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Review

The comet assay as a tool in human biomonitoring of exposure to heavy metals – A systematic review and meta-analysis

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ABSTRACT

Exposure to heavy metals such as lead, arsenic and chromium is associated with genotoxicity and increased risk of cancer. In this systematic review and meta-analysis, we have assessed effects of heavy metal exposure on levels of DNA strand breaks in leukocytes, measured by the comet assay, in human biomonitoring studies. We distinguish between traditional toxic metals (lead), semi-metals/metalloids (arsenic), transition metals (chromium), and other heavy metals. The literature search led to 66 studies, which were assessed by meta-analysis. Using standardized mean difference and 95 % confidence interval (CI), the meta-analyses show increased levels of DNA strand breaks in subjects exposed to lead (1.99, 95 % CI: 1.47, 2.51), arsenic (1.36, 95 % CI: 0.94, 1.77), chromium/welding fume (2.03, 95 % CI: 1.48, 2.57), and other heavy metals (0.81, 95 % CI: 0.45, 1.18). Subgroup analysis indicates that all studies combined from middle-income countries have higher effect size (1.99, 95 % CI: 1.63, 2.35) than have studies from high-income countries (0.81, 95 % CI: 0.37, 1.26). The lower effect size in high-income countries may be due to differences in exposure levels, related to stricter regulation of emissions or more awareness/use of personal protective equipment in the working environment. Sensitivity analysis does not unequivocally link effect size to comet assay measurement bias, inferred by insufficient information on comet assay procedures, missing assay controls, non-blinded analysis of samples, or exposure misclassification. In conclusion, this systematic review and meta-analysis shows that exposure to heavy metals - lead, arsenic and chromium – is associated with increased levels of DNA strand breaks in human leukocytes.

1. Introduction

Exposure to heavy metals in occupational and environmental settings is an important public health concern. Acute high-dose exposure to heavy metals may cause poisoning, which requires immediate medical care. However, long-term exposure to lower doses of heavy metals is also detrimental to health, including risk of cancer. Metal ions interact with cellular components, which may result in DNA damage, mutations, cell death, and carcinogenesis [1]. There is a relatively large number of human biomonitoring studies where the comet assay has been used to assess DNA strand breaks in whole blood (leukocytes) or isolated peripheral blood mononuclear cells (sometimes called lymphocytes). The

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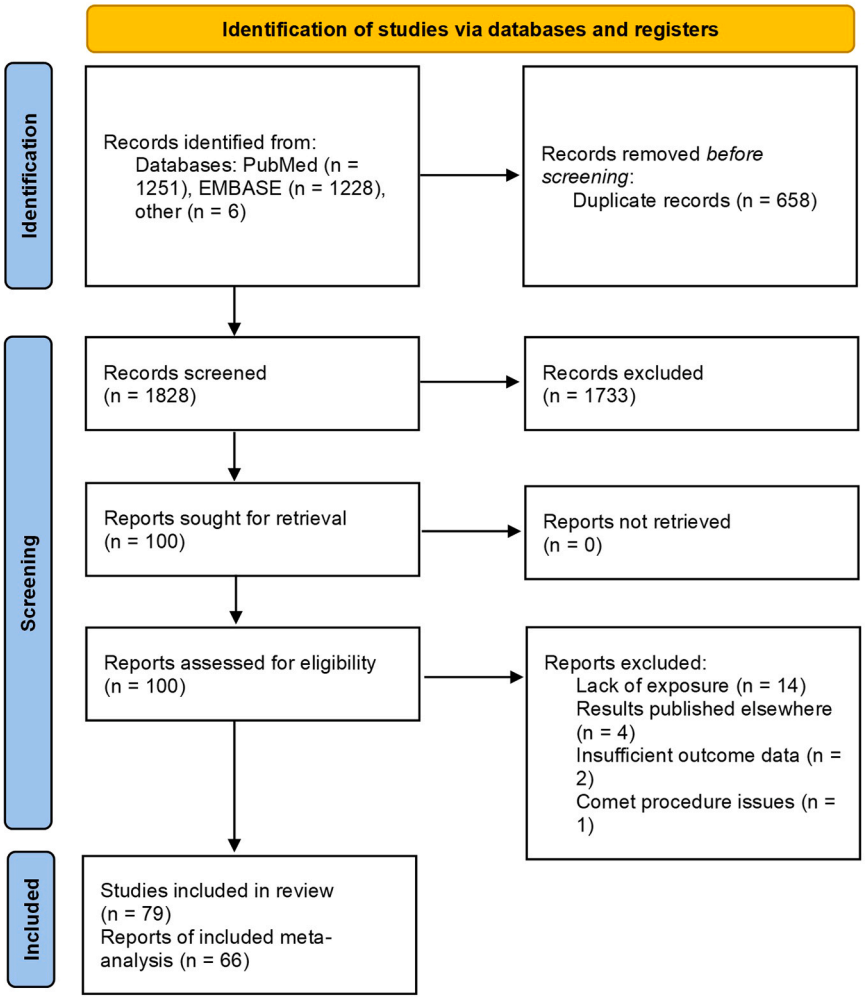

Fig. 1. Flow diagram of literature search and selection of studies for the review and meta-analysis.

standard comet assay detects DNA strand breaks and alkali-labile sites (typically called DNA strand breaks for simplicity) [2]. This has been a popular tool in human biomonitoring studies on external exposures as well as studies on DNA strand break levels in diseases, including cancer [3]. Recently, the relevance of the comet assay in human biomonitoring studies has been strengthened by results from a large prospective cohort study, showing that high levels of DNA strand breaks in leukocytes are associated with increased risk of mortality [4,5].

In a previous scoping review of human biomonitoring studies, we showed that studies on lead, arsenic and chromium dominate in the literature on heavy metals [6]. We use *heavy metals* as a term that broadly describes the exposure, because investigations typically cover complex mixtures of metals and other hazardous substances. Even so, many studies on complex mixtures have only assessed one type of heavy metal. For instance, a number of studies on the association between chromium exposure and DNA strand breaks have been done on welders, but it goes without saying that welding fumes are much more complex than just chromium. Moreover, it is desirable to apply a relatively relaxed definition of heavy metals because there is no standard definition of the term across different research fields. Heavy metal elements are typically defined by atomic mass, atomic number and/or density. However, the group of heavy metals, irrespective of the definition, contain elements that are also considered to be transition metals (especially elements in the fourth row of the periodic table), semi-metals/metalloids (e.g. arsenic and antimony) or essential trace elements (e.g. iron, copper, manganese, selenium and zinc). We loosely apply a chemical/toxicological distinction between heavy metals as (i) traditional toxic metals (i.e. arsenic, lead, cadmium and mercury), and (ii) elements that are also considered to be transition metals (mainly elements in the fourth row of the periodic table, including chromium). This segregation has the advantage of distinguishing between metals that can cause oxidative stress by production of reactive oxygen species (i.e. iron-catalysed hydroxyl radical generation by Haber-Weiss redox-chemistry reactions) and metals that are mainly toxic by inhibition of enzymes (i.e. arsenic, lead, cadmium and mercury). Notably, the traditional heavy metals can also cause oxidative stress and DNA damage, although this is related to inhibition of antioxidant enzymes and DNA repair proteins [1].

The present review is part of a series of systematic reviews on comet assay results from human biomonitoring studies on air pollution, anaesthetic gases, antineoplastic drugs, pesticides and volatile organic compounds [7–11]. The overall purpose of the systematic reviews is to compare effects of exposures on DNA strand breaks in human leukocytes, measured by the comet assay. For practical reasons, we have compiled studies into lead, arsenic, chromium/welding fumes and other heavy metals. It is based on the prevalence of articles in the literature, which probably reflect the original authors consideration of exposure levels being significant to cause toxic effects, relevance to public health, or regulatory interest. This approach enables meta-analyses on studies with a similar, although not identical, type of exposure. It is important to note that the subjects in the biomonitoring studies are exposed to many metals and other potentially genotoxic chemicals, even though the studies may focus only on one type of heavy metal.

2. Methods

The review is segregated into meta-analyses of specific heavy metals. A detailed description of the stepwise review process is available in the supplement. Briefly, associations between exposure and DNA strand breaks are assessed in (i) meta-analysis of results from papers with information on mean/median and corresponding variability measure, (ii) the full dataset of included papers (using statistical significance in the original paper as outcome), (iii) generalizability of the studies in the meta-analysis to all studies on the same type of heavy metal, (iv) subgroup analysis, and (v) sensitivity analysis. Further information on the systematic review, including background information on various methodological challenges and considerations, is published in a separate paper [12]. The systematic review protocol has been registered in PROSPERO (CRD42025636342). The review followed PRISMA 2020 guidelines (a PRISMA checklist is shown in Supplementary Table S1).

2.1. Literature search

The literature search follows the strategy laid out in our previous scoping review [6]. However, the literature search in the scoping review revealed limitations when combining diversity (i.e. many different types of emissions and exposure situations) and specificity (i.e. only human biomonitoring studies). There tend to be too few search results if "biomonitoring" is a specific term and too many results if "human" is not included in the search string. Therefore, we have used relatively broad search terms and screened studies for relevance, using the title (1st step) and abstract (2nd step). Based on the identified papers in the scoping review [6], we extended the search terms to include chromium and welders. The search string was as follows: "human AND comet assay AND (lead OR mercury OR cadmium OR arsenic OR chromium OR welders OR heavy metals). We used PubMed and EMBASE for structured literature searches. It has been standard practice to use two databases with different indexing of keywords. Traditionally, PubMed and EMBASE have been a good combination. Increasing the number of databases increases the number of publications needed to read, but it does not necessarily increase the retrieval rate of relevant publications. To increase the retrieval of relevant publications, we used Google for unstructured/exploratory searches and refence lists in the retrieved papers. Fig. 1 shows a flow diagram of the search, screening and selection of papers for the review and meta-analysis. The literature search was conducted in January 2025, covering years from 2000 through 2024. The new millennium is a good starting point because it was the year that (i) the comet assay was adopted as Medical Subject Heading (MeSH) in PubMed, and (ii) the first guideline and focused reviews on comet assay results in human biomonitoring studies were published [13–15].

2.2. Inclusion and exclusion criteria

The selection of studies was done by one reviewer, and another reviewer approved the inclusion or exclusion of studies. Both reviewers assessed the quality of studies, including exposure assessment and risk of bias. Certain studies have been excluded from the review because of (i) absence of a control with low exposure to metals, (ii) no difference in exposure between groups, (iii) no measurement of metals in external media or biological samples, or if (iv) results from the same study have been published in more than one paper. The main text only describes the included studies, whereas information on excluded studies is available in Supplemental Table S2-S5.

All studies with mean and standard deviation or standard error of the mean have been included in the meta-analysis. Studies with median and inter-quartile range (i.e. difference between 25 % and 75 % percentile) have been included in the meta-analysis as proxy of mean and standard deviation [16]. Studies using other central tendencies and variability are not included in the meta-analysis.

2.3. Generalizability

Certain studies have sufficient relevance to be included in the review, although the results are not applicable to meta-analysis. This includes studies designed for correlation or regression analysis. In addition, results reported as geometric mean and standard deviation factor cannot be incorporated into a meta-analysis with results reported as mean and standard deviation from Gaussian distribution of results. The same goes for binary data or results analysed by logistic regression. Thus, results in the meta-analyses of the present review are a subgroup of all included studies. The generalizability of the results in the meta-analyses to all studies in the review has been assessed by Z-test for comparing two proportions, with correction for continuity (test results are reported as Z-value and corresponding P-value level).

2.4. Meta-analysis

Some studies have compared levels of DNA strand breaks in exposed subjects to a control group, whereas others have segregated the study population into different exposure groups. For the latter type of studies, the control group consists of subjects with lowest exposure regardless of the dataset being segregated into two or more exposure groups. We have dichotomized exposures in studies with more than two groups (i.e. lowest exposure group versus all other groups pooled).

For the meta-analysis, we have used standardized mean difference (SMD) as effect measure because the studies have used different comet descriptors (tail length, tail intensity, tail moment and visual score). Tail intensity is obtained as the percentage of total DNA fluorescence in the tail. Values of the same comet descriptor in different studies do not correspond to the same number of DNA strand breaks because studies do not use the same comet assay protocol. SMD is the difference between groups in standard deviation units. For instance, SMD = 1 means that the difference between two groups is the same as the pooled standard deviation. The 95 % confidence interval (95 % CI) of SMD is not statistically significant if it includes zero. Similarly, there is statistically significant difference between two different meta-analyses if the 95 % CIs do not overlap. For graphical purposes, we have reproduced Forest plots from Review Manager in GraphPad Prism. Original Forest plots and accompanying Funnel plots from Review Manager are reported as Supplementary Figures S1-S8.

We have calculated the SMD and 95 % CI in random effects models using Review Manager 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration). To assess the robustness of effect sizes in the meta-analysis, we have also used non-parametric analysis to calculate the central tendencies. For this analysis, we have used the SMDs from each study for the calculation of the median and 95 % CI. The 95 % CI has been calculated by the equation as follows: rank number = n*q ± z* [SQRT(n*q*(1-q)], where n = sample size, q = median (0.5), z = critical value (1.96 for $p < 0.05$). The rank number has been rounded down or up to the nearest whole number for the lower and upper 95 % CI, respectively. These ranks have subsequently been converted to the absolute values. We refer to this outcome as SMD_{median} to distinguish the result from the regular SMD in meta-analysis.

The random effects model assumes that the outcome varies across studies because of differences in treatment effect and sampling variability. I^2 values are used as a measure of heterogeneity between studies. The I^2 value describes the percentage of the variability in an effect estimate that is due to heterogeneity rather than sampling error (chance). It is calculated as [(Q-df)/Q]*100 %, where Q is the Chi-squared statistic and df is its degrees of freedom. The Cochrane handbook uses these descriptions of I^2 values: 0–40 % "might not be important", 30–60 % "may represent moderate heterogeneity", 50–90 % "may represent substantial heterogeneity", and 75–100 % "considerable heterogeneity" (https://training.cochrane.org/handbook). Heterogeneity between studies may arise as a consequence of difference in biological effects between studies due to difference in e.g. age, sex and exposure situation.

