Toxicology Letters 213 (2012) 91–99

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

The use of biomarkers in occupational health research, practice, and policy☆

P.A. Schulte[a,*], J.E. Hauser[b,1]

[a] National Institute for Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH 45226, USA
[b] University of Cincinnati, College of Medicine, Department of Environmental Health, 3223 Eden Avenue, Cincinnati, OH 45267, USA

ARTICLE INFO

Article history:
Available online 6 April 2011

Keywords:
Biomarkers
Biological monitoring
Policy
Mechanism

ABSTRACT

Biomarkers are potentially useful tools for occupational health and safety research, practice, and policy. However, the full realization of this potential has not been achieved. In this paper, the progress made in these three usage areas is reviewed to identify what efforts can be taken to realize the full promise of biomarkers. Biomarker uses are described by a diverse taxonomy that builds on the categories of exposure, effect and susceptibility, and the continuum between exposure and disease prognosis. The most significant uses of biomarkers in occupational health have been in biological monitoring of workers. Other important uses have been in enhancing research and assessing mechanisms of action of occupational toxicants at low exposures.

Seven critical areas will influence the extent to which the potential of biomarkers in occupational health and safety is realized. These include: (1) adequate investment in validation; (2) obtaining international agreement on exposure guidelines; (3) exploring the utility of biomarkers in regulation; (4) applying biomarkers to critical occupational safety and health questions; (5) developing the exposome; (6) utilizing biomarkers to address emerging occupational health issues; and (7) continuing to address the ethical and social justice issues related to biomarkers. Overall, if biomarkers are to make a major contribution to occupational health and safety then a more holistic approach to bringing them from the laboratory to practice will be needed.

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1. Introduction

The potential of biomarkers has been extolled over the last 30 years and their usage has increased. During that time, there have been various significant contributions of biomarkers to occupational health. Examples of some of these contributions include:

- Utilizing biological monitoring as a valid tool in the practice of occupational safety and health (OSH) (Manno et al., 2010).
- Understanding biologic changes of low doses of chemicals such as benzene, formaldehyde, ethylene oxide, and polycyclic aromatic hydrocarbons (Perera and Weinstein, 2000; Yong et al., 2001; Fustinoni et al., 2005; Lan et al., 2004; Boogaard and vanSittert, 1996).
- Identifying potential hazards of nanomaterials (Shvedova et al., 2005).
- Understanding the mechanism of numerous occupational hazards (Borm, 1994; Lu et al., 2004).
- Identifying high risk subpopulations (Garte, 2008; Hemstreet et al., 2001).

However, the full promise of biomarkers for occupational safety and health has yet to be realized because the last 30 years have focused primarily on development of technologies, validation, and elucidation of processes and procedures for molecular epidemiology, analytical chemistry, and bioinformatics (WHO, 2001a; NRC, 2006; Schulte, 2007; Poste, 2011). The true promise of biomarkers will be realized when they are able to be used not only to assess known hazards and

Abbreviations: ACGIH, American Conference of Government Industrial Hygienists; ACOEM, American College of Occupational and Environmental Medicine; BAT, biological tolerance values; BEIs®, biological exposure indices; BELs, biological exposure limits; DFG, German Research Foundation; DNA, deoxyribonucleic acid; EGE, The European Group on Ethics in Science and New Technologies; ELSI, ethical legal and social issues; FIOH, Finnish Institute of Occupational Health; NIOSH, National Institute for Occupational Safety and Health; NRC, National Research Council; OELs, occupational exposure limits; OHP, hydroxyproline; OSH, occupational safety and health; OSHA, Occupational Safety and Health Administration; PAHs, polycyclic aromatic hydrocarbons; PPE, personal protection equipment; REACH, Registration Evaluation Authorisation and Restriction of Chemical substances; RELs, recommended exposure limits; RNA, ribonucleic acid; WHO, World Health Organization.

☆ *Disclaimer*: 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.

* Corresponding author at: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, 4676 Columbia Parkway, MS C-14, Cincinnati, OH 45226, USA. Tel.: +1 513 533 8481; fax: +1 513 533 8588.
E-mail addresses: PSchulte@cdc.gov (P.A. Schulte), Jennifer.Hauser@cchmc.org (J.E. Hauser).
[1] Tel.: +1 513 636 1567.

