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Review article

Systematic review of preclinical studies on the neutrophil-mediated immune response to air pollutants, 1980–2020

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ABSTRACT

Preclinical evidence about the neutrophil-mediated response in exposure to air pollutants is scattered and heterogeneous. This has prevented the consolidation of this research field around relevant models that could advance towards clinical research. The purpose of this study was to systematic review the studies of the neutrophils response to air pollutants, following the recommendations of the Cochrane Collaboration and the PRISMA guide, through 54 search strategies in nine databases. We include 234 studies (*in vitro*, and *in vivo*), being more frequent using primary neutrophils, Balb/C and C57BL6/J mice, and Sprague-Dawley and Wistar rats. The most frequent readouts were cell counts, cytokines and histopathology. The temporal analysis showed that in the last decade, the use of mice with histopathological and cytokine measurement have predominated. This systematic review has shown that study of the neutrophils response to air pollutants started 40 years ago, and composed of 100 different preclinical models, 10 pollutants, and 11 immunological outcomes. Mechanisms of neutrophils-mediated immunopathology include cellular activation, ROS production, and proinflammatory effects, leading to cell-death, oxidative stress, and inflammatory infiltrates in lungs. This research will allow consolidating the research efforts in this field, optimizing the study of causal processes, and facilitating the advance to clinical studies.

1. Introduction

Exposure to air pollutants is associated with various health problems, including asthma, increased incidence of respiratory infections, reduced lung function, and heart conditions [1, 2]. Among air pollutants, particulate matter (PM) shows a strong association with adverse respiratory (including infectious diseases [3]) and cardiovascular health effects.

PM is a mixture of particles that vary in quantity, surface area, chemical composition, origin, and size; based on the latter property, it is classified as PM_{10}, $PM_{2.5}$ (fine particles), and $PM_{0.1}$ or UFP (ultrafine particles) [4]. Exposure to these environmental pollutants can cause inflammation of the respiratory tract [5], lung damage due to oxidative stress, increased mucus secretion, and immune alterations [6]. Besides, air pollution exposure has been associated with congenital and newborn alterations [7], cardiovascular and neurological disorders, as a consequence of inflammation and oxidative stress [8, 9]. The main immunological defects that have been reported, are the humoral response [10] and its association with asthma, and the production of reactive oxygen species in the development of chronic obstructive pulmonary disease (COPD) [11]. However, assessments of the acute inflammatory response and the role of one of its main mediators, neutrophils, still require research to clarify their involvement and thus design appropriate (therapeutic) control strategies.

Recently, multiple studies have focused on the effects of PM on immune cells in the lung, including neutrophils, the main mediators of acute inflammatory reactions, and infiltrating tissue since the early hours of injury. Thanks to their high production of cytokines, lipid mediators of inflammation, oxidative radicals, and multiple hydrolytic enzymes, including metalloproteases, the neutrophils modulate the progression of lung pathologies and the exacerbation of pre-existing diseases. For instance, *in vivo* studies have shown that exposure to these contaminants promotes the infiltration of neutrophils into the lungs to eliminate PM. However, aberrant accumulation of neutrophils in the lung causes tissue damage, as seen in the triggering of asthma or COPD, related to air

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pollution [12, 13]. In this sense, studies have reported variations in cell counts, cytokine production, reactive oxygen species, immunoglobulins, and other metabolic, immunological, and even tissue damage biomarkers [14, 15, 16, 17, 18]. Also, there is a high diversity of preclinical models (laboratory based-experiments) [13, 19, 20, 21], which include multiple cell lines, primary cultures, and diverse animal models, evidencing the heterogeneity of measurements of the immune response, especially the neutrophil-mediated one.

This heterogeneity presents several implications as contradictory results when using different sources of air pollutants, evaluating pleiotropic factors such as IL-6 (with pro- and anti-inflammatory functions), or murine models with contrasting immune responses such as C57BL6/J and Balb/C mouse strains, which predominantly present Th1 and Th2 responses (antagonistic immune profiles), respectively [22].

The above shows that the preclinical evidence on the neutrophil-mediated immune response to exposure to airborne contaminants is scattered and heterogeneous, which prevents the consolidation of this research field since there are no recommendations on the cellular or animal designs, the type of exposure, or the most relevant outcomes to advance to subsequent phases of clinical research [23, 24].

Therefore, the objective of this research was to analyze the methodological characteristics of the preclinical studies that have evaluated the neutrophil-mediated immune response to air pollutants in the period 1980–2020. The specific objectives included: i) to describe the studies according to the year and place of origin; ii) to identify the different *in vitro* and *in vivo* models that have been used; iii) to describe the main pollutants and immunological outcomes used in the studies; iv) to analyze the temporal changes in the design of the selected preclinical studies; and v) to identify the immunological effects reported in the most frequently used preclinical models in this field.

This work systematically reviewed the available research that has evaluated the effect of air pollutants in the neutrophil-mediated response in *in vivo* and *in vitro* models, with a broad approach according to the Cochrane Collaboration [25], where an empirical approach of synthesis of scientific evidence in a field is implemented. Besides, the current recommendations can be updated, and allow to analyze the potential for generalization of published studies, to define hypotheses with substantial or insufficient evidence; to identify areas for further research, to locate countries in need of further research, among other relevant uses for those interested in environmental health issues, immunology, preclinical research methodologies, among others. Besides, defining the role of neutrophils in the pulmonary inflammatory response to airborne contaminants can help understand their implications in respiratory and cardiovascular disease and provides information to support decision making regarding unified methodologies for immunological assessments with airborne contaminants.

2. Materials and methods

2.1. Type of study

A systematic review of preclinical studies, following the recommendations of the Cochrane Collaboration and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guide.

2.2. PICO (Population intervention comparator outcome) question - modified

2.2.1. Experimental unit (population)

The experimental unit depended of the type of preclinical study carried out. For *in vitro* studies, it corresponded to the type of cell line or primary culture, and in the *in vivo* studies, it was the type of animal (rats, mice, hamsters, or rabbits) model.

2.2.2. Pollutant (intervention)

The atmospheric pollutants evaluated were particulate matter, Ozone, sulfur dioxide, aerosols, and others included in the preclinical studies, in different concentrations.

2.2.3. Control (comparator)

For *in vitro* studies, the control was the negative control, while, for *in vivo* studies, it was the initial or pre-exposure measurement.

2.2.4. Outcome

The outcomes were the type of neutrophil-mediated immune response, including cell count, cytokine measurement, cytokine mRNA, oxidative activity, immunoglobulins, histopathological changes.