Table 1
Summary of findings from the included studies on lead (Pb) exposure.

Author	Year	Main chemical exposure	Country	Exposure assessment or biomarkers of exposure	Population characteristics	DNA damage	Ref
Occupational exposure							
Akram	2019	**Pb**	Pakistan	Blood	200 (100 construction workers, 100 controls)	• **TL:** exposed (21.16 ± 2.19) vs. unexposed (14.31 ± 1.54); **sig.** (mean ± SEM) • **TI:** exposed (33.72 ± 3.26) vs. unexposed (13.20 ± 1.68); **sig.** (mean ± SEM) • **TM:** exposed (15.36 ± 2.87) vs. unexposed (3.00 ± 0.56); **sig.** (mean ± SEM) • **OTM:** exposed (10.09 ± 1.37) vs. unexposed (3.04 ± 0.42); **sig.** (mean ± SEM)	[19]
Arif	2018	**Pb**	Bangladesh	Blood	60 (30 automobile and repairing workers, 30 controls)	• **TI:** Exposed **(13.0** ± 0.82) vs controls (5.7 ± 0.53). **Sig.** (mean and SEM). • **TM:** exposed (5.90 ± 0.23) vs controls (2.5 ± 0.17). **Sig.** (mean and SEM)	[20]
Batra	2020	**Pb**	India	Blood	220 (110 building construction workers; 110 controls)	• **TI:** exposed (14.80 ± 1.31) vs controls (6.12 ± 1.80). **Sig** (mean and SD)	[21]
Cao	2020	**Pb**	China	Blood	267 (lead acid battery workers)	• **TI:** exposed (4th quartile: 1.40 ± 0.77, 3rd quartile: 1.24 ± 0.58, 2nd quartile: 1.26 ± 0.63, pooled: 1.30 ± 0.66) vs 1st quartile (control: 1.08 ± 0.53). **Sig** (mean and SD	[22]
Chinde	2014	**Pb**	India	Blood	400 (200 lead acid storage battery recycling and manufacturing industry workers, 200 controls)	• **TI:** exposed (12.97 ± 2.33) vs. unexposed (4.80 ± 2.57); **sig.** (mean and SD)	[23]
Coelho[3]	2013	Pb, As, Cd, Cr, Cu, Fe, Hg, Mn, Ni, Zn	Portugal	Blood, urine	81 (41 miners, 40 controls)	• **TI:** exposed (18.73 ± 7.60) vs. controls (12.40 ± 3.04); **sig.** (Mean and SD)	[24]
Danadevi	2003	**Pb**	India	Blood	81 (45 workers employed in a secondary Pb recovery unit, 36 controls)	• **VS**: exposed (44.6 ± 8.5) vs. unexposed (21.1 ± 11.7); **sig.** (mean and SD)	[25]
De Restrepo	2000	**Pb**	Colombia	Air, blood	56 (43 workers of electric battery factories exposed to lead compounds, 13 controls)	• **TL:** Group I > 40 μg/dl (55.60 [42.52–68.70]) vs. Group II 41–80 μg/dl (65.60 [52.50–78.63]) vs. Group III 81–120 μg/dl (60.53 [50.50–70.60]) vs. Group IV > 120 μg/dl (85.90 [69.21–102.53]); **sig.** between the lowest and highest concentration groups. (mean and 95 % CI)	[26]
Fracasso	2002	**Pb**	Italy	Blood	66 (37 battery plant workers, 29 controls)	• **TL:** exposed (117.1 ± 32.8) vs. unexposed (106.6 ± 25.3); **non-sig.** (mean and SEM) • **TI:** exposed (58.4 ± 15.8) vs. unexposed (40.9 ± 15.6); **sig.** (mean and SEM) • **TM:** exposed (69.0 ± 25.5) vs. unexposed (45.5 ± 19.4); **sig.** (mean and SEM) • ***Combined:*** *exposed (1.35 ± 0.42) vs controls (1 ± 0.35)*	[28]
García-Lestón	2011	**Pb**	Portugal	Blood	108 (70 workers in plants using inorganic lead, 38 controls)	• **TI:** exposed (4.4 ± 2.9) vs. unexposed (5.3 ± 2.0); **non-sig**. (mean and SD; estimated from graph)	[29]
Grover	2010	**Pb**	India	Air, blood, urine	180 (90 workers of secondary Pb recovery unit, 90 controls)	• **TL:** exposed (17.86 ± 0.88) vs. unexposed (8.15 ± 0.63); **sig.** (mean and SD)	[30]
Hernandez-Franco	2022	**Pb**	Mexico	Blood	53 (37 battery recycling workers, 16 controls)	• **TL:** exposed (37.3 ± 6.7) vs controls (34.7 ± 5.3); **non-sig.** (mean and SEM; estimated from graphs)	[31]
Iarmarcovai	2005	**Pb**, **Cd**, **Co**, **Ni**, **Mn**, Zn	France	Blood, urine	57 (27 welders, 30 controls)	• **TM:** exposed (4.54 ± 1.68) vs. unexposed (2.84 ± 0.75); **sig.** (mean and SD)	[32]
Jannuzzi	2016	**Pb**	Turkey	Blood	50 (25 storage battery workers, 25 controls)	• **TI:** exposed (9.95 ± 0.93) vs. controls (7.56 ± 0.61); **sig.** (mean ± SEM)	[33]
Kašuba	2012	**Pb**, Cd	Croatia	Blood	60 (30 pottery-glaze workers, 30 controls)	• **TL:** exposed (16.66 ± 1.20) vs. unexposed (14.10 ± 0.2); **sig.** (mean and SEM) • **TI:** exposed (3.21 ± 0.73) vs. unexposed (1.54 ± 0.73); **sig.** (mean and SEM) • **TM:** exposed (0.55 ± 0.16) vs. unexposed (0.21 ± 0.02); **sig.** (mean and SEM) • ***Combined:*** *exposed (1.51 ± 0.37) vs controls (1.00 ± 0.44)*	[36]
Kašuba[5]	2020	**Pb**	Croatia	Blood	98 (50 manufacture lead workers, 48 unexposed)	• **TL**: exposed (16.15 ± 5.33) vs. unexposed (14.27 ± 1.23); **non-sig.** (mean and SD)	[37]

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Table 1 (*continued*)

Author	Year	Main chemical exposure	Country	Exposure assessment or biomarkers of exposure	Population characteristics	DNA damage	Ref
Kayaalti	2015	**Pb**	Turkey	Blood	61 occupationally exposed to lead workers (36 low exposure, 25 high exposure)	• **TI:** exposed (2.64 ± 3.22) vs. unexposed (1.61 ± 0.74); **non-sig.** (mean and SD) • ***Combined:*** *exposed (1.39 ± 1.19) vs controls (1.00 ± 0.26)* **TL (called "DNA tail"):** High (103.94 ± 34.22) vs low (85.58 ± 24.24), **sig.** (mean and SD)**TI:** high (62219.17 ± 21180.57) vs low (46908.41 ± 11596.55). **sig.** (mean and SD) **TM:** High (4.90 ± 1.26) vs low (4.00 ± 0.62). **sig.** (mean and SD)***Combined*:** high (1.26 ± 0.38) vs low (1.00 ± 0.23)	[38]
Khisroon	2021	**Pb**, **Cd**, **Cr**, **Fe**, **Mn**, **Ni**	Pakistan	Scalp hair	118 (59 welders, 59 controls)	**VS:** exposed (121.8 ± 10.7) vs. controls (56.5 ± 17.6); **sig.** (Mean and SD)	[39]
Liu[1]	2009	**Pb**, Cd, Cr, Cu, **Fe**, **Mn**, **Ni**, **Zn**	Taiwan	Air	67 (41 foundry workers, 27 controls)	• **TM:** exposed (6.63 ± 3.99) vs controls (1.22 ± 0.76); **sig.** (Mean and SD) • **TL:** exposed (battery renovators: 34.14 ± 0.484, car painters: 33.85 ± 0.507) vs controls (30.54 ± 0.136 and 30.75 ± 0.162); **sig** (mean and SEM)	[41]
Martino-Roth	2003	Pb, organic solvents	Brazil	None	40 (10 battery renovators, 10 car painters, 20 controls)	• **VS:** exposed (battery renovators: 13.6 ± 6.18, car painters: 12.8 ± 6.67) vs controls (1.2 ± 1.03 and 1.8 ± 1.61); **sig** (mean and SEM) • ***Combined:*** *exposed (4.96 ± 2.12) vs controls (1.00 ± 0.46)*	[42]
Meng	2021	**Pb**	China	Blood	305 (201 lead battery workers, 102 controls)	• **TI:** exposed (2.20; 0.93, 2.28) vs controls (1.12; 0.79, 1.38): **sig.** (median, 1st −3rd quartiles)	[43]
Minozzo	2010	**Pb**	Brazil	Blood	106 (53 workers in recycling of automotive batteries, 53 controls)	• **VS**: exposed (21.70 ± 27.85) vs. unexposed (2.57 ± 2.79); **sig.** (mean and SD)	[44]
Muller	2022	**Pb**, **As**, **Cr**, **Ni**, **V**	Brazil	Blood	100 (50 chrome plating workers, 50 controls)	• **TI:** exposed (10.10 ± 2.16) vs controls (8.31 ± 1.32); **sig.** (mean and SD)	[45]
Olewińska	2010	**Pb**	Poland	Blood	88 (62 metalworkers exposed to lead, 26 controls)	• **TL:** exposed (86.9 ± 15.49) vs. unexposed (73.8 ± 19.12); **sig.** (mean and SD) • **TI:** exposed (60.3 ± 14) vs. unexposed (37.1 ± 17.6); **sig.** (mean and SD) • **TM:** exposed (57.8 ± 17.82) vs. unexposed (33.2 ± 19.12); **sig.** (mean and SD) • ***Combined:*** *exposed (1.51 ± 0.37) vs controls (1.00 ± 0.44)*	[46]
Palus	2003	**Pb**, Cd	Poland	Blood	84 (44 exposed, 40 controls)	• **VS**: exposed (15.6 ± 4.1) vs controls (11.3 ± 5.0); **sig. (**mean ± SD) • **TL:** exposed (28.4 ± 13.5) vs. unexposed (31.9 ± 24.4**); non-sig.** (mean ± SD)	[47]
Pawlas	2017	**Pb**	Poland	Blood	116 (78 lead and zinc smelter and battery recycling plan workers, 38 controls)	• **TI:** exposed (14.1 ± 8.8) vs. unexposed (16.2 ± 12.8); **non-sig.** (mean ± SD) • **TM:** exposed (6.5 ± 8.4) vs. unexposed (10.2 ± 15.7); **non-sig.** (mean ± SD) • ***Combined:*** *exposed (0.81 ± 0.6) vs. unexposed (1 ± 1.03)*	[48]
Shaik[2]	2009	**Pb**	India	Blood	215 (113 lead battery workers, 102 controls)	• **TL:** exposed 0.1511 ± 0.09) vs. unexposed (0.408 ± 0.04); **sig** (mean ± SEM) • **TL:** exposed (29.57 ± 9.03) vs controls (8.82 ± 6.27); **sig** (mean and SD)	[51]
Shahrokhi	2021	**Pb**, **As**, **Cu**	Iran	Air	80 (47 copper smelter workers, 33 controls)	• **TI:** exposed (25.15 ± 6.41) vs controls (8.96 ± 4.35); **sig** (mean and SD) • **TM:** exposed (17.97 ± 9.12) cs controls (1.66 ± 1.48); **sig** (mean and SD) • ***Combined:*** *exposed (5.66 ± 2.41) vs controls (1.00 ± 0.70)*	[50]
Singh	2016	**Pb**	India	Blood	70 (35 welders, 35 unexposed)	• **TL:** exposed (29.21 ± 8.8) vs. unexposed (1.47 ± 0.5); **sig.** (mean ± SEM) • **TI:** exposed (5.43 ± 1.21) vs. unexposed (1.78 ± 0.24); **sig.** (mean and SD; estimated from graph)	[52]
Wang	2018	**Pb**, Cu, Fe, Zn	China	Blood	267 (146 electronic waste processing workers, 121 controls)	• **TM:** exposed (0.98 ± 0.20) vs. unexposed (0.21 ± 0.06); **sig.** (mean and SD; estimated from graph) • **OTM:** exposed (0.79 ± 0.10) vs. unexposed (0.16 ± 0.03); **sig.** (mean and SD; estimated from graph)	[53]

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Table 1 (*continued*)

