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Brazilian workers occupationally exposed to different toxic agents: A systematic review on DNA damage

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ABSTRACT

The evaluation of genotoxicity in workers exposed to different toxic agents is very important, especially considering the association between these exposures in a chronic context and DNA damage. Assessing biomarkers of exposure and, when possible, early biomarkers of effect, contributes to elucidating the potential toxic mechanisms involved in genotoxicity and its contribution to chronic non-communicable diseases. In Brazil, the biggest country in South America, workers are exposed to hazardous physical and chemical agents. Considering that these exposures occur, in most cases, throughout the worker's whole life, this is an important public health concern in Brazil. Therefore, this systematic review aims to analyze occupational exposure to chemical and physical agents and the association with DNA damage in studies carried out in Brazil from 1980 to 2021. A systematic and comprehensive literature search was performed in different databases based on occupational exposure to chemical and physical agents and DNA damage. Only full articles on studies that investigated experimental evidence on occupational exposure in Brazil and assessed DNA damage were included, amounting to 89 articles. Five main occupational exposure groups were identified: pesticides (36%), organic solvents (20%), dust and particles (16%), metals (11%), and ionizing radiation (6%). Another group called "others" included studies (11%) that did not fall into these main groups. It was found that comet assay and micronucleus tests are the most adopted methods to detect DNA damage. Occupational exposures were most associated with DNA damage. However, further improvements in study design would be needed to better characterize the association between biomonitoring and DNA damage, particularly to account for confounding factors.

1. Introduction

There is great concern about the possible mutagenic and carcinogenic effects of genotoxic agents in human populations exposed occupationally, accidentally, environmentally, or due to lifestyle. The inevitable consequence of industrial development is human exposure to an increasing number of synthetic or natural chemical substances, including dust, fibers, organic, and inorganic chemical compounds, which can cause serious toxicological effects [1,2]. In recent years, the International Agency for Research on Cancer (IARC) evaluated more than 1000 agents and ranked more of 500 as definitely carcinogenic, probably carcinogenic, or possibly carcinogenic in humans. These include chemicals, complex mixtures, physical and biological agents, and lifestyle factors [3].

Health and safety programs have been implemented in several countries around the world, giving greater attention to the problems caused by occupational poisoning by chemical agents [4]. Workers in developed countries who are at risk of exposure to these agents have been informed about their handling; however, due to the great diversity of industry and cultural inequalities on the planet, many countries still

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ignore the importance of this for political and economic reasons. Despite regulatory measures being taken, workers continue to be exposed to genotoxic agents because they are not aware of such exposure, nor about the type and quantity of potentially hazardous substances used in their work [5]. In Brazil, the Ministry of Labor is responsible for standardizing and enforcing the prevention of accidents and occupational diseases, including the medical control of occupational health. The medical control of occupational health contemplates, among other standards, regulatory standard number 7, which establishes chemical agents, their biomarkers of exposure, and concentrations considered acceptable for occupational exposure to those chemical agents. In 2020, the standard was modified to include 45 chemical agents [PCMSO NR-7 - Programa de Controle Médico de Saúde Ocupacional (pncq.org.br)] instead of the previous 26 regulated chemical agents [6].

In toxicology, biomarkers are used to evaluate occupational and/or environmental exposure. Occupational toxicology is a science that studies biological markers, among others, aiming to prevent the development of human diseases. In this context, biomarkers of effect are very important, especially in biomarker-driven predictive toxicology, e.g. in the study of DNA damage. Biomarkers of exposure show the level of exposure to an agent in a particular time period [2]. In Brazilian regulatory standard number 7, to evaluate exposure to agrochemicals, only acetylcholinesterase and butyrylcholinesterase activities are established as biological indicators of effect with clinical significance; or blood lead concentration, which should be less than 600 μg/L for exposed workers [6]. Therefore, studies on DNA damage in workers exposed to different toxic agents are highly necessary.

The evidence indicates that environmental factors, such as inorganic and organic pollutants, may be most responsible for the development of cancer and that the work environment is still the main place where environmental exposure to potentially carcinogenic substances occurs [7,8]. The occupational environment has been one of the most favored environments for investigating the etiology and pathogenesis of cancer in humans related to specific agents. Until the 1970 s, cancer-causing substances or circumstances were found primarily in the occupational environment, and although the number of non-occupational carcinogens is currently increasing, occupationally-derived carcinogens still represent a large fraction of the total, occupying a special position among the different classes of human carcinogens [7]. Therefore, many epidemiological studies on the carcinogenic properties of different agents occur in occupational environments, where exposures are often higher than in the general environment. Through its specialized technical areas, the Brazilian Ministry of Health has sought to measure factors behind occupational and environmental cancer and intervene in them, by creating health surveillance procedures [9]. Considering the importance of such studies related with occupational activities that expose workers to chemical and physical agents and DNA damage evaluations, the present systematic review was carried out using Brazilian studies, aiming to demonstrate aspects such as the most common type of occupational exposures studied and the profile of Brazilian studies, among others, considering the types of DNA evaluation used.

2. Methods

2.1. Literature sources and search strategy

A search was conducted in Pubmed/Medline, EMBASE, Web of Science, SCOPUS, and Latin American and Caribbean Literature on Health Sciences (LILACS/BVS) to identify experimental studies that evaluated evidence on occupational exposure in Brazil and assessed DNA damage. The bibliographic search was carried out on June 30th of 2021 and included Brazilian studies in English, Spanish, or Portuguese published from 1980 to 2021. Search term combinations (developed in collaboration with a librarian) were structured using Boolean operators (AND, OR, NOT) to connect the exposure of interest (occupational exposure in Brazil to physical and chemical agents) and the adverse health outcome of interest (DNA damage biomarkers, genetic damage). The complete search strategy can be seen in Supplement 1.

The systematic review was registered in PROSPERO (registration number: CRD42021268341).

2.2. Study selection and data extraction

The study selection included experimental studies published from 1980 to 2021, in languages known by the authors (English, Spanish, and Portuguese), that indicate the genetic damage occurred in workers occupationally exposed to chemical and physical agents in Brazil.

Following the PICO acronym, the population was humans of any age, sex, or ethnic group who had been occupationally exposed to physical and chemical agents and the respective controls (unexposed individuals). The intervention/exposure was determined according to the following inclusion criterion: observational studies that investigated whether occupational exposure to physical and chemical agents alters the risk/occurrence of genetic damage in the exposed population. The exclusion criteria were as follows: 1) in vitro experimental studies, 2) in vivo and *ex vivo* studies in animals, 3) *in silico* studies, 4) studies of the effects on non-target species other than humans, 5) letters, reviews, editorials, reports, comments, theses, documents issued by regulatory bodies, and book chapters, 6) full papers not available or articles not available in English, Portuguese, and Spanish. For the comparators/controls, individuals or populations not occupationally exposed to the physical and chemical agents were used. The main outcomes were: DNA damage, numerical chromosome and/or structural abnormalities, micronuclei alterations, aneugenic effects, clastogenic effects, mutations, and others. No additional outcome was included.

After the electronic and manual search and exclusion of duplicates, at least two reviewers independently screened the relevant literature. The first screening was based on titles and abstracts. Pertinent references were screened again, basing the decision on full texts. If a disagreement persisted after being extensively discussed by the two reviewers, a third investigator (IFD) was asked to resolve it. Every step of the study selection was performed using the Rayyan software and was documented in a flow chart, according to PRISMA guidelines. A complete list is available of all references retrieved (Tables 1–7), as well as separate lists for the ones included and excluded in each step (Table Supplement 2), with the respective reason for exclusion.

A data extraction template in Excel format was developed and plotted until convergence and agreement among data extractors was reached. After extraction, an initial screening process was performed by the authors, where the inclusion of a particular article in this review was considered only if it was approved by at least two of the authors. A third author was nominated to resolve any conflicts regarding the extractions. For each study included, we extracted information to identify the study (e.g., ID, title, authors, year of publication, journal, DOI), the financial disclosures and funding sources of each author, and their affiliated organization; information about the study design (type of study, place, year, and period it was performed); information about the studies that identify genetic damage due to occupational exposure; the quality of the studies; the occupations related to the appearance of genetic damage; the most studied exposures, e.g. organic solvents (gas stations, industries, painting), pesticides, atmospheric pollution, mines, coal, crystalline silica, metals; the types of genetic tests used in the studies on occupational exposures to assess DNA damage; the test methods used, e.g. stain; how many cells were evaluated (comet and micronucleus tests); the most common biological samples; and the biological samples used to evaluate the DNA damage caused by occupational exposure.

2.3. Quality assessment

The quality score (QS) of the studies reviewed was evaluated according to eight items: (1) number of subjects in exposed and (2) control groups (*good* when 20–50 for each group; in this case two points are

Table 1
Manuscripts assessing human occupational exposure to radiation using genotoxicity assay identified by the review.

Study (QS[a])	Exposure (Type of occupation)	Duration (Mean years)	Subjects (Exposed/ Control)	Age (Mean years)	Male (%)	Current Smokers (%)	DNA Damage (Exposed/ Control)	Other Biomarkers	Radiation Exposure Assessment	Ref.
19 (QS 11)	Microcomputer users	≥ 5 years	40 (20/20)	37.8	50	NI	Micronucleus in buccal cells 3 (↑)		–	[15]
40 (QS 06)	Health professionals (technician, medical physicists, orthopedic traumatologists)	33 years	8 (6/2)	39.6	50	NI	Frequency of unstable chromosomal 2.0 (↑); Micronucleus in lymphocytes 34.8 (↑)			[12]
59 (QS 15)	Health professionals	NI	22 (11/11)	40.1	54.5	NI	Micronucleus in lymphocytes 1.3 (↑)		7.1 mSv	[10]
61 (QS 16)	Health professionals	5.9	44 (22/22)	34.8	47.7	27.3	Micronucleus in lymphocytes 1.2 (↑); Comet assay in leukocytes 2.1 (↑)		23.2 mSv	[11]
67 (QS 12)	Dentists	21.4	52 (28/24)	43.8	51.9	23	Chromosomal aberrations 0.08 (no difference);	Mitotic index 1.1 (no difference)		[14]
97 (QS 17)	Health professionals (nurses, technicians, and radiologists)	16.1	63 (27/36)	40.1	41	48	Micronucleus in buccal cells 15.7 (↑) % DNA 2.0 (↑)		< 20 mSv/ year	[13]

[a] QS, Quality Score (8–24); NI: Not informed.

given for each item); (3) age, (4) gender, (5) smoking status, and (6) alcohol intake matching (*good* when at least partly matched, with no difference with the control group; in this case two points are given for each item); (7) appropriate measurement of chemical exposure (*good* when there was at least an assessment using environmental measurements; in this case two points are given for this item); and (8) method for evaluating DNA damage according to the guideline (*good* when minimum modifications were made; in this case two points were given for this item). Each item evaluated (1–8) had a minimum of one point and maximum of three points, so the total QS possible ranged from 8 to 24. According to the QS scores, in relation to the quality of the studies, each study fits a specific category: fair (QS = 8–13), good (QS = 14–19), very good (QS = 20–23), or excellent (QS = 24). Analyses of the results using an appropriate statistical methodology and the relationship with confounding factors were also considered.

