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Review

Registered human trials addressing environmental and occupational toxicant exposures: Scoping review of immunological markers and protective strategies

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ABSTRACT

Exposure to pollution is a worldwide societal challenge participating in the etiology and progression of different diseases. However, the scarce information hinders our understanding of the actual level of human exposure and its specific effects. Inadequate and excessive immune responses underlie diverse chronic diseases. Yet, it is unclear which and how toxicant exposures affect the immune system functions. There is a multiplicity of immunological outcomes and biomarkers being studied in human trials related to exposure to different toxicants but still without clear evidence of their value as biomarkers of exposure or effect.

The main aim of this study was to collect scientific evidence and identify relevant immunological biomarkers used at the clinical level for toxicant exposures. We used the platform clinical trials.gov as a database tool. First, we performed a search combining research items related to toxicants and immunological parameters. The resulting117 clinical trials were examined for immune-related outcomes and specific biomarkers evaluated in subjects exposed to occupational and environmental toxicants. After categorization, relevant immunological outcomes and biomarkers were identified related to systemic and airway inflammation, modulation of immune cells, allergy and autoimmunity. In general, the immune markers related to inflammation are more frequently investigated for exposure to pollutants, namely IL-6, C-reactive protein (CRP) and nitric oxide (NO). Nevertheless, the data also indicated that prospective biomarkers of effect are gaining ground and a guiding representation of the established and novel biomarkers is suggested for upcoming trials. Finally, potential protective strategies to mitigate the adverse effects of specific toxicants are underlined for future studies.

1. Introduction

The presence of toxic compounds in the air, water and food is amply reported and exposure to pollutants by the different routes is a fact (Pant et al., 2018; Zhang et al., 2018; González-Mariño et al., 2021). Moreover, their diversity is enormous and includes well-defined chemical substances, e.g. metals, bisphenol A, and chemical mixtures such as cigarette smoke and air particulate matter (PM) (Pant et al., 2018; Zhang et al., 2018, 2019; González-Mariño et al., 2021). This reality brings us to a recent report by the European Environment Agency (EEA, 2021) where the health impact of air pollutants and fine PM was estimated to be responsible for more than 300,000 premature deaths in 2019.

Abbreviations: AhR, aryl hydrocarbon receptor; autoAbs, autoantibodies; B[*a*]P, benzo(a)pyrene; COX-2, cyclooxygenase-2; CRP, C-reactive protein; ENA-78, extractable nuclear antigen-78; FeNO, fractional exhaled nitric oxide; ICAM-1, intercellular adhesion molecule-1; IgA, immunoglobulin A; IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M; L-NMMA, nitric oxide synthase inhibitor NG-monomethyl-L-arginine; MMP-9, matrix metallopeptidase 9; NF-κB, nuclear factor-kappa B; NO, Nitric oxide; PAH, polycyclic aromatic hydrocarbon; PCB, polychlorinated biphenyl; PFOS, perfluorooctane sulfonate; PM, air particulate matter; SLGT2, sodium-glucose cotransporter-2; SLE, systemic lupus erythematosus; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; TCE, trichloroethylene; Th, T helper cell; VCAM-1, vascular cell adhesion molecule-1.

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Environmental and occupational exposure raises health concerns related to acute and chronic exposure to chemicals in workplaces. For example, some study cases include styrene exposure and hearing loss (Triebig et al., 2009) and exposure to nanomaterials in workplaces (Iavicoli et al., 2020).

Twenty-five years ago, Grandjean pointed out the relevance of biomarkers in epidemiology to classify and quantify environmental exposures and associated effects (Grandjean, 1995). However, the spectrum of the response (of organisms/body/human) to pollution is wide and the potential adverse effects of environmental exposures are poorly understood. The exposome paradigm is emerging as a key tool in this field (Sillé et al., 2020; Vineis et al., 2020). However, until now it mainly focused on general outcomes (e.g., mortality and hospitalizations) and specific exposure biomarkers are one of the gaps to be filled (Vineis et al., 2020).

Among other factors, environmental pollutants are one of the causes for the deregulation of the immune system affecting mechanisms of immunomodulation and inflammation (Lagoa et al., 2022; Ma et al., 2019; Winans et al., 2011). The immune system plays a critical role in the protecting the body against pathogens and inadequate and excessive immune responses underlie diverse chronic diseases. Distinct immunological mechanisms are responsible to recognize pathogens, then to act specifically and according to it and finally to provide immunological memory for prolonged protection. Moreover, the immune system is also responsible for fighting body changes that lead to disease, such as cancer which is in fact the main reason for the success of immunotherapy (Dhar et al., 2021). There is evidence that immune system is affected by exposure to polycyclic aromatic hydrocarbons (PAHs) and dioxins present, for example, in vehicle exhaust, PM, particulates from coal combustion, cigarette smoke and in foods. PAHs and some polychlorinated biphenyls (PCBs) can activate important transcription factors as the aryl hydrocarbon receptor (AhR) and nuclear factor-kappa B (NF-κB) signaling pathways, highly implicated in inflammation, cancer and immune responses (Lagoa et al., 2022; Øvrevik et al., 2017; Pinel-Marie et al., 2009; Wang et al., 2017, 2019). In addition, considering the relevance of the *in utero* immune development (Hertz-Picciotto et al., 2008) that encompasses critical steps such as cell differentiation and production of immunomodulators, it is logical to assume that prenatal exposure to toxicants will affect the postnatal immunity. In fact, mice prenatally exposed to toxicants revealed impaired immune response and increased the risk of autoimmune disease during life (Hanson et al., 2012; Elter et al., 2020). Nevertheless, by reviewing 41 epidemiological studies, Gascon and colleagues (2013) found limited evidence for the relation of prenatal exposure to persistent organic pollutants and respiratory health, allergy or the immune system in infancy, childhood and adolescence (Gascon et al., 2013).

The function and the immune system feedback depend on whether the necessary immune response is to be innate or adaptive. Depending on the response type, specific cells are called to action. Typically, basophils, eosinophils, neutrophils, mast and natural killer cells are the key players of innate immune response while B and T cells are the principal actors on adaptive immunity (Fig. 1A). Furthermore, activation and mobilization of $CD4^+$ and $CD8^+$ T cell subtypes depend on the surrounding environment with a specific expression of cytokines and chemokines and their receptors (Fig. 1B). Additionally, antibodies and cytokines, are instrumental for the immune response (Behl et al., 2021) to environmental toxicants acting either by neutralizing, subverting or, on the other hand, by exacerbating the immune response (Fig. 1C). This diversity of immunological responses leads to a multiplicity of immunological outcomes and biomarkers studied in human trials that investigate exposure to different toxicants.

We hypothesized that by gathering evidence from previous clinical trials it was possible to categorize the immunological outcomes and prioritize the corresponding biomarkers for future studies of human toxicant exposures.

Therefore, the aims of this study were:

1) To categorize the immune-related outcomes and specific biomarkers evaluated in clinical trials of subjects exposed to environmental toxicants;
2) To select established and prospective immunological outcomes that can be considered in the future when investigating human toxicant exposures;
3) To identify protective strategies investigated at the clinical level to counteract the effects of toxic environmental exposures, focusing on the immune effects.

2. Background of the classical views on the interference of environmental toxicants with the immune system

2.1. Inflammation

Inflammation is a complex immune response to insults, such as pathogens and chemicals, which involve pro- and anti-inflammatory cytokines. The anti-inflammatory signals control the pro-inflammatory response and are beneficial to prevent chronic inflammation conditions which may have a negative impact on tissues like vascular dysfunction (Shao et al., 2014). An imbalance in anti- and

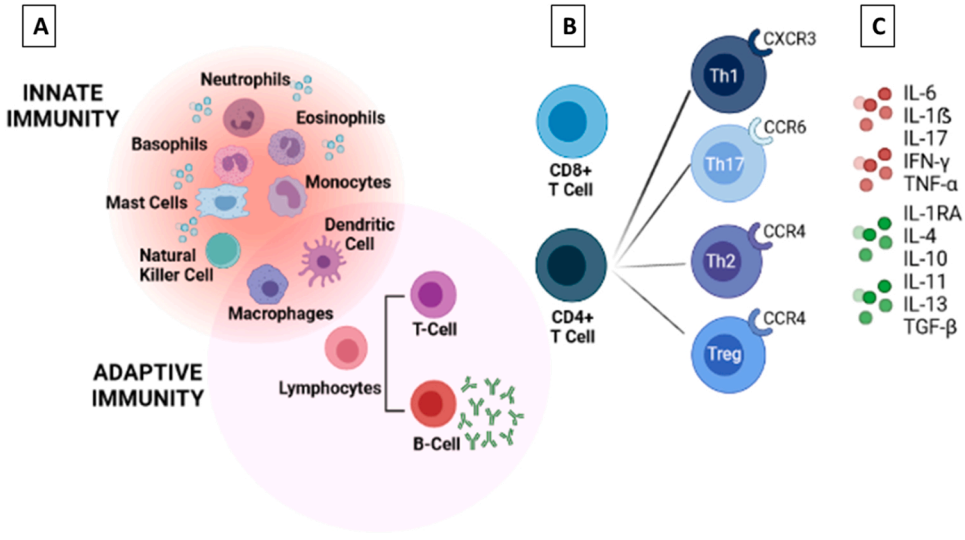


Fig. 1. – Landscape of immunological processes and markers, described in the literature to be affected by environmental toxicants. A) Cells in innate and adaptive immunity with secretion of antibodies by B cells; B) The mature T cell types and $CD4^+$ T cells' subtypes expressing specific chemokine receptors; C) The major cytokines secreted by immune cells with anti-inflammatory and pro-inflammatory actions are depicted in green and red, respectively. Image created with BioRender.com.

pro-inflammatory signals can result in chronic inflammation with the prevalence of pro-inflammatory responses (Fig. 2). The major anti-inflammatory cytokines include IL-1RA, IL-4, IL-10, IL-11, IL-13 and TGF-β, while the major pro-inflammatory cytokines include IL-6, IL-1β, IL-17, IFN-γ and TNF-α (Fig. 1C).

