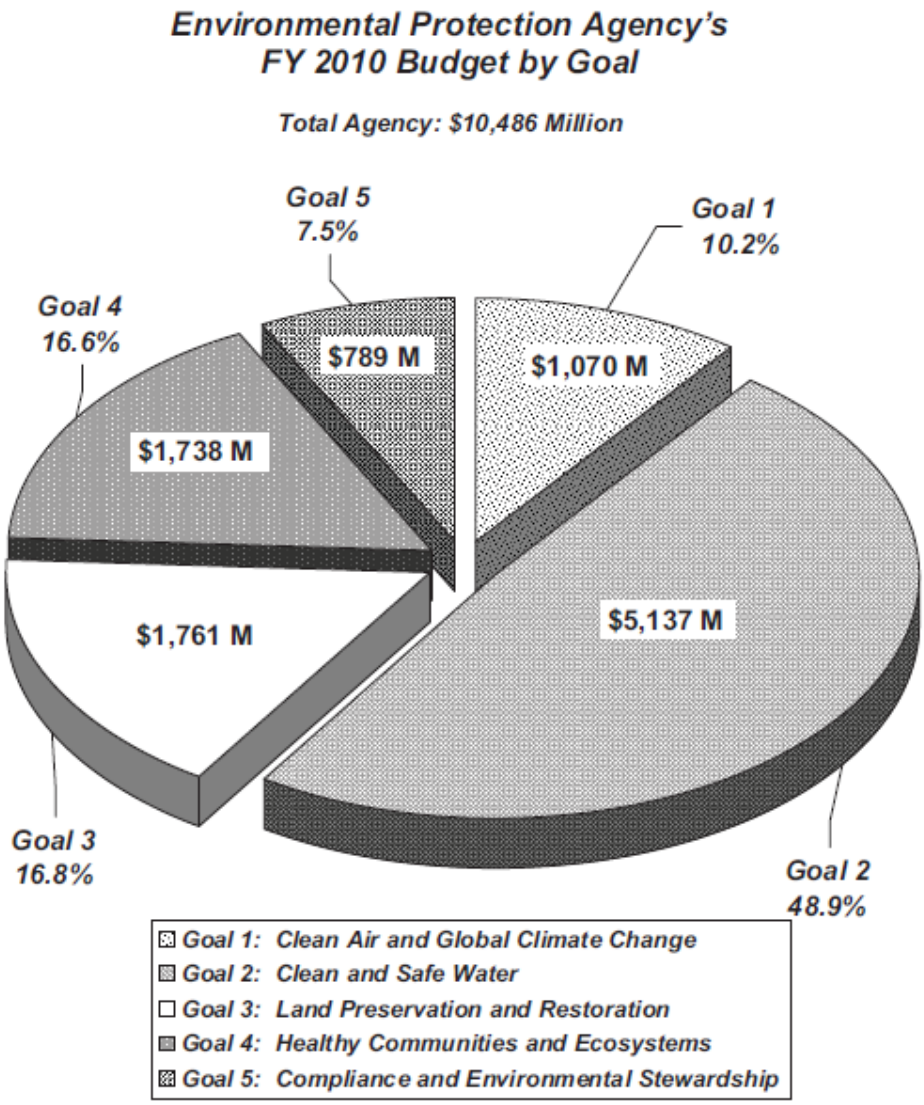

Figure A.1: EPA Budget breakdown per Goal for fiscal year 2010 (DHHS, 2009, p.9)

Key accomplishments of the EPA over the roughly forty years it has been in existence include the development and passing of the Clean Water Act and the Clean Air act in the 1970s by Jimmy Carter (EPA, 2009, Timeline). The Clean Water Act and the Clean Air Act are both extremely important as they are still in effect today, and are the basis for several environmental

policies in the US. During this timeframe, the EPA was also approved by the Supreme Court as a government agency, which solidified its involvement in the US government. During the 1980s, the EPA helped to develop emergency plans of action in response to environmental disasters, or events that could affect the quality of air, drinking water, or other environmental sources that would compromise the health of any individuals living in that area (EPA, 2009, Timeline). The 1990s brought about the Clean Air Act Amendments, which brought about stricter regulations in the areas of air pollution and reduced the amount of allowable waste and pollution industries and companies could expel into the environment. In the 2000s, the EPA began to focus on various chemical emissions such as mercury and its impact on human health as well as the environment. In 2001, the EPA responded to New York City after September 11th to test the quality of the air and ensure that citizens were not going to suffer from adverse health conditions due to the particulates in the air from the building debris.

The EPA is organized into 10 regions geographically, each with differing areas of research and the headquarters in Washington, DC. Regional offices are located in Boston, MA, New York, NY, Philadelphia, PA, Atlanta, GA, Chicago, IL, Dallas, TX, Kansas City, KS, Denver, CO, San Francisco, CA, and Seattle, WA (EPA, 2009, Regional Operations). Each region serves multiple states and provinces in the US. The locations of regional offices can be seen in Figure A.2.The EPA has over 17,000 employees worldwide.

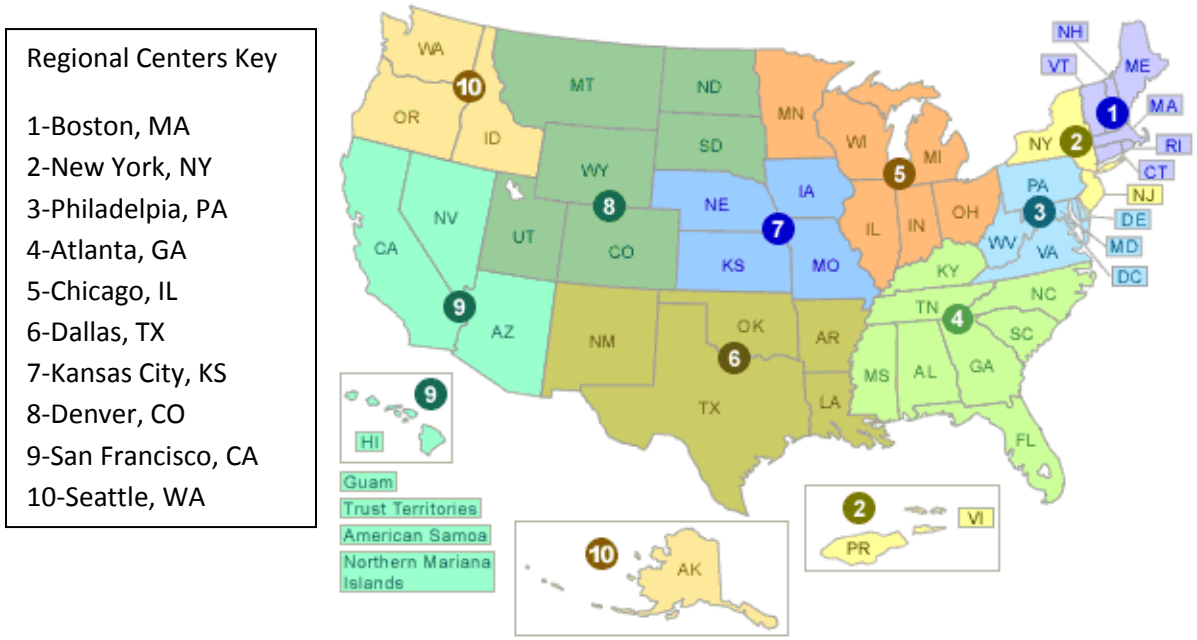

Figure A.2: Regional Offices of the EPA and areas they serve (EPA, 2009, Regional Operations).

The EPA also has several research centers around the country. Areas of research include Air and Radiation, Enforcement and Compliance, Environmental Programs, Pesticide, Policy, Economics and Innovations, Research and Developments, Science Advisory, Water, Regional Laboratories, and the Science Advisory Board (EPA, 2009, EPA Regional Facilities). These research centers are located at the various regional offices as well as the headquarters in Washington, DC. The main division, which we will be working for is the National Center for Environmental Research. Within NCER, we will be working in the Office of Research and Development in the Technology and Engineering Division in Washington, DC. The organization of NCER in the EPA and ORD can be seen below in Figures A.3 and A.4.

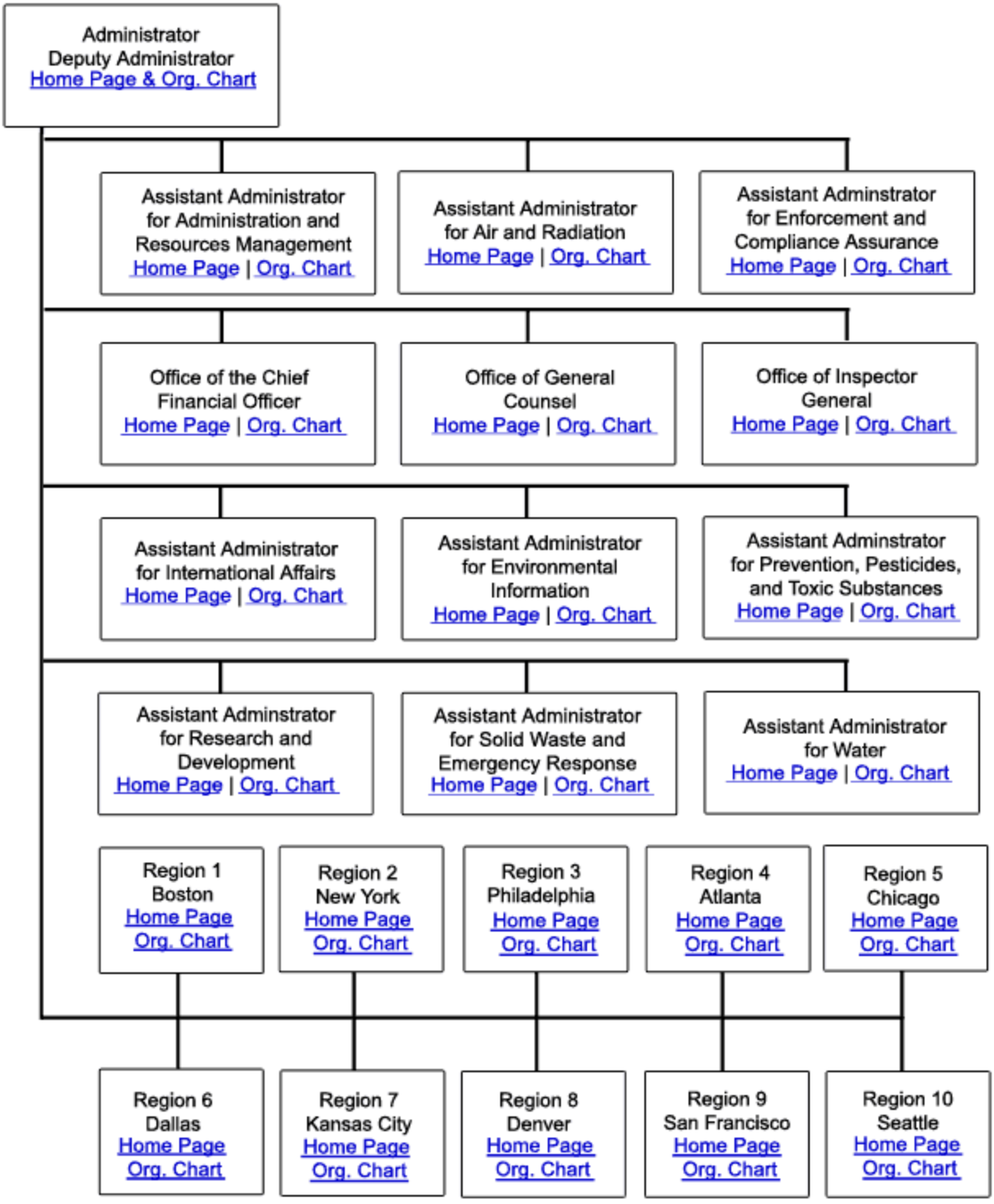

Figure A.3: EPA Organization Chart with NCER (EPA, 2009 EPA Organizational Structure).

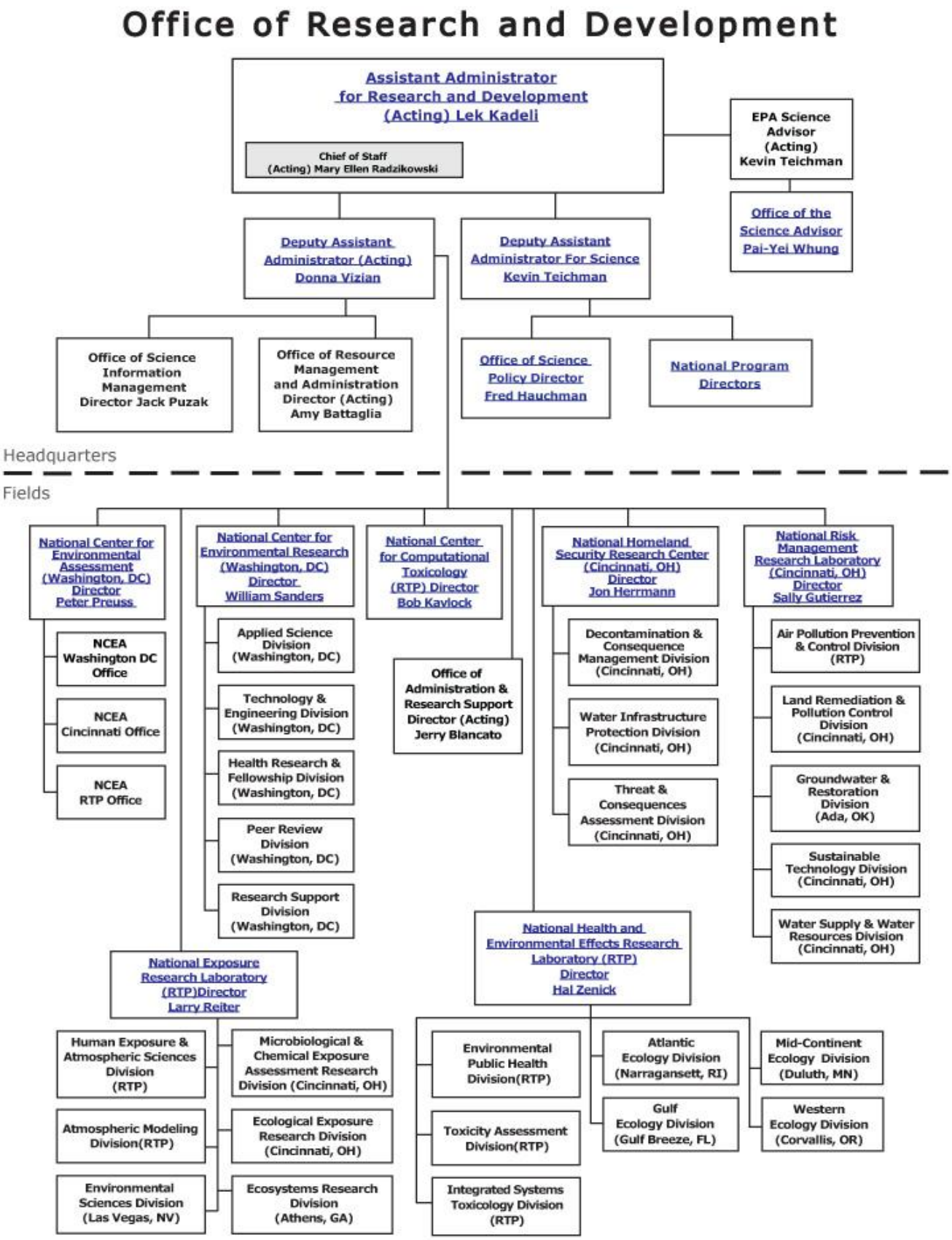

Figure A.4: EPA ORD Organization Chart with Technology and Engineering Division (EPA, 2009, Office of Research and Development).

The President of the United States chooses the EPA's Administrator. Currently Lisa P. Jackson, who is the first African American woman to lead the agency, runs the EPA. She was chosen by President Barack Obama and was inaugurated on January 26, 2009 (EPA, 2009, Administrator's Site). The purpose of the Administrator is to supervise and promote the agency. She serves as the liaison to the President on behalf of the EPA. A Deputy, three Associates, twelve Assistants, and ten Regional Administrators support the Administrator. These officers help to support and implement any decisions made by the Administrator because the EPA is such a vast organization with branches that spread far across the country.

The EPA is not the only agency in the world that works to improve the environment. Other organizations, which work on these problems include the European Environment Agency, Intergovernmental Panel on Climate Change, United Nations Environment Programme, and Earth System Governance Project among others. These organizations generally work together, or at least share information with each other. Together, they all share a common goal of protecting the environment.

Appendix B: NCER Funded Programs

STAR Grants

Science to Achieve Results (STAR) grants "fund research and graduate fellowships in numerous environmental science and engineering disciplines through a competitive solicitation process and independent peer review"(EPA, 2009, STAR Grants). STAR grants can be worth up to $350,000. The goal of the STAR program is to concentrate on research in areas of special significance to the EPA. Over the past 5 years, the budget for STAR grants has been cut almost 31 percent, which is seen in Figure B.1. From 2003-2008 the total STAR grants funded totaled 448.1 million dollars.

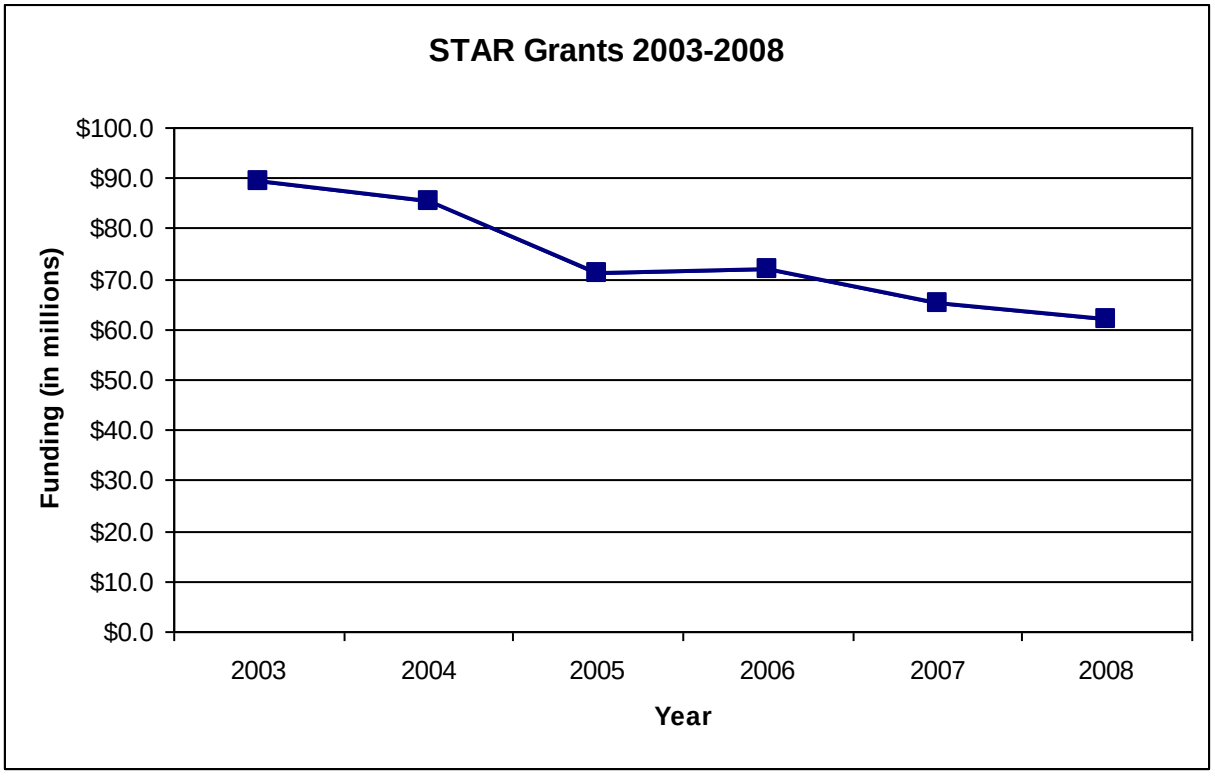

Figure B.1: STAR Grants Funding 2003-2008

P3

People, Prosperity and the Planet is a program designed by NCER to "focus on benefiting people, promoting prosperity, and protecting the planet through innovative designs to address challenges to sustainability in both the developed and developing world"(EPA, 2009, P3). P3 is a student based design program that begins with the award of phase one grants at the outset of the academic year. In April, final products for phase one as well as proposals for phase two research are due. Phase one grants can be up to $10,000, while phase two grants are up to $75,000. From the past five years, there have always been six SBIR phase two grants, but the overall projects have varied based on the year (see Figure B.2).

