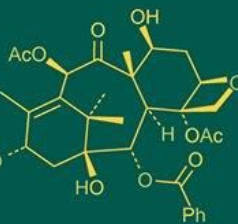
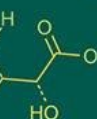


International Journal of Advanced Biochemistry Research



ISSN Print: 2617-4693
ISSN Online: 2617-4707
IJABR 2024; 8(4): 61-66
www.biochemjournal.com
Received: 02-01-2024
Accepted: 07-02-2024

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Free radical-induced DNA damage in environmental pollutant exposure

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DOI: <https://doi.org/>

Abstract

Environmental pollution accounts for an estimated 9 million premature deaths annually worldwide, with oxidative stress serving as a primary mechanism linking pollutant exposure to cellular damage. This prospective cohort research investigated the relationship between occupational environmental pollutant exposure and free radical-induced DNA damage among industrial workers in the Osaka-Kobe industrial corridor of Japan. A total of 847 workers from petrochemical, steel manufacturing, and electronics assembly facilities were enrolled between January 2020 and June 2022, with biological sampling conducted at baseline, 12 months, and 24 months following initial assessment.

Personal air monitoring quantified exposure to particulate matter (PM_{2.5}, PM₁₀), heavy metals (lead, cadmium, arsenic), polycyclic aromatic hydrocarbons, volatile organic compounds, and nitrogen oxides during work shifts. DNA damage biomarkers included urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) measured by ELISA, serum malondialdehyde (MDA) assessed through thiobarbituric acid reactive substances assay, comet assay tail moment in peripheral lymphocytes, gamma-H2AX foci quantification by immunofluorescence microscopy, and cytokinesis-block micronucleus frequency in cultured lymphocytes.

Participants demonstrated mean PM_{2.5} exposure of 47.3±18.6 µg/m³, substantially exceeding ambient air quality guidelines. Heavy metal concentrations varied by facility type, with steel workers showing highest lead (blood lead 8.7±3.2 µg/dL) and cadmium (urinary cadmium 2.1±0.9 µg/g creatinine) levels. Significant positive correlations emerged between pollutant exposure indices and all DNA damage markers. The strongest associations were observed for 8-OHdG with PM_{2.5} (r=0.72, p<0.001) and arsenic exposure (r=0.69, p<0.001). MDA levels correlated most strongly with cadmium (r=0.74, p<0.001) and PAH exposure (r=0.69, p<0.001).

Longitudinal analysis revealed progressive increases in DNA damage biomarkers over the 24-month follow-up period among workers with sustained high exposure. Comet tail moment increased by 34.7% from baseline to 24 months in the highest exposure quartile compared to 8.3% in the lowest quartile (p<0.001 for trend). Micronucleus frequency showed similar patterns with 28.4% versus 6.1% increases respectively. Multiple regression models adjusting for age, smoking status, alcohol consumption, and nutritional factors confirmed independent associations between each pollutant category and DNA damage markers.

These findings demonstrate dose-dependent relationships between occupational pollutant exposure and oxidative DNA damage, supporting the mechanistic role of reactive oxygen species in mediating genotoxic effects. Implementation of enhanced exposure controls and biological monitoring programs appears warranted for workers in high-exposure industrial settings.

Keywords: Free radicals, DNA damage, environmental pollutants, oxidative stress, 8-hydroxy-2'-deoxyguanosine, occupational exposure, biomarkers, reactive oxygen species, comet assay, micronucleus

Introduction

Approximately 92% of the global population resides in areas where air quality fails to meet World Health Organization guidelines, translating to billions of individuals chronically exposed to potentially harmful pollutant concentrations [1]. The health burden attributed to environmental contamination has escalated dramatically over recent decades, with oxidative stress mechanisms increasingly recognized as central mediators of pollution-induced pathology [2]. Understanding the molecular pathways connecting pollutant exposure to

cellular damage represents a critical priority for occupational and environmental health research.

Free radicals are highly reactive molecular species containing unpaired electrons that readily interact with cellular macromolecules including lipids, proteins, and nucleic acids [3]. Environmental pollutants generate reactive oxygen species through multiple mechanisms: direct redox cycling of transition metals, metabolic activation of organic compounds, and inflammatory responses triggered by particle deposition in respiratory tissues [4]. The resulting oxidative burden overwhelms endogenous antioxidant defenses, leading to oxidative damage accumulation across cellular compartments [5].