Author	Year	Main chemical exposure	Country	Exposure assessment or biomarkers of exposure	Population characteristics	DNA damage	Ref
Wani[4]	2017	**Pb**, (Zn)	India	Blood	130 (92 occupationally exposed to lead or lead and zinc, 38 unexposed controls were selected from neighboring with similar age)	• ***Combined:*** *exposed (4.22 ± 0.77) vs. unexposed (1.00 ± 0.20)* • **TL:** Exposed in lowest employment time group: 8.36 ± 2.16, unexposed in lowest employment time group: 6.91 ± 1.67, exposed in highest employment time group: 20.15 ± 3.53, unexposed in highest exposure time group: 12.99 ± 3.75; **sig.** (mean and SD, estimated from graph)	[54]
Wani	2019	**Pb**, Zn	India	Blood	104 (72 lead exposed workers, including car garage, workshops, car repairing, lead acid battery recycle, tyre/tube repairing; 32 controls)	• **TL:** exposed (15.65 ± 4.7) vs controls (3.83 ± 2.17). **Sig** (mean and SD; pooled results from different age groups)	[55]
Zhijian[6]	2006	**Pb**	China	Air, blood	50 storage battery workers (25 exposed, 25 unexposed)	• **TL:** exposed (2.42 ± 0.45) vs. unexposed (1.02 ± 0.55); **sig**. (mean and SEM) • **TM:** exposed (0.85 ± 0.25) vs. unexposed (0.30 ± 0.45); **sig.** (mean and SEM) • ***Combined:*** *exposed (2.6 ± 0.64) vs controls (1.00 ± 1.02)*	[58]
Environmental exposure							
Coelho[3]	2013	Pb, **As**, **Cr**, Cd, Cu, Fe, Hg, **Mn**, Ni, Zn	Portugal	Blood, urine	81 (41 subjects living near a mine, 40 controls)	• **TI:** exposure (25.58 ± 2.75) vs. unexposed (12.40 ± 3.04); **sig**. (Mean and SD)	[24]
Franken	2017	As, Cd, Cr, Pb, Ni, MeHg, PAHs, POPs	Belgium	Blood	598 adolescents (14–15 years old)	• **TI:** 4.1 (3.9–4.3); **non-sig.** (geometric mean and 95 % CI; correlation analysis)	[27]
Jasso-Pineda	2012	Pb, As	Mexico	Blood	85 exposed subjects (48 high area, 12 middle area, 25 low area)	• **TM:** low (2.5 ± 0.4) vs. middle (3.5 ± 0.4) vs. high (5.2 ± 0.6); **sig.** (geometric mean and SD)	[34]
Jasso-Pineda	2015	Pb, As, PAH, DDT/DDE	Mexico	Blood	65 children (55 exposed, 10 controls)	• **TM:** exposed (3.7 ± 1.8) vs controls (4.1 ± 1.5); **non-sig.** (mean and SD)	[35]
Koppen	2020	Pb, As, Cd, Cr, Cu, Ni, PAHs, benzene, POPs, phthalates	Belgium	Blood, urine	2040 adolescents (14–18 years old)	• **TI**: mean 2.4 [2.3–2.5] (mean and 95 % CI); **sig** (positive associated with blood Pb levels)	[40]
Sahu	2024	**Pb**	India	Blood	90 (pregnant women, stratified into low and high blood lead levels)	• **TL:** high (68.1 ± 49.5) vs low (10.8 ± 14.9); **sig** (mean and SD, calculated from raw data). • **TI:** high (19.5 ± 9.5) vs low (1.20 ± 1.96); **sig** (mean and SD calculated from raw data). • **TM:** high (16.8 ± 17.8) vs low (0.32 ± 0.95); **sig** (mean and SD, calculated from raw data). • **OTM:** high (14.4 ± 14.8) vs low (0.66 ± 1.41); **sig** (mean and, SD calculated from raw data). • ***Combined:*** *high (24.42 ± 21.79) vs low (1.00 ± 2.03)*	[49]
Wilhelm	2007	**Pb**, Cd, Cr, Ni, PAH, benzene	Germany	Blood, urine	218 children (151 near a coke oven plant, 67 rural area)	• **TM:** exposed/Duisburg (1.99, 0.55–10.65) vs controls/Borken (1.32, 0.73–2.47); **sig.** (mean and range)	[56]
Xu	2019	**Pb**, **Cr**, **Cd**	China	Blood	192 (82 exposed, 110 controls)	• **TI**: exposed (10.10 ± 3.05) vs controls (8.62 ± 3.51); **sig** (mean and SD)	[57]

Comet descriptors are segregated into visual score (VS), tail length (TL; sometimes also called comet tail length), tail intensity (TI; percentage of total DNA fluorescence in the tail), tail moment (TM; sometimes also called comet tail moment), Olive tail moment (OTM). Results have been combined for studies with more than one comet descriptor.

[1] Co-exposure to other metals (especially iron) and exposure assessment is based on air samplers.

[2] There is a discrepancy in the results from the control group. It is reported as 0.605 ± 0.14 (mean and unspecified type of variability measure) and 0.408 ± 0.04 μm (mean and SEM) in the text and table, respectively. The p-values are also reported differently ($p < 0.01$ and $p < 0.05$ in text and table, respectively).

[3] Details on exposures in different areas have been published in a different article. For the meta-analysis, we have pooled environmental and occupational exposure (exposed: 1.75 ± 0.62, n = 82; control: 1.00 ± 0.25, n = 40).

[4] Measurement of Zn is considered to be a biomarker of zinc status.

[5] All results in the paper are reported as mean and standard error. However, this appears be unlikely as it for instance implies that the subjects are 38 ± 69 years old, which is at odds with the reported age range (18–57 years). Consequently, we believe the authors mistakenly have reported standard deviations and standard errors.

[6] The first author appear as "Zhijian Chen" in PubMed (PMID: 16713056), whereas it is written as "Chen Zhijian" on the paper.

Table 2
Summary of findings from the included studies on arsenic (As) exposure.

Author	Year	Main chemical exposure	Country	Exposure assessment or Biomarkers of exposure	Population characteristics	DNA damage	Ref
Occupational exposure							
Akram	2022	**As**	Pakistan	Blood	360 (300 workers in brick kiln, furniture, pesticide, pain and welding industry, 60 controls)	• **TL:** furniture (32.07 ± 2.02), brick kiln (23.85 ± 2.24), welding (22.25 ± 1.63), pesticides (11.31 ± 0.94), paint (11.74 ± 1.33) vs controls (16.92 ± 0.78); **sig.** (mean and SEM). • **TI:** furniture (21.15 ± 2.12), brick kiln (15.13 ± 1.60), welding (17.57 ± 1.73), pesticides (10.05 ± 1.02), paint (15.29 ± 2.68) vs controls (10.02 ± 0.56); **sig.** (mean and SEM). • **TM:** furniture (6.60 ± 0.70), brick kiln (4.09 ± 0.76), welding (5.61 ± 1.01), pesticides (1.71 ± 0.19), paint (2.08 ± 0.47) vs controls (2.29 ± 0.19); **sig.** (mean and SEM). • **OTM:** furniture (7.71 ± 0.66), brick kiln (4.63 ± 0.60), welding (5.61 ± 0.64), pesticides (2.22 ± 0.23), paint (2.94 ± 0.47) vs controls (3.49 ± 0.28); **sig.** (mean and SEM). • ***Combined:*** *exposed (1.45 ± 1.40) vs controls (1.00 ± 1.14)*	[59]
Coelho[1]	2013	Pb, As, Cd, Cr, Cu, Fe, Hg, Mn, Ni, Zn	Portugal	Blood, urine	81 (41 miners, 40 controls)	• **TI:** exposed (18.73 ± 7.60) vs. controls (12.40 ± 3.04); **sig**. (mean and SD)	[24]
Muller	2022	**Pb**, **As**, **Cr**, **Ni**, **V**	Brazil	Blood	100 (50 chrome plating workers, 50 controls)	• **TI:** exposed (10.10 ± 2.16) vs controls (8.31 ± 1.32); **sig.** (mean and SD). Positive association between As exposure and DNA strand breaks in regression model (**sig**)	[45]
Palus	2005	**As**	Poland	Urine	151 (71 copper smelters, 80 controls)	• **TM:** exposed (13.2, 0–140) vs controls (2.1, 0–30); **sig.** (median and not reported type of variation)	[67]
Shahrokhi	2021	**Pb**, **As**, **Cu**	Iran	Air	80 (47 copper smelter workers, 33 controls)	• **TL:** exposed (29.57 ± 9.03) vs controls (8.82 ± 6.27); **sig** (mean and SD) • **TI:** exposed (25.15 ± 6.41) vs controls (8.96 ± 4.35); **sig** (mean and SD) • **TM:** exposed (17.97 ± 9.12) cs controls (1.66 ± 1.48); **sig** (mean and SD) • ***Combined:*** *exposed (5.66 ± 2.41) vs controls (1.00 ± 0.70)*	[50]
Vuyyuri	2006	**As**	India	Blood	365 (200 glass workers, 165 controls)	• **TL:** exposed (14.95 ± 0.21) vs. unexposed (8.29 ± 0.71): **sig.** (Mean and SEM)	[72]
Environmental exposure							
Banerjee	2008	**As**	India	Drinking water, urine, nail, hair	90 (30 exposed subjects with skin lesions, 30 without skin lesions, 30 controls)	• **TL:** exposed no skin lesions (11.85 ± 5.51) vs. exposed with skin lesions (13.54 ± 4.38) vs. unexposed (2.20 ± 0.72); **sig.** (Mean and SD) • **TI:** exposed no skin lesions (14.05 ± 4.71) vs. exposed with skin lesions (13.4 ± 3.51) vs. unexposed (4.29 ± 1.49); **sig.** (Mean and SD) • **TM:** exposed no skin lesions (2.76 ± 1.39) vs. exposed with skin lesions (2.51 ± 1.40) vs. unexposed (0.55 ± 0.83); **sig.** • ***Combined:*** *exposed (4.59 ± 1.92) vs control (1.00 ± 0.73)*	[60]
Basu	2005	**As**	India	Drinking water, urine, nails, hair	60 (30 high level exposure, 30 controls)	• **TL:** exposed (86.501 ± 5.135) vs. unexposed (21.25 ± 1.004); **sig.** (Mean and SEM) • **VS:** exposed (1.212 ± 0.049) vs. controls (0.579 ± 0.043); **sig.** (mean and SEM) • ***Combined:*** *exposed (3.08 ± 0.90) and controls (1.00 ± 0.34)*	[61]
Biswas[2]	2010	**As**	India	Water, blood	Uncertain	**TM**: exposed (4.7 ± 0.3) vs controls (1.3 ± 0.2); **sig** (mean, type of variation is not reported)	[62]
Calao-Ramos	2023	**As**	Colombia	Drinking water, blood	112 (61 exposed, 51 controls)	• **TI:** exposed (26.5 ± 1.5) vs controls (10.5 ± 7.5); **sig.** (mean and SD)	[63]
Coelho[1]	2013	Pb, **As**, **Cr**, Cd, Cu, Fe, Hg, **Mn**, Ni, Zn	Portugal	Blood, urine	81 (41 subjects living near a mine, 40 controls)	• **TI:** exposure (25.58 ± 2.75) vs. unexposed (12.40 ± 3.04); **sig**. (mean and SD)	[24]
Cruz-Esquivel[4]	2019	As, Hg	Colombia	As, Hg in blood	100 volunteers (50 exposed, 50 unexposed)	• **TL:** exposed (100.5 ± 29.1) vs. control (19.6 ± 3.4); **sig.** (mean and SD) • **TI:** exposed (36.03 ± 5.9) vs. unexposed (13.1 ± 2.1); **sig.** (mean and SD) • **VS**: exposed (42.1 ± 22.3) vs. unexposed (3.92 ± 1.81); **sig.** (mean and SD) • ***Combined:*** *Exposed (6.21 ± 2.54) vs controls (1.00 ± 0.27)*	[64]
Franken	2017	As, Cd, Cr, Pb, Ni, MeHg, PAHs, POPs	Belgium	Blood, urine	598 adolescents (14–15 years old)	• **TI:** 4.1 (3.9–4.3); **non-sig** (correlations, geometric mean and 95 % CI)	[27]

(*continued on next page*)

Table 2 (*continued*)

Author	Year	Main chemical exposure	Country	Exposure assessment or Biomarkers of exposure	Population characteristics	DNA damage	Ref
Jasso-Pineda	2007	**As**, **Pb**	Mexico	Soil, urine	60 children (12 low area, 28 medium area, 20 high area exposure)	• **TM:** low exposure (3.9 ± 0.2) vs. medium exposure (5.4 ± 0.2) vs. high exposure (4.8 ± 0.3); **sig.** (geometric mean and SEM)	[65]
Jasso-Pineda	2012	As, Pb	Mexico	Urine	85 exposed subjects (48 high area, 12 middle area, 25 low area)	• **TM:** Low (2.5 ± 0.4) vs. middle (3.5 ± 0.4) vs. high (5.2 ± 0.6); **sig.** (geometric mean and SD)	[34]
Jasso-Pineda	2015	As, Pb, PAH, POPs	Mexico	As and 1-OHP in urine Lead and total DDT/DDE in blood	65 children (40 exposed, 25 controls)	• **TM:** exposed (4.2 ± 1.3) vs controls (3.1 ± 0.5) sig.; high/low lead (3.7 ± 1.8/ 4.1 ± 1.5); **sig.** (mean and SD)	[35]
Kocadal	2021	**As**, **Cu**, Cr, **Fe**, **Ni**, **Mn**	Cyprus	Soil, blood	60 (30 exposed, 30 controls)	• **TL:** exposed (32.5 ± 5.2) vs controls (34.1 ± 9.7); **non-sig.** (mean and SD) • **TI:** exposed (3.2 ± 9.1) vs controls (1.3 ± 1.4); **non-sig.** (mean and SD) • **TM:** exposed (0.3 ± 0.2) vs controls (0.3 ± 0.4); **non-sig.** (mean and SD) • ***Combined:*** *exposed (1.47 ± 2.61) vs controls (1.00 ± 0.90)*	[66]
Koppen	2020	As, Cd, Cr, Cu, Ni, Pb, PAHs, benzene, POPs, phthalates	Belgium	Blood, urine	2040 adolescents (14–18 years old)	• **TI:** 2.4 (mean), 2.3–2.5 (95 % CI); **sig.** (positive association with blood As levels)	[40]
Quiroga	2024	**As**	Argentiva	Groundwater, urine	322 (145 exposed, 177 unexposed)	• **VS:** exposed (148.3 ± 6) vs unexposed (135 ± 4); **non-sig**. (mean and SEM)	[68]
Roy	2016	**As**	India	Water	40 (20 exposed, 20 controls)	• **TI:** exposed/tobacco chewers (4.93 ± 0.66) and exposed/non-chewers (3.44 ± 0.32) versus controls/tobacco chewers (2.46 ± 0.31) and controls/non-chewers (0.74 ± 0.08); **sig**. (mean and SD). • ***Combined:*** *exposed (3.33 ± 1.11) vs controls (1.00 ± 0.37)*	[69]
Sampayo-Reyes[3]	2010	**As**	Mexico	Drinking water, urine	286 subjects (five villages)	• **TI:** low exposure (22.90 ± 1.17) vs. medium exposure (32.76 ± 2.55) vs. high exposure (35.80 ± 3.05); **sig.** (mean and SEM)	[70]
Tirado[5]	2024	As	Bolivia	Urine	202 (correlation study)	• **TI:** No association between arsenic concentration in urine and DNA strand breaks; **non-sig.**	[71]
Yanez	2003	**As**, **Pb**	Mexico	Urine	55 children (20 exposed, 35 unexposed)	• **TL**: exposed (67.6, 58.3–79.3) vs. unexposed (41.7, 35.8–48.6); **sig.** (geometric mean and 95 % CI) • **TM:** exposed (6.8, 5.2–8.9) vs. unexposed (3.2, 2.6–3.9); **sig**. (geometric mean and 95 % CI)	[73]

Comet descriptors are segregated into visual score (VS), tail length (TL; sometimes also called comet tail length), tail intensity (TI; percentage of total DNA fluorescence in the tail), tail moment (TM; sometimes also called comet tail moment), Olive tail moment (OTM). Results have been combined for studies with more than one comet descriptor.

