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THE ROLE OF BIOMARKERS IN TOXICOLOGICAL INVESTIGATIONS

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Abstract
This article discusses the concept of biomarkers in toxicogenomics and focuses on their roles in explaining biological effects of toxic compounds at the molecular level. Biomarkers are significant indicators in exposure, effect, and susceptibility that allow prediction and evaluation of adverse outcomes. The advanced toxicogenomics has made this biomarker crucial in identifying the interaction between genes and their environment, risk assessment, and development of targeted interventions. This review article identifies the kinds of biomarkers, such as genomic, proteomic, and metabolomic markers, and potential applications of these in understanding the pathways of toxicity and variability between individuals in response to toxicants. Therefore, this study integrates cutting-edge technologies to underscore the important role that biomarkers play in moving toward precision medicine and improving our ability to mitigate environmental and pharmaceutical risks.

INTRODUCTION

Biomarkers, which are measurable indicators of biological states or conditions, are now recognized as a critical component in toxicology [1]. They provide key information on exposure to harmful substances, the physiological impact of such exposures, and individual predispositions to toxic effects. Inevitable exposure to chemicals in the environment, workplace, and pharmaceuticals in modern life underscores the importance of biomarkers as the scientific basis for understanding and mitigating such risks [2]. Biomarkers have helped to advance toxicological research and applications by providing accuracy and reliability [3].

The earlier definition of biomarkers was simply a blood or urine concentration of chemicals. Advances in molecular biology and analytical techniques have made it possible to include genetic, proteomic, and epigenetic indicators in the definition of biomarkers [4]. Advances in the field have allowed trace amounts of toxins to be detected and very subtle biological changes which result from such toxins [5]. This development was not only helpful in enhancing the precision of toxicological investigation but also broadened the scope of the study so that multifaceted interactions between toxins and biological systems could now be studied.

This review article is based on the role of biomarkers in toxicology, in classification with their application in clinical and forensic toxicology. In this paper, it also addresses the current technological developments improving the detection and analysis of biomarkers; challenges in their applications, as well as some future directions for their integration into toxicological science. Biomarkers will fill a gap between toxicology and other related areas, and could change perceptions of toxin exposure and impact upon both human health and legal systems.

Types of Biomarkers in Toxicology

Biomarkers of Exposure

Biomarkers play the most important role in the field of toxicology directly based on the measurement of the concentration of a toxic substance or its metabolite within the human body [6]. Thus developed, these biomarkers give evidence of current and past exposure, which is quite essential to find the levels and times of exposure to harmful agents [7]. Cotinine is an excellent example of a biomarker for exposure to tobacco products [8]. It is the metabolite of nicotine. In the short time, it will diagnose and treat carbon monoxide poisoning as it determines the amount of carboxyhemoglobin present in the blood [9].

Such biomarkers are commonly available in matrices such as blood, urine, hair, or saliva and would reflect different exposure windows with varied periods of stability [10]. For instance, blood and urine will expose recent exposures while possibly having hair analysis expose an exposure over a long period of time [11]. Exposures will therefore present a challenge when being biomarked because metabolizing and rates of excretion would introduce variability, thereby meaning the biomarkers could vary, so advanced analytical techniques become significant to ensure sensitivities improve, accuracy increases, and proper interpretations take place [12].

Biomarkers of Effect

Effect biomarkers are the physiological or pathological effects that the body experiences due to toxic exposure [13]. These are important in the interpretation of the biological effects of toxins, from subclinical changes to overt diseases. For example, elevated liver enzymes such as ALT and AST indicate hepatotoxicity by substances such as acetaminophen or alcohol. DNA adducts, that is the results of reactions of carcinogen with DNA are also some biomarkers for exposure to genotoxic agents and thereby to cancer risk [14, 15].

Much more valuable for diagnosis and the monitoring of therapy are biomarkers of effect. These enable toxicologists to estimate the level of exposure and its biological effect to tailor medical interventions. Equally, they greatly help in dose-response relationship studies, which are of most importance in toxicological research and regulatory decision-making. This, however calls for multi-biomarker approaches since the complexity of biological responses demands a full spectrum of effects to be captured [16].