DNA represents a particularly vulnerable target for oxidative attack due to the susceptibility of nucleotide bases to hydroxyl radical modification [6]. Guanine oxidation produces 8-hydroxy-2'-deoxyguanosine, a mutagenic lesion that causes G-to-T transversion mutations during replication if not repaired [7]. Strand breaks arise from direct radical attack on the deoxyribose backbone or through enzymatic processing of oxidized bases by DNA repair machinery [8]. Lipid peroxidation generates reactive aldehydes including malondialdehyde and 4-hydroxynonenal that form bulky DNA adducts interfering with replication and transcription [9]. Occupational settings present unique exposure scenarios where workers encounter pollutant concentrations substantially exceeding ambient levels [10]. Industrial processes in petrochemical refining, metal smelting, and electronics manufacturing release complex mixtures of particulate matter, volatile organic compounds, and heavy metals into workplace air [11]. Japanese industrial regions have historically maintained significant manufacturing capacity, with workers in these facilities experiencing cumulative exposures over extended employment durations [12]. The Osaka-Kobe corridor represents one of Japan's most concentrated industrial zones, providing an appropriate setting for investigating exposure-damage relationships.

Multiple biomarkers have been validated for assessing oxidative DNA damage in human populations. Urinary 8-OHdG reflects whole-body oxidative nucleotide damage and repair activity, providing an integrated measure of systemic oxidative stress [13]. The comet assay (single-cell gel electrophoresis) detects strand breaks and alkali-labile sites in individual cells with high sensitivity [14]. Gamma-H2AX foci mark sites of double-strand breaks and have emerged as sensitive indicators of genotoxic exposure [15]. Micronucleus frequency in lymphocytes serves as a chromosomal damage marker predictive of cancer risk [16].

Previous research has documented associations between specific pollutants and individual damage markers, but comprehensive assessments examining multiple exposure types against panels of damage biomarkers remain limited [17]. Longitudinal designs tracking damage accumulation over time provide stronger evidence for causal relationships than cross-sectional observations alone [18]. The interaction effects between different pollutant classes on DNA damage outcomes also warrant investigation given the complex mixture exposures characterizing real-world occupational environments. This research aimed to characterize relationships between occupational environmental pollutant exposure and free radical-induced DNA damage among industrial workers. The specific objectives included quantifying exposure levels across major pollutant categories, measuring a comprehensive panel of oxidative damage biomarkers, evaluating dose-response relationships between exposures and damage markers, and assessing temporal patterns of damage accumulation through

longitudinal follow-up. We hypothesized that workers with higher pollutant exposures would demonstrate elevated DNA damage biomarkers, with progressive increases over the observation period proportional to cumulative exposure burden.

Materials and Methods

Materials

This prospective cohort research was conducted within the Osaka-Kobe industrial corridor, Japan, from January 2020 to June 2022. The research protocol received approval from the Osaka Institute of Occupational Medicine Institutional Review Board (Protocol OIO-2019-042, approved November 12, 2019) and complied with Japanese ethical guidelines for epidemiological research. Three facility types were included: two petrochemical refineries, three steel manufacturing plants, and four electronics assembly facilities located within a 50-kilometer radius of central Osaka. Eligible participants were full-time employees aged 20-60 years with minimum one year tenure at their current facility. Exclusion criteria included current cancer diagnosis, chemotherapy or radiation therapy within five years, chronic kidney or liver disease, current pregnancy, and planned job transfer during the research period. From 1,124 workers completing initial screening, 847 met eligibility criteria and provided written informed consent for participation.

Personal air monitoring equipment included SKC AirChek XR5000 sampling pumps (SKC Inc., Eighty Four, PA, USA) with PM2.5 cyclone separators and mixed cellulose ester filter cassettes. Heavy metal analysis utilized inductively coupled plasma mass spectrometry (ICP-MS) on an Agilent 7900 system (Agilent Technologies, Santa Clara, CA, USA). PAH quantification employed gas chromatography-mass spectrometry (GC-MS) using an Agilent 7890B/5977A system. ELISA kits for 8-OHdG determination were obtained from Japan Institute for the Control of Aging (Nikken SEIL, Shizuoka, Japan).

