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ABSTRACT This paper describes the efforts of scientists at the National Institute of Environmental Health Sciences (NIEHS) and their allies in the National Toxicology Program to *molecularize* toxicology by fostering the emergence of a new discipline: toxicogenomics. I demonstrate that the molecularization of toxicology at the NIEHS began in a process of 'co-construction'. However, the subsequent emergence of the discipline of toxicogenomics has required the deliberate development of communication across the myriad disciplines necessary to produce toxicogenomic knowledge; articulation of emergent forms, standards, and practices with extant ones; management of the tensions generated by grounding toxicogenomics in traditional toxicological standards and work practices even it transforms those standards and practices; and identification and stabilization of roles for toxicogenomic knowledge in markets and service sites, such as environmental health risk assessment and regulation. This paper describes the technological, institutional, and inter-sectoral strategies that scientists have pursued in order to meet these challenges. In so doing, this analysis offers a vista into both the means and meanings of molecularization.

Keywords environmental health risk assessment, genomics, microarrays, molecularization, toxicogenomics, toxicology, translation

The Emergence of Toxicogenomics:

A Case Study of Molecularization

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Beginning in the 1930s, and accelerating dramatically in the 1990s, biology in particular, and the life sciences in general, have increasingly visualized life at the molecular level, focusing within the microscopic region 10^{-6} to 10^{-7} (Kay, 1993: 5). As described by numerous scholars of science, technology, and medicine, the molecularization of the life sciences has been a significant event across multiple domains and for myriad institutions, as transformations in how life is known have been translated into means for intervening in life processes (even as means of intervention themselves generate knowledge production about life) (Abir-Am, 1985, 1987; Pauly, 1987; Rabinow, 1992; Kay, 1993; Fujimura, 1996; de Chadarevian & Kamminga, 1998; Clarke, 1998; Rose, 2001). Indeed, Rose (2001: 13) observes that molecularization has not been 'merely a matter of the framing of explanations at the molecular level. Nor . . . simply a matter of the use of artefacts fabricated at the molecular level'. Rather,

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molecularization represents a 'reorganization of the gaze of the life sciences, their institutions, procedures, instruments, spaces of operation and forms of capitalization'.

At the same time, the molecularization of the life sciences has been a remarkably uneven process. That is, while some disciplines within the life sciences, such as biology, are extensively molecularized,[1] others, such as toxicology, have continued to conduct many of their operations well above the molecular level. Toxicology is 'the study of the adverse effects of xenobiotics' and includes both the study of absorption, distribution, excretion, biotransformation of such agents and the analysis of basic toxicologic processes within specific organ systems (Klaassen, 1996). Toxicology has made use of molecular biological technologies and concepts over the past 20 years, especially in the subfield of genetic toxicology (Frickel, 2004). However, many of the most important indices of toxicity studied by toxicologists exist at what they describe as the 'phenomenological' level: body weight, organ weight, level of activity, tumors, death (National Toxicology Program Toxicity Reports [abstracts and full reports], accessed at <http://ehp.niehs.nih.gov/ntp/docs/toxreports.html>). Relatedly, the 'gold standard' of toxicological testing, even while it has included molecular biological advances, continues to center on the 13-week and 2-year rodent bioassays and other forms of whole-animal studies (National Toxicology Program, 2002).

In this paper, I describe the efforts of scientists at the National Institute of Environmental Health Sciences (NIEHS) and their allies (Latour, 1987) in the National Toxicology Program (NTP) to molecularize toxicology by fostering the emergence of a new discipline: toxicogenomics.[2] I demonstrate that the molecularization of toxicology at the NIEHS began in a process of 'co-construction' (Clarke & Fujimura, 1992; Fujimura, 1996: 28). Specifically, in the course of their work to adapt cDNA microarrays (a genomic technology, described in detail below) to toxicological research, NIEHS scientists began to envision (Hedgecoe & Martin, 2003) and generate an adaptation of the discipline of toxicology. Then, as NIEHS scientists developed novel molecularized toxicological research tools (for example, the ToxChip) and work practices, the NIEHS made an institutional commitment to the conscious and deliberate 'fostering' of the molecularization of toxicology. This fostering began with the establishment of a Microarray Center at the NIEHS, which was followed by the founding of the National Center for Toxicogenomics (NCT).

The molecularization of toxicology via the emergence of toxicogenomics has not been without significant practical challenges. First, scientists have had to find ways to communicate across the myriad disciplines necessary to produce toxicogenomic knowledge. Second, emergent toxicogenomic forms, standards, and practices have required articulation (Strauss, 1988) with extant toxicological theories, technologies, and experimental systems. Relatedly, toxicogenomics must manage the tension of being grounded in traditional toxicological standards and work practices

even as it transforms those very standards and practices (Timmermans & Berg, 1997). Therefore, in the second section of this paper, I analyze the strategies of NIEHS scientists for meeting these challenges and promoting the emergence of toxicogenomics. These include interdisciplinary project teams at the NCT and, importantly, three NCT initiatives that endeavor to create stable linkages across disciplines and modes of toxicological knowledge production. Specifically, I argue that the NCT's phenotypic anchoring project and the Chemical Effects in Biological Systems (CEBS) database are designed to have the combined effects of creating linkages between traditional indices of toxicity and gene expression profiles (that is, the products of microarray analyses), establishing equivalences between old and new toxicological artifacts, and translating across traditional and emergent toxicological grammars or forms of knowledge. The NCT also funds the extramural Toxicogenomics Research Consortium (TRC), which I conceptualize as a means of enrolling participants in the process of translating toxicogenomics for toxicology.

Finally, because toxicology has traditionally been strongly identified with and valued for its applications in chemical testing, risk assessment, and regulation[3] (Schwetz, 2001), scientist entrepreneurs (Rosenberg, 1976) seeking to molecularize toxicology have had to address questions about the utility of toxicogenomics in these traditional markets for toxicological knowledge. Therefore, in the third section of this paper, I focus on NIEHS/NCT initiatives to identify and stabilize roles for toxicogenomic knowledge in risk assessment and regulation and to enroll end-users for toxicogenomics from a variety of stakeholder groups. This analysis highlights both the importance of markets for scientific knowledge in coordinating new scientific production systems (Kohler, 1982; Shapin & Schaffer, 1985; Fujimura, 1996; Clarke, 1998; Frickel, 2004) and the ways in which desired applications of a science shape the conditions of its emergence (Gibbons et al., 1994). It also contributes to ongoing efforts to describe the ways in which processes of molecularization confound the distinction between 'basic' and 'applied' sciences (de Chadarevian & Kamminga, 1998: 2). I conclude with reflections on the case of toxicology/toxicogenomics as a vista into both the means and meanings of molecularization.

From Gene Expression Profiling to the National Center for Toxicogenomics

The Advent of Microarray Technology

Microarray technologies and the gene expression profiles produced in microarray analysis have been at the center of efforts to develop a molecularized approach to toxicological research. Microarray technology made its scientific debut in 1995, when Pat Brown and his colleagues at Stanford University published a paper in *Science* entitled 'Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray'

(Schena et al., 1995). In this paper, they described a high-capacity system that they built to monitor the expression of many genes in parallel. This system relied on high-speed robotic printing of complementary DNA (cDNA) onto glass slides (often called 'chips') that were then used in quantitative expression measurements of the corresponding genes.[4] As the authors reported, this system enabled them to make differential expression measurements of 45 genes from the small flowering plant *Arabidopsis* using simultaneous, two-color hybridization.

Conceptually, microarray technology is similar to two standard laboratory techniques used to study gene expression – the Northern blot and the Southern blot (Bartosiewicz et al., 2000).[5] However, the *scale* of analysis made possible by DNA microarrays was unprecedented. For example, a Northern blot could provide information on 10 or 20 or, possibly, 100 genes at a time. In contrast, the robotized arrayer designed by Brown and his colleagues allows researchers to 'spot' up to 15,000 genes onto one glass slide and to read the gene expression of those genes (gene expression profiles) simultaneously using confocal microscopy. In essence, a cDNA microarray enables a researcher to obtain the results of thousands of Northern blot experiments simultaneously. As such, both the kind and the volume of data produced by microarray analysis are unprecedented (Rockett & Dix, 1999). In addition, the platform supports quantitative comparison of global gene expression between virtually any two biological samples: 'One can compare, for example, two different tissues, normal versus diseased tissue or untreated versus exposed cells' (Lobenhofer et al., 2001: 881). Microarray technology has been hailed by many scientists as a 'revolutionary' platform to perform genome wide expression analysis across various biological models (Lobenhofer et al., 2001: 881).

The Visible Industrialist

Biotechnology and pharmaceutical companies were among the first and most enthusiastic users and developers of microarray technology (Pollack, 2000; Lane & Pray, 2002; Pennie et al., 2004). Pharmaceutical companies were particularly eager to explore microarrays as a means of 'pre-screening' potential drug candidates, thereby potentially reducing the cost of drug development. Writing in *Toxicological Sciences* in 2000, scientists from AstraZeneca observed that 'a major part of the developmental cost of every successful new pharmaceutical or agrochemical product is the recovery costs of compounds that have failed in development, due to potential or observed toxicity' (Pennie et al., 2000: 278). Most expensive to pharmaceutical companies are the drugs that fail late in the development process, during clinical trials. In addition, as noted in a *New York Times* article on microarrays and product testing, in the late 1990s 'several drugs that were already on the market were removed because they caused harm' (Pollack, 2000). Microarrays were seen by pharmaceutical researchers as one way of meeting the imperative of the industry that dangerous compounds 'fail

fast, fail cheap' (Pollack, 2000). Moreover, microarrays were quickly put to work in the emerging field of pharmacogenomics. Varyingly defined as a science which 'decrease[s] adverse responses to therapy through determining new therapeutic agents and genetic polymorphisms that effect drug specificity and toxicity' (Wieczorek & Tsongalis, 2001: 1) and/or as an effort to reclassify and treat diseases according to their molecular phenotype (Perou et al., 2000),[6] pharmacogenomics has been hailed by pharmaceutical researchers as a means of generating 'novel approaches in drug discovery, an individualized application of drug therapy, and new insights into disease prevention' (Mancinelli et al., 2000: 1).

