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Systematic Review

Exposure and Early Effect Biomarkers for Risk Assessment of Occupational Exposure to Formaldehyde: A Systematic Review

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Abstract: The aim of the present review was to identify all the biomarkers used for assessing the internal dose and the related early effects determined by the occupational exposure to formaldehyde. For this purpose, a systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was registered in PROSPERO (ID: CRD42023416960). An electronic search of Pubmed, Scopus, and Web of Science was performed to collect all the papers concerning the focus of the review and published from the inception of each database until 18 September 2023. Articles were considered eligible if they reported data from observational studies, semi-experimental, and experimental studies on adult workers who were occupationally exposed to formaldehyde, regardless of gender or age. The quality assessment was performed using the adapted Newcastle–Ottawa Quality Assessment Scale. From 1524 articles, 52 were included. Few studies assessed the exposure to formaldehyde in occupational settings through biomarkers, especially by measuring formic acid in urine. The most common approach for evaluating the effects derived from occupational exposure to formaldehyde was the use of the cytogenetic biomarker micronucleus assay in peripheral blood lymphocytes and/or epithelial buccal cells.

Keywords: workplaces; exposure; early effects; biomarkers; formaldehyde; systematic review

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1. Introduction

Occupational exposure to formaldehyde (FA) and the related adverse effects for human health have been studied for many years and, nowadays, are still the subject of much research.

It is well known that exposure to FA is associated with a broad spectrum of negative outcomes for health, ranging from mild to severe [1]. Specifically, acute exposure to FA can lead to irritation of the eyes, nose, throat, and skin, as well as symptoms like nasal congestion, sore throat, headaches, coughing, conjunctivitis, fatigue, skin rashes, shortness of breath, nausea, and nosebleeds [2]. Besides this, FA is classified as a Group 1 human carcinogen [3], and chronic exposure to FA can lead to cancer both in humans

and animals [4]. Despite this evidence, FA finds extensive use in the manufacturing of various products, including resins, adhesives, plywood binders, plastics, synthetic fibers, paints, and insulation foams. These materials serve as the fundamental components in the production of furniture, upholstery, carpets, curtains, and various other household items [5]. Thus, FA is present ubiquitously in the environment and used in a great number of processes and activities in workplaces. The main sources of occupational exposure to FA are industrial production including resins, plastics, laminates, furniture, molding compounds, chemical manufacture, fertilizer, pesticides, paper, wood products, sanitizers, scientific supply, rubber, leather tanning, iron foundries, photographic film, textiles, and cosmetics. Other occupational settings in which occupational exposure to FA occurs are healthcare settings, especially for preserving tissue and specimens and for embalming procedures, agrifood scenarios, building, transportation, and fuel [6].

Given all the possibilities of occupational exposure to FA and the related adverse effects for human health, over the years, different mitigation strategies have been implemented in occupational environments to minimize exposure [7]. However, these procedures are not standardized and not used in all the settings in which FA is used; thus, it is essential to evaluate this specific risk in the workplace and to monitor the exposed workers for their exposure and the related adverse effects, in particular those ones at an early and reversible stage. This topic is even more relevant considering that "promoting a safe and protected working environment for all workers" represents a target of the Sustainable Development Goal 8 of the UN Agenda 2030 for Sustainable Development, that is the goal to promote sustained, inclusive, and sustainable economic growth; full and productive employment; and decent work for all. At present, the gold standard for FA risk assessment and management in workplaces is the exposure measurement. In particular, occupational exposure to FA is actually assessed by measuring the levels of airborne FA. This measurement can be carried out through portable samplers/analyzers, equipped with photoacoustic spectroscopy detectors or electrochemical detectors, with a sensitivity of the order of a few $\mu g/m^3$. More sensitive approaches are represented by active or passive environmental sampling with specific sorbent tubes containing 2,4-dinitrophenyhydrazine or 2-(hydroxymethyl) piperidine as derivatizer with a built-in ozone scrubber performed in fixed sites and/or by the use of personal samplers, then analyzed by high performance liquid chromatography mass spectrometry (HPLC-MS/MS) or gas chromatography mass spectrometry (GC-MS) [6]. However, the airborne FA level is just an estimation of the true individual exposure. After the inhalation of FA, owing to its water solubility and reactivity, a great part of it is inactivated from mucus and peribronchial fluid and the remaining amount is absorbed in the body [8]. Following its absorption, FA spontaneously reacts with glutathione (GSH) to generate hydroxy methyl glutathione (HMGSH). Subsequently, the enzyme formaldehyde dehydrogenase (FDH) oxidizes HMGSH into S-formylglutathione (FGSH). FGSH is then metabolized by S-formylglutathione hydrolase, resulting in the production of formate and the regeneration of reduced glutathione [9]. Moreover, FA can also undergo oxidation facilitated by aldehyde dehydrogenase (ALDH), in coordination with cytochrome oxidase isoenzymes including and CYP2E1 [10]. In this manner, the generated formate can be excreted in urine in the form of formic acid, interact with other biomolecules, or even be metabolized into carbon dioxide [11,12] Given the metabolism of FA, it should be very interesting to evaluate FA exposure by the use of indicators of internal dose and of early effects; however presently, official occupational health guidelines do not establish specific biomarkers for this purpose.

The aim of the present systematic review was to identify all the biomarkers used for assessing the exposure to FA in occupational environments and for evaluating the relative early adverse effects for human health.

2. Materials and Methods

2.1. Search Strategy

The systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13]. PRISMA Checklist is reported as Supplementary Materials. Additionally, the review protocol was registered in PROSPERO with the reference number CRD42023416960.

The review question focuses on the occupational exposure to FA in adult workers of all genders, to identify biomarkers of exposure used for evaluating FA exposure and/or early negative effects.

The studies selection procedure used the "PICOS" methodology (P stands for patient, population or problem; I for intervention; C for control group or comparison; O for outcome; S for study design) to generate the search query, and adherence to the following eligibility criteria was required: the population was made up of adult workers of all genders who were occupationally exposed to FA; intervention was not applicable; the outcome was the identification of all the biomarkers of exposure and/or effects used for assessing FA risk of exposure in the workplace; study design included observational, semi-experimental, and experimental studies.

We queried three electronic databases to search for articles: PubMed, Scopus, and Web of Science.