PM and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) are example of toxicants that conduct to inflammation, either by provoking an increased expression of inflammatory cytokines, such as IL-1β, IL-6 and IL-8 but also by upregulating inflammation-associated enzymes like matrix metallopeptidase 9 (MMP-9) and cyclooxygenase-2 (COX-2) (Vogel et al., 2011; Jin et al., 2016; Wang et al., 2017). The NF-κB signaling pathway is possibly related to the inflammatory processes triggered by airborne PM (Jin et al., 2016; Wang et al., 2017). And, the activation of both AhR and NF-κB signaling pathways are associated to the inflammatory processes triggered by dioxins, benzo(a)pyrene (B[*a*]P) and dioxin-like PCBs (Pinel-Marie et al., 2009; Vogel et al., 2011; Wang et al., 2019) (Fig. 2). When responding to environmental toxicants, macrophages produce oxidizing agents and inflammatory cytokines, namely IFN-γ, TNF-α and IL-6, in the so-called M1 polarization which can promote chronic inflammation, tissue injury and cancer initiation. Whereas M2 polarization can lead to immune suppression (Sepand et al., 2021).

2.2. Immune suppression

Immune suppression is one of the adverse effects of environmental toxicants happening either by reducing the number of leukocytes, affecting their function or including the expression of immunosuppressive cytokines (Wang et al., 2021b), such as TGF-β (Sepand et al., 2021) (Fig. 2).

PAHs, such as benzo[*a*]anthracene, B[*a*]P or PAH mixtures showed to alter monocyte to macrophage differentiation by altered adherence and macrophage polarization towards M1 or M2 states (Tooker et al., 2021). The M/M2 polarization is also affected by environmental toxicants like PCBs (Wang et al., 2019; Sepand et al., 2021). Indeed, a recent review recapitulates several mechanisms, related to macrophage function - like plasticity, polarization and migration – that are affected by environmental carcinogens such as arsenic, silica and ozone (Sepand et al., 2021).

In carps, cadmium caused immunosuppression accompanied by increased expression of inflammatory genes like IL-11b, IL-1β, IL-6, IFN-γ, and chemokines Cxcl18b (Chen et al., 2019a; Jiaxin et al., 2020). And, in mice exposed to tetrachlorobisphenol A and formaldehyde, immunosuppression occurred either by inducing pro-inflammatory and anti-inflammatory cytokines (IL-2, IL-12, IFN-γ, and TNF-α) (IL-4, IL-5, IL-10, GM-CSF) (Wang et al., 2021b) or via the calcineurin-NFAT signaling pathway (Park et al., 2020).

2.3. Allergies

Allergy is a hypersensitivity reaction resulting from inappropriate responses of the immune system to foreign substances, called allergens. This hypersensitivity involves imbalance on the T helper (Th) differentiation and most often exaggerated production of immunoglobulin E (IgE) (Platts-Mills and Woodfolk, 2011). After antigen encounter and depending on the cytokine milieu and other signals provided by antigen-presenting cells, $CD4^+$ Th cells differentiate into subsets, e.g. Th type 1 (Th1), Th type 2 (Th2) and Th type 17 (Th17) (Fig. 1), classified according to their partially overlapping cytokine production pattern. Allergies result mostly from Th2 and Th17 cells polarization (Crinnion, 2012) and several environmental toxicants, like perfluorooctane sulfonate (PFOS) and ambient fine particles affect the Th1/Th2 balance (Zhao et al., 2012; Zhong et al., 2016) (Fig. 2).

In fact, the development of allergies seems to result from the interplay between the internal and external exposome, including their interference with the microbiome. While the internal exposome depends on the organism's genetics, the external exposome covers every factor external to the body, including the environmental chemicals (Cecchi et al., 2018) and other factors as the social and psychological ones (Barnthouse and Jones, 2019). Nevertheless, a strong correlation exists between exposure to pesticides, solvents, and air pollutants and increasing rates of asthma and allergies (Crinnion, 2012).

The microbiome is an important factor to consider in the development of asthma and allergies (Huang and Boushey, 2015; Hershko, 2017) and it is affected by toxicants' exposure. An example is the report of air pollution provoking changes in the microbiome –denominated dysbiosis - of healthy and asthmatic children (Zheng et al., 2020).

Altered microbiota composition is associated with impaired intestinal barrier function and dysregulation of the mucosal immune system, but it is unclear if gut dysbiosis is a causal factor or an outcome of allergic diseases. Moreover, the gut microbiome is not only implicated in allergy but also in autoimmune diseases, as introduced in the next section.

2.4. Autoimmunity

Autoimmunity is a deregulated immune response against self-antigens. There is strong evidence that environmental and genetic

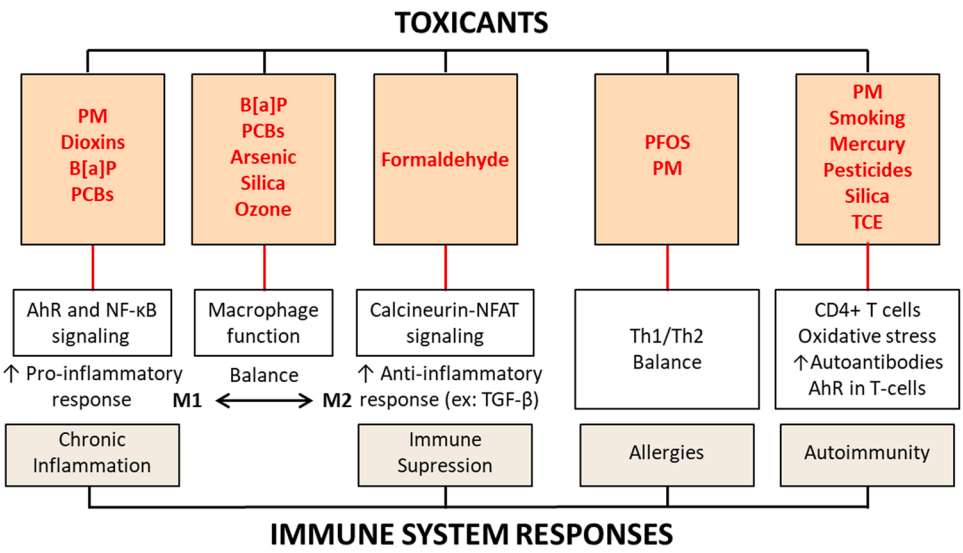


Fig. 2. – Impact of toxicants on the immune system considering the most reported outcomes: chronic inflammation, immune suppression, allergies and autoimmunity. The specific mechanisms of action are indicated. Examples of environmental toxicants are depicted in red. Abbreviations: AhR - aryl hydrocarbon receptor; B[*a*]P – benzo[*a*]pyrene; NF-κB - nuclear factor kappa-light-chain-enhancer of activated B cells; NFAT - nuclear factor of activated T cells; PCBs - polychlorinated biphenyls; PFOS - perfluorooctane sulfonate; PM – particulate matter; TCE - trichloroethylene; TGF-β - transforming growth factor beta; – affects; ↑ - increase.

factors interact in the onset or the progression of autoimmune diseases. In addition to drugs and diet, diverse environmental chemicals, pesticides and respirable PM have been associated with autoimmune diseases like systemic lupus erythematosus (SLE), rheumatic arthritis and systemic sclerosis (Khan and Wang, 2018; Pollard et al., 2021). Additionally, they also associate with subclinical autoimmunity manifestations as autoantibodies (autoAbs), autoreactive B cells and infiltrating neutrophils (Khan and Wang, 2018; Pollard et al., 2021).