Biomarkers of Susceptibility

Biomarkers of susceptibility are genetically or epigenetically determined properties that position an individual at a disadvantage for effect [4]. Such markers are well founded on the basis of intersubject variability in metabolism, immune responses, and repair, factors, which affect the toxicology of an insult. As illustrations, variation in cytochrome P450 enzymes results in polymorphism with drug or toxin metabolism to enhance susceptibility toward adverse effects [17]. Epigenetic changes, like the DNA methylation pattern, may also affect gene expression and sensitivity to environmental toxins, too [18].

These biomarkers have deeper implications in personalized medicine and preventive toxicology. Susceptibility biomarkers make interventions focused and the risk management even more efficient by allowing targeting of high-risk individuals or populations [19]. They also fine-tune risk assessment in toxicology and definitions of safety limits by accounting for variability among the exposed population. As science moves on and integrates genomics, proteomics, and other technologies of omics, then more susceptibility biomarkers shall be advanced and further propelled the prediction [20].

Type of Biomarker	Definition	Examples	Application
Biomarker of Exposure [21]	Indicates the presence of a toxic substance or its metabolite in the body	Cotinine (Tobacco exposure), Carboxyhemoglobin (Carbon monoxide exposure)	Detection of exposure levels and monitoring of environmental health risks
Biomarker of Effect [22]	Indicates physiological or pathological effects due to toxic exposure	Elevated liver enzymes (ALT, AST) indicating hepatotoxicity, DNA adducts indicating genotoxicity	Diagnosis of toxicity and monitoring of therapeutic interventions
Biomarker of Susceptibility [23]	Genetic or epigenetic factors that predispose individuals to adverse effects	Cytochrome P450 polymorphisms, DNA methylation patterns	Personalized medicine and preventive toxicology

Table 1: Types of Biomarkers in Toxicology

Biomarkers in Clinical Toxicology

Such biomarkers prove to be very helpful in diagnosing cases of poisoning and drug overdose and then managing them as well in clinical toxicology [24]. Biomarkers may immediately inform a clinician whether toxic agents are present along with the concentration of agents and how to initiate corresponding treatments [25]. For example, serum concentrations of acetaminophen must determine the severity level of overdose and whether a person is in need of antidotes like N-acetylcysteine [26]. Similarly, blood ethanol levels are automatically used to evaluate alcohol poisoning and guide supportive care [27].

Monitoring of therapy also involves biologic markers. Continuous assessments of levels help a clinician monitor how well the treatment is being tolerated and subsequently be able to change dosages to optimize outcomes appropriately [28]. As for the assessment of the lead levels in blood through chelation therapy, it has to remove efficiently without harming; such applications underscore the significance of biomarkers in personalized evidence-based medicine [29].

However, the application of biomarkers in clinical settings does have challenges. Some factors that complicate the data interpretation of biomarkers are delayed presentation, co-exposure to different substances, and individual variability in metabolism [30]. As an example, for mixed-drug toxicity cases, one finds it challenging to indicate which agent is responsible for producing clinical symptoms [31]. Such challenges need to be overcome through developing sophisticated analytical techniques and integrating comprehensive panels of biomarkers to present a real holistic view of the nature of toxic exposures and their impact [32].

Biomarkers in Forensic Toxicology

Biomarkers in forensic toxicology hold great relevance for poisoning cases, drug-induced deaths, and other toxicology matters. The reason is that biomarkers become objective evidence supporting legal procedure leading to cause and manner determination for death. For example, postmortem blood concentrations of opioids such as fentanyl or morphine confirm lethal overdose, but cyanide can be determined in tissue specimens establishing poisoning as the cause of death [33].

For instance, in drug-assisted crimes, biomarkers point out the presence of benzodiazepines or gamma-hydroxybutyrate in biological specimens. This means the evidence of drug use by suspects. Biomarkers such as hair and nail are able to prove long-term exposure to drugs, hence giving additional evidence in forensic cases. Biomarkers most of the time act as a linking factor to link suspects with crime; therefore, it has a scientific basis for legal judgments [34].

In turn, forensic biomarkers carry new complications. The post-mortem decomposition and redistribution of the body burden due to changes in fluid chemistry can make it quite confusing with alterations at the level of these markers for interpretation [35]. Moreover, environment-contaminants or endogenous, toxin mimickers result in either false-positivity or negativity that cannot easily come around during rigorous analytic validation; moreover such issues need sophisticated tools in its assay in general, mass spectrometric analysis is one in terms [36].