0378-4274/$ – see front matter. Published by Elsevier Ireland Ltd.
doi:10.1016/j.toxlet.2011.03.027

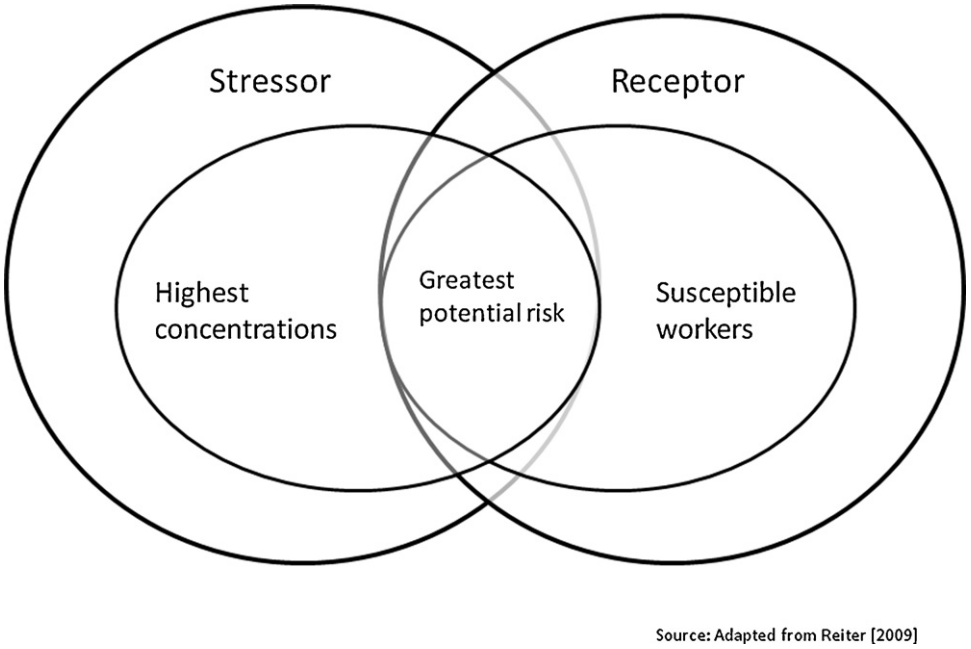

Fig. 1. Components of the stressor–receptor model.

inform control decisions, but also when they identify new hazards and groups of workers at increased risk of occupational disease, or can be used in regulatory and risk management actions.

In order to explore the use of biomarkers in occupational research, practice, and policy, it is important to describe the universe of biomarkers and define terminology that is used. This can be accomplished by building on one of the foundational concepts of occupational safety and health – the interaction of stressors and receptors (Reiter, 2009) (Fig. 1). The stressors are the chemical substances, physical and biological agents, and psychological factors that interact with receptors – workers. Historically, stressors most notably, chemical substances have been assessed in the ambient environment, the space between the source and the worker. This is the province of exposure science, and it has advanced considerably in the last 50 years (Rappaport, 1995). The ability to measure xenobiotics in biological specimens collected from workers enables the determination of exposure within the worker rather than can be measured in the adjacent environment. This is *biological monitoring* and it has a rich and useful history of contributing to occupational safety and health (Aitio et al., 1984; Que Hee, 1993; Lauwerys and Hoet, 2001; Jakubowski and Trzinka-Ochocka, 2005; Manno et al., 2010).

The concept of workers as receptors in the stressor–receptor model can be expanded to include the range of biologic responses, from the presence of xenobiotics in biologic specimens through biological changes (effects), alteration of structure and function, disability, disease, and prognosis (Fig. 2). This figure shows the well known continuum from source of exposure, through exposure to disease and disease prognosis (Schulte, 1991). At each of the steps in the continuum, various types of biomarkers can be identified from collected biological specimens, such as, blood, breathe, urine, and buccal cells, etc. These biomarkers can be considered in three categories: exposure, effect, and susceptibility. Various applications can occur in each category (Table 1). When biological monitoring for exposure focuses on genetic material in biologic specimens, it is known as *genetic monitoring*. Where there is xenobiotic interaction with genetic material, proteins, or other critical biological molecules, the monitoring may go beyond indicating exposure – it can indicate biologic effects. This can include identifying patterns of DNA or gene changes including toxicogenomic, proteinomic, or transcriptomic changes, mutational spectra, and cytogenetic effects. When monitoring is conducted to assess early health effects in asymptomatic workers, this is *medical screening*. When monitoring is conducted to identify or confirm disease, it can be *diagnostic monitoring* or medical testing. Medical tests are the cornerstone of diagnoses and also may be used to assess the effectiveness of treatment or the determination of the prognosis of individual patients. The progress along the continuum from exposure to disease (and prognosis) is influenced by various factors from variability in exposure to genetic factors that condition biological uptake, distribution, metabolism, excretion, and response. Between each step in the continuum, genetic factors can influence or modify the transitions. Assessing the genetic characteristics of workers and how those characteristics influence the effect of xenobiotics is the focus of genomics and toxicogenomics (NRC, 2007).

