Genetic Susceptibility and the Setting of Occupational Health Standards*

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Abstract

As more is learned about genetic susceptibility to occupational and environmental hazards, there will be increasing pressure to use genetic susceptibility information in setting occupational health standards. Historically, this has not been done, but a growing body of research assesses inherited genetic factors as modifiers of the effects of hazardous exposures. Additionally, acquired genetic and epigenetic characteristics could also be used in standard setting. However, for both inherited and acquired genetic characteristics, many scientific, ethical, legal, and social issues could arise. Investigators need to examine the potential role and implications of using genetic information in standard setting. In this review, we focus primarily on inherited genetic factors and their role in occupational health standard setting.

INTRODUCTION

The role of inherited genetic factors in the variation in biological response to occupational and environmental hazards has been described extensively, but to date such factors have not been used to protect workers by incorporation into standards and regulations. Genetic advances may improve risk assessments and push at the historical boundaries of the Occupational Safety and Health Act of 1970 (OSH Act), which mandates standards and regulations to assure "that to the extent feasible . . . no employee will suffer material impairment of health and functional capacity. . . ."

Historically, owing to economic and technological feasibility constraints, persistence of residual risk even after an occupational standard is adopted, and lack of consideration of genetic information in risk assessments, the OSH Act has not completely protected the American workforce, particularly those workers who could be defined by certain genetic polymorphisms as hypersusceptible. However, the U.S. Supreme Court has rejected the notion that the OSH Act requires regulation at the zero-risk level (21, 40). The Occupational Safety and Health Administration's (OSHA) health standards have not been developed with explicit concern for individual variability in response to hazardous substances. Rather, OSHA bases the standards on the assumption that substantially all employees are at a similar risk (40).

To date, no one has comprehensively examined the potential role and implications of genetic information in determining occupational exposure limits (OELs) within occupational standards. Most of the published literature on the role of genetics in occupational health has focused on discrimination, privacy, control of genetic information, use in research, or job placement, or in apportioning causation (31). This article examines the use and implications of genetic information in occupational standard setting, and it addresses the utility of developing occupational health standards based on data relating to the effects of occupational and environmental exposures on genetic material.

Inherited genetic factors: genes or genetic information transmitted between generations

Genetic polymorphisms: variation in a single nucleotide with a frequency greater than or equal to 1% in a population

OSHA: Occupational Safety and Health Administration

Occupational exposure limits (OELs): workplace atmosphere concentration levels for a specified time period that would not result in adverse health effects

Quantitative risk assessment (QRA): a methodology that evaluates and derives the probability of an adverse effect of a hazardous agent using hazard identification, exposure response assessment, and risk characterization

THE HISTORICAL APPROACH TO OCCUPATIONAL STANDARD SETTING

The historical approach to setting OELs has involved investigators observing workers as well as conducting laboratory and animal studies. The process reviewed human or animal studies to identify the highest dose of a substance that did not cause an adverse effect. This result is known as the no observed adverse effect level (NOAEL). To address uncertainty in the extrapolation of results from animals to humans or to account for the most sensitive people, a set of safety factors (e.g., dividing the NOAEL by 10) was applied. This approach was based on the assumption that if exposure to a chemical was kept below some concentration (referred to as the threshold dose) then no adverse effect would be observed. More recently, the benchmark dose (BMD) has been used in risk assessments. The BMD is defined as the maximum likelihood estimate of exposure that provides some low level (often 10%) of risk derived from a statistical model. The BMD is preferred over the uncertainty of the safety-factor approach for noncarcinogens because it utilizes all the dose-response data and provides a method to develop risk-based exposure limits (33).

The use of epidemiologic data in standard setting has increased since the 1970s, and some scholars have argued that uncertainty surrounding the exposure estimates for epidemiologic data is generally much smaller than uncertainties surrounding the extrapolation of data from animal studies to predicting human risks (47). However, when using epidemiologic data, many potential sources of uncertainty do exist, such as confounding, sample size, selection biases, and multiple exposures (48).

