Environmental Health and Genomics: (Re-)visions for Risk Assessment?

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Abstract

With the emergence of increasing amounts of genetic data in the biomedical sciences, the 'genomics of environmental response' has emerged as a new research domain. This genetic concept of 'environmental response' views individual genetic susceptibility as an important causal factor in environmentally associated disease. The issue whether 'susceptibility genes' should be taken into account has also entered debates on risk assessment. With its new objects—such as 'environmental response genes'—otherwise disjunct discourses of environmental health and of the 'genetics' of complex diseases meet and overlap. On the one hand, the conceptual link of toxicogenomics to risk assessment has stimulated expectations, promises and the provision of considerable research funds, whereas, on the other hand, the impact of this knowledge upon health risk assessments has remained highly controversial. Asking for the productivity and implications of genomics to epidemiological risk assessment, I shall argue that these shifts to individual predisposition are indicative of a larger biomedicalized reconfiguration of the environmental health and risk management discourses.

Introduction: a linkage between environmental health and genomics?

'Tying genetics to the risk of environmental disease' is the programmatic title of a 2004 *Science* feature which reviewed the emerging field of 'environmental genomics' and outlined potential implications for toxicology (Kaiser 2003). In line with many recent articles in major biomedical and environmental health journals (Masson et al. 2005; Rothman et al. 2001; Thier et al. 1999; Toraason et al. 2004) a new understanding of environmental disease is being promoted stressing the significance of individual differences in the response to environmental toxicants. The link between environmental health science with genomics is performed by introducing

individual (genetic) susceptibility as a core concept which reframes the mechanisms of how environmental agents are thought to cause disease (Khoury et al. 2004). This notion of genetic susceptibility to 'environmental challenge' may have fundamental implications on the ways the human body and determinants of health and disease are conceptualized. Further, they co-shape how health risk assessments of environmental toxicants are conducted: 'Molecular biomarker studies are likely to provide us with tools valuable to risk assessment and in the prevention of environmental cancer' (Husgafvel-Pursiainen 2002).

With regard to genomics and risk assessment, it is beyond the scope of this paper to deal with specific risk analyses as to prenatal testing or with the toxicological risks of GMOs; these topics and the concrete practices involved deserve analyses in their own right. Here, I take a rather different perspective that asks for the ways genomics transforms epidemiology and toxicology, the very disciplines providing the scientific basis for risk assessments. In doing so, I focus on the space between genomic data and the environmental health discourse which is now developing into a key area of (post)genomics. Which discursive effects occur when genomics meets the 'environment' that is often understood as opposed to the notion of genetic inheritance, as it stresses the acquired and the social spheres? What are the new sites of negotiation that emerge from this encounter between genetics and the realm of the environment? Taking up Paul Rabinow's (1996) terms 'genomic assemblages' and 'biosociality' as analytical tools, this paper aims to develop an understanding of the implications of both genomics in society and the social shaping of genomics. Using STS tools, I will follow the 'scientific narratives' and the 'travelling' of genomic data from their context of origin along their integration into epidemiologic knowledge production and, eventually, public health governance. I describe primarily the epidemiological pathways of genomic data towards environmental health science, but I also pay attention to the visions for regulatory contexts, as those bear implications far beyond the academic debate. In my analysis of research papers from environmental health journals between 1995 and 2005, I focus mainly on two key features relevant to these new developments in epidemiological and toxicological research practice: First, I