Technological Progress in Biomarker Detection and Analysis

Technologies

This is one area of biomarker detection that is under major development due to the advanced technology, which increases sensitivity, specificity, and throughput in their analysis. Techniques like LC-MS/MS, coupled with GC-MS, have brought new standards to toxicology because trace levels of toxins with their metabolites can be seen; they are invaluable in many complicated cases where other traditional assays may be impossible to meet the demands [37].

The advance in the omics technologies; namely, genomics, proteomics, and metabolomics has made detectable biomarkers more sensitive [38]. Biomarkers newly emergent via the aforementioned high throughput technologies, although revealing pathways that the toxic agent is acting on, could potentially offer better insight in them [39]. For instance, some signature that might relate to a specific toxin can be derived by metabolomic profiling and that will help in the identification and characterization of the latter [40].

Emergence Biomarkers

This can come in the molecular markers where microRNAs, exosomes, and non-coding RNAs feature as a new frontier for toxicology [41]. They bear information related to the linking of cellular response with toxic exposure and perhaps represent a basis on which further diagnosis and monitoring can take place. As such, it may eventually be shown that microRNAs feature as good biomarkers representing some form of organ damage, say, to liver or kidneys, by chemical agents [42].

All such biomarkers are supported by the development of molecular biology and bioinformatics. It is only then possible to find and validate markers of this level of specificity and sensitivity. Research will unroll the new biomarkers complementary to the classic ones and enhance sensitivity and scope of toxicological tests [43].

Point-of-Care Testing

Available POCT devices have really transformed toxicology by introducing rapid on-site biomarker detection. Of course, in emergency diagnosis, often it is quite a matter of life or death; hence portable analyzers become invaluable tools in emergency applications. Examples of very frequently used handheld devices include glucose level in blood and alcohol level in blood in both clinical as well as forensic analyses [44].

While POCT has many advantages with respect to speed and convenience, several drawbacks do exist. Results may get compromised in accuracy and reliability due to interfering environmental factors or operator errors [45]. Quality assurance of POCT devices, therefore, would require intensive testing and calibration before further application in toxicology [46].

Technology	Description	Application in Toxicology
LC-MS/MS (Liquid Chromatography-Mass Spectrometry) [47]	A method for tracing traces of toxins and metabolites	It is used for detecting complex toxic exposures and their metabolites in biological samples.
Omics Technologies (Genomics, Proteomics, Metabolomics) [38]	High-throughput technologies in the study of genes, proteins, and metabolites	It enhances the sensitivity of biomarkers and understanding of biological pathways involved in toxicity.

Point-of-Care Testing (POCT) [48]	Portable on-site devices for rapid biomarker detection	It is used in clinical and forensic toxicology for quick decision-making, such as alcohol or glucose level testing.

Table 2: Technological Progress in Biomarker Detection and Analysis

Biomarkers in Toxicology-Challenges in Use

It poses various problems that need to be solved before the full promise can be harvested from biomarkers. An important source of variability of analytical nature emanates from differences in detecting methods, sample handling techniques, and from the differences in biological matrices. Detecting biomarkers, therefore differs considerably when detection is done by utilizing hair and nails, this means an external contamination with other samples or different rates in growing; this complicates results of interpretation [49].

Biomarkers analysis is complicated by the fact that individuals have variations in their genetic, epigenetic, and environmental factors. For example, variations in genetic polymorphisms of enzymes cytochrome P450 lead to changes in drug or toxin metabolism and thus influence levels of biomarkers. Such changes mean that each person requires personal approaches to toxicological assessment, which is a time-consuming and expensive task [50].

There are ethical and legal questions even in the applications of the biomarker. Among these are questions to privacy issues, informed consent or use of sensitive information in crimes even as it poses a threat through admitting evidence of biomarker findings in courts. This needs further strict validation and standardization on analytical methods for their admittance to be effective in courts, again involving coordination with toxicologists and other legal experts to find definite ways of implementing the procedures to work around this problem [51].