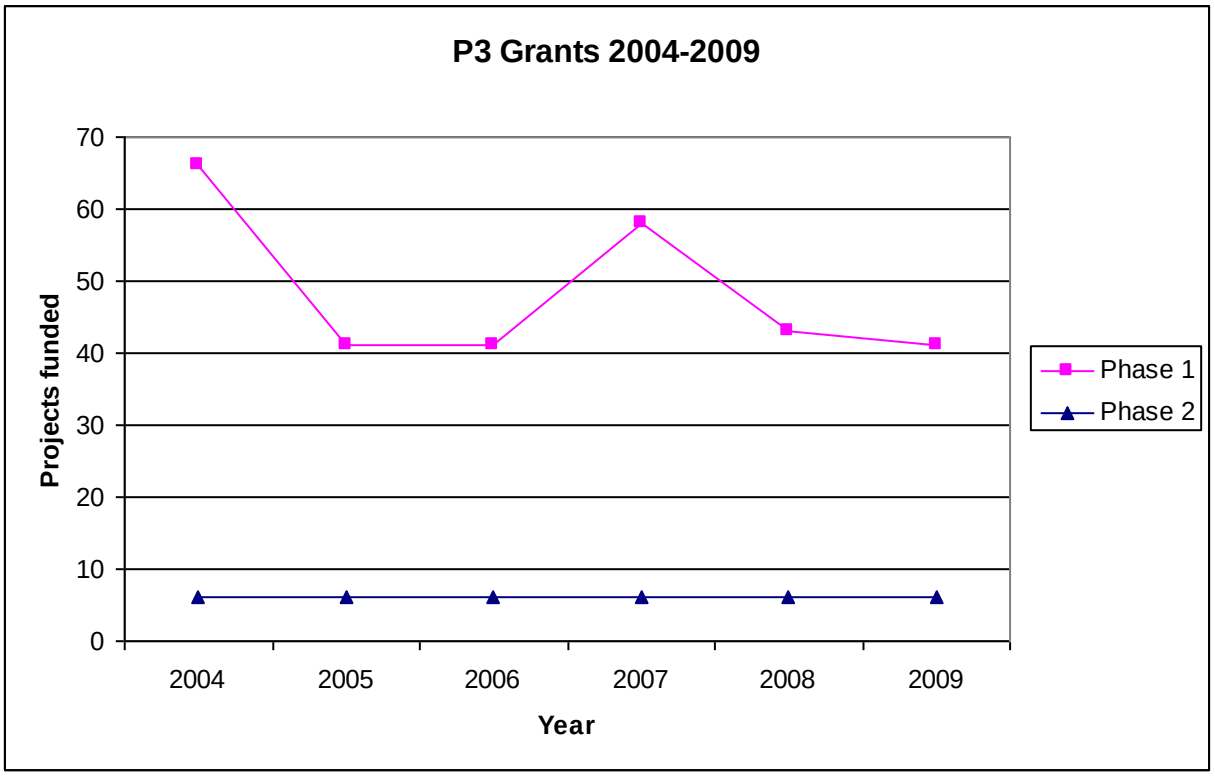

Figure B.2: P3 Projects Funded 2004-2009

SBIR

Small Business Innovation Research (SBIR) is an annual program that small businesses can apply to for funding. The stated goal of the EPA in SBIR is "to stimulate technological innovation" (EPA, 2009, SBIR). A small business is defined as one with less than 500 employees. EPA is one of 11 government agencies participating in SBIR. Phase one awards can total up to $70,000 and, upon completion of phase one, applicants can reapply for phase two grants, which can be up to $225,000. As you can see from Figure B.3, NCER funding of SBIR grants varies from year to year, but appears to be decreasing, specifically involving phase 2 grants.

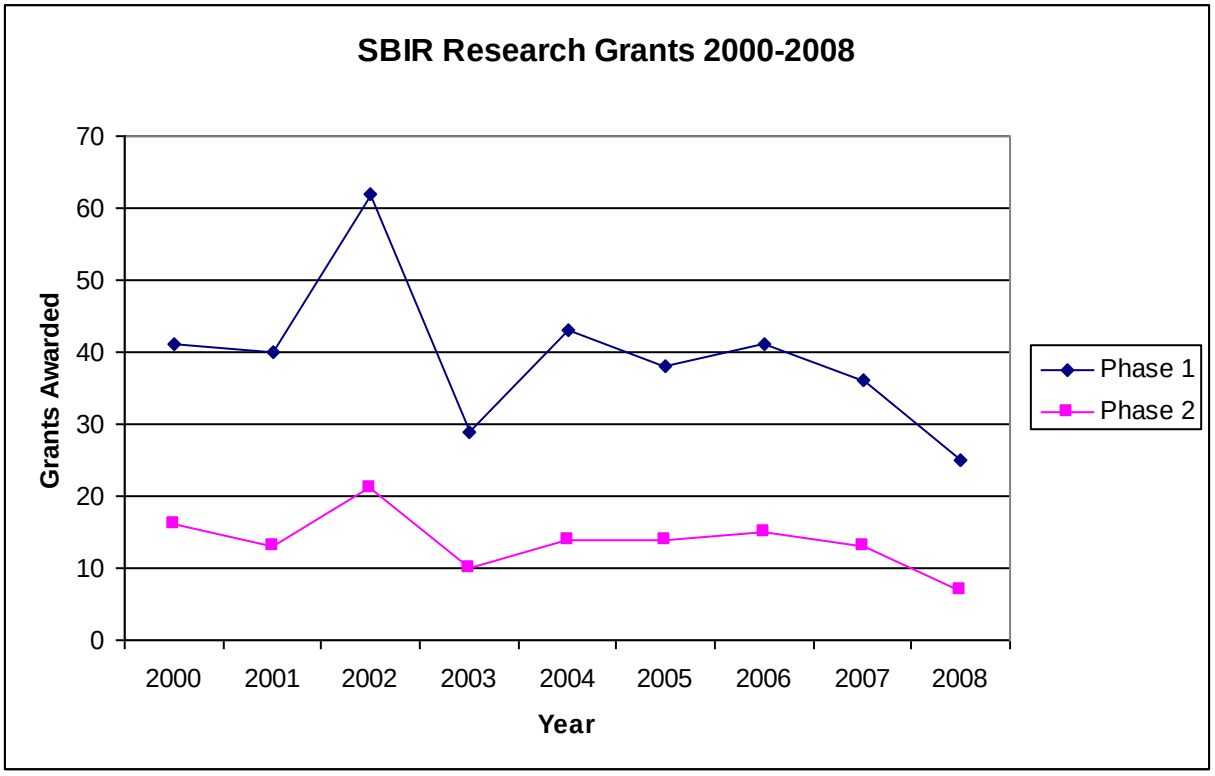

Figure B.3: SBIR Research Grants Awarded 2000-2008

Appendix C: Other Funding Agencies and their Budgets

The National Science Foundation

The National Science foundation is an independent federal agency that oversees funding of research projects within the united state. To date, the NSF has funded about 20% of research within the United States. It funds about 10,000 new research projects a year, in a wide variety of categories. The goals of the NSF include "discovery, learning, research infrastructure and stewardship" (NSF, 2009). Because of this, the NSF sponsors a wide variety of educational research. In addition, to funding research, the NSF funds expensive research equipment that one research organization could not fund individually. Unlike other organizations like the EPA or NIH, NSF does not operate any labs. The NSF's research budget can be seen in Figure C.1. This budget has been steadily increasing from 2000, with a decrease in 2008 that can be attributed to the economic climate.

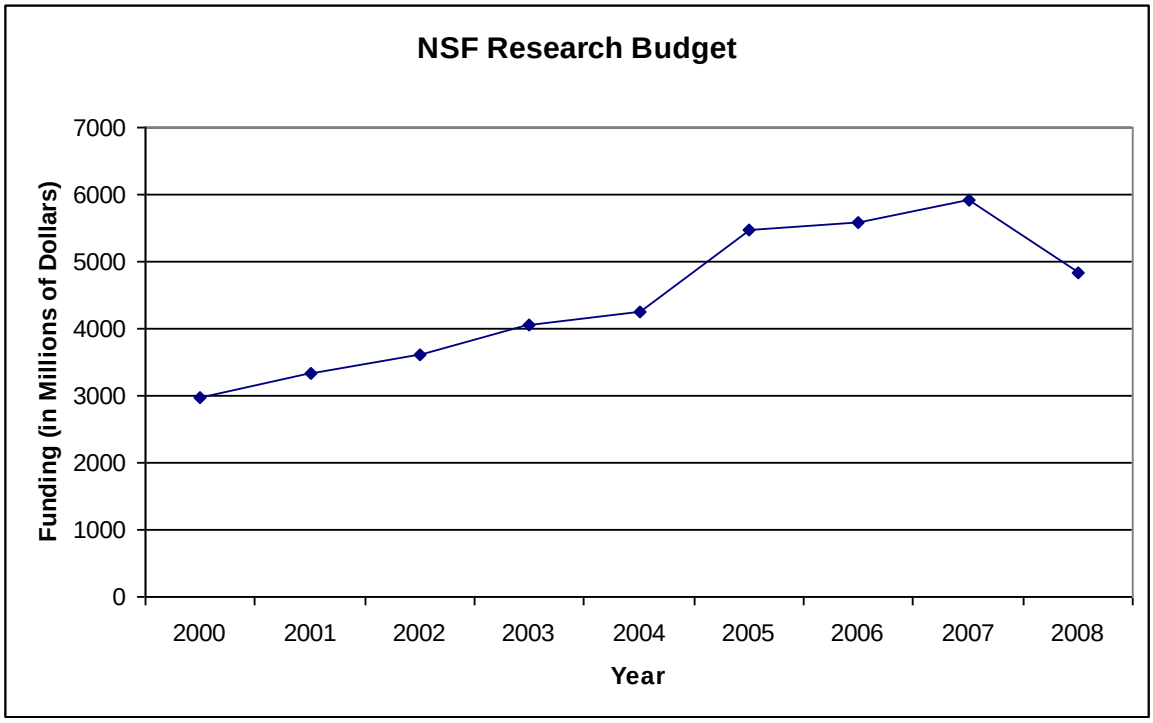

Figure C.1: NSF Research Budget

The National Institute of Health

The National Institute of Health, part of the department of Human health and Services, is the agency responsible for conducting and supporting medical research within the United States. The NIH awards over 83% of its budget to researchers at universities, medical schools, and research institutions across the United States (NIH, 2009). The NIH also runs its own labs. NIH funding resources across the past years can be seen in Figure C.2. Funding has steadily increased over the past 8 years.

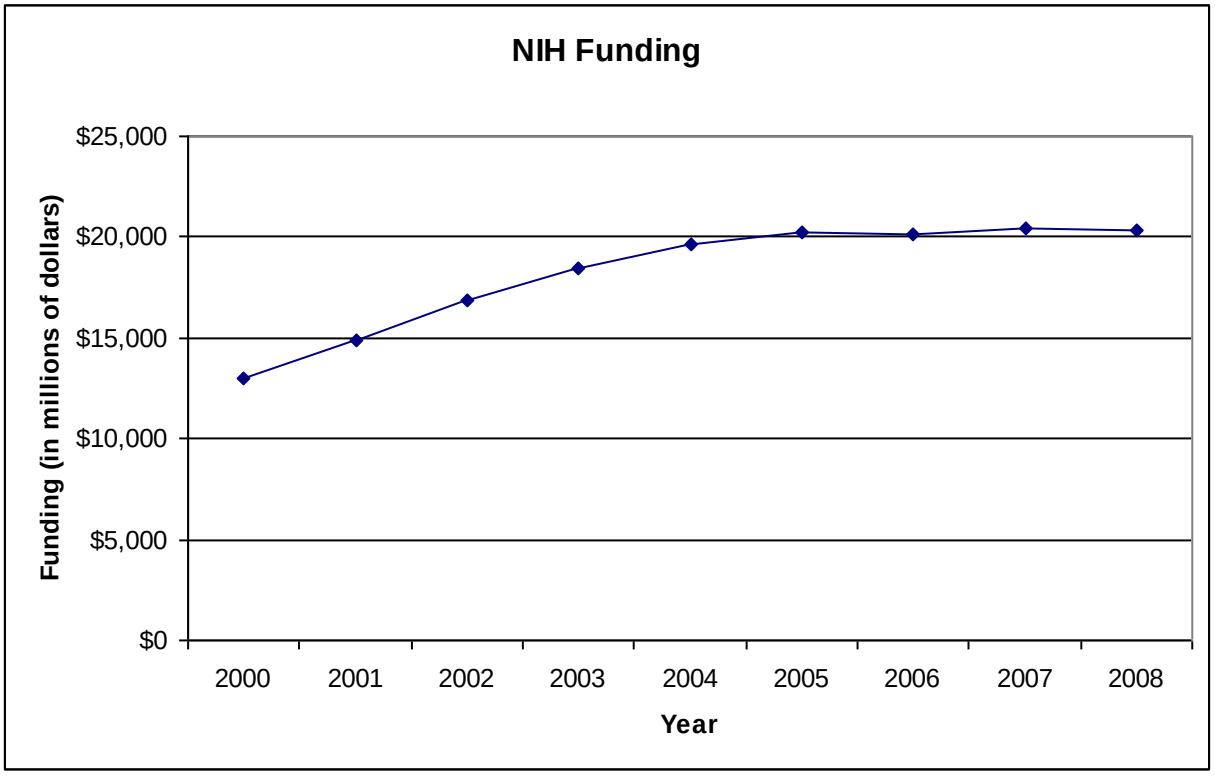

Figure C.2: NIH Funding

Figure C.2: shows how the research funding budgets of different organizations that fund research within the field of computational toxicology and/or green chemistry compares. As shown, STAR grants have an infinitesimally smaller budget compared to other organizations that fund research. Different organizations have different focuses, and the NIH have a much broader range of topics to cover, but they have much more money to work with.

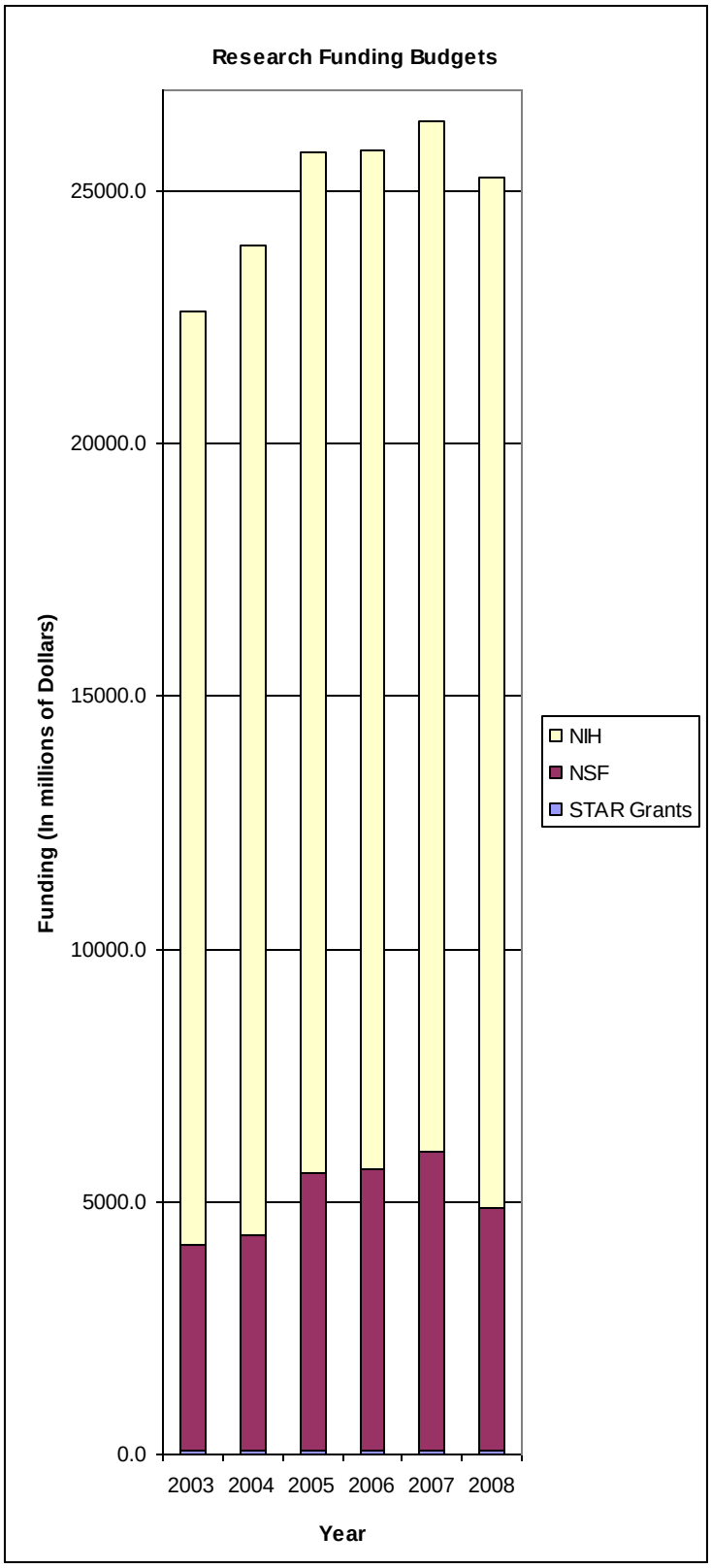

Figure C.3: Research Funding Budgets of NCER, the NIH, and the NSF

Appendix D: History of Toxicology

Toxicology is in many respects a science that relies on modern scientific discovery, but it was started thousands of years ago, before science as we know it even existed. Through trial and error, early humans discovered what substances in their environment were toxic by noticing which plants and animals made them sick (Monosson, 2007, Introduction). In many ways, early toxicology can be seen as an evolutionary process that helped early humans gain control over the natural environment.

As humans learned more about what substances could be used as poisons, toxicology became a potent weapon. According to the Greek historian Xenophon, poisoning in ancient Greece was so common that people of status often had wine tasters to ensure the food they ate was not poisoned (Monosson, 2007, Pre Industrial Toxicology). Poisons were a powerful weapon for ancient people because they were impossible to trace and not well understood. Many plagues and diseases were incorrectly blamed on mass poisonings, because ancient people did not understand what modern medical knowledge could now explain. Many stories in Greek and Roman mythology included instances of gods and goddesses using poisons. This shows what an important role poisons played in the ancient world.

During the Renaissance period, one man emerged who would change the face of toxicology and medicine, and be known as the "father of modern toxicology" (Borzelleca, 2000, Profiles in Toxicology). Paracelsus was born in Sweden and educated by his father, who was a doctor. While growing up, he studied many ancient practices, and tried to bring chemistry and the scientific method together into the medical field. This involved controversial treatment with inorganic salts (a chemical agent), which led to his famous quote "only dose determines poison" (Borzelleca, 2000, Profiles in Toxicology). He was referring to the fact that a small amount of

inorganic salts will not harm the body (and in his case actually was beneficial). He started the theory of the gradation of poisonous versus nonpoisonous substances, based on the quantity and chemical nature of the substance in question.

The industrial era was a time of great progress to modern man, but it also brought with it a host of toxicological concerns that did not exist before. Prior to this era, most poisonings were either deliberate, or only affected a relatively small number of people. As more and more people came together to work in industrial plants that produced large amounts of chemicals, occupational toxicology was born. Many factory workers became sick from the coal and mercury they worked with in factories (Monosson, 2000, Toxicology and the Chemical and Industrial Revolution). The rapid industrialization of the world has led to a host of problems caused by pollution, which has had a negative impact on overall human health and the environment in general.

Appendix E: How our Project Qualifies as an Interactive Qualifying Project

Worcester Polytechnic Institute's Interdisciplinary and Global Studies Division website defines an Interactive Qualifying Project (IQP) as a project that "challenges students to address a problem that lies at the intersection of science or technology with social issues and human needs"(WPI, 2007, Interactive Qualifying Project). Our project is an IQP because it focuses on pollution reduction techniques, which clearly affect the human population in the world. There is an obvious need to reduce pollution in the environment to maintain human health. Green chemistry and computational toxicology are at the cutting edge of technology research within the EPA, and from many other human issues arise. Communication and collaboration between the two fields is limited, and developing a relationship between the two fields will not be an easy task. In addition, because the two fields are at the cutting edge of technology, many intellectual property issues arise with sharing these data. This research has the potential to influence the environment in which humans live, as well as the overall health of humans. In analyzing the green chemistry and computational toxicology, research funded by the EPA, our project will successfully meet the qualifications to be deemed an IQP.

Appendix F: Interview Protocol

General Protocol: In an interview, it is important to be extremely polite and candid with the person you are interviewing. Basic things to remember include dressing professionally, arriving to a meeting early and prepared with a paper and pen to record information, and addressing the person you are interviewing with the utmost respect. In addition, it is important to ask the person you are interviewing if you can specifically quote or cite them in your paper.

1. **Background on Research Person**: In this part, we should ask the person we are researching some general questions to find out what their background is on the subject we are interested in, and find more general information about them. This should be completed prior to the interview. Some questions we could ask include:
    - What are your research interests?
    - What prior research have you done?
    - Have you done any research in the fields of G.C or C.T?