2.3. Search and selection protocol according to the PRISMA guide

2.3.1. Identification

A search of scientific articles was performed in four multidisciplinary databases MedLine-PubMed, Science-Direct, Scielo, LILACS. Also open searches in Google Scholar (web search engine), and four field-specific databases: Infection and Immunity (American Society for Microbiology), EPA (Environmental Protection Agency, United States), OECD i Library and HEI (Health Effects Institute), were included. A query of terms was carried out in the thesauri MeSH (Medical Subject Headings) and DeCS (Health Sciences Descriptors), and it was complemented with a process of "pearl harvest". Two terms were identified for the topic of environmental pollution: "particulate matter" and " air pollution", which were combined with the terms found for the neutrophil-mediated immune response, i.e., "neutrophils", "granulocytes" and "white blood cells". According to the above, three search strategies were applied in each database (Table 1).

2.3.2. Screening

In this phase, three inclusion criteria were applied. The first criterion was that the articles had the search terms in title or abstract; the second consisted of original investigations, with which reviews, book chapters, and abstracts were eliminated; the third inclusion criterion was that the study was classified as preclinical, thus eliminating the clinical-epidemiological studies carried out in people from different populations and the mathematical modeling studies. In this phase, the identified studies were saved in a common source in Zotero to eliminate duplicates.

2.3.3. Eligibility

At this stage, six exclusion criteria were applied, *i)* publications in other languages such as Russian or Chinese, *ii)* studies in animals, but that did not classify as preclinical, for example, studies that had dogs, fish, or horses as units of analysis but that were not *in vivo* models (animal health studies), *iii)* studies about plant species, *iv)* studies not related to air pollutant or studies that did not specify the type air pollutant, *v)* studies that did not specify the immunological outcome and *vi)* studies not available in full text or eliminated from the database.

2.3.4. Inclusion

The articles that fulfilled the two previous stages were included in this review. The variables title, authors, journal, year of publication, country, type of preclinical model (this was grouped into *in vitro* and *in vivo* models), type of *in vitro* model, type of *in vivo* model, pollutant studied, and type of neutrophil-mediated immune response (outcome) were extracted.

2.4. Evaluation of the reproducibility

The reproducibility of the search and selection protocol was validated through a review performed by two researchers independently. It was determined *a priori* that disagreements would be resolved by referral to a

Table 1. Search syntax applied in each database.

	Search 1	Search 2	Search 3
PubMed	(particulate matter [Title/Abstract] OR air pollution [Title/Abstract]) AND (neutrophils [Title/Abstract])	(particulate matter [Title/Abstract] OR air pollution [Title/Abstract]) AND (granulocyte [Title/Abstract])	(particulate matter [Title/Abstract] OR air pollution [Title/Abstract]) AND (white blood cell [Title/Abstract])
Science-Direct	Title, abstract, keywords: (particulate matter OR air pollution) AND neutrophils	Title, abstract, keywords: (particulate matter OR air pollution) AND granulocyte	Title, abstract, keywords: (particulate matter OR air pollution) AND white blood cell
Scielo	(ab:(particulate matter OR air pollution)) AND (ab:(neutrophils))	(ab:(particulate matter OR air pollution)) AND (ab:(granulocyte))	(ab:(particulate matter OR air pollution)) AND (ab:(white blood cell))
LILACS	(tw:(particulate matter OR air pollution)) AND (tw:(neutrophils))	(tw:(particulate matter OR air pollution)) AND (tw:(granulocyte))	(tw:(particulate matter OR air pollution)) AND (tw:(white blood cell))
Google Scholar	allintitle: ((particulate matter OR air pollution) AND neutrophils)	allintitle: ((particulate matter OR air pollution) AND granulocyte)	allintitle: ((particulate matter OR air pollution) AND white blood cell)
Infection and Inmunity	For abstract or title " (particulate matter OR air pollution) AND neutrophils" (match all words)	For abstract or title " (particulate matter OR air pollution) AND granulocyte" (match all words)	For abstract or title " (particulate matter OR air pollution) AND white blood cell" (match all words)
EPA	DC.title:(particulate AND DC.title:matter AND DC.title:OR AND DC.title:air AND DC.title:pollution) AND DC.title:AND ANDDC.title:neutrophils	DC.title:(particulate AND DC.title:matter AND DC.title:OR AND DC.title:air AND DC.title:pollution) AND DC.title:AND ANDDC.title: granulocyte	DC.title:(particulate AND DC.title:matter AND DC.title:OR AND DC.title:air AND DC.title:pollution) AND DC.title:AND ANDDC.title: white blood cell
OECD i Library	From (Abstract contains '(particulate matter OR air pollution)') AND from (Abstract contains 'neutrophils') AND from (IGO collection contains 'OECD')	From (Abstract contains '(particulate matter OR air pollution)') AND from (Abstract contains 'granulocyte') AND from (IGO collection contains 'OECD')	From (Abstract contains '(particulate matter OR air pollution)') AND from (Abstract contains 'white blood cell') AND from (IGO collection contains 'OECD')
HEI	(particulate matter OR air pollution) AND neutrophils	(particulate matter OR air pollution) AND granulocyte	(particulate matter OR air pollution) AND white blood cell

Note 1: The searches were carried out in Spanish without finding additional results. A total of 54 search strategies were applied (3 in English +3 in Spanish x 9 databases). Note 2: Combining the terms particulate matter OR air pollution in a unique search yielded the same studies as separating them into two searches (one for each term). This was not the case for the terms "neutrophils", "granulocytes" and "white blood cells", for which separate searches (one for each term) returned more results than a single search (with all three terms linked with "OR").

third researcher. Disagreements were dealt with in two phases: referral to a third party, then consensus among the three (the two initial parties and the third party consulted in case of disagreement). The information was extracted, filling a database in SPSS 25.0 with the study variables, independently, by two reviewers.

2.5. Analysis of the information

The included studies were analyzed by a qualitative synthesis of the extracted variables were described with absolute (n) and relative (%) frequencies. A bivariate analysis was performed using Pearson's Chi-square to compare the preclinical study type by time period. The database and the analyzes were processed in SPSS 25.0, with 95 % confidence interval.

3. Results

With the application of the search strategies in the 9 databases, 129,013 results were found. After applying the title or abstract filter and eliminating duplicates, 471 abstracts were read to apply the other selection criteria; at the end, 234 studies met the search and selection protocol (Figure 1).

The higher frequency of studies came from the United States (42.3%), China (14.3%), Canada (7.3%), Brazil (4.7%), United Kingdom (4.7%), and Japan (4.7%), with a lower frequency of studies in Latin America, Asia, Oceania and without any studies from Africa (Supplementary Figure 1).