The foundation of contemporary occupational and environmental standard setting is quantitative risk assessment (QRA). The approach to QRA is generally based on two U.S. Supreme Court cases and the National Research Council (NRC) publication, *Risk Assessment in the Federal Government: Managing the Process* (32). The NRC publication identified

four major steps of risk assessment: (*a*) hazard identification, (*b*) dose-response assessment, (*c*) exposure assessment, and (*d*) risk characterization. The U.S. Supreme Court's Benzene (21) and Cotton Dust (1) decisions set forth a three-step determination that is required to promulgate a new exposure limit: (*a*) that it is more likely than not that a significant risk of harm exists at the present level of exposure, (*b*) that it is likely that a proposed new standard will result in increased worker protection, and (*c*) that the new standard is technologically and economically feasible in the industry. These decisions encouraged the use of QRA in setting occupational exposure standards in the United States (43).

OSHA's health standards generally have not been developed with an explicit concern for individual variability in response to occupational exposures. Rather, OSHA standards have been based on the assumption that all exposed workers are at similar risk (40). To date, all risk assessments used in setting occupational standards have been based on research that, for the most part, did not involve genetic data because there was very little such research conducted from 1970 to 1990. In the 1990s, researchers began to conduct various cross-sectional and case-control studies that identified individual genetic polymorphisms, but large data sets applicable for risk assessment had not yet been developed (16, 51). Since the 1990s, more studies of occupational exposure and genetic factors have been conducted, but they have not been used in QRA.

ROLE OF GENETICS IN THE VARIABILITY OF RESPONSE TO OCCUPATIONAL EXPOSURES

Genetic factors can contribute to the variable responses of workers to occupational hazards—particularly chemical hazards and some biological and physical agents (**Table 1**) (3, 7, 10, 31, 35). Workplace exposures to chemical and physical agents are increasingly being controlled to lower concentrations, but workers with susceptible genetic profiles may still be at higher than average risk. A growing body of published evidence has shown that genetic polymorphisms are indicators of varying risk for occupational disease in exposed workers (2, 5, 7, 16, 22, 31, 34). Advances in genetic technologies have been useful in studies of occupational disease and chemical exposures, especially in understanding mechanisms and modes of action. For example, the ability to conduct analyses of whole genomes through

Table 1 Examples of occupational exposures shown to be influenced by genetic factors. Adapted from Reference 31

Exposure	Genetic factor	Disease
Beryllium	HLA–DPB1	Chronic Beryllium disease
Aromatic amines	NAT2, GSTM1	Bladder cancer
Ethylene oxide	GSTT1	Leukemia
Asbestos	NF2, NAT2, GSTM1	Mesothelioma
Benzene	CYP2E1, NQO1	Hematotoxicity
Ionizing radiation	XRCC1, XRCC5	Meningioma
Lead	ALAD	Lead toxicity
Organophosphate pesticides	PON1	Acute toxicity; respiratory effects
Silica	TNF–α	Silicosis
Chromium	SP–B	Lung cancer
Noise	AH1	Noise-induced hearing loss
Dusts, fumes, gases	α_1-antitrypsin	Respiratory disease
Electromagnetic fields	BRCA2, AR, CYP17	Male breast cancer
Aromatic, nitro, amino compounds	G6PD	Hemolytic anemia

Exposome: the environmental exposure from conception onward (including exposures from diet, lifestyle, work, and endogenous sources) that influence the etiology of disease

such approaches as whole genome analysis and genome-wide association studies (GWAS) may enhance studies of gene-environment interactions but only to the extent that environmental (occupational) data are included. The awareness of the need for environmental data to complete the gene-environment analysis is now being targeted with new vigor with the articulation of the "exposome" to balance the genome (24, 28, 29, 37, 52, 54). Detecting genetic polymorphisms can also begin to identify susceptible subgroups in exposed populations, but whether individual polymorphisms will be useful discriminators of at-risk populations is still a question. This is because most diseases involve a complex system of gene pathways that generally cannot be represented by a single gene polymorphism. However, if a single gene characteristic or specific constellation of gene characteristics can be linked to increased risk in various populations within the workforce, could and should these characteristics be used as the basis for OELs or other risk-reduction components of occupational standards?