2. **Introduction:** First, we should introduce ourselves and give a brief background of who we are. Next, we should describe our project problem, goals and objectives. As we do this, we should be sure to highlight and give more information about specific information in our topic that would be of interest for our resource person.

3. **Interview Questions:** These questions should be open-ended and ask opinion-based questions, because facts and basic information can be found from other sources, but firsthand experience with our topics is invaluable. Questions that we could ask include:
-Questions to ask a computational toxicology expert:
    - What are some advantages to computational toxicology over traditional toxicology?
    - What are some of the drawbacks you have experienced with either computational toxicology or traditional toxicology?
    - Where do you think the future of computational toxicology is headed?
    - What situations could computational toxicology be best applied to?
    - How is your specific research adding to the field of computational toxicology?

-Questions to ask a green chemistry expert:
    - What green chemistry techniques have you seen that have been successful?
    - What techniques have been unsuccessful? Why?
    - What do you do you think are the most important pollution sources that green chemistry could be used to address?
    - How do you think green chemistry could become a more popular and widespread scientific subject?
    - How have you seen computational models applied to green chemistry? Has this been successful?
    - How is your specific research adding to the field of green chemistry?

4. **Follow up:** After we have completed our interview, it is important to follow up with the person we interviewed. This would include sending a Thank you email after the interview and after our project has been completed, sending them another follow up email explaining how useful their input was, and showing them a final version of our work.

Appendix G: Interview with John MacDonald

Interview with John MacDonald, Professor of Chemistry and Biochemistry, WPI

Friday, October 2, 2009 2:00pm Gateway Park 3022

Attendees:

Taylor Mazzali (primary interviewer)

Amy Morin (secretary)

Professor John MacDonald, WPI Chemistry and Biochemistry (interviewee)

Background information on John MacDonald: Professor MacDonald is an Associate Professor of Chemistry and Biochemistry at WPI. He focuses his research in molecular nanotechnology, and has an avid interest in the field of green chemistry, but does not deem himself to be an expert in the field.

Question: What green chemistry techniques have you seen implemented?

- In industry, synthesis of products, such as polymers, rubbers, etc. are extremely important. They usually involve some form of a solvent system to carry out the reaction; however, if conducted with organic solvents, the chemicals are very volatile and toxic and when released into the atmosphere, can contribute to acid rain.
- The goal of the companies is to reduce those organic solvents to aqueous based reactions, but unfortunately, not all chemistries are compatible with water.
- If solvents do not contain Chlorine, Bromine, or Iodine, they can be burned without leeching toxic chemicals into the environment, but if they do contain those elements they must be stored or buried, and there is the potential for them to leech into the ground and end up on a course for nonpoint source pollution.
- For instance, WPI spends hundreds of thousands of dollars every year to dispose of those waste solvents created in various reactions.

- Scientists are working on finding ways to use the accumulated byproducts of these chemical reactions and use them.
- Another area to reduce the use of volatile compounds and organic solvents is through ionic liquids which are organic but have virtually zero volatility. The current methods are taking older chemistry techniques and attempting to do them with ionic liquids.
- From a safety standpoint, it would be ideal to remove hazardous reagents for reactions, and find common reagents to perform the same tasks and are not harmful to the environment
- Metals are usually very toxic, especially transition metals. Nickel-Cadmium batteries are no longer used, because even trace quantities of either substance are highly unhealthy. The transition is being made to lithium-ion batteries, which are much less harmful.
- Finding biomolecules or enzymes that will catalyze reactions as opposed to using reagents
- United States cannot survive without polymers, so moving towards using organic polymers that are cellulose derived as opposed to petroleum derived
  Environmental remediation- how to clean up toxic spills; what should be done with the cleaned up waste?
- Development of plants that can store vast amounts of metals and can begin to allow plants to return to an environment that is not compatible with life. After those plants absorb the metals, they can be burned, and the metals will be left behind to remove from the environment.
- Porous material science which can selectively absorb materials, but leave behind non-harmful chemicals/materials
- Energy: the need to move away from petroleum based energy and move towards alternative energy options

Question: What green chemistry techniques have not worked?

- Anything that was not more cost effective or a better method would not survive for long in the field of chemistry

- It is difficult to change industry because it is easier to stick with what you have working than to change.
- Pressures to change need to be positive and negative. If it is cheaper for the industry, it will be positive. A negative pressure would be in terms of fines, but if the fines are only a drop in the bucket of the profits of a large company, it is not serving its purpose

Additional Comments: Professor MacDonald encouraged us to contact John Warner who is the head of Warner Babcock Institute for Green Chemistry in Wilmington, MA. He also recommended getting in touch with the editor of the American Chemical Society Robin Rogers from the University of Alabama.

Meeting Adjourned- 3:05pm

Appendix H: Interview with John Warner

October 23, 2009 3:30pm

Warner Babcock Institute for Green Chemistry, Wilmington, MA

Meeting with Dr. John Warner

CEO of Warner Babcock Institute for Green Chemistry, Wilmington, MA

Attendees:

Amy Morin

John Warner

Notes:

Question: Is there a specific area in green chemistry that your research focuses on?

> -Dr. Warner noted that his green chemistry research focuses on the performance of the action or process, as well as the cost. By making the process more cost effective and better in performance, he also aims to make it sustainable.

Question: Does your research include computational toxicology

> -His research uses mechanistic toxicology in that it knows the substances are toxic to begin with and finds ways to reduce that toxicity in a system
>
> -Pointed out that toxicology is easy in the pharmaceutical and medical field because humans will at some point be tested, assuming the FDA approves the drug/procedure
>
> -This is more difficult outside the medical field because testing to see if a certain dye used in clothes might be cancerous will take too much time
>
> -His research uses new means of creating products, and no technology follows all twelve principles of GC

Question: Does your work always make a product or process more cost effective?

-The products are usually more cost effective, or else the industry would not be interested in changing their current methods

-Does not try to make procedure fit into the twelve principles, but creates procedure, and then analyzes extent that each follows the twelve principles

Question: Do you approach companies to make their processes or products greener?

-Companies approach him to make their processes safer/greener

-Personally interested in endocrine disruptors and renewable feedstocks

Questions: Do you have any suggestions of who to speak with when in DC?

-People to contact in Washington, DC

-Richard Engler (EPA, Pollution Prevention Office)

-Bob Peoples (American Chemical Society)

-Suggested to ask the EPA how they are planning on bringing information about research funded in GC to the everyday chemist so everyone can benefit from these greener processes

-Suggested to look at the Green Chemistry Bill (2009) that was passed in Congress, but not the Senate

Appendix I: Interview #1 with Deborah Segal

Interview with Deborah Segal, Environmental Health Scientist, U.S. EPA/ORD/NCER Monday, November 2, 2009 11:00 am NCER Office, Washington DC.

Attendees:

Alison Paquette (primary interviewer)

Amy Morin (secretary)

Deborah Segal, NCER EPA Environmental Health Scientist (interviewee)

Background information on Deborah Segal: Deborah Segal is an Environmental Health Scientist employed by the National Center of Environmental Research. She works with other EPA employees to determine how the EPA funds projects, specifically the development of the EPA's computational toxicology program.

Question: What Projects is the EPA funding within the field of CT?

-The EPA is focusing on the four STAR centers. The first two were started almost four years ago, and include the University of North Carolina (UNC) Center and the University New Jersey (UNJ) Dental Center, which focuses in bioinformatics. There are two North Carolina Centers, which develop computational models of network signaling and the resulting gene expression. This can help predict subsequent health risks of a toxin. The newest center is located in Texas, and will be opening in two weeks.

-The NCCT is also doing a lot of work with the STAR centers. Deb explained that systems biology is still extremely underdeveloped at this point, and is focusing on prioritization of chemicals rather than screening to eliminate chemicals.

-The individual centers are focusing on specific research within the field of CT. The newest center (in Texas) is focusing on developmental contaminants. The UNC is focusing specifically on liver toxicants, and the UNJ is focusing on DBP, arsenic, and other liver contaminants.

-The NCCT is using all the STAR centers to analyze ToxCast data. Many CT techniques are in the proof of concept stage, including HTS and in vitro bio-assays. The centers are trying to predict toxicity that animal testing has proven through statistical models. The NCCT does not give out grants to different researchers, but has specific contracts for the assays that they use.
-NCER gives out STAR grants that are given through a very specific system. Researchers first submit an RFA, which is subjected to an external peer review conducted by non-EPA scientists. This is followed by a programmatic review with the agency, and then the director makes the final decision about which programs are funded and how much funding each program will receive. The EPA is currently focusing on projects regarding managing CT data, and more meta-analysis.

Question: What advantages/disadvantages are there between CT vs. Traditional toxicology?

-In the future, CT could completely eliminate the need for in vitro animal testing, and could be used to screen chemicals for toxicity, but it is not developed enough for that stage. At the current time it is not developed enough to be used alone for risk assessment, and needs more research, more models, and more focus on dose response. Specifically, microarray data needs further quantification. Therefore, CT is currently only used for prioritization rather than screenings because the current modeling systems cannot be trusted enough to completely assume a chemical is not toxic.

Question: What are the current CT programs?

-ToxCast is the biggest CT initiative so far, and phase 1 is almost complete. This phase will focus on fingerprinting all the assays

Question: What are the next steps in the future of CT?

-The next steps are to decide specifically where to go, specifically what chemicals to test. Currently, the ToxCast system has been focusing on pesticide research because we have a lot of previous toxicity research on this subject. Once this data has been confirmed, CT can begin to look at other chemicals, including green chemicals. The EPA is particularly interested in the LCA aspect of CT, and how CT could trace a chemical's toxicity at different stages.

Appendix J: Interview with Rich Engler

Date: November 12, 2009 EPA NCER Conference Room North: 1:00pm

Attendees:

Rich Engler, US EPA

April Richards, US EPA

Taylor Mazzali

Amy Morin

Alison Paquette

Question: What criteria do you look for when awarding the presidential green chemistry awards?

The judging agency is an external panel run by the ACS. The judges look for three criteria:

1. Novelty: is it new and creative? This research could be incremental in development, but more innovative will probably be funded as opposed to incremental research.
2. Environmental and human health affects: Reduction of hazards, global warming
3. Broad implications: What kind of impact will this have on the environment, the economy, or both?

Question: How could computational toxicology fit into this?

Computational toxicology could be a valuable tool in evaluating hazards without actually testing the chemicals. It also shows a lot of promise, which could be a powerful tool for GC- and be easier to bring to the assembly line chemist.

Question: How could the twelve principles of green chemistry relate to computational toxicology?

CT is a good way to get info about hazards, so it could fulfill criteria regarding hazard analysis.

Question: Are there any projects or grants you know of involving CT?

He knows of nothing off the top of his head, because as he understands CT is not robust enough to understand, and he does not know of any direct applications to green chemistry.

Question: How could green chemistry impact CT? Do you know any instances of this happening?

As far as green analytical chemistry methods, there have been projects. CEM did a project involving sprint protein analysis using fluorescent markers (which are used in CT) as opposed to the traditional nitrogen analysis. This was considered green because there were less hazardous materials used. In addition, this does not require a full lab and requires much less training. In this field, there is a lot of opportunity because analytical methods need improvement, but there is only so much GC can do.

Question: Do you know anything about TSE grants?

It is an ORD cooperation, and still cooperates with SBIR.

Question: As far as GC production goes, what is the design process like? Do you conceptualize chemicals before you make them, or analyze chemicals created at a lab bench?

This depends on what it is and who is doing it. Engler thinks a holistic view is important, so function at a molecular level is initially studied. Opportunities: most efficient energy way, resource needs performance, environment, and economic benefits. Hard to do. Mostly GC is incremental, focusing on molecule with fairly understood process. How can this be minimized? Finding new solvents or changes within a molecule?

Question: What information would be useful to know when designing a chemical?

He believes you should develop ANSI standard for green chemistry in order to quantify greenness.

Question: How do you measure impact categories?

Ecotoxicity, energy, and eutrophication potential; there are 40-50 endpoints to consider.

There is a gap with the mammalian toxicology data, and CT could fulfill this existing data gap.

Question: Do green chemists use the ACToR database?

He is aware of ACToR, but does not really use it.

Toxic Substances Control Act (TOSCA). Forced them to create a huge inventory, and if a substance wasn't on the inventory, it could not be used commercially as a "catch all." This provides pre-manufacture notifications (PMN) that must be filed by companies to use a material or chemical not under the FDA or any other administration

80,000-100,000 chemicals

Chemical manufacturers will review for unreasonable risk, and believes that you should outright ban testing with rare chemicals. There are around 20,000 current PMN. This database is collecting data as it comes in (chemical Id).

This is a business process-most of the information is confidential and cannot be released to the public or other agencies.

Engler does not know the extent that other groups or organizations use ACToR.

GC usually uses Beilstein publications on organic substances as their premiere resources which is now a web database you can have access to for a fee. It contains oncologic/esosar, OPPT

Question: Why do you think people resist greening of processes?

There is a lack of knowledge: chemists only see lab applications and know how to protect themselves, only looking into short term and personal investment. If toxicity is not their direct problem, they are not concerned about it.

There is a need to design criteria at a molecular level

No GC alternatives yet: GC toolbox mostly empty

People are familiar with old methods and unwilling to change something that has been successful in the past.

Some people see GC as fluff and do not understand that it is a real field with very strong potential.

Good novel chemistry can be green, GC is Nobel caliber! (Metathesis)

Gaining access to data is a problem, and there are too many places to get data.

NIH and ToxCast data is one example

Some people have no access to these databases, due to intellectual property rights that need to be protected.

FDA data could be added to databases; ideally would like to gather all public government information together to make a database and allow access to all

Question: How could we get more information about the GC databases?

CBI-maybe work within to share externally

Rebecca Jones/Robert Morlack (RA division)

New chemicals are being input all the time in these databases.

Question: What is the future of GC?

He hopes the field will become the standard that everyone is trained in for chemistry. Chemists will consider hazards before testing with dangerous chemicals. Essentially, GC is how to do sustainability on a molecular basis.

Green chemistry should be the same thing as green engineering, because the process will be green from the start. The future in design is only going to grow.

If enough people recognize that there is money to be made in the evolution of GC, it will eventually pay for itself in terms of extra costs to "green" a system or process.

More people are considering impacts during the design phase of a product or process. Costs are associated with hazardous materials. There is much room for growth and lots for companies to do.

GC is a good business practice.

The field needs more publicity to get those ideas out there.

Appendix K: Interview #2 with Deborah Segal

Interview with Deborah Segal, Environmental Health Scientist, U.S EPA/ORD/NCER

Monday, November 12, 9:00am NCER Office, Washington DC.

Attendees:

Alison Paquette (primary interviewer)

Amy Morin (secretary)

Deborah Segal, NCER EPA Environmental Health Scientist (interviewee)

Question: How much work is the NTP doing with computational toxicology? The website makes it appear that they are not doing very much. Also, do you know why I might have a hard time accessing this information?

Deb was not very familiar with the NTP and the research they were doing. She thought that people at the NCCT might have a better idea of other research. In particular, she recommended Nadia Bauer.

Question: The NCCT has an MOU with the NCCT, how exactly does this work? Do they share resources, or information? Is it more formal or informal?

Deb explained that it was more of a sharing of information, and that the MOU was a very broad term.

Question: How do outside organizations submit information to the ACToR database? Is there a regulation or process that takes place to get this information approved?

The ACToR database is actually maintained by one man, Richard Judson. He actually looks for other databases that already exist, so we should contact him to find more information about how information is gathered within that database.

Question: Which of the 12 principles of GC would CT be best at addressing?

Deb picked out 3, 4, and 5, which was anything that was related to creating less hazardous chemicals.

Question: How reliable do you think that CT is at predicting a chemicals structure and physical and chemical properties?

The QSAR system can flag down some structures that could predict toxicity (for example a benzene ring or an abundance of pi bonds), but cannot accurately draw any conclusions at this time.

Question: Could it be used to predict the physical and chemical properties of chemicals that have not been created yet?

Sure, through the QSAR system. QSAR is a computer program that can predict chemical and physical properties. In addition the New Jersey STAR center has a program that compares two chemicals with a histogram. It can show what aspects of the chemicals are similar and which ones are different. This could help GC avoid chemicals that are too much like similar ones.

As far as the toxicology goes, the New Jersey STAR center system is only about 70% effective. It has been around for 30 years but is not reliable enough to eliminate animal testing. CT has been trying to combine the QSAR data with biological activity profiles and use statistical models to improve the accuracy of CT predictions. So far this has not been very successful. Toxigenomics is a very important aspect of CT that needs to be considered in systems, because without toxigenomics, CT could not exist. Toxigenomics is not as accurate or as simple as early Computational toxicologists thought it would be.

Question: How well publicized are the CT databases like the ACToR systems within the EPA? Would green chemists know about them?

The NCCT was extremely well publicized among computational toxicologists and within the EPA. However, people who do not pay attention or do not care about toxicology might not be aware of this information or how to properly use it. As far as chemical engineers go, Deb was not sure if they knew about the databases.

Question: Green chemistry could also be used to help the process of CT by making it greener. Do you know any instances of this?

Not sure of any examples, but the process of CT is intrinsically greener because there is less animal testing and less chemical uses.

Question: Do you know about any of the waste disposals or some of the chemicals used in GC?

The NCCT contracts out this information to outside organizations (not pharmaceutical companies), so she is not really sure about this question. It might be better to talk to the NCCT.

Appendix L: Phone Interview with Tom Knudsen

Date: November 13, 2009 1:00pm EST

Attendees: Tom Knudsen NCCT

Taylor Mazzali

Alison Paquette

STAR Grants UNC Princeton/Rutgers UHouston/Texas AM

We began with an introduction, briefly explained our project, and asked if he talked to Deb Segal about our project.

Question: What is some of the research that you have been working on within the field of computational toxicology?

He has been researching ToxCast HTS data to collect information on 300 chemicals, and potentially up to 1000 and 10000. Currently there are 467 different assays. Of these 300 chemicals, 239 are chemical based, and the rest are cell based. He is also working to build predictive models to predict signatures of toxicity.

Another aspect of his work is the virtual embryos, which are cell-based models of development to try to introduce ToxCast predictions and determine which aspects will be toxic. They are in the process of building the virtual embryo.

In the ToxCast system, phase one is complete, and they are trying to publish that data currently. There are nine different kinds of assays, and it will be published in next three months or so. Once published, the information will become public.

Question: What are some of the setbacks that CT has come across recently?

He thinks there is healthy skepticism of the field. There are many questions as to how fast and

how big this program should become before we know how effective it could be in determining toxicity. There have even been EPA, public, national, and international symposiums about it.

He believes they are doing the best they can in terms of subjecting CT to outside scrutiny.

They made the data available in April or May to everyone worldwide so that people could let them know any problems. They have found many problems through that. They have stored these chemicals in our freezer for 18 months and they have learned that most of them are still stable, but there are some that have degraded over that time. Some break down during the process and they do not know if it is during use or during testing that this happens. Chemicals have to be hydrophobic in order to use HTS due to the DMSO being too hydrophilic. When chemicals are put through the system, companies have several chemical and physical criteria to determine whether we can use HTS to test them.

Question: Is the ToxCast system reliable enough to predict toxicity? When do you think it will be ready?

They are attempting to determine this now. They find in some assays, that when using recombinant DNA it may behave differently. They are trying to determine how well it predicts in vivo effects, and currently have around a 60-70% predictive power.

Overall, he would say it is good at predicting around 239 chemical assays.

Question: Hypothetically, if there were a chemical that did not exist yet, could QSAR or any other toxicology modeling programs be used to make determinations about its chemical/physical properties like melting point, freezing point, and etcetera?

Through the NCCT website, you can look at the DSStox database. Richard maintains that database. You can search for structures and find any that are similar to it. If you have a specific structure you are interested in you can use that to determine any similarities.

Question: We understand that the ToxCast system info is deposited into ACToR. Do you know how Richard Judsen gathers information for the ACToR system? Are there any regulations/processes to determine how information gets in there?

That information is deposited into tox-miner which is a data miner and then, the ToxCast website. Data is available when it is published.

ACToR is a resource that gives you information on the diff chemicals, but the data mining itself is done through tox-miner.

The best thing to do is send him a source of that information and he will have his contractors track down the info to c if it is reliable and if it passes their quality control measures, you could do that.

Question: Do you know who uses the ACToR system, outside of the CT community?

All of this is looked over by NCCT. Tox21 is under the National Toxicology Program.

Question: In terms of the funding aspect of CT: How does the MOU work? Is it a sharing of information or a sharing of resources?

If free agencies have decided to invest their own monies into a collaborative effort, they do share published data and meet four times a year and discuss data and strategy and how to use each other's data in the best possible way.

Question: Is the NTP developing a CT system, and do you know what specifically they are working on?

