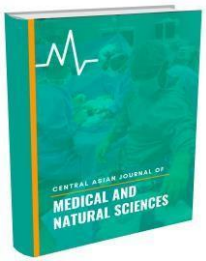

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Article

Oxidative Stress and Inflammatory Response to Indoor VOC Exposure: Biomarker Analysis in Iraqi Women

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Abstract: By producing reactive oxygen species and depleting antioxidants, volatile organic compounds (VOCs) from Household cleaning products can cause oxidative stress and inflammation. Formaldehyde levels in Iraqi homes were found to be 2.3 times higher than WHO limits (231.7 vs. 89.4 μg/m³) in our previous assessment, while benzene levels were similarly elevated. Howeve, little was known about the biological effects of such exposure. Assess inflammatory biomarker and oxidative stress in females exposed to household volatile organic compounds. A cross-Sectional Stud conducted in Kirkuk, Iraq (January -October 2024) involved 120 female housewives who were categorized as either low-exposure (n=60) or high-exposure (n=60) to indoor volatile organic compounds. Malondialdehyde (MDA), glutathion (GSH), catalase, total antioxidant capacity (TAC), nitric oxide, 8-isoprostane, protein carbonyls, and superoxide dismutase (SOD) were measured in fasting venous blood. ELISA was used to measure interleukin-6 (Il-6) and tumor necrosis factor-alpha (TNF- α). Significant oxidative and inflammatory alterations were observed in the high-exposure group: MDA rose 43% ($p<0.001$), GSH and catalase fell 37% and 33%, TAC fell 33% , and SOD fell 21% . TNF- α and lL- 6 rose by 79% and 73% , respectively (both $p< 0.001$). GSH depletion ($\beta = -0.68$) and MDA rise ($\beta =0.65$) were best predicted by formaldehyde. Women who are exposed to household VOCs experience significant oxidative stress and inflammation, which is similar to patterns observed in chronic diseases. The primary contributor, formaldehyde, emphasizes the necessity of exposure control and preventive measures based on antioxidants.

Keywords: Formaldehyde, Inflammatory Cytokines, Glutathione, Oxidative Stress, Volatile Organic Compound

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1. Introduction

Indoor air pollution from volatile organic compounds (VOCs) is an underestimated environmental health hazard affecting people worldwide.Indoor environments, where people spend roughly 90% of their time, frequently have pollutant concentrations that are two to five times higher than outdoor levels, despite the fact that outdoor air quality has received a lot of regulatory and research attention [1,2]. Formaldehyde, benzene, toluene, xylene and many other compounds are released into residential air through household cleaning products, which are a significant source of volatile organic compounds (VOCs) [3,4].

1.1 Biological VOC Toxicity

Oxidative stress, inflammatory activation, and direct cellular damage are some of the interrelated processes that mediate the health effects caused by exposure to volatile organic compounds [5]. The two main volatile organic compounds (VOCs) found in our environmental investigation, formaldehyde and benzene, are processed by cytochrome P450 (CYP450) enzymes, especially CYP2E1, which produces reactive oxygen species (ROS) as byproducts [6]. According to Wang et al. (2024), formaldehyde exposure triggers the NADPH oxidase and CYP2E1 pathways, which leads to the formation of hydrogen peroxide and superoxide anion in cellular compartments[7]. Furthermore, these substances have the ability to directly activate NADPH (NOX) oxidase complexes located on the cell membrane, thereby increasing the generation of reactive oxygen species through electron transport processes[8].

When natural antioxidant defenses are overpowered by the ensuing oxidative burden, a condition known as "oxidative stress" results, which is defined by an excess of ROS in relation to antioxidant capacity [9]. Numerous biochemical changes that have been thoroughly described in occupational and environmental exposure investigations are indicative of this imbalance:

1.1.1 Lipid Peroxidation

ROS attack polyunsaturated fatty acids in cell membranes, starting autocatalytic chian reactions that result in the stable end products of F2- isoprostanes, 4-hydroxynonenal (4-HNE), and malondialdehyde (MDA)[10]. The most extensively validated biomarker of oxidative lipid damage in human research is MDA, which is measured using thiobarbituric acid reactive substances (TBARS) assays. According to a meta-analysis by Ayala et al. (2014), increases in MDA are associated with a higher risk of cancer, development of neurological diseases, and cardiovascular events in a variety of populations. [11]. F2-isoprostanes, specifically 8-iso-prostaglandin F2α (8-isoprostane), are the gold-standard indicators of lipid peroxidation because of their specificity and chemical stability. They are produced by non-enzymatic peroxidation of arachidonic acid without the involvement of cyclooxygenase [12].

1.1.2 Oxidation of Proteins

Protein-protein crosslink formation, nitration, and carbonylation (addition of aldehyde or ketone groups) are examples of ROS-mediated protein modifications. Protein carbonyls are biomarkers of cumulative oxidative protein damage that accumulate irreversibly and are quantified by 2,4-dinitrophenylhydrazine derivatization. According to Stadtman and Levine (2003), the amount of carbonyl in proteins rises exponentially with age and oxidative stress, which leads to cellular dysfunction by deactivating enzymes and reducing protein turnover[13].

1.1.3 Depletion of Antioxidants

The main intracellular antioxidant is the tripeptide glutathione (γ-glutamyl-cysteinyl-glycine; GSH), which is found in most cells at millimolar concentrations[14]. GSH directly removes ROS through thiol-disulfide exchange reactions, acts as a cofactor for glutathione peroxidase (GPx) enzymes that reduce hydrogen peroxide and lipid hydroperoxides, and conjugates electron-loving foreign substances through glutathione S-transferase (GST) enzymes[15]. GSH is depleted by exposure to volatile organic compounds (VOCs) in three ways: (1) direct consumption during ROS neutralization; (2) the production of glutathione-formaldehyde adducts that are exported from cells; and (3) transcriptional suppression of glutamate-cysteine ligase (GCL), the enzyme that limits the rate of GSH synthesis [16]. Superoxide dismutase (SOD) and catalase are examples of complementary enzymatic antioxidants. While catalase breaks down hydrogen peroxide into water and oxygen, SOD catalyzed the dismutation of superoxide radicals into hydrogen peroxide and oxygen [17]. Through oxidative inactivation of active site residues,

reduced gene expression via redox-sensitive transcription factors, and post-translational changes that target these enzymes for proteasomal destruction, chronic oxidative stress can lower catalase and SOD activity[18]. An integrated evaluation of all plasma antioxidants, such as GSH, vitamins C and E , uric acid, and albumin, is provided by the total antioxidant capacity (TAC), which is determined by ferric reducing ability of plasma (FRAP) or oxygen radical absorbance capacity (ORAC) tests [19].