Another potential role for genetics in standard setting pertains to the design of physical environments and the goal of providing working conditions that protect all workers (36). For the most part, literature on the issue has focused on how people respond to noise, vibration, heat and cold, air quality, and light, and it concentrated on physiological and behavioral factors. Genetic factors might also be included with these considerations in the development of future standards.

THE USE OF GENETIC INFORMATION IN QUANTITATIVE RISK ASSESSMENT

QRA involves the evaluation of exposure and response data to identify levels of risk and safety at which limits can be set. Using genetic data may improve understanding of the risks of various levels of exposure. Also, many commentators have identified the importance of using mechanistic data in risk assessments (18, 35, 37, 42), and genetic data are part of the mechanistic information that can be used. Genetic information has also been useful in extrapolating from animals to humans (15, 30, 53).

QRA is the foundation on which OELs are developed in the United States, but this approach generally has not been applied to studies involving genetic polymorphisms. Many (if not all) genes that code for enzymes that metabolize occupationally relevant toxicants are polymorphic (18). A good example of the utility of genotype data in risk assessments is dichloromethane (DCM), a substance widely used in industry for degreasing metal. Lung and liver tumors have been observed in mice exposed to DCM by inhalation (13). The role of polymorphisms in genes encoding for DCM-metabolizing enzymes, such as CYP2E1 and GSTTI, was recognized as integral to the development of tumors in experimental animals (45, 46). David et al. (13) provided the most recent QRA of DCM inhalation exposure for the general population using a state-of-the-science probabilistic methodology, improved metabolic parameters for CYP2EI and GSTTI activators, and improved physiological parameters. The researchers found that the unit risk was reduced by a factor of more than 100 from previously published risk assessments. The question of the degree to which polymorphisms increase human variability in toxic response, while widely discussed, still is not well characterized (18, 22).

Also many of the concerns with QRAs stem from uncertainties in cross-species and other extrapolations, which are handled with default assumptions. Data about genetic characteristics may be useful to address such default assumptions. Mechanism-based modeling has the potential to decrease uncertainties across and within species and exposure scenarios, and it could quantify pathways and complex relationships within gene networks. Curran et al. (12, p. 755) noted that extrapolation in risk assessment presented two potential problems: "[I]f the risks are underestimated, the OELs may not provide sufficient protection for the most

susceptible workers. If the risks are overestimated, the resulting OELs may affect the economic viability of the workers' employer without providing a commensurate benefit in return." Gentry et al. (18) identified the minimum data needed to conduct a chemical-specific analysis of the effects of a polymorphism on tissue dose:

1. Well-characterized metabolic pathway, with relevant isozyme identified for all major steps;
2. Allelic frequency data available for all major polymorphic enzymes,
3. Phenotype data for the chemical of interest for each major variant allele, and
4. Existing physiologically based pharmacokinetic (PBPK) model or development of an adequate model to describe polymorphism data.

Not all genetic polymorphisms make significant contributions to the variability of the tissue dose of a toxicant. For example, Gentry et al. (18) showed that polymorphisms in the *PON1* gene that gave risk to allelic variants of paraoxonase, which is involved in the metabolism of paraoxon (a metabolite of the insecticide parathion), make only a minimal contribution to the variability of paraoxon tissue dose. In contrast, polymorphisms in the *CYP2C9* gene, which give rise to allelic variants of the major metabolic enzyme for the rodenticide warfarin, account for a significant portion of the overall (s)-warfarin tissue dose.