Exposure to aromatic and halogenated solvents, trichloroethylene (TCE) and ketones was strongly related to systemic sclerosis and, less established, to multiple sclerosis (Pollard et al., 2021). These types of exposures were observed to prevail at the occupational level with inhalation and dermal routes presenting higher toxicological risk (Pollard et al., 2021). TCE-mediated autoimmunity and hypersensitivity with altered numbers of peripheral blood $CD4^+$ T cells, and other lymphocyte subsets, was observed in workers occupationally exposed to TCE (Hosgood III, 2012). $CD4^+$ T cells are key players in autoimmunity (Dittel, 2008; Raphael et al., 2020) and, in mice, developmental exposure to TCE causes epigenetic changes in autosomal chromosomes of activated effector memory $CD4^+$ T cells that persist to adulthood (Byrum et al., 2019). Smoking and mercury exposures were associated with forms of rheumatoid arthritis, SLE or autoimmune responses without clinical disease (Khan and Wang, 2018; Pollard et al., 2021). TCE, smoking and mercury cause oxidative stress and modifications of self-protein that become immunogenic.

Mitochondrial dysfunctional mechanisms related to T lymphocyte apoptosis, production of reactive oxygen species and metabolism interfere in autoimmunity (Lenardo et al., 1999; Chen and Zhou, 2004; Qiu et al., 2021; Scherlinger and Tsokos, 2021). Mercury immunotoxicity was connected to mitochondrial changes in T cells (Khan and Wang, 2018; Pollard et al., 2021). Since oxidative stress is present in several autoimmune diseases (Fig. 2), antioxidants have been proposed as potential interventions for the clinical management of these diseases (Khan and Wang, 2018; Rengasamy et al., 2019).

Farming and prolonged exposure to pesticides are long-recognized risk factors for developing systemic autoimmune diseases like rheumatoid arthritis (Lundberg et al., 1994). Increased levels of circulating autoAbs and decreased TGF-β, were suggested to identify individuals at higher risk of systemic autoimmune diseases (Munroe et al., 2017). A recent study found that antinuclear autoAbs in farmers' serum samples correlated with greater (lifetime) use of the fumigant methyl bromide, the carbamate insecticide aldicarb and some organochlorine insecticides (Parks et al., 2019).

Epidemiology points a strong contribution of inhalable crystalline silica dust, found in construction, mining and agriculture to the development of autoimmune diseases, including SLE (Miller et al., 2012). Silica triggers lung pro-inflammatory and interferon-regulated genes upregulation, formation of tertiary lymphoid structures and autoAbs, in humans and rodents (Wierenga et al., 2020; Pollard et al., 2021). In addition, atmospheric PM aggravate autoimmune pathologies (Angelici et al., 2016). PM and PAHs changed cytokine expression and promoted Th17 differentiation in a murine model of autoimmune disease (O'Driscoll et al., 2018), and the dioxin- and PAH-sensitive AhR transcription factor was pointed as the probable mechanism sustaining T cell responses in atmospheric PM-mediated autoimmunity (O'Driscoll and Mezrich, 2018).

Fig. 2 includes the overall mechanisms affected by the described environmental toxicants in autoimmunity. Nevertheless, it is relevant to consider that autoimmunity is complex. And, if from a simplest point of view it can be interpreted as a deregulated response against self-antigens, it may also be important to consider that it is a result of complex interactions (e.g., with some bacteria and virus), such as dysbiosis. Similar to the interference of microbiome in allergies reported previously, gut dysbiosis is a response to the environmental toxicants the organism is exposed to and can contribute to autoimmunity in a close relation between oxidative stress and deregulation of the intestinal barrier function (Khan and Wang, 2020).

3. Clinical trials of exposure to environmental toxicants assessing immunological effects or protective strategies

3.1. Methodology for trial search

To identify clinical trials of exposure to environmental and occupational toxicants, we carried out a search on the clinical trials platform (www.clinicaltrials.gov in December 2020) by merging two different types of search, a general and a toxicant-specific search. The first - search A – resulted in 691 trials that combined the keywords resembling general terms for environmental and occupational exposure (Supplementary Table 1). Search B resulted in 378 trials collected using the individual and specific terms for environmental and occupational toxicants (Supplementary Table 1). Duplicates were removed and 944 trials proceeded to manual screening. After screening for relevant environmental or occupational exposure conditions, and immune or inflammation outcomes, and protective strategies, this search returned 117 trials (Fig. 3 and Supplementary Table 2). Trials not relevant to study's scope were discarded, e.g. emerged trials investigating dust mite and allergies or premature birth and high-risk pregnancy but without toxicant exposure, or trials of arsenic trioxide as drug therapy or using environmental chambers to test conditions not related to toxic exposure. The information gathered from the 117 registered clinical trials for the type of toxicant exposure, the immunological outcome and/or the protective strategy investigated, is described in the next sections. When necessary, the analysis of results is complemented with data from non-registered trials found in PubMed for the toxicant being discussed.

3.2. Trials according to the type of toxicants

We have identified 117 clinical trials addressing exposure to environmental and occupational toxicants. These trials focused on 25 different types of toxicants' exposure that were grouped into six major categories. All trials (Supplementary Table 2) received a code, to facilitate the recognition of each trial, and from now on, the reader will be directed in the text to these codes.

In more detail, Table 1 describes six categories of exposure and the number of corresponding trials. It is possible to see that clinical trials for general and specific exposure to air pollution are predominant, followed by occupational-related exposures. All six categories present a wide range regarding the number of participants enrolled without a clear trend (Supplementary Table 2). Most of the trials followed an interventional study type, except for cigarette and unspecified exposures in which all trials were observational (Supplementary Table 2).

4. Immunological outcomes

From the 117 trials collected, 99 of them evaluate immune-related outcomes. To better comprehend the possible use of these outcomes or biomarkers to assess the effects of toxicant exposure, a categorization was followed covering different clinical immunological outcomes: systemic inflammation, airway inflammation, modulation of immune cell populations and function, allergy and autoimmunity (Sup. Table 2). The different outcomes found were put into the respective category. Each or multiple inflammation/immunological outcomes were evaluated, depending on the trial. Altogether, the immunological markers found were very diverse as described in the next sections. Only 8 registered clinical trials out of the 99 evaluating immune-related outcomes, presented the study results in the clinical trials platform (www.clinicaltrials.gov on December 2020, Sup. Table 2 Codes: 6, 10, 58, 61, 63, 75, 86) with 5 showing an association regarding toxicant exposure and immunological/inflammation outcomes (Sup. Table 2 Codes: 6, 61, 63, 75, 86).

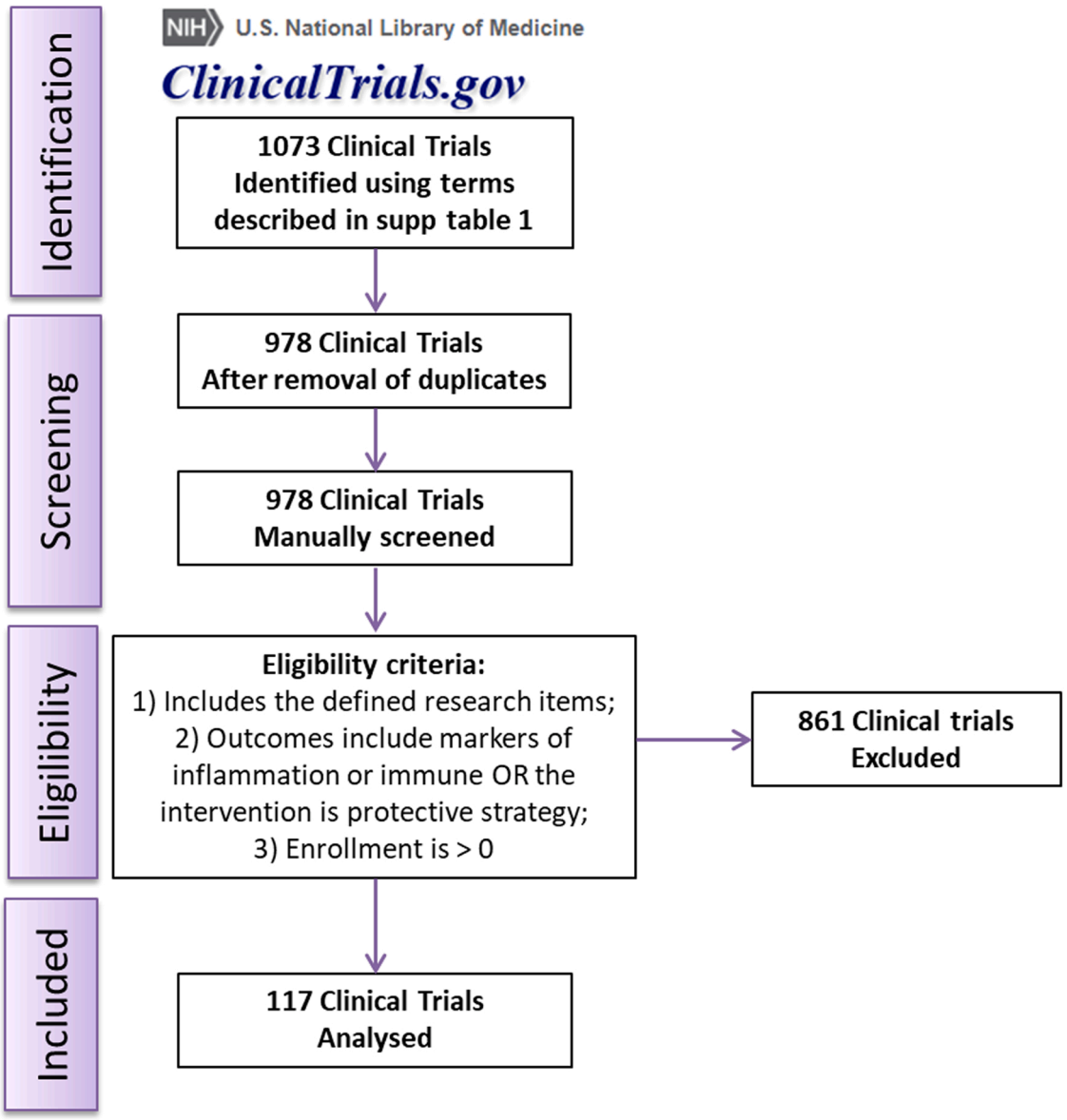


Fig. 3. – PRISMA Presentation for the research of registered clinical trials performed using the clinicaltrials.gov platform. A manual screening occurred to eliminate duplicated clinical trials and the trials not matching with the eligibility criteria. The research items used are described in Supplementary Table 1.