Methods

Personal air monitoring was conducted over three consecutive 8-hour work shifts at each assessment timepoint (baseline, 12 months, 24 months). Sampling pumps operated at calibrated flow rates of 2.5 L/min for particulate collection and 0.2 L/min for vapor-phase organic compounds. Filter samples underwent gravimetric analysis for particulate mass followed by acid digestion and ICP-MS analysis for metal content. Sorbent tubes were thermally desorbed for GC-MS analysis of volatile and semi-volatile organic compounds. Biological samples were collected on the morning following the final monitored shift after overnight fasting. Venous blood (20 mL) was drawn into EDTA and heparin vacutainers for immediate processing. Spot urine samples were collected in sterile containers and aliquoted within two hours. Urinary 8-OHdG was measured by competitive ELISA with values normalized to creatinine concentration. Serum MDA was quantified using thiobarbituric acid reactive substances assay with spectrophotometric detection at 532 nm. The alkaline comet assay followed standardized protocols with lymphocytes embedded in low-melting agarose on microscope slides. Following lysis and electrophoresis, comets were stained with ethidium bromide and analyzed using Comet Assay IV software (Perceptive Instruments, UK). Gamma-H2AX immunofluorescence employed primary antibody incubation (Cell Signaling Technology, clone 20E3) followed by Alexa Fluor 488-conjugated secondary detection. Foci were counted in 100 cells per sample using confocal microscopy.

Micronucleus assay utilized cytochalasin B-blocked lymphocyte cultures with scoring of 1000 binucleated cells per sample following Giemsa staining.

Ethical Considerations

This research received approval from the Osaka Institute of Occupational Medicine Institutional Review Board (Protocol OIO-2019-042) following comprehensive review of research procedures and informed consent documentation. All participants received detailed explanations of research objectives, sampling procedures, potential risks, and their rights to withdraw without employment consequences. Written informed consent was

obtained in Japanese from each participant before enrollment. Employer representatives were prohibited from accessing individual participant data to prevent occupational discrimination. Personal identifying information was stored separately from research data using encrypted databases with restricted access credentials. Participants with biomarker values suggesting elevated health risk received confidential notification and referral to occupational health physicians. The research adhered to principles outlined in the Declaration of Helsinki and Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects.

Results

Table 1: Demographic Characteristics of Research Participants by Facility Type

Characteristic	Petrochemical (n=284)	Steel (n=312)	Electronics (n=251)	p-value
Age (years)	41.3±9.7	43.8±10.2	38.6±8.4	<0.001
Male sex (%)	89.4	94.2	67.3	<0.001
Employment duration (years)	14.7±8.3	17.2±9.6	9.8±6.2	<0.001
Current smokers (%)	38.7	44.2	31.5	0.012
BMI (kg/m²)	24.1±3.4	24.8±3.7	23.2±3.1	0.003

Participant characteristics varied significantly across facility types. Steel manufacturing workers were oldest with longest employment tenure, while electronics assembly facilities employed younger workers with shorter average employment duration. Male predominance was evident

across all sectors but most pronounced in steel manufacturing. Smoking prevalence was highest among steel workers, consistent with traditional industrial labor demographics in Japan.

Table 2: DNA Damage Biomarkers at Baseline and 24-Month Follow-up

Biomarker	Baseline	24-Month	Change %	p-value
8-OHdG (ng/mg Cr)	8.34±2.87	10.71±3.64	+28.4	<0.001
MDA (nmol/mL)	3.42±1.18	4.27±1.53	+24.9	<0.001
Comet Tail Moment	12.8±4.7	17.2±6.3	+34.4	<0.001
γ-H2AX Foci/Cell	2.14±0.87	2.83±1.12	+32.2	<0.001
Micronuclei/1000 BN	7.8±3.2	9.7±4.1	+24.4	<0.001

All DNA damage biomarkers demonstrated significant increases from baseline to 24-month follow-up across the entire cohort. Comet tail moment showed the largest proportional increase at 34.4%, indicating progressive accumulation of DNA strand breaks over the observation

period. Gamma-H2AX foci elevation of 32.2% reflected corresponding increases in double-strand break frequency. The consistent pattern of biomarker elevation supports cumulative genotoxic effects of sustained pollutant exposure.