In pursuit of these visions of products and profits (Hedgecoe, 2003), as this researcher describes:

> pharma jumped on it [microarray technology] very quickly, moved into it very, very quickly. It was realized that this was not just a passing trend, that this was the wave of the future. So, pharma has really restructured and reorganized and brought general functional genomics/proteomics into the picture, with pharmacogenomics in particular. (Interview 35)[7]

As he noted, pharmaceutical companies 'had huge amounts of money which enabled them to move quickly in that regard ... in a very practical way because they have practical goals ... driven by marketing decisions' (Interview 35). In contrast, as this toxicologist commented, 'in the environment, it's more for the public good, without the big bucks waiting at the end of the line', which caused some scientists to worry that 'the environmental health sciences are lagging behind the pharmacological sciences pretty dramatically' (Interview 14). However, collaborations between the Brown laboratory at Stanford, the National Human Genome Research Institute (NHGRI), and the NIEHS soon brought microarray technology to the Institute's toxicologists.

Microarrays at the National Institutes of Health

In 1996, Dr Jeff Trent, then the scientific director of the NHGRI, established the first microarray facility at the National Institutes of Health (NIH). With the assistance of Stanford researchers, Trent and his colleagues built their own robot and scanners and began to explore the potential of microarray technology for analyzing gene expression patterns in human cancers (see, for example, DeRisi et al., 1996).

Given the novelty of the technology and its potential importance to biomedical research, the NHGRI leadership felt that it was important that other Institutes be able to explore microarray research. As the result of lengthy conversations between Dr Trent and Dr J. Carl Barrett, then scientific director of NIEHS, scientists from NHGRI offered to assist NIEHS in building a microarray facility. NHGRI assistance was critical at that time because, before the commercialization of the technology, as this molecular biologist recounted, 'unless you had an in with someone who knew how to build the instrumentation, you had no way to even start to do anything with it' (Interview 60). As this scientist recalled:

> [When] Pat Brown came out with his paper, there were no commercially available microarray scanners, microarray printers, you had to make your own . . . early on in the microarray days making your own equipment was the status quo, your only option. (Interview 40)

In 1997, Dr Cynthia Afshari, the Group Leader in Dr Barrett's laboratory, went to NHGRI to learn how to work with microarray technology. She also began to consult extensively with the NIH engineers who were building a robotized arrayer and a scanner for the NIEHS. Building the machinery and obtaining all the materials NIEHS researchers would need to run experiments took about a year. In 1998, with the continued support of NHGRI, the NIEHS began to operate a microarray facility.

Disciplining Microarrays at the National Institute of Environmental Health Sciences

In order to determine the utility of microarray technology for the NIEHS's intramural research program, the scientists working with the new microarray machinery were eager to see microarray analysis utilized in research projects across the Institute. Therefore, at the same time that they collaborated with NHGRI researchers in investigating the application of microarrays for research on carcinogenesis, the NIEHS scientists leading the microarray initiative made a concerted effort to engage interested intramural scientists and to explore how the technology could be applied to their varied research projects. As this researcher recalled:

> We had a lot of conversations with different people . . . to see what would they do if they had this type of technology. We had a lot of things that we wanted to do with it as far as answering basic research questions, addressing things, helping clone genes, and different kinds of small projects that we would use it for. (Interview 60)

From the outset, the leaders of the microarray initiative at NIEHS were focused on developing the applications of microarrays as a tool that could serve the extant research agendas of toxicologists:

> We didn't start initially as this big National Center for Toxicogenomics running out of NIEHS. . . . We were just starting based on [the question] what does a single, individual PI [Principal Investigator] want to do to enhance their research? (Interview 60)

However, at the same time, researchers at the NIEHS microarray facility also began to think about how microarray technology and gene expression profiles could be applied to serve the overall mission of the NIEHS. As one scientist recounted: 'This is the National Institute of *Environmental* Health Sciences. So, *we were looking for our niche*. We didn't need or want to compete with Pat Brown or Jeff Trent' (Interview 32, emphasis added). Toxicology and environmental health research constitute the niches of the NIEHS, as he further describes, 'What is distinctive here is *the National Toxicology Program, the focus on environmental insults, the practice of toxicology*'

(Interview 32, emphasis added). Conscious of such jurisdictional concerns, the researchers working in the NIEHS Microarray Center sought to define a research agenda for exploring applications of gene expression profiling specific to toxicology: ' ... then we started to think, could we really use this to advance how we conduct toxicology tests today? That's where the concepts and the ideas of toxicogenomics started to be developed' (Interview 27).

The overlapping concerns of the fields of pharmacology and toxicology and the already burgeoning use of microarray technologies in pharmaceutical research provided a jumping-off point for NIEHS researchers interested in developing microarrays as a tool for research in toxicology. Because the metabolisms of both pharmaceuticals and environmental chemicals involve similar (and sometimes identical) processes of metabolism and detoxification (Calabrese, 1996), a Stanford microarray analysis of the responses of 60 cancer cell lines (the 'NCI-60') to pharmaceutical agents suggested a specific role for microarrays in toxicology. As a scientist who worked in the Brown laboratory later recounted:

> One of the first experiments that we did was what we call the NCI-60 study, which was to do gene expression profiling on a set of sixty cell lines. These sixty cell lines were tested versus ... sixty thousand different chemical compounds. So there was a huge database of drug sensitivity on these cell lines. And we then did expression profiling to look for correlations between gene expression patterns and drug sensitivity. So from the start *a toxicology study was actually the first study that we did and published.* ... (Interview 46, emphasis added)

Of particular import to the project of developing a toxicology specific microarray research agenda, the results of that study indicated that gene expression profiling could facilitate comparisons of how different tissues responded to drugs. Therefore, it stood to reason that gene expression profiling could facilitate comparisons of how different tissues responded to environmental chemicals: 'Because if it were true for drugs, which are really just beneficial chemicals, then why wouldn't it be true for environmental chemicals?' (Interview 25). These considerations led to the development of a set of practices that NIEHS researchers called 'toxicogenomics'.

The first paper using the term 'toxicogenomics' was published in 1999 in the journal *Molecular Carcinogenesis* (Nuwaysir et al., 1999).[8] With the publication of the 1999 paper by Nuwaysir and colleagues the term 'toxicogenomics' was specifically defined as 'a new scientific subdiscipline derived from a combination of the fields of toxicology and genomics' (Nuwaysir et al., 1999: 153). While some of the authors of the paper recount that a sense of 'playing around' with words led to the coining of the word 'toxicogenomics', there was also a strong desire on the part of the authors to highlight the environmental and toxicological emphases that distinguish the research of the NIEHS from other forms of microarray research, including pharmacogenomics:

> We started thinking about, well what are *our applications*? *What's relevant to the institute?* What should we call this? . . . We weren't doing sort of classic toxicology and we wanted to get across genomics technologies. At the time pharmacogenomics was already being used . . . and we felt like that didn't really describe what we were doing, because *pharmacogenomics, while some of it does focus on toxicology, is more focused on drug targets and efficacy kinds of issues*. So we felt like ours was really different. . . . We weren't doing sort of classic toxicology and we wanted to get across genomics technologies. (Interview 30, emphasis added)

In addition, in building this new form of toxicological practice, having a specific term and a distinctive research agenda was important not only for disseminating information about the applications of microarrays to toxicological practice, but also for gaining access to the institutional and financial resources needed by the NIEHS Microarray Center: '*We were trying to justify a program and build a program* . . . and so [the question was] "what do we call it?"' (Interview 30, emphasis added). The term 'toxicogenomics' met all these needs. By referring specifically to toxicology, it highlighted the unique institutional focus of the NIEHS, while the inclusion of 'omics' made clear that this was a genomic, molecularized science. Moreover, itself a neologism, 'toxicogenomics' signaled that this was a new science, worthy of new resources.

In their 1999 paper, Nuwaysir and his colleagues described the scope of practice of toxicogenomics as 'the identification of potential human and environmental toxicants, and their putative mechanisms of action, through the use of genomics resources' (Nuwaysir et al., 1999: 153). DNA microarrays constituted the specific 'genomics resource' which the paper took as its focus; the purpose of the paper was to acquaint readers with 'the development and current state of microarray technology' and to 'present our view of the usefulness of microarrays to the field of toxicology' (Nuwaysir et al., 1999: 153). The NIEHS and National Cancer Institute (NCI) authors envisioned four general areas of application for microarrays in toxicology. First, the authors proposed that the gene expression profiles generated by microarray analysis could complement established toxicological methods for identifying the mechanisms of action of a given toxicant. Second, they suggested that the incorporation of microarray analysis in the standard 2-year rodent bioassay might dramatically enhance the sensitivity and interpretability of the bioassay and possibly reduce its cost. Third, and related, the authors argued that gene expression profiles might be developed and validated as biomarkers of environmental exposure, internal dose, damage, and/or response to treatment following a harmful exposure. Finally, these authors suggested that microarrays could be fruitfully applied to the study of 'the relationship between genetic variability and toxicant susceptibility' (Nuwaysir et al., 1999: 158).

What is remarkable about this vision of microarrays in toxicological research is the breadth of practices and foci it encompasses. In essence, Nuwaysir and his colleagues proposed that microarray analyses were relevant to *all* of the primary concerns of toxicological research focused on

human health. In addition, the authors noted that 'these considerations [for example, of microarrays in evaluating and developing animal models] are also relevant for branches of toxicology not related to human health and not using rodents as model systems, such as aquatic toxicology and plant pathology' (Nuwaysir et al., 1999: 157). Their claim was microarrays ought to be applied within most subspecialties of toxicological research.