4.1. Systemic inflammation

Systemic inflammation was the most frequent immunological outcome investigated in the registered clinical trials collected and it was evaluated using distinct markers (Fig. 4). C-reactive protein (CRP) detection in blood, plasma, and serum is the most investigated parameter of inflammation status. Its easiness for analysis probably contributes to its choice as an analytical parameter. Nevertheless, biomarkers related to blood coagulation were also explored with nitrite or nitric oxide measurements in plasma and serum. Less frequent explored are the metabolome of oxylipins (a group of fatty acids) and sera amyloid A (an opsonin), both involved in several processes including inflammation (Fig. 4A).

Specific insights are given by the trials focusing on cytokine analysis (Fig. 4B). IL-6, TNF-α and IL-8 were the most frequently investigated cytokines but IL-1β, IL-1 or IL-4 were also referred.

Some trials point to the objective to investigate systemic inflammation or cytokine profile but without specifying which parameters were explored (Sup. Table 2 Codes: 4, 6, 9, 16, 19, 29, 31, 34, 39, 41, 46, 52, 53, 57, 60, 62, 66, 70, 79, 81, and 86).

In a study, an association between exposure to PM2.5 (particulate matter with 2.5 micrometers of diameter and smaller) and CRP was found in traffic-impacted areas, but no correlation with wood smoke-impacted locations (NCT01570062) (Kajbafzadeh et al., 2015). Yet, air filtration implemented in this population with such exposure resulted in decreased levels of CRP (NCT01256957) (Allen et al., 2011). More recently, an increase in CRP, serum amyloid A and adhesion molecules (ICAM-1 and VCAM-1) was observed for a trial investigating exposure to PM2.5 (NCT03232086) (Wyatt et al., 2020) and in (Young et al., 2020). Moreover, firefighters working closer to smoke showed increases in CRP, serum amyloid A and IL-8 positively correlated to segmented-neutrophil (Adetona et al., 2017). And, PM2.5 levels are associated to the expression of IL-1, IL-6, TNF-α, toll-like receptor-2, CD40 ligand and ICAM-1 (Chen et al., 2018). Once more, air purification (for particles) was associated with a decrease in monocyte chemoattractant protein-1, IL-1β, myeloperoxidase and soluble CD40 ligand (Sup. Table 2 Codes: 8, 61; Chen et al., 2015). PM and ozone were associated with changes in IL-6, CD40 ligand, IL-1β, ICAM-1, and VCAM-1 (Li et al., 2017;

Table 1
– Categorization of environmental exposures investigated in the 117 registered clinical trials found with immune and inflammation outcomes and/or protective strategies associated. Categories include general air pollution, specific air pollution, occupational specific toxicants, environmental specific toxicants, smoking-related toxicants, and exposure to unspecified toxicants.

Categories of exposure	Types of exposures included	Number of trials found
General air pollution	Air pollution*	7
Sub-total:		**7**
Specific air pollution	Traffic-related or Diesel Exhaust*	18
	Ozone (and Nitrogen dioxide)*	17
	PM*	16
	Indoor air pollution*	9
	Combustion*	6
	Biodiesel Exhaust*	3
	Organic dust*	3
	Aerosols*	1
	Environmental toxins*	1
	PCBs, beta-hexachlorocyclohexane, waste dumping* and uncontrolled burning*	1
Sub-total:		**55**
Occupational specific toxicants	Silica dust (and PAHs)	3
	Cement	2
	Formaldehyde	2
	Pesticides (atrazine, organophosphate, insecticides, carbamates and diazinon)	2
	TCE	1
Sub-total:		**10**
Environmental specific toxicants	Heavy metals (mercury, lead, arsenic)	14
	Pesticides (Organophpsphorus pesticide, 4,4'-dichlorodiphenyltrichloroethane -DDT-, dieldrin, chlordane, toxaphene and methoxychlor)	2
	Acrylamide	1
	Bisphenol A	1
	PCBs	1
	Volatile methyl sulfides	1
Sub-total:		**20**
Smoking-related toxicants	Environmental tobacco smoke	2
	Cigarette smoking	1
Sub-total:		**3**
Unspecified toxicants	Unspecified	2
Sub-total:		**2**
Total:		**117**

* The clinical trials do not specify the chemical composition of these toxicants.

Mirowsky et al., 2017). Also, a relation was found for diesel exhaust and increased values of TNF-α and IL-6 (Törnqvist et al., 2007). A recent study, investigating farmers exposed to mixtures of pesticides revealed that IL-6 was elevated when compared to controls. In regards to blood cell counts, the same study showed that the levels of monocytes, dendritic cells, total T cells, central memory CD8 T cells and effector memory CD8 T cells were increased in farmers while the levels of total B cells, regulatory B cells and plasmablasts were decreased (Jacobsen--Pereira et al., 2020). Phthalates showed to induce changes in cytokines like IFNγ, TNFα and IL-6 (Nygaard et al., 2021) while coal induced chemokines (CCL17, CXCL5, CXCL6 and CXCL11), the serum amyloid P component, TNF-α (Wong et al., 2019). Moreover, BTX compounds (benzene, toluene, and xylene) present in gasoline increased pro-inflammatory cytokines but decreased expression of co-stimulatory markers CD80 and CD86 in monocytes (Moro et al., 2019). A recent study with adolescents showed that PM2.5 and PAHs increased CRP and the level of participants' circulating monocytes after exposure to PM2.5, carbon monoxide, nitric oxide and nitrite (Prunicki et al., 2020).

Nitrite and nitrate are common surrogate markers of nitric oxide production in inflammation. Plasma nitrite was suggested as a good indicator of air pollutant exposure (Gandhi et al., 2014) and it can be seen in Fig. 4 that is a frequent marker of systemic inflammation, whereas exhaled nitric oxide or nitrite/nitrate are valuable predictors of airway inflammation (Robroeks et al., 2007; Engel et al., 2018; Hoyte et al., 2018).

4.2. Airway inflammation

There is a higher investigation of parameters related to lung inflammation, especially in trials categorized as specific air pollution (Table 1) but no trials were found investigating inflammation specifically related to other organs/systems like for example skin inflammation. This indicates that checking inflammation in the lungs for toxicants exposure is prioritized in relation to other systems, which can be related to the importance given to the inhalation exposure route and the easiness of samples' access. In fact, lung inflammation can be assessed by fractional exhaled nitric oxide (FeNO) in the human breath test (Hoyte et al., 2018). FeNO is the best-studied non-invasive inflammatory marker (Robroeks et al., 2007) and, recently, it was used to test exposure to indoor air PM2.5 (Wang et al., 2021c). Interestingly, when using purifiers for air particles a significant decrease in FeNO levels was observed in healthy subjects (Sup. Table 2 Codes: 8, 61; Chen et al., 2015). In the trials collected in this study, FeNO is the parameter most frequently investigated in close relation to airway inflammation (Sup. Table 2 Codes: 1, 17, 36, 56, 61, 63, 65, 72, 73, 79, 82, 86 and 115).

