Asthma and Environmental Chemicals

Subjects: Respiratory System

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Asthma is one of the most common chronic diseases worldwide affecting all age groups from children to the elderly. In addition to other factors such as smoking, air pollution and atopy, some environmental chemicals are shown or suspected to increase the risk of asthma, exacerbate asthma symptoms and cause other respiratory symptoms.

asthma environmental chemicals

1. Introduction

Asthma is one of the most common chronic diseases with an estimated global prevalence of 16% appearing in all age groups. Characterization of asthma includes airway inflammation, variable airway obstruction and heterogeneous symptoms [1][2][3]. Asthma causes a high burden and economic costs for society and individuals throughout hospitalizations, disability, premature deaths and medications. Though the global prevalence of asthma is increasing, disability-adjusted life years (DALY) and mortality have decreased [1][2][3][4]. Mechanisms lying behind asthma's development are complex and include host factors such as genetics and sex, and environmental factors, like exposure to allergens or smoking [1][3]. Additionally, various environmental chemicals may affect the risk of asthma development and can escalate asthma symptoms [1][3][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24].

2. Chemicals Associated with an Increased Risk of Asthma

HBM4EU-priority chemicals associated with asthma are diisocyanates, hexavalent chromium (Cr(VI)) (both cause specific sensitization), polyaromatic hydrocarbons (PAHs) and organophosphate insecticides [8][12][18][23][24]. The following chemicals are possibly associated with asthma: phthalates, per- and polyfluoroalkyl substances (PFASs), pyrethroid insecticides, mercury, cadmium, arsenic, lead and p-Phenylenediamine (p-PDA, a potential specific sensitizer) [10][11][12][13][14][15][16][17][19][20][21][22].

2.1. PAHs

PAHs are a group of lipophilic, semi-volatile compounds with 2 to 7 aromatic benzene rings generated when organic materials are combusted incompletely (burning in high temperatures with low oxygen). PAHs are ubiquitous, widespread and released all over from both natural and anthropogenic sources and transported over long distances before precipitation into soils, sediment and vegetation. PAHs can react with ultraviolet light and other pollutants (e.g., ozone, nitrogen oxides and nitrate radicals) leading to the formation of PAH derivatives (e.g.,

nitrated and oxygenated PAHs). Factors such as temperature and humidity affect reactions. Humans are exposed directly to PAHs and PAH derivatives or through bioaccumulation in the food chain [7][18][25]. PAHs are known or suspected to be mutagenic, carcinogenic and teratogenic, yet, toxicity between PAHs and their derivatives varies and depends on concentration, time and route of the exposure [7][26][27]. There are legislation and regulations for PAHs in the EU and separate countries [7][26].

PAHs associated with fine particles enter the lungs causing inflammation and affecting respiratory health. According to epidemiological studies, there is an association between exposure to PAHs, concentrations of air pollutants and the development of allergic and non-allergic asthma, increased symptoms of asthma, risk of asthma exacerbations and lung function decrease, yet according to current data there is a low level of evidence. The strongest evidence is shown for the association between development of asthma and lung function in children [18][25][27][28]. Various mechanisms are likely to play a role in these pathophysiological processes including inflammation, immunoglobulin E (IgE), mast cells' and eosinophils' mediated reactions, oxidative stress, and epithelial and endothelial dysfunction [18][25][29][30]. The risk of asthma is associated with the duration and dose of exposure to PAHs. However, normally, PAHs are one of many air pollutants, and therefore it is difficult to study the effects of each single chemical (mixed exposure) [25][27][28].

2.2. Diisocyanates

Diisocyanates are considered as a part of the aniline family used in different industrial applications such as manufacturing polyurethanes and hardeners in various products. Mostly, used diisocyanates include methylene diphenyl diisocyanate (MDI), toluene diisocyanate (TDI) and non-aromatic hexamethylene diisocyanate (HDI). Diisocyanates are produced with an annual volume of 2.5 million tons in the EU and they are one of the most common causes of occupational asthma in Europe. To reduce the number of occupational diseases caused by diisocyanates, the EU is planning to restrict the use of diisocyanates and to set an EU-wide occupational limit value for exposure to diisocyanates in workplaces [26][25][31][32][33].