Environmental health scientists describe the 1999 paper by Nuwaysir and his colleagues as a 'concept paper' rather than a research paper. As this molecular epidemiologist put it: 'Toxicogenomics is a hypothesis really – that there is something to be learned from gene expression' (Interview 26). More specifically, toxicogenomics is the hypothesis that *toxicologists working in the environmental health sciences* have something to learn from gene expression. At the time that Nuwaysir and his colleagues published this paper, the work of testing this hypothesis – that is, of proving that there was a role for microarray technology in the toxicological armamentarium – had yet to be accomplished; toxicogenomics was still 'a promissory science' (Hedgecoe, 2003: 515). However, in articulating this vision of the uses of toxicogenomics, the authors also contributed to its technological development (cf. Hedgecoe & Martin, 2003: 328), especially in their description of the research needed in order to bridge the gap between *claiming* a role for microarrays in toxicology and actually establishing microarrays as 'the right tool for the job' (Clarke & Fujimura, 1992) of toxicological research. Specifically, the paper detailed the work of researchers at the NIEHS microarray facility to develop a custom cDNA microarray chip that contains 'genes with previously well documented involvement in cellular processes as well as their responses to different types of toxic insult' (Nuwaysir et al., 1999: 156). Research with this type of chip could demonstrate the usefulness of microarray analysis in investigating mechanisms of toxicant response, in establishing specific gene expression profiles as 'molecular signatures' of types of chemicals, and in developing biomarkers based on gene expression. In addition, the authors noted that gene expression can be affected by numerous factors, which may confound the application of gene expression profiles as biomarkers, and very briefly suggested the importance of a national database of human expression data as a resource in addressing these complications. Addressing these challenges began to emerge as priorities for researchers working in the NIEHS microarray facility, which increasingly focused *not simply on making the technology work* but *making the technology work for toxicology.*

New Tools, New Practices . . . New Science?: The Will to Discipline

The work of developing the requisite tools and practices for applying microarrays to toxicological research soon became a primary research focus for the scientists working at the NIEHS microarray facility. Central to these initial efforts was the development of a custom cDNA microarray chip, called a 'ToxChip', which contained copies of approximately 2000 human genes with which toxicologists could begin to assess the gene

expression profiles of known toxicants. Soon after, the researchers created a chip called the Human ToxChip, which contained 12,000 genes, allowing evaluation of a substantially greater number of gene expression changes in response to environmental toxicants. These ToxChips were especially important to the NIEHS researchers as they concretized a distinctive *toxicological* application of microarray research. Using ToxChips, researchers could investigate the gene expression profiles created by exposures to environmental toxicants. Such specific gene expression profiles could make contributions in research on mechanisms and pathways of toxic response, biomarkers of exposure and effect, and the classification of unknown or novel chemical compounds.

Based on early research with the ToxChips, the leadership of the NIEHS became 'bullish' about the potential of such chips in toxicology research and especially 'to revolutionize the screening of chemicals' (National Institute of Environmental Health Sciences, 2000a). In February 2000, the microarray facility was elevated from a collaborative unit within Carl Barrett's laboratory to a Center, that is, a core structure at the NIEHS. As a Center, the microarray initiative was given its own directors, faculty, staff, and resources to continue the adaptation of microarrays as tools for toxicological purposes. This included the continued development of the ToxChip.

With the development of the ToxChips and the founding of the Microarray Center, a profound shift in the focus of the NIEHS's toxicogenomics efforts occurred. Specifically, the language used to describe microarrays, chips, gene expression profiles, and their relationship to toxicology became increasingly focused on 'revolutionizing' the field of toxicology itself (National Institute of Environmental Health Sciences, 2000a). That is, rather than simply adapting a new technology to toxicological practice, there was also a growing interest in adapting toxicological practice to the new technologies – making the jobs fit the tools (Clarke & Fujimura, 1992).

As researchers working with microarrays and gene expression profiling at the NIEHS had configured microarray technology and ToxChips for the discipline of toxicology, they had also begun to reconfigure the discipline of toxicology (cf. Fujimura, 1996). In part, this reconfiguration occurred because adapting microarray technology to toxicological research has entailed a number of material and interactional changes in the daily work and practices of toxicology. For example, gene expression profiling requires new kinds of multidisciplinary collaboration and coordination. In order to do its work, the NIEHS Microarray Center had to assemble a multidisciplinary team of 12 scientists, representing the wide variety of practices implicated in toxicogenomics. As this scientist noted:

> We realized early on that we were going to have to have a really multidisciplinary team to be able to put this together. That we were going to need to have computational biologists, bioinformaticists, computer support people, bioengineers, as well as molecular biologists and toxicologists as part of our team. . . . (Interview 61)

Relatedly, as this researcher describes, bioinformatics is required to 'make sense' of microarray data for toxicological research:

> Genomics is a paradigm shift [for toxicology] because it is big science. It generates thousands of data points. So, you are dependent on bioinformatics and algorithms to help you mine the data. . . . The information is stored in the data. But we need tools to help us see what is there, to visualize the data. (Interview 32)

Indeed, scientists working with microarray analysis often refer to the amount of data they generate as 'mountains' or 'tsunamis' or 'seas' worth (Field Notes, June 2002). An NIEHS postdoctoral scientist remarked to me: 'Before this I had never worked on a study with more than 10 data points, but this one had 30,000' (Field Notes, June 2002).

In addition to requiring new collaborative relationships, the vast amounts of data produced by microarray analyses require new skills and practices of biologists and toxicologists. A biologist described the effects of these changes in the following way: 'I used to spend all my time at the bench. Now I spend all my time at the computer' (Interview 46). In addition, as noted by this scientist, taking advantage of the potentials of microarrays in hypothesis-*generating* research requires a different mind set than the hypothesis-testing model of traditional toxicology.

> [Toxicogenomics] also requires new training and a different mind-set. Because toxicogenomics can be a hypothesis testing or a hypothesis generating tool. This is a paradigm shift for NIEHS, that it can be a discovery tool. I think that it is important that the technology be used both ways – hypothesis testing and generating. It is so exciting to be in a discovery mode . . . to be thinking about different data sets and tools and how we can do discovery. It's really a tremendously exciting time. (Interview 32)

These material and conceptual changes in toxicology practice were slowly transforming what doing toxicology meant, at least within the walls of the NIEHS Microarray Center. Then, just as importantly, with the emergence of these new practices, the leadership of the NIEHS became powerfully committed to being the institution responsible for the reshaping of toxicological practice through the further development of toxicogenomics.

In December 2000, the NIEHS announced the establishment of the NCT (National Institute of Environmental Health Sciences, 2000b). The press release emphasized the 'application of powerful new techniques' with the potential to transform the discipline of toxicology. As a scientist–administrator at NIEHS commented on the founding of the NCT: 'The primary push behind it was that this technology had the opportunity *to revolutionize toxicology research*, literally, and *completely transform the way that toxicology research was done*' (Field Notes, July 2002, emphasis added). A senior scientist at the NCT recalled the process leading up to the announcement of the Center as follows:

> With the rapid progress in the genome arena it was becoming obvious that there were some technologies evolving that could have a real profound

> effect in toxicology, the capacity, used the right way, *to actually change the whole field of toxicology over a period of time.* (Interview 39, emphasis added)

The official overall objective of the NCT was to 'promote the evolution of gene and protein expression technologies and their use to understand adverse environmental effects on human health' (National Center for Toxicogenomics, 2002: 4). That is, the NCT was to 'foster development in this burgeoning field' (National Center for Toxicogenomics, 2002: 13) or, in the words of a NCT scientist, to 'create the infrastructure needed for the emergence of toxicogenomics' (Field Notes, July 2002).

With the establishment of the NCT, toxicogenomics was defined broadly as the application of 'global expression profiling, including microarray and proteomics,[9] to study the relationship between exposure and disease and to understand gene–environment interactions and their impact on human health' (National Center for Toxicogenomics, 2002: 15). The scope of the NCT also expanded on earlier microarray initiatives in two very important ways. First, while Carl Barrett had charged the microarray researchers in his laboratory to develop the applications of microarrays for toxicology, the NCT also explicitly endeavors to establish a role for toxicogenomics in chemical testing, risk assessment, regulation, and policymaking. As stated in a NCT brochure: 'The NCT aims to use and promote toxicogenomics as a means to guide federal agencies and legislators in developing guidelines and laws that regulate the levels of various chemicals in the environment' (National Center for Toxicogenomics, 2002: 13). In addition, the NCT was to create a national program to 'ensure the successful development of a broad scientific consensus on the application of toxicogenomics to the improvement of human health' (National Center for Toxicogenomics, 2002: 3).

As indicated by these statements, achieving a (molecular) revolution in toxicology requires that toxicogenomics and its products (gene expression profiles) be understandable and useful to toxicologists, risk assessors, and regulators. Establishing the utility of toxicogenomics in toxicological research and enrolling stakeholders is a major focus of the NCT. In the next sections of this paper, I examine efforts to establish toxicogenomics as a reliable, valid, and valuable toxicological science.

Towards a Molecular Grammar for Toxicology

'Let's Ground the New Technologies in the Old': Phenotypic Anchoring as a Means of Translation

Establishing the utility of toxicogenomics for toxicology, testing, and risk assessment requires a means of translation[10] across molecular/genomic and traditional toxicological modes of knowledge production. For example, at the NCT, genomics researchers have had to learn the language and practices of toxicology, while toxicologists have been required to learn the

language of genomics. This is no small undertaking for any researcher. As a self-described 'old school' toxicologist working at the NCT commented:

> For toxicologists and pathologists, the language of genomics is daunting. We don't have expertise at the genomic level. It makes you feel like you are a fish out of water. And with all the jargon and terminology relating to the genome, it's like being in another country, like being in France and not speaking French. (Interview 42)

He also noted the challenges that face researchers who want to work in toxicogenomics, but are unfamiliar with the language and practices of traditional toxicology: 'A lot of geneticists work with yeast. They're not aware of the complexities of whole animals – things like diet, circadian rhythms, and disease' (Interview 42). Indeed, in his assessment, the fact that many genomics researchers lack familiarity with the animals and animal models that are currently the primary work objects in toxicological testing, threatens the validity of their research:

> Of course they have the same problems. I asked someone at a meeting about a 'liver lobe' and he asked if I meant 'the first' when I referred to the 'left lateral'. Another example is that we do all of our work with male rats because of the menstrual cycle. The genomicists at [a university] were working with female rats. They said that they thought that 'it would even out'. This is not comforting ... there is no 'evening out' and your experiments ... are going to be misleading. (Interview 42)

Another toxicologist vividly characterized the differences between expertise of toxicologists with animal models and that of the mathematicians who provide the bioinformatics expertise required for the analysis of gene expression profiles as follows: 'These mathematicians don't know a mouse from a Ford Taurus, but they're necessary. We really need a variety of disciplines working together' (Interview 47). The NCT provides the institutional space and the resources for these disciplines to work together and gradually learn each other's languages and practices. For example, the NCT has a collaborative interdisciplinary 'Tox/Path Team', which consists of approximately 20 researchers with expertise in the fields of genomics, bioinformatics, toxicology, and pathology.