Bronchoalveolar lavage, sputum and nasal fluid were also screened for inflammation markers either by investigating cytokines, such as IL-6, IL-8, and IL-1β, or NRF2, or phase II antioxidant enzymes (Sup. Table 2 Codes: 8, 40, 55, 71, 75 and 84). Participants exposed to ozone presented an increase of IL-6 and IL-8 in nasal epithelial lining fluid (Sup. Table 2 Code: 75, NCT02857283). Another study comparing low versus high levels of exposure to fumes and aerosols of bitumen, revealed that

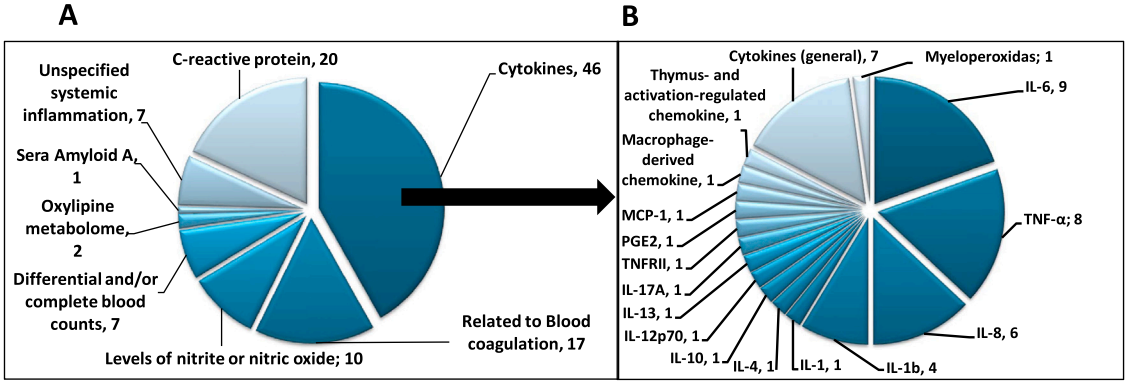


Fig. 4. – Biomarkers of systemic inflammation used in clinical trials of toxicant exposures. Panel A: General overview of the frequency of use of major groups of biomarkers; Panel B: Frequency of use of individual cytokines and related biochemical markers. Each graphic presents the biomarkers followed by the corresponding frequency number (biomarker; frequency).

high exposure to fumes and aerosols of bitumen led to irritative effects on the upper and lower airways, to significantly higher levels of IL-1β and IL-8 in the nasal lavage fluid and to higher percentages of nasal and sputum neutrophils (Sup. Table 2 Code: 86, Raulf-Heimsoth et al., 2007). Actually, blood cells and specific immune cells like neutrophils and polymorphonuclear leukocytes in these fluids were also screened in some trials where participants were exposed to toxicants (Sup. Table 2 Codes: 8, 15, 20, 26, 27, 40, 58, 71, 75, 84 and 86). Detailed information on the biomarkers related to airway inflammation found in the clinical trials is available in Fig. 5. Neutrophilic airway inflammation measured through hydrogen sulphide (H_2S) was proposed as a biomarkers for exposure to ozone (NCT00743704)(Biller et al., 2011; Suzuki et al., 2021). This correlation between exhaled gas and markers of airway inflammation opens an opportunity as future biomarkers.

Several trials test inflammatory markers associated with airway disease that, such as CRP, radioallergosorbent test, eosinophil count test and periostin (Sup. Table 2 Code: 56). Interestingly, periostin was recently proposed as a marker for allergy (Izuhara et al., 2019). Individual studies investigated airway macrophage uptake of inhaled PM and inflammation in endomucosal biopsies (Sup. Table 2 Codes: 7 and 71).

Exposure to diesel exhaust particles was also explored in non-registered trials where an increase of nasal cytokines in volunteers was observed (Diaz-Sanchez et al., 1996). For a deeper comprehension on the relation between the pulmonary immune system and PM2.5 exposure additional bibliography is suggested (Wei and Tang, 2018).

From the registered trials analyzed for airway inflammation in this work, FeNO is the predominant biomarker. However, studies suggest that more information is needed for the use of FeNO as a biomarker (Iavicoli et al., 2020). An increase of FeNO levels after exposure to several environmental toxicants such as perfluoroalkyl chemicals, arsenic, PAHs and PM was observed (Shi et al., 2016; Zhou et al., 2018; Averina et al., 2019; Shih et al., 2019; Xu et al., 2021). But, in smokers also exposed to environmental toxicants, the FeNO levels decreased (Min and Min, 2014; Zhou et al., 2018). For this topic, other authors have suggested that the extent of smoking should be considered when using FeNO (McSharry et al., 2005). Nevertheless, FeNO is considered to have clinical value in the diagnosis of occupational asthma (Engel et al., 2018; van Kampen et al., 2019). For chronic inflammatory airway disease, FeNO is a noninvasive, simple and fast method considered advantageous for patient care when compared to other parameters (Dweik et al., 2011), being recommended by guidelines and peer-reviewed articles as a biomarker for asthma (Arnold et al., 2018). Finally, to consolidate information on airway inflammation, screening cytokines and immune cells in the nasal/bronchoalveolar fluids is a useful option.

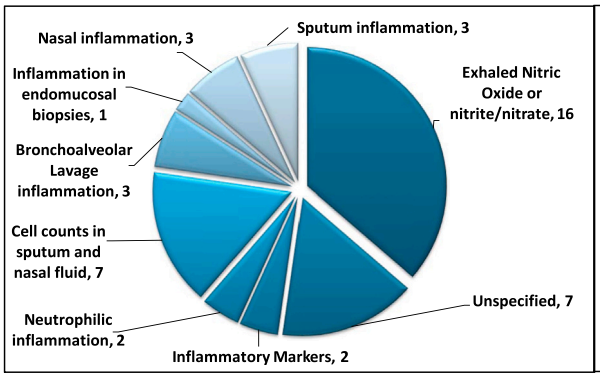
4.3. Modulation of immune cell populations and function

When looking at the effect of toxicants' exposure on the modulation of immune cells, the outcomes found in trials were centered on the type of immune cells and on specific leukocyte function or impairment. The type of immune cells is based on cell counts of different populations in peripheral blood (Sup. Table 2 Codes: 3, 32, 41, 48, 56, 81 and 85).

Phagocytosis, oxidative burst, CD markers and leukotrienes were also used as markers of toxicants exposure: CD4, CD8, CD11c, CD14, CD20, CD56, CD11b, CD14, CD64, CD16, HLA-DR, CD45, CD3, CD80, CD86, LTB4, LTC4, LTD4, LTE4, CDX2 and neutrophil elastase (Sup. Table 2 Codes: 22, 79 and 115). DNA damage and epigenetic analysis such as DNA methylation, microRNA expression and chromatin modification in immune, epithelial and lung cells are being used to assess the effect of toxicants (Sup. Table 2 Codes: 1, 37, 47, 59, 66, 81 and 77) since 2011 (Sup. Table 2 Code: 66). Fig. 6A shows the biomarkers found in clinical trials related to the modulation of immune cell populations, and panel B gives additional details of trials investigating epigenetic effects. Although low information is found in the registered clinical trials analyzed in this work for epigenetic changes, several scientific works report the environmental toxicants as causative agents of epigenetic changes, either on microRNAs expression, DNA methylation or histone modification (Vrijens et al., 2015; Sollome et al., 2016; Kotsyfakis and Patelarou, 2019; Rider and Carlsten, 2019; Shukla et al., 2019). A specific and recent example on cadmium exposure revealed that in exposed workers, the miR-221 was significantly higher. Furthermore, miR-221 and miR-155 were positively correlated with the percentage of Th17 cells that was also altered (Goyal et al., 2021). Thus, epigenetic changes will probably be considered in the close future as biomarkers of response to environmental toxicants.

Modulation of immune cell function can be seen as a target or as effector of toxicants' action as described in a recent review for cadmium toxicity (Mirkov et al., 2021). Also in cadmium exposure, exposed workers showed significant alterations in the percentage of Th17 and Treg cell populations (Goyal et al., 2021). Exposure to hexachlorocyclohexane was related to a higher number of natural killer cells (Karmaus et al., 2005) and a recent work showed a decrease in the percentage of neutrophils after exposure to PM2.5 in young healthy adults (NCT03232086) (Wyatt et al., 2020). A change in neutrophils and monocytes was also observed for ozone single exposure or ozone exposure combined with PM2.5 (Mirowsky et al., 2017). In fact, the ratio of change for the different immune cells can be a biomarker for pollutants exposure. In heavy smokers, it was observed an increase in the neutrophil-to-lymphocyte ratio that is considered a biomarker for systemic inflammation (Grieshober et al., 2018), and exposure to phthalates led to changes in innate immune cells (Nygaard et al., 2021).

A

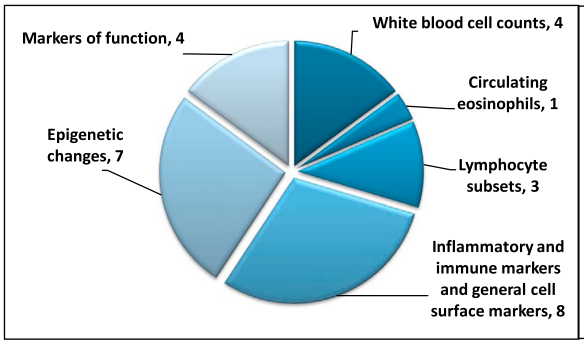


B

Trial	Toxicant	Biomarker
NCT00727714	Cement Dust	↑ FeNO
NCT02024204	WTC	↑ FeNO
NCT02239744	PM2.5	↑ FeNO
NCT02857283	Ozone	↑ IL-6 and IL-8 in Nasal ELF

Fig. 5. – Biomarkers of air inflammation used in registered clinical trials of toxicant exposures. Panel A: General overview of the frequency of use of major groups of biomarkers; Panel B: Trials with different toxicants presenting study results in which changes for specific biomarkers of airway inflammation were observed. ELF - Epithelial Lining Fluid; WTC – World Trade Center dust and fumes; ↑ - Increase.