2.4. Strategy for data synthesis

A qualitative analysis of the articles was carried out of occupational exposure and the types of genetic tests used in the studies to assess DNA damage. An analysis was performed of the following subgroups: physical and chemical agents of exposure; study design (genetic tests); occupation.

3. Results and discussion

A total of 995 articles were found in five (5) databases (Pubmed/ Medline, EMBASE, Web of Science, SCOPUS, Latin American and Caribbean Literature on Health Sciences (LILACS/BVS) – Supplement 1). After excluding all duplicates, the total number of documents retrieved by our search in the multiple electronic databases was 747 (Fig. 1). Additional records (n = 7) were also identified through other sources. Of these 754 records, 639 documents were excluded because of their titles and abstracts. Only full articles on studies that investigated experimental evidence on occupational exposure in Brazil and assessed DNA damage were included. The full text of two articles was not found, only the abstract, and so these were excluded. Moreover, six studies were theses or dissertations and so were excluded. As shown in the flow chart, 18 out of the 107 full-text articles assessed for eligibility were excluded, and the reasons for their ineligibility are given in Supplement 2. Thus, 89 full articles were included in the systematic review. It is important to observe that four articles contained mixtures of two or more chemical agents. Thus, in the Tables 1–7 there are 94 toxicological agents and the percentual calculated were about the toxicological agents and not about the article numbers. Importantly, the number of articles presented in the next tables is different from the number of articles in the flow diagram because some articles were included in more than one table due to the different exposed groups or xenobiotics evaluated. In this review, we were able to identify five main groups of occupational exposure: radiation exposure, organic solvents, pesticides, dust and particles, and metals. In addition, there is a sixth group called "others," featuring studies not included in the previous main groups (Fig. 2). The main group of publications by Brazilian scientists involved pesticides (36%), followed by organic solvents (20%).

3.1. Radiation exposure

The mutagenic effect of ionizing radiation has been studied in Brazil, and there were six studies evaluating occupational exposure to radiation in health professionals, including technicians, nurses, medical physicists, radiologists [10–13], and dentists [14], and professionals exposed to radiation emitted by cathode ray tube computer video display monitors, such as copy typists, word processor operators, and computer programmers [15]. A total of 233 individuals, including 114 exposed workers and 115 control subjects, were evaluated. Most of the studies (83%) were conducted in the South region of Brazil and just one study evaluated workers from the Northeast region. Convenience sampling was used and any study presented the sample size calculation or statistical power. In 67% of the studies, the groups were matched by age and sex. Alcohol intake and smoking habits were statistically evaluated in only 17% of the studies. In one study, no statistical analysis was performed.

Exposure to radiation was evaluated by questionnaire in 67% of the studies, while 33% used the data available at the hospital where the study was conducted. Time of exposure was evaluated in 67% of the studies. Genotoxicity was assessed by micronucleus frequency, comet assay, and/or chromosomal aberrations in 83%, 33%, and 33% of the studies, respectively. Micronucleus frequency was evaluated in lymphocyte cultures in 50% of the studies. All the studies are summarized in Table 1. A 1.2–34.8-fold increase in genotoxicity can be seen in the subjects exposed to radiation, especially evaluated by micronuclei tests. It is suggested that genotoxicity increases with exposure time to radiation. However, no study found a direct association between genotoxicity and radiation levels. According to the QS scores, 50% of the studies were considered good and 50% were considered fair. None of them was considered to be very good or excellent.

Table 2
Manuscripts assessing human occupational exposure to organic solvents using genotoxicity assay identified by the review.

Study (QS[a])	Exposure (Type of occupation)	Duration (Mean years)	Subjects (Exposed/ Control)	Age (Mean years)	Male (%)	Current Smokers (%)	DNA Damage (Exposed/Control)	Other Biomarkers[b]	Occupational Exposure Assessment	Ref.
03 (QS 14)	Laboratory workers	13.6	72 (43/29)	38.7	41.6	19.4	Chromosome breaks 1.0 (no effect); Chromosome gaps 1.3 (↑)	Total aberrant cells 1.4 (↑)	Methanol in air (0.2 ppm); Isopropyl alcohol in air (5 ppm); Chloroform in air (0.03 ppm); Formaldehyde in air (0.004 ppm); Carbon tetrachloride in air (85 ppm); Ethyl acetate in air (85 ppm)	[36]
08 (QS 16)	Laboratory workers	4.3	31 (21/10)	27	70.9	0	Micronucleus in exfoliated cells from urinary bladder 8.2 (↑); Chromosome aberration 31.9 (↑)	–	–	[38]
103 (QS 17)	Chemical laboratory workers	1 - > 20	58 (29/29)	28.6	34.5	0	Ames test in urine 1.2 (↑)	–	–	[37]
25 (QS 18)	Shoe shop workers	15.7	108 (54/ 54)	43.8	88.9	27.7	Micronucleus in lymphocytes 2.2 (↑); Total anomalies 1.7 (↑)	Binucleated cells 1.9 (↑); Cells with linked nucleus 1.2 (↑)	–	[34]
48 (QS 18)	Shoemakers	4.8	70 (45/25)	27.7	100	7.1	Comet assay in leukocytes 2.4 (↑); Micronucleus in lymphocytes; 0.9 (no effect); Micronucleus in buccal cells 1.8 (no effect)	–	Hippuric acid (0.99 g/g creatinine)	[32]
49 (QS 16)	Shoemakers	4.8	94 (39/55)	28.3	79.7	5.3	Comet assay in leukocytes 3.0 (↑); Micronucleus in lymphocytes; 0.9 (no effect); Micronucleus in buccal cells 1.4 (no effect)	Genetic polymorphisms in GSTP1 and CYP2E1	Hippuric acid (0.9 g/g creatinine) Hemoglobin (14 g/dL)	[33]
43 (QS 17)	Hairdressers	1 - > 20	124 (69/ 55)	34.5	0	23.4	Comet assay in leukocytes 1.3 (↑)	–	–	[28]
85 (QS 15)	Hairdressers	10.1	100 (50/ 50)	37.2	50	30	Micronucleus in buccal cells 5.6 (↑)	Binucleated cells 1.6 (↑); Broken egg cells 1.5 (↑); Cells with buds 3.2 (↑)	–	[29]
47 (QS 13)	Petrochemical industry workers	3–13	36 (20/16)	51.9	100	23.7	Chromosomal gaps 2.9 (↑); Chromosomal breaks 1.7 (↑)	–	–	[39]
27 (QS 18)	Gas station attendants	7	86 (51/35)	35	83.7	18.6	Chromosomal aberrations 1.0 (no effect); Chromosome breaks 4.8 (↑); Fragments 4.2 (↑); Micronucleus in buccal cells 0.6 (no effect)	Hemogram, oxidative stress markers	Benzene in air (0.01 mg/ m^3); Toluene in air (0.02 mg/m^3); trans,trans-Muconic acid (0.24 mg/g creatinine); S-Phenylmercapturic acid (3.54 μg/g creatinine)	[20]
44 (QS 14)	Gas station attendants	11.4	415 (281/ 134)	35.9	–	–	Micronucleus in buccal cells 3.8 (↑)	–	–	[16]
46 (QS 18)	Gas station attendants	11	65 (43/22)	31.3	100	0	Micronucleus in buccal cells 3.7 (no effect); Comet assay in leukocytes 1.9 (↑);	8-OHdG in urine 2.1 (↑)	trans,trans-Muconic acid (0.44 mg/g creatinine)	[17]
58 (QS 12)	Gas station attendants	0–10	147 (126/ 21)	NI	NI	NI	Micronucleus in buccal cells 3.3 (↑)	–	–	[22]
76 (QS 19)	Gas station attendants	> 0.5	311 (201/ 110)	35	61	10.9	Micronucleus in lymphocytes 3 (↑);	Immunophenotyping	trans,trans-Muconic acid (0.1 mg/g creatinine)	[23]

(*continued on next page*)

Table 2 (*continued*)

Study (QS[a])	Exposure (Type of occupation)	Duration (Mean years)	Subjects (Exposed/ Control)	Age (Mean years)	Male (%)	Current Smokers (%)	DNA Damage (Exposed/Control)	Other Biomarkers[b]	Occupational Exposure Assessment	Ref.
							Comet assay in leukocytes 1.6 (↑)			
100 (QS 13)	Gas station attendants	9.8	127 (59/ 68)	37	NI	28.3		$p14^{ARF}$ methylation 1.9 (↑); $p16^{INK4A}$ methylation 3.0 (↑); GSTP1 methylation 0.8 (no effect)	–	[21]
110 (QS 13)	Automotive workshops workers	2.4	42 (24/18)	32.2	NI	87.5	Micronucleus in buccal cells 2 (↑)	Kariorrexis 2 (↑); Kariolysis 1.5 (↑)	–	[27]
63 (QS 15)	Car painters	10.4	20 (10/10)	39.4	100	45	Micronucleus in lymphocytes 3.1 (↑); Comet tail 1.1 (↑); Comet assay in leukocytes 7.1 (↑)	–	–	[25]
92 (QS 15)	Car painters	13.7	45 (25/20)	32.8	100	24.4	Aneuploidies 2.6 (↑); Chromosome deletions 4.4 (↑)	–	–	[24]
69 (QS 18)	Industrial painters	3.8	61 (34/27)	29.1	100	14.7	Comet assay in leukocytes 2.1(↑) Micronucleus in buccal cells 1.2 (no effect)	Malondialdehyde, albumin, ischemia-modified albumin, cotinine	Blood toluene (0.07 mg/ L); Hippuric acid (0.56 g/g creatinine); Ortho-cresol (0.04 mg/L)	[26]

[a] QS, Quality Score (8–24).
[b] biomarkers that demonstrated significant association with genotoxicity.

Critically speaking, there were few Brazilian studies that focus on radiation exposure and genotoxicity detected in this review. The ones included in this review ranged from good to fair, and none of them analyzed biomarkers other than genotoxicity. Limited information on the strength of the radiation is available in the publications, therefore the conclusions drawn by these publications are weak. In this sense, there is space for more studies evaluating different biomarkers of effect in subjects exposed to fixed levels of radiation.

3.2. Organic solvent exposure

Occupational exposure to organic solvents has been evaluated in workers exposed to benzene, toluene, xylenes, ethylbenzene, methanol, isopropyl alcohol, chloroform, carbon tetrachloride, ethyl acetate, and formaldehyde. There were 24 studies evaluating gas station attendants (n = 8) [16–23], painters (n = 4) [24–27], hairdressers (n = 4) [28–31], shoemakers (n = 3) [32–34], and chemical laboratory workers (n = 5) [35–39]. The studies without a control group [18,19,30,31] were excluded from the analysis, as well as one study that measured the biomarker of exposure and genotoxicity in different groups of exposed workers [35]. Thus, the studies analyzed in this review involved the following workers: six studies were performed in gas station attendants, four studies evaluated painters, four studies were done in chemical laboratory workers, three studies evaluated shoemakers, and two studies investigated hairdressers. Importantly, most of the time workers are not exposed to a single agent, but rather to a complex mixture of solvents, such as in the case of gas station attendants exposed to benzene, toluene, ethylbenzene, and xylenes. In addition, besides their occupational exposure to organic solvents, painters are exposed to toxic metals present in the inks.