The various monitoring functions that occur along the exposure – disease continuum can be viewed in terms of what they mean for individuals and groups or populations (NRC, 2007). Thinking about monitoring at these different levels allows for different ways of protecting workers. At the individual level, monitoring results can lead to use of personal protective equipment (PPE), early treatment, and job placement. At the group or population level, monitoring data can be used to assess the effectiveness of controls, develop risk communications, and identify failures of prevention and control. There is a need for both levels of analysis to protect workers. Building on the terminology and foundation concepts, it is useful to identify more specifically how biomarkers can be used in occupational safety and health research, practice, and policy, and the extent to which they have been utilized. It is constructive to note that the use of monitoring and biomarkers in occupational safety and health needs to be seen in the context where there is increased population monitoring for xenobiotics and increasing medical and personal testing (NRC, 2006, 2007). Biomonitoring is becoming part of the social fabric with more societal expectations that "testing" of populations and individuals for environmental contaminants will occur more frequently (Paustenbach and Galbraith, 2006). This has implications for consideration and interpretation of worker testing.

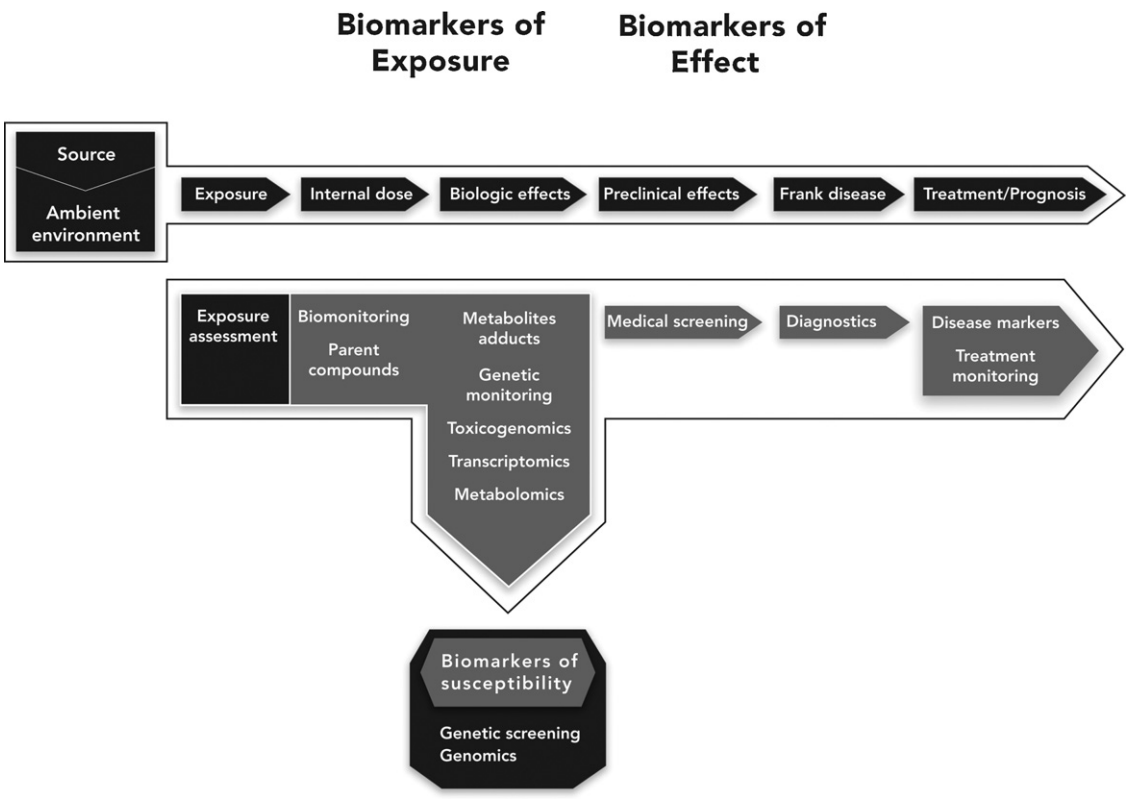

Fig. 2. Continuum of biological markers from exposure to disease prognosis.

2. Research

The use of biomarkers in research allows for the identification and clarification of the mechanism of action of chemicals and the etiology and mechanistic steps in the development of disease. In epidemiologic research, biomarkers may serve as independent or dependent variables and also as effect modifiers (Schulte, 2004). They can help reduce misclassification of exposure or effect and establish the bioplausibility of an association. Classic examples for these different research uses are shown in Table 2 . Biomarkers have begun to contribute to a "systems biology" approach to understanding specific disease and ultimately should help in the development of whole system models. Historically, the issues in using biomarkers in research include those related to specimen collection, analysis, and interpretation; privacy of findings; risk communication; the need to account for all routes of exposure; confounding factors; and the need for biomarker validation for the purpose for which it is used.