In the systematized studies, 17.5% (n = 41) used *in vitro* models, 65.8% (n = 154) *in vivo* and 16.7% (n = 39) both. Of the 80 studies that implemented *in vitro* model, 42.5% (n = 34) corresponded to primary culture, 36.3% (n = 29) cell lines and in 21.3% (n = 17) both were applied. In turn, in the 193 studies that implemented *in vivo* models, 59.6% (n = 115) were mice, 32.6% (n = 63) rats, 1.6% (n = 3) both rats and mice, and in less than 3% other models were used such as rabbits, hamsters and guinea pigs.

In the *in vitro* studies, 20 cell lines were identified, being more frequent the use of respiratory tract epithelial cells, representing 52.2% of the total number of studies with cell lines and 30% of the total number of *in vitro* studies. Likewise, 25 different primary cultures were identified, with a highest proportion of respiratory tract epithelial cells, representing 37.3% of total culture and 23.8% of the total *in vitro* studies, followed by neutrophil culture representing 19.6% and 12.5%, respectively (Table 2).

In the *in vivo* models, 34 strains of mice were identified, of which the Balb/C and C57BL6/J subtypes presented the highest proportion with 48.3% and 33.9% of the total studies in mice, respectively. Likewise, studies in rats included 11 different subtypes, more frequent Sprague-Dawley with 50%, Wistar with 25.8%, and Fischer-344 with 13.6% 11 of rats (Table 3).

Concerning the type of contaminant, 91% studied PM, with 45.7% that included the evaluation of the three types (PM_{10}; $PM_{2.5}$, and $PM_{0.1}$), and the primary immunological outcomes analyzed were cell count in 85%, measurement of cytokines (mainly proteins) in 71.4% and histopathological effects in 53.4% (Table 4).

In the most frequently used *in vitro* model (cell line or respiratory tract epithelium culture), a similar proportion of publications was found between 1980-2010 and 2011–2020; somewhat different from what was found for the most used rat models (Sprague-Dawley and Wistar), which were more used until 2010 (around 60%), while studies in mice have increased their frequency in the last decade since the period 2011–2020 was recorded 83% of studies with C57BL6/J and 66% with Balb/C; That is, the temporal analysis shows that in the last decade the study of this

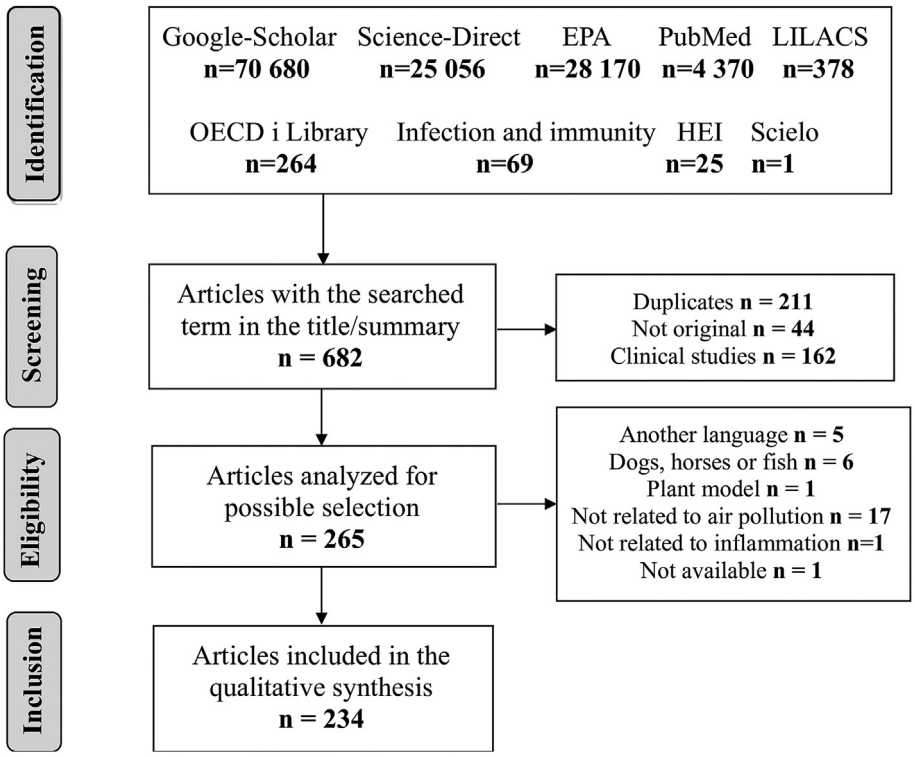

Figure 1. Study search and selection flowchart.

Table 2. Percentage distribution of in vitro studies (N = 80).

Subtype	Model	n	% between the subtype	Total % *in vitro*
Cell lines[a]	Respiratory tract epithelial cells	24	52.2	30
	RAW 264.7	5	10.9	6.3
	Human aortic endothelial cells (HAEC)	2	4.3	2.5
	Murine lung epithelial cells (MLE-12)	2	4.3	2.5
	Human monocytic cells (MM6)	2	4.3	2.5
	Subtotal cell lines	**46**	**100**	**57.5**
Primary culture[b]	Respiratory tract epithelial cells	19	37.3	23.8
	Neutrophils (unspecified)	10	19.6	12.5
	Rat/mouse/rabbit macrophages	8	15.7	10.0
	Human alveolar macrophages	8	15.7	10.0
	Dendritic cells	6	11.8	7.5
	PBMC	3	5.9	3.8
	Differentiated human monocytes in macrophages	2	3.9	2.5
	Subtotal primary culture	**51**	**100**	**63.8**

[a] **The following cell lines presented n = 1:** murine macrophages J774, THP-1, HaCaT, 3LL, HTB54, HL60, L929, 4T1, ATII, RLE-6TN, BW5147, R1, EL4, P815, and TG180.

[b] **The following primary culture presented n = 1:** human monocytes, mouse bone marrow monocytes, human neutrophils, rat neutrophils, primary tracheal epithelial cells of mouse, dendritic cells, endothelial cells, fibroblasts, rat fibroblasts Primary human keratinocytes, rat macrophages, rat alveolar macrophages, mouse bone marrow-derived macrophages, virgin CD4+ T-cells, human CD8+ T-cells, rat leukocytes, rat neonatal cardiomyocytes, and mast cells.

field with C57BL6/J and Balb/C mice has increased, with statistically significant differences ($p < 0.05$) in the three periods analyzed (Figure 2A). Likewise, it is observed that in the last decade, the proportion of studies on immunoglobulins, immunohistochemistry, histopathology, and cytokines has been statistically higher ($p < 0.05$), with a tendency to decrease the use of cell counts and other biomarkers (Figure 2B).