However, the primary strategy for the translation of toxicogenomic gene expression profiles, and one of the major research initiatives of the NCT, is *phenotypic anchoring*. NCT scientists describe this as a technique that couples the unique gene expression profiles induced by chemical exposures to visible evidence of harm (Schmidt, 2002). Put differently, phenotypic anchoring is the correlation of gene expression profiles (produced in microarray analysis) with traditional indices of toxicity, such as clinical chemistry or tissue pathology. The administration of NIEHS articulates phenotypic anchoring as a way of 'grounding' gene expression profiles in toxicological knowledge: 'Let's ground the new technologies in the old, so that we know that as we replace them, they mean the same and our interpretations are correct' (Interview 39). I conceptualize phenotypic

anchoring as a means of translation, as it makes linkages across molecular and traditional sets of indices of toxicity and their associated languages, work objects, practices, and disciplines.

Phenotypic anchoring is described by the NIEHS as a means to several inter-related ends. First, phenotypic anchoring is a means of ascertaining whether gene expression profiles can generate chemical-specific signatures, distinctive patterns that indicate known toxicological pathways and effects (Schmidt, 2002). The goal of phenotypic anchoring is to establish correlations, that is, to be able to say that a given gene expression profile will correspond to a traditional index of toxicity: 'We want to know that what the pathologist is telling you and what the gene expression profile is telling you is the same thing' (Field Notes, July 2002). This aspect of phenotypic anchoring aims to establish equivalences between the knowledge products of genomics and those of toxicology and pathology.

Second, researchers at the NCT regard phenotypic anchoring as a means of reducing subjectivity in toxicogenomic analysis. At this time, there is no consensus as to how to determine whether a change in a gene expression profile is toxicologically significant or is merely an irrelevant change in expression not indicative of toxicity. Phenotypic anchoring is pursued as an objective, and thus trustworthy (Porter, 1999), means of distinguishing between toxicologically significant versus insignificant changes in gene expression profiles: 'We are trying to make this as least subjective as possible, using histopathology, clinical chemistry, organ weight, and metabolites as the phenotypic anchorage of gene expression' (Field Notes, July 2002). Without establishing a relationship between a gene expression pattern and a meaningful physical or biochemical state, gene expression profiles cannot be meaningful biomarkers. Insofar as traditional toxicological measures provide the 'objective' data to which toxicogenomics is compared, this aspect of phenotypic anchoring also serves as a means of translation between the social worlds of genomics, toxicology, and pathology.

Finally, phenotypic anchoring is a means of identifying novel genes whose expression may be induced by a given toxicant or class of toxicants. In this way, phenotypic anchoring is a kind of 'discovery science' – a means of generating hypotheses for further scientific research. At the same time, this is accomplished through establishing linkages between traditional indices of toxicology and gene expression profiles and, as such, translates between them. Thus, in each of these instances, phenotypic anchoring works as a means of translation between two toxicological languages, linking the quantitative data and gene expression profiles of toxicogenomics to the phenomenological data, clinical chemistry, and tissue specimens of traditional toxicology.

Successful phenotypic anchoring *incorporates* – makes *corporeal* – gene expression profile data.[11] That is, phenotypic anchoring creates a chain of linkages between gene expression profiles, animal bodies, and human corporeality. This requires several moves. First, in correlating microarray data with tissue samples, organ sections, and so on, phenotypic anchoring

established connections between the colorful spotted array of a gene expression profile and the actual bodies of animals used in traditional toxicological testing and risk assessment. Second, because animal bodies 'stand in' for those of humans, phenotypic anchoring is a first step in establishing the relevance of toxicogenomic data for the health of human beings. Through phenotypic anchoring, highly abstract genomic data are brought to human matter(s); they are linked to human bodies and populations. Thus, phenotypic anchoring is a means by which gene expression profiles and toxicogenomics are inserted into already existing toxicological interests, associations, practices, and potential service roles.

At Work in the Toxicological Archives

Phenotypic anchoring as a mode of translation relies on the extensive institutional linkages between the NIEHS and the NTP[12] and, especially, on the NTP's extensive archive of toxicological data. As this NTP scientist explained:

> There is a thirty year history of toxicology testing at NIEHS and the NTP. We've tested six hundred chemicals as thoroughly as they can be tested – two week, ninety day, and two year studies. Everything [is] done up to the state of the art. We've standardized feeding cycles, light cycles, dosing. We've done necropsy of forty tissues in mice and rats, males and females – so, there are four study groups. For each chemical, this takes seven to eight years, to go from testing to a blue book.[13] (Interview 24)

The slides created during these 30 years of toxicology testing, the results of the necropsies on millions of animal bodies, and the reports of their clinical chemistry and histopathology are stored in an archive near the NIEHS campus. This archive contains the information on traditional toxicological indices needed for phenotypic anchoring and the incorporation of toxicogenomics.

Moreover, the NTP archive is invaluable for phenotypic anchoring because it contains the data from what many toxicologists regard as 'the gold standard of toxicology testing'. As this toxicologist stated:

> The NTP is extremely rigorous – and it has to be. The NTP has to fulfill every aspect of good laboratory practice, because industry sends people over here to look through the lab[oratory] books and try to find flaws. So, if there's a chance that the groups got messed up or some animals got the wrong dose, they'll contest the results. So, everything is carefully tracked and detailed. . . . *The NTP does toxicology the right way.* (Interview 42, emphasis added)

In addition, the NTP is responsible for many of the current standards of practice in contemporary toxicology testing. The standardization of laboratory techniques used to assess the risks of carcinogens and the standardization of diagnostic terminology used in interpretation of observed pathologies are regarded by many toxicologists as one of the most significant contributions of the NTP:

> The National Toxicology Program . . . is a real success story. If you think about that kind of testing, there are so many variables. They developed protocols for doing dosing, how to interpret results, and they've succeeded in having those interpretations adopted by both government and industry. (Interview 27)

The NTP blue books are not only regarded as scientifically valid, they are also politically robust, as this toxicologist emphasized: 'The NTP blue books are a bible. They are used by the regulatory agencies. They're the gold standard' (Interview 38). The NTP sets 'the standard' for toxicologists across the arena of environmental health, used by government regulatory agencies and industry alike.

Thus, while the NCT is using the NTP archive in the most material sense, that is, as a repository of the traditional indices of toxicity required to incorporate gene expression profiles, I argue that it also endeavors to use the archive in a much more expansive sense, as well. Drawing on Foucault (1972), Gottweis (1995: 35) conceptualizes archives as 'the general system of forming and transforming statements existing at a given period within a particular society'.[14] The NTP archive and the blue books based on the data it contains constitute the currently accepted 'system of forming and transforming statements' in the social worlds of toxicology and risk assessment. Therefore, the goal of establishing that gene expression profiles (and, by extension, toxicogenomics) have a valuable role in forming and transforming statements in these worlds relies on the success of phenotypic anchoring. That is, as the NCT endeavors to create a new system of forming and transforming statements about environmental exposures and their effects, it must embrace, incorporate, and transform the old system. As such, phenotypic anchoring is a strategy for 'manag[ing] the tensions among transforming work practices while simultaneously being grounded in those practices' (Timmermans & Berg, 1997: 297). Toxicogenomics, in general, and phenotypic anchoring, in particular, simultaneously invoke the authority of the NTP archive and seek to transcend its forms.

The NCT is also building a new, molecularized archive for toxicology and risk assessment. The CEBS database is a relational database that contains data from gene expression profiles, the NTP archives, the results of the phenotypic anchoring studies, and the standardization experiments of the TRC (discussed later). The CEBS database is a project of the NCT. According to the NCT, three specific goals shape the development of the CEBS database (National Center for Toxicogenomics, 2002: 25):

(1) Create a reference toxicogenomic information system of studies on environmental chemicals/stressors and their effects;
(2) Develop relational and descriptive compendia on toxicologically important genes, groups of genes, single nucleotide polymorphisms, mutants, and their functional phenotypes that are relevant to human health and environmental disease;
(3) Create a toxicogenomics knowledge base to support hypothesis-driven research.

Again drawing on Gottweis (1995), I contend that the ultimate goal of the CEBS is to create a new archive, a means of forming and transforming molecularized statements about toxicology, human health, and environmental disease. It endeavors to do this by bringing together new forms of knowledge (that is, knowledge about genes, groups of genes, single nucleotide polymorphisms, and mutations produced in toxicogenomics research) with 'functional phenotypes'. These functional phenotypes are the artifacts that populate the NTP archive and thus provide linkages between gene expression profiles and traditional indices of toxicity.

As with phenotypic anchoring techniques, the CEBS database is a means of establishing equivalences and associations between toxicogenomics and traditional toxicology, their artifacts and grammars. This is undertaken, in part, by 'creating an interface' between the CEBS database and the NTP archives. The goal is to enable researchers to link the gene expression profiles data in the CEBS with 'all the National Toxicology Program has done on the acute toxicity of over 500 chemicals' (Interview 39). *Such linkages would allow researchers to call up both sets of data with one relational query of the database.* Put differently, CEBS will answer a user's question in two languages, and, when available, will provide a means of translating between the two. Indeed, the CEBS provides 'dictionaries and explanatory text' to 'guide researchers in understanding toxicogenomics databases' (National Center for Toxicogenomics, 2002: 26). The CEBS also links to other genomics and proteomic resources on the Web, 'providing users the suite of information and tools needed to fully interpret toxicogenomics data' (National Center for Toxicogenomics, 2002: 26). Thus, the CEBS is a translational resource for environmental health scientists who want to make statements about environmental health and illness using the emergent language, artifacts, and grammar of toxicogenomics.