[1] Details on exposures in different areas have been published in a different article [24]. For the meta-analysis, we have pooled environmental and occupational exposure (exposed: 1.75 ± 0.62, n = 82; control: 1.00 ± 0.25, n = 40).

[2] The study is excluded from the meta-analysis because there is not information on the type of reported variation and the information on number of subjects differs between the text (50 in each group) and figure legend (143 and 100 in exposed and controls, respectively).

[3] Medium and high exposure groups are combined for the meta-analysis (34.1 ± 10.7, mean and SD, n = 50).

[4] The exposed population has high blood levels of both As and Hg.

[5] Excluded from meta-analysis because it is not possible to dichotomize DNA strand break results, based on exposure data.

Table 3
Summary of findings from the included studies on chromium (Cr) exposure and welding fumes.

Author	Year	Main chemical exposure	Country	Exposure assessment or Biomarkers of exposure	Population characteristics	DNA damage	Ref
Occupational exposure							
Akram	2022	Welding fumes **(As)**	Pakistan	Blood	120 (60 welders, 60 controls)	• **TL:** exposed (22.25 ± 1.63), vs controls (16.92 ± 0.78); **non-sig.** (mean and SEM). • **TI:** exposed (17.57 ± 1.73) vs controls (10.02 ± 0.56); **sig.** (mean and SEM). • **TM:** exposed (5.61 ± 1.01) vs controls (2.29 ± 0.19); **sig.** (mean and SEM). • **OTM:** exposed (5.61 ± 0.64) vs controls (3.49 ± 0.28); **sig.** (mean and SEM). • ***Combined:*** *exposed (1.45 ± 1.40) vs controls (1.00 ± 1.14)*	[59]
Aksu	2019	Welding fumes (**Cr**, **Cu**, **Cd**, Mn, **Ni**, Pb)	Turkey	Blood	96 (48 welders, 48 controls)	• **TL** (lymphocytes): exposed (6.52 ± 3.13) vs. controls (2.31 ± 1.09); **sig.** (mean and SD) • **TI:** (whole blood): exposed (8.64 ± 2.21) vs. controls (4.47 ± 2.22); **sig.** (mean and SD) • ***Combined:*** *exposed (2.38 ± 0.92) vs. unexposed (1.00 ± 0.48)*	[74]
Ambreen	2014	Cr	India	Blood	200 (100 tannery workers, 100 controls)	• **TL:** exposed (23.53 ± 5.27) vs controls (9.27 ± 2.21); **sig.** (mean and SD) • **TL:** exposed (4.21, 3.21–10.98) vs. controls (3.01, 2.68–9.40); **sig.** for exposed workers (mean and unspecified variation)	[75]
Balachandar[1]	2010	**Cr**	India	Air, urine	72 (36 leather tanning industry workers, 36 controls)	• **TI:** exposed (4.80, 4.02–11.23) vs. controls (3.20, 3.11–11.78); **non-sig.** (mean and unspecified variation) • **TM:** exposure (0.43) vs. controls (0.14); **non-sig.** (mean and variation not reported)	[76]
Coelho[2]	2013	Cr, Pb, As, Cd, Cu, Fe, Hg, Mn, Ni, Zn	Portugal	Blood, urine	81 (41 miners, 40 controls)	• **TI:** exposed (18.73 ± 7.60) vs. controls (12.40 ± 3.04); **sig.** (mean and SD)	[24]
Danadevi	2004	Welding fumes (**Cr**, **Ni**)	India	Blood	204 (102 welders, 102 controls)	• **TL:** exposed (23.1 ± 3.9) vs controls (8.9 ± 3.2); **sig.** (mean and SD)	[77]
Gambelunghe	2003	**Cr**	Italy	Urine	39 (19 chrome-plating workers, 20 controls)	• **TM:** exposed (0.42 ± 0.21) vs. unexposed (0.42 ± 0.21); **sig.** (mean and SD)	[80]
Iarmarcovai	2005	Welding fume (**Cr**, **Cd**, **Mn**, **Ni**, **Pb**)	France	Blood and urine	57 (27 welders, 30 controls)	• **TM:** exposed (4.5 ± 1.7) vs. unexposed (2.8 ± 0.8); **sig.** (mean and SD)	[32]
Khisroon	2021	Welding fume (**Cr**, **Pb**, **Cd**, **Fe**, **Mn**, **Ni**)	Pakistan	Scalp hair	118 (59 welders, 59 controls)	• **VS:** exposed (121.8 ± 10.7) vs. controls (56.5 ± 17.6); **sig.** (mean and SD)	[39]
Ko	2019	Welding fumes (Cr, Fe, Cu, Mn, Cd, As)	Taiwan	Blood	109 (60 welders, 49 controls)	• **TM:** exposed (6.17 ± 3.61) vs controls (5.20 ± 2.97); **sig.** (mean and SD)	[82]
Meibian[3]	2008	Cr	China	Air, blood, urine	90 Exposure group I: 30 tannery workers exposed to trivalent chromium from tanning department; Exposure group II: 30 tannery workers from finishing department; 30 controls.	• **TL:** moderate exposure (3.43 [2.31–8.29]) vs. high exposure (5.33 [2.90–8.50]) vs. unexposed (2.04 [0.09–3.83]); **sig.** (median and range). • **TM:** moderate exposure (3.41 [1.25 – 11.07]) vs. high exposure (6.28 [2.14 – 11.81]) vs. unexposed (0.53 [0.13–3.79]); **sig.** (median and range). • ***Combined:*** *exposed (3.09 ± 1.36) vs controls (1.010 ± 0.72)*	[84]
Muller[4]	2022	**Cr**, **Pb**, **As**, **Ni**, **V**	Brazil	Blood	100 (50 chrome plating workers, 50 controls)	• **TI:** exposed (10.10 ± 2.16) vs controls (8.31 ± 1.32); **sig.** (mean and SD)	[45]

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Table 3 (*continued*)

Author	Year	Main chemical exposure	Country	Exposure assessment or Biomarkers of exposure	Population characteristics	DNA damage	Ref
Sardas	2010	Welding fumes	Turkey	None	52 (26 welders, 26 controls)	• **TI:** exposed (13.59 ± 1.89) vs controls (6.64 ± 1.43); **sig.** (mean and SD)	[85]
Sellappa	2012	Welding fumes	India	None	126 (93 welders, 60 controls)	• **TL:** exposed (15.1 ± 4.12) vs controls (11.4 ± 3.59); **sig.** (mean and SD)	[86]
Singh	2010	Welding fume (**Pb**)	India	Blood (Pb)	70 (35 welders, 35 controls)	• **TL:** exposed (29.21 ± 8.8) vs. unexposed (1.47 ± 0.5); **sig.** (mean ± SEM)	[52]
Sudha	2011	Welding fumes	India	None	126 (66 welders, 60 controls)	• **TL:** exposed (18.6 ± 4.16) vs controls (9.30 ± 2.65); **sig.** (mean and SD, combined results from smokers and non-smokers)	[87]
Tavares	2022	Welding fumes and other occupations with Cr exposure	Belgium, Finland, Poland, Portugal	Urine	117 (74 exposed and 43 controls)	• **TI:** exposed (6.34 ± 1.83) vs controls (4.59 ± 3.26); **sig** (mean and SD)	[88]
Zhang	2011	**Cr**	China	Air, blood	250 (157 electroplating workers, 93 unexposed)	• **TL:** exposed (11.77, 3.46, 52–19) vs. unexposed (3.26, 3.00, 4.00); **sig.** (median and range) • **TI:** exposed (3.69, 0.65–16.2) vs. unexposed (0.69, 0.04–2.74); **sig.** (median and range) • **TM:** exposed (1.13, 0.14–6.77) vs. unexposed (0.14, 0.01–0.39); **sig.** (median and range)	[89]
Zhu	2001	Welding fumes	China	None	160 (120 welders, 40 managerial workers)	• **TM:** exposed (2.89, 2.63–3.19) vs controls (2.54, 2.22–2.90); **non-sig.** (geometric mean and 95 % CI)	[90]
Environmental exposure							
Balachandar[1]	2010	**Cr**	India	Cr in air and urine Cr in air	72 (36 environmental exposure subjects, 36 controls)	• **TL:** exposure (3.98, 2.98–11.27) vs. controls (3.01, 2.68–9.40); **non-sig.** (mean and unspecified variation) • **TI:** exposure (4.01, 3.81–13.28) vs. controls (3.20, 3.11–11.78); **non-sig.** (mean and unspecified variation) • **TM:** exposure (0.29) vs. controls (0.14); **non-sig.** (mean and variation not reported)	[76]
Coelho[2]	2013	Pb, **As**, **Cr**, Cd, Cu, Fe, Hg, **Mn**, Ni, Zn	Portugal	Blood, urine	81 (41 subjects living near a mine, 40 controls)	• **TI:** exposure (25.58 ± 2.75) vs. unexposed (12.40 ± 3.04); **sig.** (mean and SD) • **TL:** exposed (28.90 ± 0.80) vs. unexposed (25.16 ± 0.45); **sig.** (mean and SEM)	[24]
David[5]	2021	**Cr**, **Cd**, **Ni**, **Zn**	Pakistan	Blood	232 children (134 living at brick kiln industries, 98 controls)	• **TI:** exposed (15.02 ± 0.56) vs. unexposed (10.33 ± 0.55); **sig.** (mean and SEM) • **TM:** exposed (4.40 ± 0.23) vs. unexposed (3.96 ± 0.39); **non-sig.** (mean and SEM) • ***Combined:*** *exposed (1.24 ± 0.39) vs controls (1.00 ± 0.39)*	[78]
Espitia-Perez	2018	**Cr**, **Mn**, **Ni**, Cu, Zn	Brazil	Blood	139 (98 living in coal mining area, 41 controls)	• **TI:** exposure (50.81 ± 17.04) vs. unexposed (28.31 ± 34.41); **sig.** (mean and SD)	[79]
Franken	2017	Cr, Cd, As, Ni, Hg, Pb, PAHs, POPs	Belgium	Urine	598 adolescents (14–15 years old)	• **TI**: 4.1 (3.9–4.3) (geometric mean and 95 % CI); **sig.** (positive association with urine concentration of Cr)	[27]
Khan	2012	**Cr**	India	Blood	200 volunteers (100 exposed, 100 unexposed)	• **TL:** exposed (27.39 ± 9.50) vs. unexposed (8.89 ± 2.49); **sig.** (mean and SD)	[81]
Koppen	2020	Cr, As, Cd, Pb, Cu, Ni, PAHs, benzene, POPs, phthalates	Belgium	Blood, urine	2040 adolescents (14–18 years old)	• **TI**: mean 2.4 [2.3–2.5] (mean and 95 % CI); **non-sig** (no association with blood Cr levels)	[40]
Leon-Mejia[6]	2023	**Cr**, **Fe**, **Cu**, Zn	Brazil	Blood	270 (150 exposed, 120 controls)	• **TI:** exposed (9.61 ± 1.06) vs controls (8.11 ± 1.98); **sig** (mean and SD)	[83]
Xu	2019	**Cr**, **Pb**, **Cd**	China	Blood	192 (82 exposed, 110 controls)	• **TI**: exposed (10.10 ± 3.05) vs controls (8.62 ± 3.51); **sig** (mean and SD)	[57]

Comet descriptors are segregated into visual score (VS), tail length (TL; sometimes also called comet tail length), tail intensity (TI; percentage of total DNA fluorescence in the tail), tail moment (TM; sometimes also called comet tail moment), Olive tail moment (OTM). Results have been combined for studies with more than one comet descriptor.

[1] The study includes both environmental (indirect) and occupational (direct) exposure. The type of variation is reported as SD for tail length and % DNA tail, but the results appear to have been reported as range. For tail moment, variation is not reported. The study has been excluded from the meta-analysis.

[2] Details on exposures in different areas have been published in a separate article. For the meta-analysis, we have only included environmental exposure, because there is no difference in Cr exposure between controls and workers.

[3] The first author appear as "Z. Meibain" in PubMed (PMID:18541454), whereas it is written as "Zhang Meibain" on the paper. For the meta-analysis we have calculated mean and SD from raw results: moderate exposure (tail length: 3.73 ± 1.24, tail moment: 3.99 ± 2.36), high exposure (tail length: 5.40 ± 1.81, tail moment: 6.39 ± 2.72), and controls (tail length: 2.24 ± 1.02, tail moment: 1.25 ± 1.23).

[4] Excluded from meta-analysis because the difference in blood levels of Cr is negligible compared to differences in blood levels of Pb, As, Ni and V.

[5] The electrophoresis has been done in buffer with neutral pH.