Each of the three components has their own mission. They focus on industrial chemicals so they would have a number of chemicals that they are interested in and they have in-vivo and in-vitro assays that they have done. Several sources nominate their own chemicals.

It is actually NCCT that has the expertise. The NTP has the animal data. The NIH genomic center has the HTS data that can do 200,000 assays that way.

Question: Are there any other avenues of funding for CT research?

The NCCT gets EPA money, but they also establish collaborations with outside partners. EPA

will give NCCT compounds that they have developed. Pfizer has given NCCT 120 chemicals that they have developed and that they could not use due to toxicity, which they discovered either in testing or in clinical trials. That is valuable information even though they do not give the NCCT money.

Does CT produce less hazardous waste then regular toxicology?

The NCCT would not have to discard chemicals and would not have to use animals for testing. The EU has banned animal testing, and is trying to encourage CT. The chemicals used are probably miniscule.

EU possibly began a little earlier that the NCCT and has invested a huge amount of money, but he believes the US and the EU are working pretty close together on this as partners through the OECD that have taken a big interest in this because drugs chemicals have a large use on life

Appendix M: Interview with Devon Payne-Sturgis

Interview with Devon Payne-Sturgis, Environmental Health Scientist, U.S EPA/ORD/NCER

Monday, November 16, 2009 10:00am NCER Office, Washington DC.

Attendees:

Alison Paquette (primary interviewer)

Taylor Mazzali (secretary)

Devon Payne-Sturgis, NCER EPA Environmental Health Scientist (interviewee)

Background: Dr. Payne-Sturgis is an environmental health scientist from NCER working with exposure bio-monitoring to analyze building emissions, and working with green building engineers to build greener and healthier buildings. Devon is not an expert in GC or CT, but she could help us analyze our project in a new way by considering the social and environmental factors of GC/CT, and the long term impact of our project.

Question: What is some of the research that you are currently looking at?

Working on funding the Children's Environmental Health centers, which study environmental impacts at many different levels, from laboratory testing to socio-economic policy analysis. These centers primarily look at "classic" environmental pollutants, like lead and mercury, which have been problems for decades. These centers are also focusing on emerging new contaminants, such as phalates and plasticizers (which are commonly used in children's toys)

Question: How is Green chemistry used to construct green buildings?

Currently working on an RFA involving green buildings, which is interdisciplinary. The builders try to utilize green techniques, but do not use specific green chemistry research.

Question: How do you think the 12 principles of GC could help with your research?

She has not looked at them in depth before, but it would be extremely useful to consider. Devon took a copy of the 12 principles of green chemistry to add as an appendix or reference in future projects.

Question: How do bio-assays monitor exposure in buildings?

Bio monitoring is primarily used to monitor air samples and dust exposure. Some of the predictions are not as expected, so scientists are trying to figure out why this is true.

Question: Do you collaborate with other agencies?

No, this is surprising, because a lot of the testing is similar. There is some collaboration with the NIEHS, but not with the FDA, or CPSC. Some of these agencies test the exact same chemicals at the same time, and get different results, so interdisciplinary research and collaboration across federal agencies needs to be improved.

Question: What about collaborating with pharmaceutical companies?

As far as she knows, there are no collaborations within her division. The OPPT has some collaboration with pharmaceutical companies.

Question: What are the broader implications of CT/GC? How could either field assist environmental health scientists and improve overall public health?

CT could replace animal testing, and could verify new green chemicals. The long term impact of this is that it could accelerate the testing of chemicals. The current problem with this is that computational toxicology is not respected or trusted to analyze chemicals. Green chemists and computational toxicologists also need to reach out to people not directly involved in their field, because their work has broad implications for the field of social justice.

Question: What policy changes do you think the EPA could implement to make GC/CT more relevant to the work you do?

When testing chemicals, it is important to consider that toxic effects are not caused by one chemical at a time, so more testing needs to be done with chemical mixtures. In addition, chemical tests need to be studied in conjunction with other socio-economic factors, like stress/malnutrition. This is currently possible with in vivo models, but needs to be considered when making computational models.

Question: Since you work with green buildings, do you know how waste disposal of dangerous chemicals works, or if there are any efforts to make waste exposure greener through chemical methods?

Since there is work being done with schools, which include science lab, this actually has been considered. Devon gave us the name of Bob Axelrad, who works in the Office of Air and Radiation. He is currently working on chemical management in schools.

Appendix N: Interview with Pasky Pascual

Interview with Pasky Pascual, Environmental Scientist/Lawyer, U.S EPA/ORD/NCER

Monday, November 16, 2009 2:00pm NCER Office, Washington DC

Background: Dr. Pascual is an environmental scientist and a lawyer who is the Director for the EPA's Council for Regulatory Environmental Modeling. He is currently funding research within the field of computational toxicology, and has a lot of information about computational models and statistical models, as well as databases.

Attendees:

Alison Paquette (primary interviewer)

Taylor Mazzali (secretary)

Pasky Pascual, NCER EPA Environmental Scientist/Lawyer(interviewee)

Question: What type of projects do you fund within the field of computational toxicology?

Dr. Pascual funds research within the field of computational models and integrated assessment, which analyzes different models and tries to link them together. He also studies the legal implications of these models, and tries to understand how they would stand up in court. There needs to be a rational basis to these statistical models, or they are not valid.

Question: What are some of the other avenues of funding for the grants you give out?

Theoretically, The NSF Funds basic research, as well as the NIEHS and NIH. In reality, they have very different focuses in regards to what they are looking for.

Question: What about pharmaceutical companies?

The pharmaceutical companies cannot fund any research because it would be a conflict of research (gift authority). However, they do supply the EPA with data from the research that they have done.

Question: What are some of the setbacks to systems models?

The problems within computational models are similar to the problems of any generic model. There are many factors that need to be considered within making a model, specifically an environmental one. When analyzing data points, it is important to get a representative sample. It

is possible to use create two different modeling systems that can explain the same data. Models need to be designed to be flexible. In addition, the models being used are heavily critiqued. The way to build a statistical model is

1. Build the model.
2. Use formal techniques to defend the model
3. Figure out how to manage the data produced by the model. Another problem is the data analysis of all the different databases is like trying to find a needle in a haystack.

Question: How reliable do you think CT data is at predicting a chemicals structure and its affect on toxicity?

Computational toxicology data often studies one chemical, but in real life there are often a variety of chemicals involved in an exposure. Chemical mixtures are a lot closer to reality, and need to be taken into account with computational models.

Question: Could the QSAR system be used to analyze the structure of chemicals that have not been synthesized yet?

Hypothetically, yes. QSAR models seem stable when it comes to the descriptions and attributes of a chemical itself, but seems iffy when trying to predict the effects on human health

Question: Where do you think the future of computational toxicology is headed?

CT should be accurate enough to predict toxicity of chemicals in 10 years, sooner if computational models are correctly designed and databases are carefully maintained. There needs to be many data gathered, and it needs to be properly analyzed using statistical methods. Dr. Pascual thinks there needs to be semantic search engines instead of a single database to gather this information and make it accessible.

Question: Do you think the ACToR database is appropriately organized?

Yes, this is the direction that database management needs to go. We need to make our risk assessment analysis more like Europe's reach program, which forces companies to submit chemical tests to a single database.

Question: Is this like the TSCA database, except public?

Dr. Pascual did not know much about the TSCA database, except that it probably did not use computational toxicology modeling.

Question: What policy changes do you think that the EPA needs to make CT or GC more heavily utilized?

The CT data needs to conform to semantic web ontology (so it can go into a semantic database)

There needs to be greater clarification of what the EPA is looking for when it comes to evaluating models.

Appendix O: Phone Interview with Paul Anastas

Attendees: 10:45am 12/9/09

Paul Anastas

Taylor Mazzali

Amy Morin

Alison Paquette

We introduced ourselves and told him briefly about the work we had been doing at NCER, and then asked questions about our Conclusions and Recommendations

Question: What are your thoughts about the creation of a centralized database for GC?

-He noted the existence of the ACToR database, and that it contains much of the information on chemicals that are needed. The "A" stands for "aggregated," so it is fairly comprehensive. Also, much of the missing information such as reactivity, solubility, and chemical composition are pieces of information that can be acquired publically through experimenting with these chemicals

Question: What are your thoughts on increasing communication in GC?

-He noted the two points we were trying to make from this recommendation; first the lack of awareness, and second, the lack of resources. In terms of awareness, it is not the lack of scientific publications, but the lack of awareness in industry, the government, environmental groups, and the general public. The lack of resources also plays a role with the lack of funding in these areas.

Question: What are your thoughts on the creation of a centralized database for CT, similar to that of REACH in Europe?

-He was curious as to why we chose REACH, and encouraged us to look more into the ACToR database. The largest concern with REACH is the large amount of data entering, but no useful methods existing to analyze it.

-He pointed out that in terms of the databases we described to make sure there is a balance between data collection, and the usefulness of the data. These data should be useful for analysis in the scientific community, the academic community, as well as in the general public.

Question: What are your thoughts on increased collaboration with companies doing toxicity testing, similar to the Tox 21 initiative?

-Absolutely! He believes that this is a great idea to increase collaboration between various agencies, and possibly partnership for grants.

Question: What are your thoughts on increasing publicity of the grants, and encouraging those who apply for grants from EPA to look into grants from other government organizations such as NSF and NIH?

-He agrees that this is a great recommendation; however, some difficulties may arise with NSF. They tend to have concrete categories for their research, such as chemistry, biology, or engineering, and when you try to look for funding in something that is interdisciplinary, it becomes much more difficult to break down those established "walls" in the other organizations.

Question: What are your thoughts on increasing publicity about some of the online models available to chemists, or considering more realistic factors in those models?

-He agrees that this is a good option, but also is aware of the increase in funding that would need to occur to make this happen. He believes we want to recommend communicating to Congress to increase the EPA's budget so they can increase awareness in both GC and CT.

-In terms of more realistic models, that is a tremendous factor and challenge the field is currently facing, and would be great to recommend.

Question: In order to help connect GC and CT, what are your thoughts on increasing education and communication?

-He believes those are good recommendations, and feels that this is the direction the two fields are moving in currently. There are NAS workshops, and conferences, such as the one he just attended in India, that are getting those scientists together to begin collaborative efforts.

Appendix P: Graphs of Green Chemistry Grants

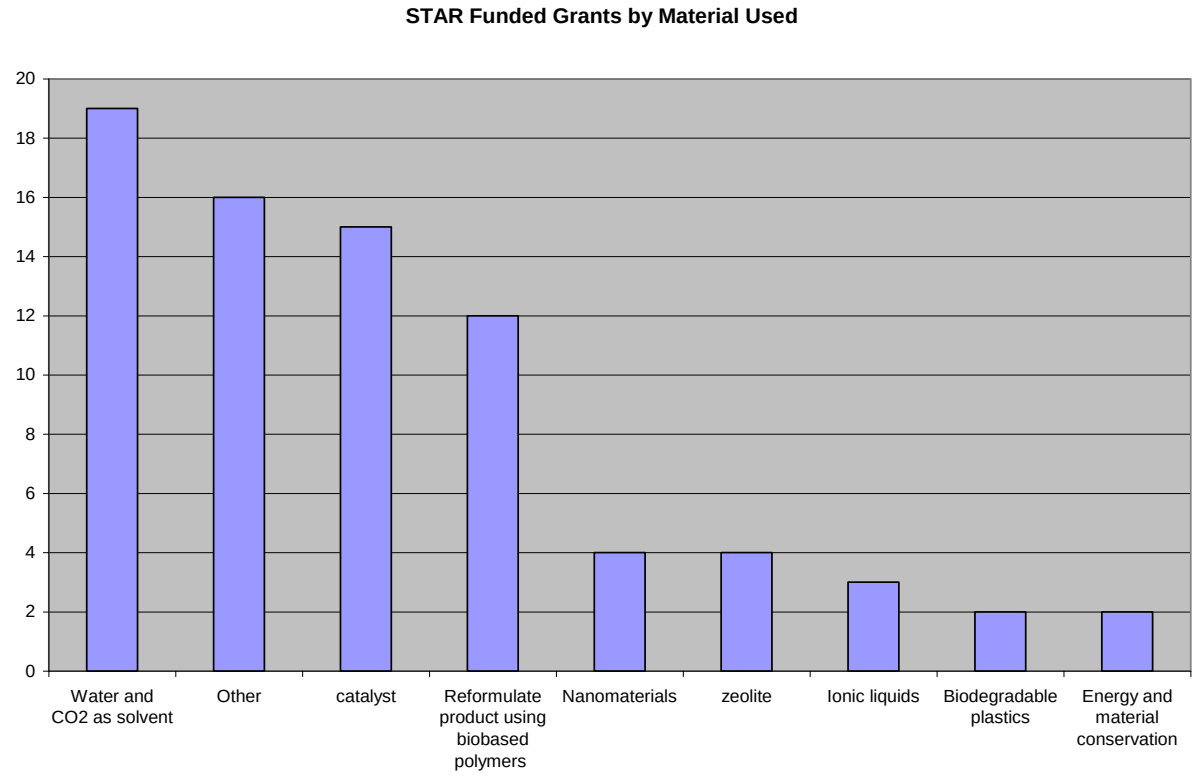

Figure P.1: Green Chemistry STAR Research by Materials Used

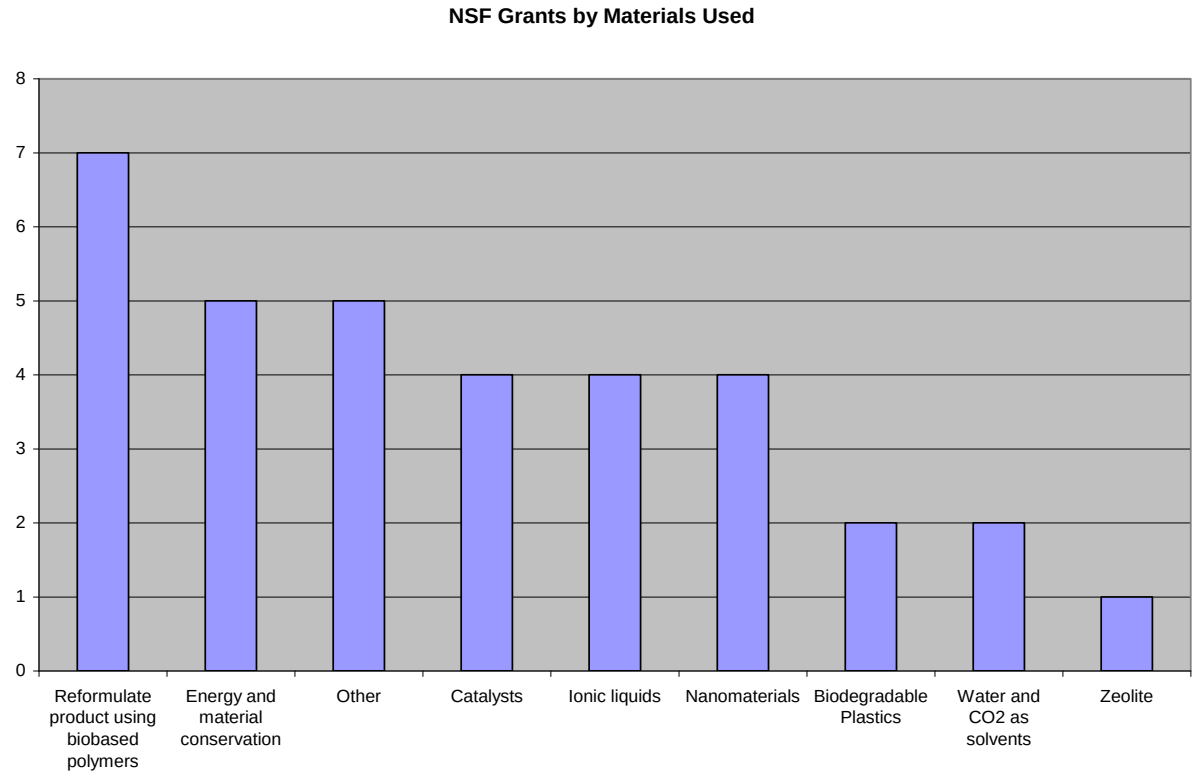

Figure P.2: Green Chemistry Research by Materials Studied (NSF)