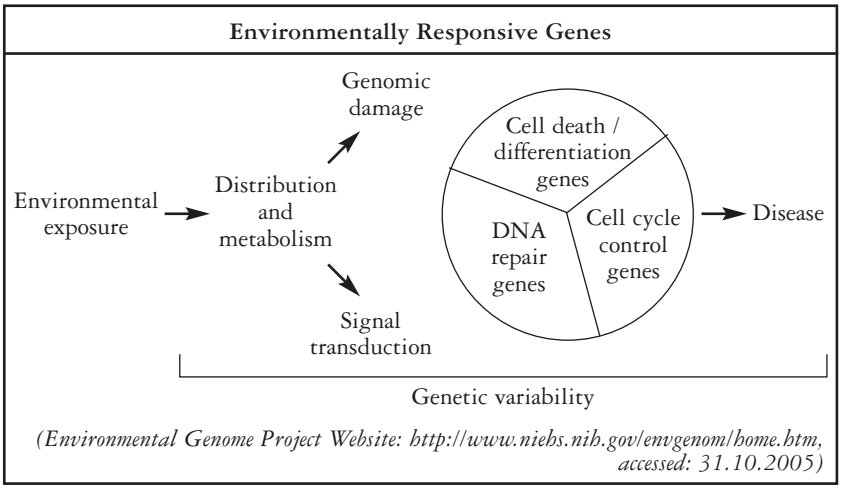
will briefly review the data generation of the Environmental Genome Project (EGP) as the cornerstone of toxicogenomics and, second, I will explore the productivity (in a Foucauldian sense) of genetic epidemiology in the generation of this knowledge. I shall argue that genomics may fundamentally change the overall concepts of health risk assessment—which, accompanied by a shift of responsibility, i.e. an individualization of environmental risk—may impact on risk management and regulatory concepts and, as a consequence, lead to modified local strategies.

The Environmental Genome Project and beyond

In 1997, the US-NIH 'Environmental Genome Project' (EGP) was initiated by the US National Institutes of Health. The EGP has been set up to identify and re-sequence polymorphisms associated with genetic susceptibility to environmental agents. For this purpose, the EGP collected blood samples of 450 persons—women and men of four 'main ethnic groups': 'European -Americans, African-Americans, Mexican-Americans/ Native Americans, and Asian-Americans'[1]—considered representative of the diversity of the US American population. The samples are stored as cell lines in the Polymorphisms Discovery Resource biobank maintained by the US Coriell Institute for Medical Research. Within the framework of the EGP the samples are re-sequenced in order to map allelic variation of several hundreds of 'environmental response' candidate genes. The goal of the EGP is to characterize human variation of several hundreds of 'environmentally responsive genes' (e.g. 'DNA repair genes, cell cycle control genes, cell death and cell differentiation genes') and to determine their role in the pathogenetic process of environmentally-related disease.

In this concept, the organism's response to environmental agents (i.e. related signal transduction processes) differs between individuals according to genetic variability as to single or combinations of genetic polymorphisms. The mechanisms of environmental response are conceptualized as genetically mediated across the whole process of pathogenesis—from exposure pathways to biologic effects on tissue, modes of interaction between parameters and manifestation of disease.

Figure 1. The concept of 'environmentally responsive genes'



(Environmental Genome Project Website: http://www.niehs.nih.gov/envgenom/home.htm, accessed: 31.10.2005)

After completing its primary goals between 1998 and 2003, EGP research reported the re-sequenced polymorphic versions of 213 environmental response genes with related haplotypes and single nucleotide polymorphisms to each of these genes by 2004 (Livingstone et al. 2004). The related sequence information—generated in the EGP—is made publicly available via the web-based SNPs database at the University of Utah and linked to the Polymorphism Discovery Resource at the Coriell Institute for Medical Research which functions as a repository for research based on the biological material of a defined group. EGP research feeds into other larger projects of genomics and post-genomics—such as the HapMap Project.[2] Phase II and III in the EGP explore the functional significance of the identified polymorphisms as well as interactions between genes by expression profiling. Epidemiological studies are conducted to investigate the association between genetic characteristics and environmental disease on a population level.