Standardizing the Grammar: The Toxicogenomics Research Consortium

At the same time, the TRC, an extramural research initiative of the NCT, endeavors to standardize this new, molecular toxicological grammar. The TRC was established in November 2001 when the NIEHS awarded grants to five institutions to participate in the TRC as cooperative research members (CRM) or 'allies' (Callon, 1986; Latour, 1987) of the NCT.[15]

The initial goal of the TRC is 'to conduct a series of cooperative gene expression experiments using shared and complementary microarray platforms' (National Center for Toxicogenomics, 2002: 14). The purpose of the cooperative experiments is to 'develop standard operating procedures and quality control standards for gene expression experiments and to develop technology standards and bioinformatics tools for data comparison across the CRM' (National Center for Toxicogenomics, 2002: 14). The development of these standards and bioinformatics tools, in turn, will allow the gene expression profiles generated by TRC members to be

submitted to the CEBS database, where it will contribute to the initial collection of toxicogenomic data available for public query.

The TRC project thus endeavors to maximize the usability of the CEBS, in particular, and toxicogenomics, in general, as resources for making molecularized toxicological statements. As alluded to in the comments of this toxicogenomics researcher, a new archive requires user guides:

> What does the data mean? That's the big question. There is so much data. It's like being given the Encyclopedia Britannica and ten seconds to find an answer. . . . You know the answer is in there somewhere, but you have to learn the rules or what volume to go to, and you have to learn the rule within that volume. Where do you look it up? And you have to learn the rules for not only reading what's there, but understanding and interpreting. . . . (Interview 35)

In order for toxicogenomics to be able to travel widely, these guides must be standardized and widely accepted (Fujimura, 1996; Timmermans & Berg, 1997). The TRC works to accomplish this standardization and to create a consistent, usable molecular grammar for toxicology.

The TRC also enrolls scientists (and, presumably, their students) at five major environmental health research centers, creating a network (Latour, 1987) of active, public sector[16] participants in the establishment of toxicogenomics as a standardized, usable molecular toxicological science. The NIEHS has made other investments in translating toxicogenomics to a scientific audience, including co-sponsoring a Society of Toxicology Workshop on 'The Use of Genomics in Risk Assessment', launching a quarterly journal (*EHP: Toxicogenomics*) as part of its *Environmental Health Perspectives*, and publishing 'perspectives on toxicogenomics' in the scientific literature (for example: Olden & Wilson, 2000; Tennant, 2001; Olden, 2002). However, as I describe in the following pages, the emergence of toxicogenomics also depends on making toxicogenomics usable in traditional markets for toxicological knowledge and these translations have required yet another set of strategies.

Molecularization and Markets

Making Use of Uncertainty

In seeking to revolutionize toxicology, the NCT endeavors to transform a science that is strongly identified with its applications and service roles in environmental health risk assessment and regulation.[17] The published literature in toxicology repeatedly emphasizes that toxicology is 'not science for the sake of science, as are many other areas of research'. Rather, toxicology is 'largely driven by issues that relate to safety of consumer products, occupational exposures, human exposure from substances in the environment, as well as the effects of chemicals on environmental species' (Schwetz, 2001: 3). Likewise, it is often noted in descriptions of toxicology

that it is 'most importantly . . . part of the risk assessment process' (Smith, 2001: 281).[18]

Toxicology's service roles are also part of the identity of the discipline and its practitioners. For example, referring to the demands and consequences of being a major contributor to risk assessment and regulatory reviews, one toxicologist commented that when working in toxicology, a scientist must understand that 'toxicology is a political science'. In making this point, he described the surprise experienced by scientists who come to toxicology from other fields when they find that their research has political consequences:

> Scientists who venture into toxicology sometimes find themselves causing uproars. They're surprised, because they're used to debating cancer pathways in the literature. But, they start one of those debates here and a product is pulled off the shelves. (Interview 42)

In this framing, being aware of this service role is a part of being a toxicologist.

Because one of toxicology's primary service roles is in risk assessment, if toxicogenomics is to succeed in reconfiguring toxicological work objects and practices, it must establish clearly that it also can be of service to environmental health risk assessment. Indeed, many of the arguments put forward in favor of the further development of toxicogenomics refer to its potential to address extant uncertainties in toxicological testing practices and their implications for risk assessment and regulation (Paules et al., 1999; Olden, 2002; Simmons & Portier, 2002). These uncertainties are characterized by NIEHS administrators as 'the intractable problems' which 'have long characterized the field' of toxicology, including the following: 'intrinsic toxicity to humans, variation in susceptibility, cross-talk or interaction between agents in mixtures, and the type, pattern and magnitude of human exposure to chemicals' (Olden, 2002: 275). These are also some of the problems highlighted by this toxicogenomics researcher's comments on the 2-year rodent cancer bioassay, which is the current gold standard for carcinogenicity testing:

> There are major obstacles in toxicology and this has been obvious to a lot of people: extrapolation from animals to humans, all the issues about exposure, because with the rats, you're giving a large dose over a concentrated period of time but humans are exposed to varying doses over longer periods of time and exposed to mixtures . . . and then there are issues of nutrition and genetic susceptibility. (Interview 32)

Researchers also emphasize the uncertainty in toxicological research that derives from issues surrounding the extrapolation of data derived from in vivo testing in animal model systems (cf. Busch et al., 2000). This regulatory scientist put it in stark terms: 'people . . . worry about the relevance of animal studies' (Interview 3). For example, in the words of this toxicologist, the 2-year rodent bioassay 'gives you the answers: (1) this does cause cancer in rodents; (2) this does not cause cancer in rodents; (3)

this might cause cancer in rodents. Then, you have to extrapolate to humans. This entire process is difficult, slow, and expensive' (Interview 2). These uncertainties also contribute to the vulnerability of regulatory decisions based on risk assessments to expensive and time-consuming legal challenges (Jasanoff, 1990, 1995).

It is therefore not surprising that toxicogenomics is being developed, in part, to improve and 'change the entire paradigm of testing' (Field Notes, July 2002). Moreover, according to one NIEHS researcher, 'toxicogenomics will continue to reveal gaps in the toxicological sciences' (Field Notes, July 2002). Therefore, toxicogenomics is promoted as a means of transforming risk assessment both by highlighting the uncertainties of extant toxicological research and providing new research methodologies that will diminish them. The NIEHS is not alone in this vision; the pharmaceutical industry has sponsored a collaborative scientific research program organized by the International Life Sciences Institute (ILSI) to investigate 'the applications of genomics to mechanism based risk assessment' of pharmaceutical products (Pennie et al., 2004).

As scientists recognize that 'people who want to promote political uncertainty will use scientific uncertainty as a basis' (Field Notes, July 2002; see also Jasanoff, 1990), reducing scientific uncertainty is of significant value to government risk assessors and regulatory scientists. However, highlighting uncertainty in environmental health risk assessment and regulation is a tricky matter. Extant methods of toxicological evaluation and risk assessment have been used to create the regulations that currently constitute environmental health protection in the USA. Moreover, as detailed earlier, NCT researchers are using traditional toxicology as the epistemological and ontological 'grounding' for toxicogenomic knowledge. Therefore, proponents of toxicogenomics must simultaneously portray toxicology and risk assessment as in need of improvement (because, as one toxicologist quipped, 'if it's not broke why fix it?' [Interview 41]), while still 'good enough' to protect public health. This tension characterized the comments of this molecular epidemiologist who stated, 'Toxicology needs to go beyond kill 'em and count 'em. But the other side of that is that this way has served the public well. If you screen out the things that kill rats, you will protect a lot of people' (Interview 26). Likewise, as noted in a paper about toxicogenomics in *Science*, although toxicology is 'a time honored way of identifying human health risks' it also ' ... can be an imprecise science' (Lovett, 2000: 536).

Scientists have identified four distinct, though not mutually exclusive, means by which toxicogenomics may reduce uncertainty in risk assessment. First, gene expression profiles are promoted as a means of elucidating mechanisms of toxicity and enhancing the knowledge base of toxicology (Burchiel et al., 2001; Hamadeh et al., 2001). This is referred to as 'mechanistic toxicology' (Pennie et al., 2000; Fielden & Zacharewski, 2001). Second, researchers are exploring the possibility that gene expression profiles may provide a basis for a new, molecular rationale for the classification (and reclassification) of toxicants (that is, grouping those

toxicants that share similar gene expression profiles) (Hamadeh et al. 2002a; Hamadeh et al., 2002b). Third, and related, scientists are actively pursuing the potential of gene expression profiles to enable the *prediction* of the toxicity of unknown compounds and thereby provide a basis for their classification (that is, without undergoing the 2-year rodent bioassay) (Bartosiewicz et al., 2000; Bartosiewicz et al., 2001a; Bartosiewicz et al., 2001b; Tennant, 2001; Hamadeh et al., 2002a; Hamadeh et al., 2002b). This is referred to as 'predictive toxicology' (Pennie et al., 2000; Fielden & Zacharewski, 2001). Fourth, gene expression profiles may serve as new molecular biomarkers of genetic susceptibility (Paules et al., 1999). The NIEHS supports the development of all of these applications of toxicogenomics.

There are two primary rhetorical strategies through which proponents of toxicogenomics seek to promote these applications of toxicogenomics for use in chemical testing and risk assessment, without thoroughly undermining current practices and the regulatory policies that rely on them. First, many statements in favor of toxicogenomics emphasize the new, molecular levels of analysis made possible by toxicogenomics and the goal of 'moving beyond classical toxicology' (National Center for Toxicogenomics, 2002). The argument is that while current toxicology and risk assessment provide the best possible system at what environmental health scientists call the 'phenomenological level', toxicogenomics offers an innovative means of conducting toxicological research 'down at the molecular level' (Field Notes, July 2002). Specifically, research at the molecular level may illuminate pathways of toxicity, where, as one regulatory scientist lamented 'oft times . . . we have no idea in the world *how* some effect comes about' (Interview 2). The hope of toxicogenomics researchers is that if 'there aren't so many black boxes', they will be able to improve the toxicological knowledge base and improve risk assessment (Field Notes, August 2002).

Second, advocates of toxicogenomics argue that gene expression profiles will provide a means of doing toxicological risk assessment that is quicker and less expensive, and that satisfies the demands of the animal rights movement for reductions in animal testing. Toxicogenomics, then, is offered as a way to 'break the bottleneck' in testing, 'deal with the backlog of chemicals that are still waiting to be tested', and 'supplant all the animal testing we do now' (Field Notes, August 2002). As one toxicologist told me:

> The idea is that we'd like to be doing it better. We'd like to be doing it cheaper. We'd like to be doing it more quickly. Because you know, at eight compounds a year, and millions and millions of dollars [per compound] we're never even going to make a dent in everything that's out there that probably needs to be tested. (Interview 27)

This comment implies that while current testing regimens provide accurate data, they are insufficient to the task of testing 'everything that's out there'.