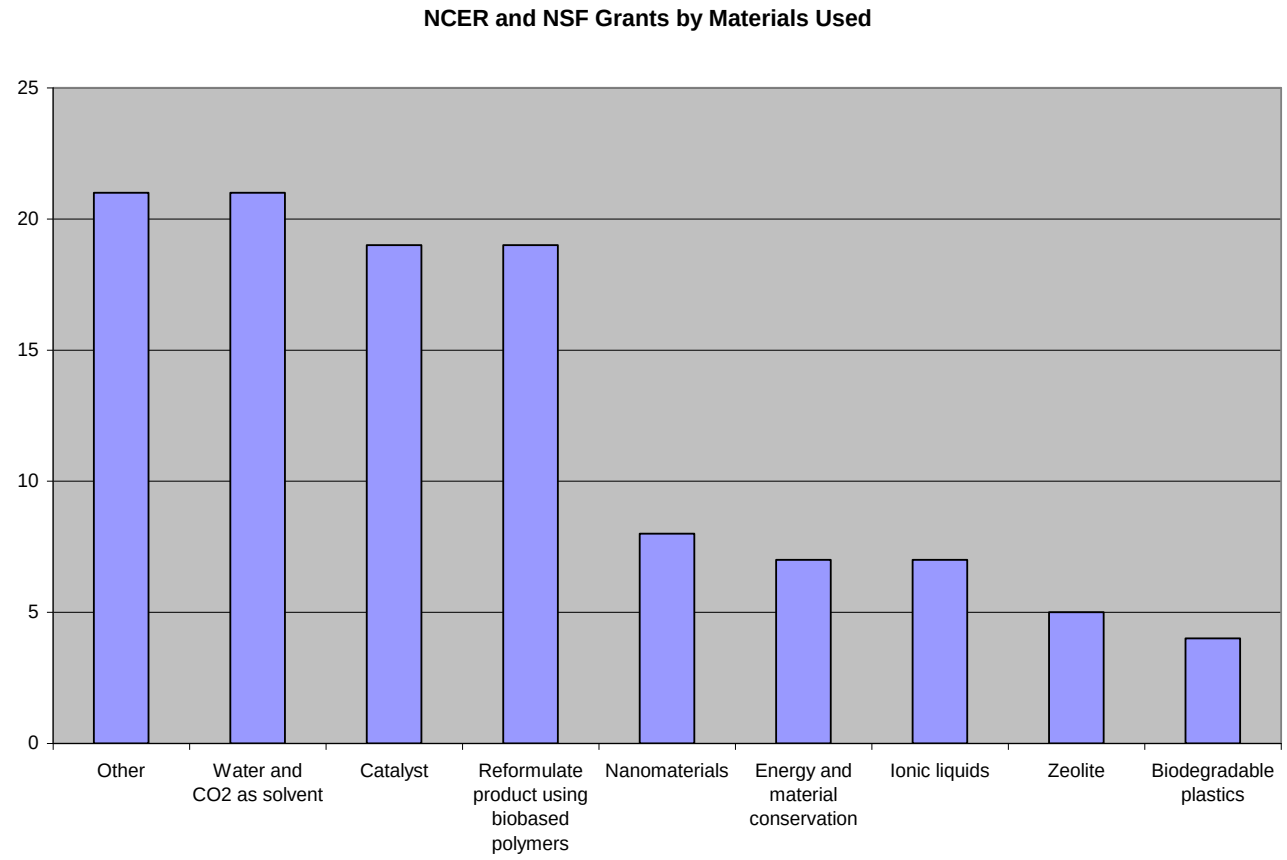

Figure P.3: Green Chemistry STAR and NSF Grants by Materials Used

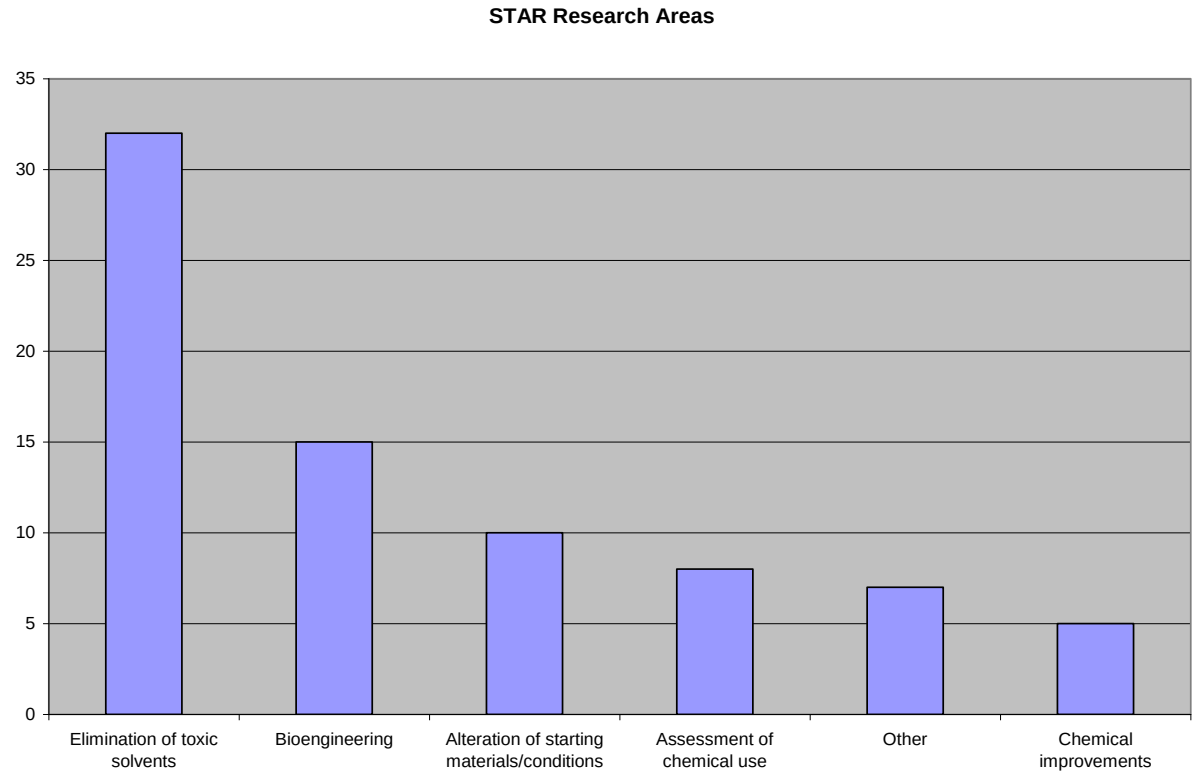

Figure P.4: Green Chemistry STAR Grants by Purpose

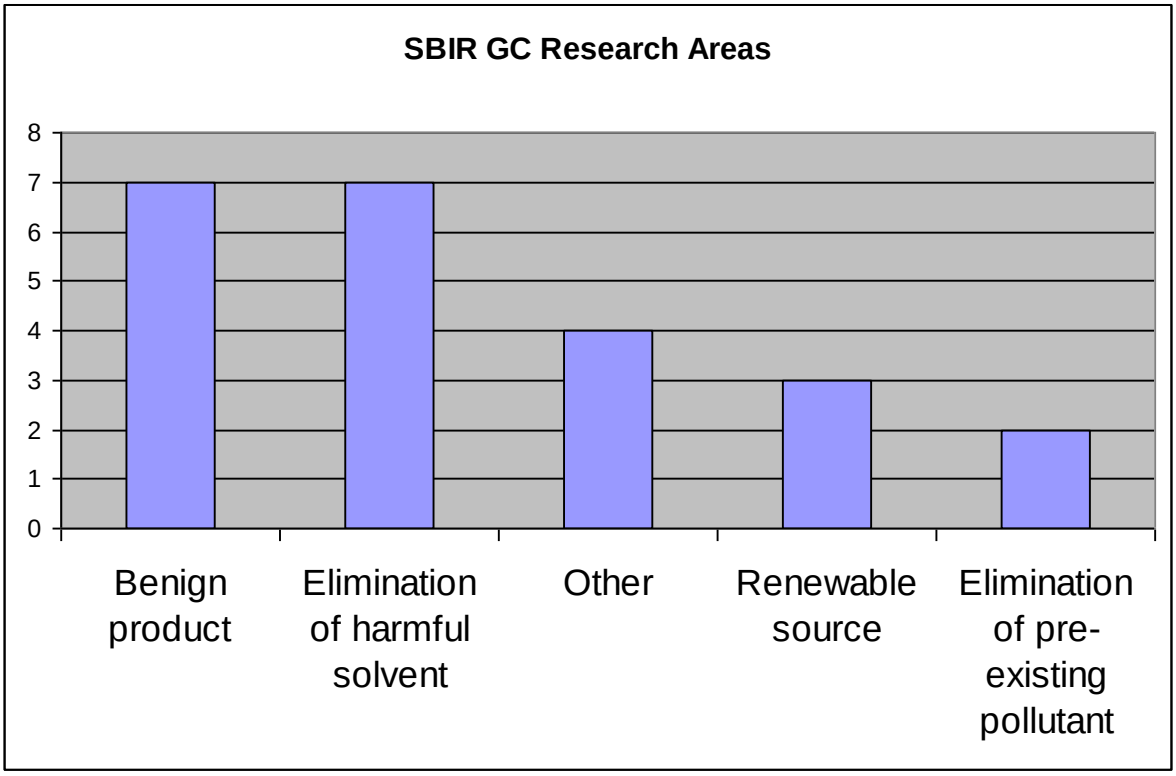

Figure P.5: Green Chemistry SBIR Grants by Purpose

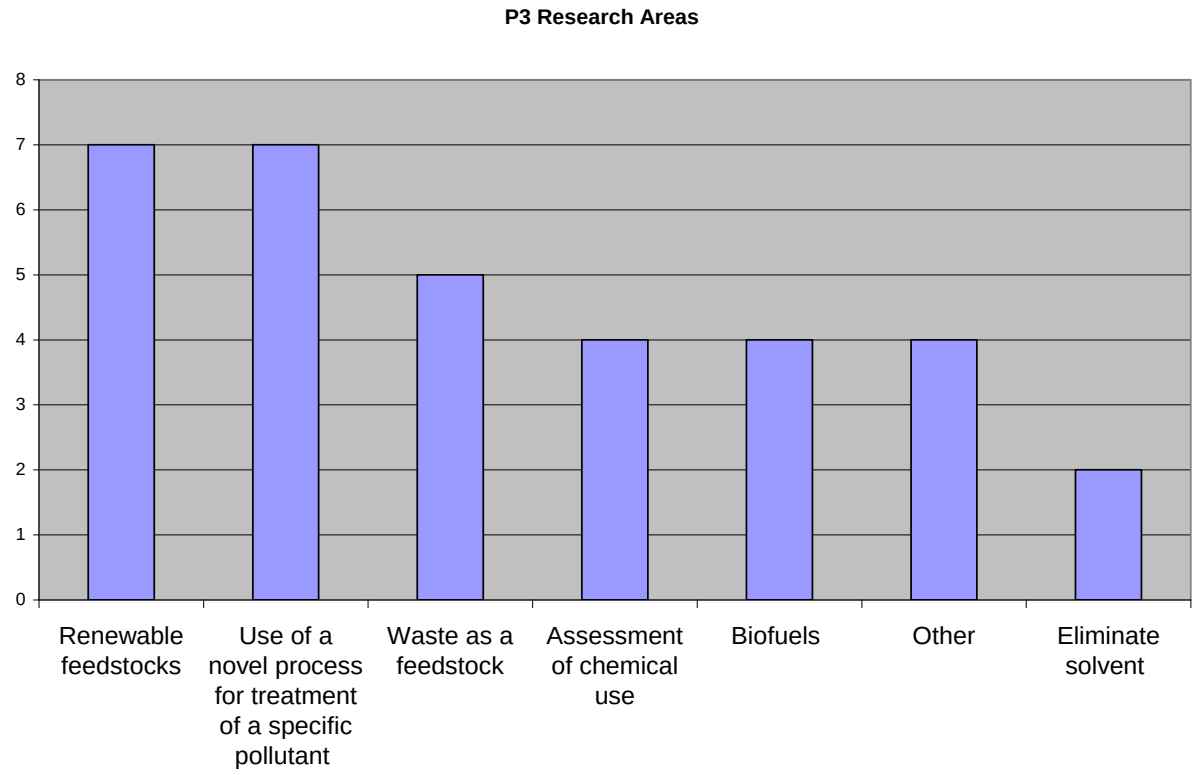

Figure P.6: Green Chemistry P3 Research by Purpose

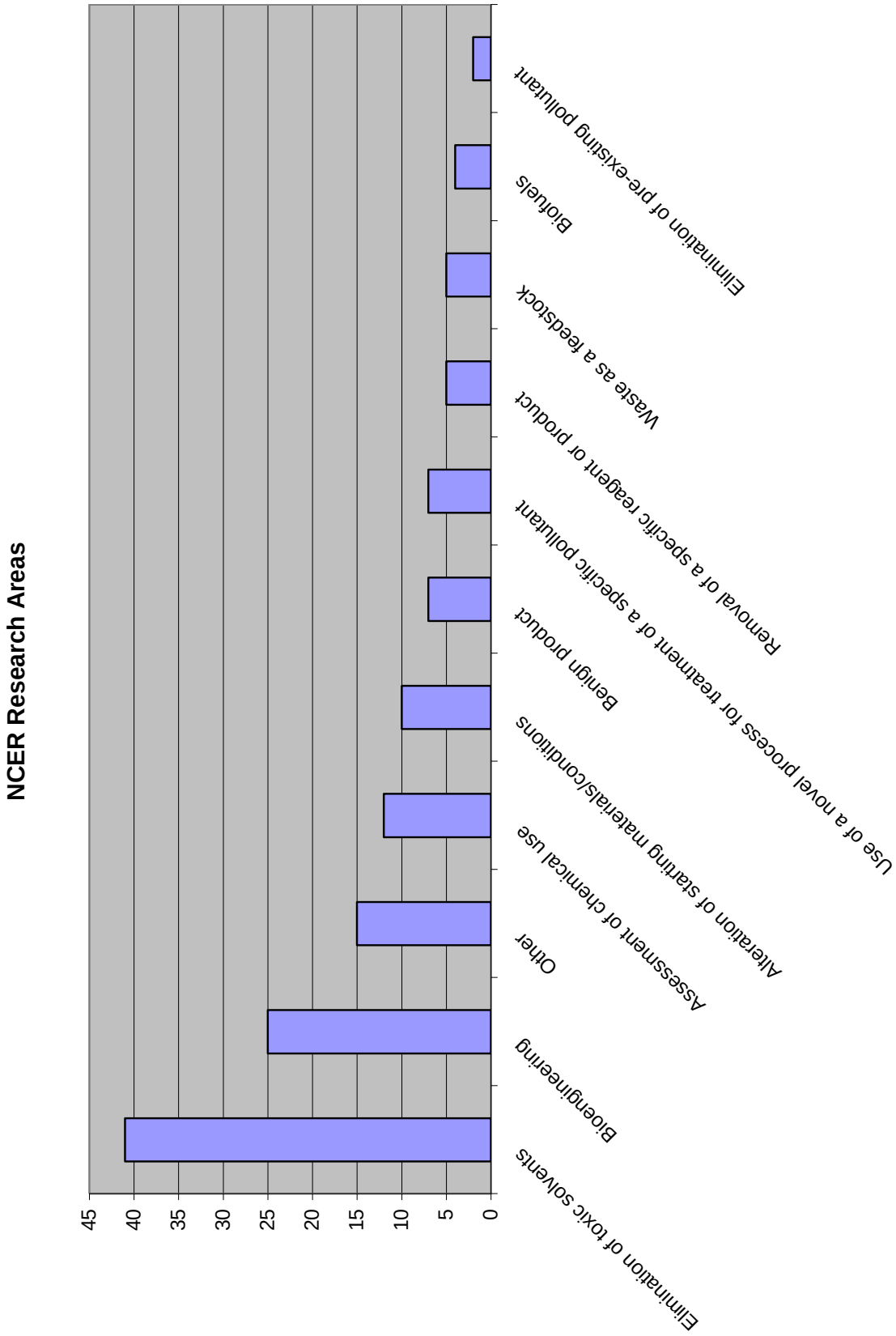

Figure P.7: Green Chemistry NCER Grants by Purpose

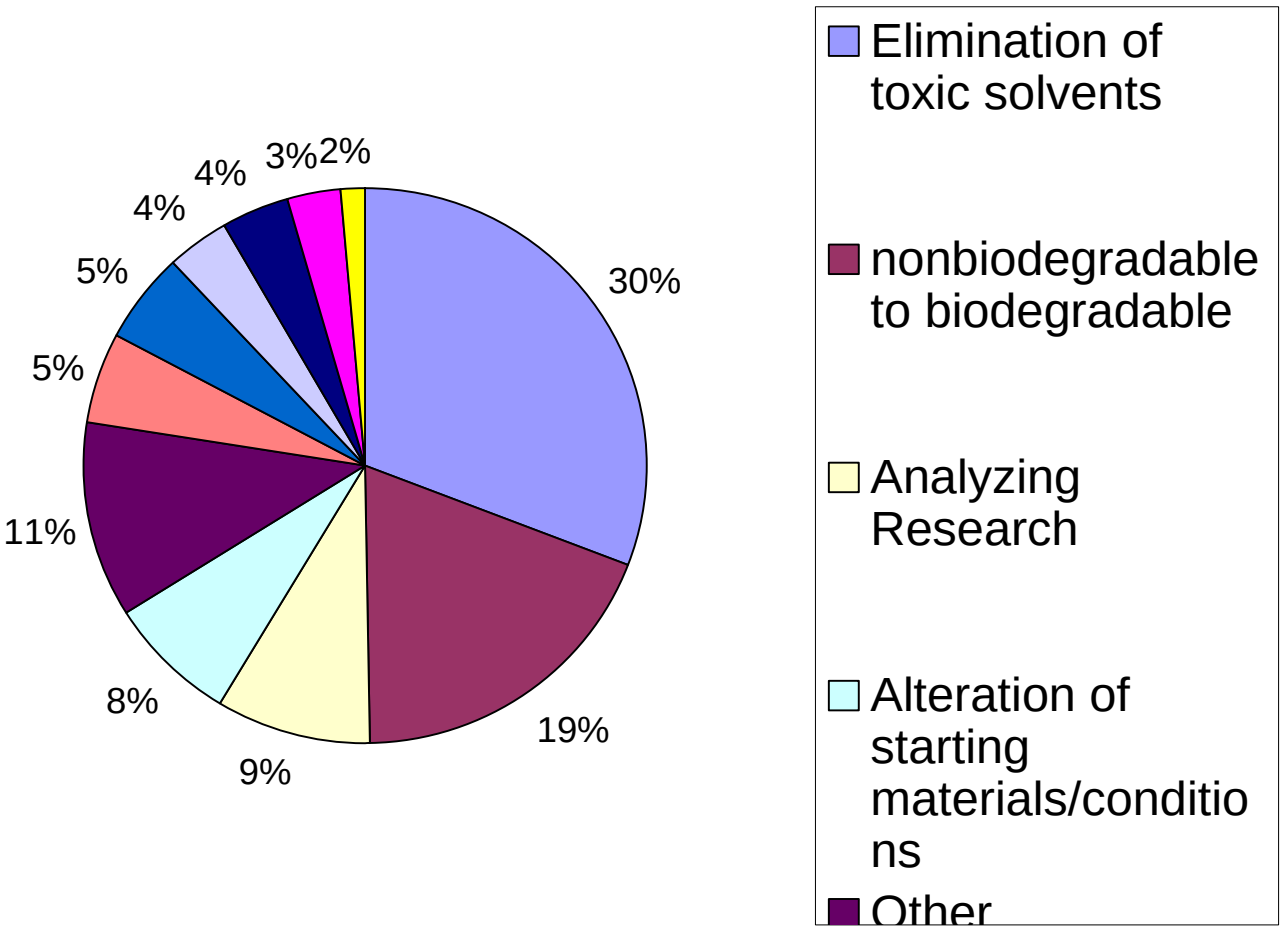

Figure P.8: Green Chemistry NCER Grants by Purpose Pie Chart

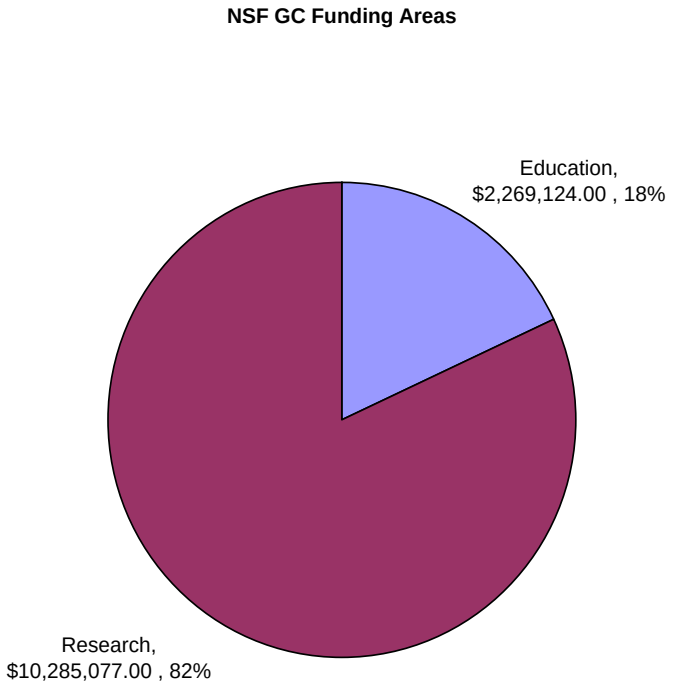

Figure P.9: Green Chemistry NSF Funding Areas

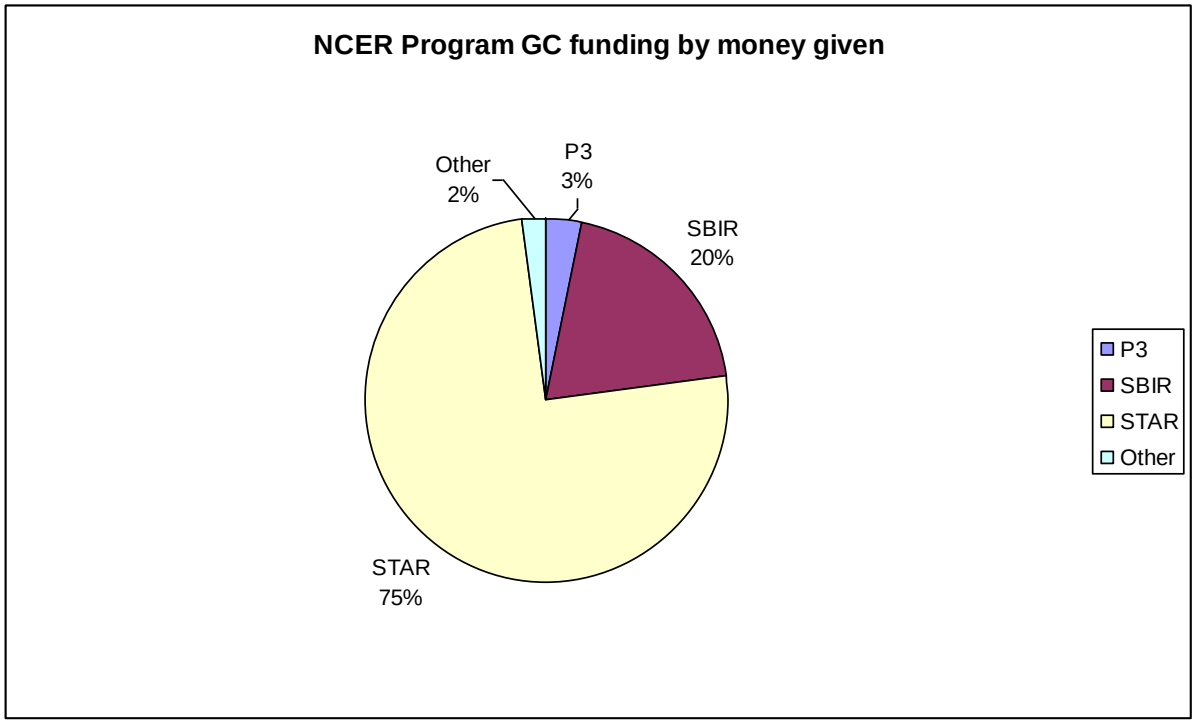

Figure P.10: Green Chemistry NCER program funding by Money

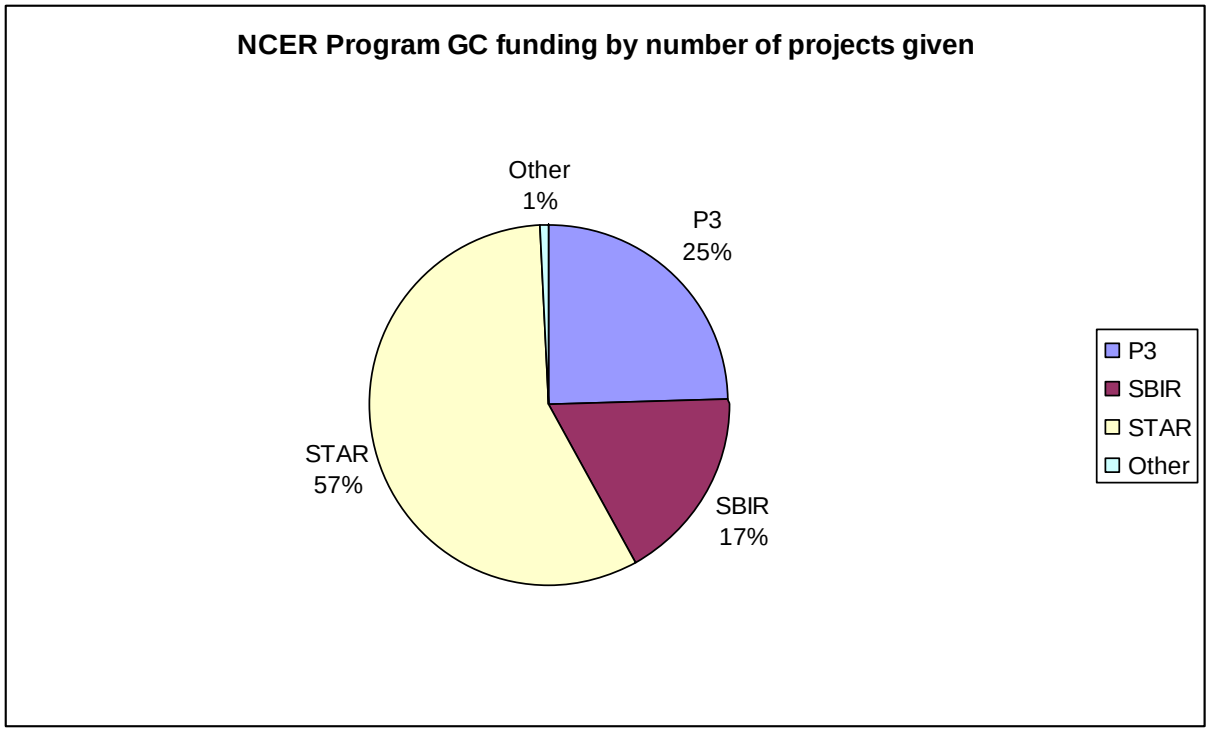

Figure P.11: Green Chemistry NCER Program funding by number of projects

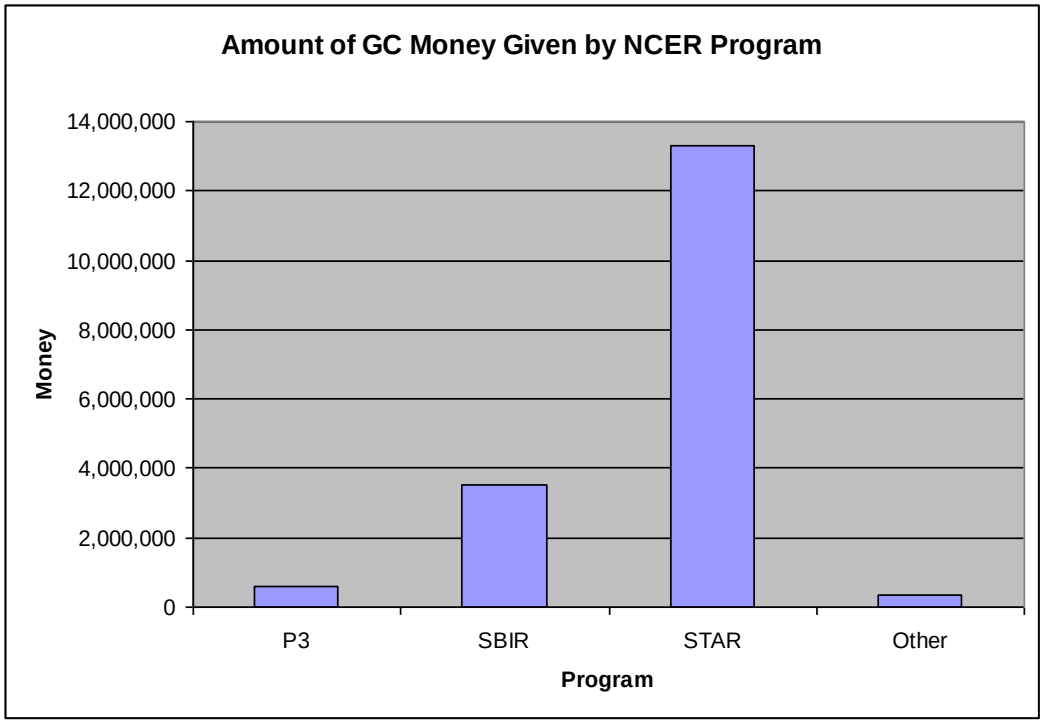

Figure P.12: Amount of Green Chemistry Money given by NCER

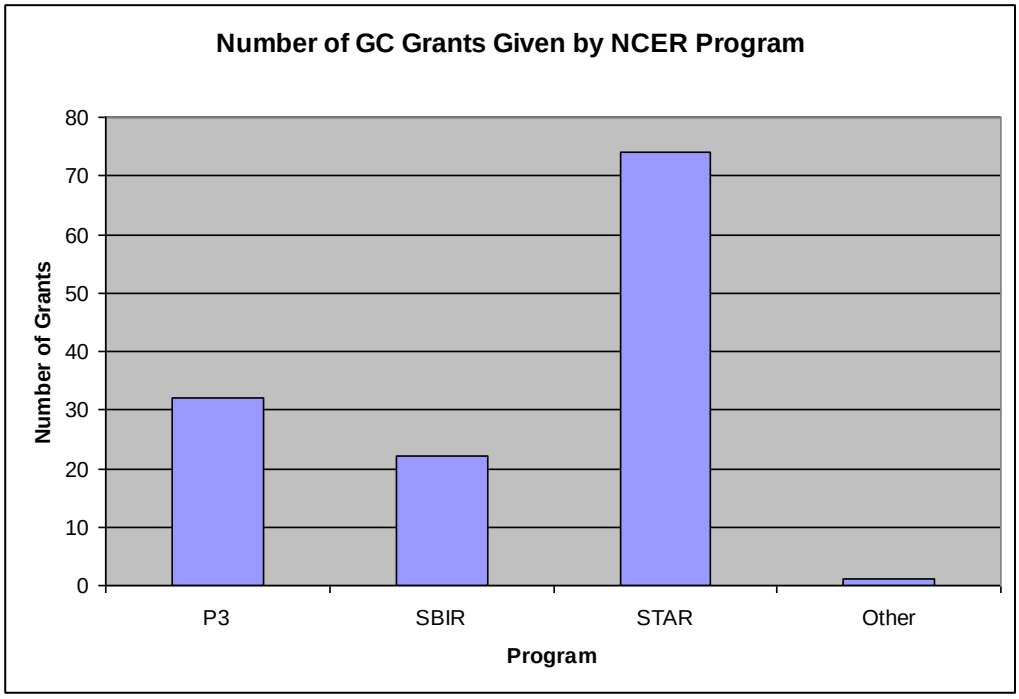

Figure P.13: Number of Green Chemistry Grants Given by NCER

Appendix Q: Tables of Green Chemistry Grants

Table Q.1 Green Chemistry STAR Grants

Type of Project	Grant #	Grant Amount (USD)	Time Period
enzymatic conversion	R831645	$190,156	June 2004 - May 2006
catalytic conversion	R831813	$350,000	June 2004 - May 2007
energy and material reduction	R831533	$375,000	Feb 2004 - Feb 2007
alteration of biodegradable plastics	R831530	335,000	Feb 2004 - Jan 2007
reformulate and improve the performance of polyurethane	R831436	350,000	Jan 2004 - July 2007
use of CO_2 as solvent to reduce waste and emissions (metal)	R831504	$349,967	Jan 2004 - Dec 2006
conversion from petroleum to renewable feedstocks	R831457	325,000	Jan 2004 - Dec 2006
conversion from petroleum to biodegradable nanocomposites	R830904	369,613	Jan 2004 - Dec 2006
evaluation of ionic liquids	R831432	325,000	Dec 2003 - Dec 2006
improving efficiency of catalytic reactions with electricity	R831495	375,000	Dec 2003 - Nov 2006
polymeric ligand exchangers to remove arsenic in water	R831431	99,452	Nov 2003 - Oct 2005
production of NaOH without CL2	R831433	319,998	Oct 2003 - Dec 2007
sulfur selective adsorption	R831471	325,000	Oct 2003 - Oct 2006
zeolites for adsorption of AS(III) and AS(V)	R831430	50,000	Oct 2003 - Sept 2004
Use of new materials to enhance membrane performance	R830909	349,000	Aug 2003 - Aug 2007
Nanomaterials environment impact	R830910	99,740	May 2003 - Apr 2005

Biodegradable nanocomposites	R830897	390,000	Jan 2003 - Dec 2005
Industrial ecosystems	R829688	334,146	June 2002 - June 2005
analyzing of nanoparticle forces	R829605	370,000	Feb 2002 - Jan 2004
plant based resins and adhesives	R829576	325,000	Jan 2002 - Dec 2004
Liquid catalyst development	R829553	325,000	Jan 2002 - Dec 2004
Organic pesticide development	R829589	180,000	Jan 2002 - Dec 2004
Improvement of catalysts and feedstock to eliminate transition metals and VOC	R829580	350,000	Jan 2002 - Dec 2004
use of CO_2 as solvent to reduce waste (plastic)	R829555	325,000	Jan 2002 - Dec 2004
zeolite use as environmental catalysts	R829600	350,000	Jan 2002 - Dec 2004
use of CO_2 to reduce organic solvent use	R829586	347,898	Nov 2001 - Nov 2004
evaluate environmental risks in Baltimore area	R828771C011	NA	Oct 2001 - Sept 2006
develop formaldehyde free binding system for wood	R828565	324,254	Sept 2000 - Sept 2003
benign solvent production	R828169	223,199	Sept 2000 - Aug 2002
use of steam or superheated water in place of solvents for degreasing	R828246	320,000	Sept 2000 - Aug 2004
zeolite coating in place of chromium coating for corrosion protection of Al	R828134	250,316	Aug 2000 - July 2004
heterogeneous catalyst development in supercritical CO_2	R828206	315,000	July 2000 - June 2004
homogeneous catalysis development in supercritical CO_2 w/ copolymer supported catalysts	R828135	315,000	June 2000 - May 2003
Near critical water as a solvent	R828130	397,910	June 2000 - June 2003

Solvent Tolerance of anaerobic bacteria	R828562	180,000	June 2000 - May 2003
Aqueous polyglycol as a benign solvent	R828133	335,000	June 2000 - May 2004
water, CO_2 and ionic liquid as solvents	R828129	310,000	June 2000 - Sept 2004
Properties of ionic liquids as solvents	R828257	375,000	May 2000 - Apr 2003
biocatalytic polyesterification	R828131	375,000	Apr 2000 - Sept 2004
Environmentally benign plastics	R826733	275,000	Nov 1998 - June 2003
CO_2 as a solvent	R826734	295,000	Oct 2000 - Sept 2001
use of bacteria in place of non renewable feedstocks	R826729	190,000	Oct 1998 - Sept 2001
liquid acrylate monomers in place of organic solvents	R826728	285,000	Oct 1998 - Sept 2001
more efficient catalysts and elimination of VOCs and solvents	R826735	330,000	Oct 1998 - Sept 2001
decrease energy and material costs with polymer use	R826732	350,139	Oct 1998 - Dec 2002
replace solvents with liquid vinyl ether monomers	R827121	328,209	Oct 1998 - Sept 2001
efficiency optimization using super critical media	R826034	125,000	Oct 1998 - May 2003
super critical fluid diagnostics	R826738	265,000	Oct 1998 - Sept 2001
development of catalysts for $CH_4(g) + CO_2(g) \rightarrow CH_3COOH(l)$	R827124	118,119	Sept 1998 - June 2002
biomimetic catalyst research for use in benign solvents	R826653	376,747	Aug 1998 - Aug 2001
development of onsite soil sampling methods	R826184	305,234	Feb 1998 - Feb 2001
Solvent development for specific processes	R826121	180,000	Nov 1997 - Oct 2000

elimination of toxic solvents through the use of nonionic surfactants and CO_2	R826115	370,000	Nov 1997 - Oct 2000
transition metal catalysts to improve benign organic reactions in water	R826120	280,000	Nov 1997 - Nov 2001
biodegradable instead of petroleum based polymeric materials	R826117	300,004	Nov 1997 - Dec 2001
biotech use to produce fuel ethanol	R826118	359,877	Nov 1997 - Oct 2000
solid acid catalyst research	R826122	150,000	Nov 1997 - Dec 2000
biocatalysis of resorcinol from glucose	R826116	337,202	Nov 1997 - Oct 2000
greening of polysaccharide materials	R826123	180,000	Nov 1997 - Oct 2001
alter the starting conditions to prevent the formation of toxic emissions	R826166	202,976	Oct 1997 - Sept 2000
elimination of harmful reagents and solvents	R826113	411,593	Sept 1997 - Aug 2000
water as solvent to rid reaction of some steps and harmful solvents	R822668	200,000	Aug 1997 - July 2000
sub critical water as a solvent to organic pollutants	R825394	374,925	Dec 1996 - Dec 1999
investigate the use of palladium catalyst for water contaminants	R825421	366,667	Nov 1996 - Oct 2001
environmental hazard of new alternative syntheses	R825329	275,235	Oct 1996 - Sept 1999
molecular assemblies to prevent water pollution	R825327	344,713	Oct 1996 - Dec 2000
environmentally benign oxidation reactions in zeolites	R825304	260,228	Oct 1996 - Sept 1999
use of subcritical water as field portable identifier of contaminants in soil	R825368	279,935	Oct 1996 - Sept 1999
Polymer synthesis in CO_2	R825338	180,000	Oct 1996 - Sept 1999

use of light to develop new synthetic reaction pathways	R825330	400,000	Oct 1996 - Sept 1999
Near critical water as a solvent	R825325	180,000	Oct 1996 - Sept 1999
investigation of CO_2 as a solvent	R824731	200,000	Oct 1995 - Sept 1997