Diisocyanates cause specific sensitization, which is associated with respiratory symptoms. Moreover, skin sensitization may occur after exposure to diisocyanates. Even a very low exposure to diisocyanates may cause sensitization and asthma. Asthma induced by isocyanates is sometimes IgE-mediated, however, often specific sensitization is observed in specific bronchial challenge tests without specific IgE. Diisocyanates may also cause asthma by irritating mechanisms (reactive airways dysfunction syndrome (RADS) [8][26][32][34].

2.3. Cr(VI)

Chromium exists in oxidation states from −2 to +6, and of those, Cr(III) and Cr(VI) are the most frequently found in the environment. Cr(VI) is mostly a manmade oxidizing compound which is mobile in nature. Contamination for Cr(VI) occurs mainly in large industrial emissions (metallurgical and chemical industries). There is a 3–4.5% annual growth in the demand of Cr in the EU [26][35]. Cr(VI) is carcinogenic, genotoxic and causes various health effects

such as skin irritation, nasal epithelium damage and lung fibrosis [26][35]. There are legislation and regulations to limit the exposure to Cr(VI) from occupational sources and from different consumer articles [26][35].

Due to the widespread use of Cr(VI) in various industrial sectors, workers can thus be considered the main vulnerable population in developing asthma. Numerous case studies revealed a link between occupational asthma and inhalation of certain particulate Cr(VI) salts/oxides mainly in electroplaters, stainless steel welders, surface treatment workers and construction workers [24][36][37][38][39]. Underlying mechanisms involved in occupational asthma caused by Cr(VI) are not fully elucidated, but may include non-immunologic and immunologic mechanisms, and the latter can be IgE-dependent or non-IgE dependent [36]. A positive association between asthma in adults and urinary Cr was observed in China [12].

2.4. Pesticides

Pesticides are a large group of chemicals with various chemical structures and from multiple substance groups used for controlling pests, such as insects and fungus [26][40]. Several pesticides are known, or suspected to be, neurotoxic, carcinogenic and/or endocrine disruptors. The use of various pesticides has varied by time and by country. The EU regulates the use of pesticides, for instance by limiting the maximal residue concentrations in food [23][26].

Organophosphate and pyrethroid insecticides are two major classes of pesticides included in the HBM4EU-project. Organophosphates are a group of chemicals of which chlorpyrifos and dimethoate are the most important ones. They are used in agriculture as insecticides and acaricides. They inhibit acetylcholinesterase activity and possess high acute toxicity, which includes, for instance, vomiting, diarrhea, abdominal cramps, dizziness, eye pain, blurred vision, confusion, paralysis, bronchoconstriction, in severe cases respiratory failure and even death (“cholinergic syndrome”) [23][26][40]. Pyrethroids are in the EU and are globally one of the major classes of insecticides which have partly replaced organophosphates. Pyrethroids are used, for instance, in plant protection, wood preservation and to combat insects in buildings and animal facilities. Chemically, they are synthetic analogs of pyrethrins, and they depolarize axonal sodium and other ion channels and have partly replaced organophosphates. An acute high exposure to pyrethroids causes instances of dyspnoea, coughing, bronchospasm, nausea, vomiting, dermal effects and peripheral neural symptoms [23][26][40].

Multiple epidemiological studies have shown associations between pesticides and asthma. The strongest association was seen for organophosphate insecticides. Use of insecticides was also associated with exacerbation of asthma among subjects with allergies. Most of the evidence comes from studies among occupationally exposed farmers and pesticide applicators, while there are fewer studies with conflicting results in the general population [23][41][42][43]. A large Canadian cohort study found an association between exposure to organophosphates and reduced lung function in the adult general population and pyrethroids and reduced lung function in children and adolescents [42][44].

