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REVIEW ARTICLE

Addressing adverse synergies between chemical and biological pollutants at schools—The 'SynAir-G' hypothesis

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Abstract

While the number and types of indoor air pollutants is rising, much is suspected but little is known about the impact of their potentially synergistic interactions, upon human health. Gases, particulate matter, organic compounds but also allergens and viruses, fall within the 'pollutant' definition. Distinct populations, such as children and allergy and asthma sufferers are highly susceptible, while a low socioeconomic background is a further susceptibility factor; however, no specific guidance is available. We spend most of our time indoors; for children, the school environment is of paramount importance and potentially amenable to intervention. The interactions between some pollutant classes have been studied. However, a lot is missing with respect to understanding interactions between specific pollutants of different classes in terms of concentrations, timing and sequence, to improve targeting and upgrade standards. SynAir-G is a European Commission-funded project aiming to reveal and quantify synergistic interactions between different pollutants affecting health, from mechanisms to real life, focusing on the school setting. It will develop a comprehensive and responsive multipollutant monitoring system, advance environmentally friendly interventions, and disseminate the generated knowledge to relevant stakeholders in accessible and actionable formats. The aim of this article it to put forward the SynAir-G hypothesis, and describe its background and objectives.

KEYWORDS
aerobiology, allergy, artificial intelligence, asthma, biosensors, children, school, virus, volatile organic compounds

See Appendix for The SynAir-G Consortium.

1 | THERE IS A MAJOR UNMET NEED TO CHARACTERISE, MONITOR AND IMPROVE AIR QUALITY TO SUPPORT HEALTH

The profound impact of air pollution on human health has been thoroughly studied and reported.[1,2] The risk involves most systems of our body, with skin, respiratory, cardiovascular and central nervous systems predominating.[2] Overall, acute and chronic illnesses, as well as exacerbations of chronic diseases, can result in humans and animals following damage of epithelial barriers, activation of inflammatory pathways, DNA damage and cell death responses.[3] The list of substances with negative potential impacts on human, as well as animal and environmental, health, is large and growing.[1] Some, such as fine particular matter (PM), O_3, CO, NOx and SO_2 are well characterized and monitored, while others, such as ultrafine particles (UPF), or radon, are uncertain or unknown. In many environments, the threat is constant and affects almost everybody. More than 10 million deaths can be attributed to air pollution every year.[4] It is both fortunate and tragic that these events are largely preventable.[2] Sadly, much of the impact predominantly involves the developing world.[2,5] Although this is not always the case, many of the adverse health effects can rapidly improve and reverse if the source of pollution is removed.[2] For example, the smoking ban in indoor places has resulted in improved health not only for hospitality workers but also for the general population.[2] Improving air quality probably has benefits even beyond the currently accepted standards. Furthermore, targeting air quality has often added considerable value to wider pollution, climate change and planetary health. There is, therefore, a major unmet need to characterise, monitor and improve air quality to support health.

2 | WE SPEND MOST OF OUR TIMES INDOORS - INDOOR AIR QUALITY (IAQ) HAS NOT RECEIVED AS MUCH ATTENTION

In the last decades, outdoor, or 'ambient', air pollution has attracted the most attention in research and media alike. However, nowadays there is increased concern and focus on household and more generally indoor air pollution.[1,2,6,7] We spend more than 90% of our time indoors; furthermore, buildings are increasingly airtight to conserve energy among others.[8,9] Some pollutants have higher concentrations in the ambient air; however, others accumulate indoors, while different outdoor–indoor gradients are generated depending on pollutant source, ventilation and local conditions.[10] Key pollutants for human health are generated by cooking, heating and cleaning. These can vary widely between households; in contrast to outdoor air pollution that can be monitored through a relatively small number of stations and geographical or atmospheric and meteorological models or remote sensors,[11] indoor air monitoring does not apply in most environments and indoor air quality can literally be unpredictable because of a huge variety of factors that influence it.[9,12] In recent years, comparative risk studies performed by the Environmental Protection Agency of the USA have consistently ranked indoor air pollution among the top five environmental risks to public health.[13]

3 | THE EFFECTS OF INDOOR AIR POLLUTION CAN BE PARTICULARLY PRONOUNCED IN DISTINCT POPULATIONS. CHILDREN WITH ALLERGY AND ASTHMA ARE A MAJOR SUCH POPULATION

