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Human semen quality and environmental and occupational exposure to pollutants: A systematic review

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Parole chiave: Fertilità umana maschile, liquido seminale, inquinamento ambientale, esposizione occupazionale, biomonitoraggio umano

Abstract

Background. *The aim of the present systematic review was to evaluate the correlation between the exposure to environmental and/or occupational pollutants and possible alteration of semen quality, focalizing the attention on the studies performed using a biomonitoring approach.*
Methods. *The review was conducted from inception to May 11 2023, according to the PRISMA Statement 2020 and using the following databases: Scopus, Pubmed and Web of Science. The protocol was registered on PROSPERO (CRD42023405607). Studies were considered eligible if they reported data about the association between exposure to environmental pollutants and alteration of semen quality using human biomonitoring. The quality assessment was carried out by the use of the Newcastle-Ottawa Quality Assessment Scale.*
Results. *In total, 21 articles were included, conducted in several countries. The main matrices used for biomonitoring were urine and blood and the most sought-after contaminants were bisphenols, phthalates, pesticides, polychlorinated biphenyls, polycyclic aromatic hydrocarbons, heavy metals and other inorganic trace elements. The results of the studies demonstrated a significant positive correlation between the increase of the pollutants' levels in the biological matrices examined and some alterations of the semen quality indicators, such as a decrease in motility, concentration and morphology of the spermatozoa.*
Conclusions. *Male fertility can be negatively affected by the exposure to environmental and/or occupational pollutants. Human biomonitoring programs may be considered a useful tool for specific surveillance programs devoted to early highlight subjects who are more exposed to environmental pollutants in order to reduce risk exposure.*

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Introduction

Over recent decades, several studies demonstrated a rapid decline in semen quality, including a reduction in semen count, volume, motility, and morphology (1). This decline often results in male infertility, considered a public health top priority because it can lead psychological distress, high economic costs and, in the future, an excessive generational imbalance. Unfortunately, in about 40% of the subjects, after an entire diagnostic check, the etiology of infertility remains hidden (2), suggesting the presence of one or more unknown risk factors (3). Scientific evidence has been highlighted that male fertility can be negatively influenced by sexually transmitted infections (4), various types of pathologies and various factors such as obesity (5) or excessive thinness (6), sedentary lifestyle or excessive physical activity (7), smoking habits (8) and exposure to chemical pollutants in living and working environments (3, 9). As for the latter risk factor, epidemiological and experimental studies recognize that the exposure to environmental and occupational pollution can be a risk factor for male infertility (3, 10). For example, healthy workers accidentally exposed to high concentrations of pollutants for short periods presented a reduction in concentration, motility and morphology of the spermatozoa, and sperm genetic anomalies compared to the general population (10). More strikingly, a very recent narrative review concluded that environmental pollutants have a significant adverse impact on semen quality (11).

Different assessing methods can be used for evaluating the exposure to contaminants present in environmental and occupational settings and for estimating potential negative effects on human health. In this context, one of the most appropriate approach is represented by human biomonitoring, which measures one or more chemicals or their metabolites or reaction products in human biological fluids, such as blood, urine, saliva, hair, breast milk, sweat, and human semen, evaluating all the pathways of exposure (ingestion, inhalation or contact) (12). This method can assess the internal dose, giving an estimate of the biologically active body burden of the chemicals and can contribute to understanding the biochemical or cellular effect whose alteration may achieve adverse health effects (13). Nowadays, there are new analytical tools that first identify and measure biomarkers, through no-invasive and cost-effective spending, quantitative endpoint, and intermediate pathways of biological tissue and fluids to identify. This is of particular importance when the altered exposure can be measured before manifesting clinical damage, early signs of functional or structural modification. In order to highlight the importance of human biomonitoring as a surveillance tool, notice that human biomonitoring is a pillar for current European strategies dedicated to health risk assessment (10).

The aim of the present systematic review was to examine the scientific literature on the correlation between environmental and/or occupational exposure to pollutants and the alteration of human semen quality, focalizing the attention on the studies performed on humans, considering both general population and workers occupationally exposed and using a human biomonitoring approach.