2.5. Phthalates and Hexamoll® DINCH

Phthalates are a group of substances with a chemical structure being esters of phthalic acid of which ortho-phthalates can be divided into high molecular weight (HMW) and low molecular weight (LMW) phthalates depending on their molecular structure. They are used in millions of tons per year globally. Most phthalates are used primarily as plasticisers as they increase the flexibility and service life of soft poly vinyl chloride (soft-PVC). Phthalates are not chemically bound to the materials and can leach, migrate or evaporate into indoor air, the atmosphere, foodstuffs or other materials. Some phthalates are known toxicants to male reproductive development and disturb the endocrine system. They can act in a dose-additive manner and thereby cause a cumulative risk for health [6][20][21][45][46]. Some, but not all, are restricted in Europe but not necessarily in other non-EU countries, and therefore, exposure to imported and to recycled old plastic products also containing restricted phthalates continues in the EU [45].

Epidemiological studies have showed a possible association between exposure to phthalates and asthma. Phthalates might exacerbate already-existing respiratory symptoms [6][20][21]. For instance, in children, exposure to phthalates at home is associated with asthma and allergies. A survey from the U.S. found that HMW phthalates may cause allergy, allergic symptoms and sensitization in adults but not in children, yet in the same survey, phthalates were associated with self-reported asthma in children [47][48]. In adults, exposure to heated PVC fumes is possibly associated with asthma. Experimental studies in vitro and in mice have reported that several phthalates may modulate the murine immune response to co-allergens and act as adjuvants in atopy and allergic reactions [6][20][21][49].

2.6. PFASs

PFASs are a large group of highly stable carbon fluorine compounds of which many are very persistent and bio-accumulative; they are widely used in major industry sectors and consumer applications. PFASs are ubiquitous contaminants and partly highly mobile in the environment; they are found in biotic and abiotic environments and food. Of PFASs, specifically PFOA and PFOS are well studied and cause harm for development, are toxic for some target organs and are suspected to be carcinogenic. In humans, the longest half-life for PFASs is up to 8.5 years, with an elimination range from 10 to 56 years [9][26][50][51][52][53]. Due to the overall concerns for human health and the environment, elements of an EU-strategy for PFASs have been worked out and a restriction proposal for PFASs for non-essential uses is currently under preparation [26][50]. Moreover, the recently published chemicals strategy for sustainability towards a toxic-free environment intends to phase out the use of PFASs in the EU, unless their use is essential [54].

There are a limited number of studies on children, adolescents and adults with no consistent results about the association between PFASs and asthma. Some studies on children and adolescents report no association between PFASs and asthma [9][55][56], allergies and IgE levels [9][55]. Two studies reported a possible association [9][57] and a third that some PFASs were associated with increased risk of self-reported asthma but not with current asthma or a wheeze [58]. In a study from Taiwan, serum concentrations of PFASs were associated with asthma, markers and severity for asthma [22], and another study from Norway showed a positive association of exposure to PFAS and clinically severe asthma in adolescents [58]. The scientific opinion of the European Food Safety Authority (EFSA)

CONTAM-panel summarises that there are no or inconsistent associations with asthma and allergies for prenatal and postnatal PFAS exposures. This is in line with two recent reviews on health effects [59] and specifically asthma related outcomes [60] of PFAS. However, the risk characterisation of EFSA is based on the effects on the immune system in humans at very low exposure concentrations, which is also supported by the effects in laboratory animals [50]. Ongoing work in HBM4EU shall provide further insight into PFAS-related effects on the immune system including asthma and allergies.

2.7. p-PDA

Aniline and its derivatives are aromatic amines which are known or suspected to be carcinogenic and genotoxic [26]. The derivative p-PDA is a common contact allergen causing skin sensitization (contact dermatitis) and exposure is possibly associated with increased risk of occupational asthma and rhinitis through sensitization [19][26][31][61]. Some anilines and their derivatives are restricted in the EU and under the REACH regulations [26][61].