Framing the potential contribution of toxicogenomics in this way emphasizes the fiscal and social costs of contemporary toxicological techniques, while leaving their scientific validity unscathed.

Using such rhetorical strategies, proponents of toxicogenomics are able to promote that approach as a means of improving toxicology and risk assessment, without discrediting current techniques and standards. This is critical to maintaining the legitimacy of the NIEHS, the NTP, and the regulatory system that their research is supposed to support. It also allows the NIEHS to enroll stakeholders in risk assessment and regulation, based on their shared interests in improving toxicological science.[19]

'Defining the Environment' for a New Environmental Health Science

To ensure that toxicogenomics is accepted as a replacement and/or adjunct to traditional toxicology, the NIEHS has begun to work at translating toxicogenomics to three categories of end-users in the domain of environmental health risk assessment and regulation. I describe these efforts here, as they highlight the ways in which potential applications and service market considerations permeate the emergence of toxicogenomics.

First, administrators at the NIEHS want to make sure that the regulatory agencies, such as the US Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) will be willing to use toxicogenomic data in regulatory reviews. As this NIEHS administrator stated:

> The ... worry is that we will have good information, mature data, and the regulatory agencies will still be hesitant to use it because they have given no thought to it. And suddenly you drop it on their doorstep, and they say, well what is this? So, you know, it could languish out there for another twenty years while they argue about it, while people die and suffer. ... (Interview 39)

Second, NIEHS/NCT scientists are also working on identifying and reaching out to the stakeholders 'that we need to build bridges with'; these include 'the chemical and pharmaceutical manufacturing industries, the green groups, environmental groups, and consumer groups, the Environmental Defense Fund, the EPA, FDA, and other regulatory agencies, and policymakers ... [and] probably staffers from Congress' (Interview 39). This list of stakeholders includes groups that are often on opposite sides of regulatory review, legislative initiatives, and litigation about environmental chemicals and their effects. Indeed, the historically adversarial relationships and potential for ongoing disagreements between these groups are one reason that the NIEHS has begun to work with them to build a consensus about the uses of toxicogenomics even before the technology is ready for those applications:

> [We] don't want this, in the end, to come to some loggerhead because labor unions are fighting industry and environmental groups. We want everybody to buy into the technology before we have it, and before

> anything is out there. Once they buy in and they have signed off on it, they can't just change their mind because they didn't like the outcome [re: a particular chemical]. . . . We want to eliminate that conflict and opposition in the end. (Interview 37)

Again, the idea is to adjudicate potential conflicts 'up front' and literally in advance of actual application so that toxicogenomics will not be kept from this market.

Finally, the NIEHS is also 'reaching out to the public' about the potential applications of toxicogenomics in risk assessment and regulation so that 'when they hear toxicogenomics five or ten years from today, it's not a Frankenstein new development. They know about it. They know exactly what it is we are doing' (Field Notes, July 2002). The fear expressed by NIEHS scientists is that toxicogenomics will meet the same kind of public opposition as genetically modified foods, an opposition they feel derives from uninformed fear and 'a lack of understanding of the technology'. Indeed, there is a pervasive belief at the NIEHS that public education about toxicogenomics will lead to its acceptance: 'if they understood it, they wouldn't object' (Field Notes, August 2002).[20]

The strategy of the NIEHS is to achieve exposure, legitimacy, and consensus regarding toxicogenomics *in advance of its applications* by 'defining the environment' in which toxicogenomics is introduced to the stakeholders in the markets of environmental health risk assessment, regulation, and policymaking. The way to do this, NIEHS's senior leadership has decided, is 'to do it up front . . . be proactive':

> I just want the technologies to have as full an impact in as short of a period as possible. And without the kind of things that we are doing to educate stakeholders, policy makers, and the American public, regulatory agencies will not be allowed to use [the new technologies], even when they decide to use them. So we have just got to bring along everybody to make sure that if three years down the road we can predict toxicity, by gosh let's do it then and let's not wait *x* number of years for everybody else to catch up. (Interview 37)

A wide variety of efforts are underway to bring toxicogenomics to its potential service markets and to enroll stakeholders in the toxicogenomic project. For example, a series of public service announcements about toxicogenomics is to run on public television and radio stations over the next three years (Field Notes, August 2002).

In addition, the NIEHS/NCT supports a working group on the 'ethical, legal, and social implications' (ELSI) of toxicogenomics. This committee consists of ethicists, lawyers, representatives from the microarray, chemical, oil, pharmaceutical, and bioinformatics industries, a representative from the environmental justice movement, and environmental health scientists from both university and government settings. Though it meets only infrequently, the ELSI Working Group has provided a high profile public forum for the discussion of toxicogenomic science among scientists, regulators, policymakers, and advocates.[21] Moreover, it has

generated a network that supports research, writing, and presentations on toxicogenomics and its ethical, legal, and social implications, especially in the domains of risk assessment, regulation, and public health.[22] Together, these activities begin to instantiate the claims of NIEHS scientists and administrators that *this is a science that will have ethical, social, and legal implications*, even if only by exploring actors' perceptions of those implications. Thus, through its activities, the ELSI Working Group contributes to the materialization and legitimation of the NCT's *definition of the situation* of toxicogenomic science (Thomas & Thomas, 1970 [1928]). Hedgecoe and Martin observe a similar role for bioethics in the emergence of pharmacogenomics: 'the creation of an ethical discourse around a controversial technology is important as it both provides a negotiation space to explore the socially acceptable limits of the technology and acts as a means of enrolling support from key actors' (Hedgecoe & Martin, 2003: 329; see also van Lente & Rip, 1998).

The most significant investment that the NIEHS has made in expressing its vision of toxicogenomics, enrolling stakeholders, and creating a social context conducive to the acceptance of toxicogenomics is its sponsorship of the National Academy of Sciences (NAS) 'Committee on Emerging Issues and Data on Environmental Contaminants' (hereafter 'the NAS Committee'). The NAS Committee was convened at the request of the NIEHS. It consists of 22 members, most of whom are university-based environmental health scientists. However, the Committee membership also includes lawyers, a scientist from the National Resources Defense Council, representatives from the Chemical Industry Institute for Toxicology and various chemical, bioinformatics/software, and pharmaceutical companies. According to a senior administrator, the NIEHS decided to invest in sponsoring the NAS Committee, in part, because:

> There's been no move by the regulatory agencies to ... anticipate the data. So, we've contracted with the NAS/NRC [National Research Council] to bring together all the stakeholders in the field: industry, scientists, lay public, unions, policy makers, environmental groups, regulatory agencies. We want to get everyone around the table to talk about toxicogenomic data, to develop case studies to explore how the data can be used. (Interview 39)

However, the NAS committee also represents an opportunity to address emerging controversies about the meaning of toxicogenomics. For example, some environmental health scientists and activists claim that the chemical industry is only interested in toxicogenomics as a means of pursuing research on mechanisms of action and that it opposes, however quietly, NIEHS's vision of gene expression profiles as a means of rapid 'predictive toxicology'.[23] Therefore, these researchers and advocates are concerned that the chemical industry will use toxicogenomics not to make risk assessment faster or more effective, but rather more complicated and time consuming, so as to delay regulatory action:

> Industries see it as a tool, a delaying action. [They say] 'I'm going to do this study first to guide me and it will take me two years'. And the

> regulatory agency says, 'Okay go ahead' and that means two more years that industry can use the product without any regulatory [oversight] . . . so it's a great delaying tactic. (Interview 40)

Activists also fear that in identifying individuals who are particularly sensitive to chemical exposures, genomic technologies may also shift the locus of responsibility for environmental health and illness, from the polluter to the susceptible individual exposed to the pollutant (Field Notes, February 2002; Shostak, 2004). In turn, representatives of the chemical industry and proponents of toxicogenomics alike have voiced concern that toxicogenomics will be 'exploited' by environmental health activists 'prematurely, to claim it says something that it doesn't indicate'. These are exactly the sorts of concerns that the NIEHS hopes that the NAS Committee will adjudicate:

> The concern is that every time there is a peak (in expression) in the data, the environmental groups will react. Or that every time there is a question about how to interpret, that industry will say the data means nothing. So, we need to get this group of people together to set standards up front. So, when we get data, we've agreed about how it will be used and it can be used immediately, so that we won't have to wait 5–10 years. (Interview 58)

The NAS was requested to facilitate this process because of its reputation for scientific excellence, neutrality, and objectivity in bringing closure to scientific debates (cf. Hilgartner, 2000). As one NIEHS scientist put it:

> The National Academy of Science is supposed to be the pure, above reproach group. And they have no stake in this. They are just trying to be the honest broker. So they are going to bring people around the table and they're going to let them argue and debate and finally get a consensus. (Interview 27)

Unlike many NAS committees, which are charged with undertaking studies and producing a consensus report to answer a specific scientific question, the NAS committee sponsored by the NIEHS is a 'standing committee' that serves 'as a forum for discussion':

> The goals are to bring issues to the forefront, to identify issues, and . . . holding symposia to focus on those particular issues, so that more issues can be identified or discussed, and different viewpoints can be brought up. Then also to develop ideas where more specific attention might be needed, either by future NAS studies or other mechanisms. (Interview 59)

While the NIEHS is, of course, clear on the fact that the committee will not produce a consensus report on any given aspect of toxicogenomics, it is hopeful that the committee will develop 'case studies' that, in time, will guide the application of toxicogenomics in risk assessment. These case studies, then, are seen as a means of producing 'blueprints' for the use of toxicogenomics by the regulatory agencies. As this scientist explained,

> There will be all of these position papers with all these case studies, and the cases will become reality with time. And we have already been given instruction as to that is what they will do to regulatory agencies as to how to use the information. So the EPA and the FDA won't have to say, 'toxicogenomics, what is that? What does this mean? And how do I use it?' They've already got a blueprint that they've agreed to and everybody's agreed to and they've been informed. (Interview 38)

In addition, the NIEHS leadership wants the NAS committee process to encourage the participation of the industries whose products are likely to be regulated using toxicogenomic data and technology. Specifically, the NIEHS scientists express hope that by providing industry with an opportunity to 'participate with government' in the process of making decisions about toxicogenomics, industry will 'know that government acted responsibly' in developing the technology and its applications in risk assessment and regulation. Again, the emphasis on defining acceptable uses, enrolling allies and creating a market for toxicogenomic knowledge is quite explicit.

