The impact of environmental factors on health status biomarkers

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INNO-SAFE-LIFE

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Conceptual Framework

Health outcomes = **f(G, E, t)**: interplay of genes (G), environment (E), and time (t).

Biomarkers represent quantifiable intermediate endpoints.

Framework:

- **Exposure → Internal Dose → Biological Effect → Disease Manifestation**

Central to **translational toxicology** and **precision public health**.

We conceptualize health as a dynamic function of genotype, environment, and time. Biomarkers occupy the causal continuum between external exposure and disease, allowing mechanistic inference and early detection.

The Exposome Paradigm

Coined by **Wild (2005)**: “The cumulative measure of environmental influences and biological responses throughout the lifespan.”

Components:

External exposome: pollutants, diet, microbiota, stressors.

Internal exposome: metabolites, hormones, reactive intermediates.

Analytical challenge: linking multi-level exposures to biological signals.

The exposome paradigm complements genomics by providing the environmental dimension of health. The complexity arises because exposures are dynamic, interrelated, and non-linear — requiring multi-omics integration for biomarker discovery.

Classification of Biomarkers

Exposure biomarkers: indicate the presence of an exogenous agent (e.g., urinary metabolites of benzene).

Effect biomarkers: represent early biological responses (e.g., oxidative DNA adducts).

Susceptibility biomarkers: reflect host factors modifying risk (e.g., GSTM1 polymorphisms).

Prognostic biomarkers: predict disease progression or resilience.

This taxonomy, endorsed by OECD and WHO, frames biomarker utility across the exposure–response spectrum. In environmental health, distinguishing effect from susceptibility biomarkers is key for causal interpretation.

Mechanistic Pathways

Environmental exposures trigger cascades:

Oxidative stress → ROS generation → lipid, protein, DNA oxidation.

Inflammation → cytokine induction (IL-6, TNF-α).

Epigenetic modulation → DNA methylation, miRNA dysregulation.

Endocrine interference → receptor antagonism, transcriptional disruption.

Mitochondrial dysfunction → altered ATP production, apoptosis.

At the mechanistic level, multiple molecular networks converge. For example, air pollutants induce ROS, activating NF-κB and AP-1 pathways that regulate proinflammatory genes. Such mechanistic biomarkers anchor toxicological plausibility.

Air Pollution as a Determinant

Primary pollutants: $PM_{2.5}$, NO_x, SO_2, ozone.

Cellular outcomes: oxidative DNA lesions (8-OHdG), lipid peroxidation (MDA).

Systemic biomarkers: CRP, fibrinogen, IL-6.

Epidemiological evidence: increased all-cause and cardiovascular mortality.

Ambient air pollution remains the most studied environmental determinant. Multi-cohort analyses show that long-term $PM_{2.5}$ exposure correlates with elevated systemic inflammation and endothelial dysfunction, measurable via CRP and IL-6 levels.

Heavy Metals and Metalloestrogens

Lead (Pb): neurotoxicity; blood Pb and δ-ALAD inhibition as biomarkers.

Cadmium (Cd): renal and bone toxicity; urinary β_2-microglobulin, metallothionein induction.

Mercury (Hg): neurobehavioral biomarkers and hair Hg analysis.

Arsenic (As): methylated metabolites (MMA, DMA) in urine; oxidative and epigenetic effects.

Metals exhibit both direct toxicity and endocrine mimicry. Speciation analysis is critical—arsenic methylation efficiency, for instance, modulates toxicity. Multi-omics profiling reveals secondary impacts on mitochondrial and DNA repair pathways.

Persistent Organic Pollutants (POPs)

Lipophilic, bioaccumulative, and resistant to degradation.

Dioxins, PCBs, PBDEs disrupt hormonal signaling.

Biomarkers:

- **Serum concentrations** (GC-MS validated).
- **Altered thyroid axis biomarkers** (T_3/T_4, TSH).
- **CYP1A1 gene induction** via AhR activation.

POPs exemplify long-term body burden biomarkers. Their quantification in serum lipid fractions provides integrative exposure indices, while AhR-related gene expression serves as functional biomarkers of effect.

Endocrine-Disrupting Chemicals (EDCs)

Phthalates, bisphenols, parabens: interact with estrogenic and androgenic receptors.

Mechanisms:

- Competitive binding to nuclear receptors.
- Alteration of steroidogenic enzyme expression.

Biomarkers: urinary monoesters, hormone panels, receptor transactivation assays.

EDCs induce subtle yet chronic endocrine perturbations. Multi-hormone profiling combined with receptor reporter assays provides mechanistic linkage between exposure and reproductive/metabolic dysfunction.

Psychosocial and Physical Environment

Chronic stress → sustained HPA axis activation (cortisol dysregulation).

Noise pollution: elevated catecholamines, endothelial dysfunction biomarkers.

Heat exposure: altered electrolyte and oxidative profiles.

Urbanicity: combined exposures—air, noise, light, stress.

The nonchemical environment contributes significantly to biomarker variability. Chronic psychosocial stress modulates inflammation and immune regulation, amplifying susceptibility to physical pollutants — the "double jeopardy" effect.