1.1.4 Activation of the Inflammatory Cascade

Redox-sensitive transcription factors, specifically nuclear factor-kappa β (NF-κβ) and signal transducer and activator of transcription 3 (STAT3), are activated by oxidative stress [20]. Inhibitor of κβ (Iκβ) proteins sequester NF-κβ dimers in the cytoplasm under baseline circumstances. Iκβ kinase (IKK) cysteine residues are oxidized by ROS, which causes Iκβ phosphorylation and breakdown and releases NF-κβ for nuclear translocation [21]. According to Wany et al.(2024), formaldehyde exposure triggers the NF-κβ pathway via ROS- dependent lKK activation, which leads to the transcriptional upregulation of cyclooxygenase-2 (COX-2), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and interleukin-1β (1L-1β) [22]. The classic pro-inflammatory cytokines, TNF- α and IL-6, cause fever by hypothalamic prostaglandin synthesis, acute-phase protein activation in the liver, and insulin resistance by interfering with insulin receptor signaling [23]. Crucially, oxidative stress and inflammation create a positive feedback loop in which ROS further activate inflammatory pathways, creating a self-perpetuating cycle, while cytokines promote more ROS production through NOX activation and mitochondrial malfunction[24].

1.2 Environmental Oxidtive Stress Vuhnerability by Gender

Due to hormonal, physiological, and behavioral reasons, women are more vulnerable to oxidative dress caused by volatile organic compounds. By activating MnSOD, catalase, and glutathione peroxidase, estrogen provides antioxidant protection; however, this defence varies with menstrual cycles and decreases after menopause. Women with higher body fat percentages are more likely to accumulate volatile organic compounds (VOCs) and have extended internal exposure, especially to lipophilic chemicals like toluene and benzene [25]. Detoxification efficiency and oxidative response are further influenced by genetic variables such GSTM1-null and CAT polymorphisms. Stronger oxidative biomarkers elevations in women exposed to air pollution were confirmed by a meta-analysis (SMD=0.34; $p < 0.001$). Housewives in areas like Iraq are more vulnerable to cumulative VOC exposure due to women's time-activity patterns, which include spending up to 22 hours indoors and frequently doing cleaning tasks[26].

Study Goals (Stortened Version)

This study sought to determine how home VOC exposure affected lraqi women 's health by:

1. Measuring inflammatory markers (IL-6, TNF- α) and oxidative stress (MDA, GSH, catalase, TAC, NO, 8-isoprostane, protein carbonyls, SOD).
2. Using regression analysis to identify VOCs that predict changes in biomarkers .
3. Investigating dose-response correlations between biological effects and VOC levels.
4. Evaluating biomarker changes in relation to predetermined thresholds for their clinical significance. The work offers mechanistic insight into VOC- related health hazards and possible intervention targets by combining exposure and biological data.

2. Materials and Methods

2.1 Ethical Approval and Study Design

From January to October 2024, this cross-sectional, comparative study was carried out in Kirkuk, Iraq. The Scientific Research Ethics Committee of the University of Kirkuk's College of Science granted ethical permission for the study protocol, and the Directorate of Health in Kirkuk officially authorized it (permission Letter No. 581, dated 22 July 2024). The principles of the Declaration of Helsinki were followed in conducting the study. After being fully informed about the goals, methods, risks, and advantages of the study, each participant signed an informed consent form. Participants were made aware of their freedom to leave at any moment and without repercussions. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Reporting requirements for Observational studies are adhered to in this paper.

2.2 Study Population and Sampling

A two-stage sampling technique was used to select samples from 120 female housewives. In summary , community health clinics and word-of-mouth referrals were used to recruit volunteers from Kirkuk's residential districts. Among the qualifying requirements were: Inclusion requirements: Housewives between the ages of 25 and 55 who are willing to give written informed permission and blood samples; who have lived in their current home for at least five years; who are unemployed or work fewer than four hours a day outside the home; Exclusion requirements:

- Pregnancy or lactation (verified by testing for β-hCG in urine).
- Chronic conditions: autoimmune disorders, liver or kidney illness, disorders, liver or kidney illness, diabetes mellitus (fasting glucose ≥126 mg/dL or proven diagnosis), hypertension (BP ≥140/90 mmHg or antihypertensive drug use), cardiovascular disease, and smoking (≥100 cigarettes lifetime).
- High levels of secondhand smoke exposure (>1 hour/ day).
- Drinking alcohol (in any quantity)
- Chemical exposure at work.
- Present usage of antioxidant supplements (vitamins C, E, selenium, N-acetylcysteine) or anti-inflammatory drugs (NSAIDs, corticosteroids).
- Acute infections within two weeks of enrollment (verified by clinical examination and , if necessary, C-reactive protein tests) Initially, 134 ladies were screened. Fourteen were eliminated: three had chronic illnesses, four were pregnant, and seven were taking antioxidant supplements. There were no dropouts during the study period, and the final sample consisted of 120 participants (60 in each group).

Exposure Classification

Based on measured indoor VOC levels recorded in our companion environmental assessment [Reference to Paper 1], participants were divided into high-exposure and low-exposure groups. The following criteria were used for classification:

- High- exposure group (n= 60): This group included homes where formaldehyde levels were above 150 μg/ m3 or benzene levels were higher than 10 μg/ m3. People in these homes used many regular cleaning products each day (eight or more), such as bleach, disinfectants, air fresheners, and surface cleaners.
- Low- exposure group (n= 60) : This group included homes with formaldehyde below 100 μg/ m3 and benzene below 5 μg/ m3. Most of these homes used natural cleaning materials like vinegar, lemon juice, and baking soda, and only a few regular products (three or fewer per day).