2.2. Inclusion/Exclusion Criteria

Articles were deemed eligible if they included data from observational studies, semi-experimental, and experimental studies, on adult workers who were occupationally exposed to FA, regardless of gender or age. We only included items published in English from the beginning of each database until 18 September 2023.

Studies including data about general population were excluded. We also excluded studies on biomarkers in workers not exposed to FA and with controls who had different socio-demographic characteristics than the exposed group, as well as controls who were not workers. Other types of studies, such as reviews, meta-analysis, case studies, qualitative investigations, book chapters, editorials, commentary studies, and so on, were not considered.

The titles and abstracts obtained from the three databases were imported into the reference management software Zotero (version 6.0.27), which was used for the initial assessment of relevance. Subsequently, the next phase involved a title and abstract screening, where potentially suitable studies were independently reviewed by five authors (A.A., A.D.G., S.Z., E.M., and V.C.). Following this, the full texts of these studies were independently examined by the same five authors, and a subsequent discussion took place regarding their potential inclusion in the review. Any disagreements that arose were resolved through consensus among the authors. All the steps were supervised by two other investigators (C.P. and M.V.).

The collected data were organized into a table that presented bibliographic details (including author, year of publication, origin country), sample size, age, and gender of participants. The table also included information about employment characteristics, biomarkers of exposure and/or early effects investigated, confounding and interfering variables considered, and the key findings of the selected studies.

2.3. Study Quality and Evaluation

We conducted the quality assessment using the Newcastle–Ottawa Quality Assessment Scale, modified for cohort and case-control studies, which enabled us to determine the overall rating. Specifically, selection, comparability, and outcome were the three evaluation categories. An overall quality rating was assigned to each eligible article according to the number of criteria met, as follows: For cross-sectional studies in the three evaluation categories of selection, comparability, and outcome: good quality (all criteria met, low risk of bias); fair quality (1 criterion not met or 2 criteria unclear, moderate risk of bias); poor

quality (2 or more criteria not met, high risk of bias). For case-control and cohort studies: good quality (3 or 4 criteria in selection domain, 1 or 2 criteria in comparability domain, and 2 or 3 criteria in outcome domain); fair quality (2 criteria in selection domain, 1 or 2 criteria in comparability domain, and 2 or 3 criteria in outcome domain); poor quality (0 or 1 criterion in selection domain, 0 criteria in comparability domain, or 0 or 1 criteria in outcome domain).

Each study was individually scored by five authors (A.A., A.D.G., S.Z., E.M., and V.C.), and any discrepancies were resolved through consensus among all the authors. The ultimate rating for each article was calculated as the average of the five authors' scores.

3. Results

3.1. Article Selection

Figure 1 shows the steps of the article selection process used for the systematic review following the PRISMA guidelines [13].

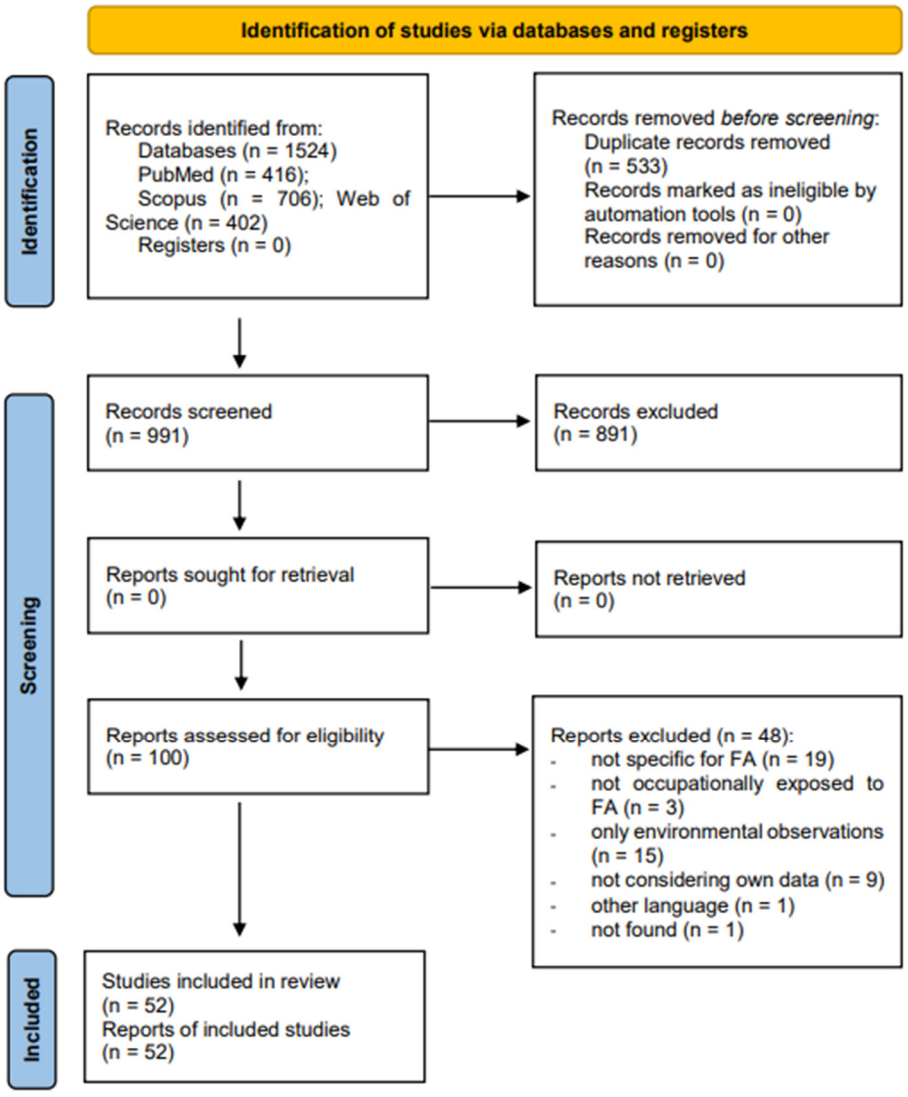

Figure 1. Flow diagram of study selection.