Additionally, the validation of biomarkers is in itself a research endeavor. While it is estimated that more than 150,000 papers have been published that claim to identify biomarkers, fewer than 100 have been validated for routine clinical practice (Poste, 2011). Validation requires extensive resources and multidisciplinary expertise to establish robust correlations between biomarkers and population health status. This is especially true with the large candidate data sets from high throughput technologies.

Table 1
Use of biomarkers.

Biomarker type	Use of biomarkers		
	Research	Practice	Policy
Exposure	• Identify mechanisms • Serve as independent and dependent variables • Assess exposure	• Biological monitoring • Genetic monitoring • Assess control effectiveness • Health surveillance	• BEI® • Use in standard setting • Exposure modeling • Compliance with REACH • Use in risk management • Use in occupational risk assessment
Effect	• Identify mechanisms • Serve as dependent variables • Useful in developing systems biology approaches	• Medical screening • Health surveillance • Early warning • Genetic monitoring • Fitness for duty	• Use in compensation deliberations • Use to screen chemicals • Use in occupational risk assessment
Susceptibility	• Identify mechanisms • Investigate new effect modifiers • Develop system biology approach	• Target high risk groups • Develop risk communication • Genetic screening	• Use in standard setting • Use in compensation deliberations • Use in occupational risk assessment

Table 2
Contribution of biological markers to occupational safety and health research.

Use of biomarkers	Research description	Literature citation
Effect modifier Independent variable: age Dependent variable: manganism Effect modifier: Mn–Fe ratio Population: smelting workers	In this study looking for an early onset manganism biomarker, age was a significant independent variable associated with a decline in fine movement coordination, regardless of manganese (Mn) exposure. When the model included Mn exposure, however, the age-related deterioration was intensified ($p = 0.009$). Exposure to Mn generally results in an increased Mn concentration and decrease iron (Fe) concentration in the blood. The Mn–Fe ratio was calculated and used as a surrogate for Mn exposure. High-exposure, low-exposure, and control groups were represented by 95, 122, and 106 participants, respectively.	Cowan et al. (2009)
Effect modifier Independent variable: hydroxyproline concentration Dependent variable: asbestos exposure/asbestosis Effect modifier: alpha-1 antitrypsin genotype Population: asbestos workers	Hydroxyproline (OHP), an amino acid in collagen, represents overall collagen catabolism. The concentration of free OHP in whole blood varied significantly among exposed asbestos workers with asbestosis (cases = 85; OHP 19.8 ± 14.7 μmol/L), exposed asbestos workers without asbestosis (exp. controls = 86; OHP 16.0 ± 12.4 μmol/L), and non-exposed hospital patients (non-exp. controls = 122; OHP 13.5 ± 6.7 μmol/L) [$p < 0.001$]. When stratified by alpha-1 antitrypsin genotype, mean OHP levels were highest for the at-risk genotype (Pi*S homozygotes: 24.5 ± 11.7; Pi*S heterozygotes: 16.6 ± 10.0; wild type: 15.9 ± 11.8). OHP reflects a dose-dependent response for asbestos exposure and disease, with demonstrated genetic effect modifiers. OHP can be applied as a biomarker of asbestos exposure (via collagen metabolism) for occupational monitoring or as a clinical diagnostic marker for asbestosis (based on its associated with the disease regardless of exposure, $p = 0.0005$).	Mas et al. (2004)
