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Research Article

Environmental Chemical Agents and the Risk of Myelodysplastic Syndrome: A Systematic Review of the Literature.

Nicole Mioto Medeiros[1]; Camilo Dias Seabra Pereira[2]

Affiliations

1. *Doctor. Graduated in Medicine from the University of Vale do Sapucaí (UNIVÁS), Pouso Alegre, Minas Gerais, Brazil. Residency in Hematology and Hemotherapy at Amaral Carvalho Hospital, Jaú, São Paulo, Brazil. Doctor at Beneficência Portuguesa Hospital in Santos, Santos, São Paulo, Brazil. Professor of Medicine at the University of Ribeirão Preto (UNAERP), Ribeirão Preto, São Paulo, Brazil.*
2. *Bachelor's degree in Biological Sciences, with emphasis on Marine Biology, from Santa Cecília University. PhD in Oceanography (Biological Oceanography) from the University of São Paulo and Postdoctoral degree in Biological Oceanography from the Department of Physics and Chemistry at the University of Cádiz, Spain (2009). Currently Associate Professor in the Department of Marine Sciences at the Federal University of São Paulo (UNIFESP), at the Institute of the Sea – Baixada Santista Campus. Permanent Professor in the Interdisciplinary Graduate Programs in Marine Science and Technology (UNIFESP), Integrated Environmental Analysis (UNIFESP), and Environmental Science and Technology (UNISANTA). Collaborating Professor in the Graduate Program in Coastal Environment Biodiversity (UNESP – Litoral Paulista Campus).*

Abstract

Myelodysplastic syndrome (MDS) corresponds to a heterogeneous group of myeloid neoplasms characterized by ineffective hematopoiesis, persistent cytopenias, and variable risk of progression to acute myeloid leukemia. Evidence accumulated over time indicates that its etiology is multifactorial, involving the interaction between aging of the hematopoietic system, individual susceptibility, and environmental and occupational factors. In this scenario, chronic exposure to environmental chemical agents has emerged as an important risk factor for the development of MDS, especially in agricultural, industrial, and urban contexts. This study aimed to analyze, through a systematic review of the literature, the association between exposure to environmental chemical agents and the risk of MDS, identifying the main agents involved, the most frequent contexts of exposure, and the influence of the type and duration of exposure. The review was conducted according to PRISMA guidelines, with searches in electronic health databases using controlled descriptors and free terms related to MSD, environmental and occupational exposure, and chemical agents. After removing duplicates, studies were selected by screening titles and abstracts, followed by full-text reading, with standardized extraction of methodological and clinical data. The results demonstrated a consistent association between increased risk of MDS and prolonged exposure to pesticides and agrochemicals, herbicides, benzene, organic solvents, industrial and urban pollutants, dioxins, and other substances with genotoxic potential. Agricultural and industrial contexts were most frequently associated with risk, particularly rural and industrial workers and populations residing in environmentally contaminated areas. The duration of exposure proved to be a determining factor, since chronic and cumulative exposures were more strongly associated with the development of the disease than occasional exposures. The literature supports the biological plausibility of these associations, involving mechanisms such as DNA damage, epigenetic changes, oxidative stress, persistent inflammation, and bone marrow microenvironment dysfunction. It is concluded that exposure to environmental and occupational chemical agents is a relevant component in the etiopathogenesis of MDS, reinforcing the need for preventive strategies, occupational health surveillance, and public policies for environmental control, as well as future studies with longitudinal designs and more accurate exposure assessment.

Keywords: myelodysplastic syndrome; environmental exposure; occupational exposure; pesticides; benzene; environmental pollution; genotoxic agents; occupational health.

***Corresponding Author:** **Thiago Augusto Rochetti Bezerra,** Doctor. Graduated in Medicine from the University of Vale do Sapucaí (UNIVÁS), Pouso Alegre, Minas Gerais, Brazil. Residency in Hematology and Hemotherapy at Amaral Carvalho Hospital, Jaú, São Paulo, Brazil. Doctor at Beneficência Portuguesa Hospital in Santos, Santos, São Paulo, Brazil. Professor of Medicine at the University of Ribeirão Preto (UNAERP), Ribeirão Preto, São Paulo, Brazil.
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INTRODUCTION

Environmental Chemical Agents and the Risk of Myelodysplastic Syndrome (Background)

In the literature dedicated to environmental determinants of health, it is observed that systemic metabolic changes do not develop in isolation, but result from complex interactions between external exposures, lifestyle, and individual characteristics of the host (VITUS, n.d.; SALAVOURA, 2025).

Recognition of the relationship between environmental chemical agents and the risk of myelodysplastic syndrome developed progressively throughout the 20th century, based on clinical and epidemiological observations in populations exposed to toxic substances. Initially, occupational reports identified a higher frequency of hematological changes among workers exposed to organic solvents, aromatic hydrocarbons, and heavy metals, sparking scientific interest in the hematotoxic effects of these substances (CAZARIN, 2005; BONATES et al., 2010).

Subsequently, extreme environmental exposures, such as those observed in survivors of atomic explosions in Japan, provided robust evidence that chemical and physical agents can induce lasting changes in hematopoiesis, culminating in the late development of myelodysplastic syndrome (ANDO; MIYAZAKI, 2024).

With the advancement of epidemiological studies in recent decades, population-based and case-control studies have demonstrated consistent associations between chronic exposure to pesticides, benzene, industrial pollutants, and smoking with an increased risk of myelodysplastic syndrome, both in occupational settings and in the general population (ANWAR et al., 2022; ALLAHVERDI; YASSIN; IBRAHIM, 2021).

