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Public health assessment of genetic information in the occupational setting

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Genetic information is information about genes, gene products, or inherited characteristics that may derive from an individual or family member (1). In the workplace, genetic information is usually the product of genetic screening or genetic monitoring, but may also be derived from a person's medical record. This chapter examines the use of genetic information in the occupational safety and health field in terms of practice, research, and regulation (see Table 11.1). In occupational health practice, *genetic monitoring* of workers exposed to various toxicants is analogous to biological monitoring for the presence or effects of any toxicant. Here the issue is to use genetic material or somatic or germline DNA to assess whether exposures or health effects are likely to have occurred. *Genetic screening*, in contrast, is rarely practiced but is aimed at identifying an asymptomatic person with a particular inherited genetic characteristic who is likely to develop a health effect related to work. For the most part, genetic screening related to occupational diseases involves hereditary characteristics that have an influence in conjunction with a particular exposure but which do not confer a risk on their own. At the present time, little scientific evidence has been found to support a link between unexpressed genetic factors and a person's ability to perform job functions. From a public health perspective, genetic monitoring and screening raise very different issues (2,3).

Genetic monitoring has many of the same strengths and limitations of any type of toxic effect monitoring such as assessing blood lead, carboxyhemoglobin, or liver-function assays. In these situations, the genetic effect must be validated for the exposure or disease—that is, the relationship between the genetic effect and exposure or disease must be known before it is used. Moreover, as with all monitoring, attention needs to be given before the

Genetic monitoring is ascertaining whether a person's genetic material has been altered over time, thus indicating exposure or providing an early warning of possible health effects. Using changes in genetic materials as exposure indicators has been well studied (15,16). Not only has genetic monitoring been used to assess damage from occupational exposures, but also from other environmental exposures and lifestyle habits such as smoking. The benefits of a monitoring program include (*1*) identifying a risk for the exposed group as a whole or for individuals; (*2*) targeting work areas for evaluation of safety and health practices; and (*3*) detecting previously unknown hazards—thus possibly decreasing health costs for employers, insurance companies, and society in general. In an Office of Technology Assessment survey conducted in 1989 of Fortune 500 companies, only one company reported currently conducting genetic monitoring (2). Five companies reported past use of genetic monitoring and two companies reported future consideration of genetic monitoring.

Ever since the late 1980s, an exponential increase in knowledge about human genetics has occurred because of the rapid progress of the Human Genome Project and technological advances in molecular biology techniques. An increase in the recognition of genetic factors in disease may present many new opportunities for prevention, detection, and treatment of occupational diseases. Adverse health effects have been associated with mutagenic toxic agents (17). These mutations occur at a significant rate above normal background levels. The relationship among genetic damage, mutation, and cancer is becoming clearer. Several types of genetic damage such as mutations and chromosomal aberrations have been associated with various cancers and tumor development in somatic cells. Most research has focused on somatic cell changes. Effects in germ cells are harder to decipher because such effects may not be seen for several generations.

Many different techniques exist for genetic monitoring. Changes can be detected on the molecular or chromosomal level by measuring DNA adducts, mutation levels, sister chromatid exchanges, micronuclei formation, DNA stability, and chromosome aberrations. At the molecular level, DNA adducts have shown much promise. Most initiating carcinogens or their metabolites can bind to DNA bases or other macromolecules forming adducts. Adducts related to the carcinogen can be measured in tissues, exfoliated cells, peripheral blood, and urine (17). A disadvantage of using adducts as a monitoring tool is that adducts are usually measured in a surrogate tissue rather than the target tissue. In addition, DNA adduct levels are dynamic, changing with various Phase I and Phase II enzyme activities, DNA repair, cell turnover, and the chemical stability of the adduct itself.

Somatic mutations in reporter genes may also have potential for genetic monitoring and have been shown to increase after exposure to toxic agents (18). Two of the most widely studied are glycophorin-A (GPA) and hypoxan-

thine phosphoribosyltransferase (HPRT). Glycophorin-A is a glycoprotein on the membrane of red blood cells. It is a polymorphic gene (M and N alleles) with 50% of the population being heterozygous. The assay measures the frequency that the M form is not expressed on red blood cells in a heterozygous person (19). The HPRT mutants can be selected, since cells with normal HPRT activity are susceptible to cytotoxicity by 6-thioguanine. These assays are highly sensitive but lack specificity for selected exposures. The relevance of these mutations to cancer is not known, but they may serve as a sentinel event for carcinogenesis.