Role of Biomarkers in Drug Development and Toxicity Testing

Biomarkers in Preclinical drug testing

Biomarkers play a crucial role in the development of drugs before clinical trials; it simply means that the scientists can determine the safety of the new compound and the potential toxicity when the compound is tested on humans [52]. In the case of animal studies, the most-used biomarkers include ALT and AST in assessing liver functions and early indicators of hepatotoxicity [53]. Creatinine and BUN levels are also an excellent indicator for renal toxicity [54]. These markers are extremely useful while studying the pharmacokinetics and pharmacodynamics of a drug; therefore, scientists will be able to predict side effects and redesign the drug accordingly. Inclusion of a biomarker during the study in preclinical will avert the late-stage toxicity of a drug during clinical development that would gobble up valuable time and dollar [55].

Biomarkers in Clinical Trails

Biomarkers are used within the clinical trials of the drugs on the basis of safety and efficacy [56]. During Phase I, they could be used to determine the highest tolerated dose because they detect early signs of toxicity, especially in healthy volunteers. Some cardiac biomarkers, such as troponin, can observe drug-induced cardiotoxicity. Similarly, inflammatory markers can be observed for immune reactions, such as CRP [57]. In later stages, biomarkers are used for dose optimization and patient stratification, thus tailoring treatments to the individual needs. Real-time data on drug responses provided by biomarkers increase the validity of clinical trials and hasten approval for new therapies [58].

Reduction of Animal Testing through In Vitro Biomarker Studies

For instance, in vitro techniques are evolving so that biomarker-based assays could be developed which may use minimal animal testing [59]. Organ-on-chip technologies emulate human organ systems, allowing researchers to study the effects and toxicity of drugs at the cellular level [60]. For example, biomarkers found in the systems include cytokines or metabolic enzymes that are vital data that may be utilized to understand toxicity without the need for live animals [61]. This is in compliance with the 3Rs principle of Reduce, Refine, and Replace, thus encouraging ethical and cost-effective research practices [62]. In

vitro biomarker studies also enable high-throughput screening of drug candidates, thereby accelerating the drug discovery process while still being in line with regulatory guidelines [52].

Biomarkers in Non-Toxicological Contexts with Toxicology Overlaps

Biomarkers in Addiction Medicine

Biomarkers are of great importance in diagnosing and in monitoring the course of treatment of a substance-use disorder in the discipline of addiction medicine [63]. For example, high cortisol levels indicate chronic exposure to alcohol or drugs: stress and shift of physiological conditions [64]. More relevant biomarkers like the metabolites of dopamine shall further present evidence on how such drugs and substances have led to alterations in brain functioning [65]. These markers have been employed in developing individually customized rehabilitation programs that will be beneficial to clinicians in monitoring recovery and even predicting relapse. These have further been used in the assessment in drug misuse workplace and forensic settings so that proper detection and intervention are enhanced [66].

Biomarkers of Risk for Chronic Diseases after Toxic Exposure

It has been proven that biomarkers of long-term exposure to environmental toxins present in the environment, such as endocrine disruptors and heavy metals, are associated with chronic diseases, including cancer, diabetes, and neurodegenerative disorders [67]. Now, since it begins with the level of biomarkers or early markers of risk development, it is the most basic tool. For example, high levels of markers of oxidative stress, such as MDA, are indicative of cellular damage by toxic exposure. They are also markers of genetic susceptibility to carcinogenesis. Thus, when they are present in the exposed, it prevents and leads to individualized treatments that gradually reduce their effect over time [68].

Biomarkers in Disaster Toxicology

Biomarkers are helpful in giving information about health effects resulting from any industrial accident, chemical spills, or environmental disasters in inhabited regions. For example, urinary metabolites can be used to assess exposure after an industrial explosion involving benzene, and serum cholinesterase levels in a victim exposed to organophosphate pesticides after an accident. These biomarkers may, therefore, be useful to quantify exposure and provide basis to guide public health responses that might extend to evacuation, decontamination, and treatment. Their role in disaster toxicology offers the advancement of the biomarker tool in human health protection toward emergency scenarios as well as development of effective methods in intervention [69].