The variability of indoor air quality, but also the differential susceptibility of discrete people groups, result in considerable inequalities and pronounced health effects in different populations.[14,15] Economy and access to clean technologies is undoubtedly a major determinant. Across populations, children are more susceptible than adults, as air pollutants may directly interfere with their development.[8,16,17] Also, in children, respiratory rate is faster, bringing in proportionally more pollutants, while airways are smaller and therefore easier to become obstructed.[8] Individuals with hypersensitivities, such as allergies and asthma, are also more susceptible: they tend to have exaggerated and persistent inflammation, triggered by specific and non-specific stimuli, including tobacco smoke, particular matter and other pollutants. Children with low socioeconomic status are also more vulnerable to air pollution effects due to higher exposure, nutrition problems, lack of capacity to anticipate, cope and adapt to the hazards, and reduced health access.[18–20] While the political connotations of socioeconomic disequilibrium are beyond the scope of this paper, an extended discussion on environmental justice and radical measures to achieve it are absolutely necessary. Furthermore, the developing diseases are not only affecting the organ of exposure, such as the respiratory system or skin; activated inflammatory cells from these organs can migrate to distant tissues and exacerbate chronic diseases there.[21] A strong link to autoimmune diseases has been reported and there is emerging data demonstrating the influence of respiratory exposure to air pollutants on neuropsychiatric conditions. Headaches, fatigue, shortness of breath, sinus congestion, coughing, sneezing, dizziness, nausea and irritation of the eyes, nose, throat and skin are some of the symptoms.[22] Risks include both increased symptoms or disease exacerbations, but also inability to prevent or treat, due to socioeconomic drawbacks.

4 | THE IMPACT OF ALLERGY AND ASTHMA

Evidently, these are not niche populations! There are more than 10–30 million people in Europe suffering from asthma.[23] Asthma is most often associated with allergy: the allergy epidemic is by itself the most common chronic condition across the life cycle, starting from early childhood, persisting through the productive years, and having an impact on healthy ageing. Allergic rhinitis, the most frequent respiratory allergy co-exists with asthma in most cases, while other forms, either organ-specific (e.g., conjunctivitis, dermatitis),

or systemic (e.g., anaphylaxis) co-exist in the same patient, increasing the personal and societal burden, and costing over €150 billion annually.[24]

5 | POLLUTANTS ARE MANY, INCLUDING CHEMICAL AND BIOLOGICAL SUBSTANCES

The definition of 'air pollution' according to the WHO is 'contamination of the indoor or outdoor environment by any *chemical*, *physical or biological agent* that modifies the natural characteristics of the atmosphere'.[25] Different groups of pollutants of public health relevance have been identified and characterized: particulate matter, gases such as carbon monoxide, nitrogen dioxide, ozone, polycyclic aromatic hydrocarbons (PAHs) and a multitude of volatile organic compounds (VOCs).[8,9] It has to be noted that more than 350,000 new chemical substances alone or in combination have been introduced to human lives with almost no regulatory control on their health effects after the 1960s. Many of them ended up as pollutants. The identities of many of these remain publicly unknown because they are claimed as confidential (over 50,000) or ambiguously described (up to 70,000).[26]

While most often the concept of pollution and pollutants has been associated with chemical substances, there is an increased realization that biological pollutants are at least equally important.[5] This gained considerable attention with the COVID-19 pandemic: while many microorganisms present in bioaerosols are part of the natural atmosphere and necessary for our microbiome, others can be highly detrimental, resulting in considerable morbidity and mortality.[27] Often, this depends upon the concentration of the microbial agent, as well as the immune status of an individual, which can be influenced by societal factors, such as congregation.[1,28,29] For the large allergic population, allergens to which they are sensitized act as pollutants. In this case, as well, it is not only the individual susceptibility that defines the pollutant, but also the result of human interventions that radically change the concentration of for example, pollen or spores in the air. The increasing abundance of pollinating plants, such as the invasive *Ambrosia* spp., and their rising atmospheric pollen concentrations as a result of global warming, is a well-established, typical example.[24,30,31] Outdoor air pollutants are a major source for indoor pollutants; in some cases, outdoor pollutants may be present in increased concentrations indoors, however, the composition of pollutants in indoor spaces—and therefore their potential interactions—can be highly variable.

6 | THERE ARE STRONG INDICATIONS THAT CHEMICAL AND BIOLOGICAL POLLUTANTS INTERACT AND POSSIBLY SYNERGISE

There is evidence suggesting that the impact of air pollutants on health goes beyond the cumulative effect of the different pollutants. Although still not completely characterised, the interactions between chemical and biological pollutants, including allergens, may be in some cases synergistic.[32]