Sister chromatid exchange (SCE) involves the breaking and rejoining of similar matching segments of DNA so that the function and viability of the cell is not compromised. The SCEs have been shown to be most useful in assessing exposure for carcinogens that form DNA adducts that are easily detected in peripheral blood (15). However, a relationship between SCEs and a health effect has not been established, thus limiting their usefulness as predictors of health risk.

Micronuclei are small fragments of DNA or chromosomes apart from the main nucleus. They indicate previous chromosomal aberrations (CAs). Micronuclei can be assayed in peripheral blood lymphocytes and in exfoliated cells from buccal mucosa and the urinary tract (19). The advent of fluorescence in situ hybridization (FISH) technology for detecting micronuclei formation will increase the speed, specificity, and sensitivity of this assay (20).

The CAs include the breaking and rearrangement of parts of chromosomes. Many different types of toxic agents can cause formation of CAs and can be used as a general biological marker to document exposure (15). As with micronuclei, FISH technology has revolutionized this assay, increasing the speed of analysis, efficiency of the assay, and improving its sensitivity (19). Of the three cytogenic markers—SCEs, micronuclei, and chromosomal aberrations—only the aberrations have been shown to be group risk factors for cancer (21,22).

Two other assays evaluate DNA stability. The first is the single-cell gel electrophoresis assay (COMET), which detects low molecular weight DNA as a result of DNA strand breaks. Advantages to this assay are (*1*) it is on the individual cell level; (*2*) any cell population can be used; and (*3*) the assay is sensitive, simple, and cost-effective (23). Another DNA stability assay that may have potential for genetic monitoring is the DNA repair assay (Challenge assay) (15). This assay is based on the premise that cells exposed to hazardous agents may be compromised in their ability to repair further insult to their DNA. Cells previously exposed to environmental agents are challenged a second time by exposure to radiation in the G_0 or G_1 phase of the cell cycle. Cells with higher levels of CAs are not able to cope with the challenge.

For genetic monitoring (as with any biomonitoring) to be useful in the workplace it should be considered within the traditional hierarchy of controls and

integrated with the other elements of health and safety programs. The hierarchy of controls establishes primary prevention by substitution and source of exposure controls before secondary or tertiary prevention. Exposure controls can be evaluated by genetic monitoring for biomarkers of exposure or exposure effects or by ambient and breathing zone monitoring. These biomarkers can also be sources of risk estimates that can be used along with morbidity and mortality statistics. If genetic biomarkers are to be useful in the workplace, they need to meet a minimum criteria, as shown in Table 11.2. Various medical surveillance requirements are included in 17 Occupational Safety & Health Administration standards, but only three of these (those for arsenic, lead, and cadmium) require specific medical monitoring; none require genetic monitoring.

Before using genetic biomarkers in monitoring workers, a plan should be in place to determine what will happen to workers with results in the extremes of the distribution of results (2,8,14). Will there be repeat monitoring, diagnostic evaluation, environmental remediations, or medical removal? One concern by critics of genetic monitoring is that the resultant action will focus only on the worker and not on changing the environment (2). Clearly, both types of actions may be warranted. The hierarchy of controls and the principles of the OSHA legislation require emphasizing changing the workplace environment by process modification, engineering controls, and, in some cases, personal protective equipment. However, a person with genetic monitoring results in the extremes of the distribution of group results may need further assessment and follow-up actions. Because many genetic markers can be influenced by nonworkplace exposures, genetic monitoring should be accompanied

Table 11.2 Minimum Criteria for Genetic Tests

Genetic Monitoring
Acceptable level of sensitivity and specificity
Acceptance by population being monitored
Established linkage to exposure or disease
Protections for privacy and confidentiality
Notification of participants
Plan for addressing abnormal results
Genetic Screening
Acceptable predictive value and reliability
Protections for privacy and confidentiality
Goals of screening should be specified
Equal access and/or random participation
Linkage of genetic factor to job requirements and duties
Demonstration that genetic factor is a bona fide qualification for adequate job performance
Definite plan for use of the data

Adapted from Murray (47) and Lappe (48).

by questionnaire to assess workers' other exposures (which could include residential ambient air, second jobs, behavioral practices, hobby exposures, and so forth). The goal of this assessment should be to explain the workplace results rather than blame the workers for their exposures.