Molecular Omics Integration

Transcriptomics: differential gene expression in detoxification (CYP, GST families).

Proteomics: quantification of oxidative and inflammatory proteins (HSP70, SOD1).

Metabolomics: disruption in lipid peroxidation, amino acid, and xenobiotic pathways.

Epigenomics: site-specific DNA methylation at CpG loci (e.g., AHRR, F2RL3).

Omics approaches offer unbiased discovery of exposure signatures. Integration through systems biology reveals pathway-level perturbations—bridging molecular biomarkers and disease phenotypes.

Oxidative Stress Network Biomarkers

Primary ROS markers: superoxide anion, hydrogen peroxide.

Secondary markers: 8-OHdG (DNA oxidation), MDA and F_2-isoprostanes (lipid oxidation).

Antioxidant defenses: GSH/GSSG ratio, superoxide dismutase, catalase activity.

Redoxomics: global thiol-disulfide homeostasis.

Oxidative stress biomarkers represent a central, conserved response mechanism. Advances in redoxomics and high-resolution mass spectrometry now permit multiplex quantification of reactive intermediates and repair capacity.

Inflammation and Immune Modulation

Acute phase reactants: CRP, serum amyloid A.

Cytokines: IL-6, TNF-α, IFN-γ.

Cellular biomarkers: leukocyte differentials, activation markers (CD40L, ICAM-1).

Chronic inflammation: pathway to cardiometabolic and oncogenic progression.

Inflammatory biomarkers are integrative: they reflect immune perturbation across multiple exposure domains. Persistent low-grade inflammation links environmental insults with metabolic syndrome and carcinogenesis.

Epigenetic Mechanisms and Biomarkers

DNA methylation: environmentally sensitive CpG sites (AHRR, LINE-1).

Histone acetylation/methylation: chromatin remodeling in response to EDCs.

miRNAs: miR-21, miR-146a as pollution-responsive regulators.

Transgenerational inheritance: stable epimutations beyond direct exposure.

Epigenetic markers represent the "molecular memory" of exposure. Unlike transient biochemical signals, these modifications can persist for decades, influencing disease risk and intergenerational health outcomes.

Metabolic and Endocrine Biomarker Networks

Insulin signaling disruption: altered fasting insulin, HOMA-IR.

Thyroid dysregulation: T_3/T_4, TSH changes linked to POPs, EDCs.

Lipidomic markers: cholesterol oxidation products (oxysterols).

Metabolic syndrome: composite biomarker panels integrating adipokines (leptin, adiponectin).

Environmental exposures often reprogram metabolic homeostasis. Multi-biomarker panels capture systemic alterations better than single endpoints, reflecting the integrative stress of the exposome.

Epidemiological Integration

Cohort studies: NHANES, EPIC, HBM4EU, MESA Air.

Use of **biobanked biospecimens** for retrospective exposure reconstruction.

Statistical frameworks:

- Multivariate regression
- Bayesian hierarchical models
- Mixture analysis (weighted quantile sum regression, BKMR)

Modern epidemiology employs mixture models to capture real-world exposures. The combination of high-dimensional exposure and biomarker data challenges traditional linear inference, requiring advanced computational tools.

Data Integration and Causal Inference

Multi-omics integration: network-based modeling (WGCNA, pathway enrichment).

Causal mediation analysis: partitioning effects of exposure via biomarkers.

Machine learning: random forest, LASSO, and deep learning for biomarker signature discovery.

Big data platforms: exposome–biobank linkages (UK Biobank, Exposome-Explorer).

Data integration and causal inference form the frontier of biomarker research. Algorithms now detect complex non-linear associations, improving prediction and revealing mechanistic pathways beyond single-variable analysis.

Ethical and Regulatory Dimensions

Ethical considerations: informed consent, genetic–environmental privacy, incidental findings.

Regulatory uses: REACH (EU), EPA IRIS, OECD biomarker validation frameworks.

Equity implications: environmental justice, unequal exposure burdens.

Ethical and regulatory dimensions shape biomarker deployment. Population-level biomonitoring must balance individual privacy with societal benefit, particularly for communities disproportionately exposed to environmental hazards.

Future Prospects

High-throughput exposomics: non-target LC–HRMS for comprehensive exposure screening.

Wearable biosensors: real-time physiological and pollutant monitoring.

Digital twins: simulation of environmental–biological interactions.

Precision prevention: individualized exposure–biomarker feedback loops.

The field is evolving toward predictive, personalized environmental health. Combining continuous exposure monitoring with biomarker-based modeling may soon enable adaptive public health interventions.

Conclusion

Environmental factors induce multi-layered biological responses detectable through biomarkers.

Integration of **molecular**, **omics**, and **systems-level** biomarkers enhances exposure–effect mapping.

Future directions: harmonized global biomonitoring, data-driven inference, and equitable application.

The biomarker framework transforms environmental science into **actionable health intelligence**.

To conclude: biomarkers bridge molecules, mechanisms, and policy. As technology, computation, and interdisciplinary science converge, biomarker-driven exposomics will redefine environmental health risk assessment and prevention.