C-C bonding in water	R824725	300,000	Oct 1995 - Sept 1997
Acid Alkylation Catalysts in Supercritical reaction media	R824729	220,000	Oct 1995 - Sept 1999

Table Q.2: Green Chemistry Non-STAR Grants

Type of Project	Grant #	Grant Amount (USD)	Time Period	Synopsis
Chicken feather H2 storage	SU834324 (P3)	$10,000	Aug 2009-Aug 2010	uses waste material to make process less expensive
Alkali-Activated Slag Cements as building material	SU834350 (P3)	$10,000	Aug 2009-Aug 2010	uses waste material to make process less expensive
Eco-Friendly Solvent Free to Synthesize Natural Products	SU833911 (P3)	$10,000	Aug 2008-Aug 2009	eliminate use of toxic solvents to remove byproducts
Directed Evolution of Iron enzymes to assist bioremediation	SU833912 (P3)	$10,000	Aug 2008-Aug 2009	learn reaction mechanism of enzyme, lead to bioremediation
Fuel Production from Coffee Wastes	SU833921(P3)	$10,000	Aug 2008-Aug 2009	increase sustainability of coffee production, safe drinking water
Novel Solid Acid Catalyst for waste oil feedstock and biodiesel production	SU833513 (P3)	$9,996	Aug 2008-Aug 2009	remove fatty acids from waste oils
Biodegradable soy-based plastic	SU833514 (P3)	$10,000	Sept 2007-Aug 2008	use soy protein based plastic instead of

products				petroleum based
eco-friendly golf tees filled with corn DDGS	SU833516 (P3)	$9,933	Sept 2007-Aug 2008	use a co-product of corn processing to make golf tees
engineering biosynthesis of styrene in yeast	SU833519 (P3)	$10,000	Aug 2007-Jul 2008	yeast produced styrene instead of petroleum based
Nutrient removal from on-site wastewater treatment systems	SU833545 (P3)	$10,000	Aug 2007-Jul 2008	iron-assisted reactor to remove phosphorus and nitrogen from wastewater
Liquid carbon dioxide based leather processing	GR833356 (other)	$322,950	Jun 2007-May 2010	assess diffusivity of CO_2 for tanning, waterproofing, dyeing etc of leather
production of biodiesel from algae for wastewater treatment	SU833154 (P3)	$10,000	Sept 2006-Aug 2007	use of alternative feedstock to provide energy for wastewater treatment
Expansion and Molding polymeric foam	SU833150 (P3)	$10,000	Sept 2006-May 2007	find a chemical agent that is benign to expand the foam
biodiesel production from algae	SU833165 (P3)	$10,000	Sept 2006-May 2007	sustainable biodiesel production using algae
self sustaining biodiesel production	SU833203 (P3)	$75,000	Sept 2006-Aug 2008	education of closed loop biodiesel systems
Natural surfactants in paper recycling	SU833151 (P3)	$10,000	Sept 2006-Aug 2007	use sugar surfactants to remove ink from recycled paper
Biocomposite material for load bearing construction components	SU833202 (P3)	$75,000	Sept 2006-Aug 2008	use recyclable materials for green building facades
Naturally occurring green tea flavonoids for cancer treatment	SU833204 (P3)	$75,000	Sept 2006-Aug 2008	new way to polymerize green tea flavonoids to use in cancer research

Recyclability index for Automobiles	SU832479 (P3)	$9,990	Dec 2005-May 2006	rate ecological impact of automobiles at the end of their life
industrial ecology and sustainable systems administration	SU832508 (P3)	$9,891	Sept 2005-May 2006	sustainable mobility practices for the future (25-30 yrs)
Trap Grease Upgrade for Biofuel Processing	SU832486 (P3)	$9,065	Sept 2005-May 2006	use trap grease to produce biofuels
Minimizing impact of construction materials in playground equipment	SU832476 (P3)	$10,000	Sept 2005-May 2006	use waste sugarcane material as playground surfacing material
UV Tube design for sustainable water disinfection	SU832462 (P3)	$75,000	Sept 2005-May 2006	uses UV light at source of water to disinfect and kill microorganisms
Renewable resources to power a university	SU832490 (P3)	$9,960	Sept 2005-Aug 2006	reducing CO_2 emissions at a university in Brazil
corn filler process as a filler in plastic resins	SU832478 (P3)	$9,933	Sept 2005-May 2006	using a corn co-product instead of petroleum based product for plastics production
encouraging toxic use reduction in academic laboratories	SU832467 (P3)	$39,852	Sept 2005-Aug 2006	survey chemicals used by MIT, and find reduction techniques, use less
Drinking water quality in developing nations	SU831833 (P3)	$10,000	Oct 2004-May 2005	use UVA radiation from sunlight and TiO2 to remove pathogens from drinking water
Implementing Biodiesel instead of petroleum diesel	SU831814 (P3)	$10,000	Oct 2004-May 2005	demonstrate environmental and economic feasibility of using biodiesel as opposed to petroleum diesel

Phosphorus recovery from sewage	SU831817 (P3)	$10,000	Sept 2004-May 2005	recover phosphorus from sewage to re-use in fertilizers… prevent eutrophication
conversion of waste oils from cooking to diesel fuel	SU831885 (P3)	$10,000	Sept 2004-May 2005	develop a pilot plant to convert waste oil to diesel fuel
Photo cross linked Immobilization of Polyelectrolytes for Template Assisted Enzymatic Polymerization of Conjugated Polymers	SU831894 (P3)	$10,000	Sept 2004-May 2005	reduce the use of lead in electronic boards and devices by photo cross-linking
TiO2 Nanoparticles for green production of photoanalytic catalysts	SU831824 (P3)	$10,000	Sept 2004-May 2005	recycling titanium waste streams to lead to green technologies for nano sized materials
cost effective photo-catalyst to remove arsenic in drinking water	SU831832 (P3)	$10,000	Sept 2004-May 2005	use a process to remove arsenic from drinking water, cheap, effective, little training required

Table Q.3: Green Chemistry SBIR Grants

Type of Project	Grant #	Purpose
Nanotech to create bioplastics	EPD07088	Renewable source
CO_2 as a replacement solvent in microelectronics manufacturing	EPD05052	Benign substance substitution, elimination of solvent
Production of ferrate as a substitute for oxidizing agents	68D02054	Benign substance substitution
Aluminum based antifouling agent	68D00272	Benign substance substitution

Environmentally friendly refrigerants	68D99082	Benign substance substitution
Cr(III) as a benign plating in place of Cr(VI)	68D50116	Benign substance substitution
nanostructures for use in dry machining	EPD05053	Elimination of harmful lubricants
Isocyanate-Free Solvent-Free Hybrid Resin System	EPD06076	Elimination of solvent and harmful reagent
Triggered-Release Biocidal Nanocomposite Coatings	EPD05054	Creation of more effective, less wasteful process
Phase I		
Production of Ti without the use of Mg or TiCl4	EPD08038	Elimination of harmful reagents
polysaccharide as a biodegradable plastic	EPD06050	Biodegradable substance
nontoxic replacements for toxic fire retardants	EPD05020	Nontoxic substance
Benign substitute for lead	EPD05008	Benign substance substitution
eutrophication of animal waste to create biofertilizer	EPD05011	Elimination of harmful pollutant
Removal of perchlorate from drinking water	EPD04040	Elimination of toxic pollutant
Environmentally safe wood preservatives	EPD04046	Benign substance substitution
Natural adhesive	EPD04043	Renewable source
Bio-based lactic acid production	68D03027	Renewable source
Ionic liquids in hydrogenation catalysis	68D00232	Non-harmful solvent
Ionic liquids as solvents	68D99042	Non-harmful solvent
Recovery of perfluoroethane	68D60028	Reuse of a greenhouse gas