Methods

1. Selection protocol and search strategy

The systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology (14) and the protocol was registered on PROSPERO with the following ID: CRD42023405607.

The literature search was conducted in three different databases (PubMed, Scopus, and Web of Science) from inception to May

11 2023 using the following keywords: “Biomonitoring”; “human semen quality”; “environmental pollution” using the Boolean Operators “AND”, “OR”.

2. Study selection

Titles and abstracts acquired from each database were transferred to the reference software Zotero systematic review manager for the relevance-assessment process. The articles were first screened for title and abstract and secondly from the reading of the full text. The screening was conducted independently by four authors (LC, IP, GDA, FG). Then, full texts were read independently by the same four authors (LC, IP, GDA, FG) with a later discussion about their inclusion in the review and disagreements were achieved by consensus among the authors.

3. Criteria for study inclusion

Studies were considered eligible if they reported data about the association between exposure to environmental pollutants and alteration of semen quality, using human biomonitoring. Only articles presenting original data deriving from observational studies were considered eligible, while clinical trials, experimental studies, reviews, meta-analysis, case studies, proceedings, editorials, commentary studies, and any other types of studies were excluded. The references of the included articles were examined to identify further eligible articles in their references. We included only articles published in English or Italian language.

4. Data extraction and quality assessment

Author, year, country, types of pollutants, the biological matrices studied and the method used for analytical determinations were collected from all studies. Besides, specific seminal fluid outcomes (motility, concentration, morphology of spermatozoa, etc) were also considered.

The quality assessment of each included article was carried out by the use of the Newcastle-Ottawa Quality Assessment Scale, adapted from cohort and case-control studies to perform a quality assessment for cross-sectional studies.

Results and discussion

The search yielded 82 articles and, after eliminating the duplicates, the remaining 69 articles were reduced to 37 by reading the title and abstract. After reading the full-text, 17 other articles were excluded, 14 because they did not involve observational studies and three because they involved animal studies. Besides, one article found from the citations of the revised articles were added. Finally, 21 articles were included in the review.

Figure 1 shows the PRISMA flow chart.

Table 1 reports a summary of the data extracted from the included studies.

The studies were conducted between the years 2000 and 2023 in various countries such as Italy (15, 16), United States (17-24), Taiwan (25), China (26-28), Poland (29), France (30), Spain (31), Turkey (32), Denmark (33), Ukraine (34), Australia (35).

Various settings were evaluated by the included studies, considering both environmental (15-20, 24-26, 28, 29, 31) or occupational (21-23, 27, 30, 32-35) scenarios. Subjects studied were, in all cases, apparently healthy males with altered semen quality.

Each included study examined many possible known causes that negatively influenced semen quality, such as chronic diseases (diabetes, hyper-hypothyroidism or other systemic diseases), prostatitis, varicocele, fever, infection, medications, exposure to X rays, history of drug abuse. Information on these causes were always obtained by questionnaires and physical examinations, including the urogenital evaluation (testis volume and trans-rectal