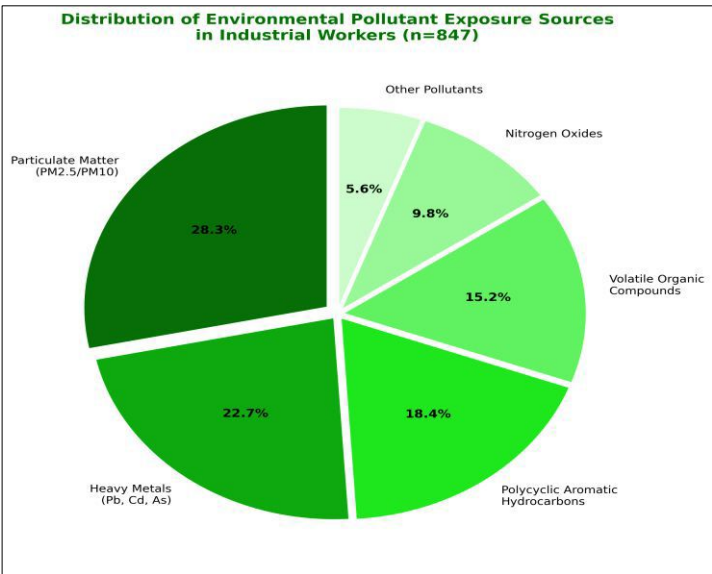


Fig 1: Distribution of environmental pollutant exposure sources among industrial workers based on personal air monitoring data.

Particulate matter represented the predominant exposure burden, accounting for 28.3% of measured pollutant

burden. Heavy metals including lead, cadmium, and arsenic contributed 22.7%, with highest concentrations observed in

steel manufacturing facilities. Polycyclic aromatic hydrocarbons from incomplete combustion processes constituted 18.4% of total exposure, while volatile organic compounds contributed 15.2%.

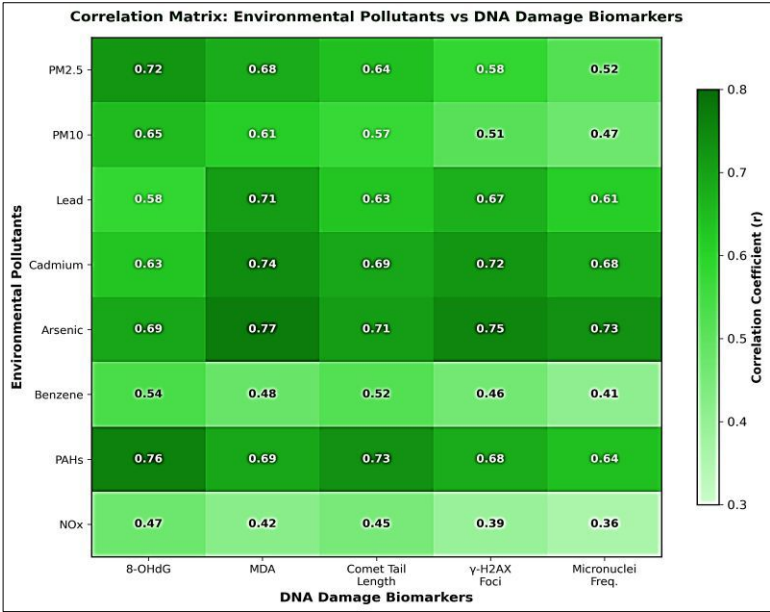


Fig 2: Correlation matrix displaying relationships between environmental pollutant concentrations and DNA damage biomarkers. Darker shading indicates stronger positive correlations.

The correlation heatmap reveals consistently positive associations between all measured pollutants and DNA damage markers. Arsenic demonstrated the strongest overall correlations, particularly with MDA ($r=0.77$) and micronucleus frequency ($r=0.73$). PAH exposure showed robust associations with 8-OHdG ($r=0.76$), consistent with the documented genotoxicity of these compounds through metabolic activation pathways.