Solvent free polymerization	68D50160	Elimination of toxic solvent

Table Q.4: Green Chemistry NSF Grants

Title	Grant #	Amount	Time Period	Synopsis	Partners?
Emerging Frontiers in Research Innovation	09-606	14 (4 year awards) $29,000,000 available	Proposals due March 1, 2010	(1) Renewable Energy Storage (RESTOR), and (2) Science in Energy and Environmental Design (SEED): Engineering Sustainable Buildings	NSF, DOE, EPA
Ordering Processes in Water, Aqueous Solutions, and Water-Biomolecule Systems	0404695	$700,000	Jul 2004-Jun 2010	use of non-crystallizing and non-perturbing solvents to study energy/kinetics of protein folding	NSF, CSC, Africa, Near East and South Asia (ANESA) Program in the Office of International Science and Engineering
Ordering Processes in Water, Aqueous Solutions, and Water-Biomolecule Systems	0404673	$840,000	Jul 2004-Jun 2010	use of non-crystallizing and non-perturbing solvents to study energy/kinetics of protein folding	NSF, CSC, Africa, Near East and South Asia (ANESA) Program in the Office of International Science and Engineering
Structure, Solvation and Dynamics in Ionic Liquids	0845026	$115,000	Sept 2009-Aug 2010	probe structures/dynamics of ionic liquids	NSF

Guiding General Chemistry Lab toward a green revolution	09242047	$192,595	Jan 2010-Dec 2011	development of green chemistry program at Armstrong Atlantic State University	NSF
Molecular Design of Nano-Carrier Materials for Reactions catalyzed by multi-enzyme complexes	0932517	$95,669	Oct 2009-Sept 2010	design nano-carrier platforms to catalyze reactions	NSF
ATR-FTIR Spectroscopy of Electrochemical Catalytic Reactions in Aqueous Systems at Doped Diamond filmed electrodes	0931749	$343,308	Sept 2009-Aug 2012	new methodology to understand conversion of organic compounds into aqueous systems	NSF
Advancing Green Reactor Engineering by Fundamental Characterization of multiphase flows	0933780	$253,625	Sept 2009-Aug 2012	develop techniques to measure flow in green reactors to increase efficiency	NSF
Chemical Dynamics and Green Chemistry strategies with organic nanocrystals	084455	$200,000	Aug 2009-July 2010	using green chemistry for synthetic applications with organic products	NSF

Reactive Polymers: Green Synthetic Applications	0910870	$160,000	Aug 2009-July 2010	development of solid-phase motifs (disks, monoliths) for reusable and regenerable main-group and transition-metal reagents/catalysts as well as the development of practical asymmetric routes to optically active targets using resin-bound asymmetric pyrrolidine catalysts in enamine-mediated reactions	NSF
EFRI-HyBi Green Aromatics by Catalytic Fast Pyrolysis of Lignocellulosic Biomass	0937895	$1,998,601	Aug 2009-July 2013	process called catalytic fast pyrolysis to convert cellulosic biomass feedstock into biofuel	NSF
Promoting Green Chemistry Education at Green Chemistry and Engineering Conference	0931906	$30,100	July 2009-Jun 2010	increase involvement in Conference by providing scholarships for students to attend	NSF, Green Chemistry and Engineering Conference
GOALI: Understanding Oxide-Polymer Interfaces to Enable Green Coating Technology	0809657	$466,148	Aug 2008-July 2011	better understand glass-polymer interactions on molecular level to develop less hazardous/more benign chemicals	NSF

Discovery Corps Fellowship: Project GREEN: Undergraduate Research, Curriculum Development and Outreach in Green Chemistry	0725117	$200,000	Sept 2007-Aug 2009	capture CO_2 using ionic liquid-based polymers	NSF
11th Annual Green Chemistry and Engineering Conference: Student Scholarships	0707686	$25,000	Mar 2007-Nov 2007	provide scholarships for students to attend conference	NSF
10th Annual Green Chemistry and Engineering Conference: Student Scholarships	0628832	$22,500	Aug 2006-Jan 2007	provide scholarships for students to attend conference	NSF
Discovery Corps Senior Fellowship: Expanding the Impact of Green Chemistry and Developing Green Products in Nigeria	0610157	$200,000	Aug 2006-July 2008	feasibility of an industry in Nigeria to produce food- and pharmaceutical-grade microcrystalline cellulose from elephant grass and other biorenewable resources	NSF
Discovery Corps Postdoctoral Fellowship: Fostering Green Chemistry and Engineering through Research, Education, and Service	0610207	$200,000	Aug 2006-Jan 2009	examine the role of membrane surface properties in the development of supercritical CO_2 separations	NSF

New Ionic Liquids for Electrochemical Devices: Fundamentals and Applications	0624620	$280,460	Jul 2006-Jun 2009	creation and use of new ionic liquid (IL) electrolytes which are environmentally clean ('green') and applicable to electrochemical devices	NSF
Chemical Dynamics and Green Chemistry Strategies with Solid-to-Solid Reactions	0551938	$527,500	Apr 2006- Mar 2010	investigate solid-state photochemical reactions and green chemistry strategies with solid-to-solid reactions	NSF
Green Chemistry in Chemical Engineering	0552702	$284,932	Mar 2006-Feb 2009	1) encourage students to continue their studies and seek research careers in chemical engineering; (2) help them to realize the employment and research opportunities available in chemical engineering aspects of sustainable technologies; (3) enhance professional development and communication skills; and (4) provide a rewarding experience by exposing them to outside classroom faculty-student interaction	NSF
Oxometal Complexes and Redox Catalysis	0553581	$437,000	Mar 2006-Feb 2009	investigate the ability of these complexes to activate dioxygen and catalyze air-	NSF

				based oxidations	
Sustainability, Energy and Engineering REU Site	0552750	$449,301	Feb 2006-Jan 2010	fund a 3 year REU at North Carolina State University	NSF
Greening the Chemistry Laboratory Curriculum	0535957	$149,760	Feb 2006-Jan 2010	integrate green chemistry concepts/practices into laboratory curriculum	NSF
Engineering ionic liquids	0547640	$565,145	Jan 2006-Dec 2010	creating ionic liquids	NSF
Collaborative Research on Bioinspired Photopolymers	0556272	$12,188	Jan 2006-Dec 2006	to develop and coordinate a collaborative research project on green chemistry, specifically working with thymine-based photopolymers	NSF
Japan-USA Workshop on Sustainable Chemical Synthesis	0603278	$27,954	Dec 2005-Nov 2006	science drivers of green chemistry in countries as complex as the US and Japan	NSF
9th Annual Green Chemistry and Engineering Conference: Workshop on Sustainability	0541524	$36,200	Aug 2005-Jul 2007	workshop sponsored by the National Science Foundation will foster the transition from a petroleum-based chemical economy to one using biorenewables by delineating key research areas and priorities	NSF

New Methods in Catalytic Organic Synthesis with Transition Metal Complexes	0516797	$420,000	Aug 2005-Jul 2008	development of new and efficient carbocyclization and higher order cycloaddition reactions, providing synthetic routes to appropriately functionalized polycyclic intermediates for the syntheses of bioactive natural and unnatural products	NSF
Discovery Corps Postdoctoral Fellowship: Greener Approaches to Chemistry Through Research and Education	0513503	$200,000	Aug 2005-Jul 2008	Involves synthesizing complex molecules that will be used in the development of a new class of molecular machines. These machines will respond collectively to mechanical, electrical, magnetic or optical stimuli develop a high school program	NSF, K-12 Outreach
Support for "Green Chemistry" Symposium at Pacifichem 2005; December 15-20, 2005; Honolulu, HI	0509841	$5,000	Jul 2005-Jul 2007	is supporting a symposium on Green Chemistry Processes	NSF
9th Annual Green Chemistry and Engineering Conference: Student Scholarships	0533126	$17,500	Jun 2005-Nov 2005	scholarships to allow students to attend conference	NSF

Joint China-USA Workshop: Determining the Green Chemistry Science Drivers and Implementation Challenges	0522369	$28,975	May 2005-Apr 2006	supporting a bilateral NSF/NSFC Workshop on "Determining Green Chemistry Science Drivers and Implementation Challenges	NSF
Synthesis and Characterization of Useful Products From Bagasse	0422729	$50,000	Jul 2004-Jun 2008	study the properties of bagasse (sugarcane cellulose residue) for utilization in production of materials for agricultural and pharmaceutical applications	NSF
RUI: Oxidative Transformation Using User- and Eco-Friendly Hypervalent Iodine Reagents	0412614	$192,000	Jul 2004-Jun 2008	developing methods for the use of water-soluble hypervalent iodine reagents as oxidation agents	NSF
8th Annual Green Chemistry and Engineering Conference: Student Scholarships	0421876	$15,000	May 2004-Oct 2004	workshop sponsored by the National Science Foundation will foster the transition from a petroleum-based chemical economy to one using biorenewables by delineating key research areas and priorities	NSF

GOALI: The Use of Sequestrants for the Dissolution of Scaling Deposits	0333091	$269,980	Apr 2004-Oct 2008	elucidate the transport and interfacial mechanisms responsible for the dissolution of mineral salts in the presence of environmentally benign chelating polymer(s)	NSF
A new low temperature generic 'green' chemistry for deposition of nanocrystalline films (TSE99-F)	0424982	$12,000	Jan 2004-Jun2004	The new approach studied in this project offers the prospect of new industrial coatings with superior properties and/or a new route to known coatings that is more sound environmentally	NSF
Functional Polymers From Renewable Resources -- Itaconic and Lactic Acids (TSE03-B)	0328002	$360,000	Aug 2003-Jul 2007	synthesize and characterize new functional polymers from renewable and sustainable resources	NSF
Making Industry Sustainable: Green Chemistry in the United States and the European Union	0327564	$22,597	Jul 2003-Jun 2005	aims to explore the ways in which green and sustainable chemistry has taken form since the early 1990s, and is generating scientific knowledge and material technologies that chemists, governments, industry, and citizens recognize as credible and legitimate for use	NSF

Support of the International Symposium on Relations Between	0334327	$5,000	Jul 2003-Aug 2003	New topics for the conference include bio-and supra-molecular catalysis, catalysis as a route to new materials, the intersections between nanoscience and catalysis, green chemistry, and emerging physicochemical or theoretical techniques	NSF
NER: Fabrication of TIO2 Nanoparticles and Films for Environmental Applications Using Ionic Liquid-Based Self Assessing Sol-Gel Methods	0304171	$100,000	Jun 2003-May 2005	investigating an innovative method to prepare nanostructured TiO2 photocatalytic powders and immobilized films with enhanced surface area, tailor-designed pore structure, and increased catalyst activity	NSF
7th Annual Green Chemistry and Engineering Conference Student Scholarships	0323271	$15,000	May 2003-Apr 2004	Student scholarships will be provided by this NSF funding for participation in the 7th Annual Green Chemistry and Engineering conference on June 23-26, 2003	NSF
From Solid State Reaction Mechanisms to Green Chemistry	0242270	$508,000	Mar 2003-Feb 2008	use of photochemical methods for the synthesis of organic compounds in the crystalline state	NSF

Green Chemistry on the Palouse	0243760	$192,000	Mar 2003-Feb 2006	10-week program will emphasize research topics in Green Chemistry	NSF
Pan-American Advanced Studies Institute on Green Chemistry	0221274	$76,420	Oct 2002-Dec 2003	activities focusing on presentations by leading experts in green chemistry, discussions on policy and economic factors driving green chemistry, group problem-solving sessions, and hands-on laboratory experiments	NSF
6th Annual Green Chemistry and Engineering Conference: Student Scholarships	0233733	$15,000	Aug 2002-Jan 2003	student scholarships for participation in Conference	NSF
New Methods in Catalytic Organic Synthesis with Transition Metal Complexes	0213216	$417,000	Jul 2002-Jun 2005	developing methodology wherein catalyst recovery and reuse are possible, thereby leading to practical green chemistry	NSF
5th Annual Green Chemistry Conference	0121728	$15,000	Jul 2001-Dec 2001	student scholarships for participation in Conference	NSF

An Environmentally-benign ('Green') Organic Chemistry Curriculum	0088986	$499,681	Feb 2001-Jan 2005	materials will be disseminated internationally through a variety of vehicles, including a published green organic chemistry laboratory textbook, workshops for teachers from all levels of educational institutions (K-12, community college, four-year college, and university	NSF
A Green Program in Extraction and Separation Chemistry for Incorporation into the Undergraduate Curriculum	0088314	$67,783	Jan 2001-Dec 2002	introduce environmentally responsible techniques of chemical separations and extractions into the undergraduate laboratory curriculum	NSF
A new low temperature generic 'green' chemistry for deposition of nanocrystalline films (TSE99-F)	9984158	$220,000	Jul 2000-May 2004	new industrial coatings with superior properties and/or a new route to known coatings that is more sound environmentally	NSF

Characterization of Optically-Active Compounds as a Means for Introducing Chemistry, Nursing, and Non-Science Majors to Environmentally-Benign Laboratory Methods	9952602	$17,279	Jan 2000-Dec 2000	integrates an automatic polarimeter into courses including Organic Chemistry, Biochemistry, Organic and Biochemistry for nursing majors, research-oriented General Chemistry laboratory, Chemistry for non-science majors, and undergraduate research	NSF

Table Q.5: NCER GC Grant Funding

Research Program	Amount spent on research	Number of projects
P3	608,620	32
SBIR	3,510,000	22
STAR	13,317,482	74
Other	$322,950	1

Table Q.6: NSF GC Funding Areas

Education	$2,269,124
Research	10,285,077

Appendix R: NCCT Publications

Table R.1: NCCT Publications

	NCCT PUBLICATIONS		
Year of Publication	**Title**	**CT Method used**	**Keywords**
2009	Inducible 70 kDa Heat Shock Proteins Protect Embryos from Teratogen-Induced Exencephaly: Analysis using Hspa1a/a1b Knockout Mice	Genetic expression	tetrogen, developmental defects
2009	Predictive Models for Carcinogenicity and Mutagenicity: Frameworks, State-of-the-Art, and Perspectives	QSAR, in silico, predictive methods,	carcinogen
2009	Mode of Action for Reproductive and Hepatic Toxicity Inferred from a Genomic Study of Triazole Antifungals	Genetic expression, biomarkers	reproductive defects, Triazole Antifungals, hepatocytes
2009	Toxicogenomic Effects Common to Triazole Antifungals and Conserved Between Rats and Humans	cross species extrapolation, microarrays, genetic expression	Triazole antifungals, hepatocytes,
2009	Profiling the activity of environmental chemicals in prenatal developmental toxicity studies using the U.S. EPA's ToxRefDB	ToxCast, ToxRef	developmental defects, pesticides
2009	Modeling Single and Repeated Dose Pharmacokinetics of PFOA in Mice	pharmokinetics, statistical analysis	PFOA, risk assessment
2009	Profiling Chemicals Based on Chronic Toxicity Results from the U.S. EPA ToxRef Database	ToxRef, Bioassay	Pesticides, Cancer, Chronic Exposure

2009	Integrated Analysis of Genetic and Proteomic Data Identifies Biomarkers Associated with Adverse Events Following Smallpox Vaccination	genetics, proteomics, algorithm	Vaccinations, immunity, AE
2009	Pharmacokinetic Modeling of Perfluorooctanoic Acid During Gestation and Lactation in the Mouse	pharmokinetics, cross species extrapolation	PFOA, developmental defects,
2009	DSSTox chemical-index files for exposure-related experiments in ArrayExpress and Gene Expression Omnibus: enabling toxico-chemogenomics data linkages	DSSTox, microarray, ArrayExpress, toxicogenomics,	exposure analysis
2009	Toward a Public Toxicogenomics Capability for Supporting Predictive Toxicology: Survey of Current Resources and Chemical Indexing of Experiments in GEO and ArrayExpress	microarray, ArrayExpress and Gene Expression Omnibus	gene expression, predictive modeling
2009	Predicting Residential Exposure to Phthalate Plasticizer Emitted from Vinyl Flooring - A Mechanistic Analysis	predictive modeling,	DEHP, Exposure analysis, phthalate plasticizers
2009	A Novel Two-Step Hierarchical Quantitative Structure Activity Relationship Modeling Workflow for Predicting Acute Toxicity of Chemicals in Rodents	QSAR, Predictive modeling	acute toxicity
2008	Biomonitoring Equivalents (BE) Dossier for Toluene (Cas No. 108-88-3)	Biomonitoring, PBPK modeling, pharmacokinetics,	toluene
2008	A Novel Approach: Chemical Relational Databases, and the Role of the ISSCAN Database on Assessing Chemical Carcinogenity	database analysis	carcinogen,
2008	Comparing Surface Residue Transfer Efficiencies to Hands Using Polar and Non-Polar Florescent Tracers	fluorescent tracers	Pesticides, exposure analysis

2008	Fetal alcohol syndrome (FAS) in C57BL/6 mice detected through proteomics screening of the amniotic fluid	cross species extrapolation, proteomics	developmental defects, alcohol
2008	Comparing Single and Repeated Dosimetry Data for Perfluorooctane Suflonate in Rats	Pharmacokinetics, systems biology	PFOA
2008	Understanding Mechanisms Toxicity: Insights from Drug Discovery Research	HTS,	drug research
2008	ACToR-Aggregated Computational Resource	HTS, ToxCast	Risk assessment, predictive modeling
2008	A Comparison of Machine Learning Algorithms for Chemical Toxicity Classification Using a Simulated Multi-Scale Data Model	Machine Learning, ToxCast, statistical analysis	Risk assessment
2008	Development of good modeling practice for physiologically based pharmacokinetic models for use in risk assessment: The first steps	pharmokinetics	Risk assessment, predictive modeling
2008	Computational Molecular Modeling for Evaluating the Toxicity of Environmental Chemicals: Prioritizing Bioassay Requirements	HTS, molecular modeling, virtual screening,	Risk assessment
2008	Comparing models for perfluorooctanoic acid pharmacokinetics using Bayesian analysis	pharmokinetics, systems biology	PFOA
2008	Understanding Genetic Toxicity Through Data Mining: The Process of Building Knowledge by Integrating Multiple Genetic Toxicity Databases	database analysis	gene expression
2008	Predicting Maternal Rat and Pup Exposures: How Different Are They?	cross species extrapolation, pharmokinetics	exposure analysis

2008	Use of Cell Viability Assay Data Improves the Prediction Accuracy of Conventional Quantitative Structure-Activity Relationship Models of Animal Carcinogenicity	HTS, QSAR	carcinogen
2007	Characterizing Uncertainty and Variability in PBPK Models: State of the Science and Needs for Research and Implementation	pharmokinetics	
2007	THE EXPANDING ROLE OF PREDICTIVE TOXICOLOGY: AN UPDATE ON THE QSAR MODELS FOR MUTAGENS AND CARCINOGENS.	QSAR	carcinogen, risk analysis
2007	DEVELOPMENT AND USE OF PBPK MODELING AND THE IMPACT OF METABOLISM ON VARIABILITY IN DOSE METRICS FOR THE RISK ASSESSMENT OF METHYL TERTIARY BUTYL ETHER (MTBE)	pharmokinetics, cross species extrapolation	MTBE, TBE, risk assessment
2007	MECHANISTIC COMPUTATIONAL MODEL OF OVARIAN STEROIDOGENESIS TO PREDICT BIOCHEMICAL RESPONSES TO ENDOCRINE ACTIVE COMPOUNDS.	molecular modeling,	EDC, reproductive defects
2007	THE TOXCAST PROGRAM FOR PRIORITIZING TOXICITY TESTING OF ENVIRONMENTAL CHEMICALS	HTS,	risk assessment, exposure analysis
2007	DISRUPTION OF TESTOSTERONE HOMEOSTASIS AS A MODE OF ACTION FOR THE REPRODUCTIVE TOXICITY OF TRIAZOLE FUNGICIDES IN THE MALE RAT	systems biology	reproductive defects, Triazole Antifungals,
2007	TOXICOGENOMIC STUDY OF TRIAZOLE FUNGICIDES AND PERFLUOROALKYL ACIDS IN RAT LIVERS ACCURATELY CATEGORIZES CHEMICALS AND IDENTIFIES MECHANISMS OF	genetic analysis	Triazole antifungals, PFOA,