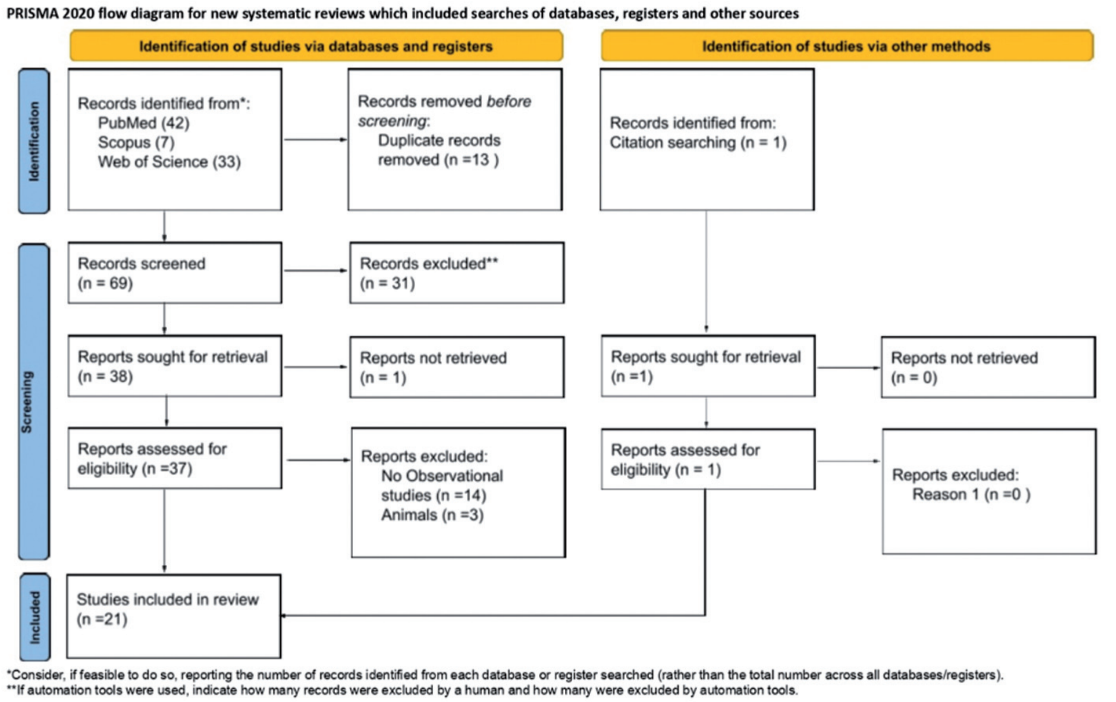

Figure 1 - Flowchart of the study selection process.

prostate evaluation). After the exclusion of all investigated causes of infertility, the influence of exposure to environmental and/ or occupational pollutants on semen quality was evaluated. The exposure to pollutants was always examined by searching for the studied compounds and/or for their metabolites in biological matrices such as urine, blood or semen. Both organic and inorganic compounds were studied. In particular, the instruments mainly used for the research of inorganic pollutants were AAS (Atomic Absorption Spectroscopy) (31, 33), ASV (Anodic Stripping Voltammetry) (31), ICP-OES (Inductively Coupled Plasma-Optical Emission Spectroscopy) (16, 32), ICP-MS (Inductively Coupled Plasma-Mass Spectrometry) (22-24, 32), IV (Inversion voltammetry) (34) and for organic pollutants were Gas Chromatography- Electron Capture Detector (GC-EDC) (30), Gas Chromatography-Flame Ionization Detector (GC-FID) (27), Gas Chromatography-Mass Spectrometry (GC-MS) (29, 35), High Performance Liquid Chromatography-Mass Spectrometry (HPLC-MS) (18), High Performance Liquid Chromatography-Tandem Mass Spectrometry (HPLC-MS/ MS) (17, 19, 24), High Performance Liquid Chromatography- Ultraviolet (HPLC-UV) (26), High Performance Liquid Chromatography with a fluorescent detector (15, 21, 28, 29, 35), High Resolution Mass Spectrometry (HRMS) (20), Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) (29, 35).

Specific compounds considered by the included studies were bisphenol A

Table 1 - Summary characteristics of the studies included in the review

Author, Year, Country	Pollutants	Exposure	Matrix	Analytical technique	Seminal fluid outcome	Quality of the study
Shih et al. 2000 China (27)	Ethylene glycol monomethyl ether	Occupational	Urine	GC-FID	Lower pH of semen	good
Bonde et al., 2002 Denmark (33)	Pb	Occupational	Semen	AAS	Decreased semen volume and total sperm count	good
McDiarmid et al. 2006 USA (22)	Uranium	Occupational	Urine	ICP-MS	Azoospermia	good
Zhang et al. 2006 China (26)	Phthalates	Environmental	Semen	HPLC-UV	Decreased of sperm motility	good
Multigner et al. 2007 France (30)	Glycol ethers	Occupational	Urine	GC-ECD	Lower sperm concentration, total sperm count, percentage of rapid progressive sperm, and percentage of morphologically normal sperm	good
Perry et al. 2007 USA (19)	Insecticide (Organophosphates, Pyrethroids) Herbicide	Environmental	Urine	HPLC-MS/MS	Decrease of sperm concentration	fair
Wirth et al. 2008 USA (18)	Phtalates	Environmental	Urine	HPLC-MS	Low sperm concentration and morphology	good
Duydu et al. 2011 Turkey (32)	Boron	Occupational	Blood, urine, semen	ICP-MS and ICP-OES	Negative connection with sperm concentration and motility parameters	good
Mendiola et al.2011 Spain (31)	Fe, Cd, Hg	Environmental	Blood and semen	ASV and AAS	Increased percentage of immotile sperms and lead and cadmium concentration in seminal plasma	good
Jeng et al. 2012 USA (21)	Polycyclic aromatic hydrocarbons	Occupational	Urine	HPLC with a fluorescent detector	Decreased normal morphology of sperm	good
Goldstone et al. 2015 USA (17)	Bisphenol A	Environmental	Urine	HPLC-MS/MS	Lower DNA fragmentation	good
Li et al. 2015 Taiwan (25)	Pb, Cd, Cr, Se, Fe, Cu, and Zn	Environmental	Blood	ICP-MS	Increased percent of immotile sperms	good