In general, the evidence available in the most frequently used preclinical models shows an alteration of the neutrophil-mediated immune response to PM, characterized by an increase in neutrophils in blood and lung tissue (accompanied by macrophages, monocytes, eosinophils, and lymphocytes), expression of biomarkers such as PAI-1, Saa3, PCR, LDH, alkaline phosphatase, GGT, NAG, ROS, chemotaxis and eicosanoids; as well as the reduction in the expression of iNOS and NADPH oxidase components, and decrease in transcriptional factors like as STAT1. There is divergent evidence in those referring to the increase or decrease of pro-inflammatory cytokines (mRNA and protein) and oxidative stress. Despite this profile's heterogeneity, in histopathological terms,

Table 3. Percentage distribution of *in vivo* studies (N = 193).

Subtype	Model	n	% between the subtype	Total % *in vivo*
Mice[a]	Balb/C	57	48.3	29.5
	C57BL6/J	40	33.9	20.7
	ICR	4	3.4	2.1
	TO	3	2.5	1.6
	Kunming	3	2.5	1.6
	CD-1	3	2.5	1.6
	C3HeB/FEJ	2	1.7	1.0
	DO11.10	2	1.7	1.0
	Subtotal mice	**118**	**100**	**61.1**
Rats[b]	Sprague-Dawley	33	50.0	17.1
	Wistar	17	25.8	8.8
	Fischer-344	9	13.6	4.7
	SH (Spontaneously hypertensive)	3	4.5	1.6
	SHR/NCrIBR	3	4.5	1.6
	WKY (Wistar Kyoto)	3	4.5	1.6
	Subtotal rats	**66**	**100**	**34.2**
Rabbits	New Zealand white rabbits	5	–	2.6
Hamster	Syrian Hamsters (*Mesocricetus auratus*)	4	–	2.1
Guinea pigs	Hartley Guinea pigs	3	–	1.6

[a] **The following mice strains presented n = 1:** Albins (*Mus musculus*), Ahr knockout, Deficient in apolipoprotein E (ApoE-/-), Deficient in MyD88 (MyD88−/−), Homozygotes with mutations in the TNFp55 (Tnfrsf1a) and p75 (Tnfrsf1b) receptor genes, Endogamic (A, AKR, C3, B6, CBA, DBA/2, FVB/N, and F1 specific crosses and backcrosses), Null mutants in EC-SOD, Transgenics (CD2-LacZ80/HazfBR), Transgenics that overexpress EC-SOD, AKR/J, B6C3F1, CB6F1, Hgu CftrTgH, IL-13−/− and IL-4-/IL-13−/−, IL-4−/− and MHC II−/−, IL-17−/−, IL17Ra−/− and IL23p19−/−, Jα18−/−, NC/Nga, NIH, Nlrp3 (−/−), Thy1. 1, TRPC6−/− and TRPC6+/-, Stat1 --, VAChT-KD and 4Get.

[b] **The following rats strains presented n = 1:** SHHF (Spontaneously Hypertensive Heart Failure), SH/NHsd, SPF HsdCpb: WU, SD, and Long-Evans.

preclinical evidence is consistent in the reporting of inflammatory infiltrates and lung tissue damage (Table 5).

4. Discussion

Environmental pollution is a major social, economic, and health problem worldwide. According to the World Health Organization (WHO), about 90% of people living in urban areas are exposed to air quality levels that exceed the accepted limits for $PM_{2.5}$ and PM_{10} (10 or 20 μg/m^3, respectively) [68]. This exposure has been associated with an increase in cardiovascular and respiratory adverse effects [69] and has contributed to decreased cognitive functions, depressive symptoms, and neurodegenerative pathologies [70]. Also, it has generated an economic impact for the countries, represented by an increase in mortality and morbidity, cost overruns for the care of related health events, loss of working hours, school and work absenteeism due to illness or the need to care for a sick person, a decrease in family income and a reduction in productivity [69, 71].

Against this background, in recent years, awareness of the impact of air pollution has increased, leading to changes in public policies. In addition, an increase in research focused on elucidating the mechanisms by which exposure to PM affects human health has been performed, focused on this field, in which preclinical studies play a determining role, given the limitations of human research to establish physiopathological and organic causality [72]. In this work, *in vitro* (primary cell culture and cell lines) and *in vivo* (rat, mouse, rabbit and hamster) models were analyzed to evaluated the effect of air pollutants on the neutrophil-mediated immune response. A total of 324 studies were systematically reviewed, in which were used 90 different preclinical models, with high heterogeneity of study sites, type of contaminant, and immune outcomes.

Most of the studies were carried out in the United States and China. In the case of the United States, the findings of this review demonstrate a greater interest in having substantial preclinical evidence, which in turn is related to previous studies that have reported the association between $PM_{2.5}$ exposure and death from cardiovascular and cerebrovascular disease, COPD, type 2 diabetes, lung cancer, pneumonia, chronic renal disease, hypertension, and dementia [73]. Although the average annual concentration of $PM_{2.5}$ has decreased by 42% between 2000 and 2015 in

Table 4. Percentage distribution of the types of contaminant and immunological outcome studied.

	n	%
Type of contaminant		
PM_{10}, $PM_{2.5}$, $PM_{0.1}$	107	45.7
$PM_{2.5}$	45	19.2
PM_{10}	35	15.0
$PM_{0.1}$	26	11.1
Ozone (O_3)	16	6.8
Sulfur dioxide (SO_2)	1	0.4
Secondary Organic Aerosols (SOA)	1	0.4
Zinc Sulfate ($ZnSO_4$) Aerosol	1	0.4
Concentrated environmental particles (CAP) and ozone (O_3)	1	0.4
Nicotine	1	0.4
Immunological outcome		
Differential counts[a]	164	85.0
Histopathology[a]	103	53.4
Immunohistochemistry[a]	35	18.1
Immunoglobulins[a]	22	11.4
Cytokines	167	71.4
Cytokine mRNA[b]	18	10.8
Cytokine proteins[b]	109	65.3
RNA and cytokine proteins[b]	40	24.0
Biomarkers	92	39.3
Oxidative Activity	67	28.6

[a] N = 193 since it only applies to *in vivo* studies.

[b] N = 167 since it only applies to studies that measured cytokines.