2.8. Mercury

Mercury (Hg) is a highly toxic heavy metal which bio-accumulates in food chains and remains in circulation for thousands of years when released. There are natural and anthropogenic sources for Hg which travel over long distances in the air. Mercury exists in various forms, of which exposure sources, target organs, toxicity and metabolism differ [26][35][62]. Organic methylmercury compounds cause the highest risk to human health because they accumulate in the food chain—mainly in large predatory fish—and cause severe and irreversible effects on the central nervous system, even at very low levels [26][35][62]. The use and emission of Hg is restricted with several regulations in the EU and globally [26][35].

There is no definite association between asthma and exposure to Hg. In children, the blood concentration of Hg was shown to both, associate [11] and not to associate with asthma [10][63]. The body burden of Hg might be associated with acute atopic eczema and total IgE measured in children [64].

2.9. Cadmium

Cadmium (Cd) is a heavy metal with cumulative toxic effects. The yearly global consumption is 22,000 metric tons. Cd is released from natural sources, for instance in volcanic eruptions and forest fires, and anthropogenic sources, for instance corrosion protection of steel and soldering metal in alloys [26][35]. Cd is carcinogenic and its main target organs are kidneys and bone. The level of exposure affects toxicity, yet only moderate environmental exposure might increase the risk of osteoporosis and age-related decrease in kidney function. There are restrictions in the EU and globally on the use of cadmium [26][35].

Exposure to inhaled Cd might be associated with asthma, however smoking confounds this association while cigarettes include cadmium and smoking is associated with asthma. In smokers, the blood concentration of Cd was associated with wheeze and asthma and in all subjects with lower forced expiratory volume in 1 s (FEV_1) per

forced vital capacity (FVC) and fractional exhaled nitric oxide (FeNO) [15] and urinary concentration of Cd with asthma [12]. The blood level of Cd had an association with self-reported asthma [63].

2.10. Arsenic

Arsenic (As) is a chemical element and a significant global environmental toxicant released from natural and anthropogenic sources, appearing everywhere in our environment and circulating in water, air and living organisms and concentrating in soil for years. There are multiple forms of As of which inorganic arsenic (iAs) combined with other elements, such oxygen and sulphur, is the most toxic [13][26][35]. The major toxicity of iAs originates from the natural geological sources such as contaminated drinking water. iAs is for instance carcinogenic and causes vascular diseases and neurotoxicity. Various compounds have various physicochemical properties and toxicity and vary between individual metabolisms related to age, gender and life stage such as pregnancy [13][26][35]. There are international regulations for the use of As [26][35].

There are a limited number of studies on the association between exposure to iAs and its methylated forms and asthma and, therefore the association is undetermined. Chronic exposure to As was associated with various respiratory symptoms, decrease in lung functions, dyspnoea, asthma and increased IgE [13][14], and respiratory symptoms in children in China [38]. A recent study clearly indicates that chronic exposure to As in Bangladesh is associated with characteristic features of asthma [65].

2.11. Lead

Lead (Pb) is a toxic heavy metal found in air, water and soil, especially in urban and industrial areas. Lead is used up to 10,000,000 tons per year in the EU and the human exposure to Pb occurs mainly from anthropogenic sources. Pb is present in different inorganic and organic forms which have various properties [26][35]. Inorganic lead compounds are neurotoxic. Foetuses and young children are especially vulnerable because their nervous system is particularly sensitive to the effects of Pb [26][35]. The EU and separate countries have introduced different regulations on Pb [26].

There are quite a few studies investigating the association between exposure to lead and asthma, and therefore, the association is undetermined. Increased Pb blood levels are associated with bronchial hyperresponsiveness, total IgE and decrease in FEV_1 and FVC [16][17][26][66]. In a recent study the blood Pb level was associated with self-reported asthma [63].

References

1. Reddel, H.K.; Fitzgerald, J.M.; Bateman, E.D.; Bacharier, L.B.; Becker, A.; Brusselle, G.; Buhl, R.; Cruz, A.A.; Fleming, L.; Inoue, H.; et al. GINA 2019: A fundamental change in asthma

management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. Eur. Respir. J. 2019, 53.

2. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir. Med. 2017, 5, 691–706.
3. Masoli, M.; Fabian, D.; Holt, S.; Beasley, R.; Global Initiative for Asthma (GINA) Program. The global burden of asthma: Executive summary of the GINA Dissemination Committee report. Allergy 2004, 59, 469–478.
4. Bahadori, K.; Doyle-Waters, M.M.; Marra, C.A.; Lynd, L.D.; Alasaly, K.; Swiston, J.; Fitzgerald, J.M. Economic burden of asthma: A systematic review. BMC Pulm. Med. 2009, 9, 24.
5. Briggs, D. Environmental pollution and the global burden of disease. Br. Med. Bull. 2003, 68, 1–24.
6. Jaakkola, J.J.; Knight, T.L. The role of exposure to phthalates from polyvinyl chloride products in the development of asthma and allergies: A systematic review and meta-analysis. Environ. Health Perspect. 2008, 116, 845–853.
7. Kim, K.H.; Jahan, S.A.; Kabir, E.; Brown, R.J. A review of airborne polycyclic aromatic hydrocarbons (PAHs) and their human health effects. Environ. Int. 2013, 60, 71–80.
8. Tarlo, S.M.; Liss, G.M. Diisocyanate-induced asthma: Diagnosis, prognosis, and effects of medical surveillance measures. Appl. Occup. Environ. Hyg. 2002, 17, 902–908.
9. Rappazzo, K.M.; Coffman, E.; Hines, E.P. Exposure to Perfluorinated Alkyl Substances and Health Outcomes in Children: A Systematic Review of the Epidemiologic Literature. Int. J. Environ. Res. Public Health 2017, 14, 691.
10. Heinrich, J.; Guo, F.; Trepka, M.J. Brief Report: Low-level Mercury Exposure and Risk of Asthma in School-age Children. Epidemiology 2017, 28, 116–118.
11. Kim, K.N.; Bae, S.; Park, H.Y.; Kwon, H.J.; Hong, Y.C. Low-level Mercury Exposure and Risk of Asthma in School-age Children. Epidemiology 2015, 26, 733–739.
12. Huang, X.; Xie, J.; Cui, X.; Zhou, Y.; Wu, X.; Lu, W.; Shen, Y.; Yuan, J.; Chen, W. Association between Concentrations of Metals in Urine and Adult Asthma: A Case-Control Study in Wuhan, China. PLoS ONE 2016, 11, e0155818.
13. Ratnaike, R.N. Acute and chronic arsenic toxicity. Postgrad. Med. J. 2003, 79, 391–396.
14. Das, D.; Bindhani, B.; Mukherjee, B.; Saha, H.; Biswas, P.; Dutta, K.; Prasad, P.; Sinha, D.; Ray, M.R. Chronic low-level arsenic exposure reduces lung function in male population without skin lesions. Int. J. Public Health 2014, 59, 655–663.