Louis et al. 2015 USA (24)	Benzophenone-type ultraviolet (UV) filter	Environmental	Urine and blood	LC-MS/MS	Decreased sperm concentration, percentage of straight and linear movement, percentage of other tail anomalies, and an increased number of immature sperm	good
Mumford et al. 2015 USA (20)	Persistent organic pollutants	Environmental	Serum	HRMS	Increased sperm concentration and elongation factor, percentages of abnormal morphology, decreased sperm head length, percent round	good
Bergamo et al. 2016 Italy (16)	Al, As, Ba, Be Ca, Cd, Co, Cr, Cu, Fe, K, Li, Mg, Mn, Mo, Na, Ni, Pb, Sb, Se, Sr, Zn	Environmental	Blood and semen	ICP-OES	Decreased motility and increased sperm DNA damage	good
Jurewicz et al. 2016 Poland (29)	Phthalates, pyrethroids, polycyclic aromatic hydrocarbons	Environmental	Urine, saliva	HPLC with a fluorescent detector, GC-MS, LC-MS/MS	Lower Y:X sperm chromosome ratio among men	good
Onul N. et al. 2018 Ukraine (34)	Pb	Occupational	Blood and semen	Inversion voltammetry	Azoospermia, asthenozoospermia, oligozoospermia	good
Song et al. 2018 China (28)	Perfluoroalkyl acids	Environmental	Seminal fluid	HPLC-MS/MS	Lower sperm concentration and motility	good
McDiarmid et al. 2019 USA (23)	Uranium	Occupational	Urine, blood, and semen	ICP-MS	Higher U concentrations in all fluid	good
Caporossi et al. 2020 Italy (15)	Phtalates and Bisphenol A	Environmental	Urine	HPLC-MS/MS	Sperm genetic anomalies and lower DNA fragmentation. Decrease of spermatozoa's motility	good
Engelsman et al. 2023 Australia (35)	Polycyclic aromatic hydrocarbons, metals, phthalates, organophosphate esters, polybromodiphenyl ethers	Occupational	Urine, blood	LC-ICP/MS, LC-MS/MS, GC-MS, HPLC with a fluorescent detection	No alteration of the seminal parameters	Good

AAS = Atomic Absorption Spectroscopy; ASV = Anodic Stripping Voltammetry; GC-EDC = Gas Chromatography- Electron Capture Detector; GC-FID = Gas Chromatography-Flame Ionization Detector; GC-MS = Gas Chromatography-Mass Spectrometry; HPLC-MS = High Performance Liquid Chromatography-Mass Spectrometry; HPLC-MS/MS = High Performance Liquid Chromatography-Tandem Mass Spectrometry; HPLC-UV = High Performance Liquid Chromatography-Ultraviolet; HPLC with a fluorescent detector = High Performance Liquid Chromatography with a fluorescent detector; HRMS = High Resolution Mass Spectrometry; ICP-MS = Inductively Coupled Plasma-Mass Spectrometry; ICP-OES = Inductively Coupled Plasma-Optical Emission Spectroscopy; LC-MS/MS = Liquid Chromatography-Tandem Mass Spectrometry