A total of 2293 individuals were evaluated, including 1483 exposed workers and 810 control subjects from different regions of the country. Around 58% of the studies were conducted in the South and Southeast regions of Brazil, while 12.5% were from the Federal District, 8% were from the Northeast, and just 4% were from the North region of Brazil. Convenience sampling was used and no study presented the sample size calculation or statistical power. Most of the studies were partly matched by age and sex. Alcohol intake and smoking habits were also evaluated, but the individuals were only excluded in three studies.

A summary of the studies is described in Table 2. Most of the studies (around 58%) evaluated organic solvent exposure by questionnaire, which could be considered a limitation of these studies. In 20% of the studies, organic solvent exposure was verified by biological monitoring, while in 12.5% the exposure was accessed by environmental monitoring. In 8% of the studies, occupational exposure was evaluated by both environmental and biological monitoring. Therefore, the lack of proper exposure monitoring is a limitation in most of the studies. Another limitation is the lack of a control group for a proper comparison between occupationally and not occupationally exposed subjects; this was observed in five studies, which were not included in the table.

Genotoxicity was assessed by micronuclei frequency, comet assay, chromosomal aberrations, and DNA methylation in 67%, 37%, 21%, and 8% of the studies, respectively. Micronucleus frequency was evaluated in lymphocyte cultures in 25% of the studies. A 1.2–31.9-fold increase in genotoxicity can be seen in the subjects exposed to organic solvents. However, any finding of a direct association between genotoxicity and organic solvent levels is limited mainly because few studies applied environmental and/or biological monitoring. According to the QS scores, most of the studies were considered good (79%; average QS = 16) and 21% were considered fair. None of them was considered to be very good or excellent.

In addition, the evaluation of individuals' responses through the presence of gene polymorphisms was performed in two studies. A significant increase in DNA damage was observed for *GSTP1 Ile/Val* or *Val/Val* footwear-workers relative to those with *GSTP1 Ile/Ile*, especially in younger subjects. Furthermore, about 25% of levels of the DNA damage was associated with genetic polymorphisms in GSTP1 and CYP2E1 in this population [31]. In gas station attendants, the GSTP1 heterozygote genotype presents any association with methylation status [19].

The publications on Brazilian studies evaluating occupational exposure to organic solvents and DNA damage included 21% with no control group and so they were excluded. Of those analyzed, 79% were good, but none were very good or excellent. The micronuclei test for genotoxicity was performed the most and 58% of the publications evaluated occupational exposure to organic solvents using questionnaires alone, which is a very important limitation when the aim is to associate occupational exposure to toxic agents and its damaging effect, in this case DNA damage.

Table 3
Manuscripts assessing human occupational exposure to pesticides in multiple crops using genotoxicity assay identified by the review.

Study (QS[a])	Exposure	Duration (mean years)	Subjects (Exposed/ Control)	Age (mean years)	Male (%)	Current Smokers (%)	DNA Damage (Exposed/ Control)	Other Biomarkers[b]	Chemical Exposure Assessment	Ref.
1 (QS 18)	Organophosphorus, Organophosphorus, Biological insecticide, Organophosphate, Triazine	14	162 (100/62)	39	100	37	Micronucleus in buccal cells 2.2 (↑)	Buccal cells: karyorrhexis 3.7 (↑), karyolysis 3.1 (↑), Binucleated cells 1.3 (↑); Butyrylcholinesterase (BChE) activity 1.1 (no effect); lipid profiles (no effect); hematological markers (no effect)	–	[46]
17 (QS 13)	NI	3.6	34 (24/10)	34.2	100	56	Chromosome aberrations 21.3 (↑), aneuploidy 17.0 (↑), total breaks 13.3 (↑), centromeric breaks 14.3 (↑), mitotic index 2.7 (↑)	Acetylcholinesterase (AChE) 1.2 (↓); Hepatic enzymes: (no effect), alkaline phosphatase (AP) 1.3 (↑)	Cu, Zn (no effect), Mn 3.6 (↓);	[70]
21 (QS 14)	2,4D dimethylamine, Malathion, Atrazine, Glyphosate, Cyfluthrin, Imidacloprid.	Most participants > 10; 2.4% participants < 5	152 (84/68)	52.5	NI	10	Micronucleus in leukocytes (no effect)	Thiobarbituric acid reactive substances (TBARS) 1.2 (↓), Superoxide dismutase (SOD) 1.2 (↓), Glutathione peroxidase (GPx) activity 1.2 (↓), glutathione reductase (GSH) 1.2 (↓), carbonil, Catalase activity 1.1 (CAT) (no effect); Biochemical markers: total cholesterol (TC) 1.1 (↓), renal profile albumin 1.2 (↓), hepatic profile: alkaline phosphatase (ALP) 1.3 (↓)		[71]
22 (QS 16)	N-substituted glycine, 2,4-D, 2–4 in combination with other pesticides	19.3/7.5- farmers off season	152 (97/55)	36.2	100	26	Micronucleus in buccal cell 3.5 (↑), 1.25 (↑) of Micronucleus in non-PPE workers comparison user-PPE); chromosome aberrations 8.0 (↑); (significant to discentric and ring)	Relation high micronucleus in smoking, radiation-exposed, alcohol, and meat consumer workers.	–	[72]
26(QS 14)	Fosfonometil + Glyphosate, Paraquat, Tebuconazole, Tiabendazole	> 10	90 (80 = 50 commercial farming (CF) + 30 family farming (FF)/10 organic farming (OF))	45.7	98	18	Chromosome aberrations 11/0 11.0 (↑), more aneuploidies)	Gene expression: CF (XPG, CSA, ATM, LIG4 (↓)) in relation to OF, FF (XPG, LIG4 (↓)) in relation to OF, CF + FF individual with ≥ 12 years of exposure (XPC, XPG, CSB, ATM, LIG4 (↓)) in relation to < 12 years of exposure, CF + FF with CA (BRCA2 (↓)) in relation to CF + FF group without CA.	–	[74]
28 (QS 14)	Tararom or Methamidophos, Lanate, Vertimec, Benlate	20.7	36 (20/16)	35.7	100	17	Chromosome aberrations: (no effect)	Mitotic index 1.9 (↓); Polymorphisms: no influence of GSTM1	–	[58]
50 (QS 18)	Paraquat, glyphosate, aryloxy phenoxy propionic acid, deltamethrin, captan, triazol	34.64	125 (50/46 +29 – rural (Ac) and urban city (Fp) controls individuals)	42.6	60.8	10	Comet in lymphocyte damage index 5 (↑); (no difference between control cities); Micronucleus in lymphocytes 1.2 (↑) in relation to Ac city and 5.6 (↑) in relation to Fp city	Lymphocytes: nuclear buds 1.2 (↑), NPB 5 (↑); no difference between control cities. TBARS 3.5 (↑) in relation to Fp city; 3.1 (↑) in Ac city in relation to Fp city; CAT 1.7 (Ac) 2.2 (Fp) (no effect); BChE 1.1 (↓) in relation to control group, AChE 1.0 (no effect)	–	[48]
56 (QS 14)	Glyphosate, fenpropathrin, carbofuran	17	73 (41/32)	83.7	94.5	27	Lymphocyte comet % DNA 5 (↑); Micronucleus in binucleated cells 8 (↑)	–	–	[53]

(*continued on next page*)

Table 3 (*continued*)

Study (QS[a])	Exposure	Duration (mean years)	Subjects (Exposed/ Control)	Age (mean years)	Male (%)	Current Smokers (%)	DNA Damage (Exposed/ Control)	Other Biomarkers[b]	Chemical Exposure Assessment	Ref.
57 (QS 16)	α-cypermethrin, cypermethrin, deltamethrin, temephos, malathion, azoxystrobin, cyproconazole, pyraclostrobin, epoxiconazole, profenofos, lufenuron, thiamethoxam	5.28	59 (29/30)	29.7	100	34	Micronucleus in buccal cells 3.3 (↑)	Buccal cells: nuclear buds 4.6 (↑), necrotic 2.3 (↑)	–	[54]
62 (QS 13)	Glyphosate and 2,4-D	NI	36 (18/18)	22–71 (range)	100	0	Comet in lymphocyte damage index 1.8 (↑); Micronucleus and nuclear abnormalities in buccal cells 2.9 (↑)	–	–	[55]
74 (QS 14)	Organophosphates, dithiocarbamates	9.4	63 (32/31)	33.5	100	1	Comet in lymphocyte damage index 2.9 (↑); Chromosome aberrations: (no effect)	–	–	[59]
83 (QS 17)	2,4-D, Atrazine, Carbendazim, Copper oxychloride, Deltamethrin, Diflubenzuron, Diuron, Glyphosate, Imazethapyr, Imidacloprid, Mancozeb, Methamidophos, Methiocarb, Monocrotophos, Paraquat, Permethrin, Simazine, Tebuconazole	25.7	57 (37/20)	40.0	100	33	Comet in leukocytes damage index 6.9 (↑); MN in buccal cells (no effect)	BchE 1.2 (↓), ALA-D (no effect); hematological (no effect); lipid parameters (no effect)	–	[61]
99 (QS 17)	Disulfoton, chlorpyrifos, acephate, dimethoate, glyphosate, paraquat, urea, triazoles, dithiocarbamate, carbamates, organochlorines, pyrethroids, pyrethrins	15.9	238 (188 = 94 without organophosphates + 94 with organophosphates/ 50)	38.0	NI	8	Micronucleus in buccal cells 3.4 (↑)	Buccal cells: nuclear buds 4.1 (↑), condensed chromatin 58 (↑) and karyolytic 2.4 (↑) in organophosphates group, binucleated cells 4.2 (↑), karyorrhectic 4.3 (↑), pyknotic 5.6 (↑) in two groups in relation to control group; levels of urinary dialkyl phosphates (↑); activity of total cholinesterase 1.4 (↑)	–	[63]
101 (QS 16)	Glyphosate, Cypermethrin, Chlorpyrifos	Pesticides: 14.8; pesticides+cigarettes: 8.3	120 (60/30)	29	46.7	50	Micronucleus in buccal cells 10.1 (↑)	Buccal cells: nuclear abnormalities 7.2 (↑)	–	[64]

[a] QS, Quality Score (8–24).
[b] biomarkers that demonstrated significant association with genotoxicity. NI: Not informed.

Table 4
Manuscripts assessing human occupational exposure to pesticides: type of exposure, using genotoxicity assay identified by the review.