15. Yang, G.; Sun, T.; Han, Y.-Y.; Rosser, F.; Forno, E.; Chen, W.; Celedon, J. Serum Cadmium and Lead, Current Wheeze, and Lung Function in a Nationwide Study of Adults in the United States. J. Allergy Clin. Immunol. Pract. 2019, 7, 2653–2660.e3.
16. Pak, Y.S.; Oh, A.; Kho, Y.L.; Paek, D. Lung function decline and blood lead among residents nearby to industrial complex. Int. Arch. Occup. Environ. Health 2012, 85, 951–959.
17. Min, J.Y.; Min, K.B.; Kim, R.; Cho, S.I.; Paek, D. Blood lead levels and increased bronchial responsiveness. Biol. Trace Elem. Res. 2008, 123, 41–46.
18. Karimi, P.; Peters, K.O.; Bidad, K.; Strickland, P.T. Polycyclic aromatic hydrocarbons and childhood asthma. Eur. J. Epidemiol. 2015, 30, 91–101.
19. Helaskoski, E.; Suojalehto, H.; Virtanen, H.; Airaksinen, L.; Kuuliala, O.; Aalto-Korte, K.; Pesonen, M. Occupational asthma, rhinitis, and contact urticaria caused by oxidative hair dyes in hairdressers. Ann. Allergy Asthma Immunol. 2014, 112, 46–52.
20. Kimber, I.; Dearman, R.J. An assessment of the ability of phthalates to influence immune and allergic responses. Toxicology 2010, 271, 73–82.
21. North, M.L.; Takaro, T.K.; Diamond, M.L.; Ellis, A.K. Effects of phthalates on the development and expression of allergic disease and asthma. Ann. Allergy Asthma Immunol. 2014, 112, 496–502.
22. Humblet, O.; Diaz-Ramirez, L.G.; Balmes, J.R.; Pinney, S.M.; Hiatt, R.A. Perfluoroalkyl chemicals and asthma among children 12–19 years of age: NHANES (1999–2008). Environ. Health Perspect. 2014, 122, 1129–1133.
23. Mostafalou, S.; Mostafalou, S.; Abdollahi, M.; Abdollahi, M. Pesticides: An update of human exposure and toxicity. Arch. Toxicol. 2017, 91, 549–599.
24. Park, H.S.; Yu, H.J.; Jung, K.S. Occupational asthma caused by chromium. Clin. Exp. Allergy 1994, 24, 676–681.
25. Delfino, R.J. Epidemiologic evidence for asthma and exposure to air toxics: Linkages between occupational, indoor, and community air pollution research. Environ. Health Perspect. 2002, 110 (Suppl. 4), 573–589.
26. HBM4EU Project. Available online: (accessed on 5 March 2020).
27. Lag, M.; Ovrevik, J.; Refsnes, M.; Holme, J.A. Potential role of polycyclic aromatic hydrocarbons in air pollution-induced non-malignant respiratory diseases. Respir. Res. 2020, 21, 1–22.
28. Pope, C.A. Epidemiology of fine particulate air pollution and human health: Biologic mechanisms and who’s at risk? Environ. Health Perspect. 2000, 108 (Suppl. 4), 713–723.
29. Jenerowicz, D.; Silny, W.; Danczak-Pazdrowska, A.; Polanska, A.; Osmola-Mankowska, A.; Olek-Hrab, K. Environmental factors and allergic diseases. Ann. Agric. Environ. Med. 2012, 19, 475–

481.