> Rather than assume that any exposure to any chemical is harmful—an ill-informed position that could have severe economic repercussions—we need to develop and use new technologies to investigate potential threats to human health. Many of

> these technologies are spin-offs of the human genome project. We are using and further developing these techniques in an environmental genome study of how disease-susceptibility genes vary from person to person in the population. We and collaborating scientists are re-sequencing the human genome to discover the variations in the population's so-called 'susceptibility genes' that may cause one child to develop leukemia while a neighbor remains healthy, one smoker to die of lung cancer while another escapes, or one chemistry worker to become infertile, while another sires a half-dozen children (Olden, Guthrie & Newton 2001).

Exposure to environmental pollutants is no longer understood as primarily a matter of external toxic agents, environmental management, clean-up or exposure prevention. Another factor, the response of the individual—that is conceptualized as genetically predisposed—comes into play. It allows researchers to re-consider their notion of stochastic effects: Instead of rough collective probability estimates for the entire population, it appears possible to open the 'black box between exposure and disease' and provide more precise and individualized predictions. This transforms the concept of cancer as a 'stochastic effect' which, for non-threshold effects such as cancer, was an important argument to support precautionary policies. Thus, there is a shift in reasoning from general probabilities of stochastic cancer effects to the quest for differential knowledge, as the 'risk estimate' can be gradually 'individualized' to smaller subgroups. In this process, environmental health risks become entirely compatible with biomedical agendas and furthermore, they can embark on a tradition that promises 'more rational' risk analysis. Many environmental health researchers have embraced this promise, which they expect to shape the future of the discipline. Emerging research fields have been envisioned using analogies to forensics and are thereby recast as a new type of environmental health research:

> The job of the environmental health researchers is much like that of a forensic scientist. Both painstakingly examine the crime scene for clues to identify both the offender and the process by which the act was carried out. In both cases, the hope is that by identifying the offender and the weapon(s) used, further adverse outcomes can be prevented. In the case of the toxicologist, the 'crime scene' (i.e. the human genome) has become more circumscribed, and the investigative tools more powerful in terms of precision and specificity. So, there is now considerable

> optimism to that prevention of chronic diseases is within our grasp (Olden & Guthrie 2001, 9).

The metaphor of the crime and the narrative of the researcher as a detective investigator has a long tradition which can be traced in epidemiologic textbooks (Bauer 2004; Fox, Hall & Elveback 1970). Researching environmental health and making contributions to public health and to prevention is described as an activity that converges with genomics and forensics. It centres on the genome and re-conceptualizes its work from there—how is this linkage between genomics and environmental health further implemented in research practice?