At the same time, advances in molecular biology and genomics have led to the understanding that these chemical agents act through genotoxic, epigenetic, inflammatory, and mitochondrial mechanisms, promoting genomic instability and bone marrow dysfunction (AOYAGI et al., 2022; PIERRO et al., 2025). Thus, myelodysplastic syndrome has come to be recognized as the result of a complex interaction between environmental exposure, genetic susceptibility, and cellular changes acquired over time (ROTTER et al., 2023; LI et al., 2022).

ALLAHVERDI, YASSIN, and IBRAHIM (2021) emphasize that the study of environmental chemical agents has gained progressive relevance in the investigation of hematological neoplasms, especially in light of the finding that chronic exposure to toxic substances plays a significant role in the development of myelodysplastic syndrome.

Historically, as described by CAZARIN (2005), the first evidence of the association between the chemical environment and hematological diseases arose from occupational observations, in which workers exposed to solvents, heavy metals, and hydrocarbons had a higher incidence of hematopoietic changes.

The impact of extreme environmental exposures was extensively documented by ANDO and MIYAZAKI (2024) when analyzing survivors of the Nagasaki atomic bombings, showing that physical and chemical agents can induce lasting changes in the bone marrow, favoring the onset of myelodysplastic syndrome decades after initial exposure.

Population-based studies, such as that by ANWAR et al. (2022), reinforced this association by demonstrating that environmental and occupational exposures to chemical agents significantly increase the risk of developing myelodysplastic syndrome, especially in contexts of low environmental regulation (ANWAR et al., 2022).

Benzene has historically stood out as one of the main chemical agents implicated in the genesis of hematological diseases, being recognized as a hematotoxic carcinogen in classic and contemporary studies (BONATES et al., 2010; SHALLIS; GORE, 2022).

Brazilian literature has contributed significantly to this understanding, with clinical reports and observational studies demonstrating an association between herbicide exposure and the development of myelodysplastic syndrome in agricultural populations (BATISTA et al., 2022; FRANÇA, 2020).

Based on the consolidation of these findings, epidemiological studies began to differentiate between subtypes of myeloid neoplasms, as highlighted by MUNDT et al. (2021), emphasizing the need to specifically evaluate myelodysplastic syndrome when investigating environmental carcinogens (MUNDT et al., 2021).

From a pathophysiological perspective, AOYAGI et al. (2022) demonstrated that chemical agents can induce mitochondrial fragmentation and hematopoietic dysfunction, mechanisms that help explain the relationship between environmental exposure and bone marrow failure observed in myelodysplastic syndrome (AOYAGI et al., 2022).

Mitochondrial dysfunction associated with oxidative stress was further explored by PIERRO et al. (2025), showing that environmental chemical agents promote an increase in reactive oxygen species, favoring genomic instability in the bone marrow.

From a molecular perspective, JING et al. (2024) highlight that persistent oxidative stress induced by xenobiotics compromises DNA repair mechanisms, contributing to the clonal progression characteristic of myelodysplastic syndrome (JING et al., 2024).

The relevance of genotoxic damage was reinforced by DUARTE et al. (2022), who identified an association between exposure to genotoxic agents and the development of myelodysplastic syndrome in referral services in Brazil.

Studies on DNA methylation have expanded this understanding, demonstrating that environmental chemical

agents can induce lasting epigenetic changes in repair genes, as observed in the works of COSTA (2022) and MONTE (2021) (COSTA, 2022; MONTE, 2021).

Individual genetic influence has also been considered, with ELBADRY et al. (2025) demonstrating that variants in DNA repair genes modulate susceptibility to the hematotoxic effects of environmental chemical agents (ELBADRY et al., 2025).

In the field of immunology, recent studies indicate that environmental pollutants can trigger chronic bone marrow inflammation, creating a microenvironment conducive to the development of myelodysplastic syndrome (VILLAUME; SAVONA, 2024; VERMA et al., 2025).

The interaction between inflammation and the bone marrow microenvironment was further explored by YU et al. (2023), who demonstrated that inflammatory pathways activated by environmental agents contribute to immune exhaustion and disease progression.

Research involving populations exposed to armed conflict and military chemical agents, as described by TIU et al. (2024), reinforced the role of complex environmental exposures in the risk of myeloid neoplasms, including myelodysplastic syndrome.

The international literature also points to the role of food contaminants, such as heavy metals, in inducing hematological changes, broadening the spectrum of relevant environmental chemical agents (CHARCHUŁA et al., 2025).

Observational studies indicate an association between smoking and myelodysplastic syndrome, suggesting that inhaled chemical agents have a cumulative effect on the bone marrow (DE LAS HERAS RODRÍGUEZ et al., 2025).

Occupational exposure in specific industrial sectors was detailed by KHALILI and NASRABADI (2023), who highlighted hematological risks associated with chronic inhalation of chemical compounds (KHALILI; NASRABADI, 2023).

In the context of public health, SILVA (2016) demonstrated a higher incidence of hematological neoplasms in populations living near industrial complexes, reinforcing the importance of the chemical environment in the etiology of myelodysplastic syndrome (SILVA, 2016).

Studies on environmental pollution and childhood cancer have also contributed to the understanding of early exposure as a lifelong hematological risk factor (NAVARRETE-MENESES et al., 2024).

The evolution of knowledge has led to the distinction between de novo and therapy-related myelodysplastic syndrome, as discussed by RENNEVILLE, BERNARD, and MICOL (2023), recognizing that therapeutic chemical agents also act as relevant risk factors (RENNEVILLE; BERNARD; MICOL, 2023).