6.1 | Interactions of chemical pollutants with allergens

Diesel exhaust (DE) emissions have been shown to be able to underpin allergen sensitisation[33] but also augment allergen-induced airway disease. In vitro exposure of peripheral blood mononuclear cells of allergic patient to DE, together with the major mite allergen Der p1, synergistically increased the production of the neutrophil chemoattractant IL-8.[34] In a French epidemiological study, levels of aldehydes in the house had a significant synergistic effect with the presence of the major dog allergen Can f1, although this was not the case for other interactions.[35] Using an in vivo exposure model in humans, allergic individuals were exposed for 2 h to particulate matter, followed by a bronchial allergen challenge. Levels of eosinophils, IL-5 and ECP were increased.[36] Additive, but not synergistic, effects have also been shown in a similar experimental setting, on the expression of microRNAs.[37] In contrast, in another epigenetic study, when exposure was separated by a 4-h time interval, differential methylation was observed to a much larger extent; furthermore, the timing of exposure altered the results.[38] In yet another human study, co-exposure to DE and allergen (house dust mite, birch or grasses) not only altered the allergen-mediated secretome by enhancing or suppressing specific proteins but also induced protein changes unique to co-exposure.[39] Lastly, there is evidence of interaction between chemical air pollutants and pollen grains. Chemical pollutants might facilitate pollen allergen release, act as adjuvants to stimulate IgE-mediated responses, modify allergenic potential and enhance the expression of some allergens in pollen grains.[39]

6.2 | Interactions of viral infections with allergens

The allergen–virus interaction has been particularly studied in the context of asthma. In studies assessing exposures of either adults or children hospitalized for an acute exacerbation of asthma, it has been shown that the risk for such an event increased synergistically when they were infected and also exposed to an allergen to which they are sensitized.[20,40] A typical upper respiratory infection, most often associated with human rhinoviruses, may induce airway hyperresponsiveness (AHR) even in healthy individuals.[41] AHR is a cardinal characteristic of asthma and can be prolonged up to five times, in atopic children through repeated infections.[42] An allergen can act either through IgE recognition or directly on the epithelium through protease activity.[19] Timing of exposure appears to be crucial, as both in vitro[19] and in vivo[18] studies showed that synergy may not occur when allergen exposure happens first. Interestingly, recent observations suggested that allergen exposure, in sensitized individuals, may in fact protect them from infection with SARS-CoV2![43] However,

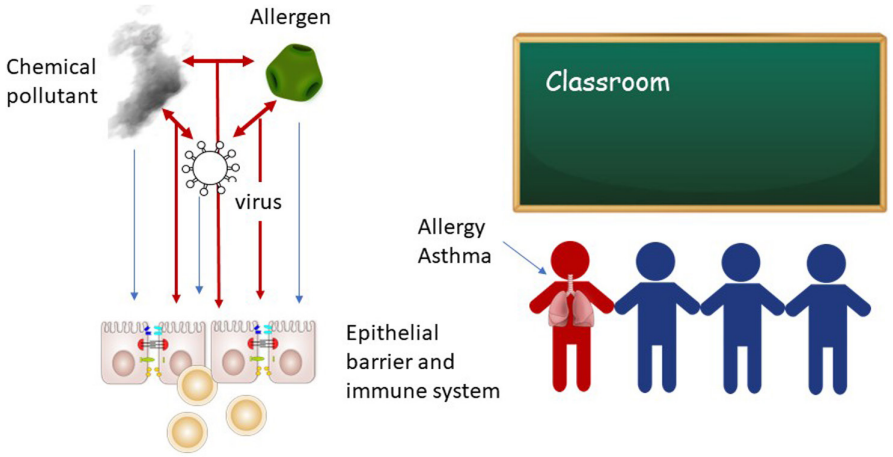

FIGURE 1 Chemical pollutants, allergens and viruses affect the epithelial barrier and the immune system compromising health. While direct effects (blue lines) have been studied extensively, the interactions between chemical and biological pollutants (red lines) have not been adequately evaluated. Although all may be affected, young children and particularly those with allergy and asthma, are more susceptible to high indoor concentrations of pollutants at school.

pollen exposure is associated with an increased risk of viral infections, including both rhinoviruses (RVs) and SARS-Cov2.[41,44–46] Therefore, when evaluating the impact of combined exposures, it is important to consider the immune background of individuals or groups, as well as the type and sequence of exposures.

6.3 | Interactions of chemical pollutants with viruses

Epidemiological data from children demonstrate more severe viral-induced asthma symptoms and worse lung function outcomes in the presence of increased exposure to high concentrations of chemical air pollutants.[46,47] Ambient PM and DE particles compromise the integrity of the epithelial barrier, while NO_2 exposure increases epithelial expression of ICAM-1, the major receptor for RVs.[48] Indeed, PM increases susceptibility to RV epithelial infection in vitro.[49] Furthermore, exposure to air pollutants increases substantially oxidative stress, which can diminish Th1 and favour Th2 responses, but also disrupt the balance between Th1 and cytotoxic T lymphocyte responses, potentially affecting the antiviral defence mechanisms.[50] A large body of data has recently confirmed the effect of ambient pollution on susceptibility to SARS-CoV2 and the development of severe disease.[28]

It should not be overlooked that additional interactions within the wide groups of 'chemical' and 'biological' pollutants have also been identified or suggested to different extents, such as interactions between viruses and bacteria[51] or between ozone and other chemicals,[52] as well as in the presence of allergens.