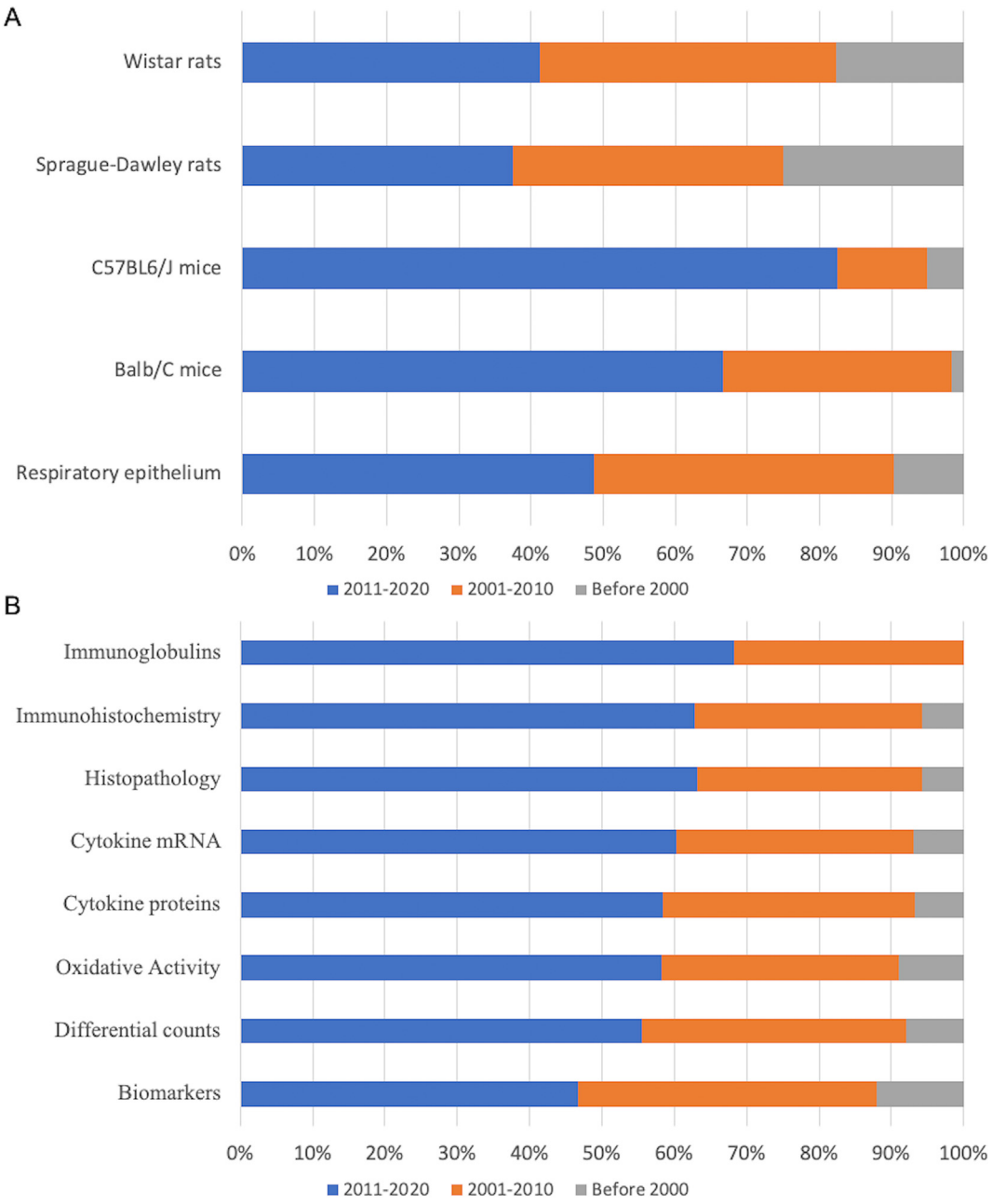

Figure 2. Percentage distribution of the leading preclinical models and immunological outcomes identified according to the publication period. A. Preclinical models, according to the study period. B. Immunological outcomes, according to the study period.

this country, as well as the mortality associated with $PM_{2.5}$ exposure [74], there is evidence that long-term exposure to fine PM contributes to the risk of mortality, especially from lung and cardiopulmonary diseases, including cancer [75].

In addition, China's air pollution problem has become the fourth largest health threat [76]. A study reported that exposure to polycyclic aromatic hydrocarbons (PAH) by inhalation resulted in a higher incidence of lung cancer [77], the most common cancer in the Chinese population [78]. PM_{10} exposure has resulted in about 1.5 million premature deaths in China [79]. Besides, during 2014–2015, the economic cost of health impact due to PM_{10} exposure represented 2.94% of China's gross domestic product (GDP) [79].

In this review, the effect of air pollutants on the neutrophil-mediated response was addressed. Most of the studies included used PM (including mixtures of PM_{10}, $PM_{2.5}$, and $PM_{0.1}$), the main air pollutant [80]. Although considering the availability of monitoring stations in the world, especially those that can collect $PM_{0.1}$, the experimental approaches must be focused on PM_{10} and $PM_{2.5}$, independently, to allow precise comparisons among the studies.

Regarding air pollutants, an increase in macrophages, neutrophils, eosinophils and lymphocytes was observed in the alveolar lavage fluid of mice exposed to PM [18, 26, 29, 30]. Furthermore, it has previously been reported that the inflammatory response may differ according to the type of PM [30, 80, 81, 82]. For instance, $PM_{0.1}$ induces grater eosinophilic

Table 5. Main immunological results in murine, rat, and neutrophil culture models exposed to air pollutants.