On a total of 1524 articles found in all searched databases (416 from PubMed, 706 from Scopus, and 402 from Web of Science); after duplicate deletion, 991 records were screened for inclusion; of the remaining studies, 891 were deleted after analyzing the title and abstract. Then, the full texts of 100 articles were assessed for eligibility and evaluated considering the inclusion and exclusion criteria. After the evaluation, 48 articles were

excluded on the basis of the exclusion criteria and specifically for the following reasons: 19 articles because they were not specific to FA, 15 articles only considered environmental monitoring, 9 did not consider original data, 3 did not assess an occupationally exposed population, 1 because it was in a different language from English, and 1 because it was not found. Finally, 52 articles met the inclusion criteria, and were included in the analysis.

3.2. Main Characteristics of the Included Studies

The included articles were grouped based on the studied occupational scenarios, as follows: healthcare and research (Table 1), industrial (Table 2), and other settings or miscellanea of settings (Table 3). These groups were chosen on the basis of the results of a recent systematic review [6], which categorized those exposed to FA according to the activities carried out in the work environment. The included articles studied different categories of workers who were grouped as miscellanea of settings.

Table 1. Main characteristics of studies (n = 21) involving healthcare and research settings included in the systematic review.

Reference Country Working Context	Sample Size Age (Mean Value ± SD and/or Range) Gender (%)	Biomarkers of Internal Dose and/or Early Effect	Confounding and Interfering Factors	Main Results	Quality Evaluation According to NOS Scale
Bellisario et al., 2016 [14] Italy Hospital operating theatre	94; 30 exposed and 64 controls; 45 ± 8 years; 0 males (0%) and 94 females (100%)	Biomarkers of effect: levels of 15-F2t-isoprostane and malondialdehyde in urine samples	Smoking habits, log-FA, UVS, urinary cotinine, age, body mass index	Statistically significant increases in urinary levels of 15-F2t-isoprostane and malondialdehyde in nurses using FA, in particular in those workers using liquid FA	Fair
Bono et al., 2010 [15] Italy Pathology wards	76; 44 exposed and 32 controls; 32% <30 years, 31% 30–39 years, 37% >39 years; 22 males (29%) and 53 females (71%)	Biomarkers of effect: levels of leukocyte malondialdehyde-deoxyguanosine adducts	Gender, age, smoking habits, exposure status, air-FA measurements	Statistically significant increases in malondialdehyde-deoxyguanosine adducts in exposed with respect to controls. The effect becomes stronger when the evaluation of air-FA exposure was based on personal samplers	Fair
Bouraoui et al., 2012 [16] Tunisia Hospital pathology anatomy laboratory	62; 31 exposed and 31 controls; 43 ± 9 years; 21 males (40%) and 41 females (60%)	Biomarkers of effect: micronucleus frequencies in peripheral lymphocytes	Gender, age, smoking habits, use of individual protection, professional class, presence of respiratory and ocular effects	Statistically significant increases in micronucleus frequency in the exposed group compared to controls	Fair
Costa et al., 2008 [17] Portugal Hospital pathology anatomy laboratory	60; 30 exposed and 30 controls; 38 ± 9 years; 20 males (33%) and 40 females (67%)	Biomarkers of effect: micronucleus frequencies, sister chromatid exchanges, comet tail length in peripheral lymphocytes	Age, gender, smoking habits, years of employment	Statistically significant increases in micronucleus frequency, sister chromatid exchanges, and comet tail length in the exposed group compared to controls	Fair
Costa et al., 2013 [18] Portugal Hospital pathology anatomy laboratory	70; 35 exposed and 35 controls; 40 ± 10 years; 11 males (16%) and 59 females (84%)	Biomarkers of effect: micronucleus frequencies and sister chromatid exchanges in peripheral lymphocytes, T-cell receptor mutations in mononuclear leukocytes	Age, gender, smoking habits, years of employment	Statistically significant increases in micronucleus frequency and sister chromatid exchanges in the exposed group compared to controls. No significant differences were found for T-cells receptor mutations	Fair
Costa et al., 2015 [19] Portugal Hospital pathology anatomy laboratory	171; 84 exposed and 87 controls; 39 ± 10 years; 39 males (23%) and 132 females (77%)	Biomarkers of effect: chromosomal aberrations in peripheral lymphocytes and percentage of DNA in the comet tail in peripheral mononuclear cells	Health conditions, general medical history, medication, diagnostic tests (X-rays, etc), age, gender, smoking habits, alcohol consumption, dietary habits	Statistically significant increases in chromosomal aberrations and percentage of DNA in the comet tail in the exposed group compared to controls	Fair
Costa et al., 2019 [20] Portugal Hospital pathology anatomy laboratory	172; 85 exposed and 87 controls; 40 ± 10 years; 138 males (80%) and 34 females (20%)	Biomarkers of internal dose: urinary formic acid concentrations Biomarkers of effect: micronucleus frequencies in peripheral lymphocytes and in exfoliated buccal cells, sister chromatid exchanges in peripheral lymphocytes, T-cell receptor mutations in mononuclear leukocytes, percentages of different lymphocyte subpopulations	Health conditions, general medical history, medication, diagnostic tests (X-rays, etc), age, gender, smoking habits, alcohol consumption, dietary habits	Statistically significant increases in urinary formic acid, micronucleus frequency and sister chromatid exchanges in the exposed group compared to controls. Statistically significant alteration of percentages of different lymphocyte subpopulations in the exposed group compared to controls. No significant differences were found for T-cells receptor mutations	Fair