OCCUPATIONAL EXPOSURE LIMITS

We currently have no examples in which OELs have been based on genetic characteristics or risks in a population subgroup. Nor do we have an example of one OEL for the general working population and a different OEL for a genetic subpopulation. Nonetheless, studies have suggested risks below established OELs for significant numbers of workers. Examples include exposure to substances such as benzene, ethylene oxide, polycyclic aromatic hydrocarbons, beryllium, manganese, and silica. See *Genetics in the Workplace—Implications for Occupational Safety and Health* (31) by the National Institute for Occupational Safety and Health (NIOSH) for an overview. As new genetic data are applied to risk assessments, the policy judgments involved in standard setting will become more complicated. For example, the concept of a single threshold delineating safe from unsafe levels of noncarcinogens will become increasingly difficult to support as new genetically susceptible groups are identified. If evolving genetic science supports regulation at doses approaching background regulation, standards that depart from the science may need to be justified on social policy grounds (19). If it is not feasible to control risks to background levels, there may be pressure to invoke cost considerations as the reason why various genetically defined subgroups may not receive maximum protection.

The establishment of a recommended level of exposure with some margin of safety is an important aspect of QRA. In the occupational field, the historical approach involved the use of uncertainty factors to account for cross-species and interindividual variability. Genetic factors could be used to address uncertainties and provide more precise risk assessments and to identify specific subgroups with different risks.

The availability of more extensive genomics data is likely to invigorate the debate over the relative merits of health-based and technology-based standards (19). Health-based standards solely utilize risk of adverse effects (and adjustment for uncertainties) as the basis, whereas technology-based standards include consideration of technological feasibility and economic impact. OSHA standards are currently technology based, whereas NIOSH recommendations are more health based, although they include some feasibility considerations such as the availability of an analytical method to assess exposure. New genomic information may allow for more precision in risk assessments and less use of default assumptions to address uncertainties pertaining to extrapolation from animals to humans as well as in the identification of population subgroups at higher risk.

Toxicogenomics, metabolomics, proteomics, transcriptomics: technologies used to study the impact of agents on multiple genes or their expression

Hence, health-based standards could become even more protective than technology-based standards. Substituting direct biological measurements for arbitrary defaults may permit protection of vulnerable worker groups while avoiding over- or underregulation (12, 19, 33).

Determining the role of genetics in occupational health standards may be illuminated by assessing how genetic information has been considered for use in the regulation of air pollutants (11, 26, 27). An EPA report, *Interim Policy on Genomics* (49), described the potential of genetic information to enhance assessments and better inform the decision-making process. The U.S. Clean Air Act explicitly guarantees the protection of sensitive human populations from adverse effects associated with air pollution exposure. Kramer et al. (26) explored the extent to which genomic information has the potential for use in setting health-based air pollution standards directed at protecting susceptible subpopulations. Using the case of particulate matter and asthmatics, investigators identified a number of important issues in the risk assessment process, including using genetic information to improve sensitivity analysis. However, the Interim Policy on Genomics states that "while genomics may be considered in decision-making at this time, these data are insufficient as a basis for decision-making and will be considered on a case-by-case basis" (26, 49). Kramer et al. (26) also identified regulatory criteria for for identifying key asthma genes. These criteria may be applicable more generally when considering genetic information for regulatory purposes. Criteria include the following:

1. The gene product must be relevant to the pathophysiology of a clearly defined and consistent phenotype.
2. Gene function must be associated with exposure to a regulated pollutant or, at the very least, to a disease-progression process known to be associated with exposure to the chosen regulated pollutant.
3. The mutation must be functionally relevant.
4. The magnitude of frequency of occurrence in the population must be measured, and variation across populations (e.g., geography, race) must be considered.
5. There must be a high magnitude of association (i.e., preferably a relative risk >1.5) to an adverse health effect for the phenotype of interest.