A genetic monitoring result may require that a particular worker be moved from one job location to another. This is known as *medical removal.* This practice has been used with traditional biological monitoring, such as for lead in blood where a health risk is associated with a certain blood level, and where exposure controls are difficult to implement in a timely fashion. With measures like blood lead or zinc protoporphyrin, which are continuous, an employer may have more options than with a discrete measure such as an acquired *p*53 mutation, which is either present or absent.

One issue with medical removal is whether an employee will retain the same pay rate and benefits. This issue is termed *rate retention* and was mandated in the lead standard [(24) CFR 1910.1025 (k) (1)]. A known association, as seen with lead and disease, does not yet exist with most markers that might be used in genetic monitoring. However, a growing body of data has linked cytogenetic markers and somatic mutations in reporter genes with cancer risks in groups of workers (18). Whether this risk would apply to individuals in those groups has not been established. This highlights a confusion in the literature between group risk assessment and individual risk assessment. Epidemiologic research identifies risks for groups and not individuals in the groups. Individual risk functions can be calculated from group risk data when there are individual risk variables (25), but this is not commonly practiced. The potential exists for establishing individual risk profiles based on exposure factors, data from tests on effects of exposure (including genetic monitoring), and hereditary characteristics. Still, this will only be a probalistic determination, much like insurance company ratings of individuals with high risk factors. This kind of risk profiling will put further pressure on insurers and employers to remove or exclude workers rather than correct environmental exposures.

Genetic monitoring of workers requires considering what information workers should be given about the monitoring (so that they participate) and about their test results (26,27). The question of who has access or should have access to the results of genetic monitoring data needs to be considered before implementation of the testing. Participants should be informed about the access that others have to their data.

The question for society and policymakers on the horizon is: Does genetic monitoring indicate a health problem, a potential health problem, or compensable damage? The answers to this question will be affected by the state of science and public policy. At present, genetic monitoring is not validated widely as indicating individual risk of disease or a compensable condition. This situation could change as additional research is conducted.

Genetic Screening

Genetic screening in the workplace could be used in job placement or relocation to ensure that employers place workers most susceptible to a specific risk in the least hazardous environments (2). It could also be used to provide information to prospective or current employees so that they can decide if they wish to work in a particular environment.

Two types of genetic information might be used in occupational genetic screening. One is information about single genes that are strongly associated with rare diseases—for example, the HLA-B27 gene and ankylosing spondylitis, or the gene for hereditary diseases like the retinoblastoma gene (RBI) and eye cancer. In contrast, and more relevant to the occupational environment, are genes that code for enzymes involved in the metabolism (Phase I or Phase II) of occupational toxicants or carcinogens. These genes have multiple alleles and are sometimes called "metabolic polymorphisms." (A *polymorphism* is defined as a gene for which more than 1% of the population has a "variant" nonmajority allele.) They generally do not confer risk on their own but only in combination with a specific exposure (28,29). Examples are CYP2D6 and B(a)P exposure in lung cancer and *N*-acetytranferase-2 (NAT2) and aromatic amines in bladder cancer.

As was noted, genetic screening is rarely used in industrial medical practice because most genetic tests have not been validated—that is, their predictive value for occupational disease has not been determined. The 1989 survey of Fortune 500 companies showed that 12 were using biochemical genetic screening, and none were using direct DNA screening (2). Moreover, the ethical, legal, and social issues surrounding routine genetic screening of workers (mostly before employment or job change) have not been adequately debated. Nonetheless, in most jurisdictions, employers are not prohibited from requiring genetic screening, even if sufficient evidence does not exist for using such information as the basis of employment (1). Even if employers do not use genetic screening, they may still have access to medical records of employees and prospective employees. Employers may be able to learn if these individuals have predispositions to some diseases, although most of these predispositions probably will not pertain to occupational risks. Generally, for the workplace, genes for enzymes that are polymorphic with variants having different metabolic capabilities are likely to be candidates for genetic screening. The rationale is that workers with a particular characteristic can be excluded from exposure or will decide to exclude themselves, and these actions will result in prevention of occupational disease. This assumption may not always be correct, as was determined for one candidate for genetic screening [*n*-acetyltransferase (NAT) phenotype—discussed later].