[6] The authors used Mann Whitney *U* test and concluded that the difference between exposed and controls is not statistically significant. However, Student's *t*-test demonstrate a highly significant effect ($t = 7.96$, $P < 0.0001$). We have considered the results on DNA strand breaks as statistically significant.

The latter might be due to difference between occupational and environmental exposure studies. Heterogeneity might also be due to different workplaces being more or less apt to implement/enforce protective procedures to avoid exposure of workers to hazardous compounds. It is virtually impossible to assess the magnitude of exposure, except by comparing metal concentrations in biological samples of studies that have reported concentrations in the same unit. In addition, heterogeneity in effect sizes might be dependent on the researcher's control of variation that occurs in biological techniques such as the comet assay. This applies to both blinded scoring of samples and inclusion of samples with contrasting exposures in the same comet assay experiment (i.e. analysis of matched pair of pre and post samples or exposed/controls in the same comet assay experiment). Randomized analysis of samples and matched pairs are acceptable analytical designs, but comparison of effect sizes between these experimental designs might cause heterogeneity in a meta-analysis.

2.5. Subgroup analyses

The studies have been stratified into populations from high-income and middle-income countries, according to the 2025 World Bank classification (https://data.worldbank.org/). In the present dataset, high-income economies include Belgium, Croatia, Cyprus, Germany, Finland, France, Italy, Poland, Portugal and Taiwan. Countries in the group of middle-income countries include Argentina, Bangladesh, Brazil, China, Colombia, India, Iran, India Mexico, Pakistan and Turkey. In another subgroup analysis, we have stratified the database into studies that have assessed (i) lead vs multiple metals, (ii) arsenic vs multiple metals, and (iii) chromium vs welding fumes.

2.6. Sensitivity analyses

Uncertainties (potential bias) related to comet assay experiments and exposure assessment have been assessed on a scale with low, moderate or high risk of bias/exposure misclassification. The classification system is described in detail in the supplementary material. In brief, the comet assay experiments have been rated according to the recommended Minimum Information for Reporting on the Comet Assay (MIRCA) [17], inclusion of assay controls and blinded/coded analysis of samples or slides. The exposure assessment has increasing certainty of exposure: (i) grouping based on work categories or areas, (ii) environmental monitoring assessment, and (iii) biomarkers of exposure (internal and/or effective dose). For visual presentation, we have used traffic light plots where red, yellow and green colours refer to studies with high, moderate and low risk of bias/exposure misclassification. The traffic light plots have been generated in robvis (https://mcguinlu.shinyapps.io/robvis/) [18]. Differences in distributions have been tested by χ^2-test.

3. Results

Overall, the literature search identified 100 articles, of which 79 are included in the review and 66 have been used in meta-analyses. Many studies have assessed environmental or occupational exposure to lead, either as the only measured metal or in combination with other metals/chemicals. The same goes for occupational chromium exposure, which has typically been assessed in welders. Lastly, a number of studies have assessed genotoxicity in populations with environmental exposure to arsenic. In the results section, we only describe studies that have been included in the review, including meta-analyses. The results have been segregated into studies on lead (Table 1), arsenic (Table 2), chromium/welding fumes (Table 3) and other metals (Table 4). Table 5 summarizes effect sizes in meta-analysis of the different heavy metals as well as effects in subgroup analyses. Table 6 shows results from sensitivity analyses on stratification of studies according to risk of bias due to missing information on blinding/coding of samples, assay controls and comet assay procedures, and exposure misclassification. Excluded studies are described in the Supplemental Tables S2-S5.

3.1. Lead [Pb]

The literature search generated a total number of 40 studies on occupational or environmental lead exposure [19–58] (Table 1).

3.1.1. Generalizability

Thirty-four out of the 40 included studies have found statistically significant increased levels of DNA strand breaks [19–26,28,30,32–34,36,38–47,49–58]. Six studies have shown unaltered levels of DNA strand breaks between lead exposed subjects and controls [27,29,31,35,37,48]. Most of the included studies in the review are also included in the meta-analysis (35 out of 40 studies). There does not appear to be a major difference in proportions of positive results in the studies that have been included (89 %, 31 out of 35 studies) and excluded (80 %, 4 out of 5 studies) in the meta-analysis (Supplementary Table S6). There is not a sufficient statistical power to assess a difference in proportions of positive associations between datasets of included and excluded studies in the meta-analysis.

3.1.2. Meta-analysis

A total of 35 studies out of the 40 included studies have been included in the meta-analysis [19–26,28–33,36–39,41–55,57,58]. Fig. 2 shows results from the meta-analysis of the studies. The meta-analysis shows a SMD of 1.99 (95 % CI: 1.47, 2.51). There is a large heterogeneity in effect size between the studies ($I^2 = 98$ %). In particular, a study by Grover et al., 2010 stands out as having an effect size that is much higher than effects found in other studies [30]. The study does not appear to be unusual with regard to the level of lead exposure (3.2 versus 30 μg/dL blood lead in unexposed and exposed, respectively). However, the within-group variation is relatively low (coefficient of variation: 7.7 % and 4.9 % in controls and exposed, respectively). This is also visually clear in the Funnel plot where the study gives rise to an isolated data point in the lower right-hand corner, indicating that the study has an effect size and variability that differ from other studies (Supplementary Figure S2). Excluding the study by Grover et al., 2010 [30] reduces the effect size (SMD = 1.72, 95 % CI: 1.24, 2.20), although

Table 4
Summary of findings from the included studies on various heavy metals.

Author	Year	Main chemical exposure	Country	Exposure assessment or Biomarkers of exposure	Population characteristics	DNA damage	Ref
Occupational exposure							
Cavallo[2]	2002	Sb	Italy	Air (personal air samplers)	46 (23 workers assigned to different fire-retardant treatment tasks in the car upholstery industry, 23 controls)	• **TM:** exposed group A: 15.0 ± 8.9, exposed group B: 18.9 ± 9.4 vs control: 16.7 ± 6.9; **non-sig.** (mean and SD)	[91]
De Boeck	2000	Co	Belgium, Norway, Finland, Sweden, England	Urine	99 (35 cobalt dust, 29 carbide-cobalt, 35 unexposed)	• **TI:** Co (0.50 ± 1.44) vs. hard metals (0.57 ± 1.24) vs. unexposed (0.51 ± 1.35); **non-sig.** (geometric mean and SD) • **TL:** Co (0.71 ± 1.38) vs. hard metals (0.65 ± 1.23) vs. unexposed (0.64 ± 1.25); **non-sig.** (geometric mean and SD) • **TM:** Co (0.37 ± 1.85) vs. hard metals (0.40 ± 1.45) vs. unexposed (0.34 ± 1.47); **non-sig.** (geometric mean and SD)	[92]
De Olivera	2012	Cu, Fe, Zn	Brazil	Blood	22 (11 copper-smelters, 11 controls)	• **VS:** exposed (17.6 ± 10.2) vs. unexposed (4.29 ± 2.53); **sig.** (mean and SD)	[93]
Liu[4]	2017	Indium	China	Air, urine	120 (57 indium exposed workers, 63 controls)	• **TL**: exposed (16.36 ± 7.56) vs. unexposed (10.80 ± 5.63); **sig.** (mean and SD) • **TI**: exposed (5.01 ± 3.08) vs. unexposed (2.69 ± 1.61); **sig.** (mean and SD) • ***Combined:*** *exposed (1.69 ± 0.92) vs controls (1.00 ± 0.56)*	[94]
Pandeh[3]	2017	Fe	Iran	Iron status (including serum iron)	56 (30 steel company workers, 26 controls)	• **TL**: 15.88 (8.94–20.44) vs. 6.17 (5.57–8.07); **sig.** (median, 1st−3rd quartiles) • **TI**: 8.98 (5.81–11.37) vs. 3.97 (30.7–4.84); **sig.** (median, 1st−3rd quartiles) • **TI:** 24.59 (11.74–29.53) vs. 20.19 (17.50–22.26); **sig.** (median, 1st−3rd quartiles) • **TM**: 3.42 (1.60–6.01) vs. 0.68 (0.53–0.93); **sig.** (Median, 1st−3rd quartiles) • ***Combined:*** *exposed (2.77 ± 2.52) vs controls (1.00 ± 0.42)*	[95]
Environmental exposure							
Calderon-Segura[1]	2024	Heavy metals (Fe, Mn, Pb, As)	Mexico	None	202 (101 children from mining site, 101 controls)	• **TL**: exposed (60.89 ± 6.18) vs controls (36.59 ± 1.86); **sig** (mean and SEM) • **TI:** exposed (37.68 ± 4.59) vs control (18.38 ± 1.52); **sig** (mean and SEM) • **TM**: exposed (19.79 ± 3.50) vs controls (4.24 ± 1.54); sig (mean and SEM) • ***Combined:*** *exposed (2.78 ± 4.17) vs control (1.00 ± 1.68)*	[96]
Miranda-Guevara	2023	Cr, **Fe**, Ni, Zn	Columbia	Urine	270 (150 exposed, 120 conttrols)	• **VS:** exposed (76.6 ± 32.8) vs controls (45.4 ± 16.8); **sig** (Mean and SD)	[97]

Comet descriptors are segregated into visual score (VS), tail length (TL; sometimes also called comet tail length), tail intensity (TI; percentage of total DNA fluorescence in the tail), tail moment (TM; sometimes also called comet tail moment), Olive tail moment (OTM). Results have been combined for studies with more than one comet descriptor.

1 Heavy metals have not been assessed in the study (exposures are presumed from previous studies of contaminants in drinking water).

2 Air measurements have only been done in the two groups of exposed workers. The exposure groups have been pooled for the meta-analysis (16.0 ± 9.0). Estimated from graph.

3 Inter-quartile range has been used as proxy-measure of SD in the meta-analysis.

4 Procedure described as “neutral condition”, but reference to detail procedure indicates it is alkaline condition.

it does not affect the heterogeneity between studies (I^2 = 98 % for datasets with or without Grover et al., 2010). Using non-parametric analysis to calculate the central tendency produces a substantially lower effect size (SMD_{median} = 1.29, 95 % CI: 0.63, 2.36).

Blood lead is the preferred biomarker of exposure, which typically represents a steady-state exposure over a couple of months as lead is mainly found in erythrocytes ($T_{½}$ of which in blood is 1–2 month in adults). A number of the studies have reported blood lead concentrations, which makes it possible to assess dose-response relationships between exposure and DNA strand break levels [19–23,25,26,28–33,36,37,44,46–49,52–55,57,58]. Fig. 3 shows an analysis of the relationship between the lead exposure gradient and effect sizes. The difference in

Table 5
Summary of meta-analysis of exposure to lead, arsenic and chromium/welding fumes.

Metal	Papers (No)	Subjects (No)	Overall analysis (SMD)	Subgroup analysis (SMD)	Median (SMD)
Lead	35	4913	1.99 (1.47, 2.51)[a]	Lead-only: 2.01 (1.34, 2.68) [23] Mixed: 2.07 (1.19, 2.94) [12] High-income: 0.76 (0.32, 1.20) [10] Middle-income: 2.49 (1.81, 3.18) [25]	1.29 (0.63, 2.36)
Arsenic	14	2187	1.36 (0.94, 1.77)	Arsenic-only: 1.25 (0.76, 1.74) [8] Mixed: 1.48 (0.75, 2.21) [6] High-income: 0.83 (−0.32, 1.98) [2] Middle-income: 1.45 (0.99, 1.91) [12]	1.12 (0.37, 2.42)
Chromium (welding fumes)	20	2664	2.03 (1.48, 2.57)	Chromium: 1.77 (1.04, 2.51) [9] Welding fumes: 2.24 (1.38, 3.11) [11] High-income: 1.87 (0.47, 3.27) [4] Middle-income: 2.07 (1.45, 2.69) [16]	1.48 (0.71, 3.52)
Other metals	6	716	0.81 (0.45, 1.18)	Not applicable	Not analysed

Standardized mean difference (SMD) is reported with 95 % confidence interval.
[a] Effect without outlier (SMD = 1.72, 95 % CI: 1.24, 2.20).

Table 6
Sensitivity analysis of effect sizes in studies according to use of blinded analysis, inclusion of assay controls and description of comet assay procedure.

Item (risk of bias)	Lead (Pb) studies	Arsenic (As) studies	Chromium (Cr) or welding fume studies
Blinding			
High	1.49 (1.03, 1.96) [26]	1.29 (0.56, 2.01) [7]	1.35 (0.85, 1.85) [14]
Low	3.52 (1.93, 5.12) [9]	1.43 (0.86, 2.01) [7]	3.72 (2.05, 5.38) [6]
Inclusion of assay controls			
High	2.11 (1.56, 2.65) [32]	1.42 (0.96, 1.89) [12]	2.03 (1.48, 2.67) [19]
Low	0.71 (−0.73, 2.14) [3]	1.02 (−0.56, 2.59) [2]	0.71 (0.32, 1.10) [1]
Comet assay description			
High	3.16 (1.65, 4.66) [9]	0.35 (0.19, 0.51) [1]	1.35 (0.24, 2.47) [3]
Moderate	2.14 (0.96, 3.32) [8]	1.41 (0.62, 2.20) [6]	3.53 (1.77, 5.28) [4]
Low	1.37 (0.89, 1.85) [18]	1.49 (0.87, 2.10) [7]	1.76 (1.08, 2.44) [13]
Exposure assessment			
High	2.53 (1.68, 3.38) [1]	No results	2.50 (0.88, 4.11) [3]
Moderate	2.42 (1.83, 3.01) [1]	1.85 (0.31, 3.40) [3]	No results
Low	1.96 (1.42, 2.50) [33]	1.24 (0.80, 1.68) [11]	1.95 (1.35, 2.55) [17]
Combined			
High	1.89 (0.12, 3.66) [4]	0.36 (0.21, 0.52) [2]	1.35 (0.24, 2.47) [3]
Moderate	1.97 (1.40, 2.54) [29]	1.75 (1.08, 2.43) [7]	1.94 (1.29, 2.59) [14]
Low	2.49 (−1.33, 6.32) [2]	1.22 (0.58, 1.87) [5]	3.12 (0.69, 5.56) [3]

Standardized mean difference (SMD) is reported with 95 % confidence interval (number of studies are shown in brackets). Not applicable (NA)

lead exposure is calculated as delta values of blood lead concentration between exposed and controls, or differences in "after" and "before" working periods. In general, there does not appear to be a relationship between lead exposure and DNA strand breaks. Today, there is no safe lower limit of exposure to lead, but WHO recommends that a blood lead concentration of 5 μg/dL should be a trigger to assess sources of personal exposure and actions to reduce/avoid the exposure. In comparison, the difference in lead exposure is substantial.