Although the authors infer that these five points generally refer to studies in humans, animal data may be used when their relevance to humans has been established. Kramer et al. (26) also highlighted that with many complex diseases multifactorial considerations are necessary when developing epidemiologic studies. Many of the early phases of genetic association research in human populations showed poor replication of results (23). More recently, the funding of large studies with more statistical power and control of confounders (8, 9) has been advocated to validate genetic expression.

USING INFORMATION ON THE EFFECTS OF ENVIRONMENTAL EXPOSURES ON GENETIC MATERIAL

Many of the -omic technologies [toxicogenomics, the study of changes in the expression of numerous genes or gene products due to toxicant-induced exposures; metabolomics, investigation into the genetic underpinnings of metabolism; proteomics, the study of the full complement of proteins required for the structure and function of an organism, and transcriptomics, the study of the full complement of DNA transcripts (RNA molecules) required for the structure and function of an organism] generally represent acquired genetic effects. Hence, these technologies enhance the specific focus of genetic monitoring as a subset of the broad area of biological monitoring. In genetic monitoring, investigators aim to assess the impact of environmental or occupational risk factors on a person's somatic or germ cell genetic material. Genetic monitoring has many of the same strengths and limitations of toxic-effect monitoring, such as assessing blood lead, carboxyhemoglobin, or liver function

assays (44). In terms of standard setting, -omics data could be used as end points in QRAs once such data were validated as predictors or surrogates of disease or disease risks (6). The line between inherited and acquired genetic effects has always been blurry because even if genetic effects (e.g., mutations) are linked to specific exposures, they, as well as all types of biologic effects, are conditioned by host genetic effects that regulate absorption, metabolism, and excretion of xenobiotics.

Moreover, the line is further blurred by findings from the relatively new field of epigenetics. Epigenetics links environmental and genetic influences on the traits and characteristics of a person. Although the epigenetic hazards do not change the genetic code per se, they impact the genetic sequence, which in turn affects whether, when, and how specific segments of the genetic code are activated or expressed. The relationship between the genetic code and epigenetics has been characterized as the relationship between computer hardware and software: The genetic code is the hardware, but epigenetic information may be analogized as parameters for operating the software (14, 41). Epigenetic changes may also be passed from the exposed generation to subsequent generations. Toxicogenomics and epigenetic data may also obscure the line between health and disease (19). If these data are used as end points in risk assessments, criteria will be needed for when they are valid end points. Ultimately, both inherited and acquired genetic effects may play a role in standard setting, particularly in terms of defining the shape of the dose-response relationship at low exposures and the use of data rather than default assumptions to determine or eliminate some uncertainty factors (10, 50).

ISSUES AND IMPLICATIONS

Considerations for the use of genetic information in the occupational health standard setting:

- The technical basis for considering a genetic factor in standard setting is whether the genetic factor is a major effect modifier or describes a significant occupational exposure-disease association. In addition, the magnitude of the genetic effect is important. The size of the population attributable risk (PAR) for the genetic factor is likely to indicate the extent that it affects a significant fraction of the disease incidence in question. A genetic factor that does not represent a significant PAR may not be a useful candidate for setting an occupational health standard. For some genetic factors, both absolute and relative risks to individuals who have these factors will be high, but the PAR is small. In contrast, other types of genetic factors confer modest absolute and relative risks to relatively large numbers of individuals, and the PAR is high (5). However, it does not take very many genetic variants with weak-to-moderate effects to combine to form a sizeable PAR (55).

