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Agency for Toxic Substances and Disease Registry

Genotoxicity, Toxicological Profiles, and Protecting Communities at Risk

Editor's Note: As part of our continued effort to highlight innovative approaches to improve the health and environment of communities, the *Journal* is pleased to publish regular columns from the Agency for Toxic Substances and Disease Registry (ATSDR) at the Centers for Disease Control and Prevention (CDC). ATSDR serves the public by using the best science, taking responsive public health actions, and providing trusted health information to prevent harmful exposures and diseases related to toxic substances. The purpose of this column is to inform readers of ATSDR's activities and initiatives to better understand the relationship between exposure to hazardous substances in the environment, its impact on human health, and how to protect public health.

The findings and conclusions in this column are those of the authors and do not necessarily represent the official position of CDC, ATSDR, or the National Center for Environmental Health. The use of product names does not constitute an endorsement of any manufacturer's product.

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Introduction

Protecting communities from harmful hazardous exposures is the central mission of the Agency for Toxic Substances and Disease Registry (ATSDR). One critical challenge facing environmental public health today is understanding how hazardous substances, particularly metals, damage genetic material and initiate disease processes long before clinical symptoms appear. Genotoxicity, defined as adverse effects on DNA integrity and stability, represents a foundational mechanism linking toxic exposures to cancer, neurodegeneration, and other chronic health outcomes (Shoeb et al., 2023). Through decades of applied toxicological research, community engagement, and development of toxicological profiles for several hazardous substances (Agency for Toxic Substances and Disease Registry [ATSDR], 2022, 2024), ATSDR has built a scientific framework that translates genotoxic evidence into public health action.

This column highlights work led and supported by ATSDR on metal-induced genotoxicity, telomere biology, and toxicological profiles, emphasizing how these efforts support community health protection, risk assessment, and prevention strategies. Recent advancements—particularly those integrating telomere alteration (Shoeb, Joseph et al., 2017; Shoeb, Kodali et al., 2017), shelterin complex dysregulation, and DNA damage response (DDR) pathways (Antonini et al., 2019; Shoeb et al., 2019, 2020, 2021, 2024)—underscore the value of genotoxic biomarkers (Figure 1) by suggesting populations at risk and providing timely intervention strategies.

Genotoxicity as a Public Health Risk

Genotoxicity is a summation of DNA alterations, including DNA strand breaks, chromosomal aberrations, DNA repair inhibition, epigenetic modification, and telomere alteration (Shoeb et al., 2021, 2023). ATSDR (2026) has systematically cataloged these endpoints within its Toxicological Profiles (Tox Profiles) to create a comprehensive framework for evaluating the strength, consistency, and relevance of evidence across hazardous substances. Furthermore, these genotoxic endpoints are not just abstract laboratory observations, but they could represent early biological events that precede disease and thus offer strategies for intervention.

Our recent studies suggested that metals commonly encountered at hazardous waste sites and in occupational settings, such as chromium, nickel, arsenic, cadmium, lead, and mercury, might result in the activation of multiple genotoxic pathways (Beddingfield et

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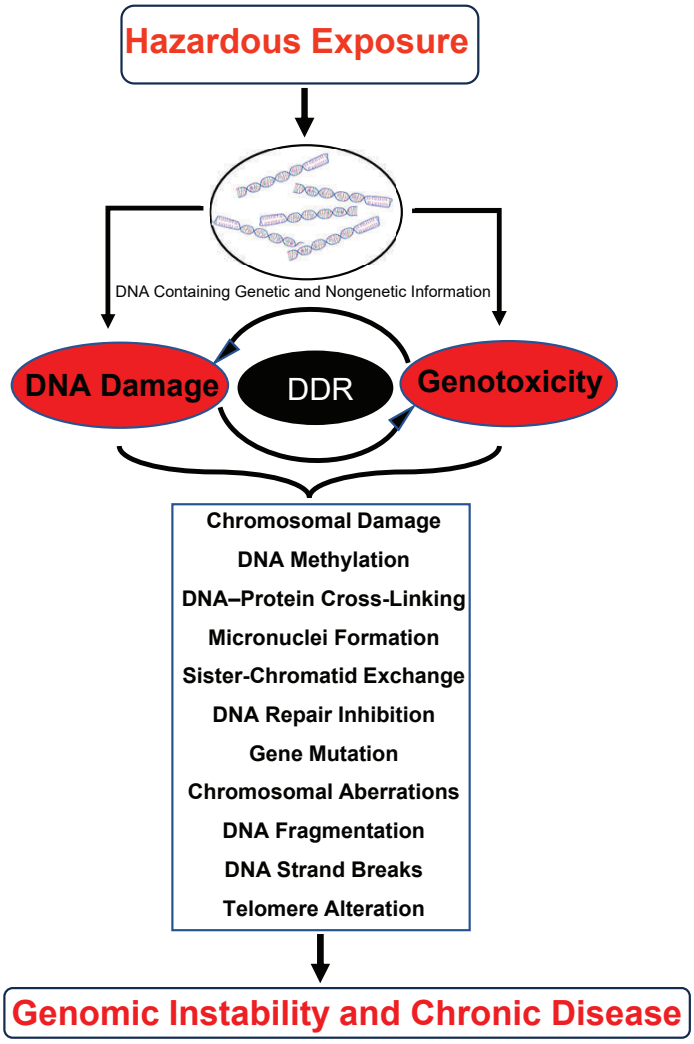
FIGURE **1**