(15, 17), phthalates (15, 18, 26, 29, 35), insecticides (19), herbicides (19), persistent organic pollutants (19), pyrethroids (29), polycyclic aromatic hydrocarbons (21, 35), organophosphate esters (35), polybromodiphenyl ethers (35), glycol ethers (30), ethylene glycol monomethyl ether (27), perfluoroalkyl acids (28), benzophenone-type ultraviolet filter (24), metals and other inorganic elements (Al, As, B, Ba, Be Ca, Cd, Co, Cr, Cu, Fe, K, Li, Mg, Mn, Mo, Na, Ni, Pb, Sb, Se, Sr, Zn, Hg, Se, U) (16, 22, 23, 25, 31-35). All these substances are well-known environmental contaminants and they can be present both in environmental matrices and/or in occupational settings. Thus, there are many occasion to be exposed: intake by inhalation, ingestion and, to a lesser extent, dermal contact from contaminated air, water and food.

The evaluation of the traditional indicators of seminal quality (vitality, motility and morphology of the spermatozoa) was performed in all cases by the use of a microscope, while the determination of spermatic DNA fragmentation in seminal fluid was performed using one of the following techniques: comet assay (single cell gel electrophoresis), TUNEL (terminal deoxyuridine nick end labeling assay), SCSA (Sperm Chromatin Structure Assay), and SCD (Sperm Chromatin Dispersion assay).

All the included studies demonstrated an association between the exposure to environmental and/or occupational exposure and the alteration of some indicators of semen quality, and such evidence should be considered robust because almost all studies had a good overall quality, except for one case in which the quality resulted fair (19). These findings can be attributed to the fact that some chemical factors can function as potential sources of damage to the testis and accessory glands and spermatogenesis dysfunction (3) and some others could interfere in the endocrine functions by simulating the activity of endogenous steroid hormones (36-41).

The present review has some limitations. Firstly, we did not conduct a meta-analysis of the results of the included studies because they were different in terms of exposure scenarios, type of pollutants, exposure assessment methodologies, and study design. Thus, statistical heterogeneity and publication bias were not assessed. Secondly, we included only articles published in English or Italian language, excluding a priori potentially useful results published in other languages. Finally, we considered just the studies that evaluated the exposure by the use of human biomonitoring and excluded those reported results obtained with environmental monitoring. However, it is well-known that human biomonitoring is the most appropriate way to perform an exposure assessment study.

Conclusions

The results demonstrated that male fertility can be negatively affected by the exposure to environmental and/or occupational pollutants. Further studies should be carried out to produce more robust scientific evidence and to understand the mechanisms underlying the association between exposure to pollutants and semen alterations. Besides, human biomonitoring programs may be considered a useful tool for specific periodic surveillance programs devoted to early highlight subjects who are more exposed to environmental pollutants in order to reduce risk exposure. It would be advisable to conduct studies to identify threshold levels below which there are no alterations in the quality of the semen and, consequently, to protect male fertility.

Riassunto

Qualità del seme umano ed esposizione ambientale e occupazionale ad inquinanti: una revisione sistematica

Premessa. Lo scopo della presente revisione sistematica è stato di valutare la correlazione tra l'esposizione a inquinanti in ambienti di vita e/o di lavoro e la possibile alterazione della qualità dello sperma, focalizzando l'attenzione sugli studi condotti utilizzando un approccio di biomonitoraggio.

Metodi. La revisione è stata condotta dalla data di inizio di ogni banca dati all'11 maggio 2023, secondo il PRISMA Statement 2020 e utilizzando le seguenti banche dati: Scopus, Pubmed e Web of Science. Il protocollo è stato registrato su PROSPERO (CRD42023405607). Sono stati considerati eleggibili gli studi che riportavano dati sull'associazione tra esposizione a inquinanti ambientali e alterazione della qualità dello sperma utilizzando il biomonitoraggio umano. La valutazione della qualità è stata effettuata utilizzando la scala Newcastle-Ottawa.