Issues in complying with occupational standards based on genetic factors:

- If an occupational standard is set using genetic information, numerous questions arise when risk managers attempt to comply with the standard. Would there be a need for specific risk communication to workers with, and workers without, the genetic factors? Genetic standards could raise questions among workers or employers about who had the genetic factor and who did not. Would an employer have the responsibility to provide worker genetic testing for the factor (4)? Would employers have to inform workers that other genetic risk factors not specified in the standard might play a role in occurrence of the health effect at issue in the standard? Additionally, it is not clear which compliance measures employers must take to protect the health of employees who, because of their genetic factors, do not receive sufficient protection under the relevant OSHA standard (39). As Rothstein (40) noted, "In the

Genetic susceptibility: an inherited genetic propensity that increases an individual's risk of an adverse effect from exposure to an exogenous agent or for disease

PAR: population attributable risk

> Benzene case, the Supreme Court arguably support[s] additional precautions when it upholds the principle of 'action level' medical testing. . . . [A]ccording to the Court, testing employees exposed at an action level below the permissible exposure level 'could ensure that workers who were unusually susceptible. . .could be removed from exposure before they suffered any permanent damage.'" Although the Genetic Information Nondiscrimination Act of 2008 (GINA) (17) prohibits the use of genetic information to discriminate in hiring, firing, compensation, or other terms and conditions of employment, applicants for jobs in which there is established scientific evidence of genetic variability in response to substances in the workplace may need to be offered optional genetic testing through independent physicians and laboratories, and the results disclosed only to the individuals (40). Section 202(b)(5) of GINA expressly permits employers to offer optional genetic monitoring to detect effects of exposure, but there is no comparable provision permitting employers to offer pre-exposure genetic testing to determine whether an individual may have increased risk (e.g., from beryllium exposure).

Ethical and institutional parameters of using genotype variation in risk assessments must be considered:

- Including genetic information in risk assessments may make standards based on those risk assessments more protective than those without them. However, there is a danger that the genetic risk analysis will be inhibited by the tendency to favor it as the sole explanation for occupational disease rather than occupational exposures. Once standards are set with genetic components, would they signal that it was appropriate for employers or employees to utilize genetic information in workers' compensation proceedings or tort lawsuits (38)? With regard to workers' compensation, this would represent a change from existing laws under which an employer would take the worker "as is" (38).

Stigmatization and discrimination could result:

- Occupational standards set using genetic information would protect the entire workforce and particularly those with a genetic susceptibility factor. If it becomes necessary to identify individual workers who are susceptible, would such workers be candidates for stigmatization and discrimination? How would such workers be protected?
- Hansson (20) has asked whether every exposed person, including the most sensitive people, should be protected, rather than basing protections on the population average. Two approaches to protecting a group have been identified: (*a*) special standards for the group (differentiated protection) and (*b*) general standards strict enough to protect all its members (unified protection). Hansson identified six major factors that are relevant for choice between these two strategies: (*a*) difference in the risk, (*b*) costs of abatement, (*c*) identifiability of sensitive individuals, (*d*) privacy, (*e*) social exclusion, and (*f*) previous discrimination.

CONCLUSION

We do not know to what extent, if at all, future occupational health standards will be developed to take advantage of the genetic variability that influences disease occurrence in workers (40). However, as more research identifies genetic factors as effect modifiers of significant occupational exposure-disease associations, it seems likely that risk assessors will include this information in risk assessments. Standards based on those risk assessments would include genetic information, directly or indirectly.

In terms of epigenetic effects, which were identified in this article but were not its main focus, it is likely that when validated, they too

could be used as end points in risk assessments and, ultimately, in standards. If genetic variability is to be considered in risk assessments and occupational health standards, it will be important to have criteria for how that analysis will be accomplished and to consider the implications. Use of genetic information in standards may signal to society that other societal actions such as workers' compensation, litigation, and job placement may have a genetic basis as well.

Although using genetic information in occupational risk assessments and health standards may better protect the entire workforce at the level of workers' genetic constitution, we should avoid the simplistic view that genetic (or epigenetic) factors are the primary cause of occupational disease (25). Clearly, this is not the case; occupational exposures are the primary cause of occupational disease and will remain the responsibility of the employer to control. Genetic information, however, is likely to be a useful tool for increasing the precision of risk assessments and the protectiveness of occupational health standards.

DISCLOSURE STATEMENT

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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