Murine models		
C57BL6/J mice	BALB/c mice	Type of pollutant
Increased neutrophils in blood and lung tissue, accompanied by other cell types such as macrophages, monocytes, eosinophils, and lymphocytes [26, 27, 28, 29]	Increased neutrophils in blood and lung tissue, accompanied by other cell types such as macrophages, monocytes, eosinophils, and lymphocytes [30, 31, 32, 33]	Particulate matter (PM_{10}, $PM_{2.5}$, $PM_{0.1}$), and DEP.
Increased pro-inflammatory cytokines (mRNA and protein)* [29, 34, 35]	Increased pro-inflammatory cytokines (mRNA and protein)* [5, 31, 36]	Cigarette smoke and Particulate matter (PM_{10}, $PM_{2.5}$).
Increased oxidative stress** [37, 38]	Increased oxidative stress** [39, 40]	ROFA, Diesel, DEP, and PM_{10}
Increased expression of plasminogen-1 activator inhibitor (PAI-1), Saa3, and CRP [5, 41]	Increased release of LDH (lactate dehydrogenase), alkaline phosphatase, and Saa3 [42] [5] [43].	Particulate matter ($PM_{2.5}$, PM_{10}), DEP, O_3 and tobacco smoke.
Inflammatory infiltration and lung tissue damage [34, 37]	Inflammatory infiltration and lung tissue damage [27, 44, 45]	$PM_{2.5}$, ROFA, and DEP.
Rat Models		
Sprague-Dawley Rats	**Wistar Rats**	
Increased neutrophils in blood and lung tissue, accompanied by other cell types such as macrophages, monocytes, eosinophils, and lymphocytes [21, 46, 47, 48]	Increased neutrophils in blood and lung tissue, accompanied by other cell types such as macrophages, monocytes, eosinophils, and lymphocytes [49, 50, 51, 52]	Particulate matter (PM_{10}, $PM_{2.5}$, $PM_{0.1}$) DEP, CFA, and O_3
Increase in pro-inflammatory cytokines (mRNA and protein) [46, 53, 54]	Increase in pro-inflammatory cytokines (mRNA and protein) [50, 55, 56]	DEP, CAP, ROFA, O_3, and PM_{10}.
Increased oxidative stress [57, 58, 59]	Increased oxidative stress [50, 51, 60]	Particulate matter (PM_{10}, $PM_{2.5}$, $PM_{0.1}$), DEP, and secondary organic aerosols (SOA).
Increased expression of CRP [61]. Increased release of LDH (lactate dehydrogenase) [47, 48, 53]	Increased release of LDH (lactate dehydrogenase), γ-glutamyl transferase (GGT), and n-acetyl glucosaminidase (NAG) [50, 51]	Particulate matter (PM_{10}, $PM_{2.5}$, $PM_{0.1}$), and CAP.
Inflammatory infiltration and lung tissue damage [21, 48, 54]	Inflammatory infiltration and lung tissue damage [56, 62, 63]	CFA, Particulate matter (PM_{10}, $PM_{2.5}$), ROFA, and DEP.
Primary neutrophils culture		
Human primary neutrophils	**Murine primary neutrophils**	
Increase in pro-inflammatory cytokines [64]	Increase in pro-inflammatory cytokines [19] Reduction of the TNFα production [65]	Particulate matter (PM_{10}, $PM_{2.5}$, $PM_{0.1}$)
Production of free oxygen radicals (ROS) [13, 64, 66, 67]	Decreased expression of iNOS and NADPH oxidase components [65]	Particulate matter (PM_{10}, $PM_{2.5}$, $PM_{0.1}$).
Eicosanoid enhancement (LTB_4, LTC_4, and PGE_2) [64]	Reduction in STAT1 activation [65]	Particulate matter (PM_{10}, $PM_{2.5}$, $PM_{0.1}$).

* Some reports indicate a decrease in pro-inflammatory cytokines.
** Some reports indicate a decrease in oxidative stress.

inflammatory effect than $PM_{2.5}$ [83], and also show increased potential for vascular dysfunction and heart damage [81]. Further, Cho et al. [81] observed an increased number of neutrophils in CD-1 mice exposed to PM_{10} compared to those exposed to $PM_{2.5}$ and $PM_{0.1}$ [81]. These results could be associated with chemical agents present in PM_{10} such as Al, Fe, Si, Cu and Ti [84, 85], and higher levels of endotoxin [80, 81, 86] in comparison with other PM [80].

On the other hand, it has been reported that PM stimulates ROS production and release in resting neutrophils, causing tissue damage, thus initiating, or exacerbating the inflammatory response [64, 87] (Figure 3). By the way, Miyake et al. found that endocytosis of neutrophils was involved in the triggering of ROS production. However, these cells endocytosed $PM_{2.5}$, but not PM_{10} [88], suggesting that oxidative response differed according to the type of PM [84, 88]. In this regard, it was identified that PM_{10} was more potent in inducing cytokines but not ROS than $PM_{2.5}$ and $PM_{0.1}$ [84]. In contrast, Li et al. identified the oxidative properties of PM_{10} by increased lactate dehydrogenase concentrations in BALF of syngeneic Wistar-derived rats [89]. These apparently contradictory results indicate that the oxidative stress in response to exposure to PM_{10} was different from that induced by $PM_{2.5}$, the latter being dependent on neutrophil endocytosis.

With respect to cytokine profiling, *in vitro* and *in vivo* studies suggest that IL-6, TNF-α and keratinocyte chemoattractant (KC) may represent key mediators of the inflammatory response induced by PM exposure [20, 25, 90, 91]. Particularly, Vieira et al. found an association between the cytokines release and the recruitment and activation of neutrophils in the BALF of BALB/c mice exposed to PM [90]. Van der Toorn et al. [92] reported that PM induced an increase in cytokines such as MIP-1α (macrophage inflammatory protein-1α), MCP-1 (monocyte chemotactic protein-1), KC, IL-5, and GM-CSF (granulocyte-macrophage colony stimulating factor) in the lungs of BALB/c mice [92]. Besides, Hitzfeld et al. [67] demonstrated that exposure to PM caused the release of IL-8 by neutrophils, inducing the accumulation of these cells at the sites of inflammation due to an autocrine mechanism [67](Figure 3). This cytokine was also released in the human bronchial epithelial cells [25] and the human nasal septum cells [91], indicating its important role in recruiting neutrophils in tissues affected by PM. Additional to the above, exposure to SO_2 in C57BL/6J mice induced infiltration of neutrophils in the alveolar space and release of cytokines such as TNF-α, IL-1β and IL-6. This stimulates the bone marrow stromal cells (mainly adipocytes) and regulates hematopoiesis. As result, alterations of the blood cell counts are observed in leukocytes, erythrocytes and platelets [93].

Besides, previous studies have shown a negative correlation between PM_{10} and O_3 [94], reflecting the importance of research studying the effect of contaminants other than PM. The exposure to O_3 caused the infiltration of neutrophils, macrophages, lymphocytes and eosinophils into the lungs of rabbits [95], mice [96] and rats [97, 98]. Also, Bosson et al. [88] found that O_3 exposure enhanced MPO (Myeloperoxidase)