Three people were moved to a different group after comparing what they reported with the actual air test results, to make sure the grouping matched real exposure levels.

2.3 VOC Exposure Assessment:

The detailed steps for collecting indoor air samples and measuring VOCs are explained in another related paper [Reference to Paper 1]. In summary, Tenax TA thermal desorption tubes connected to calibrated pumps were used to collect indoor air samples from living rooms, kitchens, and bedrooms (100 mL/ min , 8 hours). Over the course of four weeks, samples were taken twice a week while doing routine domestic tasks. Gas chromatography- mass spectrometry (GC-MS, Agilent 7890B/ 5977A) was used to measure the VOC concentrations, and multi-point calibration curves and internal standards were used for quantification. Additionally, formaldehyde was quantified using 2,4-dinitrophenylhydrazine (DNPH) cartridges and HPLC-UV analysis at 360 nm. Formaldehyde detection limits were 2.5 μg/ m3 and benzene detection limits were 0.8 μg/ m3, with recoveries of 92 ± 7% and 95 ±5%, respectively. We used the mean VOC concentrations for each household over all sample time points for the current biomarker study. The VOC exposure levels for the two groups are summarized in Table 1.

Table 1. Indoor VOC Concentrations by Exposure Group.

Compound	Low-Exposure Group (n=60) Mean ± SD (μg/m³)	High-Exposure Group (n=60) Mean ± SD (μg/m³)	p-value	Cohen's d
Formaldehyde	89.4 ± 28.1	231.7 ± 65.4	<0.001	2.78
Benzene	6.2 ± 2.4	17.1 ± 4.7	<0.001	2.89
Toluene	42.1 ± 15.6	149.8 ± 41.5	<0.001	3.44
Xylene	28.9 ± 11.3	94.2 ± 25.3	<0.001	3.24

2.4 Blood Sample Collection

Blood samples (10mL) were collected from participants in the morning between 8:00 and 10:00 a.m. after fasting overnight for at least 8 hours. To avoid changing caused by daily biological rhythms, samples from each person were taken within the same 30-minute period on the same day of the week. Blood was drawn from the antecubital vein by trained personnel using standard venipuncture methods.

Samples were placed into:

- EDTA tubes (5mL) : for plasma cytokine testing (IL-6, TNF- α).
- Heparinized tubes (5mL): for oxidative stress marker analysis (MDA, GSH, catalase, TAC, NO, 8-isoprostane, protein carbonyls, SOD). Right after collection, tubes were gently turned upside down 8-10 times to mix the anticoagulant properly and then kept on ice until further analysis. Within 30 minutes of blood collection, the samples were centrifuged at 3000xg for 15 minutes at 4 ° C using a refrigerated centrifuge (Eppendorf 5810R). The plasma layer was then carefully separated without disturbing the buffy coat and divided into 500 μL cryovials (Corning). Each portion was rapidly frozen in liquid nitrogen and stored at – 80 °C in a Thermo Scientific freezer equipped with temperature control and an alarm system.

Quality Control During Collection:

1. Hemolysis Check: Plasma samples were visually examined for any pink or red color that indicates hemolysis. Absorbance at 414 nm was also measured using a BioTek ELx800 microplate reader. Samples with absorbance values higher than 0.2 AU were considered hemolyzed and excluded, and participants were contacted to provide a new blood sample.Three samples were found to be hemolyzed and were successfully replaced.
2. Storage Duration: All samples were analyzed within six months of collection to prevent degradation. The storage time was similar between the two groups (p=0.64).

3. Freeze-Thaw Cycles: Samples experienced only one freeze-thaw cycle before testing. Aliquots were thawed on ice and used immediately.

2.5 Biomarker Analyses

Biomarker tests were performed in the Biochemistry Laboratory at the University of Kirkuk, College of Science. Samples were analyzed in four batches of 30, with 15 from each group per batch, to manage workload and reduce batch effects. Each batch included pooled quality control samples prepared from leftover plasma not used for participant testing. All assays were carried out by laboratory staff who were blinded to the participants' exposure groups.

2.5.1 Oxidative Stress Biomarkers

Malondialdehyde (MDA)

MAD levels, representing lipid peroxidation, were measured using the thiobarbituric acid reactive substances (TBARS) method (Cayman Chemical, Cat. No. 10009055). In brief, 100 μL of plasma was mixed with 100 μL of SDS solution and 4 mL of thiobarbituric acid reagent. The mixture was heated at 95 °C for 60 minutes and then cooled on ice. After centrifuging at 1600 xg for 10 minutes, absorbance was recorded at 532 nm and compared to a standard curve (0-50 nmol/ mL). The concentration was expressed as nmol of MDA per mL of plasma. The intra-assay CV was 4.2% , and the inter-assay CV was 6.8%

Reduced Glutathione (GSH):

GSH concentration was determined using a colorimetric assay kit (Sigma- Aldrich, Cat. No. CS0260). The method relies on the reaction of GSH with 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB, Ellman' s reagent) to form 5-thio-2-nitrobenzoic acid (TNB). Plasma samples (10 μL) were mixed with 5% sulfosalicylic acid to precipitate proteins, then centrifuged. The resulting supernatant was reacted with DTNB, and absorbance was read at 412 nm using a GSH standard curve (0-10 mg/dL). The results were expressed as mg/dL. The intra-assay coefficient of variation was 3.8%, and the inter-assay coefficient was 5.9%.

Catalase Activity:

Catalase activity was assessed using a kinetic assay kit (Cayman Chemical, CAT.No. 707002). The method measures the decrease in hydrogen peroxide concentration at 540 nm after adding plasma containing catalase. Enzyme activity was calculated from a formaldehyde standard curve and expressed as units per millilitre (U/mL). One unit represents the amount of enzyme that forms 1.0 nmol of formaldehyde per minute at 25°C. The intra-assay CV was 4.5%, and the inter-assay CV was 7.2%.

Total Antioxidant Capacity (TAC):

TAC was evaluated using the ferric reducing antioxidant power (FRAP) assay (Sigma-Aldrich, CAT. No. MAK369). For this test , 5 μL of plasma was added to the FRAP reagent containing 2,4,6-tripyridyl-s-triazine (TPTZ) in an acetate buffer. The antioxidants in the sample reduce Fe3+ TPTZ to Fe2+ TPTZ, producing a blue color that was read at 593 nm. Values were determined using a Trolox standard curve and expressed as mmol/L of Trolox equivalents. The intra-assay CV was 3.2% , and the intra-assay CV was 5.4%.