Genetic screening to prevent workplace disease may have a range of controversial, ethical, and social effects that could include violating the decision-making autonomy of workers and promoting discrimination of racial and

ethnic groups with a particular genetic characteristic (26,30). Moreover, the attempt to focus on a single metabolic polymorphism, such as NAT, fails to acknowledge that the body's processing of a xenobiotic toxicant requires numerous genes and enzymes. In the near future, however, new high-throughput technologies may allow for the simultaneous analysis of hundreds or thousands of genes, gene segments, and expression products (31). Statistically and functionally analyzing these multiple markers and interpreting them will be a major methodological problem and may raise new ethical and social issues.

However, as more is learned, it should be possible to identify more realistic combinations of genes and expression products that may provide a profile of individual risks of a given exposure. These technological advances will need to be considered against a backdrop of workers' and employers' rights and responsibilities. Workers have rights to self-determination, privacy, access to their results, and to employment. Employers have the responsibility to provide safe and healthful workplaces. When useful and valuable information can affect occupational risks, it is not likely to be ignored (4). The question is what policy and social controls will be implemented to avoid workers being unfairly and prejudicially treated. Currently, the laws to protect abuse of genetic screening and monitoring data are perceived as few, cumbersome, and difficult to enforce (8). These may include the Civil Rights Act, Title VIII (which prohibits discrimination based on race, religion, gender, and natural origin); the Americans with Disabilities Act (ADA) (which prohibits discrimination on the basis of a disability); and the National Labor Relations Act (which determines what subjects can be bargained).

The question with the ADA is whether a genetic trait is considered a disability. Most genes with polymorphisms for metabolic enzymes are not disease risks by themselves but indicate risk only with exposure. The ADA indicates that to qualify as a disability a condition must "substantially limit an individual in a major life activity." Whether being at risk in a particular job meets this definition is yet to be determined.

Another law, the Health Insurance Portability and Accountability Act, may provide some protection to workers because they will not be as readily subject to health insurance restrictions due to a preexisting genetic condition. This also remains to be widely tested. In addition, numerous laws against genetic discrimination are being considered in various state legislatures (4,9).

Research

Subsequent to development in the laboratory, research involving genetic information is generally along the lines of validating an assay, developing it for use, or determining the role of a genetic marker as a risk factor for disease.

Laboratory Validation

Validity of a marker in the laboratory generally means that the procedure or test responds in the presence of a marker and does not respond in its absence. The first step in laboratory validation is characterization of a genetic marker. Assessing the following characteristics are crucial: dose response, marker persistence, variability within and among individuals, correlation with other markers, and correlation with a critical response (32).

In developing a procedure for use in genetic monitoring, certain characteristics of the procedure must also be known. The test should be sensitive (i.e., it measures the desired effect at low levels of change). The test must have a high degree of accuracy or specificity. Accuracy is the "trueness" of the result. The test must also have precision, which is reproducibility of standards throughout the analyses.

Genetic tests for monitoring are subject to a great deal of variability, because the body actively collects, distributes, and eliminates xenobiotics (32). Repair of damaged DNA also occurs, which adds to the variability. Laboratory procedures can have three basic sources of error: (*1*) technical variability or error in laboratory measurement, (*2*) biological change from time to time in the person, and (*3*) biological changes among individuals (33). Technical variation is largely a result of instrumentation, reagents, and human error in sample labeling, preparation, and test performance (34). Technical variability must be determined to minimize its effect on discerning true differences. The contribution of the variation about biologic changes in an individual or among individuals can be factored in if characteristics and confounders of a genetic marker have been established.

Technical variability can be controlled using appropriate quality-assurance procedures. The first step is to develop a written standard operating procedure that specifies details of the reagents, storage conditions, equipment, sampling and analytical procedures, and calibration and quality-control methods (35). Changes should not be made to the operating procedures unless the impact on sensitivity, accuracy, and precision is known. An operating procedure is critical for monitoring tests so that the same procedure is maintained for subsequent analyses. Using an operating procedure also aids in identifying and minimizing laboratory drift (a change in response with time). Preparing quality-control samples at the beginning of analysis can also determine laboratory drift.

Protocols need to be established for collecting and documenting the samples. Timing the collection of the sample may depend critically on what the test is measuring. Protocols also need to be developed to establish transportation and storage procedures in the preanalytic phase. It is generally accepted that samples should be coded so that the identity or case of exposure of the person's samples is not known to the analyst.