30. Klingbeil, E.C.; Hew, K.M.; Nygaard, U.C.; Nadeau, K.C. Polycyclic aromatic hydrocarbons, tobacco smoke, and epigenetic remodeling in asthma. Immunol. Res. 2014, 58, 369–373.
31. Baur, X.; Bakehe, P. Allergens causing occupational asthma: An evidence-based evaluation of the literature. Int. Arch. Occup. Environ. Health 2014, 87, 339–363.
32. Health Council of Netherlands, di- and Triicocyanates. Available online: (accessed on 2 April 2020).
33. Collins, J.J.; Anteau, S.; Conner, P.R.; Cassidy, L.D.; Don, M.; Wang, M.L.; Kurth, L.; Carson, M.; Molenaar, D.; Redlich, C.A.; et al. Incidence of Occupational Asthma and Exposure to Toluene Diisocyanate in the United States Toluene Diisocyanate Production Industry. J. Occup. Environ. Med. 2017, 59 (Suppl. 12), S22–S27.
34. Wisnewski, A.V.; Redlich, C.A. Recent developments in diisocyanate asthma. Curr. Opin. Allergy Clin. Immunol. 2001, 1, 169–175.
35. Rahman, Z.; Singh, V.P. The relative impact of toxic heavy metals (THMs) (arsenic (As), cadmium (Cd), chromium (Cr)(VI), mercury (Hg), and lead (Pb)) on the total environment: An overview. Environ. Monit. Assess. 2019, 191, 1–21.
36. Fernandez-Nieto, M.; Quirce, S.; Carnes, J.; Sastre, J. Occupational asthma due to chromium and nickel salts. Int. Arch. Occup. Environ. Health 2006, 79, 483–486.
37. Schneider, B.C.; Constant, S.L.; Patierno, S.R.; Jurjus, R.A.; Ceryak, S.M. Exposure to particulate hexavalent chromium exacerbates allergic asthma pathology. Toxicol. Appl. Pharmacol. 2012, 259, 38–44.
38. Zeng, X.; Xu, X.; Boezen, H.M.; Huo, X. Children with health impairments by heavy metals in an e-waste recycling area. Chemosphere 2016, 148, 408–415.
39. Walters, G.I.; Moore, V.C.; Robertson, A.S.; Burge, C.B.; Vellore, A.D.; Burge, P.S. An outbreak of occupational asthma due to chromium and cobalt. Occup. Med. (Lond.) 2012, 62, 533–540.
40. Koureas, M.; Tsakalof, A.; Tsatsakis, A.; Hadjichristodoulou, C. Systematic review of biomonitoring studies to determine the association between exposure to organophosphorus and pyrethroid insecticides and human health outcomes. Toxicol. Lett. 2012, 210, 155–168.
41. Ratanachina, J.; De Matteis, S.; Cullinan, P.; Burney, P. Pesticide exposure and lung function: A systematic review and meta-analysis. Occup. Med. (Lond.) 2019, 70, 14–23.
42. Ye, M.; Beach, J.; Martin, J.W.; Senthilselvan, A. Urinary Dialkyl Phosphate Concentrations and Lung Function Parameters in Adolescents and Adults: Results from the Canadian Health Measures Survey. Environ. Health Perspect. 2016, 124, 491–497.

43. Benka-Coker, W.; Loftus, C.; Karr, C.; Magzamen, S. Association of Organophosphate Pesticide Exposure and a Marker of Asthma Morbidity in an Agricultural Community. J. Agromed. 2020, 25, 106–114.
44. Ye, M.; Beach, J.; Martin, J.W.; Senthilselvan, A. Urinary concentrations of pyrethroid metabolites and its association with lung function in a Canadian general population. Occup. Environ. Med. 2016, 73, 119–126.
45. (48) Koch, H.M.; Angerer, J. Phthalates: Biomarkers and Human Biomonitoring. Biomarkers and Human Biomonitoring; RSC Publishing: Cambrige, UK, 2012.
46. Wittassek, M.; Koch, H.M.; Angerer, J.; Bruning, T. Assessing exposure to phthalates—The human biomonitoring approach. Mol. Nutr. Food Res. 2011, 55, 7–31.
47. Odebeatu, C.C.; Taylor, T.; Fleming, L.E.; JOsborne, N. Phthalates and asthma in children and adults: US NHANES 2007–2012. Environ. Sci. Pollut. Res. Int. 2019, 26, 28256–28269.
48. Hoppin, J.A.; Jaramillo, R.; London, S.J.; Bertelsen, R.J.; Salo, P.M.; Sandler, D.P.; Zeldin, D.C. Phthalate exposure and allergy in the U.S. population: Results from NHANES 2005–2006. Environ. Health Perspect. 2013, 121, 1129–1134.
49. Bornehag, C.G.; Nanberg, E. Phthalate exposure and asthma in children. Int. J. Androl. 2010, 33, 333–345.
50. European Food Safety Authority (EFSA). Risk to Human Health Related to the Presence of Perfluoroalkyl Substances in Food. Draft Scientific Opintion Part, I. EFSA J. 2020. Available online: (accessed on 1 June 2020).
51. Fischer, S. Known uses of PFASs. In Nordic Workshop; Swedish Chemicals Agency: Stockholm, Sweden, 2017.
52. KEMI. Occurrence and Use of Highly Fluorinated Substances and Alternatives; Swedish Chemicals Agency: Stockholm, Sweden, 2015; ISSN 0284-1185. Available online: (accessed on 2 December 2020).
53. OECD. Risk Reduction Approaches for PFASs—A Cross Country Analysis; Series on Risk Management No. 29; Environment Directorate: Paris, France, 2015.
54. EU European Environment Strategy. Available online: (accessed on 6 January 2021).
55. Gaylord, A.; Berger, K.I.; Naidu, M.; Attina, T.M.; Gilbert, J.; Koshy, T.T.; Han, X.; Marmor, M.; Shao, Y.; Giusti, R.; et al. Serum perfluoroalkyl substances and lung function in adolescents exposed to the World Trade Center disaster. Environ. Res. 2019, 172, 266–272.
56. Smit, L.A.M.; Lenters, V.; Høyer, B.B.; Lindh, C.H.; Pedersen, H.S.; Liermontova, I.; Jonsson, B.A.G.; Piersma, A.H.; Bonde, J.P.; Toft, G.; et al. Prenatal exposure to environmental chemical contaminants and asthma and eczema in school-age children. Allergy 2015, 70, 653–660.