A



B

Trial	Investigated Epigenetic Changes	Cell type
NCT01864824	microRNA expression DNA methylation	T-helper cells
NCT02765529	microRNA expression	Leukocytes
NCT04012385	DNA methylation	Lymphocytes

Fig. 6. – Biomarkers related to immune cell populations and function in clinical trials of toxicant exposures. Panel A: General overview of the frequency of use of major groups of biomarkers; Panel B: Trials investigating the effect of air pollution on epigenetic changes affecting immune cells, none of them present study results.

4.4. Allergy outcomes

The relation between allergies and exposure to pollutants has been studied in controlled trials (Table 2). The production of IgE is a common characteristic of allergies. In a small trial with healthy subjects exposed to diesel exhaust particles there was an increase of cytokines that contributed to the increment of the IgE levels relevant to respiratory allergic disease (Diaz-Sanchez et al., 1996). In psoriasis patients, dermal exposure to PAHs also increased the total serum IgE levels (Mastrangelo et al., 2003). Moreover, prenatal exposure to PFOS was positively correlated with cord blood IgE levels (Wang et al., 2011). Likewise, an association between exposure to different toxicants - such as smoke, exhaust, herbicides or pesticides – was found for early-onset persistent asthma in children (Salam et al., 2004).

Depending on the toxicant type, a different immune response can happen. For example, in the work developed by Karmaus and colleagues (2005), PCBs were associated with increased immunoglobulin M (IgM) levels and, on the contrary, exposure to hexachlorocyclohexan was inversely related to IgM (Karmaus et al., 2005). Lead correlated to increased IgE levels and dichlorodiphenylethylene to increased IgE, immunoglobulin G (IgG), and immunoglobulin A (IgA) levels (Karmaus et al., 2005).

In the analyzed trials, the immune response to organic dust and diesel exhaust in bronco alveolar lavage was investigated using Th1/Th2 cell populations and anti-allergen IgE/IgG4 as biomarkers, however without results (Table 2, Sup. Table 2 Codes: 54, 56 and 67). A focus on studying the effect of PM on allergy, more specifically in asthma condition, is visible in recent works (Dėdelė et al., 2019; Lee et al., 2020; Sompornrattanaphan et al., 2020). The estimated risk of allergies is two-fold higher for individuals more exposed to PM10 when compared to those less exposed (Dėdelė et al., 2019). Recently, epidemiological studies support the fact that exposure to PM can be a cause for the development of asthma, allergic rhinitis, and aeroallergen sensitization (Sompornrattanaphan et al., 2020). Practical measures to reduce PM2.5 inhaled levels, like filter use, showed a decrease in the levels of PM2.5 followed by a significant reduction regarding the medication need in children with asthma (Lee et al., 2020) (Table 2). Interestingly, a positive association between microbiome and asthma biomarkers such as FeNO, blood eosinophil, IgE and IL-4 levels, was revealed in a study investigating the gut microbiome of allergic and non-allergic asthmatic patients (Zou et al., 2021). Moreover, depicting FeNO reference values for allergy, it was recently suggested to consider the type and degree of IgE sensitization (Zaigham et al., 2021). This study showed that individuals with a high degree of IgE sensitization (to allergens) had higher FeNO levels than non-atopic subjects (Zaigham et al., 2021).

Despite no registered trials being found for epigenetic screening related to allergy, environmental exposures promote allergy-related epigenetic modifications that can lead to future specific biomarkers of effect (Potaczek et al., 2017). In fact, epigenetic modifications influence the differentiation of T cell lineages and the balance of Th cell populations (Potaczek et al., 2017). Specifically, DNA methylation, histone modifications and also miRNAs are suggested as potential biomarkers for allergy and asthma (Alhamwe et al., 2020, 2021). In asthmatic patients exposed to traffic-related air pollution, there was an increased methylation of the *TET1* promoter region (Somineni et al., 2016).

Table 2
– Biomarkers found in registered and non-registered trials for allergy derived from exposure to environmental toxicants.

Biomarker	Toxicant	Reference	Number of participants - Condition
Th1, Th2cell populations Anti-allergen IgE and IgG4, IgA, IgM	Diesel Exhaust	NCT01792232	18 - Allergy
	Diesel exhaust	NCT02017431	13 – Non-smoker and allergy
	Diesel exhaust	Diaz-Sanchez et al. (1996)	14 - Healthy nonsmoking
	Diesel exhaust (PAHs)	Mastrangelo et al. (2003)	32 - Acute psoriatic lesions
	Explosion dust and fumes	NCT02024204	94 - Breathing problems
	Organic dusts	NCT02540408	400 - COPD and healthy matched controls
	Organochlorines (DDE, HCB, PCBs) and lead	(Karmaus et al., 2005)	331 - Children
	Perfluorinated chemicals (perfluorooctanoic acid, perfluorooctane sulfonate, perfluorononanoic acid and perfluorohexane sulfonic acid)	Wang et al. (2011)	40 - Atopic dermatitis 80 - Controls
PEFR, FeNO, urine microbiome and phthalate	PM2.5	Lee et al. (2020)	30 - Asthma
DNA methylation of the *TET1* promoter region	Traffic-related air pollution	(Somineni et al., 2016)	12 – Asthmatic African American children and their nonasthmatic siblings.

Abbreviations: DDE – dichlorodiphenylethylene; HCB – hexachlorobenzene; PEFR - Peak expiratory flow rate.

4.5. Autoimmunity

Exposure to toxicants was also assessed by investigating the risk for autoimmune diseases through the level of autoAbs, or other markers of

autoimmune diseases like anti-extractable nuclear antigen-78 (ENA-78) antibodies (Sup. Table 2 Codes: 48, 107). Additionally, thyroid autoimmune disease risk was also considered, and the role of the polymorphic inheritance of genes related to the susceptibility to Graves' disease (Sup. Table 2 Code: 114). The biomarkers related to autoimmunity found based on exposure to toxicants are present in Table 3.

Several non-referenced trials showed an association between pollutants and autoimmunity. For example, individuals exposed to chlorpyrifos showed a higher incidence of autoimmune disease (Thrasher et al., 1993), while the presence of autoAbs was detected in chronic smoke exposures of mice and humans with lung disease (Newkirk et al., 2012). More recently, a relation was observed between the increase of autoAbs (Table 3) and the proximal distance for the main road in Delhi (Kumar et al., 2020). A higher prevalence of autoAbs was observed in individuals residing within 200 m of the main road (Kumar et al., 2020). And, for rheumatoid arthritis patients it was shown a correlation between PM2.5 exposure and the concentrations of the autoantibody against cyclic citrullinated peptide antibody (Alex et al., 2020).

Table 3
– Biomarkers found in registered and non-registered trials for autoimmunity derived from exposure to toxicants.

Biomarker	Toxicant	Reference	Number of participants - Condition
Risk for autoimmune diseases*	Environmental exposures (including smoking and occupational exposures)	NCT00047970	50,884 - sisters of women who have had breast cancer
Auto-antibodies*	DDT, dieldrin, chlordane, methoxychlor and the metabolites of DDT and methoxychlor	NCT02530814	20 - Organochlorine pesticide exposure
Autoimmunity (autoAbs directed to smooth muscle, parietal cell, brush border, thyroid gland, myelin, and antinuclear antibodies)	Chlorpyrifos	(Thrasher et al., 1993)	12 – Chlorpyrifos exposure
Thyroid autoimmune diseases risk; GSTT1, GSTM1, GSTP1, CYP1A1 and 72TP53 polymorphic inheritance on the susceptibility to Graves' disease	Cigarette smoking	NCT00505011	1998 – GST, CYP and TP53 Gene Polymorphisms inheritance and controls
ENA-78	Diesel exhaust	NCT01867450	109 - work with diesel fuel (and control subjects) Caucasian
Rheumatoid factor, anti-CCP, and anti-HSP70 autoAbs	Cigarette smoke	Newkirk et al. (2012)	20 - healthy 20 - smokers 20 – COPD North American Native 20 – non-smokers 20 - smokers
	PM2.5	Alex et al. (2020)	557 – history of rheumatoid arthritis for 13 years
	Air pollution	Kumar et al. (2020)	500 – Delhi residents

Abbreviations: anti-CCP – anti-cyclic citrullinated peptides, ENA-78 - Extractable nuclear antigen-78, marker for autoimmune diseases; COPD – Chronic obstructive pulmonary disease.

* The clinical trials do not specify the types of biomarkers investigated.

5. Investigated strategies against the effects of environmental toxicants' exposure

The idea of a protective strategy reflects the possibility to counteract the adverse effects of toxicants' exposures to human health.