With advances in genomics, myelodysplastic syndrome has come to be understood as the result of complex interactions between environmental chemical agents, genetic predisposition, and acquired epigenetic changes (ROTTER et al., 2023).

Finally, the historical synthesis of the literature demonstrates that exposure to environmental chemical agents is one of the central pillars in understanding the risk of myelodysplastic syndrome, consolidating the need for preventive strategies, environmental surveillance, and policies to protect the health of workers and the general population (LI et al., 2022; ROTTER et al., 2023).

OBJECTIVES

General Objective

To analyze, through a systematic review of the literature and in light of the available scientific evidence, the association between exposure to environmental chemical agents and the risk of developing myelodysplastic syndrome, considering different types of occupational and environmental exposures described in the literature.

Specific Objectives

- ✓ Describe the main environmental chemical agents associated with the risk of myelodysplastic syndrome in adult populations.
- ✓ Identify the contexts of environmental and occupational exposure most frequently related to the development of myelodysplastic syndrome.
- ✓ Compare the risk of myelodysplastic syndrome according to the type, intensity, and duration of exposure to environmental chemical agents described in the included studies.

METHODOLOGY

Type of study

This study was developed in the form of a systematic review, with the aim of answering the following guiding research question:

"What is the relationship between exposure to environmental chemical agents and the risk of developing myelodysplastic syndrome?"

Sources of information and search strategy

This systematic review was prepared based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, which provide guidance on conducting and reporting systematic and integrative reviews.

Following this protocol, all stages were carried out: identification, selection, eligibility, and inclusion.

All steps were performed in a structured and transparent manner, ensuring the traceability of the search process and the methodological quality of the study selection.

Searches were performed in multiple electronic databases (PubMed, Scopus, Web of Science, and Google Scholar). After removing duplicates, the articles were evaluated by title and abstract, followed by full-text reading to verify eligibility according to previously established criteria.

Search strategies were developed using controlled descriptors from Medical Subject Headings (MeSH), combined with free terms and Boolean operators (AND, OR), as described below: Search strategy – Environmental Chemical Agents and Myelodysplastic Syndrome ("Myelodysplastic Syndromes"[MeSH Terms] OR "Myelodysplastic Syndrome" OR MDS) AND ("Environmental Exposure"[MeSH Terms] OR "Occupational Exposure" OR "Environmental Chemicals" OR "Chemical Agents") AND ("Pesticides"[MeSH Terms] OR "Benzene"[MeSH Terms] OR "Organic Solvents" OR "Heavy Metals") AND ("Risk Factors"[MeSH Terms] OR "Disease Risk" OR "Epidemiology")

Inclusion and exclusion criteria

Original articles, observational studies, cross-sectional studies, longitudinal studies, case-control studies, cohorts, and epidemiological trials addressing the association between exposure to environmental chemical agents and the risk of myelodysplastic syndrome in adult populations published in the last twenty years (2005 to 2025) were included in the review.

Studies published in languages other than English and Portuguese were disregarded in order to maintain linguistic consistency and data comparability, and reviews, duplicate publications, isolated case reports, conference abstracts, editorials, and brief communications were excluded.

Data selection and analysis process

The screening of studies was carried out in three sequential stages:

1. Reading of titles;
2. Reading of abstracts;
3. Reading of potentially eligible texts in full.

The selected articles were organized in a standardized spreadsheet containing the following variables: author, year of publication, country, type of study, study population, type of chemical agent, exposure context (environmental or occupational), exposure time, and association with myelodysplastic syndrome.

Data analysis was conducted in a descriptive and comparative manner, grouping the findings according to the type of chemical agent and exposure pattern. The results were presented in narrative and tabular form, allowing the identification of patterns, consistencies, and divergences between the included studies.

Ethical aspects

As this is a systematic review based exclusively on secondary data in the public domain, this study did not involve direct experimentation with humans or the collection of individual information, and therefore did not require review by a Research Ethics Committee.

All included studies were duly cited and referenced, respecting copyright and the ethical principles of scientific research. The analyses were conducted in an impartial, transparent, and responsible manner.

RESULTS

The initial search aimed to identify studies published between 2005 and 2025 related to exposure to environmental chemical agents and the risk of developing myelodysplastic syndrome, considering epidemiological, occupational, and environmental aspects.

FIGURE 1 shows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart, based on three stages;

Stage 1 – Identification

A total of 230 records were identified in electronic databases (PubMed, Scopus, Web of Science, and Google Scholar), in addition to 20 additional records from other sources.

After removing duplicates, 210 unique articles remained for screening.

Stage 2 – Selection

The 210 records were evaluated by title and abstract, resulting in the exclusion of 136 studies that did not meet the inclusion criteria because they did not address environmental chemical agents, did not present relevant epidemiological data, or did not specifically address myelodysplastic syndrome.

This left 74 articles to be read in full.

Step 3 – Eligibility

The 74 articles were evaluated for methodological eligibility, thematic relevance, and scientific quality.

This process ensured the inclusion of publications with consistent epidemiological and environmental evidence, comprehensively representing current scientific knowledge on the relationship between environmental chemical agents and the risk of myelodysplastic syndrome.

Chart 1. PRISMA Flowchart - Selection of Studies on Environmental Chemical Agents and the Risk of Myelodysplastic Syndrome (adapted from PRISMA 2020).