57. Jackson-Browne, M.S.; Eliot, M.; Patti, M.; Spanier, A.J.; Braun, J.M. PFAS (per- and polyfluoroalkyl substances) and asthma in young children: NHANES 2013–2014. Int. J. Hyg. Environ. Health 2020, 229, 113565.
58. Averina, M.; Brox, J.; Huber, S.; Furberg, A.S.; Sorensen, M. Serum perfluoroalkyl substances (PFAS) and risk of asthma and various allergies in adolescents. The Tromso study Fit Futures in Northern Norway. Environ. Res. 2019, 169, 114–121.
59. Fenton, S.E.; Ducatman, A.; Boobis, A.; DeWitt, J.C.; Lau, C.; Ng, C.A.; Smith, J.S.; Roberts, S.M. Per- and Polyfluoroalkyl Substance Toxicity and Human Health Review: Current State of Knowledge and Strategies for Informing Future Research. Environ. Toxicol. Chem. 2020.
60. Kvalem, H.E.; Nygaard, U.C.; Lodrup Carlsen, K.C.; Carlsen, K.H.; Haug, L.S.; Granum, B. Perfluoroalkyl substances, airways infections, allergy and asthma related health outcomes—Implications of gender, exposure period and study design. Environ. Int. 2020, 34, 105259.
61. Malvestio, A.; Bovenzi, M.; Hoteit, M.; Fortina, A.B.; Peserico, A.; Corradin, M.T.; Filon, F.L. p-Phenylenediamine sensitization and occupation. Contact Dermat. 2011, 64, 37–42.
62. Esteban, M.; Castano, A. Non-invasive matrices in human biomonitoring: A review. Environ. Int. 2009, 35, 438–449.
63. Koh, H.Y.; Kim, T.H.; Sheen, Y.H.; Lee, S.W.; An, J.; Kim, M.A.; Han, M.Y.; Yon, D.K. Serum heavy metal levels are associated with asthma, allergic rhinitis, atopic dermatitis, allergic multimorbidity, and airflow obstruction. J. Allergy Clin. Immunol. Pract. 2019, 7, 2912–2915.e2.
64. Weidinger, S.; Kramer, U.; Dunemann, L.; Mohrenschlager, M.; Ring, J.; Behrendt, H. Body burden of mercury is associated with acute atopic eczema and total IgE in children from southern Germany. J. Allergy Clin. Immunol. 2004, 114, 457–459.
65. Siddique, A.E.; Rahman, M.; Hossain, I.; Karim, Y.; Hasibuzzaman, M.; Biswas, S.; Islam, S.; Rahman, A.; Hossen, F.; Mondal, V.; et al. Association between chronic arsenic exposure and the characteristic features of asthma. Chemosphere 2020, 246, 125790.
66. Wang, I.J.; Karmaus, W.J.J.; Yang, C.C. Lead exposure, IgE, and the risk of asthma in children. J. Expo. Sci. Environ. Epidemiol. 2017, 27, 478–483.