Table 1. *Cont.*

Reference Country Working Context	Sample Size Age (Mean Value ± SD and/or Range) Gender (%)	Biomarkers of Internal Dose and/or Early Effect	Confounding and Interfering Factors	Main Results	Quality Evaluation According to NOS Scale
Ghelli et al., 2021 [21] Italy Hospital pathology laboratory	105; 57 exposed and 48 controls; 41.4 ± 9.3 years; 54 males (52%) and 51 females (48%)	Biomarkers of effect: formation of chromosomal aberrations on peripheral blood lymphocytes	Sex, age, personal habits (smoking) during the last year, work characteristics (length in years of service working and type of work)	Statistically significant increases in chromosomal aberrations in the exposed group compared to controls. Significant positive correlations were found between chromosomal aberrations frequency and air-FA concentration	Fair
Ghelli et al., 2022 [22] Italy Hospital pathology laboratory	105; 57 exposed and 48 controls; 41.4 ± 9.3 years; 54 males (52%) and 51 females (48%)	Biomarkers of effect: formation of sister-chromatid exchanges in peripheral blood lymphocytes	Sex, age, smoking habits referring to the last year, working characteristics (working years and task and personal protective equipment use).	Statistically significant increases of sister-chromatid exchanges in the exposed group compared to controls	Good
Jakab et al., 2010 [23] Hungary Hospital pathology laboratory	74; 37 exposed and 37 controls; 43.2 ± 2.0 years; 0 males (0%) and 74 females (100%)	Biomarkers of effect: formation of chromosomal aberrations, sister-chromatid exchange, HPRT mutations, UV-induced unscheduled DNA-repair synthesis, premature centromere division and of cells with a high frequency of SCE in peripheral blood lymphocytes	Age, medication, lifestyle (smoking and drinking habits), medical and work histories in relation to known or suspected chemical mutagens and/or to exposure to ionizing radiation, use of protective devices during work	Statistically significant increases in the apoptotic activity and chromosomal aberrations levels in the exposed group compared to controls	Fair
Ladeira et al., 2011 [24] Portugal Hospital-associated histopathology laboratories	141; 56 exposed and 85 controls; 35.9 ± 9.8 years; 50 males (35%) and 91 females (65%)	Biomarkers of effect: micronuclei in peripheral blood lymphocytes and exfoliated cells from the buccal mucosa, nucleoplasmic bridges, common poor repair and/or telomere fusion and nuclear buds in peripheral blood lymphocytes	Age, gender, smoking habits and alcohol consumption, use of protective devices during work	Statistically significant increases in the investigated biomarkers in the exposed group compared to controls	Good
Ladeira et al., 2013 [25] Portugal Hospital-associated histopathology laboratories	136; 54 exposed and 82 controls; 36.3 ± 9.8 years; 48 males (35%) and 88 females (65%)	Biomarkers of effect: micronuclei in peripheral blood lymphocytes and exfoliated cells from the buccal mucosa, nucleoplasmic bridges and nuclear buds in peripheral blood lymphocytes	Age, gender, smoking habits, alcohol consumption	Statistically significant increases in the investigated biomarkers in the exposed group compared to controls	Good
Motta et al., 2021 [26] Italy Anatomic pathology unit	16 exposed	Biomarkers of internal dose: urinary formaldehyde concentrations	-	Workers' urinary formaldehyde levels were minimal, but the statistical analysis highlighted a slight weekly accumulation	Poor
Musak et al., 2013 [27] Czech Republic Hospital laboratories	355; 105 exposed and 250 controls; 39 ± 10 years; 50 males (14%) and 305 females (86%)	Biomarkers of effect: structural chromosomal aberrations in peripheral blood lymphocytes	Age, gender, job category, smoking habits	Statistically significant increases in the chromosomal aberrations levels in the exposed group compared to controls	Good
Pala et al., 2008 [28] Italy Cancer research institute laboratories	36; 27 low exposed and 9 high exposed; 40.14 (range 27–52) years; 12 males (33%) and 24 females (67%)	Biomarkers of internal dose: formaldehyde human serum albumin conjugate Biomarkers of effect: chromosome aberrations, micronuclei, sister chromatid exchanges in peripheral blood lymphocytes	Age, gender, smoking habits, exposure to other chemicals	Statistically significant increase in the biomarker of exposure in subjects with high exposure, but not of the biomarkers of effect	Poor

Table 1. *Cont.*

Reference Country Working Context	Sample Size Age (Mean Value ± SD and/or Range) Gender (%)	Biomarkers of Internal Dose and/or Early Effect	Confounding and Interfering Factors	Main Results	Quality Evaluation According to NOS Scale
Santovito et al., 2011 [29] Italy Pathology wards	36; 20 exposed and 16 controls; 43.9 ± 2.34 years; 13 males (36%) and 23 females (64%)	Biomarkers of effect: frequency of chromosomal aberrations in peripheral blood lymphocytes	Age, years of employment	Statistically significant increase in the frequency of chromosomal aberrations per cell and in the percentage of cells with aberrations in peripheral lymphocytes in the exposed group compared to controls	Poor
Shaham et al., 1996 [30] Israel Anatomy and pathology laboratories	20; 12 exposed and 8 controls; 42.5 ± 10.1 years	Biomarker of effect: amount of DNA–protein crosslinks in white blood cells	Age, smoking habits, medical history, hygiene habits	Statistically significant increase in the levels of DNA–protein crosslinks in peripheral white blood cells in the exposed group comapred to controls. Linear positive relationship between years of exposure and the amount of DNA–protein crosslinks	Poor
Shaham et al., 1997 [31] Israel Anatomy and pathology department	33; 13 exposed and 20 controls; 40.5 ± 12 years	Biomarker of effect: sister chromatid exchanges in peripheral blood lymphocytes	Age, gender, smoking habits, years of FA exposure, occupational and medical histories, hygiene habits	Statistically significant increase in the mean numbers of sister chromatid exchanges in the exposed group compared to controls	Poor
Shaham et al., 2003 [32] Israel Pathology wards	399; 186 exposed and 213 controls; 43.9 ± 10.3 years; 186 males (47%) and 213 females (53%)	Biomarkers of effect: DNA–protein crosslinks and p53 "wild type" and mutant (pantropic p53) in peripheral lymphocytes	Age, gender, smoking habits, years of education, origin	Statistically significant higher level of pantropic p53 in the exposed group compared to controls	Fair
Suruda et al., 1993 [33] USA Anatomy laboratory	29; 23.6 years; 22 males (76%) and 7 females (24%)	Biomarkers of effect: micronuclei in buccal cells, nasal cells, and peripheral blood lymphocyte; lymphocyte sister chromatid exchange	Age, gender, smoking status, performed embalming in 90 days prior to study	Statistically significant increase in micronucleus frequency during the study period compared to pre-exposure levels in epithelial cells from the buccal area, nasal cells, and blood cells in the low exposed group, and a decrease in lymphocyte sister chromatid exchange	Poor
Tompa et al., 2006 [34] Hungary Hospital operating theater	180; 86 exposed and 94 controls; 42.4 ± 1.7 years; 14 males (7.8%) and 166 females (92.2%)	Biomarkers of effect: chromosome aberrations, sister chromatid exchange, ratio of lymphocyte subpopulations, lymphocyte activation markers and leukocyte oxidative burst	Age, smoking, drinking, exposure to known or suspected mutagens, occupational history, use of protective devices during work	Statistically significant increase in the mean sister chromatid exchange frequency was observed in the exposed group compared to controls	Fair

Table 2. Main characteristics of studies (n = 23) involving industrial settings included in the systematic review.