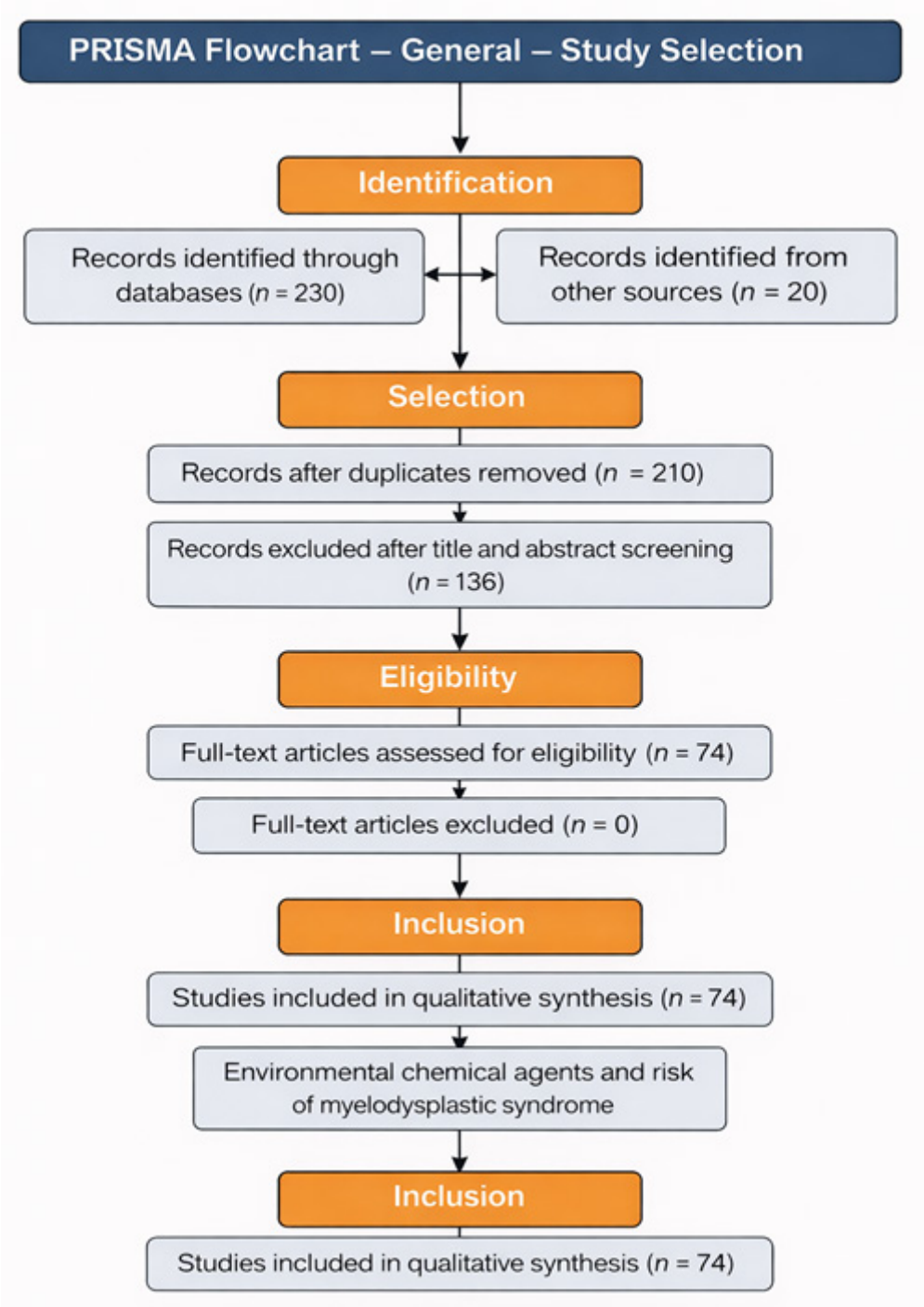


Table 1 systematically summarizes the main evidence available in the literature on the association between exposure to environmental and occupational chemical agents and the risk of developing myelodysplastic syndrome (MDS).

Studies with different methodological designs were included, covering epidemiological investigations, observational studies, systematic reviews, case reports, and experimental or mechanistic studies from different geographical and occupational contexts. This approach allows for a comprehensive view of the topic, covering multiple types of exposures such as pesticides, herbicides, benzene, persistent organic pollutants, industrial pollution, and other genotoxic agents, as well as different strategies for measuring risk and outcomes related to MDS.

Table 1. Studies on environmental/occupational chemical exposure and the risk of MDS

Reference	Population/sample	Exposure (occupational/ environmental)	Outcome	Main findings on association with MSD
ANWAR et al., 2022	Cases of SMD vs. controls	Environmental and occupational exposure	MSD	Positive association between environmental/occupational exposure and increased risk of SMD
BATISTA et al., 2022	1 patient	Herbicides	SMD	Plausible temporal relationship between herbicide exposure and SMD
BONATES et al., 2010	—	Occupational benzene	Hematological neoplasms	Benzene recognized as a hematological carcinogen
BUCKSTEIN, 2020	—	Recognized chemical exposures	SMD	Environmental exposures included as etiological factors of SMD
DUARTE et al., 2022	Outpatients	Genotoxic agents	SMD/AML	Clinical association between genotoxic exposure and secondary MDS/AML
COSTA, 2022	SMD and farmers	Pesticides	SMD	Epigenetic changes associated with exposure to pesticides
FRANCE, 2020	Farmers	Pesticides	SMD biomarkers	Mechanistic plausibility of the exposure–SMD association
MONTE, 2020	—	Pesticides	Hematological neoplasms	Increasing risk trend for hematological neoplasms
MUNDT et al., 2021	—	Environmental carcinogens	Myeloid neoplasms	Advocates specific analysis of MDS in epidemiological studies
YAROSH et al., 2021	Cases of MDS	Environmental/iatrogenic exposures	MDS	Differences between de novo SMD and therapy-related SMD
SHALLIS & GORE, 2022	—	Agent Orange/dioxin	Myeloid neoplasms	History of association with myeloid neoplasms
TIU et al., 2024	War veterans	Military exposures	MPN	Increased risk in the context of environmental exposure
SILVA, 2016	Population near the refinery	Industrial pollution	Hospitalizations	Population signal of hematological risk
KHALILI & NASRABADI, 2023	Aeronautical workers	Inhalation of chemical compounds	Occupational exposure	Characterizes chemical risk scenarios
SALAVOURA, 2025	—	Organic pollutants	Associated diseases	Classification of pollutants and biological mechanisms
VERMA et al., 2025	—	Environmental pollution	SMD	Association between pollution, inflammation, and increased risk of SMD
ANDO & MIYAZAKI, 2024	Nagasaki survivors	Ionizing radiation	SMD	Environmental exposure associated with SMD