Study (QS[a])	Exposure (Type of occupation and exposure)	Duration (Mean years)	Subjects (Exposed/ Control)	Age (Mean years)	Male (%)	Current Smokers (%)	DNA damage (Exposed/ Control)	Other Biomarkers[b]	Chemical Exposure Assessment	Ref.
12 (QS 18)	Soybean: Organophosphorus, carbamates, pyrethroids organochlorines	≥ 30	146 (81/ 46)	49	57	0	Comet in lymphocyte damage index 2.0 (↑); Micronucleus in buccal cells 2.3 (↑)	Buccal cells: nuclear buds 1.7 (↑), binucleated 1.2 (↑), condensed chromatin 1.6 (↑), karyorrhectic 1.6 (↑), karyolytic 1.4 (↑); Butyrylcholinesterase (BChE) 1 (no effect)	Inorganic elements in buccal cells: increased but no difference	[47]
13 (QS 21)	Soybean: organophosphorus, carbamates, pyrethroids organochlorines	30	220 (137/ 83)	46	100	NI	Comet in lymphocyte damage index 1.3 (↑); Comet in lymphocyte damage index hOGGss 7.0 (↑); Micronucleus in buccal cells 4.7 (↑)	Buccal cells: nuclear buds 4.3 (↑), binucleated 2.2 (↑), karyorrhectic 1.5 (↑), Pyknotic 2.7 (↑), karyolytic 1.8 (↑); Global DNA methylation 1.2 (↑); BChE 1 (no effect); hematological markers (no effect); biochemical parameters (no effect)	Inorganic elements: Al (↑), P (↑).	[50]
14 (QS 15)	Soybean: Strobilurin/ Triazolinthione, Dithiocarbamate, Pyrethroid/ Organophosphate	31	24 (12/ 12)	43.9	100	8	Comet in lymphocyte damage index: high exposure in relation to low exposure 12 (↑), in relation to control group 60 (↑)	BChE: high exposure in relation to low exposure 1.1 (↓)	–	[62]
16 (QS 14)	Soybean: Organochlorine, Pyrethroid, Organophosphate, Pyrethroid, Benzoylurea	16	66 (29/ 37)	37.9	100	56	Micronucleus in buccal cells 2 (↑)	–	–	[68]
35 (QS 22)	Soybean, carbamates and organophosphates: Thiamethoxam, Chlorantraniliprole, Profenofos, Glyphosate and Carbendazim	> 1	148 (76/ 72)	33.3	100	0	Micronucleus in buccal cells 3.6 (↑); telomere length (no effect)	Buccal cells: nuclear buds 2.6 (↑), binucleated cells 1.1 (↑), Condensed chromatin 1.9 (↑), Karyorrhectic 1.7 (↑); BChe 1 (no effect); polymorphisms: influence of *XRCC1 Trip/-* and *PON1 Arg/-*	Inorganic elements: Br (↑), Pb (↑), Rb (↑)	[77]
45 (QS 16)	Soybeans: Glicine, Strobilurin/triazole, Glycolates, Triazin, Oxime methyl carbamate, Strobilurin, Phthalic acid diamide	15	163 (74/ 89)	36.4	65	15	Comet in lymphocyte OTM 1.6 (↑)	Acetylcholinesterase (AChE) (no effect); biochemical tests: aspartate aminotransferase (ASA), alanine aminotransferase (ALT), lipid profile, glycemia (no effect); polymorphisms: (no effect).	–	[80]
73 (QS 14)	Wheat and soybeans[c]	10.7	60 (30/ 30)	41.1	90	20	Micronucleus in lymphocytes 2 (↑)	–	–	[57]
81 (QS 18)	Mainly soybean and corn crops: glyphosate, 2,4-D, cypermethrin, deltamethrin, and atrazine	16.3	360 (180/ 180)	46	69.4	19	Comet in whole blood damage index 1.2 (↑)	Immune dysfunction: influence of *CD3 +CD4 +*, *CD3 +CD4 +CD25 +*, *CD3 +CD4 +CD25-FOXP3 +*; polymorphisms: influence of *TNF-α*.	–	[60]
30 (QS 20)	Tobacco, organophosphate	30.34	159 106/ 53	42.1	51	6	Micronucleus in buccal cells: 13.5 (↑)	Buccal cells: nuclear buds (↑ 13.0), binucleated in differentiated cells (↑ 1.3), karyolytic (↑ 3.8), basal cells (↑ 1.2), Micronucleus in basal cells (↑ 1.8); Cotinine 6 (no effect); BChE 1.1 (no effect); polymorphisms: influence of *PONIGln192Arg* and *CYP2A6*[c]*9(248 T > G)*.	–	[75]
31 (QS 19)	Tobacco, organophosphate, carbamate, dithiocarbamate and pyrethroid, glyphosate	29.23	60 (30/ 30)	41.1	53	0	Micronucleus in lymphocytes 1.5 (↑); Comet in lymphocyte damage index 1.8 (↑)	Cotinine 1 (no effect); BChE 1.2 (no effect)		[76]

(*continued on next page*)

Table 4 (*continued*)

Study (QS[a])	Exposure (Type of occupation and exposure)	Duration (Mean years)	Subjects (Exposed/ Control)	Age (Mean years)	Male (%)	Current Smokers (%)	DNA damage (Exposed/ Control)	Other Biomarkers[b]	Chemical Exposure Assessment	Ref.
52 (QS 18)	Tobacco: glyphosate, flumetralin, clomazone, imidacloprid and sulfentrazone	29.0	130 (56/ 74)	42.0	26	28	Comet in lymphocyte damage index 25 (↑); telomere length 1.2 (↓)	Global DNA methylation 1.4 (↓), p16 methylation with smallest telomere 1.3 (↓) unmethylated, Cotinine 13.0 (↑); total antioxidant capacity (TEAC) 1 (no effect), thiobarbituric acid reactive substances (TBARS) 1.1 (↑)	Inorganic elements: P (↑), S (↑), Cl (↑)	[49]
53 (QS 21)	Tobacco: glyphosate, mancozeb, magnesium aluminum phosphide, copper	28.3	80 (40/ 40)	45.3	47.5	0	Micronucleus in lymphocytes 2.1 (↑); telomere length 1.1 (↓)	Lymphocytes: NPB ridges 2.3 (↑), nuclear buds 2.0 (↑), binucleated cells 2.0 (↑); Global DNA methylation 1.2 (↓); polymorphisms: influence of *MTHFR CT/TT* and *TERT GT/TT*.	Vitamin B12 (↑); trace elements: Al (↑), As (↑), Cr (↑), Cu (↑), Mo (↑), Ni (↑), K (↑), Se (↓), Zn (↑)	[51]
54 (QS 16)	Tobacco: glyphosate, flumetralin	29	124 (62/ 62)	41.5	48	14	Telomere length 1.1 (↓)	TBARS 1.1 (↑), TEAC 1.1 (↑)	Inorganic elements: (no difference)	[52]
Ad_01 (QS 17)	Tobacco: organophosphate, carbamate	NI	137 (77/ 60)	89.6	63.5	25	Micronucleus in buccal cells 5.4 (↑); comet in whole blood damage index 2.9 (↑)	Polymorphisms: influence of *PON1 Gln/Gln*; hemogram (no effect); SOD 10.1 (↑)	Inorganic elements: Zn (↑), Mg (↑), Al (↑)	[67]
23 (QS 16)	Banana farming[c]	> 1	41 (21/ 20)	35.9	100	0	Micronucleus in buccal cells 9.5 (↑)	Buccal cells: karyorrhexis 30.6 (↑)	–	[73]
29 (QS 17)	Vineyard workers: Cymoxanil, Maneb, mancozeb, glyphosate, Parathion, Fenthion, Methidathion, Paraquat, 2,4-D	29.8	173 (108/ 65)	39.7	100	5	Micronucleus in lymphocytes 1.7 (↑); Comet in lymphocyte damage index 4.6 (↑)	Polymorphisms: influence of micronucleus in *PON Gln/Gln* in relation *PON Arg/-* and an association between *GSTM1*, *GSTT1* and *CYP2E1*.	–	[69]
105 (QS 15)	Floriculturists: Glyphosate, Mancozeb, Procymidone, Iprodione, Thiophanate-methyl, Abamectin	9.7	74 (37/ 37)	36.3	54	5	Micronucleus in buccal cells (no effect); comet in whole blood 2.8 (↑)	–	–	[65]
64 (QS 12)	Aviators[c]	> 10	67 (50/ 17)	40.4	NI	4	Micronucleus in buccal cells 3 (↑), binucleated 2.5 (↑)	–	–	[56]
42 (QS 14)	Health agents: Diflubenzuron, Novaluron, Deltamethrin, Malathion	7.4	249 (161/ 88)	35.2	49	12	Comet in lymphocyte OTM 1.6 (↑)	Polymorphisms: influence of *GSTM1;* gene expression: influence in *CCL3, CXCL5, IGJ, IGL, IGF2R, LRP1, NBPF* genes.	–	[79]
106 (QS 15)	Workers IAPAR: Organophosphates, carbamate	11.1	46 (23/ 23)	38.0	100	72	Chromosome aberrations 1.9 (↑)	–	–	[66]

[a] QS, Quality Score (8–24).
[b] biomarkers that demonstrated significant association with genotoxicity. NI: Not informed.
[c] No information on the type of pesticide used.

3.3. Pesticide exposure

Brazil has been the country that uses the most agrochemicals in the world since 2008. It is no wonder that 34 (38%) of the articles on occupational exposure in this review involve exposure to pesticides. The use of pesticides in Brazilian agriculture is a public health problem, given the high levels of occupational exposure of farmers, environmental pollution, and, as a result, water and food poisoning of the human population [40–42]. High exposures are associated with the application of these compounds in agriculture or for public health protection purposes, such as in preventing malaria. A number of pesticides have been characterized as possible or probable human carcinogens by the IARC based on human and experimental animal data showing links between some pesticides and cancer in multiple sites [43]. Cancer of the lung, prostate, lymphatic, and hematopoietic systems are most often associated with exposure to pesticides in epidemiological studies [44, 45].

Thirty-five studies evaluating DNA damage from human exposure to pesticides were evaluated in this review [46–80]. The main results of these studies are summarized in Tables 3 and 4. Only one study was excluded from the analysis because it did not include a control group [78]. All 34 remaining articles studied occupational exposures, where 40% of the farmers were involved in different crops (the specific type was not identified) (Table 3) and 60% received a specific type of exposure (either from health agents or a single type of crop) (Table 4). 57% of these studies were of farmers in the South region of Brazil. The average age of the workers was 40 years old and the average exposure time was 18 years. A total of 2174 workers and 1615 non-exposed

Table 5
Manuscripts assessing human occupational exposure to dust and particulate matter using genotoxicity assay identified by the review.