3.1.3. Subgroup analysis

A relatively large number of studies in the meta-analysis have only assessed lead exposure (23 out of 35 studies). A stratification of the studies according to the exposure assessment does not indicate a substantial difference between studies that have only reported exposure to lead levels (SMD = 2.01, 95 % CI: 1.34, 2.68) as compared to studies that also have assessed other heavy metals (SMD = 2.07, 95 % CI: 1.19, 2.94).

There are more studies on lead exposure from middle-income (n = 25) than high-income countries (n = 10) in the meta-analysis. Studies from middle-income countries have higher effect size (SMD = 2.49, 95 % CI: 1.81, 3.18) as compared to high-income countries (SMD = 0.76, 95 % CI: 0.32, 1.20).

3.1.4. Sensitivity analysis

Fig. 4 summarizes the risk of comet assay measurement bias and exposure misclassification. The overall results indicate that the majority of the studies have moderate risk of comet assay measurement bias, including insufficient information on comet assay procedures (49 % in the moderate and high risk category, 17 out of 35 studies), lack of reporting on blinding/coding of samples (74 %, 26 out of 35 studies) and assay controls (91 %, 32 out of 35 studies). However, most of the studies have low risk of exposure misclassification (89 %, 31 out of 35 studies). Overall, the majority of the studies have moderate risk of bias (89 %, 31 out of 35 studies).

The sensitivity analysis does not unequivocally indicate that the effect size depends on potential risk of comet assay measurement bias and exposure misclassification (Table 6). Studies with reporting of blinded/coded analysis of samples seem to have higher effect size (SMD = 3.52, 95 % CI: 1.93, 5.12) than studies without such information (SMD = 1.49, 95 % CI: 1.03, 1.96). On the other hand, the risk of comet assay measurement bias related to information on comet assay procedure description increases from low risk (SMD = 1.37, 95 % CI: 0.89, 1.85) to moderate (SMD = 2.14, 95 % CI: 0.96, 3.32) and high risk (SMD = 3.16, 95 % CI: 1.65, 4.66).

3.1.5. Summary

Collectively, the meta-analysis of 35 studies indicates a positive association between lead exposure and levels of DNA strand breaks. Depending on the type of analysis of this dataset, the effect size is 1.99 (95 % CI: 1.47, 2.51) or 1.29 (95 % CI: 0.63, 2.36) using either parametric or non-parametric estimate of the central tendency, respectively.

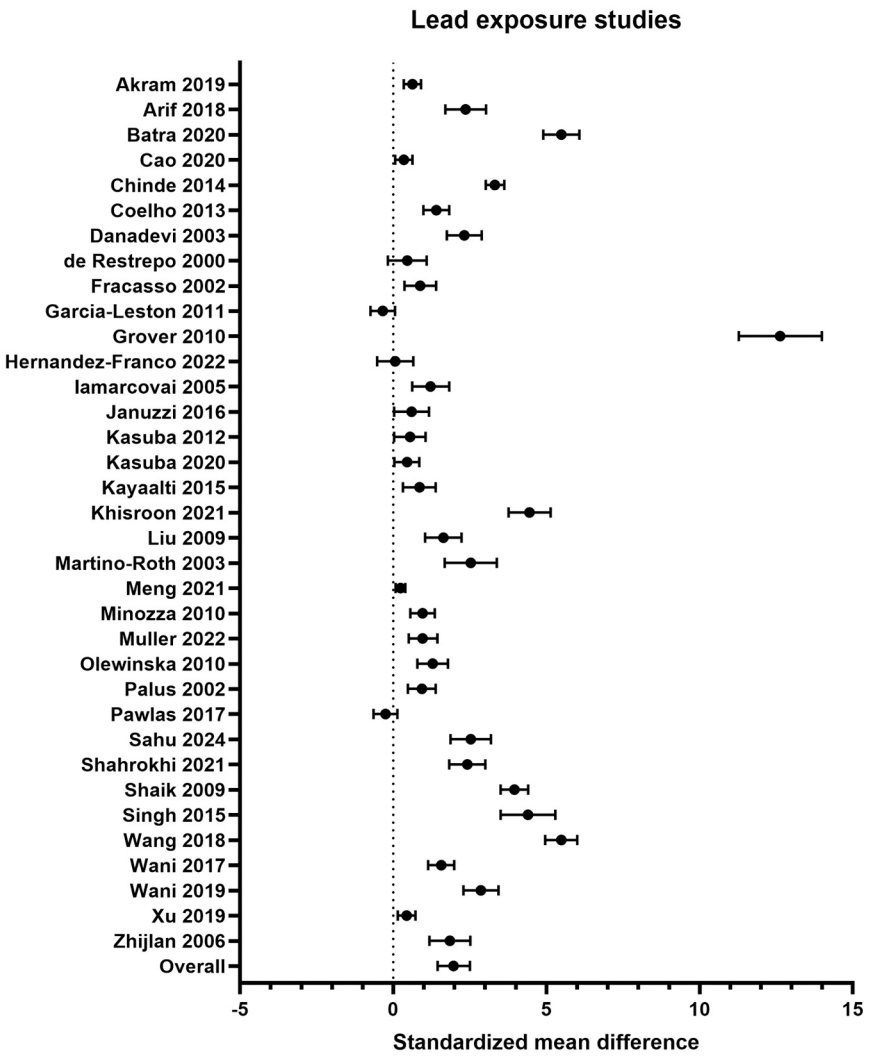

Fig. 2. Effect sizes in studies on environmental (n = 2), occupational (n = 32) and mixed environmental/occupational exposure (n = 1) to lead. Symbols and lines are mean and 95 % confidence intervals. Effects are statistically significant if they do not cross the vertical line at x = 0. The forest plot has been reproduced for graphical purposes. Original Forest and Funnel plots are included in Supplementary Figs. S1 and S2, respectively.

3.2. Arsenic [As]

We have included 22 studies with data on arsenic exposure and DNA strand breaks in the review [24,27,34,35,40,45,50,59–73] (Table 2). Fourteen out of the 22 studies are included in the meta-analysis.

3.2.1. Generalizability

Among the included studies, there is an over representation of studies that show genotoxicity of arsenic exposure (18 out of 22 studies) [24,34,35,40,45,50,59–65,67,69,70,72,73], compared to null effect studies (4 studies) [27,66,68,71]. There is no difference in the proportions of studies with positive association in the meta-analysis (83 %, 12 out of 14 studies) and excluded studies (75 %, 6 out of 8 studies, Z-value = 0.05, P > 0.05) (Supplementary Table S7).

3.2.2. Meta-analysis

Fourteen studies have been included in the meta-analysis [24,35,45,50,59–61,63,64,66,68–70,72]. Three studies have assessed occupational exposure to arsenic [45,59,72], one study has assessed both occupational and environmental exposure [24], and 10 studies have assessed environmental exposure [35,50,60,61,63,64,66,68–70]. The meta-analysis shows a SMD of 1.36 (95 % CI: 0.94, 1.77), which is skewed due to the heterogeneity in effect between studies (Fig. 5). Using a non-parametric test to calculate the central tendency produces a slightly lower effect size (SMD_{median} = 1.12, 95 % CI: 0.37, 2.42).

3.2.3. Subgroup analysis

The studies that have assessed arsenic only have a similar effect size (SMD = 1.25, 95 % CI: 0.76, 1.74) as compared to studies with measurement of arsenic and other metals (SMD = 1.48, 95 % CI: 0.75, 2.21). Subgroup analysis of effect sizes according to the origin of the study is uncertain, as 12 out of 14 studies originate from middle-income countries. The effect size for high-income countries is 0.83 (95 % CI: −0.32, 1.98) and for middle-income countries it is 1.45 (95 % CI: 0.99, 1.91).

3.2.4. Sensitivity analysis

Fig. 6 shows the results of assessment of risk of comet assay measurement bias and exposure misclassification. The overall results indicate that the majority of studies have moderate risk of bias related to the comet assay procedure, including insufficient information on comet assay procedures (50 % in the moderate and high risk category, 7 out of 14 studies), lack of reporting on blinding (50 %, 7 out of 14 studies) and assay controls (86 %, 12 out of 14 studies). However, most of the studies have low risk of exposure misclassification (79 %, 11 out of 14 studies). Overall, the majority of the studies have moderate risk of bias (93 %, 13 out of 14 studies).

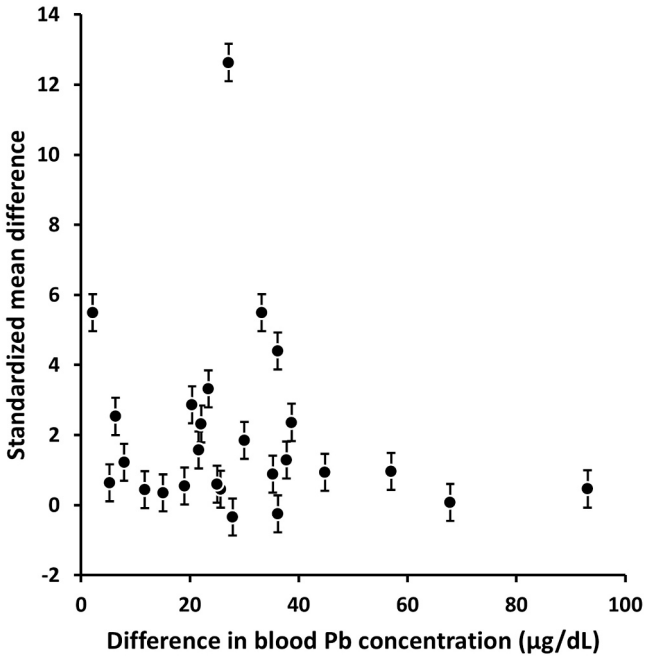

Fig. 3. Relationship difference between environmental (n = 2) and occupational (n = 24) lead exposure and DNA strand breaks in leukocytes. Each symbol is one study (mean and 95 % confidence interval (CI)). There is no difference between studies that are included in this analysis (standardized mean difference (SMD) = 1.98, 95 % CI: 1.34, 2.62, N_{study} = 26, $N_{subjects}$ = 3248) and other studies that are not included in the graph (SMD = 2.04, 95 % CI: 1.02, 3.05, N_{study} = 9, $N_{subjects}$ = 1665). The results in the graph cannot be fitted to linear or polynomic regression lines (i.e. r^2-values are less than 0.05).

In general, sensitivity analysis of effect sizes is uncertain because of the low number of studies in each group (Table 6). However, groups with somewhat similar number of studies do not seem to differ substantially (i.e. low vs high risk of bias related to blinding, and low *vs* moderate risk of bias comet assay description).

3.2.5. *Summary*

Collectively, the meta-analysis of 14 studies shows a positive association between arsenic exposure and levels of DNA strand breaks. Depending on the type of analysis on this dataset, the SMD is 1.36 (95 % CI: 0.94, 1.77) and 1.12 (95 % CI: 0.37, 2.42) using either parametric or non-parametric estimate of the central tendency.

3.3. *Chromium [Cr] and welding fume*

We have included 26 studies with information on chromium exposure and/or welding fumes [24,27,32,39,40,45,52,57,59,74–90] (Table 3). Twenty out of the 26 studies are included in the meta-analysis. The studies in the meta-analysis have assessed DNA strand breaks in populations of chromium-exposed subjects [24,57,75,78–81,83,84] and/or welders [32,39,52,59,74,77,82,85–88].

3.3.1. *Generalizability*

A total of 24 out of the 26 studies have reported positive associations between exposure to chromium/welding fume and DNA strand breaks. There is a slightly higher proportion of studies with positive results in the meta-analysis (100 %, 20 out of 20 studies) as compared to the studies that have not been included in the meta-analysis (67 %, 4 out of 6 studies, Z-value = 1.30, P > 0.05) (Supplementary Table S8).

3.3.2. *Meta-analysis*

The meta-analysis shows a SMD of 2.03 (95 % CI: 1.48, 2.57) (Fig. 7). Using non-parametric analysis to calculate the central tendency

Fig. 4. Risk of comet assay measurement bias and exposure misclassification (traffic light plot) in studies on environmental (n = 2), occupational (n = 32) and mixed environmental/occupational (n = 1) lead exposure.

produces a slightly lower effect size (SMD_{median} = 1.48, 95 % CI: 0.71, 3.52).