Role of Biomarkers in Toxicogenomics

Gene Expression Profiling and Biomarkers

The gene expression profiling has totally made toxicogenomics what it is today [70]. It's for the reason that through its ability to show the kind of biomarker which represents the reaction by the body to the toxin at molecular levels. Biomarkers were one which was in change form resulting from measurements on various forms of high throughput techniques through either microarray, or even RNA sequencing [71]. For example, it is induced for the DNA repair genes, like p53 under stress caused by genotoxic agents. Their subsequent biomarkers track the subsequent strength of exposure and extent of damage inflicted on cellular parts. This gene expression technique offers the information regarding the toxic effect mechanism rather than the methods that have been integrated for traditional toxicity testing [72].

Gene expression biomarkers, therefore also important while trying to differentiate acute versus chronic toxicological effects [72]. For instance, long term exposures to heavy metals like cadmium would impact the level of metallothionein gene over long time or acute exposure that would result in the short time response. The Biomarkers can be pretty helpful in while investigating the dose-response relationship and in case of time toxicity patterns [73]. Thus, they are an essential application in clinical and regulatory toxicology. In addition, with recent technology developments, the integration of machine learning into the analysis of gene expression makes even more excellent predictions for the determination of toxicants [74].

Epigenetic Biomarkers in Toxicology

Epigenetic marks that include DNA methylation, histone acetylation, and microRNA control mark are utilized for the assessment of the long-term effects of exposures of toxins [75]. These changes are heritable but reversible, so that they have high relevance in understanding how environmental exposures influence gene expression without altering the primary DNA sequence. For example, some specific CpG sites were identified as a biomarker of exposure to carcinogens, such as benzene and arsenic, based on DNA methylation. These biomarkers tell the exposure story, and that will also be useful for risk assessment regarding disease, such as cancer, probably due to that exposure [76].

MicroRNAs-small noncoding RNAs that regulate expression post-transcriptionally-emerge as rather sensitive epigenetic markers. Toxins that include dioxin and PCBs have been reported to modify the microRNA profiles detectable through biofluids such as blood and urine. The reason these may be highly useful for monitoring toxicological effects specifically in susceptible populations such as pregnant women and children is that as a non-invasive approach [77]. Thus, new epigenomics technologies will make it relatively easier to discover new epigenetic biomarkers for early diagnosis and personalized interventions in toxicology.

Biomarker Type	Examples	Role in Toxicology
Gene Expression Biomarker [78]	p53 (DNA repair genes), Metallothionein	Indicate the cellular response to toxins, track exposure strength, and assess damage.
Epigenetic Biomarker [79]	DNA Methylation (e.g., CpG sites), MicroRNAs (e.g., dioxin exposure)	Reflect long-term exposure effects, potentially reversible, and linked to carcinogens.
MicroRNA Biomarker [80]	Noncoding RNAs regulating post-transcriptional expression (e.g., PCBs)	Used for non-invasive monitoring of toxicological effects, especially in susceptible populations.

Table 3: Gene Expression and Epigenetic Biomarkers in Toxicogenomics

Toxicogenomics in Predictive Toxicology

Predictive toxicology concerns adverse effects because of toxicants before the stage of exposure and includes very vital biomarkers [81]. On these lines, with the information attained through toxicogenomics capable enough to predict individual susceptibility to toxins, the pattern study of the gene expression or change in the epigenetic level will be of much concern [82]. For example, it is found that the biomarker of SNP, detoxifying cytochrome P450 or enzyme exists in this way. Applications are mainly there in drug development due to the scope because biomarkers predict adverse reactions. This will be put to service the patient by personalizing as per his demands [83].

Biomarkers of toxicogenomics also enable the evolution of models of toxicity. These biomarkers would enter into machine learning algorithms to simulate the toxicological response in silico; therefore, the dependency on the animal goes down. For instance, the oxidative-stress transcriptomics biomarkers have been added to predictive models regarding the toxicity of new chemicals. This is the hope that toxicogenomics biomarkers would really revolutionize the nature of risk assessment, regulatory decisions, and public health strategies by providing accurate and reliable predictions of toxicological outcomes [84].