Study (QS[a])	Exposure (Type of occupation)	Duration (Mean years)	Subjects (Exposed/ Control)	Age (Mean years)	Male (%)	Current Smokers (%)	DNA Damage (Exposed/ Control)	Other Biomarkers[b]	Chemical Exposure Assessment	Ref.
2 (QS 18)	Mineral coal (Miners)	At least 1 year	102 (51/ 51)	20–40[c]	100	NI	Micronucleus in buccal cells 3 (↑); Chromosomal aberration 3.6 (↑)	–	Metals, fluorides and PAHs in plasma	[100]
15 (QS 19)	Outdoor air pollution (Traffic controllers, taxi drivers)	At least 1 year	57 (39/18)	49[d]	100	0	Micronucleus in buccal cells 2.4 (↑); Micronucleus in lymphocytes 2.1 (↑)	–	$PM_{2.5}$ and NO_2	[96]
20 (QS 19)	Outdoor air pollution (Professional motorcyclists)	8	74 (44/30)	33.8[d]	100	29.7	Micronucleus in buccal cells 2.1 (↑)	Catalase (CAT) activity 22.4 (↑), Superoxide dismutase (SOD) activity 22.4 (↑), Lipid peroxidation 12.5 (↑)	NO_2 and O_3; metals in urine	[101]
33 (QS 17)	Particulate matter (Mixed categories)	NI	30 (24/6)	20–61[c]	NI	0	Comet in buccal cells: Damage index 5.35[d] (↑); Damage frequency 9.18[d] (↑)	–	PM_1; $PM_{2.5}$; PM_4; PM_{10}	[102]
36 (QS 20)	Particulate matter (Cashew nut roasting workers)	NI	193 (77/ 116)	27.8[d]	51	0	Micronucleus in buccal cells 5.1 (↑); Nuclear buds 1.37 (↑), Binucleated 2.03 (↑),	Pyknosis 1.80 (↑), Karyolysis 2.23 (↑), Karyorrhexis 1.59 (↑), Condensed chromatin 1.64 (↑), Basal cells 1.18 (↑)	TSP, PM_1; $PM_{2.5}$; PM_{10} and urinary 1-OHP	[105]
39 (QS 18)	Particulate matter (Street vendors)	NI	96 (48/48)	32.2[d]	50	50	Micronucleus in buccal cells 4.3 (↑) Binucleated 1.1 (no difference)		$PM_{2.5}$	[97]
46 (QS 18)	Outdoor air pollution (Taxi drivers)	17.2	56 (34/22)	37	100	0	Micronucleus in buccal cells 1.8 (no difference); Damage Index 2.0 (↑)	8-OHdG 1.5 (↑)	Urinary t,t-MA and COHb	[17]
55 (QS 19)	Wood smoke (Charcoal Workers)	NI	132 (98/ 34)	34	100	50	Ames test YG1041 +S9 2.36 (↑) high exposure 1.48 (no difference) low exposure	–	2-NAP, 1-OHP in urine	[106]
77 (QS 18)	Dust and gases Tunnel workers	NI	26 (15/11)	42.5	100	0	Micronucleus in buccal cells 9.1 (↑)	–	2-NAP, 1-OHP in urine	[108]
80 (QS 17)	Dust and concrete constituent (Construction workers)	14.7	40 (20/20)	35.5[d]	100	0	Micronucleus in buccal cells 2.2 (↑)	–	–	[92]
86 (QS 17)	Mineral coal (Miners)	13.8	70 (41/29)	41.77	NI	0	Micronucleus in buccal cells (basal cells) 17 (↑); Micronucleus in buccal cells (differentiated cells) 14.8 (↑); Nuclear buds 1.1 (no difference) Binucleated 1.23 (↑)	Karyolysis 1 (no difference), Karyorrhexis 1.08 (no difference), Condensed chromatin 0.49 (↓), Basal cells 14.34 (↑)	Metals in blood	[103]
94 (QS 18)	Particulate matter and PAHs (Construction workers)	At least 1 year	108 (59/ 49)	39	100	0	Micronucleus in lymphocytes 2 (↑)	Methylation of *CDKN2A* 1.32 (↑), *APC* 1.38 (↑), and *MLH1* 1.19 (↑); methylation of *LINE-1* 0.98 (↓)	$PM_{2.5}$, Metals in blood	[98]
96 (QS 16)	Mineral coal (Miners)	11.6	206 (158/ 48)	44	99	18.4	Micronucleus in buccal cells 2.72 (↑); Comet in blood cells: % DNA 1.26 (no difference)	–	–	[104]
98 (QS 16)	Biomass burning (Rural workers)	NI	53 (23/30)	30.8	100	22.6[d]	Micronucleus in buccal cells 2.34 (↑); Micronucleus in lymphocytes 6.47 (↑)	–	–	[99]
109 (QS 20)	Dust and outdoor air pollution (Street Sweepers)	At least 4 months	40 (20/20)	35.7	100	0	Micronucleus in lymphocytes 2.6 (↑)	Pyknosis 1.32 (no difference), Karyolysis 1.76 (no difference), Karyorrhexis 1.45 (no difference)	–	[107]

[a] QS, Quality Score (8–24).
[b] biomarkers that demonstrated significant association with genotoxicity.
[c] min-max.
[d] arithmetic mean between groups.

Table 6
Manuscripts assessing human occupational exposure to metals using genotoxicity assay identified by the review.

Study (QS[a])	Exposure (Type of occupation)	Duration (Mean years)	Subjects (Exposed/ Control)	Age (Mean years)	Male (%)	Current Smokers (%)	DNA Damage (Exposed/Control)	Other Biomarkers[b]	Metal Exposure Assessment	Ref.
20 (QS 20)	Professional motorcyclists	8	74 (44/30)	33.7	100	31.8	Micronucleus in buccal cells 2 (↑)	Catalase (CAT) activity 22.4 (↑), Superoxide dismutase (SOD) activity 22.4 (↑), Lipid peroxidation 12.5 (↑)	Sb, Pt, As, Cd, V, Mn, Co, Pb, Cr and Ni in fingernails	[101]
34 (QS 15)	Copper smelters	5.3	22 (11/11)	43.4	100	55	Comet assay in peripheral blood leukocytes 4 (↑)	–	Cu, F, Zn, Na, Mg, Al, P, S, Cl, K, Ca, V, Co, Br, Pb in blood	[116]
38 (QS 14)	Tannery workers	8.21	60 (30/30)	34.42	100	36.66	Frequencies of chromosomal aberrations 27.2 (↑) and Micronucleus in lymphocytes 2.9 (↑)	–	–	[121]
59 (QS 15)	Workers of a hospital (exposed to Pb (solder))	NI	22 (11/11)	38.8	90.9	NI	Micronucleus in lymphocytes 1 (↑)	Delta-aminolevulinic acid levels in urine	–	[10]
63 (QS 18)	Battery renovators	10.2	20 (10/10)	33.3	100	40	Micronucleus in buccal cells 3.3 1 (↑); Comet assay in blood 11.33 (↑)	–	–	[25]
65 (QS 15)	Workers employed in the recycling of automotive batteries	5.62	55 (26/29)	30.81	100	38.5	Micronucleus in peripheral blood lymphocytes 2.6 (↑)	–	Pb in blood	[118]
66 (QS 22)	Workers employed in the recycling of automotive batteries	9.80	106 (53/ 53)	36.00	100	28.3	Cytokinesis-block Micronucleus (CBMN) cytome assay 3 (↑); Comet assay in peripheral blood lymphocytes 8.4 (↑)	–	Pb in blood	[119]
68 (QS 15)	Tannery workers	5.8	20 (10/10)	34.1	100/ 100	40.0	Frequency of chromosomal aberrations (CA)/cell 1.07 (↑)	–	–	[122]
70 (QS 18)	Chrome plating workers	6.97	100 (50/ 50)	34.3	100	13.10	Comet assay in whole blood 1.2 (↑) and Micronucleus in buccal cells	b-2 integrin 1.5 (↑), ICAM-1 6.4 (↑), and L-selectin 8.2 (↑) surface protein expression (%) in lymphocytes; Lipid peroxidation biomarker (MDA 1.2 (↑); protein carbonyl levels 1.6 (↑)	Cr, Pb, As, Ni, and V in blood; Cr in urine	[117]
72 (QS 10)	Welders	14	44 (22/22)	41.34	100	NI	Micronucleus in buccal cells 0.6 (↑)	–	–	[120]

[a] QS, Quality Score (8–24).
[b] biomarkers that demonstrated significant correlation with genotoxicity; NI: not informed.

controls were evaluated (the vast majority were men), and a significant difference in DNA damage was observed in the exposed subjects with respect to the controls in 30 out of 34 studies (88%), showing 1.1–36-fold increases. Only two studies (6%) did not demonstrate a significant increase in DNA damage for exposed individuals (both had a QS of 14 and did not identify the kind of crop). In the review carried out by Bolognesi and Holland [42], it is also described that most studies on exposure to pesticides demonstrate a significant increase in DNA damage. After performing a meta-analysis study, Pinto et al. [81] demonstrated that occupational exposure to pesticides increases DNA damage and mutation rate, and after making categorizations related to the comet assay and micronucleus test, they showed significant differences between the exposed and control groups, regardless of gender or crop.

According to the QS scores, in relation to the quality of the studies, each study fits in a specific category. Most of the studies were considered good (73%; average QS = 16), 12% were considered very good, and 15% were considered fair. None of them was considered to be excellent. The main problem observed in the studies was related to the number of subjects evaluated and the quality of the controls. For pesticide exposure, this is a factor that deserves much discussion, as the controls are generally from the same region. Thus, although they are not occupationally exposed, they live in the regions sprayed, and are thus also exposed to some extent. Another important factor was the lack of suitable analyses of the results. In some cases age and time of exposure were collected, but no correlation analysis was conducted in relation to biomarkers. Data regarding nutrition were not obtained in any study. The studies were developed from 1998 to 2021 (average JCR = 3.63), and the increasing quality during these years was clear in relation to collected data, measurements, and discussions about mechanisms of action of compounds. The statistical analyses of biomarker data employed parametric methods such as the Student t-test and ANOVA, while the Kruskal-Wallis and Mann-Whitney U tests were the most frequently used non-parametric methods.

Increases in cell micronuclei, nuclear bridges, comet cells, and chromosome aberrations (chromatid and chromosome alterations) were generally observed. All of the studies considered at least one of the following DNA damage biomarkers: micronuclei in lymphocytes (18%; studies [48,51,53,57,69,71,76]), micronuclei in buccal cells (38%;

Table 7
Manuscripts assessing human occupational exposure to "other agents" using genotoxicity assay identified by the review.