Nitric Oxide (NO):

Plasma nitric oxide was estimated by measuring total nitrite and nitrate (NOx) through the Griess reaction (Invitrogen, Cat. No. EMSNO). In this procedure, nitrate was reduced to nitrite reacted with sulfanilamide and N- (1- naphthyl) ethylenediamine dihydrochloride to form a colored azo compound, and absorbance was read at 540 nm. Results were reported in μmol/L. The intra-assay CV was 5.1% , and the inter-assay CV was 7.8%.

Isoprostane:

Plasma levels of 8-iso-prostaglandin F2 α were determined using a competitive enzyme immunoassay kit (Cayman Chemical, Cat. No. 516351). Samples were purified by solid-phase extraction before testing. The assay employs a monoclonal antibody specific for 8-isoprostane along with an acetylcholinesterase- linked tracer. Absorbance was measured at 412 nm , and concentrations were calculated using a standard curve (0.8-500 pg/mL). Results are expressed in pg/mL. The intra-assay CV was 6.2%, and the inter-assay CV was 9.4%.

Protein Carbonyls:

Protein oxidative damage was evaluated by measuring protein carbonyls using the 2,4- dinitrophenylhydrazine (DNPH) method (Cayman Chemical, Cat. No. 10005020). Plasma proteins were derivatized with DNPH, precipitated with trichloroacetic acid, washed, and than dissolved in guanidine hydrochloride. The amount of protein- bound DNPH was measured at 370nm and normalized to protein content determined by the Bradford assay.

Results are expressed as nmol carbonyl per mg protein. The intra-assay CV was 5.8%, and the inter-assay CV was 8.6%.

Superoxide Dismutase (SOD):

Total SOD activity was measured using a colorimetric assay kit (Cayman Chemical, Cat.No. 706002). The method relies on the inhibition of tetrazolium salt reduction by xanthine oxidase. One unit of SOD is defined as the amount of enzyme that produces 50% dismutation of the Superoxide radical. Absorbance was measured at 450 nm, and enzyme activity was calculated using a standard curve. Results are expressed in U/mL. The intra-assay CV was 4.9%, and the inter-assay CV was 7.5%.

2.5.2 Inflammatory Cytokines

Interleukin-6 (IL-6) and Tumor Necrosis Factor- α (TNF-α):

Plasma IL-6 and TNF- α levels were determined using commercial ELISA kits (ELK Biotechnology, Cat. No. ELK6087 for IL-6 and ELK1396 for TNF- α) according to the manufacturer's protocol. Briefly, 100 μL of standards or plasma samples were added to wells coacted with capture antibiotics and incubated for 90 minutes at 37°C. After washing, biotinylated detection antibodies were added, followed by streptavidin-HRP. TMB substrate was used to develop color, and the reaction was stopped with sulfuric acid. Absorbance was measured at 450nm with a 570nm reference using a BioTek ELx800 microplate reader. Concentrations were calculated using four-parameter logistic regression from the standard curves and expressed as pg/mL.

- IL-6 : Detection range 15.6-1000 pg/mL; sensitivity <9.38 pg/mL; intra-assay CV 5.3%, inter-asssy CV 8.1%.
- TNF- α: Detection range 7.8-500 pg/mL; sensitivity <4.69 pg/mL; intra-assay CV 4.7%, inter-assay CV 7.9%

All samples were analyzed in duplicate, and the average of the two readings was used for statistical analysis. Samples with duplicates differing by more than 15% were re-assayed.

Batch Effect Control:

To monitor and minimize batch effects, pooled quality control (QC) samples were included in all four analytical batches. The CV for these QC samples remained below 10% for every biomarker. ANOVA analysis confirmed no significant batch effects for any marker (all $p>0.38$). Each batch contained an equal number of samples from both exposure groups, with 15 high-exposure and 15 low-exposure samples per batch.

2.6 Statistical Analysis

Statistical analysis were carried out using SPSS version 26.0 (IBM Corp., Armonk, NY) and R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value <0.05 was considered statistically significant.

Data Distribution and Descriptive Statistics:

Normality of continuous variables was checked using the Shapiro-Wilk test and Q-Q plots. Levene's test was used to assess homogeneity of variance. Variables with a normal distribution are presented as mean± standard deviation (SD), while non-normally distributed variables are shown as median (interquartile range). Categorical variables are reported as counts and percentages.

Univariate Comparisons:

For normally distributed variables, differences between high-and low-exposure groups were assessed using independent samples t-tests. Mann-Whitney U tests were used for non-normally distributed variables. Effect sizes were calculated using Cohen's d for t-test and r for Mann-Whitney tests. Ninety-five percent confidence intervals were reported for all comparisons. Categorical variables, including demographics and lifestyle factors, were compared using chi-square tests or Fisher's exact tests when expected counts were <5.

Correlation Analysis:

Pearson correlation coefficients were calculated to examine relationships between individual VOC levels (formaldehyde, benzene, toluene, xylene) and biomarkers. Spearman's rank correlation was applied for non-normally distributed data. Correlation matrices were generated, and p-values were adjusted for multiple testing using the Benjamini-Hochberg false discovery rate (FDR) method

Multiple Regression Modeling:

Multiple linear regression analysis were conducted to identify independent predictors of key biomarkers (MDA, GSH, IL-6), controlling for potential confounders. Multicollinearity was assessed using Variance Inflation Factors (VIF); variables with VIP>5 were not included in the same model. Because formaldehyde and benzene were highly collinear (VIP= 6.8), separate regression models were created for each.

3. Results

3.1 Participant Characteristics

The study included 120 women, all of whom completed the study with no dropouts. Table 2 summarizes the demographic and household characteristics. The high-exposure and low-exposure groups were comparable in terms of age, BMI, number of children, house size, education level, monthly income, ventilation, type of cooking fuel, season of sampling, and home age (all p> 0.05). This balance suggests that differences in biomarker levels are attributable to VOC exposure rather than demographic or lifestyle factors.