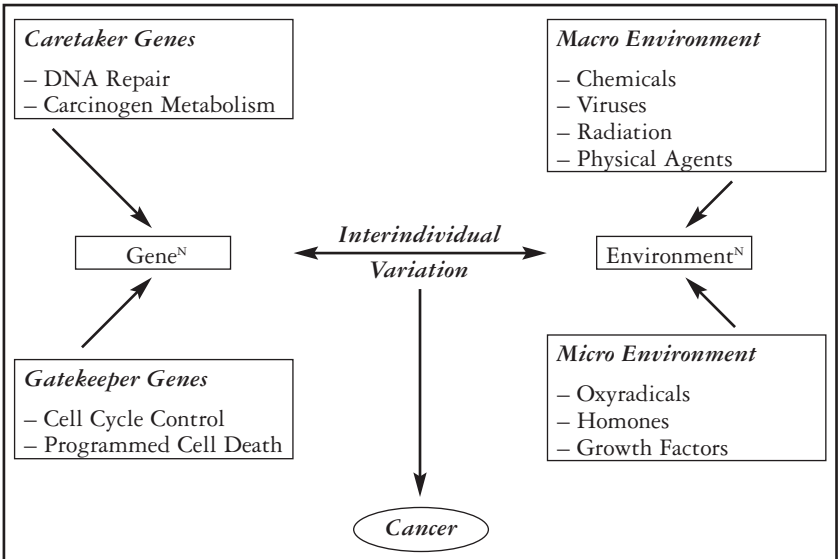
Assigning meaning: genetic epidemiology

In the risk assessment of environmental chemicals, transferring toxicological information derived from experiments with animals or cell lines is considered to be problematic and to involve uncertainties due to inter-species variation. Therefore, in addition to toxicology, epidemiological studies play a major role in providing more direct dose-response data and risk estimates obtained from the observation of human populations (Wichmann 1999). A common textbook definition of epidemiology describes epidemiology as 'the science of the distribution and determinants of health-related states or events in specified populations and the application of this study to central health problems' (Last 1993). In other words, as an epidemiologist put it in the 1970s: 'The history of epidemiology is really the story of evolution of our ideas as to disease causation' (Fox, Hall & Elveback 1970). The scientific framework of epidemiology, in a very general sense, comprises the search for causal factors in disease aetiology (environment or genes discourse),[3] the evaluation of treatment and 'preventive measures' as well as a risk assessment tool. Observational studies are used to examine the statistical significance of associations between risk factors and the occurrence of disease in human populations. Epidemiological studies are also increasingly being used to translate and examine human genome data with respect to their role in disease causation. Epidemiological studies conducted on gene-environment interactions include

studies on lead or benzene toxicity and genetic polymorphisms (Kelada et al. 2001; Nebert et al. 2002). Thus, known environmental carcinogens are being refocused in order to investigate individual differences in the response to these chemicals.

The concept of genetic susceptibility is introduced into risk factor epidemiology, not only as 'environmental genomics' but also as 'caretaker genes' and 'gatekeeper genes'—terms that have been coined as descriptive metaphors for DNA repair, cell cycle control and apoptosis, respectively. The bodily reaction to environmental response is understood as coping with a challenge and described in terms of an individualized and geneticized 'environmental response machinery' (Shields & Harris 2000).

Figure 2. Visualisation of the role of genes and the environment in the carcinogenetic process (Shields & Harris 2000)



(…) Many genes and environmental exposures contribute to the carcinogenic process. The effects can be additive or multiplicative, which are modifiable by interindividual variation in genetic function. We propose to include carcinogen metabolic activity and detoxification genes as caretaker genes involved in maintaining genomic integrity.

The translation of genomic data into risk assessment is done in terms of association studies of candidate genes or polymorphisms with a particular disease. Epidemiological studies are designed to test hypotheses on the associations between environmental exposures and disease with the goal of deriving quantitative effect estimates of the risk per unit dose of exposure to an environmental chemical. This risk estimate per unit dose (which then enters risk assessment) is now further differentiated according to degrees of genetic susceptibility, which can be determined by new technologies such as genetic tests for polymorphisms or by expression profiling using new test technologies such as micro-array chips. Thus, risk assessment changes from aiming to one approximative estimate[4] as a basis for regulation to stratified profiles which construe different subpopulations according to genetic variation.

With the generation of differential risk estimates between 'genetic risk profiles', it becomes possible to target population subgroups to different degrees in public health interventions (Brand et al. 2004). The images that are used to illustrate this discourse in the scientific journals evoke spaces of surveillance and screening as well as the policing of difference according to susceptibility profiles just made visible. This moment of new, genetically grounded, fragmentation is accompanied by an iconography of surveillance where profiles are made visible and are screened according to the grids and categories used in epidemiologic studies. Furthermore, an individualization in setting the research agenda can be observed both in the new emphasis on susceptibility as well as in the conceptualization of prevention in terms of the management of lifestyle according to individual risk profiles.

The epidemiologic gaze on the population[5] traditionally embraces a wide range of 'risk factors'—relating phenomena of different contexts to each other within multifactorial frames—localized in the realms of environmental or socio-economic conditions, in individual lifestyle as well as in biological parameters. As genomics becomes complex, epidemiological methods are prominent tools to sort things out, to determine the status of a variable as a significant risk factor or as a confounder and to evaluate the role of interactions between variables. Epidemiological studies are used to specify risks according to susceptibility status and under further

reference to routinely included analytical categories, such as gender, ethnicity and socio-economic status (Shim 2002). In this way, they perform repeated risk profiling used in public health interventions and health promotion campaigns.