Study (QS[a])	Exposure Type of occupation)	Exposure (Type of exposure)	Duration (Mean years)	Subjects (Exposed/ Control)	Age (Mean years)	Exposed Male (%)	Current Smokers (%)	DNA Damage (Exposed/ Control)	Other Biomarkers[b]	Chemical Exposure Assessment	Ref.
4 (QS 21)	Farmers	Nicotine	26.9	80 (40/40)	42	50	0	Comet assay Damage Index 2.4 (↑); Comet assay - Damage Frequency 2.1 (↑)	Alterations of the redox status by quantification of the total antioxidant capacity (TEAC) (↑) and of thiobarbituric acid reactive substances (TBARS) (no effect); Cotinine levels (↑)	–	[128]
31 (QS 17)	Tobacco farmers	Nicotine	29.23	60 (30/30)	42	56.6	0	Comet assay Damage Index 1.9 (↑); Comet assay - Damage Frequency 2.2 (↑); MN in lymphocytes 1.3 (↑)	Plasma cholinesterase activity (no effect) and Cotinine levels (↑)	–	[76]
59 (QS 15)	Workers from Hospital de Clínicas de Porto Alegre (HCPA)	Lead, ionizing radiation, ethylene oxide and cytostatic drugs	NI	84 (42/42); Lead (11); ionizing radiation (11); ethylene oxide (10); cytostatic drugs (10)	Lead (38.8); Ionizing radiation (40.4); ethylene oxide (35.8); cytostatic drugs (29.8)	64.28	NI	Micronucleus in lymphocytes cytostatic drugs 1.7 (↑); ionizing radiation 1.3 (↑)	–	–	[10]
60 (QS 11)	Pharmacists and nurses	Antineoplastic drugs	4 (a follow up study was carried out 4 years after an initial evaluation)	First evaluation: 20 (10/10); Second evaluation 24 (12/ 12)	29.8; 34.7	NI	NI	Micronucleus in lymphocytes 1.4 (↑); Dicentric bridges 1.7 (↑); Comet assay Damage Index 2.6 (↑)	–	–	[129]
84 (QS 11)	Workers employed in an industry in Brazil using EtO as an intermediate	ethylene oxide (EtO)	7	Chromossome aberrations: 75/22; Micronucleus in lymphocytes: 16/11; Micronucleus buccal cells: 75/22	32.6	100	17.3	Micronucleus in buccal cells 1.2 (↑); Micronucleus in lymphocytes 3.6 (↑)	Hemoglobin adduct (HOEtVal) determination (↑)	–	[130]
Ad04 (QS 16)	Anesthetists	Inhalational anesthetics: isoflurane and sevoflurane	At least 2 continuous years	80 (40/40)	39	65	0 (non-inclusion criteria)	Micronucleus in buccal cells 1.8 (↑)	Telomere Length measurement (no effect)	–	[131]
Ad05 (QS 21)	Anesthetists	Waste anesthetic gases (WAGs). Halogenated sevoflurane and isoflurane and to a lesser degree to halogenated desflurane and N2O gas	15 years. At least 3 years for a minimum of 12 hr per week	60 (30/30)	38	66	0 (non-inclusion criteria)	Comet in lymphocyte Damage Index 1.2 (↑)	Lipid peroxidation; Nitric oxide (NO) metabolites; Lipophilic antioxidants; Antioxidant status; Relative telomere length; markers of inflammation; gene expression. (no effect)	–	[132]
Ad06 (QS 18)	Anesthetists	Isoflurane and sevoflurane (inhalational anesthetics) and nitrous oxide (anesthetic gas; commonly known as laughing gas)	At least 3 years	63 (32/31)	28	62,5	0 (non-inclusion criteria)	Comet in lymphocyte Damage Index 1.6 (↑); Micronucleus in buccal cells 2.3 (↑)	Oxidative stress (no effect) and inflammatory markers (↑); Antioxidant assays (no effect); Waste anesthetic concentrations in operating rooms (↑)	–	[133]
Ad07 (QS 18)	Anesthetists	Isoflurane, sevoflurane, desflurane and N_2O.	At least 2 years	60 (30/30)	40	67	0 (non-inclusion criteria)	Comet in lymphocyte Damage Index 1.1 (↑) Micronucleus in lymphocytes 2.2 (↑);	–	–	[134]

(*continued on next page*)

Table 7 (*continued*)

Study (QS[a])	Exposure Type of occupation)	Exposure (Type of exposure)	Duration (Mean years)	Subjects (Exposed/ Control)	Age (Mean years)	Exposed Male (%)	Current Smokers (%)	DNA Damage (Exposed/ Control)	Other Biomarkers[b]	Chemical Exposure Assessment	Ref.
Ad08 (QS 15)	Pharmacists, pharmacy technicians and nurses	Antineoplastic drugs	8	64 (29/35)	41	24,1	0 current smoking habits	Nuclear buds 1.5 (↑); Condensed chromatin 1.1 (↑); Karyorrhexis 1.3 (↑); Piknosis 1.5 (↑); Karyolysis 1.1 (↑) Comet in lymphocyte Damage Index 1.0 (↑); Micronucleus in buccal cells 0.9 (↑)	Oxidative stress parameters	NI	[135]

[a] QS, Quality Score (8–24).
[b] biomarkers that demonstrated significant correlation with genotoxicity; NI: not informed.

studies [46,47,50,54–56,61,63–65,67,68,73,75,77]), comet assay (47%; studies [40,47–50,53,55,59,61,62,65,67,69,76,79,80]), and chromosome alterations (CA; 12%; studies [58,59,66,70,72,74]). 27% of the studies used at least two of these biomarkers. In addition, one study used a modified comet assay (with the FPG enzyme; study [50]) and four measured telomere length [49,51,52,77]. Some studies [49,51,52] found a decrease in telomere length when the farmers investigated were exposed to pesticides in tobacco crops. Alterations in telomeric length may be related to the mechanisms suggested for the formation of the nucleoplasmic bridges [82], progression of aging and oxidative stress [83].

All the studies that performed comet assays of the blood samples to check for DNA damage found positive effects for genotoxicity, this being the most used biomarker among the studies that investigated the effects of exposure to pesticides. Alkaline comet assay modified by repair endonuclease (FPG) was used to detect oxidized purines. Some of the damaged bases that are recognized and removed by FPG include 8-oxoG, 8-oxoadenine, fapy-guanine, methy-fapyguanine, fapy-adenine, aflatoxin B1-fapy-guanine, 5-hydroxy-cytosine, and 5-hydroxy-uracil [84,85]. Multiple mechanisms are likely to be involved in the effects of pesticide, but most of the published literature points to DNA and protein damage mediated by oxidative stress [86,87]. Some pesticides are also related to diseases related to chronic inflammation and immune system [60,79,88] and the induction of epigenetic changes [42,49–51].

The second most used test in the studies was micronuclei in buccal cells, with 13 studies showing an increase in micronucleus frequencies and other abnormalities in buccal cells, although three studies found no effect in these cells [56,61,65]. In relation to the use of micronuclei in lymphocytes, six studies observed alterations in this biomarker and only one study observed no effect in the group exposed to pesticides in relation to the non-exposed group [78]. The use of micronuclei in lymphocytes is considered an excellent tool for human pesticide biomonitoring, mainly due to its sensitivity in detecting damage induced by clastogenic and aneuploidogenic mechanisms [42,89]. There is a direct relationship between micronuclei in the buccal cells and lymphocytes [90], and it is understood that micronucleus frequency is an indirect way of evaluating chromosomal aberrations [91]. The chromosome aberration test was used in six studies, and only one did not observe an increase in chromosomal damage in individuals exposed to complex mixtures of pesticides [58].

In addition, other methods were used seeking to understand the heterogeneity of individuals' responses, such as gene polymorphisms. Regarding the association between biomarkers, Da Silva et al. [69] observed a significant increase in micronucleus frequencies in *PON Gln/Gln* individuals in addition to the influence of GSTM1, GSTT1, and CYP2E2 polymorphisms. Oliveira et al. [77] also observed the influence of polymorphism of *PON* in combination with *XRCC1 Trip/-* genotypes, which induced an increase in binucleated cells (exposed group) and nuclear buds (non-exposed group) in buccal cells. Other studies also found a relationship between polymorphisms and the modulation of biomarkers of DNA damage in subjects exposed to complex mixtures of pesticides [51,67,69,75,77,79,92]. In relation to confounding factors that influenced the increased MN frequency in the CBMN assay, a significant correlation was detected with age, gender [48], years of exposure [49], and smoking and alcohol consumption [72]. One study found that increases in DNA damage in the comet assay were significantly correlated with age (males) and gender (females) [60]. A correlation was also observed between other confounding factors, such as radiation exposure, meat consumption, and sweetener consumption [72]. When compiling the studies on occupational exposure to pesticides and the use of Personal Protective Equipment (PPE), it was observed that only three studies found a correlation between increased DNA damage and the non-use of PPE [53,60,72]. Bolognesi and Holland [42] presented the relevance of PPE, whose adequate use can reduce genotoxic risk, suggesting the promotion of educational programs for safe pesticide use.

In relation to biomarkers, cholinesterase, hematological and

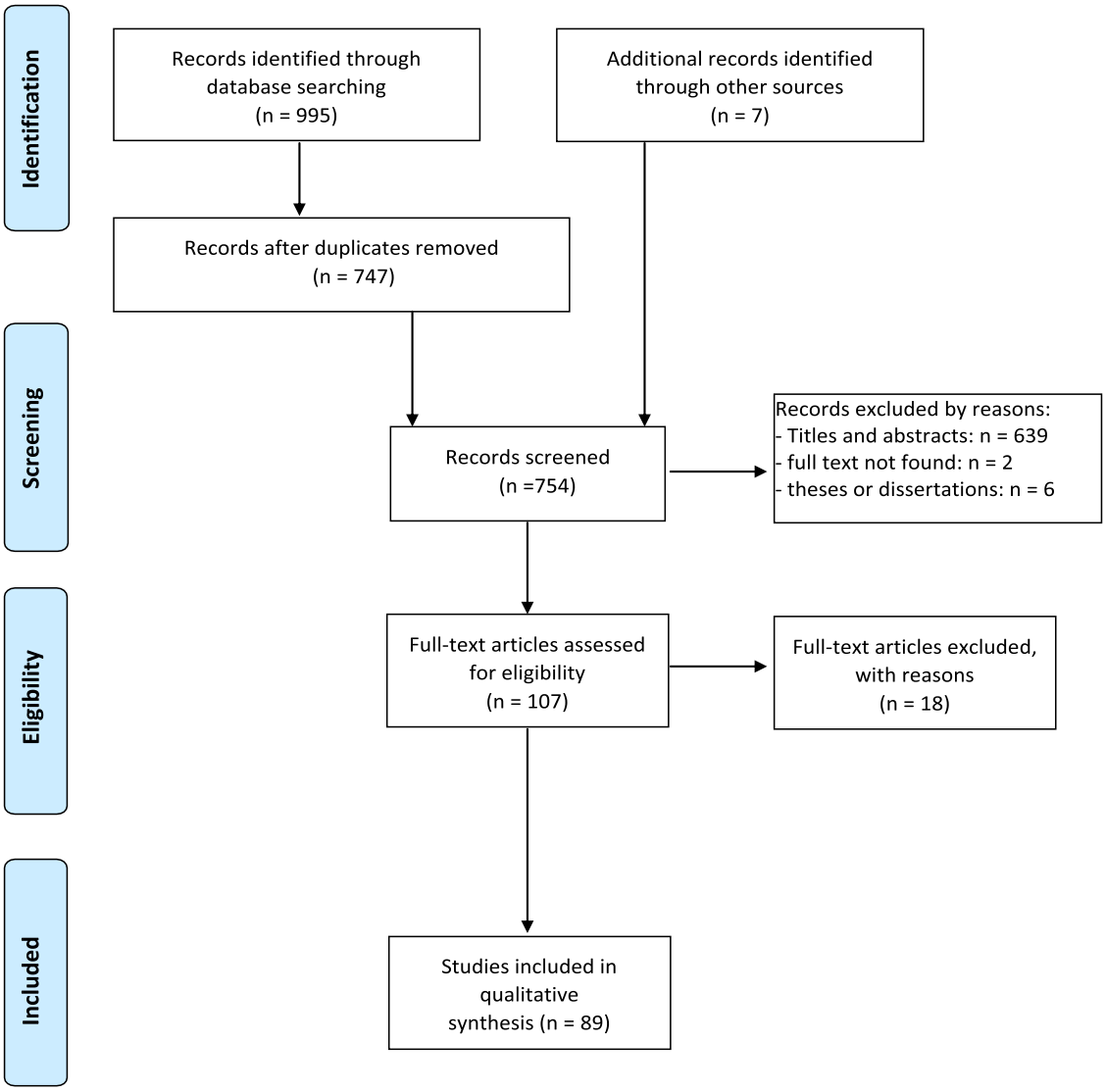

Fig. 1. Flow diagram of selection experimental studies for inclusion in the systematic review. *Pubmed/Medline, EMBASE, Web of Science, SCOPUS, "Latin American and Caribbean Literature in Health Sciences (LILACS/BVS) and Science Direct.