7 | SCHOOLS ARE PARTICULARLY IMPORTANT FOR CHILDREN

Children spend up to 10 h a day at school, most of the time indoors[6,8] and the density of persons per square meter during this time is much higher than in the usual working place or at home. Concentrations of particulate matter and PAHs higher than those required by international guidelines have been found in around 30% of schools.[8,53–55] Levels of exposure are amenable to change, as it has been shown for example, following school building renovation.[56] Nevertheless, it is not surprising that the highest levels of chemical pollutant exposure happen in schools located in highly polluted, low socioeconomic background areas. Simple field interventions, such as ventilation schedules and/or using air purifiers, have the capacity of reducing some of the effects, however many rely on changing habits, which is challenging.[9,12,57] Furthermore, schools are the breeding grounds of respiratory viruses. The risk of transmission of SARS-CoV2 in schools has attracted a lot of attention; while the extent and relative importance of this mode of transmission is still scrutinized, there is no doubt that viral transmission either through aerosols or by hand contact is important.[58] Typically, high peaks of respiratory infections, followed by asthma attacks in susceptible individuals and their families, take place during the month of September in the Northern Hemisphere, coinciding with the return of schoolchildren after their summer vacation—the so-called 'September epidemic',[59] attributed mostly to rhinoviruses. At the same time, cat allergens, brought from home on the clothes of children are present in increased concentrations within classrooms. French data suggested that the combined action of sensitization to house dust mites and viruses on asthma attacks during the epidemics among the pupils might be quantitatively increased by the presence of stress as assessed objectively through the Strength and Difficulties Questionnaire.[60,61] Many more allergens, such as cockroaches, mites and moulds, with the potential to sensitize and produce symptoms in sensitized individuals, are present at schools.[60] It is therefore plausible that schools are ideal grounds for interacting pollutants to affect the health of children—particularly those with hypersensitivity.

8 | THE SynAir-G HYPOTHESIS

To further explore the nature and impact of interactions between common chemical and biological pollutants, and in the context of the Horizon Europe project 'SynAir-G' (Disrupting Noxious Synergies

of Indoor Air Pollutants and their Impact in Childhood Health and Wellbeing, using Advanced Intelligent Multisensing and Green Interventions) we have generated the following working hypothesis: 'We hypothesise that major indoor air effects on respiratory, immune and mental health are modulated by synergistic interactions between biological and chemical pollutants' (Figure 1). This hypothesis needs to be evaluated both epidemiologically, in different populations and subgroups, and mechanistically, using state-of-the-art in vitro and in vivo models.

9 | NEEDS AND PROJECTED ACTIONS AND INNOVATION

The above hypothesis will be evaluated thoroughly in real-life conditions, as well as in experimental systems in the context of SynAir-G, with the participation of 18 partners from 11 countries. Details about the protocols and technical approaches used can be found in the project's website.[62] SynAir-G will develop and deploy novel sensor technologies in schools, as well as intelligent wearable devices,[63] and evaluate the impact of the exposome on health, combining mathematical, statistical and computational means, including advanced methods from machine learning and artificial intelligence (AI). Citizen science and participatory design principles will be used in the establishment and follow-up of the cohorts. Recent studies indicate that when air pollution sensors are coupled with physiological sensors and location, a stronger connection can be made between a person's exposure environment and health indicators.[64] SynAir-G builds on the cross-fertilisation and analysis of data collected from various sources (questionnaires, sensors, wearables), accounting for privacy and embedding ethics in the development of innovative AI methods.[65] Several interventions, including air filtering and a green wall, will also be evaluated. Socioeconomic determinants will also be put into context. While it is expected that these investigations will improve our targeting and capacity for addressing the problem, the list of needs and potential mitigation measures is large and should not be delayed. Monitoring systems, air filtration measures as well as lifestyle interventions to develop healthy habits, are imminently required, together with measures to address inequalities, to support the next generation to develop and retain optimal health. Coordinated efforts by all stakeholders including scientists from different disciplines and regulatory authorities are urgently needed, to implement novel discoveries and opportunities highlighted here.[66]

AUTHOR CONTRIBUTIONS

Study conception: NGP. Study design: All authors. Critical revision of the manuscript: All authors.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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APPENDIX

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