Biomarkers and Legal Considerations in Toxicology

Role in Cases of Litigation and Liability

Biomarkers are of utmost significance in toxicology cases involving issues with litigation and liability, especially such exposures from the environment and occupation [85]. It can help produce scientific evidence linking exposures to pathogenic health effects resulting from a given toxicant. An example includes metabolites of benzene in urine, found in many cases brought forward about chemical exposure

at industries for sure, definitive contact with toxicants. These biomarkers will, therefore, aid in the quantification of the level of exposure, which is important in claiming compensation and liability arising out of negligence or inadequacy of safety [86].

Other than providing information related to the timeframe and intensity of exposure, both have the same degree of value as quantification regarding determining causation. In particular, certain biomarkers like polychlorinated biphenyls, due to a tendency to last for an extended period in either blood or fatty tissues of the body may give insight into extended durations of environmental toxins exposition [87]. This may be very applicable in situations of delayed toxic effects like cancers or chronic illnesses whose exposure has been decades ago. Through the association of biomarkers with specific exposure scenarios, attorneys and toxicologists can formulate a strong case either for the plaintiffs or defendants [88].

However, litigation through biomarkers comes with its own set of problems. Legal teams most often have to find an angle of presenting complex scientific data before the judges and juries. Other interested parties could even debate specificity and legitimacy of a given biomarker. They can claim that some other factors caused the observed health effects. To overcome such challenges, it is important to make sure that there are well-tested biomarkers that have already appeared in peer-reviewed literature, plus expert testimony. This would ensure that not only would there be admissibility but also persuasiveness that would sway the outcome of legal cases [89].

Biomarker Forensic Validations

Forensic validation of biomarkers is the critical step in ensuring credibility in using biomarkers for legal and investigative purposes. Validating biomarkers simply means demonstrating specificity, sensitivity, and reproducibility under different conditions. For instance, in forensic toxicology, the reliability of biomarker blood alcohol concentration is well validated, for instance, in the case of DUI cases. Analogously, drug metabolites biomarkers are validated through controlled studies to ensure accuracy regarding drug use or overdose detection. If not well validated, then, in most legal settings, the use of biomarker evidence will be dismissed, and thereby, this will undermine the utility of biomarkers in toxicology cases [90].

A major challenge in validating biomarkers in forensic applications is that confounding factors do not allow biomarkers to be independently affected. Such differences in metabolism or concomitant exposure to other chemicals may make cholinesterase levels change, for example in pesticide exposure. Thus, age, gender, genetic predisposition, and pre-existing medical conditions have to be considered when validating studies. International organizations, for instance the International Organization for Standardization (ISO), play a very significant role in attaining agreement and reliability in validation biomarkers by providing standardized protocols and guidelines [91].

Improved forensic techniques also incorporate the use of high-resolution mass spectrometry that further increases the accuracy levels of the analysis. These technologies enable the detection of low-abundance biomarkers and provide the discrimination between isomers, therefore increasing the specificity levels. Therefore, validated biomarkers are increasingly viewed as powerful evidence in court cases that link science findings to judicial processes. Consequently, continuing research and innovation in forensic biomarker validation is very important [92].

Ethical Considerations of Biomarkers

Biomarkers in toxicology pose many problems of privacy and informed consent. Biomarkers in general tend to reveal sensitive information about health, lifestyle, and predispositions to disease in people if mishandled. Some examples include occupational exposure studies where disease predisposing factors may be revealed resulting in discrimination in employment. Ethical requirements include obtaining informed consent before biomarker testing and a right to control the use of their data [93].

The second ethical issue is disclosure of results of biomarkers to third parties, such as an insurance company or legal authorities. Biomarker evidence can prove to be very useful in toxicology cases, but disclosure must be balanced against the right to confidentiality of the individual. There will be regulatory frameworks governing such matters as the Health Insurance Portability and Accountability Act in the case of the United States. But such

continuous debates indicate that more stringent policies are needed so that biomarkers can be used in toxicology without compromising either scientific integrity or legal fairness [94].

Biomarkers in Occupational Toxicology

Biomarkers of Exposure in Monitoring Occupational Exposure

Biomarkers of exposure to harmful chemicals, among the integral components of workplace biomarkers, play an essential role. People exposed include agricultural workers, industrial or manufacturing site employees, and those employed in mines as miners, as such a large population of the work group faces exposure due to harmful chemicals [95]. Biomarkers of exposure such as urinary cotinine in scenarios involving exposure to nicotine or blood levels of lead in heavy metal exposure cases help in both identification and quantification. Such measurements provide employers with objective data by which to base interventions that will reduce toxic risks and improve the safety of the workplace [96].