Effect modifier Independent variable: chemical exposures Dependent variable: chromosomal aberrations Effect modifier: genetic polymorphisms Population: railroad transit workers	Train shipments from Russia to Finland frequently contain complex chemical mixtures, such as fuel oil, pyrolysis resin, and mixtures of bitumen. This study examined tank car workers ($n = 51$) and age-matched controls ($n = 40$; office workers), all of whom were nonsmokers. Polymorphisms in genes of xenobiotic metabolism, DNA repair, and folate metabolism were studied. Exposure duration and chromosomal aberrations (CAs) were positively associated, suggesting that damage (prior to the institution of new safety measures) remained in experienced workers' cells. Levels of CAs in exposed workers were significantly less than in the controls, especially for MTHFR and XRCC3 polymorphisms. The genotoxic risk associated with tank car work seems to be modified by genetic polymorphisms, which could be tested as susceptibility genotypes.	Catalan et al. (2009)
Mechanistic insight Independent variable: α_1-microglobulin Dependent variable: proximal tubule damage Exposure: trichloroethylene Population: metal, paper, and wood-processing workers	Long-term occupational exposure to high levels of trichloroethylene is associated with increased incidence of renal cell cancer. Repetitive, intense exposures lead to nephrotoxicity, a presumed promoter of tumor development. Proximal tubule damage is an event on the disease continuum and can be identified through the excretion of tubular marker proteins, such as α_1-microglobulin. Median α_1-microglobulin levels were significantly different for exposed ($n = 39$) vs. non-exposed ($n = 359$) persons ($p = 0.0090$). Among cancer cases, exposed ($n = 20$) vs. non-exposed ($n = 79$) had higher excretions ($p = 0.0005$). Additionally, exposed cases ($n = 20$) had higher α_1-microglobulin excretions than exposed controls ($n = 18$) [$p = 0.0004$]. The data support the applicability of the α_1-microglobulin biomarker of proximal tubule damage.	Bolt et al. (2004)
Mechanistic insight Independent variable: metallothionein gene expression Dependent variable: renal toxicity Exposure: cadmium Population: cadmium workers	Metallothioneins (MTs) bind cadmium (Cd) and aid in the detoxification of toxic metals. Previous studies indicated MT protein could potentially be a marker for Cd exposure and Cd-related kidney dysfunction. In this study, MT gene expression in peripheral blood lymphocytes (PBLs) showed a decreased sensitivity to developing Cd-related renal dysfunction. This mechanistic approach resulted in an inverse relationship between MT-mRNA levels in PBLs and the likelihood of renal toxicity. (See also: Lu J, et al. Metallothionein gene expression in peripheral lymphocytes from cadmium exposed workers. Cell Stress Chaperones 2001;6:97–104.)	Lu et al. (2004)
Mechanistic insight Independent variable: GSTTI genotype Dependent variable: hemoglobin adduct formation Exposure: ethylene oxide Population: hospital workers	Ethylene oxide (EtO) is widely used as an industrial chemical intermediate as well as a sterilant for agriculture and medical products and equipment. *Glutathione-S-transferase TI (GSTTI)* and *M1 (GSTTI)* genotypes were studied with respect to hemoglobin adducts and sister chromatid exchanges (SCE) in 58 exposed hospital workers. Four-month cumulative EtO exposure was estimated using air sampling measurements. After adjusting for potential confounders, EtO exposure correlated significantly with adducts and SCE. In particular, the *GSTTI*-null genotype was significantly associated with higher EtO-hemoglobin adducts ($\beta = 1.62$, $p = 0.02$) and lower SCE ($\beta = -1.25$, $p = 0.003$). This research suggests that "workers with *GSTTI*-null genotype may be more susceptible to the genotoxic effects of occupational EtO exposure."	Yong et al. (2001)