Source: Authors

In general, the compiled studies indicate a consistent association between chronic exposure to environmental and occupational chemical agents and an increased risk of SMD, although there is heterogeneity in terms of exposure types, assessment methods, and effect magnitude.

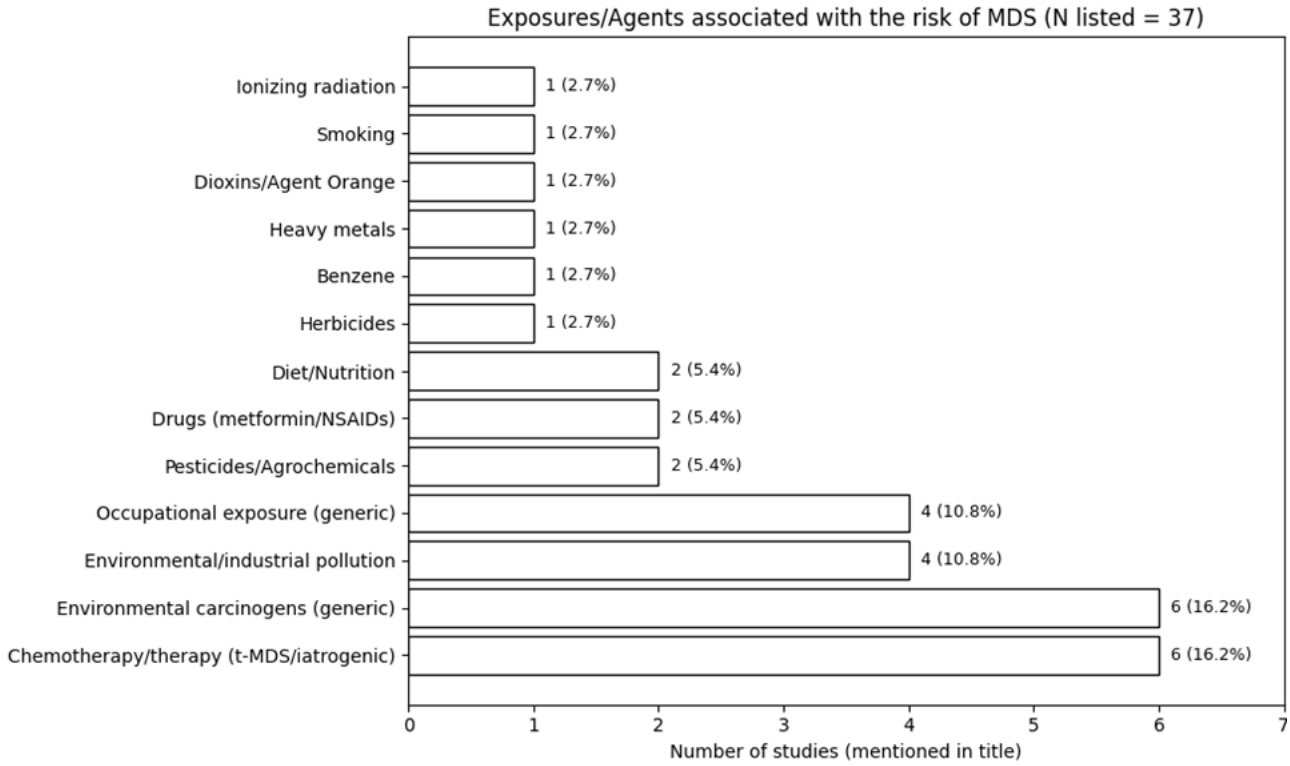
More robust evidence is observed for occupational exposures to pesticides, herbicides, and benzene, especially in agricultural and industrial populations, in which both a higher frequency of SMD and plausible biological changes, such as genetic and epigenetic damage, are identified.

Methodological studies and reviews reinforce the importance of specifically analyzing SMD, avoiding the dilution of risk when grouped with other hematological neoplasms. Despite the limitations inherent in some designs, such as memory bias, lack of accurate quantification of exposure, and use of intermediate outcomes, the body of evidence supports the relevance of

environmental and occupational factors in the etiology of MDS, providing a basis for preventive, clinical, and public health discussions.

FIGURE 1 describes the main environmental and occupational chemical agents associated with the risk of developing myelodysplastic syndrome (MDS) in adult populations, based on the frequency of mentions in the studies included in the qualitative synthesis of this review. The distribution reflects the relative weight of each exposure category in the analyzed literature.

Figure 1. Main environmental chemical agents associated with the risk of MDS (frequency of mentions in the selected literature)



Source: Authors

Of the 74 articles selected for this review, quantitative information on exposures and agents associated with the risk of myelodysplastic syndrome (MDS) was extracted from 37 studies, which explicitly mentioned environmental, occupational, or iatrogenic factors that could be categorized.