Figure 3. The Environmental Genome Project and susceptibility screening

(*Environmental Health Perspectives* 110 (12): A757, 2002)

Epidemiological studies can thus be understood as technologies to produce risk differentials. They function as complex biopolitical assemblages (Rabinow 1996) tying together otherwise disparate contexts and are constitutive of how we perceive individual bodies in historically contingent matrices. Accounting for 'genetic susceptibility status', genomics-driven analytical grids find their way into risk assessment.

Post-genomic visions and promises: 'more rational' risk assessments?

The risk assessment paradigm widely employed for the analysis of environmental health risks by many government agencies and international bodies such as the WHO comprises the steps of hazard identification, dose-response analysis, exposure assessment and risk characterization, a scheme that is applied in different contexts—from environmental chemicals to physical or biological agents. How do the new genomic data enter this conceptual framework—and subsequently the 'regulatory road' (Freeman 2004)?

Figure 4. Toxicogenomics and the 'regulatory road ahead'

(*Environmental Health Perspectives* 112 (12): cover page, 2004)

In the words of the EGP initiators:

> [O]ne of the biggest potential benefits of this new knowledge is that environmental health regulatory agencies will be able to develop more rational policies. At present, human genetic variation is not implicitly considered in estimating dose-response relationships, nor is it considered when setting exposure limits. Data on the prevalence and characteristics of susceptibility genes offers the potential to reduce guesswork in risk assessment (…) (Olden & Wilson 2000, 152).

The applications in both environmental and occupational health contexts promise to 'reduce guesswork' and enable 'more rational policies' (Toraason et al. 2004) that are expected to reduce uncertainty and to increase efficiency by 'limiting the necessity' for precaution. Thus, EGP representatives argue for a separation of science and policy and for the primary role of science, a paradigm which has been questioned by STS: Science policy studies consider risk analysis, assessment and management rather as a continuum and as a political process. In this context, the concept of the precautionary principle has been proposed in order to deal with the involved uncertainties. Which discursive effects do the renewed shifts towards 'more rational politics' with the new genetics—which again evoke the authority of rational science for regulation—implicate?

In December 2004, the US Environmental Protection Agency (EPA) published a *Genomics Task Force White Paper* outlining regulatory applications of genomics in two main fields: toxicity assessment and human health risk assessment, the latter being mainly concerned with the incorporation of individual susceptibility into risk assessment. Despite the uncertainties stressed in most epidemiological papers which clearly state that populations testing is 'premature'—EPA emphasizes the importance of mechanistic insights and uses the concept of individual genetic susceptibility in a rhetoric of cost-effective management. The EPA paper anticipates that dose-response assessments will be improved and expects that this will lead to more rational, optimized and cost-effective measures, since less conservative (and less precautious) extrapolations 'may be sufficient' for some environmental risks. How is the consideration of susceptibility differences envisioned in the context of the regulation of chemicals? The EPA paper provides two examples—one concerned with labelling industrial chemicals, the other one with clean-up measures at contaminated sites:

> If genomics technologies are successful in identifying populations susceptible to specific pesticides or industrial chemicals, product labeling will probably be necessary. For example, labels might include warnings for particular populations known to exhibit higher frequencies of an at-risk genetic polymorphism. The pharmaceutical industry already includes warnings to susceptible populations on drug labels (EPA 2004, 26).