Biomarkers Application

Biomarkers also determine cumulative exposures that are not quite very evident from the standard monitoring done. For example, through biomarkers in blood or adipose tissue, exposure to POPs can be measured in terms of long-term accumulation [97]. This is quite useful in identifying delayed health effects such as chronic diseases or cancers which may occur due to low-level and long-time exposures. Indeed, biomarkers provide a preventive approach to occupational health, which flags early signs of overexposure in regular monitoring.

Improved technologies, like metabolomics and proteomics, are realized through new biomarkers' expanded possibilities that present more complete evaluation of exposures in the workplace. Such techniques can detect even subtle metabolic changes following toxicants exposure, thus allowing to bring physiological responses to the fore. This innovation enhances possible identification of at-risk workers and introduces combined strategies reducing exposure so that compliance with occupational health standards will be bettered [98].

Early Detection of Occupational Diseases

Biomarkers have become essential now in the earlier stages of occupational diseases that allow interventions before reaching the worst situation. Take for example the measurement in which one finds a decrease of cholinesterase activity when the exposure is due to pesticide for farmers and agricultural personnel that has started neurotoxic manifestation even before clinical symptoms manifested. Urinary cadmium levels also act as an early warning for kidney dysfunctioning in exposed workers. Such early warnings are very crucial to prevent the onset of diseases developed due to increased duration exposure [99].

Biomarkers fill gaps between exposure and disease manifestation by indicating preclinical changes. They are much useful in chronic occupational diseases such as silicosis, asbestosis, and occupational asthma. This is very helpful in making an early suggestion of pulmonary damage even before the onset of radiological abnormalities, as noted by biomarkers such as surfactant proteins in the lavage fluid of the bronchoalveolar [100]. Here, health professionals would be able to inform about some form of change in the working conditions or measures of protection for less likely serious cases [101].

Frameworks of Regulation over Biomarkers in Occupational Safety

Occupational toxicology biomarkers apply within a framework of appropriate application that guarantees reliability and safety in use [102]. For example, OSHA and the ECHA provide guidelines on how to go about the use of biomarkers. The frameworks help in applying only valid biomarkers with a suitable sampling method and proper interpretation standards to ensure that assessments are consistent and accurate [103].

Conversely, the regulatory frameworks have focused on worker privacy and informed consent much more than do the biomarker-based monitoring programs. In this regard, the employers are supposed to communicate with workers on the purposes, benefits, and risks of biomarker testing. It is possible to remove the ethical objections concerning discrimination that could arise from biomarker-based results through measures of high data confidentiality. On reference to these regulations, the employment

of biomarkers in workplace health programs would serve its intended purpose without infringing on the rights of the employees [104].

Biomarkers in Environmental Toxicology

Biomarkers of exposure to environmental pollution

Biomarkers have revolutionized the assessment of environmental pollution, as they are specific, quantifiable, and measurable indices of exposure to environmental pollutants [105]. For example, mercury and arsenic blood concentration or urinary metabolites of PAHs are indicative of exposure to industrial and agricultural sources of heavy metals and vehicular emissions of air pollutants, respectively. Biomarkers are markers of both exposure and effect [106].

Long-term biomarker studies give insight into the cumulative effects of pollution on human health. Biomarker studies have, for instance, shown that POPs are associated with endocrine disruption and other reproductive issues, thus calling for regulation of these substances. Coupling biomarker data with environmental monitoring will help draw out correlations between pollutant levels in the environment and their biological effects, thus making regulatory actions more specific and targeted [107].

Ecotoxicological Biomarkers in Wildlife

Biomarkers are also heavily employed in ecotoxicology in assessing the level of impacts from environmental toxins in wildlife. For instance, a shift in the quantity of certain enzymes, like depressed activity of acetylcholinesterase in fish, is biomarkers of pesticide exposure in water ecosystems. Equally, metallothioneins in mollusks are biomarkers of heavy metal contamination with significant information useful in ecological risk assessment [108].