Table 2. Demographic and Household Characteristics.

Variable	Control group (n=60)	Experimental group (n=60)	p-value
Age (years)	36.8 ± 7.9	38.2 ± 8.4	0.327
Body Mass Index (BMI)	25.9 ± 3.8	26.8 ± 4.2	0.211
Number of children	2.9 ± 1.1	3.1 ± 1.2	0.369
House area (m^2)	138.7 ± 26.1	142.5 ± 28.3	0.435

Educational level - university (%)	35.0	31.7	0.694
Monthly income - average (%)	58.3	61.7	0.712
Ventilation (ACH)	0.8± 0.31	0.75	0.267
Gas cooking (%)	71.7	75.0	0.682
Winter sampling(%)	50.0	50.0	1.00
Home age (years)	18.2	19.6± 10.2	0.428

3.2 Oxidative Stress and lnflammatory Biomarkers

Significant differences were observed in plasma biomarkers between the two exposure groups. The high-exposure group showed increased oxidative stress, reduced antioxidant capacity, and elevated inflammatory cytokines compared with the low-exposure group(Table 3)

Table 3. Blood Biomarkers.

Indicator	**(Control group) Mean ± SD**	**(Experimental group) Mean ± SD**	**(p-value)**	**Cohen's d**	**% Change**
MDA (nmol/ml)	5.1 ± 1.4	7.3 ± 1.9	< 0.01	1.32	+43.1%
GSH (mg/dl)	3.8 ± 1.0	2.4 ± 0.8	< 0.01	-1.57	-36.8%
Catalase (U/ml)	68.5 ± 15.6	46.2 ± 12.7	< 0.01	-1.59	-32.6%
TAC (mmol/L)	1.89 ± 0.39	1.26 ± 0.35	< 0.01	-1.72	-33.3%
NO (μmol/L)	28.1 ± 5.2	31.3 ± 9.4	0.026	0.42	+11.4%
IL-6 (pg/ml)	6.2 ± 2.0	11.1 ± 3.9	< 0.01	1.59	+79.0%
TNF-α (pg/ml)	9.3 ± 2.4	16.1 ± 5.2	< 0.01	1.68	+73.1%
8-Isoprostane(pg/ml)	28.4±8.2	42.7±12.6	< 0.001	1.36	+50.4%
Protein carbonyls(nmol/mg)	1.8±0.6	2.9±0.9	< 0.001	1.45	+61%
SOD(U/ml)	124.6± 28.2	98.2±24.7	< 0.001	-0.99	-21.2%

MDA= malondialdehyde; GSH= reduced glutathione; TAC= total antioxidant capacity; SOD = superoxide dismutase; NO= nitric oxide; lL-6= interleukin-6; TNF- α = tumor necrosis factor-alpha.

Lipid Peroxidation:

Women in the high-exposure group showed clear evidence of intensified lipid oxidation . MDA concentrations were 43.1% higher than those in the low-exposure group ((5.1 to 7.3) nmol/mL, p<0.001, Cohen's d=1.32). A similar trend was seen for 8-isoprostane, which rose by 50.4% ((28.4 to 42.7) pg/mL, p<0.001, Cohen's d=1.36). These large effect sizes point to extensive oxidative damage affecting cell membranes.

Protein Oxidation:

Protein carbonyl levels increased markedly by 61.1% in the high-exposure group ((1.8 to 2.9) nmol/mg protein, p<0.001, Cohen's d=1.45), indicating ongoing oxidative modification of plasma proteins that could impair their stability and function

Antioxidant Defense Systems:

A consistent reduction was observed in all antioxidant indicators among highly exposed participants. GSH fell by 36.8 % ((3.8 to 2.4)mg / dL, p<0.001, Cohen's d=-1.57), catalase activity by 32.6% ((68.5 to 46.2) U / mL, p< 0.001, Cohen's d= -1.59), and TAC by 33.3% ((1.89 to 1.26) mmol/L, p<0.001, Cohen's d=-1.72). SOD activity decreased by 21.2% ((124.6 to 98.2) U/ mL, p<0.001, Cohen's d=-0.99). Together, these changes reflect a clear depletion of antioxidant reserves and heightened oxidative pressure.

Nitric Oxide:

NO levels rise slightly but significantly by 11.4% in the high-exposure group (28.1 to 31.3 μmol/ L, p=0.026, Cohen's d= 0.42), suggesting mild nitrosative stress and potential involvement of inducible nitric oxide synthase activity.

Inflammatory Cytokines:

Marked increases were observed on pro-inflammatory cytokines. IL-6 nearly doubled ((6.2 to 11.1) pg/mL, p<0.001, Cohen's d=1.59), while TNF- α increased by 73.1%((9.3 to 16.1) pg/mL, p<0.001, Cohen's d=1.68). These elevations signal strong activation of inflammatory pathways consistent with systemic oxidative stress.

3.3 Multiply Regression Analysis: predictors of Biomarkers Alterations

Regression models indicated that formaldehyde was the main independent factor associated with changes in oxidative stress and inflammatory biomarkers , even after controlling for age, BMI, ventilation, and other household characteristics (Table 4).

Multiple Regression Analysis

Table 4. Factors affecting oxidative stress and inflammatory biomarkers.

Model 1: Malondialdehyde (MDA) as Dependent Variable

Adjusted $R^2 = 0.64$, $F(4,115) = 42.3$, $p < 0.001$

Independent Variable	β	95% CI	SE	t	VIF	p-value
Formaldehyde (μg/m³)	0.65	0.49 to 0.81	0.08	8.13	2.3	<0.001
Age (years)	0.12	0.01 to 0.23	0.05	2.08	1.2	0.041
BMI (kg/m²)	0.08	-0.05 to 0.21	0.07	1.14	1.1	0.258
ACH (air changes/hour)	-0.18	-0.32 to -0.04	0.07	-2.57	1.4	0.012

Model 1 lnterptation:

Formaldehyde was identified as the strongest predictor of MDA (β= 0.65, p< 0.001), explained most of the variability in lipid peroxidation. Each standard deviation increase in formaldehyde was associated with a 0.65 standard deviation increase in MDA, controlling for other factors. Age showed a small positive effect (β= 0.12, p= 0.041), consistent with gradual increases in oxidative stress with age. Higher air change rates (ACH) were linked to lower MDA levels (β= -0.18, p= 0.012), indicating that improved ventilation reduces oxidative damage from VOCs. BMI and season did not significantly influence MDA. The model accounted for 64% of the variance in MDA (adjusted R 2 = 0.64), demonstrating substantial predictive strength.