Table 2 (*Continued*)

Use of biomarkers	Research description	Literature citation
Mechanistic insight Independent variable: PARK gene expression Dependent variable: Mn-induced Parkinsonism Exposure: manganese Population: animals exposed to welding fumes	Welding fumes are complex mixtures of gases and respirable metal particulates, including manganese (Mn). Chronic human Mn exposure has previously been linked with neurological dysfunction similar to Parkinson's disease (PD). This study examines pulmonary exposure to welding fumes and its potential association with mitochondrial dysfunction, oxidative stress, and alterations in PD-related (PARK) proteins leading to dopaminergic toxicity. Rats were dosed with fumes representative of one year and 5 years of worker exposure. These repeated exposures caused alterations in PARK gene expression in dopaminergic brain areas.	Sriram et al. (2010)
Etiology (independent variable) Independent variable: urinary and blood lead concentration Dependent variable: osteoporosis Population: storage battery plant workers	Lead may have direct biological effect on osteoblast and osteoclast function and an indirect effect on bone turnover through kidney dysfunction. This study hypothesizes that occupational lead exposure at a storage battery plant is associated with low bone mass ($n = 249$ workers). Lead concentration in urine (UPb) and blood (BPb) were the exposure biomarkers; bone mineral density (BMD) and osteoporosis were the outcomes of interest. High UPb (vs. low UPb) significantly decreased BMD ($p < 0.05$). A strong dose–response relationship was demonstrated for osteoporosis with both UPb and BPb ($p < 0.01$), with the UPb marker showing the closest association.	Sun et al. (2008)
Etiology (dependent variable) Independent variable: job type/circadian disruption Dependent variable: urinary metabolite of melatonin Population: airline attendants	Circadian disruption can be measured by melatonin production. This epidemiologic study investigated the relationship between occupationally related sleep pattern disturbances and the urinary metabolite of melatonin, 6-sulfatoxymelatonin (6SMT), a correlate of plasma melatonin levels and circadian rhythm biomarker. The exposed worker population was comprised of airline attendants ($n = 45$) while the controls were minimally flying schoolteachers ($n = 26$). Results showed that flight attendants have greater melatonin rate variance (2.8×10^5 ng/h) than teachers (1.0×10^5 ng/h) [$p = 0.04$], which infers increased circadian disruption for these exposed workers.	Grajewski et al. (2003)
Etiology (dependent variable) Independent variable: occupational stress Dependent variable: salivary cortisol Population: call center workers	Prior studies indicate that stress is involved in dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis. The relationship between job-related stressors and salivary cortisol is examined in this study. Call center employees in Northern Italy ($n = 36$) responded to questionnaires and contributed salivary samples from two workdays and one weekend. Cortisol was recorded as cortisol awakening response (CAR) and was significantly influenced by job stress ($p < 0.01$).	Maina et al. (2009)
Etiology (dependent variable) Independent variable: ETS Dependent variable: urinary metabolites of nicotine Population: restaurant workers	Environmental tobacco smoke (ETS) exposure was assessed by air nicotine measurements in readings near employees' breathing zones. Urinary metabolites (cotinine, 3-hydroxycotinine) were measured during one work week. Three types of restaurants were evaluated: food-oriented (lunch, dinner), socialization-oriented (pubs), and nightlife (discos, nightclubs). Study participants were 12 female and 13 male nonsmoking restaurant workers ($n = 25$). Pubs and nightclubs produced significantly higher concentrations of nicotine in the air. Correlation for the urinary metabolites and breathing zone nicotine was 0.66, with increases throughout the week in 80% of workers (particularly those in pubs and nightlife establishments). Sixty percent of the employees exceeded the level of heavy exposure (9 ng cotinine/$mg_{(creatinine)}$) at least once during the week. Data was gathered prior to the National Tobacco Act which restricted smoking in restaurants.	Johnsson et al. (2003)
Etiology (dependent variable) Independent variable: naphthalene exposure Dependent variable: urinary naphthols Population: air force personnel	This study examined the dose-response relationship between naphthalene exposure and urinary naphthols. "The exposure-smoking interaction was consistent with induction by smoking of one or more steps in the metabolism of naphthalene and naphthalene-1,2-oxide (NapO)." Naphthalene was metabolized at different rates in smokers vs. nonsmokers which suggests two or more biologic pathways are involved.	Serdar et al. (2004)

3. Practice

The greatest success of biomarkers in occupational health has been their use in biologic monitoring (Aitio et al., 1984; Zielhuis and Henderson, 1986; Que Hee, 1993; Lauwerys and Hoet, 2001; Manno et al., 2010). This has generally been for exposure assessment and is standard practice in many companies with various potentially hazardous exposures and in some regulations (OSHA, 2005). Biological monitoring is a means to assure the effectiveness of risk management and prevention programs. Biological monitoring is also used as part of health surveillance to provide the correct interpretation of doubtful clinical tests, especially when environmental monitoring data are unavailable (Manno et al., 2010). Genetic monitoring, a subset of biological monitoring, continues to expand with the development of new technologies that allow assessing the impact of stressors on genetic structures, DNA, RNA, and proteins on a large scale using high throughput technologies (NRC, 2007). The use of biomarkers in medical screening has increased in gen-

eral medicine but is still not widely practiced for workers who are asymptomatic for occupational diseases. However, because many of the diseases that affect the workforce are not solely work-related, general screening conducted by workers' physicians may have workplace implications. Some common diseases can be exacerbated by occupational exposures (Schulte et al., 2008). A recent conference on nanomaterials identified various tests that could be used to screen workers for respiratory and cardiovascular conditions that, while related to nanomaterial exposures, are common in the population (Trout and Schulte, 2010). Since nanomaterials may cause these conditions, screening workers for indicators of disease without causal attribution may be warranted. This is not to preclude the use of epidemiologic research to assess causality of these conditions and association with workplace hazards.

Biomarker assessments can also be used to target high risk groups within a worker population and ultimately develop risk communications (Hemstreet et al., 2001). When this targeting involves genetic biomarkers, various ethical issues arise, and the practice of genetic screening of worker populations has generally not been recommended or sanctioned by governments and authoritative organizations (Van Damme et al., 1995; EGE, 2003; ACOEM, 2005; NIOSH, 2010). In fact, in the U.S., the Genetic Information Nondiscrimination Act of 2008 prohibits use of genetic information in workplace decision making including hiring, firing, and compensation. That does not exclude the use of genetic information in occupational disease diagnosis and treatment, and it is still allowable in medical examinations related to compensation and litigation. However, the use of genetic biomarkers to apportion causation has been criticized (Schulte and Lomax, 2003).