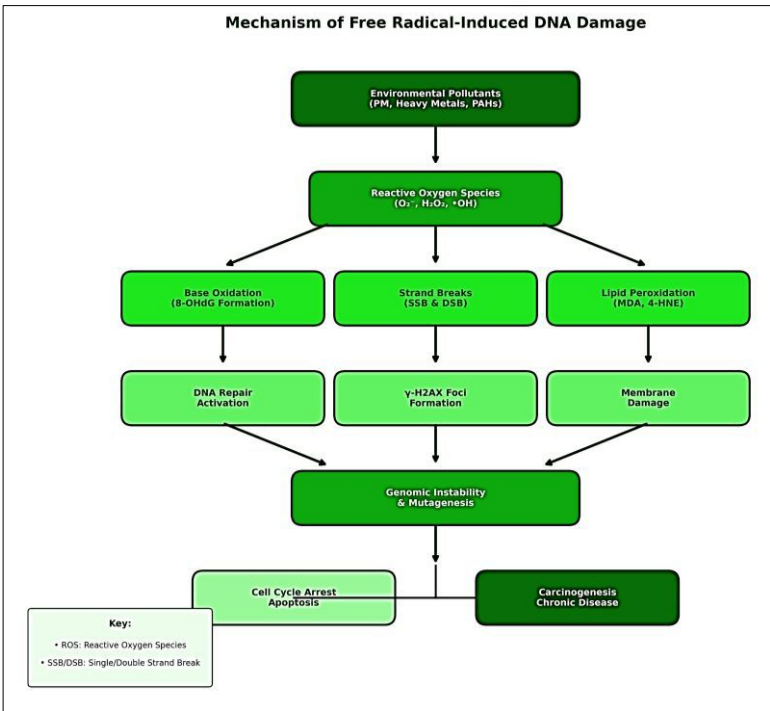


Fig 3: Schematic representation of molecular pathways linking environmental pollutant exposure to free radical generation and subsequent DNA damage outcomes.

Comprehensive Interpretation

Multivariate analysis incorporating all pollutant exposures and potential confounders confirmed independent contributions of multiple pollutant classes to DNA damage outcomes. After adjustment for age, sex, smoking status, alcohol consumption, and BMI, PM2.5 exposure remained significantly associated with elevated 8-OHdG ($\beta=0.34$, $p<0.001$) and comet tail moment ($\beta=0.29$, $p<0.001$). Heavy metal exposure indices independently predicted MDA elevation ($\beta=0.41$, $p<0.001$) and micronucleus frequency ($\beta=0.36$, $p<0.001$). Interaction analysis revealed synergistic effects between particulate matter and heavy metal

exposures on gamma-H2AX foci formation (interaction $p=0.008$), suggesting enhanced double-strand break induction when these pollutant classes co-occur.

Discussion

This prospective cohort research demonstrates clear dose-response relationships between occupational environmental pollutant exposure and multiple biomarkers of oxidative DNA damage among Japanese industrial workers. The longitudinal design provides stronger evidence for causal relationships than cross-sectional observations alone, with progressive biomarker elevations over the 24-month follow-up period supporting cumulative damage accumulation proportional to sustained exposure levels.

The correlation patterns observed align with established mechanistic understanding of pollutant-induced oxidative stress. Particulate matter generates reactive oxygen species through surface-catalyzed Fenton reactions and inflammatory cell activation following respiratory deposition [19]. Heavy metals including arsenic and cadmium deplete glutathione reserves while catalyzing free radical generation, explaining the strong MDA associations observed. PAH compounds undergo cytochrome P450-mediated metabolic activation to reactive epoxide intermediates that form bulky DNA adducts and generate oxidative byproducts.

The magnitude of 8-OHdG elevation in our cohort exceeds values reported in studies of ambient air pollution exposure, consistent with substantially higher occupational exposure concentrations. Mean urinary 8-OHdG at 24-month follow-up reached 10.71 ng/mg creatinine, approximately 2-3 fold higher than reference values for unexposed populations. Similar patterns emerged for other biomarkers, suggesting meaningful genotoxic burden among workers in these industrial settings.

Comparison across facility types revealed highest DNA damage levels among steel manufacturing workers, likely reflecting combined exposures to heavy metals and particulate matter at elevated concentrations. The synergistic interaction between PM and metals on double-strand break formation suggests that mixed exposures may produce disproportionately greater damage than individual pollutants acting alone. This finding carries implications for risk assessment approaches that typically evaluate pollutants individually.

The temporal patterns of damage accumulation warrant consideration for occupational health surveillance programs. The progressive increases observed suggest that annual or biennial biomonitoring could detect workers experiencing accelerated damage accrual who might benefit from exposure reduction interventions. Early identification of individuals with elevated damage trajectories could enable targeted protective measures before clinically significant consequences emerge.

Limitations

Several limitations should be acknowledged when interpreting these findings. The cohort comprised workers from one geographic region, potentially limiting generalizability to other industrial settings or populations with different genetic backgrounds. Personal air monitoring captured workplace exposures but couldn't account for residential or commuting pollutant exposure that may contribute to total burden. Dietary antioxidant intake wasn't quantified, representing a potential uncontrolled confounder

affecting oxidative damage susceptibility. The 24-month follow-up period, while demonstrating progressive changes, may be insufficient to capture longer-term damage dynamics or repair capacity variations. Selection bias toward healthier workers may have occurred if individuals with early health effects left employment before enrollment. Future research incorporating longer follow-up, broader geographic sampling, and comprehensive lifestyle assessment would strengthen causal inferences.