Model 2: Reduced Glutathione (GSH) as Dependent Variable

Adjusted $R^2 = 0.58$, $F(5,114) = 34.7$, $p < 0.001$

Independent Variable	β	95% CI	SE	t	VIF	p-value
Formaldehyde (μg/m³)	-0.68	-0.82 to -0.54	0.09	-7.56	2.3	<0.001
Toluene (μg/m³)	-0.16	-0.28 to -0.04	0.06	-2.67	1.8	0.009
Age (years)	-0.09	-0.21 to 0.03	0.06	-1.50	1.2	0.137
BMI (kg/m²)	-0.05	-0.18 to 0.08	0.07	-0.71	1.1	0.481
Cooking fuel (gas vs. electric)	0.11	-0.02 to 0.24	0.07	1.57	1.3	0.120

Model 2 Interprtation

Formaldehyde remained the primary factor linked to GSH reduction (β= - 0.68, p< 0.001), demonstrating that higher Formaldehyde exposure significantly weakened antioxidant defenses. Toluene also showed an independent but smaller association with GSH decline (β =-0.16, p= 0.009). The negative relationship indicates that as VOC concentrations increased, GSH levels dropped – consistent with its utilization in neutralizing reactive oxygen species and forming detoxification adducts. Other factors, including age , BMI, and tybe of cooking fuel, had no significant influence. The model explained 58% of the variation in GSH levels (adjusted R 2 = 0.58), suggesting strong predictive accuracy.

Model 3: Interleukin-6 (IL-6) as Dependent Variable

Adjusted $R^2 = 0.61$, $F(5,114) = 38.5$, $p < 0.001$

Independent Variable	β	95% CI	SE	t	VIF	p-value
Formaldehyde (μg/m³)	0.52	0.38 to 0.66	0.07	7.43	2.3	<0.001
Xylene (μg/m³)	0.27	0.11 to 0.43	0.08	3.38	1.9	0.001
Age (years)	0.14	0.02 to 0.26	0.06	2.33	1.2	0.022
BMI (kg/m²)	0.10	-0.03 to 0.23	0.07	1.43	1.1	0.156
ACH (air changes/hour)	-0.15	-0.28 to -0.02	0.07	-2.14	1.4	0.035

Model 3 Interpretation:

Formaldehyde was identified as the main driver of IL-6 elevation (β = 0.52, p < 0.001), explaining most of the variance in inflammatory response . Xylene also contributed significantly (β =0.27, p= 0.001), suggesting that simultaneous exposure to several VOCs can enhance inflammatory activation. Age was positively related to IL-6 levels (β=0.14, p= 0.022), which aligns with the gradual increase in systemic inflammation observed with aging. In contrast, better ventilation (β=-0.15, p= 0.035) showed a protective role, helping to limit the rise in inflammatory biomarkers. BMI did not significantly affect IL-6 levels. The model accounted for 61% of the variation in IL-6 concentrations (adjusted R 2 = 0.61), indicating a strong and reliable predictive fit.

Regression Diagnostics:

All models fulfilled the standard regression assumptions. The residuals were normally distributed (Shapiro-Wilk tests: Model 1, p = 0.18; Model 2, p =0.24; Model 3, p = 0.31) and exhibited homoscedasticity (Breusch- pagan tests: all p> 0.15). No significant autocorrrlation was detected (Durbun – Watson values ranged between 1.89 and 2.12). Variance Inflation Factor (VIF) values were below 2.5, confirming the absence of problematic multicollinearity. Sensitivity tests conducted after excluding outliers (n= 4 observations > 3 SD from the mean) produced consistent results, reinforcing the robustness and stability of the regression analyses.

3.4 Correlation Analysis: VOCs and Biomarkers

Correlation analyses using both Pearson and Spearman methods revealed significant and robust associations between individual VOC levels and several oxidative and inflammatory biomarkers (Table 7). Formaldehyde displayed the highest correlation strength across nearly all biomarkers, followed sequentially by benzene, toluene, and xylene, indicating a graded pattern of biological impact related to VOC exposure.

Table 5. Correlation Coefficients between VOC Concentration and Blood Biomarkers.

Compounds	MDA	GSH	Catalase	TAC	NO	IL-6	TNF-α
Formaldehyde	0.75**	-0.68**	-0.64**	-0.60**	0.61**	0.70**	0.66**
Benzene	0.57**	-0.53**	-0.49**	-0.50**	0.44**	0.61**	0.54**
Toluene	0.50**	-0.48**	-0.45**	-0.47**	0.39*	0.48**	0.47**
Xylene	0.46**	-0.44**	-0.41**	-0.45**	0.38*	0.50**	0.45**

*P< 0.05; **P< 0.01(two- tailed). All significance values were corrected for multiple testing using the Benjamini-Hochberg false discovery rate (FDR) method.

Formaldehyde Correlations:

Formaldehyde showed the strongest and most consistent associations across all biomarkers. It correlated positively with oxidative stress indicators (MDA: r = 0.75, p< 0.01; NO: r=0.61, p<0.01) and inflammatory cytokines (IL-6: r= 0.70, p<0.01; TNP- α: r= 0.66, p< 0.01), while exhibiting strong negative correlations with antioxidant defenses (GSH: r =-0.68, p< 0.01; catalase: r= -0.64, p<0.01; TAC: r= -0.60, p< 0.01). This pattern-elevated oxidative and inflammatory markers alongside depleted antioxidants indicates a mechanistic link between formaldehyde exposure and oxidative stress-driven inflammation.

Benzene Correlations:

Benzene displayed moderate to strong relationships with multiple biomarkers, though generally weaker than formaldehyde (r =0.44 - 0.61). Its highest correlation was with IL-6 (r= 0.61, p< 0.01), followed by MDA (r = 0.57, p < 0.01), suggesting that benzene exposure contributes significantly to inflammatory activation and lipid oxidation.