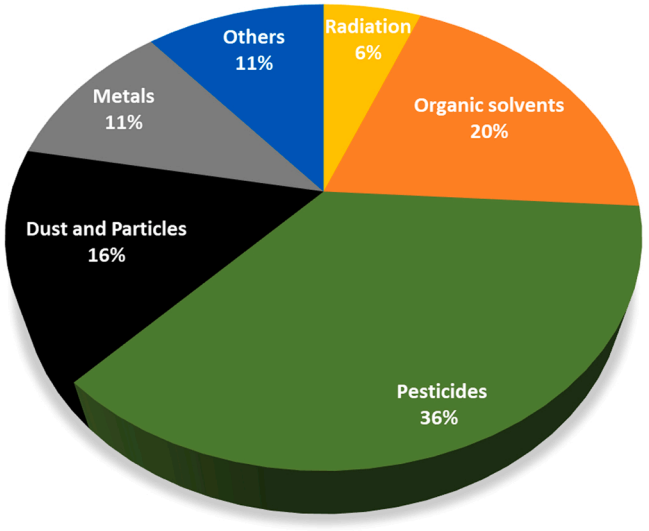

Fig. 2. Main groups of occupational exposure in Brazil (N = 89 articles, but were 94 toxicological agents and the percentual was calculated on this).

biochemical parameters were also evaluated. Chemical exposure to inorganic elements was assessed in 23% of the studies [47,49–52,67,70,77]. Specific biomarkers for specific pesticides were not found in these studies. Some studies evaluated the effects of detoxification and cumulative exposure to a complex mixture of pesticides, quantifying specific metabolites in urine and blood samples [46–48,50,61–63,70,75–77,80]. Measurements of blood levels of cholinesterase enzymes are used as a biomarker of effect to cholinesterase-inhibitor insecticides. Pesticides such as carbamate and organophosphorus insecticides have the potential to inhibit the enzyme acetylcholinesterase and decrease its activity [87]. Of the studies that quantified acetylcholinesterase activity, only 33% observed changes in this biomarker. The conflicting results are due to the fact that complex mixtures of pesticides and prolonged exposures to low doses may influence acetylcholinesterase activity levels [47]. A biomarker of exposure is essential to analyze acetylcholinesterase activity levels before the time of application (basal level) of these insecticides and after the time of application to compare if there was an alteration in acetylcholinesterase activity levels. Additionally, enzymatic inhibition is reversible and also occurs in the gradual synthesis in response to the cumulative effects of this exposure [50]. In addition, chemical exposure by inorganic elements was assessed in 23% of the studies [47,49–52,67,70,77].

Several pesticides were reported as routinely used among workers involved with different crops in the studies included in this review, mainly organophosphates, pyrethroids, and carbamates. In relation to this, some studies only described the pesticide categories or mentioned the chemical group of pesticides and two studies did not report which pesticides were used by the exposed group [56,73]. All workers in the exposure group used at least one pesticide reported as moderately or highly hazardous to human health [93]. In Brazil, as well as in several low-to-middle-income countries, farmers use a mixture of pesticides to combat the variety of pests that attack crops [94] and measuring the effects of these complex mixtures is more difficult, due to the synergistic and antagonistic effects of these combinations [81]. The main pesticides used by workers mentioned above are well described as capable of acting in the human body via multiple mechanisms, causing genotoxic effects, mainly inducing chromosomal damage, mediated by oxidative stress, mitochondrial dysfunction, and epigenetic changes [42].

3.4. Exposure to particulate matter

A total of 16 original studies were included on genotoxicity in workers exposed to particulate pollutants. After evaluating the quality criteria proposed in the study, a single study was excluded [95], as it did not have a control group. The final score of all the studies was between 16 and 20 points. The studies were conducted in 12 cities in eight Brazilian federative units, with six studies using workers in the Southeast region [92,96–99], six studies using workers in the South region [100–104], and three studies conducted in the Northeast region of Brazil [105–107].

The set of articles evaluated 736 exposed workers and 532 subjects classified as the control group. The sample size of the studies ranged from 20 to 158 for the exposed group (mean= 53; median= 44) and from six to 116 for the control subjects (mean = 35.4; median 30). The studies were interested in evaluating genotoxicity in workers engaged in activities related to coal mining (n = 3) [100,103,104], biomass burning (n = 3) [99,105,106], construction (n = 2) [92,98], transport and roads (n = 4) [17,96,101,108], outdoor occupations (n = 2) [97,107], and one study evaluated a mixture of occupations in an urban environment [102]. Among the control subjects, eight studies reported that they were unexposed workers or residents, four studies used administrative workers, and three studies used education workers.

Selecting subjects also seems to be a challenge for studies involving the assessment of genotoxicity among workers exposed to dust and particulate matter. Among the 15 studies included, only one was census-based [104] and another used a random sampling strategy [105]. All the other studies either reported convenience sampling or did not report detailed information on subject selection. No study presented the sample size calculation or statistical power. The lack of detail on the formation of the sample of individuals in the control group seems even more accentuated. Only one study indicated the use of random sampling [105], but without any details of the randomization criteria. Although most studies showed information on the sample characterization, many lacked information on matching (exposed vs. control), current and previous occupation, and environmental exposure.

Levels of particulate matter as a measure of environmental monitoring of the occupational environment were reported in only five of the 15 studies [96–98,102,105] and four of these also evaluated levels in the control environment [96,97,102,105]. Regarding biomarkers of exposure, only eight studies revealed levels of some chemical or its metabolites, including metals, fluoride, and PAHs in plasma [100], metals in nails [101] and blood [98,103], and urinary hydrocarbon metabolites [17,105,106,108].

All the studies collected socioeconomic, demographic, occupational, lifestyle, and health conditions information through the application of a questionnaire and 11 of the 15 studies used lifestyle or some health conditions as an exclusion criterion for participants, especially smoking [17,92,96,98,102,103,105,107] and chronic diseases or the continuous use of medication [17,96,98,100–102,107]. Although all the studies had information to characterize their sample, any investigation of these variables as confounding factors or associated factors was precarious in most studies. Four studies [92,96,99,107] did not make any adjustment for confounding factors and most of the other studies were concerned with evaluating smoking, drinking, and age as relevant factors for genotoxicity. The census study by Da Silva Júnior et al. [104] evaluated a series of factors using the Poisson regression model, including age, height, weight, ethnicity, health status, family history of cancer, chronic diseases, lifestyle, diet, smoking habits, medication, alcohol and illicit drug consumption, occupation, time of service, and radiation exposure.

Regarding biological material, oral mucosa cells are the priority target of genotoxicity studies of workers exposed to particulate material (n = 13 studies). Genetic damage was evaluated in blood cells in six studies, five of which [17,96,99,104,108] also used cells from the oral mucosa. Finally, a single study [106] used urine to assess mutagenicity through the Salmonella/microsome assay. The micronuclei test was the most widely used test for mutagenic evaluations (n = 13 studies), followed by the comet assay (n = 3) and the nuclear abnormalities test (n = 2) and the chromosomal aberration test and the Ames test (1 study each). Of the total, five studies used two bioassays, including the micronuclei test and comet test [17,104], micronuclei and nuclear abnormality [97,105], and micronuclei and chromosomal aberrations [100]. It should be noted that most studies used recognized protocols for preparing the bioassays. Even so, we should emphasize that blinding for the analysis of slides was only reported in one study [96].

The ratio of genotoxic responses between the exposed and control groups is shown in Table 5. In all the studies investigated, there was at least one biomarker that showed a significant increase between the exposed and control groups, showing the impact of occupational activities related to the release of particulate matter. The average difference between exposed and control groups ranged from 1.1 to 17-fold.

Occupational exposure to particulate matter is known to cause harmful health effects [109,110], and studies have shown the relationship between related activities and the appearance of genotoxic damage [111,112]. The set of studies included in this review showed an increase in genetic damage among exposed workers and this can help guide further scientific research. First, it is important to emphasize that the number of studies on the subject is still very small (n = 13) and that there are certainly numerous other occupational activities exposed to dust and particulate matter in which health damage needs to be studied. Even so, the groups studied refer to an important portion of workers in the country.

Besides expanding the studies on the activities already studied, contemplating research in other regions of the country and in other scenarios, and including other potential occupational activities exposed to particulate matter, it is important to expand the investigations on the relationship between toxic agents and the mechanisms triggered by exposure. Frequent contact with dust and particles during the workday exposes the worker to known carcinogenic constituents adhered to particulate matter, such as PAHs and some metals, as well as possibly leading to inflammatory processes related to lung diseases, including lung cancer [113]. In this sense, efforts must be made in order to expand the studies that contemplate the environmental monitoring of these constituents, as well as, whenever possible, using biomarkers of exposure (internal dose) to better determine the cause-effect relationship. Regarding biomarkers of effect, the use of the micronuclei test in oral mucosa cells seems to be very useful as an early indicator of mutagenic damage, and although other bioassays can be used, the low cost of this bioassay combined with its non-invasiveness is an advantage of the tool in large-scale and long-term studies in the occupational environment.

Obviously, additional care should be taken in future studies. These precautions include better detailing of the sample (sample calculation or statistical power and well-defined sampling criteria) and the control group; the use of an information collection instrument that includes socioeconomic, demographic, diet, lifestyle, and health conditions,

which are taken into account in models to adjust for cofactors or assess risk and protective factors; and clear information that can guarantee the credibility and replicability of the bioassays used (blinding of the analysis, clear ways of expressing the results, detailing the statistical criteria used, etc.).

3.5. Metal exposure

Metals pose significant potential risks to human health in both occupational and environmental settings. Some metals are essential as trace elements for human organisms to function. Of these, some can be toxic at only elevated exposure levels, as is the case of copper (Cu). Other essential elements, when exposure occurs at high concentrations, can lead to diseases including Parkinson's-like syndrome, caused by manganese (Mn). On the other hand, other metal(loid)s, such as lead (Pb), mercury (Hg), and arsenic (As), are xenobiotic and cause toxic effects even at low levels of exposure [114].

Eleven studies evaluating the genotoxicity of Brazilian subjects occupationally exposed to metals were found in the literature, as shown in Table 6, with the exception of one study that was not included in the table because it did not have a control group [115]. The workers investigated include professional motorcyclists [101]; copper smelters [116]; chrome plating workers [117]; workers exposed to Pb, employed in automotive battery factories [115], in the recycling of automotive batteries [118,119], and in storage battery repair [25]; workers at a hospital (exposed to solder) [10]; welders [120]; and tannery workers [121,122]. Regarding quality scores, all the studies ranged between 10 and 22 points. Curiously, with the exception of the study of Do Amaral et al. [121], which was carried out using workers in the Northeast region of Brazil, and the study of Monteiro Neto et al. [122], which investigated workers from the Midwest Brazilian region, all the other studies were carried out using workers in the South region (n = 9; 81.8%).