Among the clinical trials found in this study, 32 investigated potential protective strategies addressing toxicant exposures to different environmental toxicants, mainly to air pollutants known to affect large populations (Supplementary Table 2). The trialed strategies were grouped into 3 types: dietary (n = 21), pharmacological (n = 10) and devices (n = 1). Table 3 represents the protective strategies found and the corresponding toxicant exposures.

Four clinical trials showed significant effects in conditions of toxicant exposures (Sup. Table 2 Codes: 2, 6, 51 and 101). Interestingly, three interventions were found to influence toxicant metabolism. In adults exposed to arsenic in Bangladesh, a preliminary study showed that the supplementation with choline bitartrate, betaine or both, decreased the percentage of urinary levels of arsenic metabolites (monomethyl arsenic and inorganic arsenic) (NCT01749982). Also by measuring the excretion levels of benzene-mercapturic acids, a metabolite of benzene, it was observed that a high dose of broccoli sprout beverage significantly enhanced the detoxification of this toxicant with the results showing a 63.2% increase of metabolites in urine (Chen et al., 2019b, NCT02656420). An additional study showed that probiotic yogurt in pregnant women counteracted the increases of mercury and arsenic levels in the blood (Bisanz et al., 2014; NCT01904513). In fact, strategies focused on higher excretion of toxic compounds or metabolites resemble the olestra usage for persistent lipophilic compounds described in 1999 (Moser and McLachlan, 1999). And more recently, it was reported the use of thiazide diuretics and sodium-glucose cotransporter-2 (SLGT2) inhibitors for the removal of phthalates metabolites (Mengozzi et al., 2021) and lentils rich in selenium that resulted not only in higher urinary excretion of arsenic but also in lower incidence of asthma and allergy (Smits et al., 2019).

Regarding to effects of air pollution particles, the study of Lin and collegues (2019; NCT03255187) investigated the influence of fish-oil on several biomarker classes, including biomarkers of inflammation. The levels of PM2.5 exposure were highly associated with CRP, TNF-α and IL-6, the latter found to have a significant difference when compared to the placebo group. The increment of IL-6 arising from exposure to PM2.5 was 32.7% and 33.5% smaller in the fish oil group at 24 h and 48 h after exposure, respectively (Lin et al., 2019; NCT03255187).

Additional studies investigated N-acetylcysteine and ascorbate, or L-NMMA and norepinephrine as strategies against diesel exhaust exposure (Table 4), but without evident results (Cosselman et al., 2012 - NCT00434005; Langrish et al., 2013 - NCT01060930. Sup. Table 2 Codes: 11 and 28, respectively).

Fourteen trials explored the potential protective strategies of immunomodulators but only one study retrieved significant results for fish oil (Lin et al., 2019; NCT03255187). Additional studies pointed to fish oil or n-PUFAS as possible preventing allergy-related diseases consequent from air pollution or tobacco exposure (Dotterud et al., 2013; Hansell et al., 2018). In the same line, dietary supplementation with ω-3 HUFAs attenuated silica-triggered lupus flaring in a mouse model (Wierenga et al., 2020). In fact, fish oil is associated with immunomudulatory and anti-allergic effects that seem to be at least partly mediated by epigenetic modifications (Harb et al., 2017; Acevedo et al., 2019).

Other natural compounds like phytochemicals or polyphenols are often described as protective agents. Recently, due to its antioxidant activity, a polyphenolic extract was observed to protect splenocytes

Table 4
– Potential protective strategies assessed in completed clinical trials of subjects exposed to toxicants.

Type of Intervention	Protective Strategy (last update)	Toxicant Exposure	Number of participants - Intervention	Trial identifier (Code in Table S1)
Dietary	Mediterranean diet (2020)	Firefighters	486 - Mediterranean diet OR controls	NCT02941757 (76)
	Beet and orange juice (2017)	Air pollution	24 - Beet OR orange juice	NCT02027415 (1)
	Tea polyphenols and AOB-w (2017)	Acrylamide	110 - Tea polyphenols & acrylamide OR AOB-w & acrylamide OR placebo & acrylamide	NCT03118167 (110)
	Fish oil (2020)	Ozone	64 - fish oil & acute ozone exposure OR fish oil and sham exposure OR soy oil and ozone exposure OR soy oil and shame exposure	NCT03697499 (80)
	Fish oil (2020)	Air pollution	70 - Fish oil supplementation OR sunflower seed oil supplementation	NCT03255187 (6)
	Omega-3 fatty acids (2011)	Air pollution	29 – Fish oil OR olive oil	NCT01442480 (33)
	Omega-3 and Omega-6 fatty acids (2015)	Mercury and lead	280 – Observational study	NCT00013858 (93)
	Selenium (2017)	Arsenic	40 - Anhydrous selenite OR control	NCT02377635 (104)
	High-selenium lentils (2017)	Arsenic	400 - Low-Se lentils OR high-Se lentils	NCT02429921 (105)
	Selenium (2011)	Arsenic	819 – Selenium OR placebo	NCT01442727 (99)
	Creatine and folic acid (2012)	Arsenic	600 - Folic Acid 400 ug OR 800 ug daily OR creatine 3 mg daily OR creatine 3 mg & folic acid 400 ug daily	NCT01050556 (97)
	Iron and folic acid (2017)	Arsenic	42 – 21 Iron & Folic acid OR 21 placebo	NCT02908581 (109)
	Vitamin E (2016)	Arsenic	45 – Vitamin E & Palmar Arsenical Keratosis OR vitamin E & exposed to arsenic OR vitamin E & healthy volunteers	NCT02468518 (106)
	Garlic oil (2012)	Arsenic	60 – Garlic oil & Palmar Arsenical Keratosis OR garlic oil & exposed to arsenic OR garlic oil & healthy volunteers	NCT01748669 (100)
	Spirulina (2012)	Arsenic	30 - Spirulina & Palmar Arsenical Keratosis OR spirulina & exposed to arsenic OR spirulina & healthy volunteers	NCT01752972 (102)
	Choline bitartrate and betaine (2014 *)	Arsenic	60 – Placebo OR Choline bitartrate OR Betaine OR Choline bitartrate & Betaine	NCT01749982 (101)
	Cock's comb extract (2018)	Arsenic	25 - Cock's comb extract	NCT03127657 (111)
	Sulforaphane-rich broccoli sprout homogenate (2015)	Ozone	16 - Broccoli sprout homogenate OR Alfalfa sprout homogenate	NCT01625130 (40)
	Broccoli sprout-derived beverage (2019 *)	Air Pollution	170 – Placebo OR broccoli sprout high dose OR medium dose OR low dose	NCT02656420 (2)
	Flavonoids and prebiotics (2017)	Volatile organic compounds	27 - Placebo, Flavonoids, flavonoids & prebiotics OR placebo, flavonoids & prebiotics, flavonoids OR flavonoids, placebo, flavonoids & prebiotics	NCT02871596 (108)
	Probiotic yogurt (2017)	Environmental toxins	44 – Yogurt supplemented with L. rhamnosus GR-1 OR pasteurized whole milk	NCT01904513 (51)
Pharmacological	L-NMMA and Nor-epinephrine (2011)	Diesel exhaust	14 - Diesel exhaust exposure OR air exposure	NCT01060930 (28)
	Montelukast (2009)	Airborne ultrafine and fine PM	24 - Exercise in high levels of ultrafine and fine particulate air pollution & Montelukast OR placebo OR Exercise in low levels of ultrafine and fine particulate air pollution & Montelukast OR placebo	NCT00814281 (20)
	N-acetylcysteine (2017)	Diesel exhaust	26 - Filtered air with placebo OR diesel exhaust with placebo OR diesel exhaust with N-acetylcysteine	NCT01699204 (42)
	N-acetylcysteine and ascorbate (2013)	Diesel exhaust	24 - Diesel exhaust OR filtered air	NCT00434005 (11)
	Neem extract, propylene glycol and salicylic acid combination (2016)	Arsenic	30 - Neem plus propylene glycol plus salicylic acid OR salicylic acid	NCT02352987 (103)
	Pralidoxime (2004)	Organophosphorus pesticide	200 - Pralidoxim	NCT00333944 (95)
	DMSA - dimercaptosuccinic acid (2008)	Heavy metals	80–1 round of DMSA, followed by 3 months of placebo OR 7 rounds of DMSA over 4 months	NCT00811083 (96)
	Anti-IL17A (AIN457, secukinumab) (2010)	Ozone	24 – Anti-IL17A OR placebo OR oral corticosteroid	NCT00920933 (26)
	PUR118 (calcium lactate) (2013)	Ozone	24 - PUR118 low dose OR mid dose OR low dose	NCT01690949 (Holz et al., 2015) (41)
	Bimosiamose (2010)	Ozone	18 – Bimosiamose OR placebo	NCT00962481 (27)
Devices	IonCLeanse footbath (2011)	Heavy metals	6 - IonCLeanse Footbath	NCT01125592 (98)

Abbreviations: AOB-w - water-soluble antioxidant of bamboo leaves; L-NMMA - nitric oxide synthase inhibitor NG-monomethyl-L-arginine; * - trials presenting results.

against oxidative stress provoked by the pesticides malathion and chlorpyrifos (Zhao et al., 2020). Likewise, protective interventions using polyphenols to address cancer risk related to toxicant exposure were recently reviewed, including strategies acting in inflammation and immunomodulation (Lagoa et al., 2022). For a deeper understanding of the potential of phytochemicals as immunomodulators, the reader is referred to a recent review (Behl et al., 2021).