Reference Country Working Context	Sample Size Age (Mean Value ± SD and/or Range) Gender (%)	Biomarkers of Internal Dose and/or Early Effect	Confounding and Interfering Factors	Main Results	Quality Evaluation According to NOS Scale
Attia et al., 2016 [35] Egypt Cosmetic industry	60; 40 exposed and 20 controls; 29 ± 11 years; 12 males (20%) and 48 females (80%)	Biomarkers of internal dose: urinary formic acid concentration Biomarkers of effect: levels of p53 mutations and malondialdehyde in serum samples	Gender, age, smoking habits, alcohol consumption	Statistically significant increase in serum malondialdehyde in exposed workers compared to controls	Fair
Bono et al., 2006 [36] Italy Plywood and laminate factory	51; 21 exposed and 30 controls; 35 ± 8 years; 37 males (73%) and 14 females (27%)	Biomarkers of effect: alkylation of hemoglobin to form a terminal N-methylenvaline residue	Age, gender, residence, smoking habits, professional activity	Statistically significant higher prevalence of N-methylenvaline in the exposed group compared to controls	Fair
Bono et al., 2012 [37] Italy Laboratory and plastic laminate plant	173; 95 exposed and 78 controls; 40 years; 89 males (51%) and 84 females (49%)	Biomarkers of effect: alkylation of hemoglobin to form a terminal N-methylenvaline residue	Age, gender, smoking habits, place of residence, hobbies, therapies, smoking habits, profession, environmental and personal protective equipment	Statistically significant higher concentration of N-methylenvaline in the exposed group compared to controls	Fair
Bono et al., 2016 [38] Italy Plastic laminate plant	95; 50 exposed and 45 controls; 44 ± 10 years; 95 males (100%) and 0 females (0%)	Biomarkers of effect: frequency of 3 (2-deoxy-β-D-erythro-pentafuranosyl) pyrimido [1,2-α] purin-10 (3H)-one deoxyguanosine adducts	Age and smoking habits, jobs, personal formaldehyde exposure	Statistically significant increase in frequency of deoxyguanosine adduct in the exposed group compared to controls.	Good
Burgaz et al., 2002 [39] Turkey Shoes factory and anatomy and pathology laboratory	68; 50 exposed and 18 controls; 30 ± 8 years; 55 males (81%) and 13 females (19%)	Biomarkers of effect: micronucleus frequencies in epithelial buccal cells	Gender, age and smoking habits, duration of exposure	Statistically significant increases in micronucleus frequency in the exposed group compared to controls	Fair
El Far et al., 2006 [40] Egypt Chemical industries	80; 65 exposed and 15 controls; 26–60 years; 80 males (100%) and 0 females (0%)	Biomarkers of effect: levels of carcinoembryonic antigen, alpha-fetoproteins, prostate-specific antigen	-	Statistically significant higher serum concentration of carcinoembryonic antigen, alpha-fetoproteins, and prostate-specific antigen in the exposed group compared to controls	Fair
Ghelli et al., 2021 [41] Italy Wood industry plants	238; 127 exposed and 111 controls; 42 ± 16 years; 161 males (68%) and 77 females (32%)	Biomarkers of effect: levels of oxidative stress markers as 15-F2t-IsoP and 8-oxo-dGuo in urine samples	Age, gender, body mass index, smoking habits, residence, working years, wheezing, asthma-like symptoms, allergies, eczema, personal protective equipment use	Statistically significant higher concentrations of 15-F2t-IsoP and 8-oxo-dGuo in the exposed group compared to controls	Good
Hosgood et al., 2012 [42] China Melamine resins and plastic utensils factories	94; 43 exposed and 51 controls; 30.5 ± 6.5 years; 81 males (86%) and 13 females (14%)	Biomarkers of effect: major lymphocyte subsets	Age, gender, smoking habits, alcohol consumption, recent infections (flu or respiratory infections in the previous month), body mass index	Statistically significant decrease in counts of NK cells, regulatory T cells, and CD8+ effector memory T cells in the exposed group compared to controls	Fair
Lan et al., 2015 [43] China Melamine resins plant	52; 29 exposed and 23 controls; 31 ± 5 years; 47 males (90%) and 5 females (10%)	Biomarkers of effect: chromosomal aneuploidy and structural chromosome aberrations in myeloid progenitor cells	Age, gender, smoking habits, alcohol consumption, recent infections (flu or respiratory infections in the previous week), use of medication, body mass index	Statistically significant increase in the frequencies of monosomy, trisomy, tetrasomy, and structural chromosome aberrations of multiple chromosomes in exposed group compared to controls	Good