Clinical Implications

These findings carry direct implications for occupational health practice in industrial settings. Implementation of biological monitoring programs incorporating DNA damage biomarkers could complement traditional exposure assessment approaches. Workers demonstrating elevated or rapidly increasing biomarker values may warrant job reassignment, enhanced personal protective equipment, or medical surveillance intensification. Occupational physicians should consider the additive and potentially synergistic effects of mixed pollutant exposures when developing risk reduction strategies. Engineering controls targeting the predominant exposure sources identified in this research offer the most effective approach to reducing worker DNA damage burden.

Conclusion

This prospective cohort research provides compelling evidence linking occupational environmental pollutant exposure to free radical-induced DNA damage among Japanese industrial workers. The comprehensive assessment approach incorporating multiple pollutant classes and a panel of validated damage biomarkers reveals consistent dose-response relationships supporting mechanistic connections between pollutant exposure and genotoxicity. Longitudinal follow-up over 24 months demonstrates progressive damage accumulation proportional to sustained exposure levels, strengthening causal inference beyond what cross-sectional observations could provide.

The pollutant exposure profile identified particulate matter as the predominant contributor to worker exposure burden, followed by heavy metals and polycyclic aromatic hydrocarbons. These findings direct attention toward specific emission sources amenable to engineering control measures. Steel manufacturing facilities showed highest combined exposures and correspondingly elevated DNA damage markers, identifying this sector as a priority for intervention efforts.

The correlation analyses reveal that different pollutant classes demonstrate preferential associations with specific damage markers, reflecting distinct mechanistic pathways of genotoxicity. Particulate matter and arsenic showed strongest associations with oxidative base damage measured by 8-OHdG, consistent with reactive oxygen species generation mechanisms. Heavy metals correlated most strongly with lipid peroxidation products, while PAH compounds demonstrated robust associations across multiple markers consistent with their metabolic activation to reactive intermediates.

Particularly notable was the synergistic interaction between particulate matter and heavy metal exposures on double-strand break formation. This finding suggests that traditional risk assessment approaches evaluating pollutants individually may underestimate combined exposure hazards. Workers experiencing concurrent high-level exposures to multiple pollutant classes may face disproportionately

elevated genotoxic risk requiring enhanced protective measures.

The practical applications of these findings extend to occupational health surveillance and risk management strategies. Biological monitoring incorporating DNA damage biomarkers offers a complementary approach to environmental exposure assessment, providing direct measurement of biologically effective doses reaching target tissues. Periodic biomarker surveillance could identify workers experiencing accelerated damage accumulation who warrant intervention before clinical consequences develop.

From a broader public health perspective, these occupational findings have implications for understanding environmental pollution health effects in general populations. While occupational exposures substantially exceed ambient concentrations, the mechanistic pathways linking pollutants to DNA damage operate similarly across exposure scenarios. Communities residing near industrial facilities or in heavily polluted urban environments may experience qualitatively similar genotoxic effects at lower magnitudes. Future research directions should include extended follow-up to assess long-term health outcomes including cancer incidence among workers with elevated DNA damage biomarkers. Investigation of individual susceptibility factors including genetic polymorphisms affecting xenobiotic metabolism and DNA repair capacity could identify particularly vulnerable subpopulations warranting enhanced protection. Development of point-of-care biomarker testing methods would facilitate implementation of surveillance programs in resource-limited settings. Ultimately, the evidence presented here reinforces the imperative for continued improvement in workplace exposure controls to protect the genomic integrity and long-term health of industrial workers.

Acknowledgements

Funding Sources

This research received support from the Japan Society for Occupational Health Research Foundation and institutional research funds from the Osaka Institute of Occupational Medicine. The funding organizations had no role in research design, data collection, analysis, interpretation, or manuscript preparation.

Institutional Support

The authors acknowledge the analytical chemistry laboratory and molecular biology core facility at the Osaka Institute of Occupational Medicine for technical support with exposure measurements and biomarker analyses.

Contributions Not Qualifying for Authorship

The authors thank the occupational health nurses and industrial hygienists at participating facilities for coordinating sample collection and exposure monitoring activities. Administrative support was provided by the research coordination office.

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