In conjunction with the formal NAS committee, the NIEHS has organized a Federal Liaison Group, consisting of members of federal institutions that have interests in toxicology and risk assessment.[24] This Group is a critical component of the overall project, as representatives of federal agencies (including the NIEHS) cannot participate in NAS committees. The Federal Liaison Group attends the NAS committee meetings (which are also open to the public), as well as conducting its own deliberations. The Federal Liaison Group also presents reports on its discussions and concerns at NAS committee meetings.

The NAS Committee and its Federal Liaison Group constitute a 'staged intersection' designed to create a space in which toxicogenomics can be effectively translated to stakeholders in important service markets for traditional toxicology. As conceptualized by Garrety (1998: 403), staged intersections are 'conferences, hearings, symposia, etc. which intentionally brought people together from diverse social worlds for the express purpose of persuasion and public adjudication'. Indeed, as detailed earlier, these are the exact purposes of the NAS and Federal Liaison Group Committee meetings. Moreover, in additional to the actual meeting of the NAS Committee and Federal Liaison Group, the NAS Committee also occasions two ongoing, virtual staged intersections. First, it maintains a website, which provides audio-clips and slides from the presentations made at committee meetings and symposia, the Committee's mission statement, upcoming events, and extensive links to other NIEHS and NAS websites. The committee also maintains a mailing list and a listserv, by which it distributes its newsletter 'Emerging Issues in the Environmental Health Sciences' (National Academy of Sciences, 2002–2004). The contents of the newsletter include brief reports on the proceedings of committee meetings and symposia, the agenda for upcoming committee events, book and journal reviews pertinent to toxicogenomics, and lists of 'hot topics' that might be considered by the

committee over the coming years. Thus, the translation and adjudication of toxicogenomics may extend far beyond the individuals who attend any given meeting or symposium at the NAS.

As noted earlier, the NAS is a crucial setting for this intersection, as it is perceived as neutral and objective by many in the environmental health sciences. However, the tremendous credibility and prestige of the NAS are also of value in the translation of toxicogenomics. As this environmental health scientist noted, 'any significant NAS report or workshop ... can signal the official definition of a field' (Field Notes, July 2002). Moreover, the National Research Council (NRC) of the NAS wrote the so-called Red Book, which is 'the Bible' for risk assessment at the federal agencies; it sets the standards to which all federal agencies are held accountable. Indeed, one potential 'hot topic' proposed by the NIEHS to be addressed by the NAS committee is 'Should the NRC report *Risk Assessment in the Federal Government: Managing the Process*, the so-called "Red Book" be updated to address the new technologies and their potential impact on risk assessment?' (National Academy of Sciences, 2003: 3). To revise the NRC Red Book would be a tremendous step towards establishing service markets for toxicogenomics, as it would be no less than a re-standardization of the entire risk assessment process. That such a revision was suggested at the very first meeting of the NAS committee is certainly suggestive of its potentially pivotal role in articulation of a molecularized toxicology.

Conclusions: Disciplining Toxicology

As I have demonstrated in this paper, the emergence of toxicogenomics can be understood as a deliberate effort to molecularize the field of toxicology. Indeed, the success of toxicogenomics relies on the molecularization of toxicology's technologies, 'language', practices, and markets. Clearly, novel technologies, the development of their toxicological applications, and subsequent transformations in toxicological practices have contributed to the emergence of toxicogenomics. However, this paper also highlights the role of scientific institutions, such as the NIEHS and the NTP, in 'fostering' this new science, through their extensive efforts to translate, standardize, and stabilize markets for toxicogenomics. In this conclusion, I argue that the emergence of toxicogenomics therefore offers an important vista into the significance of molecularization for contemporary environmental health scientists, their institutions, and their service markets.

Drawing on Foucault (1980: 131–33) and his expositors, I contend that toxicogenomics moves toxicology more firmly within the 'regime of truth' in the contemporary life sciences (Rose, 2001). A 'regime of truth' is:

> the body of practices and the types of discourses that a society accepts and makes function as true; the mechanisms and instances that enable one to distinguish true and false statements and the means by which each is

> sanctioned; the techniques and procedures accorded value in the acquisition of truth; and the status of those who are charged with saying what counts as true. (Lenoir, 1997: 48)

Increasingly, the regime of truth in the life sciences is molecular (de Chadarevian & Kamminga, 1998; Rose, 2001). Therefore, in order to fully participate in knowledge production in the contemporary life sciences (for example, to receive funding, to have access to technologies and experimental systems, to find venues for the publication of one's research, to establish service roles for one's products), scientific disciplines are increasingly required to participate in the discursive practices of molecular biology, genetics, and/or genomics.

Toxicologists speak eloquently of such pressures to molecularize their discipline. Indeed, at the same time that many toxicologists express enthusiasm for the potentials offered by toxicogenomics, they talk about being afraid that unless they incorporate genomic science in their research practices, toxicology will become an 'anachronistic science' (Field Notes, December 2001). As one toxicologist told me, 'The genomics revolution is washing over us. Either we incorporate it or we'll be left behind' (Field Notes, July 2002). Likewise, in discussing the founding of the NCT, several scientists and researchers at the NIEHS reported that they felt that toxicology was in danger of 'becoming irrelevant' in the age of genomics. As noted by this toxicologist, toxicology was already far behind the leading edge of science and therefore stands to gain tremendously from a transformation of its tools, objects and practices:

> There is just enormous potential. There is more potential in toxicogenomics than in any of the other -omics, and the reason for that is that toxicology as a science was not at the leading edge of academic science. So this is an opportunity to bring toxicology research to an entirely new level of power and sophistication as a research enterprise; and that has enormous potential for human public health benefit, with respect to toxicology research. We have more to gain than any other discipline. (Field Notes, June 2002)

This potential was highlighted, in part, by developments and investitures in pharmacogenomics. 'Drug discovery science' has long been one of the major 'drivers' of demand for toxicity assessment; the other being the build up of thousands of as-of-yet untested chemical and physical pollutants in the environment and ongoing concerns and controversies about their effects on human health (Olden, 2002). As pharmacogenomics was developed in the private sector, the NIEHS began to foster toxicogenomics for applications in the public sector.

Indeed, toxicologists fear that being 'left behind' would undermine not only their laboratory research, but toxicology's relevance to many of the most critical service markets for the environmental health science: environmental health risk assessment, regulation, and policymaking. For example, one toxicologist stated that he was concerned that if it failed to incorporate genomics, 'then the NTP would be a toxicology program of only historical

interest' (Interview 32). Relatedly, the administrators at the NIEHS firmly believe that active engagement with genomics is critical to their institutions status:

> So, we started [the genomics initiatives] . . . and the National Institute of Environmental Health Sciences has become a major player at the National Institutes of Health. It used to be, quite frankly, that they didn't see us as important to the mission of the National Institutes of Health, to protecting public health. But now we are a major part of the Institutes – we are integrated with the National Cancer Institute, the National Human Genome Research Institute – and they see how important our work is for public health. (Field Notes, December 2001)

This paper has highlighted the central role of the scientists and leadership of the NIEHS and the NTP in the development and fostering of toxicogenomics. Thus, its emergence must also be understood within the context of the pressures to molecularize experienced by environmental health scientists and their institutions.

Even amidst these pressures, toxicologists express concerns about the molecularization of their field. Some fear that toxicogenomics will be used by the chemical industry to undercut the validity of the current gold standard of toxicology testing, the two-year rodent bioassay, thereby impeding the regulation of environmental chemicals. As this researcher noted,

> People who want the environment protected are concerned that by siphoning resources away from the chronic studies that are already readily accepted by the agencies, into something that may not be as accepted by them, is to [create] either a longer time to regulatory intervention or [to] actually preclude it. (Interview 1)

Relatedly, some toxicologists believe that the resources that the NIEHS has invested in genomic technologies would be better spent testing the many chemicals in the environment via the two-year rodent bioassay:

> People . . . were saying that . . . [toxicogenomics], it's just a glitzy, fly by night kind of thing, a here-today-gone-tomorrow kind of technology. Why do you want to invest so much in it? Especially in the early days when we had to build all the instrumentation ourselves, they [asked] . . . why are you going to spend years developing this technology when it's going to be gone before you know it? (Interview 60)

Others note that the expense associated with microarray research may create a 'biotechnological divide' that disadvantages actors and institutions without access to molecularized toxicological tools (Field Notes, August 2002).

The emergence of toxicogenomics and its consequences remain very much a work in progress. At the time of this writing, phenotypic anchoring, the development of the CEBS database, the work of the TRC, and the deliberations of the NAS Committee are all ongoing. Moreover, what toxicogenomics ultimately will mean for the environmental health risk

assessment, regulation, and policy will be subject to both ongoing and emergent struggles in the arena of environmental politics (Shostak, 2004). Relatedly, while the NIEHS's expansive definition of toxicogenomics and its applications has, thus far, allowed it to support and foster the emergence of toxicogenomics most broadly, transformations in the production of or demand for toxicogenomic knowledge may have as-of-yet unknowable effects on the scope of this emerging form of toxicological practice. For all of these reasons, toxicogenomics, the challenges it meets in the laboratory and in its service markets, its successes and failures, will continue to provide an opportunity for sociologists and historians of science to explore both the processes and the meanings of molecularization in the environmental health sciences.

Notes

It is the generosity with which many busy people met my requests for their time, their stories, their aspirations, their concerns, and their insights that made this ethnographic case study possible; I owe them all a great debt. I am deeply grateful to Adele Clarke, Howard Pinderhughes, Paul Rabinow, and Sharon Kaufman and the members of our UC San Francisco writing group, each of whom, in their own remarkable way, made significant contributions to various iterations of this work. I thank Cynthia Afshari for her review of the manuscript for technical accuracy. Thanks also to three anonymous reviewers, Lucy Suchman, and Mike Lynch at *Social Studies of Science* for tremendously helpful comments. I gratefully acknowledge the generous support of the National Science Foundation (award no. 035381) and the University of California Toxic Substances Research and Teaching Program. Of course, for the analysis presented in this manuscript and any errors it contains, I take sole responsibility.