In general, the studies evaluated a small number of workers, with four studies (36.4%) investigating < 19 workers [10,25,116,122], six studies (54.5%) assessing 20–50 workers [101,117,118,120,121], and only two studies (18.2%) evaluating > 50 workers [115,119]. Only one study did not have a control group [115]. There were a total of 367 workers and 256 individuals classified in the control group in all the studies evaluated.

Biomonitoring of metal exposure provides valuable information regarding the risk of exposure and, for this, different biological samples may be used, including blood, nails, hair, and urine [123]. Among the 11 studies evaluated, only seven (63.6%) performed metal exposure biomonitoring. Carvalho et al. [101] dosed the following elements in the fingernails of professional motorcyclists from Porto Alegre, in Rio Grande do Sul: antimony (Sb), platinum (Pt), As, cadmium (Cd), vanadium (V), Mn, cobalt (Co), Pb, chromium (Cr), and nickel (Ni), using an inductively coupled plasma mass spectrometer (ICP-MS). With the exception of Pb, Cr, and Ni, all the other elements had significantly ($p < 0.05$) higher concentrations (ng/g) in the professional motorcyclist group than in the office workers group. De Oliveira et al. [116] determined blood metal content [Cu, iron (Fe), zinc (Zn), sodium (Na), magnesium (Mg), aluminum (Al), phosphorus (P), sulfur (S), chlorine (Cl), potassium (K), calcium (Ca), V, Co, bromide (Br), and rubidium (Rb)] using the particle-induced X-ray emission (PIXE) technique in smelters employed in smelting plants located at Cachoeirinha, in Rio Grande do Sul. Although no significant difference was observed in blood metal concentrations (ppm) between the copper smelter workers and the unexposed controls, the copper smelter workers had higher blood levels of Cu, Fe, Al, V and Rb than the control group. Pb concentrations were assessed in blood and plasma samples by Devóz et al. [115] in workers employed in automotive battery factories in Paraná state, using ICP-MS. This study did not have a control group, but the Pb levels in blood (μg/dL) and in plasma (μg/dL) were in accordance with Brazilian law (up to 60 μg/dL for individuals occupationally exposed to Pb). In two studies, Minozzo et al. [118,119] determined blood Pb levels in workers employed in the recycling of automotive batteries around Porto Alegre, using atomic absorption spectrophotometry. In both studies, blood Pb concentrations (μg/dL) were significantly ($p < 0.05$) higher in the workers exposed to the metal than in the control groups. In chrome plating workers from two plating companies located at Rio Grande do Sul, biological monitoring was performed through quantification of Cr, Pb, As, Ni, and V in the blood using ICP-MS [117]. In the same study, Cr was also quantified in urine samples from the workers. The blood (μg/L) and urine (μg/g creatinine) concentrations of Cr were significantly ($p < 0.01$) higher in the exposed group in relation to the unexposed group. Regarding the other metals, there were significant ($p < 0.05$) increases in blood levels of Pb, As, Ni, and V in the exposed group when compared with the non-exposed group. The study of Maluf and Erdtmann [10] selected individuals exposed to Pb, who were solder workers from a hospital in Porto Alegre, to participate in their evaluation based on their levels of the biomarker delta-aminolevulinic acid in urine (mg/L), but they concluded that the delta-aminolevulinic acid urinary levels in these subjects represented apparently no dangerous exposure to Pb since the mean was 5.4 ± 1.1 mg/L and only levels > 15 mg/L can be considered dangerous. Pb causes the inhibition of the enzyme delta aminolevulinic acid dehydratase (ALA-D) activity in erythrocytes. The ALA-D inhibition results in an increased blood delta aminolevulinic acid (ALA), substrate of ALA-D, and, consequently, in a higher urinary excretion of ALA (ALAU). Of toxicological importance, studies demonstrated that ALA could exhibit pro-oxidant properties under physiological conditions. In this line, ALAU is very useful for the biomonitoring of occupational Pb exposure [124–127].

With regard to biological matrices to assess DNA damage, peripheral blood was the most used (n = 9; 81.8%), and only two studies (18.2%) exclusively used oral mucosa cells. In relation to genotoxicity assays, the following biomarkers were used: micronuclei in buccal cells in four studies (36.4%), micronuclei in lymphocytes in four studies (36.4%), comet assay in four studies (36.4%), chromosome alterations in two studies (18.2%), and DNA global methylation in one study (9.0%). Four of these studies (36.4%) simultaneously used two of these biomarkers.

One of the main limitations of the studies evaluated was the lack of a direct association between metal biomarkers and DNA damage biomarkers. Among the studies that performed biomonitoring of metal exposure (n = 6; 54.5%), only two found significant associations between metal biomarkers and genotoxicity biomarkers. In the study of Muller et al. [117], the blood levels of As, Ni, and V of chrome plating workers were significantly ($p < 0.05$) correlated with the comet assay (percentage of tail DNA). In workers from automotive battery factories, Devóz et al. [115] found negative correlations ($p < 0.05$) between blood and plasmatic levels of Pb and global DNA methylation percentage. According to the authors, the consequences may result in impairment in the regulation of gene expression, leading to several adverse health effects. Also, the authors mentioned that their study was, to the best of their knowledge, the first to propose the use of plasma Pb as a biomarker of exposure associated with epigenetic status in individuals occupationally exposed to the metal.

Taking all of the evaluated studies into account, the most important limitations were: the lack of biomonitoring of metal exposure in most of the studies – only seven (63.6%) performed this evaluation, with the other studies evaluating exposure to metals by questionnaire; the lack of a control group, which was observed in just one study [115]; and, finally, the small number of workers in most of the studies.

3.6. Occupational exposure to other chemical agents

The main results of these studies are summarized in Table 7, including the average ratio between the exposed and control groups. It was possible to observe that between the studies carried out in Brazil featured in ten published articles.

Four studies were found that evaluated occupational exposure to some inhalation anesthetics and gases, such as isoflurane, sevoflurane,

desflurane, and N_2O [131–134]. A total of 132 workers and 131 non-exposed controls were evaluated. The four studies found were carried out in the city of Botucatu, in the state of São Paulo. The studies had a quality score ranging between 16 and 21. The biological samples used to assess DNA damage were peripheral blood (100%) and oral mucosa cells (50%). A slight increase in the frequency of DNA damage was observed in the studies evaluated.

Regarding occupational exposure to cytostatic/antineoplastic drugs, three studies were found. One was carried out using workers from Hospital de Clínicas de Porto Alegre (HCPA) [10], one used pharmacists and nurses at a hospital in southern Brazil [129], and another study was carried out on pharmacists, pharmacy technicians, and nurses also at the HCPA [135]. All three studies were carried out in hospitals in the South region of Brazil. A total of 61 exposed workers and 67 workers in the control group were evaluated. The studies had a quality score ranging between 11 and 15. Three studies used blood samples for genotoxicity assays (micronucleus test and comet assay) and one study [135] used oral mucosal cells for the micronucleus test. The three studies found a significant increase, indicating an association between occupational exposure to cytostatic/antineoplastic drugs and genotoxic damage.

Two studies were found related to occupational exposure among tobacco farmers to nicotine [76,128]. A total of 70 exposed workers and 70 workers in the control group were evaluated. Alves and collaborators [128] included 40 exposed and 40 unexposed workers and Da Silva and collaborators [76] included 30 exposed and 30 unexposed workers. Both studies were carried out in the South region of Brazil. One study [128] had a quality score of 21 and the other study [76] had a quality score of 17. The two studies assessed genotoxicity using the comet assay and one of them also assessed it using the lymphocyte micronucleus assay. The biological material used in the assays was peripheral blood. Cotinine levels were also assessed in both studies. A significant increase in genotoxic response was observed in both studies, indicating an association between occupational exposure to nicotine and genotoxic damage.

Two studies evaluated occupational exposure to ethylene oxide (EO). One was carried out on workers from HCPA [10] and one used a worker employed in an industry in Brazil using ethylene oxide (EtO) as an intermediate [130]. The study carried out with industrial workers exposed to ethylene oxide indicated that occupational exposure resulted in a statistically significant increase in chromosomal aberrations and micronuclei in lymphocytes. The study carried out in a hospital with workers in the sterilization area, on the other hand, did not find a positive relationship between occupational exposure to ethylene oxide and an increased frequency of genetic alterations, after performing the micronucleus test in peripheral blood.

The articles published on occupational exposure to other chemical agents demonstrated that most performed the MN test, four articles analyzed also oxidative stress biomarkers, and only three articles did not other biomarkers. The groups found were inhalation anesthetics and gases (40%), cytostatic/antineoplastic drugs (30%), tobacco farmers (20%), and ethylene oxide (20%). It was possible to observe that most articles were related to exposure in workers employed in health systems, e.g. hospitals.

4. Final considerations

Our systematic review indicated comet assays and micronucleus tests as the preferred methods for detecting DNA damage in occupational exposures in Brazil, probably because they are simpler and cheaper techniques that can be used to answer research questions. In the last 40 years in Brazil, the methods used to detect DNA damage have changed from chromosomal aberrations and the Salmonella test, to comet assays and micronucleus assays. These tests have become more robust, including other biomarkers in parallel, but little has been done considering individual chemical and environmental assessments.

The main mechanism proposed as being involved in DNA damage is mostly the production of reactive oxygen species associated with exposure mainly to complex mixtures. This process could induce genetic alterations expressed by different methods. However, further improvements in study design will be needed in future studies in order to better characterize exposure, especially using biomonitoring and/or atmospheric air analyses, considering confounding factors (e.g. gender, age, lifestyle factors, and diet), and other mechanisms of DNA damage in addition to oxidative stress. Important individual factors end up causing confusion in the analysis of genomic instability in population biomonitoring, and each of these can play a role in the induction or expression of DNA damage.

Another factor that draws attention is the need for more robust statistical analyses, making better use of the findings and correlating the data. Another point to consider is that Brazil, with its 220 million inhabitants, has published few manuscripts on occupational exposure to chemical and physical agents and genotoxicity. For example, in the case of pesticides exposure alone, Brazilian workers are the most exposed in the world, but only few articles have been published in 41 years. Additionally, the articles showed that biomonitoring and/or atmospheric air were scarcely considered in the design and results obtained, the most studies applied questionnaires, in a qualitative and not really quantitative manner. The main conclusion of our analysis was the lack of the use of protective equipment and adequate safety measures to reduce the exposure to toxic agents and, thus, genotoxic risk, suggesting the need for the promotion of educational programs. On the other hand, more studies are needed that evaluate the effects of chemical and physical agents on the health of workers in Brazil, especially on DNA damage, conducted in a more robust and complete manner to demonstrate the real contribution of these exposures to chronic non-communicable diseases.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mrgentox.2022.503519.

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