Possible Activation of DNA Damage-Induced Genotoxic Endpoints After Hazardous Exposures



Note. This schematic illustrates how hazard exposure-induced DNA damage response (DDR) can activate genotoxic endpoints and possibly contribute to genomic instability and disease outcomes. Adapted from Shoeb et al., 2023.

al., 2024). For example, welding fumes are complex mixtures of cytotoxic and genotoxic metals capable of inducing oxidative stress, DNA damage, and telomere dysregulation (Shoeb, Kodali et al., 2017; Shoeb et al., 2020, 2024). Evidence suggests that even subchronic exposure to welding fumes can lead to measurable genomic instability in peripheral blood mononuclear cells (PBMCs) and target tissues (Antonini et al., 2019; Shoeb, Kodali et al., 2017; Shoeb et al., 2024), reinforcing concerns for exposed occupational workers and surrounding communities.

Telomeres Biology and Metal-Induced DNA Damage

Growing scientific evidence supports the integration of genotoxicity into toxicological evaluation. Telomeres are specialized DNA–protein structures that protect chromosome ends and regulate cellular aging, senescence, and genomic stability (Barthel et al., 2017; Beddingfield et al., 2024; Blasco, 2005; Shoeb et al., 2021, 2023). Alterations in telomere length, either shortening or inappropriate elongation, can disrupt normal DNA function and might increase susceptibility to cancer and other chronic disease conditions.

ATSDR investigators reported that pulmonary exposure to metal-rich welding fumes induces telomere elongation in both PBMCs and lung tissue without activation of telomerase reverse transcriptase (TERT) (Shoeb et al., 2024). Instead, this effect is mediated by dysregulation of the shelterin complex, which normally safeguards telomere integrity. From a public health perspective, these mechanistic insights are critical. Telomeres and their regulatory proteins might serve as early biomarkers to evaluate genotoxic events, allowing identification of exposed populations before irreversible pathologies occur. This identification aligns with ATSDR's emphasis on prevention, early detection, and evidence-based community health decision-making approaches.

Toxicological Profiles: Translating Science Into Action

ATSDR's Tox Profiles are cornerstone documents that synthesize epidemiological, mechanistic, and animal experimental evidence to inform risk assessment and public health guidance. By organizing data around defined genotoxic endpoints, Tox Profiles enable comparison across hazardous substances and identification of data gaps. Depending on the ATSDR Substance Priority List of identified hazardous substances commonly found at hazardous waste sites that pose the greatest potential threat to human health (ATSDR, 2022, 2024), evidence of genotoxicity often supports the classification of known, probable, or suspected human carcinogens, reinforcing the need for exposure reduction and regulatory action.

Importantly, ATSDR develops minimal risk levels (MRLs), which are estimations of daily human exposure to a hazardous substance likely to pose minimal risk for noncancer health effects. Derivation of MRLs is included in ATSDR Tox Profiles, which can be used as health-based comparison values when investigating hazard exposure scenarios relevant to real communities. Residents living near superfund sites,

workers in metal-processing industries, and sensitive populations such as children, pregnant women, older adults, and people with preexisting disease conditions might experience cumulative or mixed exposures. ATSDR's scientific framework acknowledges these complexities and supports the use of mechanistic biomarkers, including telomere alteration (Beddingfield et al., 2024; Kim et al., 2025), to refine health assessments and community outreach.

Implications for Communities

Communities disproportionately burdened by environmental contamination often face limited access to health resources and delayed recognition of exposure-related disease. Genotoxic biomarkers offer a pathway to earlier identification of exposure-related health risks, empowering communities and public health practitioners with intervention strategies. ATSDR's work underscores that DNA damage is not merely a molecular endpoint but could be a warning signal informing target audiences of where to focus interventions and exposure mitigation strategies.

By linking genotoxic events to Tox Profiles and community health practice, ATSDR continues to raise awareness among communities affected by harmful environmental exposures. Understanding how hazardous exposures disrupt genomic integrity strengthens the scientific basis for site cleanup, occupational protections, and community education, ensuring that prevention efforts are grounded in the best available science.

Conclusion

ATSDR efforts will continue to integrate emerging genotoxic biomarkers into toxicological evaluation and public health practice to shed light on the toxic effects of hazardous exposures. Expanding longitudinal studies, incorporating mixture effects, and translating mechanistic findings into accessible community guidance remain priorities. As the science of genotoxicity and related biomarkers advances, ATSDR's mission to prevent harmful exposures and protect public health remains a priority.

Through rigorous research, transparency, and commitment, ATSDR will continue to transform genotoxicity science into meaningful public health action.

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