Another important way to decrease technical variation is laboratory enroll-

ment in a proficiency testing program. Proficiency testing increases the confidence in the results generated by that laboratory. In the absence of a formal proficiency testing program, which may be the case if the test used is not in routine use, comparison of results with other laboratories may suffice. Finally, laboratory validation, including an evaluation of technical variability, must be accomplished before a procedure is even considered for genetic monitoring or genetic screening. Establishing a quality-assurance program is essential before any monitoring program is put in place.

Population Validation

Subsequently, an assay must to be validated in terms of its utility in various population groups. This process entails understanding interperson variability according to demographic and behavioral characteristics, determining the underlying prevalence of the marker, and identifying the optimal handling and logistic considerations. Ultimately, validation requires determining the predictive value and attributable proportion (36). Critical in population validation is that exposure assessment should receive as much attention as marker measurement (37). Moreover, in research particularly, whole assay techniques are being developed, and thus some degree of genetic risk factor misclassification will almost inevitably occur in population-based studies. Evaluation of the phenomena in the context of marker prevalence is important in explaining disparate findings in the literature (38).

Many issues of using genetic markers in research are similar to their use in occupational medical practice. The greatest difference is that, in research, less certainty exists about the meaning of the markers, hence the need for the research. Moreover, much of the research is to establish specifications, performance characteristics, and mechanistic information about the marker or the assay, and this has no specificity about individual or group risks. At this level of uncertainty, much debate is triggered concerning what subjects and, in some cases, their close relatives as well should be told about research during recruitment, when reporting test results, or when reporting study results. Debate ranges from proposals to report only clinically relevant findings to proposals to report all results regardless of their relevance for individual risk or health. The issue is further exacerbated by technological and scientific developments that lead to the ability to identify new markers and assays long before their "meaning" is known. This advance, coupled with the increasing practice of storing or banking biological samples containing DNA, presents some unusual logistical and ethical dilemmas (29,39).

Historically, when research subjects agreed to participate in studies, they routinely agreed or were not aware that specimens were going to be stored for subsequent and generally related research. The recent explosion of data about genetic assays has provided researchers with many new opportunities for testing specimens for a wide range of genetic characteristics. The

following questions arise: To what extent is further consent required from the initial participants? What feedback on subsequent tests is appropriate? The latter question depends in part on the nature of the initial informed consent. Was the consent to a specific assay, or to broader research questions, a research topic, or area? Were banking and results notification mentioned? Some have argued that in the workplace genetic research setting, informed consent is practically an impossibility in that neither the investigator nor the participant is truly informed of the meaning of the research, or the extent of social or legal jeopardy to which a participant might be subject (40). Also, the consent is often seen as being given within a coercive framework tied to the power relationships in the workplace.

In addition, little research has been conducted to assess whether research participants have subsequently been harmed by stigmatization, job or insurance discrimination, psychological loss of self-esteem or in other ways. Some anecdotes supporting these contentions have been noted. The lack of research on the deleterious effects of participating in investigations with genetic components may not indicate the size of the problem but rather the difficulty in assessing it.

Another problem area is researcher and commercial efforts to market assays before they are validated (41). This stems in part from researchers' conducting poorly designed studies (in terms of sample size, control for bias, and confounding), and then failing to conduct the necessary follow-up work to determine the degree to which the finding is generalizable to other populations. Much of the problem is based on overinterpreting the results of a single small study by the researchers and inappropriate implication by scientific journals, translational newsletters and services, and ultimately by the popular press. Another interpretation problem is the incorrect practice of attributing the cause of complex social and biological phenomena to single-gene explanations.

Regulation

Genetic monitoring or screening and the use of genetic markers are not currently proscribed in workplace regulations, but such efforts are not prohibited. Although some occupational health standards require certain biomonitoring, much debate continues about whether future standards will require genetic testing (screening or monitoring) (9,13). This situation could change as more validated markers become identified and as more is learned about the genetic role in occupational disease. Society is faced with a difficult issue. As one observer (9) has noted: "If society's goal is to protect the welfare of workers, is it a basic contradiction of this goal, as embodied in both statutory law as well as common law, to interpret antidiscrimination laws as protecting the

rights of ostensibly healthy individuals to eventually decide to disable themselves in the name of freedom of choice?" Most regulations involving genetic testing or use of genetic markers will most likely be of the protective variety, namely to prevent civil rights abuses involving genetic information. At present, no uniform protection exists against the use or misuse of, or access to, genetic information in the workplace (1). However, federal legislation such as HR 2215, The Genetic Nondiscrimination in the Workplace Act. Was proposed but not passed in 1997. Often, the laws that have been passed have not been related to genetic factors that would interact with workplace exposures, but rather to genetic conditions that of themselves rarely might lead to prematurely reducing an employee's ability to work.

