Do Environmental Toxicants Contribute to Allergy and Asthma?

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Abstract

The rates of asthma and allergy (Type 1 hypersensitivity disorders) have been increasing worldwide for the last few decades. Various theories have been proposed to account for this alarming trend. One of these is the impact of environmental toxicants. Epidemiological research has correlated exposure to environmental chemicals (such as pesticides, solvents, and air pollutants) with increasing rates of both asthma and allergies. Research has documented chemicals as causal agents capable of producing immune system imbalances characteristic of type 1 hypersensitivity. *In vitro* studies and *in vivo* animal models have demonstrated that many of the environmental chemicals and pollutants that have been epidemiologically associated with increased allergic tendency have been shown to enhance Type 2 helper T cell (Th2) dominance, which is consistent with the T-helper cell pattern found in asthma, allergic rhinitis, and other Type 1 hypersensitivity disorders. Depletion of glutathione is one possible mechanism for this T-helper cell imbalance. Preliminary evidence suggests the possibility that repletion of glutathione levels (with oral supplementation of N-acetylcysteine), and enhancement of glutathione transferase function (using sulforaphanes), might be therapeutic options for countering type 1 hypersensitivity disorders caused by environmental chemicals. *(Altern Med Rev* 2012;17:6-18)

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Background

Allergies and asthma (as well as other atopic disorders) are considered type 1 hypersensitivities (immediate hypersensitivity), which are reactions provoked by re-exposure to a specific type of antigen referred to as an allergen. Rates of these disorders have been increasing around the world in the last few decades. Most countries report rates of allergies in their population between 15-35 percent, with the worldwide average being 22%.[1] The prevalence of asthma has been increasing since the early 1980s and, by 2004, 1 in every 15 residents in the United States had asthma (20 million), with half of those cases being allergic asthma.[2] But, by 2007, the same organization (the United States Centers for Disease Control) stated that the number of people with asthma increased to 1 out of every 9, for a total of 34 million in the U.S.[3] From 2001 through 2009, asthma rates rose almost 50 percent among black children. Asthma was linked to 3,447 deaths (about 9 per day) in 2007. Asthma costs in the U.S. grew from about $53 billion in 2002 to approximately $56 billion in 2007, nearly a 6 percent increase.[4]

Type 1 (Th1) and Type 2 Helper T (Th2) Cell Model

Communication in the immune system occurs by chemical messengers that are typically referred to as cytokines or lymphokines. Included in these chemicals are interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), a number of interleukins, and a host of other compounds. T-helper cells (Th cells) are also important chemical messengers, functioning to activate or direct other immune cells.

Th cells are a sub-group of lymphocytes that play an important role in the adaptive immune system. As seen in figure 1, the cellular immune system response begins once a macrophage consumes an antigen. It sends out chemical messengers to alert the immune system to the presence of this antigen, and, in so doing, turns on the cellular immune response that is dominated by Th and B cells. When