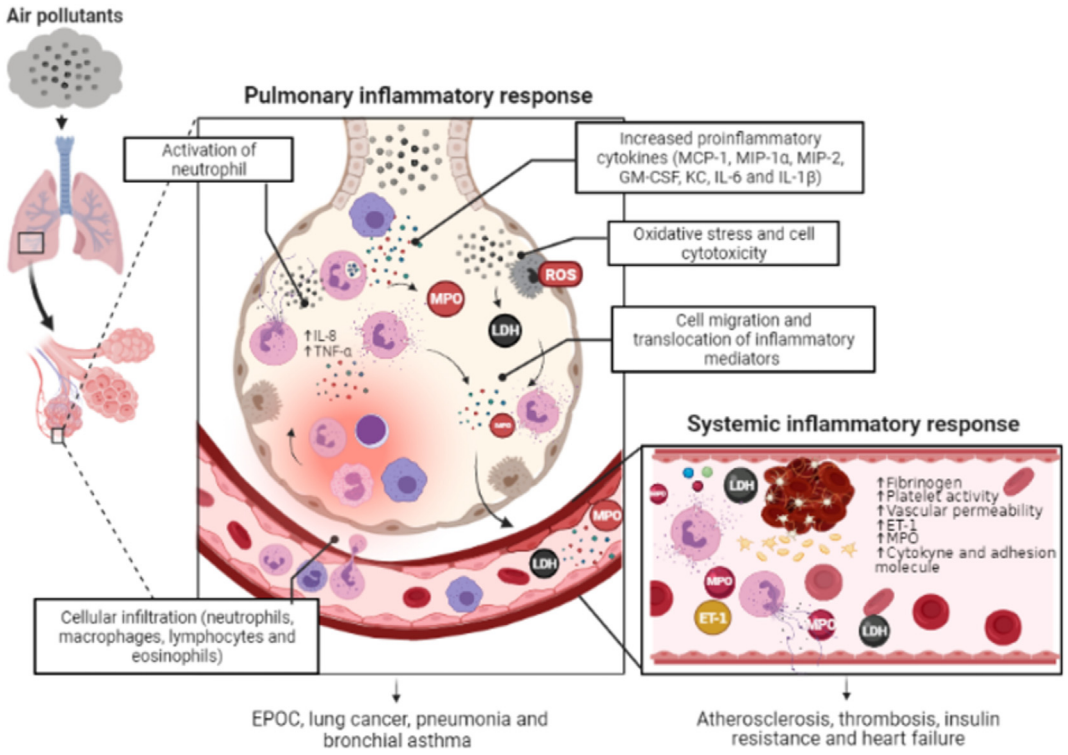

Figure 3. Immunological effects of PM, on neutrophil activation, and pulmonary and systemic homeostasis. Inhalation and deposition of PM in the lungs trigger inflammatory responses leading to the release of inflammatory cytokines (MCP-1, MIP-1α, MIP-2, GM-CSF, KC, IL-6 and IL-1β); and recruitment of innate immune cells (neutrophils, macrophages, lymphocytes and eosinophils). Neutrophil activation (degranulation, phagocytosis and NETs) induces the production of ROS and the release of inflammatory mediators. These cellular mechanisms also promote changes at the pulmonary level, including increased oxidative stress, and cellular cytotoxicity with LDH release. These events are associated with increased circulating levels of adhesion molecules, inflammatory mediators (MPO and ET-1), cytokines, increased platelet activity and vascular permeability. Together, these responses favor the development of pulmonary diseases such as COPD, lung cancer, pneumonia and bronchial asthma; and systemic inflammatory responses that are related to pathologies such as atherosclerosis, thrombosis, insulin resistance and heart failure.

release in induced sputum [88]. These findings suggested that the activated neutrophils induced MPO release, and ROS production, causing cell damage [88, 99].

Regarding aerosol and volatiles, there was a limitation in the number of studies. However, the *in vivo* toxicity resulting from secondary organic aerosols exposure evidenced ROS generation and lung inflammation [59]. Likewise, prolonged exposure to SO_2 caused chronic lung inflammation and pulmonary fibrosis in mice [93]. Moreover, a study evaluating the effect of nicotine present in electronic cigarettes showed higher levels of neutrophils and alveolar macrophages in bronchoalveolar lavage fluid of SR rats than in unexposed rats [100]. Contrary to what was observed for other pollutants, exposure to ZnSO4 was not associated with a change in the number of macrophages or neutrophils [101]. Therefore, although the evidence indicates that exposure to these pollutants affects the respiratory system, given that those pollutants can be generated from different sources of emission, complementary studies are still required.

Furthermore, the evidence indicates that PM exposure may contribute to morbidity and mortality from cardiac diseases. The proposed mechanisms include increased oxidant production, direct cardiac effects, and systemic mediators leading to cardiac responses [102]. Farina et al. [103] demonstrated that the inflammatory response in the lungs after exposure of BALB/c mice to PM_{10}, is also associated with translocation of inflammatory mediators like as MPO and ET-1, from the lungs to the bloodstream, thus triggering systemic and cardiac effects. On the other hand, ET-1, a marker of inflammation implicated in the progression of cardiovascular diseases, has been found to be increased in plasma and cardiac tissue of rats exposed to O_3 and diesel exhaust particles [104, 105, 106]. The increased oxidative stress, limited antioxidative compensation and cytotoxic potential of PM have been implicated in the pathogenesis of cardiovascular diseases in humans and animal models, including those with systemic hypertension and other complications such as atherosclerosis, stroke, and myocardial infarction [107, 108]. Previous studies have reported an increase in blood neutrophils and an attenuated antioxidant response in rats exposed to residual oil fly ash (ROFA) [109], showing PM-induced cardiophysiological changes such as acute depression in ST-segment area of electrocardiography [102]. It has been reported that neutrophil activation (with the expression of inflammatory cytokines, and adhesion molecules) induces endothelial dysfunction through ROS formation, and increased vascular permeability, thus resulting in structural damage of the arterial wall with smooth muscle cell proliferation, and atherosclerotic plaque formation [110, 111, 112]. Exacerbation of vascular oxidative stress in ApoE −/− mice exposed to PM has been reported, which enhanced vascular inflammation and atherosclerosis [113]. Further, a study by Haberzettl et al. [114] showed that exposition of mice to $PM_{2.5}$ suppressed endothelial insulin-stimulated nitric oxide synthase (eNOS) phosphorylation and suppresses vascular insulin signaling, thus suggesting that vascular insulin resistance could be one such "sensitive" target of $PM_{2.5}$ that in turn affects processes such as tissue perfusion, endothelial function, and atherogenesis [115, 116, 117]. The suppression of insulin-stimulated phosphorylation of eNOS results in alteration of the vascular tone, thrombosis, and atherogenesis [115, 117, 118]. Collectively, these changes could increase cardiovascular risk and mortality in humans exposed to PM.

In addition to oxidative stress and neutrophilic inflammation, PM exposure has been associated with activation of the coagulation and fibrinolytic system [119, 120]. Cascio et al [121] found, in a mouse

model, that after exposure to ultrafine particulate matter (UFP) there was an increase in the platelets, plasma fibrinogen, and soluble P-selectin levels, with reduced bleeding time, implying an increased thrombogenic potential. Increased expression of adhesion molecules by pulmonary capillary endothelium in hypertensive rats exposed to ROFA induces neutrophil migration and activation that consequently alter fibrin degradation and stimulate fibrinogen synthesis, ultimately leading to hyperfibrinogenemia [109]. Aberrant fibrinogen increase is a risk factor for cardiovascular disease in humans as by increasing blood viscosity, recruits platelets, and promotes thrombi [122].