Toluene and Xylene Correlations:

Both toluene and xylene showed moderate yet significant correlations with oxidative stress and inflammation (r = 0.38-0.50), confirming their involvement in redox imbalance. Their relatively lower correlations with NO (toluene: r=0.39; xylene: r=0.38; p<0.05) suggest distinct mechanistic pathways from those of formaldehyde and benzene.

Mechanistic Interpretation:

These findings align with established toxicological pathways. Formaldehyde's high reactivity promotes direct ROS generation through metabolic oxidation and adduct

formation with proteins and DNA, leading to inflammation. Benzene is metabolized by CYP2E1 into reactive intermediates that deplete GSH and trigger NF- κβ- mediated inflammatory signaling. Toluene and Xylene, converted into less reactive metabolites (benzoic and methylhippuric acids), cause milder oxidative effects.

Dose- Response Evidence:

The stepwise decrease in correlation magnitude (formaldehyde > benzene > toluene ≈ xylene) supports a dose-response trend consistent with chemical reactivity and toxic potency. Furthermore, the consistent direction of associations-positive with oxidative and inflammatory markers, negative with antioxidants, across multiple biomarkers reinforces the causal nature of these relationships and reduces the likelihood of random associations.

4. Discussions

4.1 Principal Findings

The present study provides clear biomarker evidence that prolonged residential exposure to volatile organic compounds (VOCs) from household cleaning products induces significant oxidative stress and systemic inflammation in Iraqi women. Women in the high-exposure group showed a pronounced oxidative profile, including: (1) increased lipid peroxidation, with MDA and 8-isoprostane rising by 43-50% ; (2) marked depletion of antioxidants, with GSH, catalase, TAC, and SOD reduced by 21-37%; (3) elevated protein oxidation, indicated by a 61% increase in protein carbonyls; and (4) strong inflammatory responses, reflected by 73-79% higher levels of TNF- α and IL- 6. Regression analysis pointed to formaldehyde as the main driver of these effects ($\beta = 0.52\text{-}0.68$ across models), with benzene, toluene, and xylene also contributing independently. The observed magnitude of these biomarker changes is comparable to or exceeds that seen in chronic diseases such as cardiovascular disorders, metabolic syndrome, and asthma, emphasizing the significance of indoor VOC exposure as a preventable public health concern.

4.2 Mechanistic Framework: From VOC Exposure to Biological Damage

4.2.1 Formaldehyde as primary Oxidative Stressor

Formaldehyde was the strongest predictor in our regression analyses, explaining 40-46% of the variance in individual biomarkers when considered alone, reflecting its high chemical reactivity. After inhalation, formaldehyde is rapidly metabolized by alcohol dehydrogenase(ADH) and aldehyde dehydrogenase (ALDH) in the respiratory epithelium and red blood cells, producing formate and reactive oxygen species (ROS) as byproducts [27]. It also activates CYP2E1 in liver and lung cells, generating superoxide anions ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2) through uncoupled electron transfer [28]. Wang et al. (2024) showed that chronic exposure to formaldehyde at levels similar to our high-exposure group stimulates NADPH oxidase complexes, particularly NOX2 and NOX4, leading to a 3-4 fold increase in ROS 72 hours[7]. This combination of ROS generation through metabolism and enzymatic activation accounts for formaldehyde 's strong oxidative effects. The increases in MDA and 8-isoprostane indicate lipid peroxidation of polyunsaturated fatty acids in membrane, producing reactive aldehydes that perpetuate oxidative damage [29]. Elevated protein carbonyls reflect oxidative modifications of amino acids such as lysine, arginine , proline, and threonine , which can impair enzymatic activiy and disrupt cellular functions [30].

4.2.2 Antioxidant Defense Exhaustion

The substantial GSH depletion in high-exposure women (37% reduction) indicates a critical weakening of cellular antioxidant defenses. GSH is essential for neutralizing ROS directly, acting as a cofactor for glutathione peroxidase to reduce hydrogen peroxide and lipid hydroperoxides, and conjugating electrophilic VOC metabolites through glutathione S-transferases [31]. Our findings suggest that chronic VOC exposure overwhelms the cell' s capacity to regenerate GSH, with consumption surpassing synthesis despite reported

compensatory increases in γ-glutamylcysteine ligase (GCL) activity [32]. Formaldehyde contributes to GSH loss by forming S- formylglutathione adducts, which are exported via multidrug resistance- associated proteins (MRPs) , irreversibly removing GSH from the cellular pool[33]. The observed strong negative correlation between formaldehyde and GSH (r=- 0.68) and the the regression coefficient (β= -0.68) indicate that each standard deviation rise in formaldehyde (~65 μg/m³) corresponds to a 0.68 SD decline in GSH (~ 0.68 mg/ dL). The declines in catalase and SOD activity (33% and 21% , respectively) likely result from both direct oxidative inactivation and reduced gene expression. Persistent ROS exposure can oxidize catalase's home iron and the active sites of SOD (Cu^{2+}/Zn^{2+} or Mn^{3+}), lowering enzymatic processes [34], while transcriptional suppression of antioxidant genes can occur via oxidative modification of Nrf2 and FOXO transcription factors [35]

4.2.3 Inflammatory Cascade Activation

The substantial rises in IL-6 (79%) and TNF- α (73%) indicate strong activation of inflammatory signaling, primarily via the NF- κB pathway. VOC-indicate ROS oxidize cysteine residues in lκB kinase (IKK), leading to phophorylation and proteasomal degradation of lκB inhibitory proteins [36]. This releases NF- κB dimers (mostly p65/p50), which translocate to the nucleus and bind κB elements in gene promoters, increasing expression of lL-6, TNF- α, IL-1β, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS)[37]. Wang et al (2024) demonstrated that formaldehyde activates NF-κB through both oxidative IKK activation and direct adduct formation with lκBα, accelerating its degradation [23]. The resulting cytokine production creates a positive feedback loop: TNF- α and IL-6 enhance ROS generation via NOX enzymes and mitochondrial dysfunction, while ROS further stimulate NF- κB, sustaining information [38]. The 11% increase in NO likely reflects iNOS induction downstream of NF- κB activation. Although NO has protective roles in antimicrobial defense and vasodilation , excessive NO in the presence of superoxide generates peroxynitrite (ONOO -) , a highly reactive species that nitrates tyrosine residues and damage DNA[39]. This nitrosative stress contributes to overall oxidative burden and is consistent with the positive correlation between NO and MDA (r = 0.61 with formaldehyde).