	TOXICITY		
2007	Novel methods for detecting epitasis in pharmacogenomics studies	data-mining, genetic analysis	epitasis, pharmogenomics
2007	Issues in the Design and Interpretation of Chronic Toxicity and Carcinogenicity Studies in Rodents: Approaches to Dose Selection	pharmokinetics, cross species extrapolation	chronic exposure, carcinogen, risk assessment
2007	Predicting Age-Appropriate Pharmacokinetics of Six Volatile Organic Compounds in the Rat Utilizing Physiologically Based Pharmacokinetic Modeling	pharmokinetics, cross species extrapolation	volatile organic compounds, developmental defects
2007	USING BIOMARKERS TO INFORM CUMULATIVE RISK ASSESSMENT	biomarkers	risk assessment, exposure analysis
2007	Implications of gender differences for human health risk assessment and toxicology	pharmokinetics, systems biology	gene expression, reproductive defects, developmental defects, risk analysis
2007	EXTRAHEPATIC METABOLISM IN CYP2E1 IN PBPK MODELING OF LIPOPHILIC VOLATILE ORGANIC CHEMICALS: IMPACTS ON METABOLIC PARAMETER ESTIMATION AND PREDICTION OF DOSE METRICS.	pharmokinetics	volatile organic compounds, risk assessment
2006	METABOLISM OF MYCLOBUTANIL AND TRIADIMEFON BY HUMAN AND RAT CYTOCHROME P450 ENZYMES AND LIVER MICROSOMES.	pharmokinetics, systems biology	Triazole antifungals
2006	MEASURING POTENTIAL DERMAL TRANSFER OF A PESTICIDE TO CHILDREN IN A CHILD CARE CENTER	algorithms	pesticide, exposure analysis

2006	GENE EXPRESSION PROFILING IN THE LIVER OF CD-1 MICE TO CHARACTERIZE THE HEPATOTOXICITY OF TRIAZOLE FUNGICIDES	genetic analysis, microarrays,	Triazole antifungal, hepatocytes,
2006	NTP-CERHR EXPERT PANEL UPDATE ON THE REPRODUCTIVE AND DEVELOPMENTAL TOXICITY OF DI(2-ETHYLHEXYL) PHTHALATE.		reproductive defects, developmental defects, phalate
2006	A MATHEMATICAL MODEL FOR THE ANDROGENIC REGULATION OF THE PROSTATE IN INTACT AND CASTRATE ADULT MALE RATS	PK modeling, mathematical modeling	reproductive defects
2006	CHEMICAL STRUCTURE INDEXING OF TOXICITY DATA ON THE INTERNET: MOVING TOWARDS A FLAT WORLD	database analysis	risk assessment, toxicity prediction
2006	THE FUTURE OF TOXICOLOGY-PREDICTIVE TOXICOLOGY: AN EXPANDED VIEW OF CHEMICAL TOXICITY	QSAR, HTS	toxicity prediction
2006	Gene Expression Profiling in Liver and Testis of Rats to Characterize the Toxicity of Triazole Fungicides	genetic analysis, microarrays	Triazole antifungals, gene expression
2006	MICROARRAY QUALITY CONTROL PROJECT: A COMPREHENSIVE GENE EXPRESSION TECHNOLOGY SURVEY DEMONSTRATES MEASURABLE CONSISTENCY AND CONCORDANT RESULTS BETWEEN PLATFORMS	microarray, gene expression	
2006	GENOMIC IDENTIFICATION OF POTENTIAL RISK FACTORS DURING ACETAMINOPHEN-INDUCED LIVER DISEASE IN SUSCEPTIBLE AND RESISTANT STRAINS OF MICE	genetic analysis,	drug research, hepatocytes, gene expression

2006	THE ART OF DATA MINING THE MINEFIELDS OF TOXICITY DATABASES TO LINK CHEMISTRY TO BIOLOGY	data mining, QSAR	toxicity prediction

Appendix S: NCER funded Research

Table S.1: NCER funded CT Research

Identifier	Name	time period	CT Methods	Keywords	grant amount
STAR Grant R833856	Development of an In Vitro Test and a Prototype Model to Predict Cellular Penetration of Nanoparticles	July 1, 2008 through June 30, 2011	computational chemistry,QSAR	nanoparticles	$399,628
R832739	Systems Approach to Assessing Cumulative Exposure to Endocrine Disrupting Chemicals	October 1, 2005 through September 30, 2009	systems biology,reporter gene approach,	EDC, gene expression	$585,206
R831847	Estrogen Elicited Gene Expression Network Elucidation in the Rat Uterus	September 1, 2004 through August 31, 2007	systems biology, Genetic algorithms,HTS, QRT-PCR	EDC, gene expression	$747,960
R831846	Chemical Induced Changes in Gene Expression Patterns Along the HPG-axis at Different Organizational Levels Using a Small Animal Model	September 1, 2004 through August 31, 2007	systems biology,HTS,whole animal systems approach, QRT-PCR	EDC,gene expression, aquatic systems	$749,904
R831848	Systems Biology Modeling of Fathead Minnow Response to Endocrine Disruptors	August 1, 2004 through July 31, 2007	systems biology,microarrays	EDC, aquatic systems,	$722,851
R831300	Mechanistic Approach to Screening Chemicals and Mixtures for Endocrine Activity Using an Invertebrate Model	September 1, 2003 through August 31, 2007	invertebrate models, systems biology, HTS,	EDC, hazard analysis	$391,598
R829358	Mechanistic Evaluation of the Toxicity of Chemical Mixtures	September 24, 2001 through September 23,	algorithms,systems biology,	hazard analysis, chemical mixtures, hazardous waste,	$465,281

Appendix T: Non EPA funded CT Research

Table T.1: Non-EPA funded CT Research

Identifier	Title	Grantee	Amount	Keywords
NIH				
Y2ES7020-4-0-1	TOXICITY PROFILING USING HIGH THROUGHPUT SCREENING (HTS)	NIEHS	$3,500,000	Tox 21, HTS
5T32ES007126-27	PRE- AND POSTDOCTORAL TRAINING IN TOXICOLOGY	UNIVERSITY OF NORTH CAROLINA CHAPEL HILL	$522,776	Post doctoral Training in CT
5K25ES012909-05	BIOCHEMICAL REACTION NETWORK MODELING OF PCB MIXTURES	COLORADO STATE UNIVERSITY-FORT COLLINS	$137,338	Computer modeling, PCB
NSF				
0714028	CRC: High Throughput and Massively Parallel Synthesis of Nanostructured Materials	Michigan State University	$457,500	HTS
0945802	SBIR Phase I: Development of new materials for a low cost high throughput ion channel measurement platform	Librede Inc.	$149,770	HTS
0944910	SBIR Phase I: High Throughput Microfluidic Cell Injection for Cell Reprogramming	Zaiput Technologies LLC	$150,000	HTS
0927736	High Throughput Process Screening and in-situ Characterization for Graphene Synthesis	GA Tech Research Corporation - GA Institute of Technology	$365,002	HTS
			$1,122,272	

Appendix U: Glossary of Terms

Acute: exposure that takes place over a very short period of time, sometimes a matter of hours or even minutes (Stelljes, pg 191, 2000)

Ames test: A common mutagenicity test involving salmonella (Crosby, 1998, p.151)

Assay: a test to determine the presence, absence or quantity of a substance (Merriam-Webster Online Dictionary. ASSAY." 2009.)

Atom economy: the percentages of raw materials and reagents that end up in the product (Hoag, 2009, Chemical Heritage Newsmagazine).

Aluminum trichloride ($AlCl_3$): a toxic reagent made up of three chlorine atoms attached to an aluminum atom

Bayesian modeling: a statistical modeling technique in which evidence is used to predict the probability of something to be true

Benign: Non-harmful (Thefreedictionary, 2009, Benign)

Bio assays: Determination of the effectiveness of a compound by measuring its effect on animals or tissues in comparison with a standard preparation. (Glossary, BIO, 2009)

Bio Monitoring: Monitoring conducted to determine existing environmental conditions, pollutant levels, rates, or species in the environment.(SFEI, 2009, glossary)

Biochemical reactions: a chemical reaction in a living organism (BIO, 2009, glossary)

Biofuel: Fuel created with renewable, naturally occurring starting material

Blood/brain barrier: The protective membrane that separates circulating blood from brain cells (*UK HealthCare*, 2007, B Glossary)

Breeding: having animals reproduce to gather new animals for scientific purposes

Cancer: the growth of hazardous tumors that can grow and expand without limit (*Merriam-Webster Online Dictionary*, 2009, cancer).

Carbon tetrachloride (CCl_4): a toxic solvent made up of four chlorine atoms attached to a carbon atom

Carcinogens: a substance that causes cancer

Catalyst: a substance, usually used in small amounts relative to the reactants, that modifies and increases the rate of a reaction without being consumed in the process (Houghton Mifflin Company, 2009, catalyst).

Chem-informatics: computer software and hardware used in drug discovery and for chemical analysis (*Drug Development Technology*, 2009, Cheminformatics Glossary Definition).

Chronic: an exposure that lasts over a period of more than 7 years (Stelljes, 2000, p.192).

Closed loop biodiesel production: Self-sustaining system to produce biodiesel

Computational biology: using computers to study complex biological models that involve many intermolecular reactions (*Rational MD,* 15 June 2008, Cell Biology Glossary).

DEHP: a chemical used in plasticizers that has been shown to cause developmental defects (ethylhexyl) phthalate (DEHP) (*ToxFacts* , 2007, ATSDR).

Dioxin: a carcinogen produced from the chlorine bleaching process (Gross, Keaty, 2009, Dioxin).

DNA: a molecule that carries the genetic information for most living systems (BIO, 2009, Glossary).

Dose-response assessment: is the characterization of the relationship between exposure or dose and the incidence and severity of the adverse health effect. It includes consideration of factors that influence dose-response relationships such as intensity and patterns of exposure and age and lifestyle variables that could affect susceptibility. It can involve extrapolation of high-dose responses to low-dose responses and from animal responses to human responses (NRC, 1994).

Dose-Response Information Analysis [DORIAN] System: a computational system created by the Environmental Bioinformatics Center

DuPont: Currently the world's second largest chemical company (Thefreedictionary, 2009, DuPont).

Enantiomer: a compound that is not identical to its mirror image

Endocrine disrupting chemicals: a foreign substance that alters the function of the endocrine system (*GreenFacts*, 2009, Endocrine Disruptors).

Endocrine system: a system of glands in the body that produce hormones (*GreenFacts*, 2009, Endocrine Disruptors).

Environmental toxicology: The study of environmental toxins and natural pollutants in the environment (*Medterms*, 2004, Environmental toxicology definition).

Enzyme: A protein that increases the rate of a chemical reaction (Voet, 2008, g-9)

Epidermis: the outer layer of skin

Estimational Program Interface (EPI):a series of programs that can determine physical/chemical property and environmental fate estimation programs, developed by the EPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation (*OPPT*, 2 June 2009, Estimation Program Interface (EPI) Suite).

Ethane(C_2H_6) : a two carbon hydrocarbon

Exposure assessment: the determination of the intensity, frequency, and duration of actual or hypothetical exposure of humans to the agent in question (NRC, 1994).

European Chemical Agency: Located in Helsinki, Finland, and oversees the REACH program (European Chemicals Agency, 2009, ECHA)

European Commission: a subsidiary of the European Union that oversees the REACH database

European Union: organization of twenty-seven European nations for economic and political benefits for all members

Ex vivo: testing done outside of an organism

Feedback loops: the return to the input of a part of the output (Economicswebinstitute, 2004, Feedback loops).

Feedstock: Raw material required for an industrial process (Houghton Mifflin Company, 2009, feedstock).

Fetus: an unborn or unhatched vertebrate especially after attaining the basic structural plan of its kind (Merriam-Webster, 2009, Fetus).

Fluorescent markers: a substance that fluoresces to light, which can be useful for studying organisms.

Gene activation: activation of a gene so that it is expressed

Genetic analysis: analysis of different aspects of the genetic makeup of an organism

Genetic mutation: A change in normal DNA structure (Stelljes, 2000, p. 197)

Greenhouse gas: components of the atmosphere that contribute to the greenhouse effect (Thefreedictionary, 2009, Greenhouse Gas)

Hepatocyte metabolism: liver cell metabolic pathways

High throughput screening (HTS): using automated assays run by computers to search through large numbers of substances to scan for specific properties (Drug Discovery & Development Glossary)

Hormone: A chemical produced in one part of an organism that has the ability to affect other parts of the organism through a chemical process (Stelljes, 2000, p. 195).

Hormone mimic: A compound that mimics a hormone

Ibuprofen: a non-steroidal anti-inflammatory drug (MedlinePlus, 2009, Ibuprofen).

In silico: using computer modeling systems

In vivo: Experiments performed on living organisms

In vitro: Experiments using only cell or tissue cultures

Intercalate: To insert, interpose, or interpolate. (Thefreedictionary, 2009, Intercalate)

Isobutyl-benzene: a hydrocarbon with a methyl group attached to the second carbon, and a benzyl ring attached to the fourth carbon

Lethal: Causing death

LD50: Dose of a chemical that is lethal to 50% of organisms in a laboratory study (Stelljes, 2000, p. 196).

Life cycle assessment: consideration of not only the product's impact on the environment, but the entire process to create the product, use, and eventually dispose of it (EPA, 2009, Life-Cycle Assessment)

Mass spectroscopy: the use of spectroscopy to determine the masses of small electrically charged particles (Princeton, 2009a, Mass Spectroscopy).

Metal carbine: a compound bearing a formal carbon-metal bond (Thefreedictionary, 2009, Metal carbine)

Microtiter plate: a plate that holds chemicals to be screen through High Throughput Screening (Cambridge Healthtech Institute, 19 Nov. 2009, Biopharmaceutical Assays & screening glossary).

Microarrays: A high throughput technology that enables the detection of gene expression levels (CARDIODX, 2009, Glossary).

Molybdenum: Element with 42 protons

Methyl Tert-Butyl Ether (MTBE): a chemical compound that is manufactured by the chemical reaction of methanol and isobutylene (EPA, 2009, MTBE).

Mutagen: a chemical that can cause a mutation in DNA

Mutagenicity tests: a way to test chemicals for mutagens

Nanomaterials: a field of materials science on the nano-level

Nervous system: the sensory and control apparatus consisting of a network of nerve cells (Princeton, 2009b, Nervous system).

Nonpoint source pollution (NPS): pollution that is not from a single known source, but rather various factors that include but are not limited to agricultural fertilizers, oil, or sediments, and end up deposited in a body of water (EPA, 2009, What is Nonpoint Source (NPS) Pollution? Questions and Answers).

Paracelsus: a scientist known for revolutionizing the field of computational toxicology (Profiles in Toxicology, 2000, Borzelleca).

Perfluorooctanoic Acid (PFOA): a chemical that has been used by industry for many years as a processing aid in the manufacture of fluoropolymers representing a wide range of high-

performance products that are versatile and durable and possess unique properties such as non-stick characteristics and heat and chemical-resistance (DuPont, 2009, PFOA).

Petri dish: a cylindrical dish used for cell culture experiments

Pfizer: The world's largest research-based pharmaceutical company (Pfizer. 2009. 1)

Pharmokinetics: The behavior of chemicals inside the body, including the processes of uptake, distribution, metabolism, and excretion. (Environmental Law Glossary, 2009, Environmental Lawyers).

Pharmacological toxicology: the study of the toxicity of drugs

Pneumoconiosis: a respiratory illness caused from inhaling dust and other particles in the air

Point-source pollution (PS): pollution from a single known source, can include but is not limited to smokestack from a factory, drainage pipe, or ditch (EPA, 2009, What is Nonpoint Source (NPS) Pollution? Questions and Answers).

Polymer: Any of numerous natural and synthetic compounds of usually high molecular weight consisting of up to millions of repeated linked units, each a relatively light and simple molecule (Thefreedictionary, 2009, Polymer)

Predictive modeling systems: a model created to predict an outcome

Principal Investigators (PIs): lead investigator in a scientific research project

Propene: (C_3H_6): a three carbon hydrocarbon with two of its carbons linked by a double covalent bond

Proteomics: "The study of the set of proteins produced (expressed) by an organism, tissue or cell, and the changes in protein expression patterns in different environments and conditions." (University of Indiana, 2000, Genomics Glossary)

QRT-PCR(Quantitative Real Time PCR): A technology used to quantify DNA sequences (CardioDX, 2009, Glossary)

Quantitative risk assessment: A way to quantitatively understand the risk of a situation.

Quantitative Structure Activity Relationships (QSAR) Models: The process by which a chemicals structure can be related to its physical and chemical properties and the effect that it has on biological systems. It was initially developed by drug companies, but it is now widely used by computational toxicologist to predict a compound's toxicity (Richon, 2008).

Reagent: A substance used in a chemical reaction to detect, measure, examine, or produce other substances. (Thefreedictionary, 2009, Reagent)

Receptors: A specific molecule of a cell that recognizes and binds with other specific molecules (ligands), such as hormones."(ARIMIDEX, 2009, Glossary).

Receptor/ligand binding: The binding of a receptor to a ligand

Registration, Authorization and Restriction of Chemical Substances (REACH): new EU regulation on chemical use through the creation of a public database (European Chemicals Agency, 2009, About Reach)

Reporter genes: a certain type of gene that researchers can use for analysis because they are easily identifiable.

Reproductive system: organs and tissues involved in the production and maturation of gametes and in their union and subsequent development as offspring (Princeton, 2009, Reproductive System).

Salmonella: a gram-negative, rod-shaped bacilli that can cause diarrheal illness in humans, often the cause of food poisoning (USDA, 2009, Salmonella).

Separation agent: a reagent used to separate bound and free tracers in radioassay (Thefreedictionary, 2009, Separation agent)

Signaling pathways: a series of biochemical reactions (orchestrated by enzymes) that sends different signals throughout the body (TargetmTOR, 2009, Glossary)

Solvent: A substance in which another substance is dissolved, forming a solution. (Thefreedictionary, 2009, Solvent).

Sub-lethal dose: an amount of a toxin that is harmful but will not cause immediate damage (Stelljes, 2000, p.36).

Subchronic: exposure that occurs over a period of several years, but not over an entire lifetime (Stelljes, 2000, p. 200).

Substrate: A substance that is acted upon by a protein (Voet, 2008, g-28).

Systems biology: The study of biology from a holistic perspective, using modern technology to understand how different biological levels interact and affect each other, from biochemical reactions to protein production and signaling to tissue function. (21st Century Science, 2008, Systems Biology).

Tetrogen: a substance toxic to human development (Chacha, 2009, Tetrogen).

Thalidomide: A drug produced in the 1950s that caused a wide variety of defects due to its chemical structure. (Stelljes, 2000, p.52).

Toluene: An aromatic hydrocarbon used in the manufacture of benzene derivatives, caprolactam, saccharine, pharmaceuticals, dyes, perfumes, TNT and detergents. It is used in fuels (anti-knock additive) and as a solvent for paints and coatings, rubber, resins, thinners in nitrocellulose lacquers and adhesives. (German Federal Ministry for Economic Cooperation and Development, 2008, Toluene).

Toxicology: The study of how chemicals affect the body

Toxico-genetic modeling: "application of genetic and genomic methods to the study of toxicology" (UCSF School of Pharmacy, 8 July 2009, Glossary).

ToxCast system: A system developed by the NCCT to predict toxicity using high throughput screens.

Tox 21 Memorandum of Understanding (MOU): chemical testing process mandated by the National Institutes of Health Chemical Genomics Center, which uses high throughput screening toxicity testing of chemicals (Schmidt, 2009, Tox 21: New Dimensions of Toxicity Testing)

Toxic Substances Control Act Database: online chemical database mandated by the EPA to organize chemicals under the Toxic Substances Control Act. It lists chemicals manufactured, processed, or imported in the US (EPA, 2009, TSCA Inventory Reset).

Toxin: A chemical that has the ability to cause adverse affects (Stelljes, 2000, p. 200).

Triazole antifungals: azole derivatives with broad-spectrum antifungal activity; includes fluconazole and itraconazole. (Thefreedictionary, 2009, Triazole antifungals)

Tumorigens: a chemical that causes tumor growth

Volatile Organic Compounds (VOC): are emitted as gases from certain solids or liquids, and may have short- and long-term adverse health effects. (EPA, 2009, VOC)

Xenobiotics: a compound not normally found within the body, including drugs or toxins.

Appendix V: Twelve Principles of Green Chemistry

1. **Prevention**
   It is better to prevent waste than to treat or clean up waste after it has been created.
2. **Atom Economy**
   Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. **Less Hazardous Chemical Syntheses**
   Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. **Designing Safer Chemicals**
   Chemical products should be designed to affect their desired function while minimizing their toxicity.
5. **Safer Solvents and Auxiliaries**
   The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6. **Design for Energy Efficiency**
   Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7. **Use of Renewable Feedstocks**
   A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8. **Reduce Derivatives**
   Unnecessary derivitization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.
9. **Catalysis**
   Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. **Design for Degradation**
    Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.
11. **Real-time analysis for Pollution Prevention**
    Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. **Inherently Safer Chemistry for Accident Prevention**
    Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

(EPA, 2009, Twelve Principles of Green Chemistry).