3.3.3. *Subgroup analysis*

There does not appear to be a difference in effect sizes between studies on chromium in welding fume (SMD = 2.24, 95 % CI: 1.38, 3.11) and studies on chromium exposure in other settings (SMD = 1.77, 95 % CI: 1.04, 2.51). Subgroup analysis by locations is uncertain because most

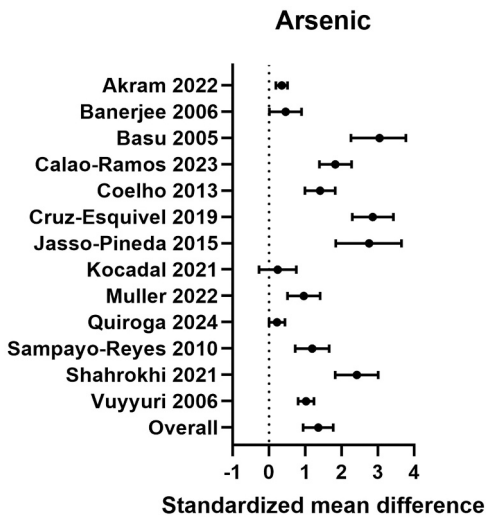

Fig. 5. Effect sizes in studies on environmental (n = 9), occupational (n = 4) and mixed environmental/occupational (n = 1) exposure to arsenic. Symbols and lines are mean and 95 % confidence intervals. Effects are statistically significant if they do not cross the vertical line at x = 0. The forest plot has been reproduced for graphical purposes. Original Forest and Funnel plots are included in Supplementary Figs. S3 and S4, respectively.

studies originate from middle-income countries (16 out of 20 studies). Studies from middle-income countries have slightly higher effect size (SMD = 2.07, 95 % CI: 1.45, 2.69) than have studies from high-income countries (SMD = 1.87, 95 % CI: 0.47, 3.27).

3.3.4. *Sensitivity analysis*

Fig. 8 shows the results of assessment of risk of comet assay measurement bias and exposure misclassification. The overall results indicate that most of studies have moderate risk of bias related to the comet assay procedure, including insufficient information on blinding (70 %, 14 out of 20 studies) and assay controls (95 %, 19 out of 20 studies). However, most of the studies have low risk of exposure misclassification (85 %, 17 out of 20 studies). Overall, most of the studies have moderate risk of bias (80 %, 16 out of 20 studies). In general, sensitivity analysis of effect sizes is uncertain because of uneven number of the studies between groups (Table 6).

3.3.5. *Summary*

Collectively, the meta-analysis of 20 studies shows a positive association between chromium or welding fume exposure and levels of DNA strand breaks. Depending on the type of analysis, the SMD is 2.03 (95 % CI: 1.48, 2.57) or 1.48 (95 % CI: 0.71, 3.52) using either parametric or non-parametric estimation of the central tendency.

3.4. *Other heavy metals*

A few studies have assessed occupational exposure to heavy metals

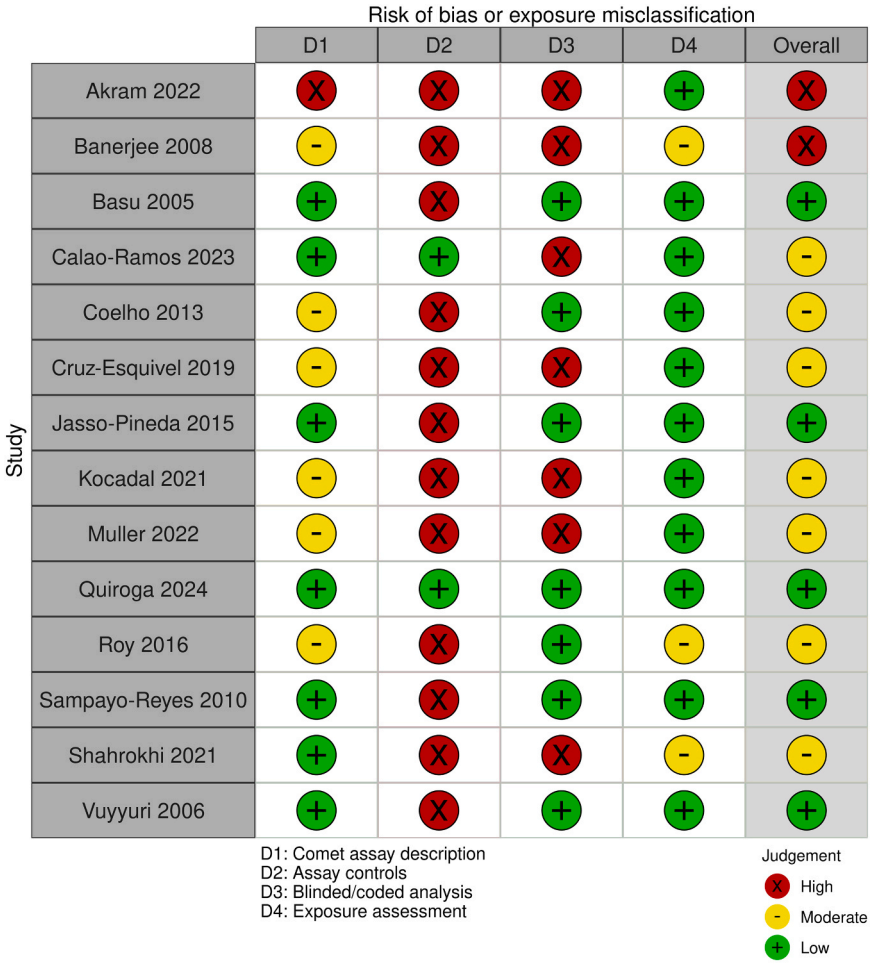

Fig. 6. Risk of comet assay measurement bias and exposure misclassification (traffic light plot) in studies on environmental (n = 9), occupational (n = 4) and mixed environmental/occupational (n = 1) arsenic exposure.

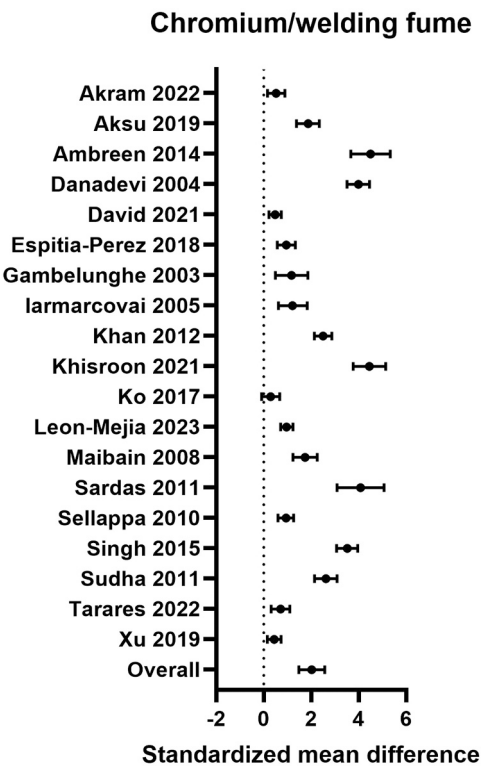

Fig. 7. Effect sizes in studies on environmental and occupational exposure to chromium (n = 9) or welding fumes (n = 11). Symbols and lines are mean and 95 % confidence intervals. Effects are statistically significant if they do not cross the vertical line at x = 0. The forest plot has been reproduced for graphical purposes. Original Forest and Funnel plots are included in Supplementary Figs. S5 and S6, respectively.

other than lead, arsenic and chromium (Table 4). Studies on occupational exposure to antimony [91] and cobalt [92] have shown null effects on DNA strand breaks. However, genotoxic effects have been seen in studies on copper smelters [93], indium-exposed workers [94], iron-rich fumes in steel company workers [95], and subjects living near mining sites [96,97]. Six of the seven studies have reported DNA strand break results, which can be assessed by meta-analysis. This shows a modest effect size (SMD = 0.81, 95 % CI: 0.45, 1.18; Fig. 9, Forest and Funnel plots are shown in Supplementary Figure S7 and S8). There are too few studies to assess risk of bias related to experimental procedures bias and exposure misclassification (Fig. 10).

4. Discussion

The meta-analyses in the present systematic review show that exposures to lead (SMD = 1.99), arsenic (SMD = 1.36), chromium/welding fumes (SMD = 2.03) and other heavy metals (SMD = 0.81) are associated with elevated levels of DNA strand breaks. The effect sizes are similar, which may be because the exposure situations involve complex mixtures, even in those studies that may only have measured one type of heavy metal. The combined data, encompassing 66 studies and 9020 subjects show an effect size of 1.74 (95 % CI: 1.43, 2.05). As highlighted in the results section, there are too few studies for subgroup and sensitivity analysis in each dataset. Therefore, we have merged all datasets on heavy metal exposures to obtain more robust estimates of central tendencies. The effects are discussed in the same stepwise manner as in the results section. Subsequently, we highlight results from previous meta-analyses on DNA strand breaks in human biomonitoring and provide general comments on the evidence of carcinogenicity of heavy metals.

4.1. Generalizability of meta-analysis results

The generalizability of the results in meta-analyses has been assessed by comparing the proportion of statistically significant associations to the results in the dataset of all included studies in the review. Each of the four datasets on lead, arsenic, chromium/welding fume and other heavy metal exposure have relatively few null effect studies. Thus, we have pooled the four datasets to increase the statistical power. This shows a slightly higher proportion of studies with positive associations in the meta-analysis (91 % positive studies; 61 out of 68) as compared to the proportion in the excluded studies (70 % positive studies; 14 out of 20 studies, Z = 1.61, P > 0.05, Supplementary Table S9). A slight overestimation of DNA strand break generation by heavy metals in the meta-analyses cannot be ruled out.

4.2. Subgroup analyses

Individual datasets on lead and arsenic do not indicate that studies with assessment of one type of heavy metal have markedly different effect size as compared to studies with assessment of several heavy metals (Table 6). Studies on chromium-exposed populations and welders have similar effect sizes too. In as much as lead, arsenic and chromium/welding fume have similar genotoxic potency, it is interesting to note that occupational exposure studies (mainly lead and chromium/welding fume) might have slightly higher effect size than environmental exposure studies (mainly arsenic). This is in agreement with the notion that exposure levels tend to be higher in occupational than environmental settings.

There are insufficient studies in the separate datasets to assess differences in effect sizes between high- and middle-income countries. Thus, for this subgroup analysis we have pooled studies from different heavy metal exposures and excluded replicates (i.e. each study is only included once in the analysis). This shows that studies from middle-income countries have higher effect size (2.00, 95 % CI: 1.64, 2.37, n = 51) than do studies from high-income countries (0.84, 95 % CI: 0.41, 1.26, n = 15).

It is possible that the higher effect size in middle-income countries is due to the level of exposure. High-income countries may have less exposure due to the type of work that exposes subjects to heavy metals. However, it is also possible that stricter control of especially occupational exposures is a key factor for the lower effect size in high-income countries.

4.3. Sensitivity analyses

The assessment of comet assay measurement bias indicates a substantial uncertainty in the quality of the experiments as 89 % (59 out of 66 studies) and 70 % (46 studies) have not reported the use of assay controls and blinded analysis of samples, respectively. The papers with information on assay controls tend to have been published recently. Four out of 6 studies have been published between 2022 and 2024 [31,63,68,88], whereas two papers were published in 2011 [29] and 2003 [42]. In addition, the distribution of studies according to the comet assay description indicates that 38 (58 %), 18 (22 %) and 13 (20 %) of the studies have low, moderate and high risk of bias, respectively. Lastly, it should be emphasized that most studies have low risk of exposure misclassification as they have measured metals in biological samples (85 % of the studies in the meta-analysis, 56 out of 66 studies). The risk of comet assay measurement bias and exposure misclassification is not related to studies being done in high- and middle-income countries (Supplementary Table S10).

We have pooled individual datasets on different types of heavy metals to obtain robust effect sizes (Table 7). Stratification of studies according to risk of comet assay measurement bias indicates an incremental increase in effect size as the risk of bias increases from low (1.39, 95 % CI: 1.09, 1.70), to moderate (1.96, 95 % CI: 1.20, 2.72) and high

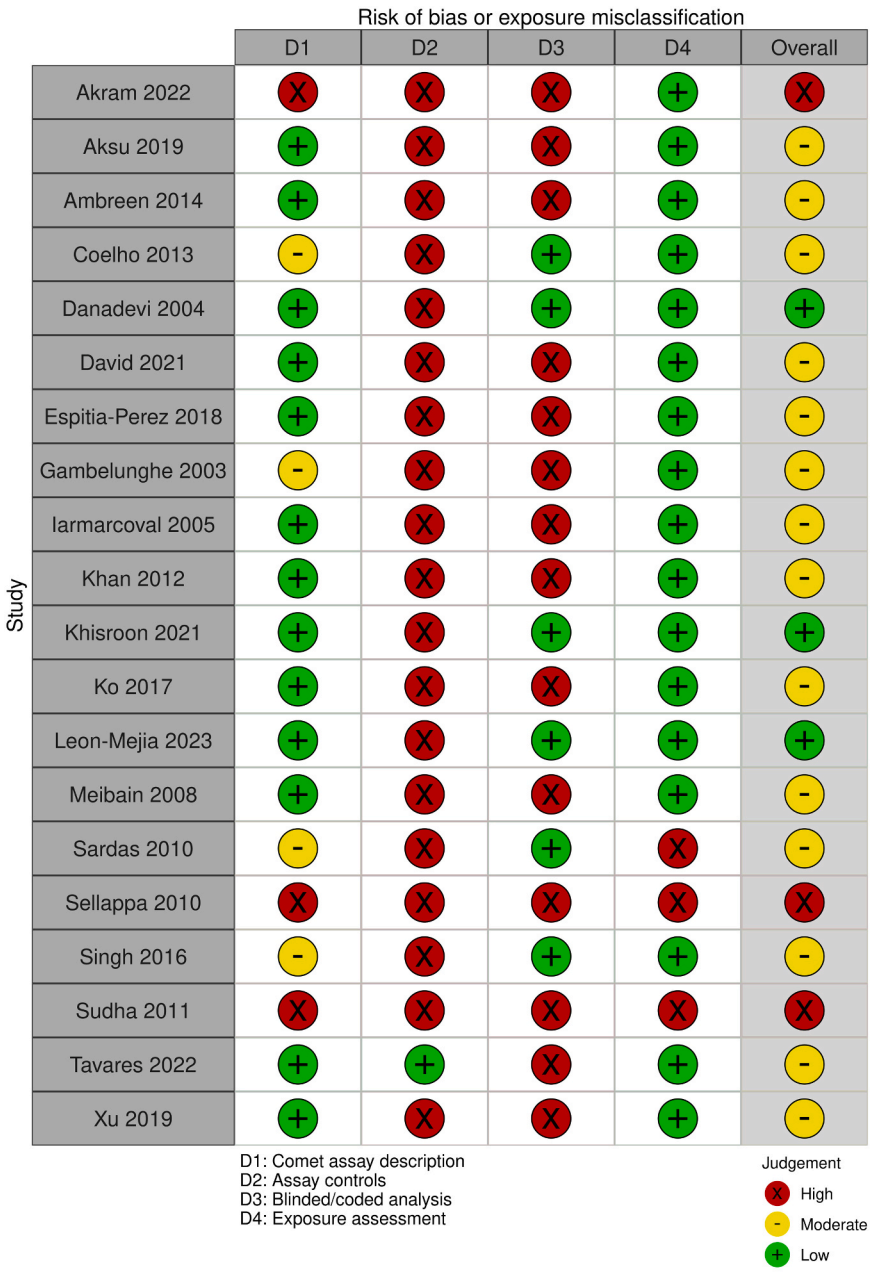

Fig. 8. Risk of comet assay measurement bias and exposure misclassification (traffic light plot) in studies on chromium (n = 9) and welding fume (n = 11) exposure.

risk (2.51, 95 % CI: 1.54, 3.48). There is also a higher effect size for studies without inclusion of assay controls (1.82, 95 % CI: 1.50, 2.14) as compared to studies with assay controls (0.90, 95 % CI: 0.25, 1.55). On the contrary, studies with blinded/coded analysis have higher effect size (2.59, 95 % CI: 1.88, 3.30) than have studies without reporting blinded analysis (1.38, 95 % CI: 1.08, 2.05). The effect size does not appear to be different between studies with low (1.74, 95 % CI: 1.41, 2.07) and moderate/high risk of exposure misclassification (1.66, 95 % CI: 0.99, 2.33).