Table 2. *Cont.*

Reference Country Working Context	Sample Size Age (Mean Value ± SD and/or Range) Gender (%)	Biomarkers of Internal Dose and/or Early Effect	Confounding and Interfering Factors	Main Results	Quality Evaluation According to NOS Scale
Lyapina et. al. 2004 [44] Bulgaria Carbamide FA glue employees	50; 29 exposed and 21 controls; 38.5 ± 12.5 years; Exposed: 13 males (26%) and 16 females (32%)	Biomarkers of effect: neutrophil respiratory burst activity; haematologic alterations	Age, gender, smoking habits	Statistically significant negative correlation between the duration of exposure to formaldeyde and erythrocyte count and haematocrit level, and lower neutrophil respiratory burst activity in the exposed group with upper respiratory tract findings and frequent and long-lasting infectious inflammatory relapses	Poor
Maniscalco et al., 2018 [45] Italy Friction system manufacturing plant	30; 20 exposed and 10 controls; 36.5 ± 6.5 years; 30 males (100%) and 0 females (0%)	Biomarkers of effect: changes in metabolic profiles in exhaled breath condensate	Smoking habits	Statistically significant increase in the concentration of propionate, isopropanol, lactate, acetoin, methanol, 1,2-propanediol, ethylene glycol, 3-hydroxyisobutyrate, and phenylalanine in the exposed group compared to controls	Good
Orsiere et al., 2006 [46] France Anatomy laboratory	96; 59 exposed and 37 controls; 44.3 ± 8.3 years; 20 males (20.9%) and 76 females (79.1%)	Biomarkers of effect: DNA damage by chemiluminescence microplate assay and cytokinesis-blocked micronucleus assay in peripheral lymphocytes	Age, gender, smoking habits, alcohol consumption, recent X-ray diagnostic or radiotherapy history, use of mutagenic or reprotoxic drugs	Statistically significant higher frequency of micronuclei in the exposed group compared to controls	Fair
Oztan et al., 2020 [47] Turkey Fiber manufacturing company	198; 116 exposed and 82 controls; 35.3 ± 6.68 years; 198 males (100%) and 0 females (0%)	Biomarkers of internal dose: urinary formic acid concentration Biomarkers of effect: proinflammatory cytokines, pulmonary function tests, serum AST, ALT, GGT, and creatinine	Chronic disease, medications, smoking status	Statistically significant increase in mean level of FA, TNF-α, and IL-6; significant decrease in FEV1 and FVC in the exposed group compared to controls	Fair
Peteffi et al., 2016 [48] Brazil Furniture manufacturing facility	91; 46 exposed and 45 controls; 35 ± 11.4 years; 41 males (45%) and 50 females (55%)	Biomarkers of internal dose: urinary formic acid concentration Biomarkers of effect: micronucleus test in exfoliated buccal cells and comet assay in peripheral lymphocytes	Age, gender, smoking habits, alcohol consumption	Statistically significant increase in damage frequency and damage index in the comet assay, frequency of micronuclei, and formic acid concentration in urine in the exposed group compared to controls	Poor
Phillips et al., 2022 [49] USA Factories	71; 31 exposed and 40 controls; 30.6 ± 6.7 years; 59 males (83%) and 12 females (17%)	Biomarkers of effect: DNA methylation in peripherical blood cells	Age, gender, occupational and medical history, environmental exposures, smoking habits, alcohol consumption	Statistically significant decrease in methylation variability in the DUSP22 gene promoter and hypomethylation of the HOXA5 promoter region in the exposed group compared to controls	Fair
Regazzoni et al., 2017 [50] Italy FA production factory	30; 15 exposed and 15 controls; 9 males (30%) and 21 females (70%)	Biomarkers of internal dose: formaldeyde human serum albumin conjugate	Smoking habits	No increase of formyl adducts in exposed subjects compared to controls	Fair
Romanazzi et al., 2013 [51] Italy Decorative laminates industry	105; 51 exposed and 54 controls; 40 ± 10 years; 105 males (100%) and 0 females (0%)	Biomarkers of effect: levels of 15-F2t-isoprostane in urine samples	Age, place of residence, hobbies, therapies, smoking habits, professional use of environmental and personal protective devices	Statistically significant increase in 15-F2t-isoprostane in exposed group compared to controls	Poor

Table 2. *Cont.*

Reference Country Working Context	Sample Size Age (Mean Value ± SD and/or Range) Gender (%)	Biomarkers of Internal Dose and/or Early Effect	Confounding and Interfering Factors	Main Results	Quality Evaluation According to NOS Scale
Seow et al., 2015 [52] China Resins and plastic factories	94; 43 exposed and 51 controls; 30.5 ± 6.5 years; 43 males (46%) and 51 females (54%)	Biomarkers of effect: circulating immune/inflammation markers	Age, gender, smoking habits, alcohol consumption, recent infections or medication use, body mass index	Statistically significant decrease in immunomodulating markers in the exposed workers compared to controls	Good
Van der Laan et al., 2022 [53] China Resins and plastic factories	70; 31 exposed and 39 controls; 30.7 ± 6.7 years; 12 males (17%) and 58 females (83%)	Biomarkers of effect: DNA methylation in peripheral blood cells	body mass index, smoking habits, alcohol consumption, self-reported recent infection	No statistically significant differences in methylation in peripheral blood cells were observed in the exposed group compared to controls	Fair
Zendehdel et al., 2016 [54] Iran Melamine dish preparation plant	67; 35 exposed and 32 controls; 17–59 years	Biomarkers of effect: erythrocyte acetylcholinesterase activity	Age, gender, smoking habits, socioeconomic status, genotype of acetylcholinesterase	Statistically significant increase in the acetylcholinesterase activity in the exposed group compared to controls	Fair
Zendehdel et al., 2018 [55] Iran Melamine tableware plant	87; 53 exposed and 34 controls; 28.8 ± 7.9 years; 80 males (92%) and 7 females (8%)	Biomarkers of effect: DNA damage by comet assay	Age, gender, smoking habits, alcohol consumption, work experience	Statistically significant increase in DNA tail lengths at comet assay in the exposed group	Good
Zhang et al., 2010 [56] China Melamine resins plant	94; 43 exposed and 51 controls; 30.5 ± 6.5 years; 81 males (86%) and 13 females (14%)	Biomarkers of effect: hematopoietic function disruption and leukemia-related chromosome changes by fluorescence in situ hybridization (FISH)	Smoking habits, alcohol consumption, age, gender, flu or respiratory infections in the previousmonth, body mass index	Statistically significant decrease in total white blood cell counts in the exposed group	Fair
Zhitkovich et al., 1996 [57] Bulgaria Chrome-platers factory	16; 10 exposed and 6 controls; 37.8 ± 6.8 years	Biomarkers of effect: DNA-protein crosslinks in peripheral blood lymphocytes	Smoking habits, age, gender, weight, alcohol consumption, occupational exposure to chromium	No statistically significant differences of levels of DNA-protein crosslinks in peripheral lymphocytes in the exposed group	Poor

Table 3. Main characteristics of studies (n = 8) involving other settings or miscellanea of settings included in the systematic review.