While several studies have reported the link between cardiopulmonary mortality and exposure to air pollution, few reports have focused on the central nervous system (CNS). In BALB/c mice exposed to ultrafine particles, increased brain biomarkers of oxidative stress and tissue injury have been observed [123]. Similarly, the acute O_3 exposure in mice induces neurological issues and an increase in infiltrating neutrophils [124]. A study found that Alzheimer's and Parkinson's patients have significantly elevated levels of neutrophil-mediated oxidative stress compared with healthy donors [125]. As neutrophils are potent producers of ROS, including those in response to PM exposure, these cells could induce an oxidative imbalance and consequent oxidative injury to neighboring tissues, thus contributing to the pathogenesis of neurodegenerative disorders [124]. However, additional research should address the effects of neutrophil activation following exposure to air pollution and the related effects on neuroinflammation and neurotoxicity.

Recent studies link neutrophils as one of the most important players in the effects of pollutant exposure and cancer development. Rocks et al. [126] demonstrated that O_3 exposure greatly facilitates lung metastasis by inducing tissue injury and neutrophilic inflammation in a mouse model. Furthermore, O_3 exposure influences metastasis and activates the release of neutrophil extracellular traps (NETs) that favor tumor cell colonization in the lungs. However, there are limited studies that focus on evaluating this effect in the presence of PM, therefore, the cellular and molecular mechanisms linking neutrophils to cancer development and progression in relation to PM exposure should be further explored. This may be an important explanation for the epidemiological correlation between exposure to environmental pollutants and high rates of hospitalization and mortality from cardiovascular complications [110, 111].

Preclinical study models, also called basic medical research, include experiments on animals, cellular studies, among others that seek to clarify biochemical, genetic, physiological, or immunological mechanisms for various purposes such as improving analytical, diagnostic, or therapeutic processes, as well as consolidating (and in some cases discarding) scientific knowledge that is indispensable for the subsequent development of research on patients. Animal models make it possible to visualize the neutrophil-mediated immune response in a physiologically relevant environment that includes cellular interactions or specific signals that can be evaluated by *in vitro* models [127, 128]. In this review, it was evidenced that most of the studies included an *in vivo* model, in which mainly mice and rats were used. This trend has been maintained over time. It is worth mentioning that, since the 20th century, mice have represented a key element in the investigation of the immune response [129]. Moreover, given the metabolic and physiological similarities between humans and rats, the latter are widely used in immunological, pharmacological, and toxicological studies [130]. Nonetheless, primary research and characterization of leukocyte subpopulations in this species are less well known than for research in mouse models, limiting the development of complex immunological studies [131].

Although the use of animal models has been a critical element in biomedical research, it implies high costs and strict ethical considerations, which restrict their use [132]. With this limitation, the *in vitro* models represent a useful tool in the study of the effect of environmental contamination; although, in this model, in particular, there are different factors such as the concentration of the contaminants that can limit the conclusive and comparable information between the different studies [133]. Besides, few differences have been reported in the neutrophil's markers, depending on the mice or rat strain, because those different types of animals show differences in adaptive immunity, without affecting the innate immunity cells. In this sense, the PM concentrations that demonstrate a significant effect *in vitro* can be greater than the PM density that reaches the respiratory tract. Despite the above, these problems can also occur in animal models, so the use of *in vitro* models remains relevant [133].

In this work, primary cultures were the main *in vitro* models used in the studies. However, there were a limited number of *in vitro* studies that used neutrophils as a cellular model. Their selection instead of the cell line could be because the genetic manipulation of the cell lines can alter their phenotype, functionality, and capacity of response to stimuli, so it is possible that they do not adequately represent the primary cells and could provide deleterious results [134]. The general recommendations for *in vitro* experiments should be the use of primary human neutrophils, which can be easily obtained, compared with animal cells.

In general, this review showed high heterogeneity in the type of model used in the studies to evaluate the effect of air pollution, which may represent a limitation for the passage to clinical studies since it is difficult to determine the consistency of the results and the selection of the most significant exposures [135]. However, the identification of biological markers, that explain the effects of air pollutants is important itself, as provides information for experimental design looking for the understanding of molecular mechanisms. Besides, limited information was found on Ozone, SO_2 and $ZnSO_4$, evidencing the need to increase research focused on these pollutants.

Considering the studied outcomes, it is clear the natural change in the methodologies, promoted by the advances in molecular techniques, multiplex assays, and modern biochemical and immunological tools that allow, besides the classic measurements of cellular counts, functional aspects of them, including respiratory explosion and transcriptional expression of cytokines and other inflammatory factors, among others. These new measurements provide new information regarding the state of cell activation and the magnitude of the immune response in response to airborne contaminants, which could explain the alterations observed in the long term in individuals exposed to airborne contaminants, including increased susceptibility to infectious diseases of the respiratory tract.

Consistent with the characteristics of Cochrane's broad approach, we must declare some intrinsic limitations to this type of review, such as the impossibility of delving into the findings of some hypotheses on specific immunological outcomes or the mechanisms of damage of PM, especially those associated to the activity of the neutrophils.

5. Conclusions

The analysis of the studies and their heterogeneity allows us to recommend practical options that can be unified in future studies to obtain comparable data to move on to clinical studies, which will support the epidemiological observations widely reported in the area. These recommendations include the use of primary cultures of human neutrophils, considering that human donors' genetic variability allows a precise approximation to the expected results in the general population. Regarding the outcomes, the measurement of pro-inflammatory cytokines, either at the protein level in culture supernatants and BALF, by ELISA, or mRNA by RT-PCR, are widely used measures that allow building meta-analysis and understanding of global variations in response to contaminants found in different latitudes. Secondly, there is the use of BALBc or C57BL6/J murine models (understanding that it is not available in all research entities), and in this, the histopathological analyses (infiltrates counts and lung damage measures) that allow understanding of the expected immunopathological potential in the human population exposed to air pollutants.

Finally, the studies included in this review suggest that environmental pollutants induced neutrophil recruitment as the first sign of inflammation. The effect of neutrophils depended on the type, concentration and size of the PM particles. These cells release pro-inflammatory

cytokines and ROS that cause damage to lung tissue and contributes to the systemic inflammatory response related to cardiovascular diseases. The importance of future research to clearly establish the relationship between neutrophilic activation after exposure to air pollutants with the development of cancer and neurodegenerative diseases was also identified. Future studies with potential for clinical approaches include the use of primary cells, especially those obtained from pulmonary samples, such as bronchoalveolar lavages in human populations from different geographical areas with monitoring programs for air pollution. However, basic experimental studies are still incipient, indicating the need to improve and increase these investigations before the studies in human populations.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data associated with this study has been deposited at https://doi.org/10.6084/m9.figshare.13140176.v1.

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Declaration of interests statement

The authors declare no conflict of interest.

Additional information

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