There appears to have been a change of habit to report results on assay controls (or maybe including assay controls in experiments) in human biomonitoring studies. This may be due to increased awareness of the importance of demonstrating reliable results. The importance of reporting results on assay controls is emphasized in summary notes from comet assay workshops, description of experimental protocols and recommendations on reporting procedures and results [2,17,98]. Ensuring a reliable determination of DNA strand breaks by blinded analysis is pivotal for the interpretation of results, irrespective of the main finding of the studies being statistically significant or not. The dataset on heavy metal exposures shows that too many studies do not report whether investigators were blinded to the identity of samples or slides in the comet assay.

4.4. Previous meta-analyses

A few earlier studies have assessed associations between exposure to heavy metals and DNA strand breaks by meta-analyses of human biomonitoring studies. Nagaraju and co-authors have reviewed genotoxic effects of lead and cadmium exposure in human biomonitoring studies [99,100]. Most relevant to the present review is the meta-analysis on lead exposure. The systematic review included 16 biomonitoring studies that had assessed comet assay results in lead exposed subjects [100]. That meta-analysis too showed an increase in DNA damage measured by the comet assay in exposed workers. However, there are substantial

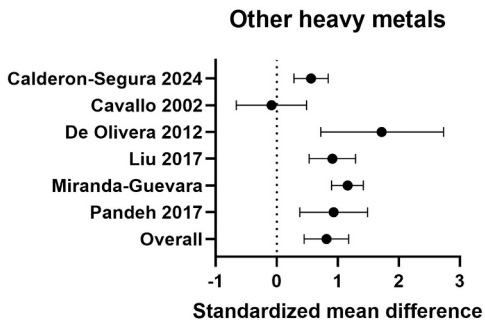

Fig. 9. Effect sizes in studies on environmental and occupational exposure to other heavy metals. Symbols and lines are mean and 95 % confidence intervals (n = 6). Effects are statistically significant if they do not cross the vertical line at x = 0. The forest plot has been reproduced for graphical purposes. Original Forest and Funnel plots are included in Supplementary Figs. S5 and S6, respectively.

methodological differences between this and our meta-analysis. In the review by Nagarujo and co-authors, one included study had barely any gradient of lead exposure between exposed workers and controls [74], one study used the Fpg-linked comet assay [101], and incorrect values were abstracted from one paper [102]. Moreover, the literature search missed 12 studies, which we have included in our review [20,22,23,25,26,44,47,51,53–55,58]. It is surprising that the systematic review should fail to find pioneer studies such as Danadevi et al., 2003 [25], which is cited in a number of the identified papers [21,30,33,37,38,46,48,101,102]. Lastly, the meta-analysis is based on mean differences, which is not meaningful for primary comet assay descriptors because they depend on the assay conditions (e.g. longer electrophoresis time is positively related to longer comets). We believe that our meta-analysis is much more complete, providing an accurate picture of the effect of lead exposure on DNA strand breaks in human leukocytes.

One meta-analysis on arsenic exposure has specifically assessed DNA damage by the comet assay in human biomonitoring studies [103]. The last literature search was done in 2019. Overall, the meta-analysis included 13 articles, including four papers in Chinese journals that have not been available to us. On the other hand, our review includes more studies because the search period ends in 2024. Contrary to our meta-analysis, the authors used mean ratio between exposed and controls, and the meta-analysis was done for separate comet descriptors. Importantly, this meta-analysis and ours have used different methodology, but both analyses show that exposure to arsenic is associated with increased level of DNA strand breaks in leukocytes from humans.

4.5. *Mechanism of action and evidence of carcinogenicity*

Our meta-analyses show that exposure to various heavy metals is associated with increased levels of DNA strand breaks in human leukocytes. However, it does not address how these lesions occur or whether the exposures are associated with increased risk of cancer. The International Agency for Research on Cancer (IARC) has evaluated the scientific evidence for carcinogenicity linked to exposure to several heavy metals. The IARC monographs on heavy metals cover a period of 15 years, which have aligned with structures in 1991, 2006 and 2019 preambles. Especially evidence from mechanistic studies has gained increasingly more weight in the overall evaluation of carcinogenicity to humans. This has been formalized as ten key characteristics (KCs) of carcinogens in the 2019 preamble [104]. Below we summarize/interpret the mechanistic evidence in terms of the contemporary KCs, together with the IARC evaluation of the evidence of cancer to humans.

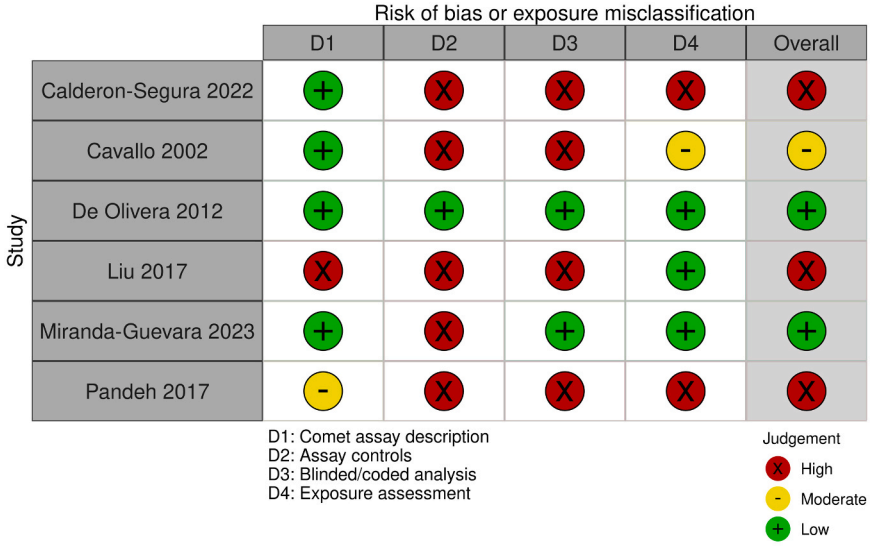

Fig. 10. Risk of comet assay measurement bias and exposure misclassification (traffic light plot) in studies on exposure to other heavy metals (n = 6).

Table 7
Effect size of all studies according to risk of comet assay measurement bias and exposure misclassification (mean, 95 % CI).

Item	Low risk (green)	Moderate risk (yellow)	High risk (red)
Comet assay description	**1.39 (1.09, 1.70)**	**1.96 (1.20, 2.72)**	**2.51 (1.54, 3.48)**
Assay control	**0.90 (0.25, 1.55)**		**1.82 (1.50, 2.14)**
Blinding/coding	**2.59 (1.88, 3.30)**		**1.38 (1.08, 2.05)**
Exposure misclassification	**1.74 (1.41, 2.07)**	**1.66 (0.99, 2.33)**	
Overall	**1.72 (1.09, 2.35)**	**1.85 (1.43, 2.27)**	**1.29 (0.70, 1.88)**

(i) Lead compounds were evaluated in 2004, categorizing inorganic and organic forms of lead in Group 2A and 3, respectively [105]. The classification is based on limited and sufficient evidence of carcinogenicity in humans and animals, respectively. Cancer of the lung and stomach have been the main outcomes in epidemiological studies. In the evaluation, IARC highlighted a mechanism of indirect generation of DNA damage by increased reactive oxygen radical production (equivalent to KC "Induce oxidative stress" in the current 2019 preamble) and interaction with proteins, including DNA repair proteins (equivalent to KC "Alters DNA repair or causes genomic instability").

(ii) Arsenic (inorganic form) was evaluated to be in Group 1, causing lung, bladder and skin cancer, and moreover showing positive association with kidney, liver and prostate cancer [106]. IARC noted that arsenic is weakly genotoxic by direct DNA damage, whereas it causes inhibition of enzymes, including DNA repair proteins. The latter is considered to cause genomic instability (equivalent to KC "Affects DNA repair and induces genomic instability"). This is partly mediated by increased reactive oxygen species production, oxidative stress and oxidative damage to DNA (equivalent to KCs "Induce oxidative stress" and "Is genotoxic").

(iii) Chromium compounds causes lung cancer (IARC Group 1), with mechanisms on genotoxicity, oxidative stress and cell transformation (similar to KC "cell proliferation/cell death") [106]. The IARC monograph on welding fumes has been produced close to the implementation of the preamble from 2019 and it has a somewhat contemporary structure and wording. Exposure to welding fumes is associated with lung cancer, and there is a positive association between exposure and kidney cancer (Group 1) [107]. Nevertheless, the studies show some differences in composition as well as differences over time, including area-specific differences due to heterogeneity in the implementation of protective measures. Main metal components are chromium, nickel and manganese. The experimental evidence ranges from strong (chronic inflammation and immunosuppressive effect), to moderate (genotoxicity, oxidative stress and cell proliferation/cell death) to weak (modulate receptor-mediated effects) [107].

In general, exposure to the heavy metals in the present systematic review - lead, arsenic and chromium/welding fume – appears to be associated with tumours at the first point of contact in the human body (e.g. lungs) and secondary organs (e.g. kidney). Mechanistic studies indicate that genotoxicity occurs by indirect mechanism of action through induction of oxidative stress and/or inhibition of DNA repair. Oxidative stress is a condition where the content of oxidants exceeds the capacity of the antioxidant defence system, which leads to cellular damage such as breakage of DNA strands [1]. Chromium, like certain other transition metals, can increase the production of reactive oxygen species. Arsenic, cadmium and lead tend to affect the capacity of enzymes in the antioxidant defence system, whereby reactive oxygen species are not removed. By a similar mechanism, arsenic, cadmium and lead may inhibit the activity of DNA repair proteins, which may stall the repair process at stages between incision and ligation of DNA strands.

4.6. Limitations

The comet assay has certain limitations that affect both inter-laboratory comparison of results and predictive value of statistically increased DNA strand breaks for disease outcomes. These limitations pertain to all biomonitoring studies on comet assay results and meta-analyses of comet assay results from biomonitoring studies in different laboratories. The limitations are summarized below:

(i) Unfortunately, researchers use different comet assay protocols, and they report different comet descriptors. The meta-analysis, using SMD, is a valid procedure for results in different metrics or methods. However, it is based on assumption that the mean and variability in DNA migration values can be compared between studies. Certain ring trials have assessed the variation in DNA migration in samples that have been produced in one laboratory and distributed to other laboratories. These ring studies have demonstrated a large variation in both levels of comet descriptors and effect sizes, even though the samples had the same level of DNA strand breaks [108,109]. Reporting of comet assay results as absolute value, such as lesions per million base pair, would have made it possible to calculate unstandardized mean differences.

(ii) There is heterogeneity between studies on the control for confounding factors. Many studies control effect of confounders by restriction criteria or matching. It should also be noted that most of the studies have co-exposures, which may or may not have been assessed in the study or included as confounder in statistical analyses. It is likely that the difference in controlling for confounding causes heterogeneity between studies in the meta-analyses. Publication bias is another likely source of heterogeneity between studies.

(iii) A general limitation of comet assay results is the paucity of studies on the predictive value of high levels of DNA strand breaks. There are several studies showing that DNA damage in patients with non-communicable and high-prevalence diseases have higher levels of DNA strand breaks than disease-free controls [3,110]. However, there is still only one prospective study that has shown a positive association between high levels of DNA strand breaks and increased risk of mortality [5]. This makes it challenging to convert comet assay results from occupational and environmental monitoring programs to public health regulations.

4.7. Overall summary

This systematic review of human biomonitoring studies with comet assay results in subjects with lead, arsenic and chromium/welding fume exposure shows increased levels of DNA strand breaks in leukocytes. An overall assessment of effect sizes suggests that studies on subjects exposed to lead and chromium/welding fumes have found slightly higher effect sizes as compared to studies on arsenic. A lower genotoxic effect of arsenic might be due to exposure situation (mainly environmental exposure) and exposure route (mainly oral exposure compared to inhalation in occupational exposure studies). More pronounced is a difference between effect sizes in high- and middle-income countries, which might be due to high exposures in the latter. Further research is necessary to fully understand the potential of some metals (alone or combined with other metals and substances) to generate DNA damage in human leukocytes.

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. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mrrev.2025.108567.

Data availability

Data will be made available on request.

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