Human Biomonitoring in Environmental Health Studies

Biomarker-based human biomonitoring programs are now a tool for environmental health studies [12]. Overall, these programs consist of systematic collection and analysis of population-based biomarker data concerning the level of exposure that would result in corresponding adverse health risks. In America, NHANES provides public health policy and interventions direction based on the biomarker exposures [109].

Biomarkers in Drug-Induced Toxicity

Prediction of Adverse Drug Reactions

Adverse drug reactions are a problem in the clinic, associated with patient morbidity, prolonged hospitalization, and escalating health care expenses. Biomarkers have been found to play an essential role in adverse drug reaction prediction. The treatment course can now be differently targeted based on genetic biomarkers, such as variants of the CYP2D6 gene, that control drug metabolism, and respond better to antidepressants and beta-blockers. Such predispositions, should they be found in such patients, may prevent adverse outcomes by guiding a change in dose or alternative treatments [110].

In addition to genetic biomarkers, metabolic and proteomic biomarkers also have the ability to show the risk of ADR. Drugs or endogenous metabolites may be used as biomarkers that may indicate altered pathways predisposing patients to toxic effects [61]. For instance, higher plasma levels of certain cytokines have been reported to have a risk for hypersensitivity reactions caused by drugs. Furthermore, incorporation of these biomarkers into clinical practice can also improve therapeutic safety and efficacy [111].

Advances in the field of biomarker discovery in the form of machine learning and artificial intelligence have increased the prospect of ADR prediction even further. Computational models could then process big data to discover intricate biomarker patterns correlated with specific toxicities. Such advancements would help reduce the burden of ADRs by having real-time risk assessment and making dynamic alterations in patient care [112].

Biomarkers for Hepatotoxicity and Nephrotoxicity

Drug-induced hepatotoxicity is the most common cause of liver failure and the main reason for the withdrawal of drugs from the market [113]. Routine use of markers such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) has been routine for monitoring liver health [114]. However, microRNA-122 and fragments of keratin-18 are some of the novel markers which are more

sensitive and specific. These can detect damage in the liver at much early stages hence allowing early interventions that consequently prevent irreversibly damaging parts of the organ [115].

Similar cases include nephrotoxicity, which, most of the time is caused by a range of drugs; for instance aminoglycosides and NSAIDs can be traced using the new generation biomarkers [116]. Some conventional markers such as serum creatinine are quite insensitive, especially for the earliest stages of renal damage. In contrast, the recently developed markers are neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1), which can predict and monitor early renal damage. Including them in screening protocols reduces the incidence of drug-induced kidney failure [117].

Biomarkers in Drug Development and Safety Evaluation

The integration of biomarkers into drug development has changed the assessment of drug safety and efficacy. Biomarkers are now used during preclinical studies to predict potential toxicities, and unsafe compounds can be terminated at an early stage. For example, cardiac biomarkers such as troponins are used to test for cardiotoxic effects of new drugs during the preclinical stages. Such early evaluations prevent costly failures in later stages of drug development [61].

Biomarkers are thus used in clinical trials to predict both therapeutic outcomes and adverse effects. This accelerates the drug approval process because reliable data on drug performance would be delivered. For example, in oncology trials, biomarkers such as ctDNA measure drug response and disease progression. The ability to design adaptive trials using a biomarker allows for adjusting protocols with real-time biomarker information, increasing the efficiency and safety of the trial [118].

Regulatory agencies, such as FDA and EMA, have embraced the concept of biomarker-driven strategy with guidelines on validation and use in drug development. Further, it ensures that only valid markers are used in the safety evaluation for consistency and reliability. As the concept of personalized medicine continues to gain momentum, biomarkers will remain at the forefront in drug development between innovation and safety [119].

Conclusion

Biomarkers have been found to be the most crucial tool in toxicogenomics that reveals profound knowledge concerning the mechanism behind toxicity, hence human health. It gains direct real-time information related to exposure and biological impact; therefore, the strategy adapted for the assessment of risk and also for therapeutics gets individualized. Such research further reinforces the significance of biomarkers and closes gaps between toxicological research and clinical applications, in opening up the scope for further innovation in precision medicine, so that, through enhancing knowledge of complex interplays between genetic and environmental influences, biomarkers can change the face of toxicology in the making of a safer environment and pharmaceutical practice.

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