It is the 'subgroup-specific risks' in 'particular populations' that are now targeted by a genomics informed risk assessment as to environmentally associated disease. This includes the computation of specific probabilities for subpopulations of so-called slow metabolizers—a group brought into being by genetic micro-array tests.[6] However, predictions are being made even without genetic tests based purely on known allele frequencies in population subgroups, e.g. as construed for different ethnic backgrounds.[7] In this context, the category 'ethnicity' is often used as a proxy for genetic make-up. Similar arguments are used when it comes to negotiating remediation and environmental clean-up of contaminated sites:

> If, for example, a genomics study were to identify a susceptible population at risk due to exposure to a contaminant at a Superfund site (hazardous waste clean-up site) through a correlation of genomic analysis of local populations and measured or expected exposure levels, the Agency might choose to reduce the RfD/RfC[8] value and propose more strict remediation measures. This, of course, presupposes an established linkage of the genomic endpoint and an adverse effect. Use of new genomics tools could, however, limit the extent of remediation measures by more accurately predicting the potential for exposure of the sensitive population. Thus, genomics tools may play a key role in determining intensity and extent of clean-up practices and have large implications for time and cost of such procedures (EPA 2004, 26).

As the terms of negotiation of environmental justice are changing towards genomic levels, these resources and technologies are needed by local agencies to engage in environmental justice (cf. EPA 2004, 44). Will this lead to more and new inequalities or to a different understanding of 'environmental justice' that takes into account genetic susceptibility? US EPA considers populations with proven susceptibility to be entitled to a higher degree of clean-up, whereas non-susceptible people are assumed

to be able to live with a certain exposure at the same degree of disease risk.[9] Will this—justified by increased efficiency—keep environmental measures to a minimum? As this debate is moving away from the precautionary principle towards a system of optimization, cost effectiveness and evidence-based prevention, associated political struggles in this biosocial space can be expected to centre on the burden and modes of proof. How will oppositional strategies, for example by environmental health activists, NGOs and patient groups be affected by these changes? Environmental activists increasingly make use of genetic susceptibility data to argue for zero-risk or for specific clean-up measures. This is also the case for Multiple Chemical Sensitivity (MCS) patient groups whose bodily conditions have not been recognized by biomedicine and who use concepts of genetic susceptibility in line with 'metabolic diversity' or 'biochemical individuality'. Here, the term individualization is used in order to argue for diversity to oppose standardization and generalization and to create a space for diversity within biomedicine. Yet, at what 'costs' can individual genetic susceptibility be used to legitimize bodily experiences that are currently not accepted by biomedicine? Genomics shapes not only society but also individual and collective strategies both of health governance as well as on the level of oppositional strategies. A genomics-informed biological citizenship (Petryna 2002; Rose & Novas 2004) may emerge or, in terms of Didier Fassin, 'biolégitimité' (Fassin 2000) becomes a core social feature, along which health and disease are classified and new biosocial segregations are based on biological data.

'Biosocial' effects of the 'environmental genomics' discourse

Susceptibility profiling constructs and performs differences between and within populations and individuals which then restructure social relations: In the context of occupational medicine, susceptibility reasoning tends to shift the responsibility towards the exposed worker by localizing the 'problem' in the exposed individual rather than in unsafe working conditions. With the new concepts, the point of reference for prevention strategies is about to change. Equality—and equity—are replaced by a differential system of who is to be protected to what extent in order to

achieve just distributions of risk. 'High risk' groups are constructed as 'in need for protection' from environmental exposures or as to be given advice for better self management in order to compensate for susceptibility, for example by avoiding other risk factors.

The examples I have provided display some of the multiple biosocial negotiations pursued by many actors (governments, environmental activists, patient groups) albeit with different political agendas. Environmental justice conflicts enter a new site of negotiation with the genomic data used to prove or disprove exposure, effect and susceptibility.

The new genetics have moved from genetic determinisms to a contested site of negotiation concerning inequality, diversity and justice. When environmental regulation is discussed in the light of individual susceptibilities, environmental hazards appear to be re-negotiated within our bodies and become subject to (bio)medicalization and *in vivo* management. The rhetorics of environmental genomics ('adaptive response', 'oxidative stress', 'epigenetic stress') appear to recast the environment as a biomedicalized space within human physiology.