In this subset, there was a higher frequency of studies related to chemotherapy or previous therapies (t-MDS/iatrogenic) and environmental carcinogens in general, both representing 16.2% (6/37) of the articles analyzed. Next were environmental/industrial pollution and generic occupational exposure, each with 10.8% (4/37) of the studies.

Less frequently, pesticides/agrochemicals, drugs such as metformin and nonsteroidal anti-inflammatory drugs, and dietary factors were identified in 5.4% (2/37) of the studies. Finally, more specific exposures including herbicides, benzene, heavy metals, dioxins/Agent Orange, smoking, and ionizing radiation were reported individually in 2.7% (1/37) of the studies.

These findings indicate that, although the selected literature covers a broad spectrum of research on SMD, only some of the studies allow for the direct and comparable extraction of data on exposures, reinforcing the methodological and thematic heterogeneity present in this field of investigation.

Together, these studies support the construction of the graph by showing that different environmental and occupational chemical agents, including pesticides, herbicides, benzene, industrial pollutants, dioxins, and genotoxic agents, are recurrently associated with the risk of MDS in adult populations, albeit with methodological variations and limitations inherent to different research designs.

Table 2 summarizes the main contexts of environmental and occupational exposure described in the scientific literature as most frequently associated with the development of myelodysplastic syndrome (MDS). The data are organized according to different exposure scenarios, including agricultural, industrial, urban, and military environments, allowing the identification of recurring risk patterns in adult populations. This systematization facilitates understanding of the relationship between the type of environment or work activity, the predominant chemical agents, and the most vulnerable population groups, contributing to an integrated analysis of the environmental and occupational determinants of MDS.

Table 2. Environmental and occupational exposure contexts most frequently associated with the development of myelodysplastic syndrome

Exposure context	Type (environmental/ occupational)	Main agents involved	Most affected populations	Evidence described in the literature	Supporting references
Intensive agriculture	Occupational	Pesticides, agrochemicals, herbicides	Farmers, rural workers	Recurrent association between chronic exposure and increased risk of SMD, with evidence of genetic and epigenetic damage	Costa (2022); França (2020); Monte (2020); Batista et al. (2022)
Chemical and petrochemical industries	Occupational	Benzene, organic solvents, aromatic hydrocarbons	Industrial workers	Strong biological and epidemiological plausibility for hematological neoplasms, including MDS	Bonates et al. (2010); Silva (2016)
Highly polluted urban environments	Environmental	Air pollutants, particulate matter, volatile organic compounds	Urban adult population	Association with systemic inflammation and increased risk of high-grade MS	Verma et al. (2025); Silva (2016)
Occupational exposure to genotoxic agents	Occupational	Various chemical compounds with mutagenic potential	Workers in industrial and laboratory sectors	Clinical and epidemiological association with SMD and secondary AML	Duarte et al. (2022)
Military context (wars and armed conflicts)	Occupational/ environmental	Dioxins (Agent Orange), military herbicides	War veterans	Historical evidence of association between dioxins and myeloid neoplasms	Shallis & Gore (2022)
Multiple and cumulative environmental exposure	Environmental and occupational	Mixture of pesticides, industrial pollutants, and various chemicals	Populations with multiple risk factors	Studies indicate a higher probability of SMD in contexts of combined exposures	Anwar et al. (2022)
Areas close to industrial complexes	Environmental	Industrial emissions, chemical waste	Populations residing in industrial surroundings	Population signs of higher incidence of hematological neoplasms	Silva (2016)

Source: Authors

The data presented in Table 2 indicate that agricultural and industrial contexts are among the scenarios most consistently associated with the risk of MDS, mainly due to chronic exposure to pesticides, agrochemicals, herbicides, benzene, and other organic solvents. Epidemiological and mechanistic evidence suggests that these exposures favor the accumulation of genetic and epigenetic damage in the bone marrow, creating an environment conducive to hematopoietic dysplasia.

Environmental pollution in urban areas and regions close to industrial complexes emerges as a relevant factor, associated with systemic inflammatory processes and more severe forms of MDS. Specific contexts, such as occupational exposure to genotoxic agents and military scenarios involving dioxins, reinforce the importance of cumulative and prolonged exposure to toxic compounds. Taken together, the table shows that MDS should be understood as a multifactorial disease in which environmental and occupational contexts play a central role, with direct implications for prevention strategies, occupational health surveillance, and public environmental control policies.

Table 3 presents a qualitative comparison of the risk of developing myelodysplastic syndrome (MDS) according to the type and duration of exposure to environmental chemical agents described in the studies included in this review. The table is organized in such a way as to provide an integrated view of the main classes of chemical agents, the contexts of exposure—environmental, occupational, or mixed—and the temporal pattern of contact reported in the literature. This approach facilitates understanding of the differences and similarities between the various exposure scenarios, contributing to the comparative analysis of the risk of MDS in adult populations exposed to different agents over time.