Risultati. In totale, sono stati inclusi 21 articoli, condotti in diversi Paesi. Le principali matrici utilizzate per il biomonitoraggio sono state l'urina e il sangue e i contaminanti più ricercati sono stati bisfenoli, ftalati, pesticidi, policlorobifenili, idrocarburi policiclici aromatici, metalli pesanti e altri elementi inorganici in traccia. I risultati degli studi hanno dimostrato una significativa correlazione positiva tra l'aumento dei livelli di inquinanti nelle matrici biologiche esaminate e alcune alterazioni degli indicatori di qualità dello sperma, come la diminuzione della motilità, della concentrazione e della morfologia degli spermatozoi.

Conclusioni. La fertilità maschile può essere influenzata negativamente dall'esposizione a inquinanti ambientali e/o professionali. I programmi di biomonitoraggio umano possono essere considerati uno strumento utile per specifici programmi di sorveglianza dedicati a evidenziare precocemente i soggetti più esposti agli inquinanti ambientali, al fine di ridurre l'esposizione a rischio.

References

1. Levine H, Jørgensen N, Martino-Andrade A, et al. Temporal trends in sperm count: a systematic review and meta-regression analysis of samples collected globally in the 20th and 21st centuries. Hum Reprod. 2023 Mar 1; **29**(2): 157-76. doi: 10.1093/humupd/dmac035.
2. Krausz C, Escamilla AR, Chianese C. Genetics of male infertility: from research to clinic. Reproduction. 2015 Nov; **150**(5): R159-74. doi: 10.1530/REP-15-0261.
3. Tang Q, Wu W, Zhang J, Fan R, Liu M. Environmental factors and male infertility. In: Meccariello R, Chianese R, Eds. (Internet). InTech; 2018. Available on: http://dx.doi.org/10.5772/68063.
4. Goulart ACX, Farnezi HCM, França JPBM, et al. HIV, HPV and Chlamydia trachomatis: impacts on male fertility. JBRA Assist Reprod. Oct 2020; **24**(4): 492-7. doi: 10.5935/1518-0557.20200020.
5. Palmer NO, Bakos HW, Fullston T, Lane M. Impact of obesity on male fertility, sperm function and molecular composition. Spermatogenesis. 2012 Oct 1; **2**(4): 253-63. doi: 10.4161/spmg.21362.
6. Guo D, Xu M, Zhou Q, Wu C, Ju R, Dai J. Is low body mass index a risk factor for semen quality? A PRISMA-compliant meta-analysis. Medicine (Baltimore). 2019 Aug; **98**(32): e16677. doi: 10.1097/MD.0000000000016677.
7. Ilacqua A, Izzo G, Emerenziani GP, Baldari C, Aversa A. Lifestyle and fertility: the influence of stress and quality of life on male fertility. Reprod Biol Endocrinol. 2018 Nov 26; **16**: 115. doi: 10.1186/s12958-018-0436-9.
8. Harlev A, Agarwal A, Gunes SO, Shetty A, Plessis SS. Smoking and male infertility: an evidence-based review. World J Mens Health. 2015 Dec; **33**(3): 143-60. doi: 10.5534/wjmh.2015.33.3.143. Epub 2015 Dec 23.
9. Deng Z, Chen F, Zhang M, et al. Association between air pollution and sperm quality: a systematic review and meta-analysis. Environ Pollut. 2016 Jan; **208**(Pt B): 663-9. doi: 10.1016/j.envpol.2015.10.044.
10. Montano L, Bergamo P, Andreassi MG, Lorenzetti S. The role of human semen as an early and reliable tool of environmental impact assessment on human health. In: Meccariello R, Chianese R, Eds. (Internet). InTech; 2018. Available on: http://dx.doi.org/10.5772/68063.
11. Kumar N, Singh AK. Impact of environmental factors on human semen quality and male fertility: a narrative review. Environ Sci Eur. 2022; **34**(1): 6. doi: 10.1186/s12302-021-00585-w.
12. World Health Organization (WHO). Regional Office for Europe‎. Human biomonitoring: facts and figures. World Health Organization. Regional Office for Europe; 2015. Available on:

https://apps.who.int/iris/handle/10665/164588.
13. Longo V, Forleo A, Giampetruzzi L, Siciliano P, Capone S. Human biomonitoring of environmental and occupational exposures by GC-MS and gas sensor systems: a systematic review. Int J Environ Res Public Health. 2021 Sep 29; **18**(19): 10236. doi: 10.3390/ijerph181910236.
14. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021 Mar 29; **372**: n160. doi: 10.1136/bmj.n160.
15. Caporossi L, Alteri A, Campo G, et al. Cross sectional study on exposure to BPA and phthalates and semen parameters in men attending a fertility center. Int J Environ Res Public Health. 2020 Jan 13; **17**(2): 489. doi: 10.3390/ijerph17020489.
16. Bergamo P, Volpe MG, Lorenzetti S, et al. Human semen as an early, sensitive biomarker of highly polluted living environment in healthy men: A pilot biomonitoring study on trace elements in blood and semen and their relationship with sperm quality and RedOx status. Reprod Toxicol. 2016 Dec; **66**: 1-9. doi: 10.1016/j.reprotox.2016.07.018. Epub 2016 Sep 1.
17. Goldstone AE, Alexandra E, Chen Z, Perry M, Kannan K, Louis GM. Urinary bisphenol A and semen quality, the LIFE Study. Reprod Toxicol. 2015 Jan; **51**: 7-13. doi: 10.1016/j.reprotox.2014.11.003. Epub 2014 Nov 11.
18. Wirth J, Rossano MG, Potter R, et al. A pilot study associating urinary concentrations of phthalate metabolites and semen quality. Syst Biol Reprod Med. 2008 May-Jun; **54**(3): 143-54. doi: 10.1080/19396360802055921.
19. Perry M J, Scott A V, Dana BB, Xiping X. Environmental pyrethroid and organophosphorus insecticide exposures and sperm concentration. Reprod Toxicol. 2007 Jan; **23**(1): 113-8. doi: 10.1016/j.reprotox.2006.08.005. Epub 2006 Sep 1.
20. Mumford SL, Sungduk K, Zhen C, Gore-Langton R E, Barr D B, Louis GM. Persistent organic pollutants and semen quality: The LIFE Study. Chemosphere. 2015 Sep; **135**: 427-35. doi: 10.1016/j.chemosphere.2014.11.015. Epub 2014 Nov 28.
21. Jeng HA, Pan CH, Lin WY, et al. Biomonitoring of polycyclic aromatic hydrocarbons from coke oven emissions and reproductive toxicity in nonsmoking workers. J Hazard Mater. 2013 Jan 15; **244-245**: 436-43. doi: 10.1016/j.jhazmat.2012.11.008. Epub 2012 Nov 26.
22. McDiarmid MA, Engelhardt SM, Oliver M, et al. Biological monitoring and surveillance results of gulf war i veterans exposed to depleted uranium. Int Arch Occup Environ Health. 2006 Jan; **79**(1): 11-21. doi: 10.1007/s00420-005-0006-2. Epub 2005 Aug 2.
23. McDiarmid MA, Gucer P, Centeno JA, Todorov T, Squibb KS. Semen uranium concentrations in depleted uranium exposed gulf war veterans: correlations with other body fluid matrices. Biol Trace Elem Res. 2019 Jul; **190**(1): 45-51. doi: 10.1007/s12011-018-1527-3. Epub 2018 Oct 6.
24. Louis GM, Chen Z, Kim S, Sapra KJ, Bae J, Kannan K. Urinary concentrations of benzophenone-type ultraviolet light filters and semen quality. Fertil Steril. 2015 Oct; **104**(4): 989-96. doi: 10.1016/j.fertnstert.2015.07.1129. Epub 2015 Aug 5.
25. Li CJ, Yeh CY, Chen RY, Tzeng CR, Han BC, Chien LC. Biomonitoring of blood heavy metals and reproductive hormone level related to low semen quality. J Hazard Mater. 2015 Dec 30; **300**: 815-22. doi: 10.1016/j.jhazmat.2015.08.027. Epub 2015 Aug 20.
26. Zhang YH, Zheng LX, Chen BH. Phthalate exposure and human semen quality in Shanghai: A cross-sectional study. Biomed Environ Sci. 2006 Jun; **19**(3): 205-9.
27. Shih TS, Hsieh AT, Liao GD, Chen YH, Liou SH. Haematological and spermatotoxic effects of Ethylene Glycol Monomethyl Ether in copper clad laminate factories. Occup Environ Med. 2000 May; **57**(5): 348-52. doi: 10.1136/oem.57.5.348.
28. Song X, Tang S, Zhu H, et al. Biomonitoring PFAAs in blood and semen samples: investigation of a potential link between PFAAs Exposure and semen mobility in china. Environ Int. 2018 Apr; **113**: 50-4. doi: 10.1016/j.envint.2018.01.010. Epub 2018 Feb 6.
29. Jurewicz J, Radwan M, Sobala W, et al. Exposure to widespread environmental endocrine disrupting chemicals and human sperm sex ratio. Environ Pollut. 2016 Jun; **213**: 732-40. doi: 10.1016/j.envpol.2016.02.008. Epub 2016 Mar 28.
30. Multigner L, Ben Brik E, Arnaud I, Haguenoer JM, Jouannet P, Auger J, et al Glycol Ethers and semen quality: a cross-sectional study among male workers in the Paris municipality. Occup