Reference Country Working Context	Sample Size Age (Mean Value ± SD and/or Range) Gender (%)	Biomarkers of Internal Dose and/or Early Effect	Confounding and Interfering Factors	Main Results	Quality Evaluation According to NOS Scale
Aglan and Mansour 2020 [58] Egypt Hairdressing salon	120; 60 exposed and 60 controls; 20–36 years; 0 males (0%) and 120 females (100%)	Biomarkers of effect: micronucleus frequencies in epithelial buccal cells and peripheral blood lymphocytes	Age, residency, nutritional habits, socio-economic standard	Statistically significant increase in micronucleus frequency in hairstylists involved in hair straightening procedure for >5 years with respect to the controls	Fair
Barbosa et al., 2019 [5] Brazil Hairdressing salon	49; 8 males (16%) and 41 females (84%)	Biomarkers of effect: global DNA methylation in whole blood	Age, gender, alcohol consumption, smoking habits	Statistically significant increase in global DNA methylation in higher-exposed group.	Fair
Norbak et al., 2000 [59] Sweden School buildings	234	Biomarkers of effect: acoustic rhinometry and eosinophil cationic protein, myeloperoxidase, lysozyme, albumin in nasal lavage	Age, gender, smoking habits, atopy and mean classroom temperature in the school	Statistically significant increase in eosinophil cationic protein and of lysozyme in the exposed group. A lower degree of nasal patency was found at higher concentrations of respirable dust, nitrogen dioxide, and formaldehyde	Fair
Peteffi et al., 2016 [11] Brazil Hairdressing salon	50	Biomarkers of internal dose: urinary formic acid concentration Biomarkers of effect: micronucleus test in exfoliated buccal cells and comet assay in peripheral lymphocytes	Age, gender, weight, smoking, smoking-related habits, allergic symptoms, whether they wear personal protection equipment	Statistically significant variation in damage frequency and damage index in the comet assay, frequency of micronuclei, and formic acid concentration in urine before and after the exposure, respectively	Fair
Squillacioti et al., 2020 [60] Italy Traffic police officers	154; 85 outdoor workers and 69 indoor workers; 45.8 ± 7.7 years; 88 males (57%) and 66 females (43%)	Biomarkers of effect: urinary F2t-isoprostane; FeNO as a marker of airway eosinophils inflammation	Age, gender, smoking habits, body mass index, sampling location, job duties, cities	Statistically significant positive correlation between the air concentration of formaldehyde and 15-F2t-isoprostane	Fair
Triebig et al., 1989 [61] Netherlands Anatomic theatres, pathological laboratories, chipboard manufacturers	153	Biomarkers of internal dose: urinary formic acid concentration	Workplaces	No significant relationship between FA exposure and formic acid excretion in urine	Poor
Vargova et al., 1993 [62] Slovakia Woodsplinter materials plant	39; 20 exposed and 19 controls; 42.3 years	Biomarkers of effect: structural chromosome aberrations in peripheral blood lymphocytes	Age, lifestyle factors, social status, health conditions	Statistically significant higher percent of aberrant cells and breaks per cell in the exposed group compared to control	Poor
Viegas et al., 2010 [63] Portugal Resin production plant, pathology and anatomy laboratories	165; 80 exposed and 85 controls; 34.8 ± 8.9 years; 79 males (48%) and 86 females (52%)	Biomarkers of effect: micronucleus test in exfoliated epithelial cells from buccal mucosa and peripheral blood lymphocytes	Age, gender, smoking habits, health conditions, medical history, medication, lifestyle factors	Statistically significant higher frequency of micronuclei in the exposed group, both in peripheral blood lymphocytes and in epithelial buccal cells in the exposed group compared to control. Moderate positive correlation between years of exposure and frequency of micronuclei in peripheral blood lymphocytes and in epithelial cells	Good

In total, 21 articles out of a total of 52 included in the present review were focused on healthcare and research settings, 23 in industrial scenarios, and 8 in other settings.

The included articles were published between 1989 and 2023 and performed in several countries: 15 from Italy [14,15,21,22,26,28,29,36–38,41,45,50,51,60], 7 from Portugal [17–20,24,25,63], and 5 from China [42,43,52,53,56]. Other countries were less represented: Egypt [35,40,58], Brazil [5,11,48], and Israel [30–32] had three studies each; Iran [54,55], USA [33,49], Hungary [23,34], Turkey [39,47], and Bulgaria [44,57] had two studies each; only one study was conducted each in Slovakia [62], Tunisia [16], Sweden [59], Czech Republic [27], France [46], and the Netherlands [61].

Most of the studies involved both males and females, while three studies studied only females [14,23,58], five only males [38,40,45,47,51], and nine did not state the gender of the participants [26,30,33,54,57,59–62]. All the studies included subjects with a range of 17–60 years, with a sample size ranging from 16 [26,57] to 399 individuals [32] and a study period considered ranging from 3 weeks [49] to 13 years [34].

Nine articles [11,20,26,28,35,47,48,50,61] investigated the levels of biomarkers of internal dose, using the urinary concentration of formic acid [11,20,35,47,48,61] or FA [26] or FA human serum albumin conjugate [28,50]. Statistically significant increases in the concentration of biomarkers of internal dose in the exposed group with respect to the control were recovered in four studies [20,26,28,48], and higher levels of formic acid were found after the exposure in one study [11].

As regards to the biomarkers of early effects for human health, the included articles monitored one or more of these biomarkers. The most common investigated effect was the micronucleus frequency in peripheral blood lymphocytes and/or epithelial buccal cells (used in 14 [11,16–18,20,24,25,28,33,39,46,48,58,63] of the 49 included studies evaluating biomarkers of effect), which was statistically significantly increased in those exposed compared to controls, with the exception of Pala et al. [28], which did not find any cytogenetic effect. Nine studies analyzed structural chromosomal aberrations [19,21,23,27–29,34,43,62] and nine articles evaluated sister chromatide exchanges [17,18,20,22,23,28,31,33,34]; they found significantly increased effects in the exposed workers compared to controls.

Several factors extrinsic to occupational exposure can affect the FA exposure levels and the related frequency of observed early biological effects; hence, with the exception of one study [26], all the included studies considered some potential confounding and/or interfering factors on biomarkers measurements, such as age, sex, body mass index, current cigarette smoking status and alcohol consumption, recent infections, current use of medication, and duration of exposure. For this reason, in order to adjust the results related to the biomarkers of exposure or effects, these variables were included in models if they were significant at $p < 0.05$ or if there was evidence of confounding (e.g., greater than a 15% change in the regression coefficient). In the multiple linear regression analysis, adjustments were made for possible influence of such variables and selected biomarkers were subsequently tested using the adjusted multiple linear regression.

4. Discussion

The present systematic review was focused on the identification of biomarkers used for assessing the exposure to FA in occupational environments and the relative early negative effects for human health.