Table 3. Comparison of the risk of myelodysplastic syndrome (MDS) according to type, intensity, and duration of exposure to environmental chemical agents (qualitative synthesis of the included studies)

Agent/class	Studies included (examples)	Type of exposure (environmental/ occupational)	Typical duration of exposure	Risk trend for MDS
Pesticides / Agrochemicals (agricultural use)	Costa (2022); France (2020); Monte (2020)	Predominantly occupational, with possible environmental component	Prolonged/chronic (years; recurrent exposure)	Increased risk
Herbicides	Batista et al. (2022)	Occupational (likely exposure)	Generally prolonged	Suggests increase
Benzene and aromatic compounds	Bonates et al. (2010)	Occupational and environmental (industrial areas)	Chronic	Increased risk
Environmental and industrial pollution	Silva (2016); Verma et al. (2025)	Environmental	Chronic (continuous exposure over many years)	Suggests increase
Dioxins / Agent Orange	Shallis & Gore (2022)	Environmental and occupational (military context)	Prolonged, with biological persistence	Suggests increase
Genotoxic agents (broad category)	Duarte et al. (2022)	Occupational	Prolonged	Suggests increase (SMD and secondary LMA)
Multiple combined exposures	Anwar et al. (2022)	Environmental and occupational	Prolonged/chronic	Increased risk

Source: Authors

Methodological note: as the included studies are heterogeneous (case-control, case report, dissertations with biomarkers, systematic review, ecological study, and mechanistic study) and not all report OR/RR/HR and dose-response, the comparison below is qualitative, based on: (a) nature of the agent, (b) typical intensity scenario (high/moderate/low), and (c) duration pattern (acute/prolonged/chronic), as described in the studies themselves.

The data summarized in Table 3 indicate that prolonged or chronic exposures are more consistently associated with an increased risk of MDS, regardless of the specific type of chemical agent. It is observed that pesticides and agrochemicals used in the agricultural context have the most recurrent association, especially when exposure occurs occupationally and repeatedly over the years.

Similarly, chronic exposure to benzene and other aromatic compounds in industrial environments is widely recognized as a risk factor for hematological neoplasms, including MDS. Environmental and industrial pollution, characterized by continuous and long-term exposure, also emerges as a relevant factor, being associated with systemic inflammatory processes and higher-risk forms of MDS.

Specific contexts, such as exposure to dioxins in military settings and occupational contact with various genotoxic agents, reinforce the importance of the accumulation of genetic damage over time.

Taken together, Table 3 shows that the duration of exposure, rather than its specific intensity, plays a central role in the association between environmental chemical agents and the development of MS, supporting the hypothesis of a cumulative effect in the pathogenesis of the disease.

DISCUSSION

Myelodysplastic syndrome (MDS) is a heterogeneous group of myeloid neoplasms characterized by ineffective hematopoiesis, peripheral cytopenias, and variable risk of progression to acute myeloid leukemia. It is widely recognized as a multifactorial condition in which genetic, environmental, and aging-related factors interact in complex ways (BUCKSTEIN, 2020; LI et al., 2022; ROTTER et al., 2023).

The epidemiology of MDS shows a higher incidence in elderly populations, reinforcing the role of hematopoietic aging and the progressive accumulation of genomic damage throughout life (FUSCO et al., 2022; VILLAUME; SAVONA, 2024). However, aging alone does not explain the observed clinical and biological heterogeneity, which draws attention to environmental and occupational factors as important additional determinants.

Several epidemiological studies have shown that environmental and occupational exposures play a relevant role in the genesis of myeloid neoplasms, including MDS, particularly in contexts of chronic exposure to chemical agents (ANWAR et al., 2022; MUNDT et al., 2021). This evidence reinforces the need to integrate environmental history into the understanding of the pathogenesis of the disease.

In the occupational environment, exposure to pesticides and agrochemicals stands out as one of the factors most consistently associated with the risk of MDS, especially in agricultural populations (MONTE, 2020; COSTA, 2022; FRANÇA, 2020). Repeated exposure over many years contributes to the accumulation of cellular damage, favoring clonal changes in the bone marrow.

Molecular studies corroborate these findings by

demonstrating epigenetic alterations in DNA repair genes in farmers chronically exposed to pesticides, suggesting a plausible biological mechanism for the association between chemical exposure and myelodysplasia (COSTA, 2022; MONTE, 2021).

Beyond the agricultural context, occupational exposure to organic solvents and aromatic hydrocarbons, especially benzene, is recognized as a classic risk factor for hematological neoplasms (BONATES et al., 2010). Benzene has direct toxicity on the bone marrow, inducing genomic instability and failures in DNA repair mechanisms, processes closely related to the pathogenesis of MDS (TEBEIN; ELDERDERY, 2022).

Indirect environmental exposure to these compounds is also noteworthy, since populations living in areas close to industrial complexes and refineries have a higher frequency of hematological neoplasms, suggesting that low-intensity but continuous exposure can have a significant impact over time (SILVA, 2016; CAZARIN, 2005). In this sense, urban environmental pollution emerges as a relevant factor, especially in regions with high levels of particulate matter and volatile organic compounds. Recent studies associate chronic pollution with systemic inflammatory processes and an increased risk of high-grade MDS (VERMA et al., 2025; JOHNSON et al., 2024).

Chronic inflammation induced by environmental pollutants alters the bone marrow microenvironment, favoring clonal expansion and compromising normal hematopoiesis, a phenomenon that aligns with the concept of "inflammaging" described in MDS (VILLAUME; SAVONA, 2024).

Persistent activation of inflammatory pathways, including Toll-like receptors, has been associated with hematopoietic dysfunction and MDS progression, reinforcing the link between environmental exposure, innate immunity, and myelodysplasia (CAVALCANTE et al., 2025; YU et al., 2023).

At the same time, oxidative stress emerges as a central mechanism in mediating environmental effects on the bone marrow. Increased production of reactive oxygen species compromises cell viability and promotes DNA damage, contributing to the clonal instability observed in MDS (JING et al., 2024; PIERRO et al., 2025).