4. Policy

Biological markers may play a role in policy matters (Bertazzi and Mutti, 2008). Biomarkers of exposure are the focus of guidance for safe biomonitoring levels such as biological exposure indices (BEIs)® and biological tolerance values (BAT) promulgated by various organizations and government standards (DFG, 2009; ACGIH, 2010). The ACGIH has established 46 BEIs® for over 100 chemical exposures including pesticides and polycyclic aromatic hydrocarbons (PAHs), and Germany has established BATs for over 100 chemicals (DFG, 2009; ACGIH, 2010). Literature that is used in developing occupational standards often includes studies of various types of biological markers. However, at present, there are few examples where biologic markers are endpoints in studies that are evaluated in quantitative risk assessments and used as the basis of health standards but this is likely to change as more gene–environment interaction research is conducted based on high throughput genomic and toxicogenomic technologies. Nonetheless, biological markers have been used, but not widely, as the basis for corporate policies for risk management (Boogaard and vanSittert, 1996; Boogaard, 2008). As more preventative strategies get incorporated into law, such as through REACH or revisions to Toxic Substance Control Act, governments may accept biomarker data as surrogates for disease endpoints.

5. Critical development and investment needs

If the potential of biomarkers to contribute to occupational health and safety is to be realized, efforts need to be focused and new investments made. Biomarkers are not a panacea for preventing all worker illnesses and injuries, but if focused on particular issues, their use can contribute to improved protection.

5.1. Adequate investment in validation

The critical issue for use of biomarkers in occupational health research, practice, and policy, is the extent to which biomarkers have been validated – that whether the parameters of the relationship between a biomarker and what it marks are known (WHO, 2001b). This is not an all-or-none condition but one dependent on the state of knowledge about aspects such as sensitivity, specificity, reliability, predictive value, and interpretability (Schulte, 2005; Schulte and Talaska, 1995; WHO, 2001a). These issues may be more complex when biologic markers are not single measurements but patterns of output from high throughput platforms (e.g., toxicogenomics, proteomics, transcriptomics, and metabolomics) (Vineis et al., 2009). The large sample sizes required to validate these outputs require extensive resources and large scale partnerships (Poste, 2011).

In part, validation builds on specimen collection, degree of standardization, sufficiency of sample size, and quality control. Large scale databases and multidisciplinary expertise may be required to establish robust correlations between biomarkers and workers health status. A critical interpretive question is putting biomonitoring data in a risk context for workers and others. The mere presence of xenobiotics in a biological specimen does not equal risk. The ability to measure xenobiotics is far outpacing the ability to interpret its meaning (Bahadori et al., 2007). Research is needed to link biomonitoring data quantitatively to health risk (Smolders et al., 2008).

5.2. Obtaining international agreement on occupational exposure guidelines

Global markets and commercial transfer of chemicals makes a globally harmonized system of exposure guidelines an important consideration. Already the Globally Harmonized System for labeling of chemicals has been widely adopted (UN, 2005). Ultimately, there may be a role of exposure guidelines either as occupational exposure limits (OELs) or biological exposure limits (BELs). Regarding BELs, the four impediments to international agreement have been identified. These include:

1. The specification of the biological monitoring guidelines as ceiling or average values.
2. Whether carcinogenic substances should be treated differently from agents with other toxic outcomes.
3. The method of accounting for variability among individual workers.
4. The extent to which these guidelines should be extended to include specific biomarkers such as genetic markers, indicators of susceptibility, or indicators of early biological response (Morgan and Schaller, 1999).

5.3. Explore the utility of biomarkers in regulation

Biomarkers can be used in regulation as illustrated by the U.S. OSHA regulation to control lead in blood (OSHA, 2005). However, this use has only rarely occurred. The voluntary use of BEI® and BATs illustrate the potential for regulatory or corporate policies to use biomarkers of exposure (Morgan and Schaller, 1999; Bolt and Thier, 2006; Manno et al., 2010). Biomarkers of effect (e.g. sputum and bladder cytology, liver function) have occasionally been used in regulations; however, this has been rare (California Code of Regulation, Title 8). Additionally, acquired genetics effects and epigenetic markers could be used in occupational standards (NRC, 2007). Biomarkers of susceptibility have not been used to develop occupational standards in the past but they are likely to be used in the future. There is a growing body of research that assessed

inherited genetic factors as modifiers of the effects of hazardous exposure. This type of information could be used in risk assessments that serve as the basis for developing OELs (Scheepers and Heussen, 2005; Bertazzi and Mutti, 2008; Schulte and Howard, 2011).