The first relevant result is related to the use of specific biomarkers of occupational exposure to FA. Indeed, just about one-sixth of the articles included have monitored an exposure biomarker using urinary concentrations of formic acid [20,35,47,48,61] or unmodified FA [26] or FA human serum albumin conjugate [28,50], and the results showed a statistically significant increase in the levels of these substances in the exposed group compared to control in only half of the studies [20,26,28,48]. In particular, the urinary concentration of formic acid was found significantly higher in FA-exposure with respect to the control by Costa et al. [20] and by Peteffi et al. [11,48], but not by the other included studies. These contrasting results can be due to the influence of other individual or external

factors beyond FA-exposure on the excretion of formic acid in the urine. For example, food composition can determine inter- and intra-individual daily fluctuations of urinary formic acid concentrations [64]. Indeed, it has been reported that an excessive intake of proteins and carbohydrates seems to increase the formic acid excretion in urine [65]. Besides this, age presents a positive correlation with the urinary levels of formic acid [20]. Furthermore, it has been demonstrated that a non-negligible level of formic acid can be produced by endogenous FA [8]. All these influences on the concentrations of formic acid make this substance a poor biological index for the human biomonitoring of exposure to FA. As regards urinary unmodified FA, Motta et al. [26] evidenced a potential FA weekly accumulation, but the same authors highlighted that the use of urinary FA as a biomarker of exposure poses severe limitations because of its very short half-life [26]. Regarding FA human serum albumin conjugate, Ref. [28] recovered a statistically significant increase in this biomarker; in contrast, the results found by Regazzoni et al. [50] did not confirm the association between FA exposure and the formation of the adduct. This difference can be due to several factors, such as the levels and the duration of exposure, the methods used for measuring the adducts, the exposure to other substances as well as differences in the genetic polymorphism for specifying metabolizing enzymes.

Another important finding is linked to the biomarkers of early adverse effects for human health. Except for three studies [26,50,61] evaluating only biomarkers of exposure, the other included articles monitored also one or more biomarkers of effects in workers exposed to FA. The most common studied effect was the cytogenetic one by micronucleus assay in peripheral blood lymphocytes and/or epithelial buccal cells followed by the structural chromosomal aberrations and sister chromatide exchanges. Among the other studied early effects there were oxidative stress, DNA damage, and DNA protein crosslink. The results of almost all the included articles agree in demonstrating a statistically significant increase in early effect biomarkers in FA-exposed workers with respect to controls. These results confirm that occupational FA exposure is associated with a large number of early adverse effects and these risks should be carefully evaluated and managed. Besides this, these findings evidence that there are many effects related to FA exposure that are detectable early; consequently, these can be a useful tool for assessing the risks linked to this occupational exposure and for predicting the possibility of diseases, including cancer. A research agenda in this field is represented by the choice of which early effect indicators to use. In fact, there are some critical issues that need to be considered.

All the included studies take into account several confounding and/or interfering variables on the exposure to FA or on the levels of biomarkers, such as age, sex, body mass index, current cigarette smoking status and alcohol consumption, recent infections, current use of medication, and duration of exposure. As regard to sex and gender differences, a recent review highlighted that in the last few decades, given the increasing number of women workers, the difference between male and female populations in terms of occupational health has become evident and the effect of risk factors and work-related exposures is intrinsically different in male and female workers. However, further research in this field is needed in order to study in depth the extent of sex and gender differences in the context of occupational health [66]. Besides this, for the interpretation of biomarkers of exposure and effects, the issue of confounding factors such as age, sex, and gender differences; genetic make-up; and other exogenous confounding factors including lifestyle habits such as smoking habit, alcohol consumption, and others should have been addressed and discussed in previous research, and they should be carefully taken into account in future studies [67].

In addition to the aforementioned interfering and confounding factors that can influence the levels of biological indices of effects, it must be considered that the indicators studied by the articles included in the present review are not only determined by exogenous FA, but also by endogenous FA and, therefore, it is necessary to find appropriate ways to exclude this quota produced within the organism. Furthermore, the identified indicators of early effect are not specific to the exposure to FA, but they can also form following

exposure to other toxic and/or carcinogenic substances in workplaces. Several studies demonstrated that DNA damage and other early adverse effects can be determined by the occupational exposure to a large number of inorganic and organic compounds, such as cadmium [68], cytostatic/antineoplastic drugs [69], benzene and other polycyclic aromatic hydrocarbons [70], organochlorides [71], and others.

Regarding the setting groups, we found no differences in the results of the studies involving healthcare and research or industrial or other scenarios. This result is in line with the findings of a previous review [6], reporting that airborne FA was found at concentrations higher than outdoors in almost all the studied scenarios/activities.

The results of this systematic review add some scientific evidence on the use of the biomarkers for evaluating the exposure and the related early effects related to occupational exposure to FA. This evidence can support appropriate choices in the risk assessment and management process, necessary for helping to achieve the target of "promoting a safe and protected working environment for all workers" in the Sustainable Development Goal 8 of the UN Agenda 2030 for Sustainable Development.

This systematic review has some limitations. First of all, only studies published in the English language were considered, excluding articles published in other languages a priori. Besides this, a formal meta-analysis was not carried out because the results of the articles included in the review were different in term of populations, number of participants (from 16 to 399), study period (ranging from 3 weeks to 13 years), working context, study design, methodological approach for estimating exposure and effects, confounding and/or interfering factors considered, and kinds of biomarkers of exposure or effects investigated. Thus, publication bias and statistical heterogeneity were not assessed. This choice is supported by Cochrane, who recently declared that meta-analysis should be considered only when the studies are adequately homogeneous for participants, interventions, and outcomes [72]. However, in our knowledge, this is the first systematic review of the scientific literature that gives a complete picture of biomarkers of exposure and early effects used in the assessment of FA exposure in occupational settings.

5. Conclusions

The results of the included articles evidenced that the use of biomarkers of exposure for assessing occupational exposure to FA is under debate. Further studies are needed to find suitable biological indicators of FA exposure.

Almost all the studies show a statistically significant increase in early effect biomarkers (particularly cytogenetic assays) in FA-exposed workers with respect to controls demonstrating their usefulness for biomonitoring studies of exposed workers. FA exposure in working contexts should be eliminated or reduced as much as possible thanks to the use of individual and collective protective equipment and mitigation strategies. Besides this, biomarkers of early effect can be used for evaluating the health hazards to human health in a very early and reversible phase. In particular, micronucleus assays on buccal cells are interesting and promising for their sensitivity and also because of their non-invasiveness, which makes them easily usable and acceptable to workers.

Additional efforts must be made to eliminate the effect due to simultaneous exposure to other toxic and carcinogenic substances and the influence of confounding and interfering factors.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/su16093631/s1, PRISMA Checklist.

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