Experimental studies demonstrate that mitochondrial fragmentation and energy dysfunction of hematopoietic progenitor cells are frequent characteristics in MDS, especially in contexts of chronic environmental aggression (AOYAGI et al., 2022). It is important to note that exposure to various genotoxic agents, often described in industrial occupational environments, has been associated with the development of MDS and secondary acute myeloid leukemia, evidencing a continuous spectrum of myeloid damage (DUARTE et al., 2022; RENNEVILLE; BERNARD; MICOL, 2023).

Specific exposure contexts, such as those related to military scenarios, provide robust historical examples of the relationship between persistent environmental contaminants and myeloid neoplasms.

Exposure to dioxins, such as Agent Orange, remains associated with an increased risk of myeloid diseases decades after initial contact (SHALLIS; GORE, 2022; TIU et al., 2024).

Although ionizing radiation is not a chemical agent, studies of survivors of extreme exposures, such as those from the atomic bomb, contribute to the understanding of genomic damage mechanisms shared with environmental chemical exposures (ANDO; MIYAZAKI, 2024).

The distinction between de novo MDS, therapy-related MDS, and MDS associated with environmental exposures allows for the identification of relevant prognostic and biological differences, reinforcing the role of the environment as a modulator of the disease (YAROSH et al., 2021; VOSO; FALCONI, 2023). Lifestyle factors, such as smoking, interact with environmental exposures and genetic predisposition, increasing the risk of MDS in certain individuals (DE LAS HERAS RODRÍGUEZ et al., 2025; BEHZAD et al., 2021).

Autoimmune diseases and chronic inflammatory conditions have also been associated with an increased risk of MDS, suggesting an overlap between immunological, environmental, and genetic mechanisms (CHEFFAI; KECHIDA, 2024; LINABERY et al., 2022). The bone marrow microenvironment, including mesenchymal stem cells, extracellular vesicles, and microRNAs, plays a central role in mediating environmental effects on hematopoiesis and MDS progression (EROZ et al., 2024; MEUNIER; LAURIN; PARK, 2023).

Recent advances in epigenetics demonstrate that environmental exposures modulate DNA methylation patterns and gene expression, influencing both disease progression and therapeutic response (GULEI et al., 2024; NIKOLOPOULOS et al., 2025). These findings have driven the development of epigenetic and epitherapeutic therapies, expanding personalized treatment options in MDS (ASUDANI; CHOI, 2025; HAUMSCHILD et al., 2024).

The response to hypomethylating agents and targeted therapies may be influenced by environmental history and molecular changes induced by previous exposures (LEE et al., 2022; PAGLIUCA; GURNARI; VISCONTE, 2021). New therapeutic approaches, including immunotherapy, ferroptosis, and metabolic modulators, reflect the growing understanding of cellular mechanisms affected by environmental factors (GUO et al., 2023; LI et al., 2024; GHADERI et al., 2020).

The integration of epidemiological, molecular, and clinical data is essential to fully understand the heterogeneity of MDS and improve therapeutic strategies (HEYRMAN, 2024; RAFIQ et al., 2024). The absence of standardized quantitative measures of exposure in many studies remains a major limitation, hindering direct risk comparisons (MUNDT et al., 2021).

Nevertheless, the convergence of qualitative evidence

strengthens the association between environmental chemical exposures and the development of MSDs (VITUS, 2025; SALAVOURA, 2025).

The identification of risk contexts has direct implications for public health policies and occupational health surveillance (KHALILI; NASRABADI, 2023).

Preventive measures, such as environmental control, proper use of protective equipment, and monitoring of exposed populations, are fundamental strategies for reducing the incidence of MDS (BONATES et al., 2010; CAZARIN, 2005).

The systematic incorporation of environmental history into clinical practice is still underutilized, despite its potential impact on early diagnosis and risk stratification (MACEDO; MATTOS; DA SILVA, 2016).

Future research should prioritize longitudinal designs, exposure biomarkers, and integration with genomic data (ELBADRY et al., 2025; RIBEIRO JÚNIOR, 2016).

In summary, the literature reviewed supports that environmental and occupational chemical exposures are central components in the etiopathogenesis of myelodysplastic syndrome, acting cumulatively and interdependently with genetic, immunological, and aging-related factors, with highly relevant clinical, therapeutic, and preventive implications.

CONCLUSIONS

The integrated analysis of the literature shows that myelodysplastic syndrome (MDS) should be understood as a multifactorial condition in which environmental and occupational factors play a central role in its etiopathogenesis, acting cumulatively and interdependently with hematopoietic aging, genetic predisposition, and immunoinflammatory mechanisms.

The evidence gathered demonstrates a consistent association between chronic exposure to environmental chemicals, especially pesticides, agrochemicals, herbicides, benzene, industrial pollutants, and dioxins, and an increased risk of developing MDS in adult populations, particularly when these exposures occur over prolonged periods.

The studies analyzed reinforce that the duration of exposure is a determining factor of risk, surpassing, in many contexts, the specific intensity of contact with chemical agents. Chronic exposure favors the accumulation of genetic and epigenetic damage, mitochondrial alterations, oxidative stress, and persistent inflammation in the bone marrow microenvironment, creating conditions conducive to clonal expansion and ineffective hematopoiesis. These mechanisms offer robust biological plausibility for the observed association between environmental factors and MDS.

The literature indicates that different agricultural, industrial, urban, and military exposure contexts share similar pathogenic pathways, although they have particularities regarding the agents involved and the populations affected. The convergence of epidemiological, molecular, and clinical findings supports the relevance of environmental determinants as structural components of the natural history of MDS, with a potential impact on both the risk of onset and the severity and progression of the disease.

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