5.4. Applying biomarkers to critical occupational health and safety questions

The ultimate utility of biomarkers in occupational health and safety is the extent to which they lead to prevention and control of occupational disease. Clearly, biomonitoring has made a contribution in that regard. However, ultimately, if biomarkers are to be of significant utility, they need to be used to identify new hazards or clarify important questions of mechanism or etiology that can lead to new or better control efforts. The barriers to identifying new hazards is agreement on the extent to which biomarkers represent exposure, significant biologic effect/disease, or important susceptibility indicators, that is, their degree of validation. In part, this issue is related to the previously mentioned issues of putting biological monitoring data in a risk context.

Additionally, utilizing susceptibility data in developing occupational regulation may be an important contribution of biological markers (Bertazzi and Mutti, 2008; Schulte and Howard, 2011). Although there are various technical, ethical, legal, and societal issues (ELSI), genetic and epigenetic data could be used in standards development. As more research identifies genetic and epigenetic factors as effect modifiers of significant occupational exposure-disease associations, risk assessors will be induced to include such research to more precisely improve certain controls in quantitative risk assessments that serve as the basis of standards.

5.5. Developing the exposome

The exposome is the constellation of all exposure events (exogenous and endogenous; including lifestyle) from conception to death (Wild, 2005). The challenges to characterizing the exposome include addressing the scale, complexity, and changes of exposure over time. Ultimately, when integrated with knowledge from the genome it may be possible to address all the factors that affect the health of the workforce and better control those that are work-related (Rappaport and Smith, 2010). This is an immense task but the nascent-effort to complement the genome with an exposome is an appropriate first step.

5.6. Utilizing biomarkers to address emerging occupational health issues

While traditional occupational hazards still abound, many countries are increasingly moving to "knowledge and service" economies, where work-related, psychosocial factors are leading to risk of common mental disorders, and depression (Stansfeld and Candy, 2006; Kivimaki et al., 2010). The WHO estimated that by 2020, unipolar depression will be the second-most frequent cause of disability in the world (WHO, 2001b). Psychosocial stress in humans is a complex phenomenon not readily captured by bodily biochemical modification. However, animal models have begun to illuminate translational mediating events and various biomarkers have been identified that can be useful for screening and early intervention in workers under prolonged psychosocial stress (Asberg et al., 2009).

Another characteristic of contemporary and future workplaces is the aging workforce (Costa et al., 2005). Increasingly, it may be important to distinguish biological from chronological aging and determine the workability of the workforce. Biomarkers may contribute to this topic however, the history establishing informative biomarkers of aging has been problematic due to "... the extensive variability between individuals that makes generalization difficult; the overlapping of aging and disease processes; uncertainty regarding benign versus pathogenic age-related change; the point at which a process begins to do damage to an organism, and if so, when does it occur; and when to distinguish critical damage from non-critical damage" (Butler et al., 2004). Nonetheless, biomarkers of aging may provide important data on how work affects age-related changes and vice versa.

5.7. Continuing to address ethical and social justice issues related to biomarkers

Much has been written about ethical issues related to using biologic markers (Ashford et al., 1984; Schulte, 1992; Van Damme et al., 1995; Schulte et al., 1997; Van Damme and Casteleyn, 2003; Vahakanges, 2008; NIOSH, 2010). Of importance, for future consideration are such issues as the inappropriate discriminatory effects on workers from employer uses of biomarkers related to behavior, personality, neurophysiologic characteristics (such as stress), and epigenetic influences. There is also concern from a social justice viewpoint about investing scarce occupational and public health resources in specimen collection and analysis when other uses of funds may be of equal or better value. This may be the case, sometimes, with studies of genomic biomarkers in workers (Schulte, 2007).

6. Conclusion

While the use of biomarkers has a rich history in biological monitoring of workers, their overall contribution to occupational safety and health has been limited. This is, in part, due to the fact that focusing and validating biomarkers requires extensive effort. Large scale research and validation efforts may be a way to address some development and validation efforts. Additionally, a broad range of disciplines will be needed to address massive data sets that may be generated. Moreover, expertise associated with end uses of biomarkers, such as from regulatory or policy domains, will be needed to help inform development and validation efforts. Overall, if biomarkers are to fulfill the expectations that have arisen for them, then a more holistic approach to bringing them from the laboratory to the field will be needed.

Conflict of interest

The authors declare that there are no conflicts of interest.

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