In describing the stabilization of scientific knowledge, my aim was to unfold the scientific hybridization of genomics in the context of a field that was previously viewed as representing perhaps the 'other' than the gene in the gene-environment dichotomy, i.e. the role of the environment as to health. What has been understood as genetic for a long time, is being reconfigured: individual (genetic) constitution is conceptualized as co-shaped by the environment—for example in the concept of embodiment (Krieger & Davey Smith 2004). The old dichotomy appears to be taken over by a genetification that is itself becoming increasingly complex while it is used in environmental health with different political agendas.

Epilogue: symptomatic metaphors

The debate on genes and the environment is a site of multiple negotiations, where genes and environments can take the shape of pieces of evidence or of a culprit in a crime scene or are described in narratives of loaded guns and triggers mutually reversing the blame for harm:

> The relationship between genes and the environment can be compared to a loaded gun and its trigger. A loaded gun in itself causes no harm; it is only when the trigger is pulled that the potential for harm is released. Genetic susceptibility creates an analogous situation, where the loaded gun is one or a combination of susceptibility genes (alleles) and the trigger is an environmental exposure (Olden & Wilson 2000, 149).

These metaphors are also indicative of a new mode of evidence generation and of what can count as 'evidence' in public health in the age of biotechnology. While the concept of genetic susceptibility—or 'metabolic individuality'—is working in an 'economy of promises' (Fortun 2000), of scientific progress, new therapeutics, valuation of diversity and better health, it brings about new frameworks for public health interventions and prevention. Public health genetics on a population level tends to privilege individualized risk management over other options for primary prevention—such as exposure reduction.

Notes

1 See Websites of the Environmental Genome Project (http://www.niehs.nih.gov/envgenom/home.htm) and Coriell Institute (http://ccr.coriell.org/), accessed: 31.10.2005.

2 The 'HapMap Project' is a large-scale multinational project studying genomic diversity performed by a research consortium based in the US, Canada, UK, Nigeria, China, and Japan, http://www.hapmap.org/index.html.en, accessed: 31.10.2005.

3 In the late 19th century epidemiology's primary focus was on infectious diseases (bacterial and viral agents) and the etiological concept comprised the agent, the host and the environment. 20th century 'modern epidemiology' experienced an extension towards general determinants of (chronic) 'disease'. Since the 1960s, 'multiple causation' has constituted the paradigm of risk factor epidemiology (web of causation). By the end of the 20th century, postgenomic epidemiology is increasingly serving as a tool for molecular biology (Bauer 2004).

4 It should be noted that—apart from differentiations for genetic profiles—there are on-going efforts to develop risk estimates not only for a 'standard human', but also for different age groups and for differences ascribed to gender.

5 With the 'epidemiological gaze' I make reference to the Foucauldian notion of the 'clinical gaze' (Foucault 1973).

6 See http://www.roche-diagnostics.com/media/pdf/presskit/final_technology_behind_cyp450.pdf (accessed: 31.10.2005) for a (pharmaco)genetic test approved in the European Union.

7 Cf. http://www.niehs.nih.gov/envgenom/abstract/r01-6717.htm, http://www.niehs.nih.gov/envgenom/abstract/p01-5622.htm, accessed 31.10.2005.

8 Reference doses: RfC: Inhalation Reference Concentration, RfD: Oral Reference Doses.

9 Contrary to EPA, no documents dealing with the implications of genomics for health risk assessment were available at the European Environmental Agency. In the German context, the issue of susceptibility is mentioned, yet referring to life stage and specific susceptibilities of children and the elderly. So-called life stage susceptibility windows are considered in terms of different ages in regulation, but genetic susceptibility is not an issue in regulation so far. However, European researchers increasingly draw on the genomic data mentioned in this article. A study issued by the German Friedrich Ebert Stiftung on Public Health Genetics pointed out the importance of this field (Brand et al. 2004).

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