Pharmacological approaches for auto-inflammatory diseases, such as anti-IL-17 (secukinumab), were also tested but without results (NCT00920933). However, it is a promising tool, based on the efficiency for the treatment of psoriasis (McInnes et al., 2015) by disrupting IL-17 signaling responsible for the amplification of the inflammatory response (Hawkes et al., 2018). PUR118 (calcium lactate) was also investigated to counteract the effects of ozone exposure but failed in reducing ozone-induced airway inflammation (Holz et al., 2015 - NCT01690949). Yet high PUR118 dose treatment led to relevant alterations in sputum and blood leukocytes and slightly attenuation of the levels of CRP which require further investigation of their potential protective role (Holz et al., 2015).

Overall, the strategies tested in trials deserve more investigation for their protection against environmental exposure effects, with fish oil and anti-IL-17 showing more evident immunological benefit and better

understanding of their mechanism of action. Nevertheless, careful use of fish oil is needed due to fish contamination by toxicants such as methylmercury, dioxins, PCBs and PAHs (Gil and Gil, 2015). But benefits of fish oil can be considered if species of origin are taken into consideration and risk assessment is done (Gil and Gil, 2015). Additionally, the described strategies promoting higher toxicants' excretion can be taken into account.

6. Limitations of this work

This work focus on immune markers and protective strategies investigated in 117 registered clinical trials of toxicant exposure. Most of the works investigated do not specify the dose or the chemical composition of the toxicant as is the case of the trials found for general air pollution where the predominant toxicant is not identified (diesel exhaust, or ozone or other…). In addition, some clinical trials also do not specify the biomarkers investigated. Nevertheless, we used bibliographic data from research works found in PubMed to complement the information and the discussion of findings.

7. Final remarks and Future perspectives

In general, the trials represented in this work demonstrated a dispersion of immunological biomarkers explored as outcomes of environmental and occupational toxicant exposures. This can be a major issue for the investigation of toxicants' effects at the clinical level where a more precise standardization of biomarkers is needed. In this work, we performed a categorization for the immunological outcomes assessed in the human trials. From established to prospective markers, Fig. 7 represents a selection of markers from the analyzed trials as a practical resource for the design of future trials of toxicant exposure.

More specific highlights/final remarks from the present work are:

1) IL-6, IL-8 and TNF-α showed a strong association with toxicant exposure. Recently, IL-6 was also evidenced as a marker of PAH toxicity (Wang et al., 2021a).
2) FeNO is a strong biomarker for airway inflammation (Engel et al., 2018; van Kampen et al., 2019), but the smoking history and the type and level of IgE sensitization of the individuals should be considered (Zaigham et al., 2021).
3) Hydrogen sulphide is a potential biomarker for neutrophilic airway inflammation based on the correlations found by (Suzuki et al., 2021).
4) Alterations in immune cell levels revealed to be a good biomarker for exposure to toxicants (Mirowsky et al., 2017; Grieshober et al., 2018; Wyatt et al., 2020; Mirkov et al., 2021; Nygaard et al., 2021).
5) Epigenetic changes and miRNAs as biomarkers for acute and chronic environmental exposures were proposed (Kotsyfakis and Patelarou, 2019; Lagoa et al., 2022; Vrijens et al., 2015), but are not yet established.
6) IgE is the biomarker more associated with environmental toxicant-related allergies (Diaz-Sanchez et al., 1996; Mastrangelo et al., 2003), while periostin is emerging (NCT02024204) as a potential biomarker for allergy (Izuhara et al., 2019).
7) Rheumatoid factor and autoAbs are the most explored biomarkers for toxicant exposures and the risk of autoimmune diseases (Newkirk et al., 2012; Alex et al., 2020; Kumar et al., 2020).

In regards to protective strategies facing exposure to environmental toxicants, the dietary strategies were predominant but most of the results are not available. Dietary strategies of three trials showed changes for the presence of the toxicants in blood or excretion metabolites after

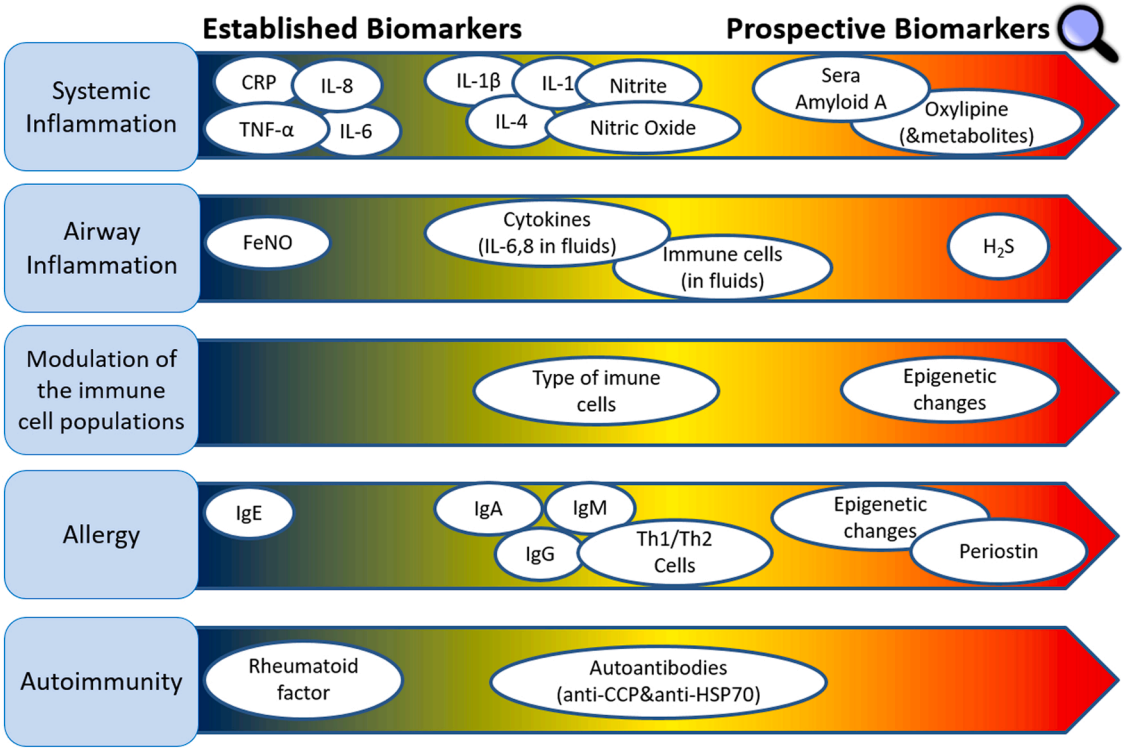


Fig. 7. – Immune markers used in clinical trials for toxicant effects depending on the categorization proposed in this work. Colorful gradient represents the qualitative scale for immune biomarkers and distinguish between those already established (blue) and those less explored and considered prospective (red).

probiotic yoghurt, choline bitartrate and broccoli sprout beverage intervention (Bisanz et al., 2014; Chen et al., 2019b; Sup. Table 2 Codes: 2, 51 and 101). In the literature, we found additional studies for strategies promoting higher toxicant excretion and they can be considered.

One study observed the effect of fish oil in alleviating the impact of air pollution, focusing on inflammation/immunological markers showing that fish oil counteracted the increment of IL-6 derived from fine particulate air pollution (Lin et al., 2019; NCT03255187). As referred previously, fish oil or n-PUFAS are considered possible protective strategies against the development of allergy-related diseases resulting from air pollution or tobacco exposure (Dotterud et al., 2013; Hansell et al., 2018). However, the adoption of fish oils as a protective method requires further evaluation to assure no contamination by chemical toxicants like PCBs.

Finally, the categories less explored in the registered clinical trials for toxicant exposures were allergy and autoimmunity in which some of the identified biomarkers were unspecific. This gap can be counteracted by an effort to investigate these categories in future clinical trials of toxicant exposure with the opportunity to assess specific biomarkers indicated in Fig. 7.

In conclusion, this study provides established and prospective immunologic biomarkers that reflect, at the clinical level, the effects of dangerous environmental exposures and can be useful to consider in following trials. The potential strategies identified to mitigate the damaging effects of toxicants' exposure can gather further evidence in the future.

CRediT authorship contribution statement

Dorinda Marques-da-Silva: Conceptualization, Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing, Project administration. **Paula Alexandra Videira:** Validation, Writing – review & editing. **Ricardo Lagoa:** Conceptualization, Writing – original draft, Validation, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

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

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.etap.2022.103886.

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