In the conclusion to a visionary book (1988) on variation in human susceptibility, Hornig (42) stated that the central public policy question is: "How should variation in the sensitivity of groups and individuals be taken into account in occupational laws and regulations?" Historically in the occupational arena, susceptibility has not been a major factor in determining permissible exposure levels. The Occupational Safety and Health Act (OSHAct) requires that a standard should be set "which most adequately insures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity." Moreover, a policy strategy that focuses on the worker instead of the workplace, while counter to the spirit of the OSHAct also may not be as effective as it might appear.

For example, the preventive advantage of preselecting and removing individuals who are slow acetylators (with a particular allele for NAT) from a workforce was compared with removing a chemical bladder carcinogen from the work environment. For the worker removal, the attributable proportion was 25% for a twofold association (OR = 2) and 43% for an eightfold association (OR = 8), whereas for removing the carcinogen, the attributable proportions were 50% and 88%, respectively (given that the whole excess risk is not concentrated only among the slow acetylators) (30,43). (*Attributable proportion* is the fraction of the association that can be accounted for by the genetic factor.) Thus, in the above example, removing the carcinogen would account for a larger reduction in the cancer risk than removing the worker.

The use of genetic screening would reinforce the trend in the health promotion field to focus only on those employees identified as "at-risk." This approach can be contrasted with a public health approach that recognizes that most people will have a variety of genetic, environmental, and behavioral risk factors that can contribute to occupational disease. Focusing on just one subgroup can miss many others (44). The extent to which it is possible to identify genetic subgroups that will suffer material impairment may have an impact on the interpretation of the law. Moreover, the implication of such capabilities to

identify subgroups leads to arguments for genetic screening, which could result in denying career opportunities to some people and result in their being labeled "unfit." From an employer's perspective, using genetic information to prevent occupational disease or injury may be worthwhile and cost-effective. From the worker's perspective, the potential loss of opportunity and the emphasis on excluding the worker rather than controlling the workplace is unfair and inappropriate.

Additionally, excluding people with a particular genotype does not assure that individuals with another genotype who replace them still will not have some risk. Also taking part in this debate are the insurers who argue that they should be able to use all risk factors—exogenous and endogenous—in considering insurance risks (45). These are the debates that are likely to occur in the next decade.

Workers' compensation is the existing legal framework for protecting workers. Within this framework, the role of a genetic trait as part of the etiology for an occupational disease will depend on a jurisdiction's statutory definition (9). Generally, claimants must prove that the disease is work-related and not one of the "ordinary diseases of life." For example, if a worker had a gene for thalassemic anemia that was activated by lead exposure in the workplace, whether it was compensable would depend on whether this is an ordinary disease of life for this worker just by virtue of his genotype (9). Conversely, it might be argued that such a condition might not have been triggered without the workplace exposure.

Another area where genetic information may impact regulation is in the area of qualitative and quantitative risk assessments. The current requirements for various regulatory agencies is to be able to describe the level of risks and the effect of recommended reduction of exposures [Industrial Union Department v. American Petroleum Inst., 448 USC 607, (1980)] (10). Risk assessment is the practice of determining the extent to which a hazard causes a risk, injury, or disease. It involves establishing the existence of an exposure–response relationship and the area of no or lowest observed effect levels. This can be accomplished qualitatively or by statistical and mathematical modeling.

For example, quantitative risk assessment (QRA) entails extrapolating risks from animal species to humans and from high to low exposures. The use of genetic information can possibly enhance QRAs by providing mechanistic information to judge the appropriateness of extrapolating between species and to describe biological conditions with high and low doses (12,46). There is a great deal of uncertainty in QRA because of the lack of data and the need to make assumptions about relationships between species, and the nature of the exposure–response relationship at low exposures. Understanding the role of genetic factors and impact of xenobiotics may provide more useful information for risk assessors to recommend occupational safety and health standards.

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