4.3 Clinical and Public Health Significance

4.3.1 Disease- Associated Biomarker Comparison

The alterations in biomarkers among the high-exposure group reached or even exceeded clinical thresholds linked to chronic diseases, underscoring their health relevance. MDA concentrations (7.3 nmol/mL) were comparable to values reported in cardiovascular disease patients (6.8-7.5 nmol/ mL) [40], while IL-6 levels (11.1 pg/mL) surpassed the cardiovascular risk cutoff 10 pg/mL [41]. Similarly, GSH depletion (2.4 mg/ dL) and TNF- α elevation (16.1 pg/mL) reflected oxidative and inflammatory patterns typical of metabolic syndrome [42,43]. Elevated 8-isoprostane level (42.7 pg/mL) also exceeded those linked to asthma and COPD exacerbations [44,45]. These results suggest that prolonged VOC exposure represents a preventable yet serious contributor to chronic disease risk, comparable in significance to smoking or obesity.

4.3.2 Gender-Speciific Vulnerability

Women demonstrated greater oxidative vulnerability due to a combination of biological and environmental factors. Reduced estrogen levels after age 40 are associated with lower antioxidant enzyme activity [46], while higher adipose tissue facilitates VOC accumulation [47]. Additionally, genetic factors such as the GSTM1-null and CAT C262T polymorphisms, which are common among lraqi women [48,49], further weaken detoxification mechanisms. Lifestyle conditions intensify these risks: extended indoor time (20-22 hours per day) and frequent cleaning activity (3-5 hours daily) substantially increase cumulative VOC exposure [50].

4.4 Comparison with Global Literature

The biochemical responses observed here align with findings from international research but appear more pronounced in this Iraqi cohort. Compared to Chinese studies [51], MDA and GSH changes were higher (43% vs. 38% and 37% vs. 29%, respectively), likely reflecting elevated VOC concentrations in Kirkuk. European studies [52] reported smaller IL-6 increases (20-30% vs, 79%), likely due to stricter indoor air quality controls. U.S. occupational research [52] showed greater biomarker alterations, though under short-term, high-level exposures. This investigation is the first to comprehensively examine oxidative and inflammatory biomarkers related to VOC exposure in a Middle Eastern setting, offering strong, region- specific evidence that indoor VOCs contribute significantly to systemic oxidative stress and inflammation[53].

4.5 Limitations

Although this study was carefully structured and methodologically robust, several limitations should be taken into account when interpreting the results:

- Cross- sectional design: The study's cross-sectional nature limits the ability to establish direct cause-effect relationships between VOC exposure and oxidative or inflammatory alterations. However, the inclusion of participants with long-term household exposure (8-12 years) provides strong evidence of a likely temporal connection. Longitudinal studies are needed to confirm causality.
- Geographical limitation: Since all participants were recruited from Kirkuk city, the findings may not fully represent populations in other regions with different building materials, ventilation systems, or lifestyle patterns. Nonetheless, because oxidative stress and inflammatory mechanisms are universal, the biological relevance of these results likely applies to similar environmental settings.
- Restricted VOC assessment: Only seven key VOCs were analyzed, meaning that other compounds present in household cleaning emissions might not have been captured. Still, the measured compounds-especially formaldehyde and benzene-are dominant contributors and suitable indicators of overall VOC exposure.
- Single – time biomarker collection: Biomarkers were measured once , preventing assessment of temporal changes. However, standardized sampling conditions (morning, fasting) and the consistent trends observed across multiple biomarkers suggest the findings reflect chronic rather than transient exposure.
- Sample size and subgroup analysis: While the sample of 120 participants was adequate for primary comparisons, it was insufficient for more detailed subgroup analyses (e.g. , based on menopausal status, BMI, or genetic polymorphisms). Larger – scale studies could help identify specific high- risk subgroups.
- Self-reported exposure information: Certain exposure details , such as frequency and duration of product use, were self- reported and may contain minor recall inaccuracies. However, these were cross- validated with measured indoor VOC concentrations, reducing the potential for bias.
- Unmeasured dietary influences: The study did not account for participants' dietary antioxidant intake, which can affect oxidative balance. Future research should include dietary assessments to better control for nutritional confounding factors.

5. Conclusions

This study clearly demonstrates that long -term exposure to volatile organic compounds (VOCs) emitted from Household cleaning products leads to pronounced oxidative stress and systemic inflammation among lraqi women. Participants with higher

VOC exposure exhibited substantial increase in oxidative damage biomarkers (MDA, 8-isoprostane, protein carbonyls), along with marked depletion of antioxidant defense systems (GSH, catalase, TSC, SOD) and elevated pro- inflammatory cytokines (IL-6, TNF-α). Formaldehyde was identified as the strongest independent predictor of biochemical disturbance, showing consistent dose-response and correlation patterns that support its mechanistic role in oxidative injury. These findings establish indoor VOC exposure as a significant yet preventable public health issue-particularly in households with inadequate ventilation and frequent use of chemical cleaning products. The mechanistic pathway identified-VOC inhalation triggering reactive oxygen species (ROS) generation, antioxidant exhaustion, and activation of inflammatory cascades- suggests clear opportunities for preventive strategies through improved ventilation, safer product formulations, and public education on chemical exposure risks. Clinically, the biochemical alterations observed indicate elevated susceptibility to chronic diseases driven by oxidative and inflammatory stress, such as cardiovascular, respiratory, and metabolic disorders. At the policy level, the outcomes highlight the urgent need for stronger regulation of VOC emissions in household products, along with targeted health campaigns promoting safer domestic practices. In conclusion, this work underscores that indoor air pollution caused by household cleaning agents represents a serious and modifiable health hazard. Immediate preventive actions- combined with longitudinal and interventional research-are essential to confirm causal relationships, define exposure limits, and develop evidence- based policies to protect public health.

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