Environ Med. 2007 Jul; **64**(7): 467–73. doi: 10.1136/oem.2005.023952. Epub 2007 Mar 1.

31. Mendiola J, Moreno JM, Roca M, et al. Relationships between heavy metal concentrations in three different body fluids and male reproductive parameters: a pilot study. Environ Health. 2011 Jan 19; **10**(1): 6. doi: 10.1186/1476-069X-10-6.
32. Duydu Y, Başaran N, Üstündağ A, et al. Reproductive toxicity parameters and biological monitoring in occupationally and environmentally boron-exposed persons in Bandirma, Turkey. Arch Toxicol. 2011 Jun; **85**(6): 589-600. doi: 10.1007/s00204-011-0692-3. Epub 2011 Mar 19.
33. Bonde J P, Joffe M, Apostoli P, et al. Sperm count and chromatin structure in men exposed to inorganic lead: lowest adverse effect levels. Occup Environ Med. 2002 Apr; **59**(4): 234-42. doi: 10.1136/oem.59.4.234.
34. Onul NM, Biletska EM, Stus VP, Polion MY. The role of lead in the etiopathogenesis of male fertility reduction. Wiad Lek. 2018; **71**(6): 1155-60.
35. Engelsman M, Banks APW, He C, et al. An exploratory analysis of firefighter reproduction through survey data and biomonitoring. Int J Environ Res Public Health. 2023 Apr 11; **20**(8): 5472. doi: 10.3390/ijerph20085472.
36. Singh S, Li SS. Epigenetic effects of environmental chemicals bisphenol A and phthalates. Int J Mol Sci. 2012; **13**(8): 10143-53. doi: 10.3390/ijms130810143. Epub 2012 Aug 15.
37. Ho SM, Cheong A, Adgent MA, et al. Environmental factors, epigenetics, and developmental origin of reproductive disorder§§§s. Reprod Toxicol. 2017 Mar; **68**: 85-104. doi: 10.1016/j.reprotox.2016.07.011. Epub 2016 Jul 12.
38. D'Angelo S., Scafuro M., Meccariello R. BPA and nutraceuticals, simultaneous effects on endocrine functions. Endocr Metab Immune Disord Drug Targets. 2019; **19**(5): 594-604. doi: 10.2174/1871530319666190101120119.
39. Patisaul H. Achieving CLARITY on bisphenol A, brain and behaviour. J Neuroendocrinol. 2020 Jan; **3**(1): e12730. doi: 10.1111/jne.12730. Epub 2019 May 26.
40. Santoro A, Chianese R., Troisi J, et al. Neurotoxic and reproductive effects of BPA. Curr Neuropharmacol. 2019; **17**(12): 1109-32. doi: 10.2174/1570159X17666190726112101.
41. Li K, Gao P, Xiang P, Zhang X, Cui X, Ma LQ. Molecular mechanisms of PFOA-induced toxicity in animals and humans: Implications for health risks. Environ Int. 2017 Feb; **99**: 43-54. doi: 10.1016/j.envint.2016.11.014. Epub 2016 Nov 18.

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