1. As noted by a scientist in a 2002 interview 'We still call it "molecular biology". But then biology is actually kind of a marginalized area . . . traditional biology is actually probably a smaller component of biology than molecular biology is now . . . '.
2. This analysis draws on data from a multi-sited ethnographic project on disciplinary emergence in the environmental health sciences that I conducted from September 2000 through September 2002. The primary mode of data collection for this project was in-depth qualitative interviews (*N* 59). The majority of these interviews were with scientists formally educated and/or working in the fields of molecular biology, genetics, genomics, epidemiology, and toxicology, as well as scientists working in molecular epidemiology, environmental genomics, and toxicogenomics. In addition, I interviewed seven regulatory scientists and administrators based at the US Environmental Protection Agency or the Food and Drug Administration and two scientists working in the chemical and pharmaceutical industries. A second set of interviews was conducted with environmental advocates, community activists, and lawyers. I also conducted participant observation at a variety of scientific conferences, meetings, and symposia and, for three months, as an intern at the NIEHS. Secondary data were generated by a comprehensive review of the literature on genetics/genomics and the environmental health sciences, 1950–2000. All of the data detailed earlier were coded and analyzed using the general principles of grounded theory (Glaser & Strauss, 1967; Strauss, 1987; Strauss & Corbin, 1990).
3. Risk assessment refers to 'the systematic scientific characterization of potential adverse health effects resulting from human exposures to hazardous agents or situations' (National Research Council, 1983: 1). The results of risk assessment serve as the empirical basis for decision-making about regulatory standards or policy actions to deal with the hazards identified in the risk assessment. Jasanoff (1990, 1995) has written extensively on the history and politics of risk assessment in the US federal government.

4. cDNA refers to an identical copy of a gene that would usually be produced in a living cell which has been produced via 'reverse transcription' from RNA in a laboratory (Schmidt, 2002). The construction of a cDNA microarray usually involves immobilization of cDNA sequences corresponding to research genes of interest on the surface of a glass slide. These spotted sequences can represent either sequenced genes of known function, or partially sequenced cDNA derived from expressed sequence tags corresponding to mRNA from genes of unknown function. mRNA isolated from the biological samples of interest is converted to fluorescently labeled targets via a reverse transcriptase reaction. The labeled targets are then competitively hybridized on the microarray chip, scanned by a laser at frequencies corresponding to the respective fluorescent tags, and analyzed using digital imaging and bioinformatic techniques (Lobenhofer et al., 2001).
5. These are techniques used to separate, identify, and measure pieces of RNA. Also, these techniques use radioactive tags, whereas microarray analysis relies on fluorescence and confocal microscopy (Interview 40).
6. Hedgecoe & Martin (2003) provide a detailed analysis of the differences in these definitions and 'visions' of pharmacogenomics and their consequences.
7. Per the requirements of my Human Subject Research protocol, I do not reveal the names of any of my respondents. Institutional affiliation has been revealed only for those subjects who consented to be interviewed 'on the record', as well as for those whose comments were recorded in my field notes during ethnographic observation. In order to better contextualize quotations from interviews, I provide the respondents' scientific background (for example, 'epidemiologist', 'toxicologist') whenever possible. I have also provided codes for interview respondents (for example, 'Interview 45'), so that they may be understood as unique 'voices', however anonymous. Although my total sample of interviews was 59, these interview codes may be of higher numbers, as, during recruitment, some code numbers were assigned to potential respondents who later declined to be interviewed.
8. The first author of the paper, Emile Nuwaysir was a postdoctoral researcher at NIEHS, working with Cynthia Afshari. His co-authors were the NHGRI and NIEHS scientists who brought microarrays to the NIEHS: Afshari and Barrett from NIEHS's Laboratory of Molecular Carcinogenesis, and Trent and Bittner from the NHGRI's Laboratory of Cancer Genetics.
9. Whereas genomics focuses on gene expression, proteomics refers to the global analysis of protein expression, including protein folding. The two fields are conceptually and technologically related, as proteomics draws on many of the same fundamental technologies that have supported the emergence of genomics (for example, chips, robotized arrayers, databases, bioinformatics software). Many scientists believe that proteomics will be 'the next frontier' for the life sciences and will improve greatly on DNA microarray approaches. As this scientist noted, 'the problem with [DNA] microarrays is that they tell you what genes are being expressed. They don't tell you why those genes are being expressed. They don't tell you whether those genes are being translated into proteins that are being produced. They don't tell you whether those proteins that are being produced are then being excreted or expressed . . . [and] are, in fact, having a biological effect'.
10. My use of the term 'translation' is informed by actor network theory's conceptualization of translation as the means by which one entity gives a role to others (Latour, 1987: 109; Callon, 1995). I also draw upon insights from the actor network theory on the importance of attending to 'the operations that link technical devices, statements, and human beings' (Callon, 1995: 50). Similarly, I am interested in how the definition of technical problems contributes to the definition of the space of circulation for the knowledge that is produced (Callon, 1995: 52). However, my analysis also diverges from the actor network theory in several ways. In contrast to a narrative of 'a great man and the network he created' (Hess, 1997: 110), my intention is to include a wide range of actors, social worlds, and institutions in my analysis of translation. Relatedly, as I do not assume that translation is a one-way endeavor (Star,

1991), my analysis focuses on the processes through which multiple social worlds and social actors in the environmental health arena negotiate the translation of emergent forms and disciplines and thereby reshape, resist, and reinvent them. Finally, as Law (1999: 8) notes, 'this term "translation" tells us nothing at all about how it is that links are made'. In contrast, my analysis focuses on the specific technologies and practices that constitute the *work* of translation.

11. I thank Adele Clarke for our conversations about the concept of incorporation.
12. Approximately 95% of the scientists working in the NTP also have faculty positions at the NIEHS. In addition, the Director of the NIEHS is also the Director of the NTP. While the NTP has facilities around the country, its 'home' is on the NIEHS campus in Research Triangle Park, NC, USA. The NTP is often referred to as 'the other side of the house' at the NIEHS (Field Notes, 2002).
13. The NTP reports have a blue cover and are commonly referred to as the 'blue books'.
14. Gottweis particularizes Foucault's notion of the archive, reconceptualizing it as the 'reservoir of narratives' available to be mobilized to make statements in a society (Gottweis, 1995: 87). His shift is from Foucault's concern with overarching historical archives, 'the rules from within which we speak', to specific archives. This distinction is critical, as Foucault argued that it is not possible for us to describe our own archive (Dreyfus & Rabinow, 1983: 86). However, it should be possible to identify the archives of particular discourses, such as toxicology, which is my goal here.
15. The five institutions awarded funding to participate in the TRC were the University of North Carolina, the Fred Hutchinson Cancer Research Center, the Oregon Health and Science University, The Massachusetts Institute of Technology and Duke University. The initial grant funding for all five centers combined was US$37 million over 5 years. The NIEHS Microarray Center also participates in the TRC as a cooperative research member (National Center for Toxicogenomics, 2002: 13).
16. The pharmaceutical and chemical industries have organized a similar program, under the auspices of the International Life Sciences (ILSI) Health and Environment Science Institute (HESI) (Pennie et al., 2004).
17. Sellers (1997) provides an excellent history of the development of the relationship between toxicology and risk assessment. Frickel (2004) has written a sophisticated analysis of the import of this relationship for the emergence of genetic toxicology.
18. Of course, toxicology is just one component of risk assessment and management, and toxicologists are well aware that political and economic concerns are also important determinants of final rulings. For example, one toxicologist pointed out to me that the EPA is required to hold hearings as part of the regulatory review process 'even when the science is clear'. That is, published toxicological studies alone, no matter how definitive, are insufficient to settle matters of risk assessment and regulation.
19. Although there is significant evidence that the chemical, lead, and tobacco industries are heavily invested in creating uncertainty in the risk assessment process (Proctor, 1995; Ong & Glantz, 2001; Markowitz & Rosner, 2002), the credibility of industry as a participant in risk assessment prohibits them from publicly opposing the development of more accurate scientific techniques.
20. This assumption runs counter to current scholarship on the public understanding of science (Irwin & Wynne, 1996).
21. In July 2002, the group convened at the Woodrow Wilson Center in Washington, DC. The first part of the meeting consisted of a 'public forum' on toxicogenomics, part of the Woodrow Wilson Center's ongoing project 'Genomics and Our Environmental Future'. The forum was widely publicized and drew an audience from the NAS, the federal regulatory agencies, environmental health advocacy groups, and the press. Speakers at the forum addressed the science of toxicogenomics, the applications of toxicogenomics in regulatory settings, and legal perspectives on toxicogenomics (with special attention to occupational settings). The ELSI working group then convened for two days of 'working sessions' that addressed the following issues: (1) Public Health and Regulatory Applications of Toxicogenomics; (2) Toxicogenomics in the Courtroom and the Workplace; (3) Ethical Considerations in Toxicogenomic Research; and (4)

Next Steps in the Development of a White Paper on the Implications of Toxicogenomics (Field Notes, July 2002).

22. For example, one member of the group organized a panel on toxicogenomics for a national conference on human genetics by writing to group members and inviting their participation.
23. At the same time, the toxicogenomic interests of the drug and chemical industries are not necessarily synonymous. As suggested by the pharmaceutical industry's massive investment in pharmacogenomics, the pharmaceutical industry likely stands to gain more from microarray technologies than does the chemical industry. As this scientist noted, 'Pharma has been a lot more proactive and they have reason to be, because they want to get their compounds through the pipeline faster' (Interview 1). If the differing motives and markets of these industries continue to shape differing relationships to toxicogenomics, new alliances in the area of risk assessment and regulation may emerge.
24. These include the EPA, FDA, Department of Agriculture, Department of Energy, Department of Defense, Occupational Safety and Health Administration, National Institute for Occupational Safety and Health, National Center for Environmental Health, and the Agency for Toxic Substances and Disease Registry.

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