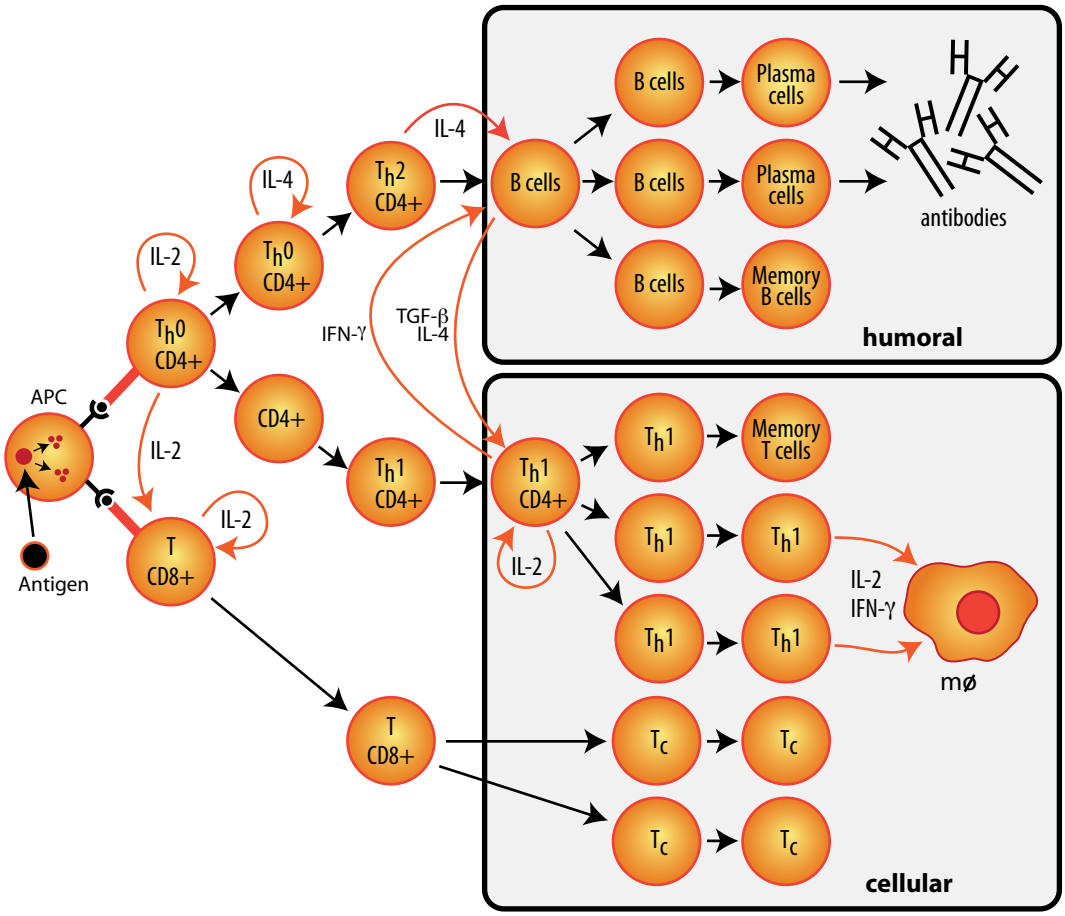
Key Words: allergies, asthma, hypersensitivity, Th2, Th1, chemical, glutathione, sulforaphane, Brassica, NAC, N-acetylcysteine, perflourocarbons, smoke, diesel, DEP, triclosan, phthalates, plastics, solvents, herbicides, pesticides

Th cells proliferate they develop into (1) effector Th cells, (2) memory Th cells, or (3) regulatory Th cells. Effector Th cells subsequently differentiate into two major subtypes known as Type 1 and Type 2 helper T cells (Th1 and Th2 cells, respectively).

Th1 cells primarily produce IFN-γ and possibly interleukin-2 (IL-2). Th1 cells stimulate cell-mediated immune function and are involved with maximizing the killing efficacy of macrophages, the proliferation of cytotoxic CD8+ T cells, and the production of opsonizing antibodies. Because of this, Th1 cells play a critical role in fighting viral and bacterial pathogens, type 4 hypersensitivity (delayed-type hypersensitivity [DTH] that results in chronic inflammation and cytokine release), and defense against cancer cells.

Th2 cells produce higher levels of interleukin-4 and 5 (IL-4 and IL-5, respectively) and they stimulate the humoral immune system and influence B-cell proliferation, B-cell antibody class switching, and the production of neutralizing antibodies. In the Th1/Th2 model, Th2 overexpression is involved with the promotion of type 1 hypersensitivity (immediate hypersensitivity disorders [e.g., allergies and asthma]), type 2 hypersensitivity (cytotoxic hypersensitivity [e.g.,

Figure 1. Human immune system lymphocyte response to antigen presence



Antigen-producing cells (APC) consume an invading organism (antigen) and display the antigenic signature of this invader, as well as send out chemical messengers to alert the immune system of the antigen's presence. Generic T helper cells (Th0) can then be stimulated to produce Th1 or Th2 cells. Th2 cells stimulate the development of antibody-producing B cells. Th1 cells attack invaders directly, and produce memory cells, so that if the antigen shows up again the immune system will respond more rapidly. T-cytotoxic cells (Tc) are also produced.

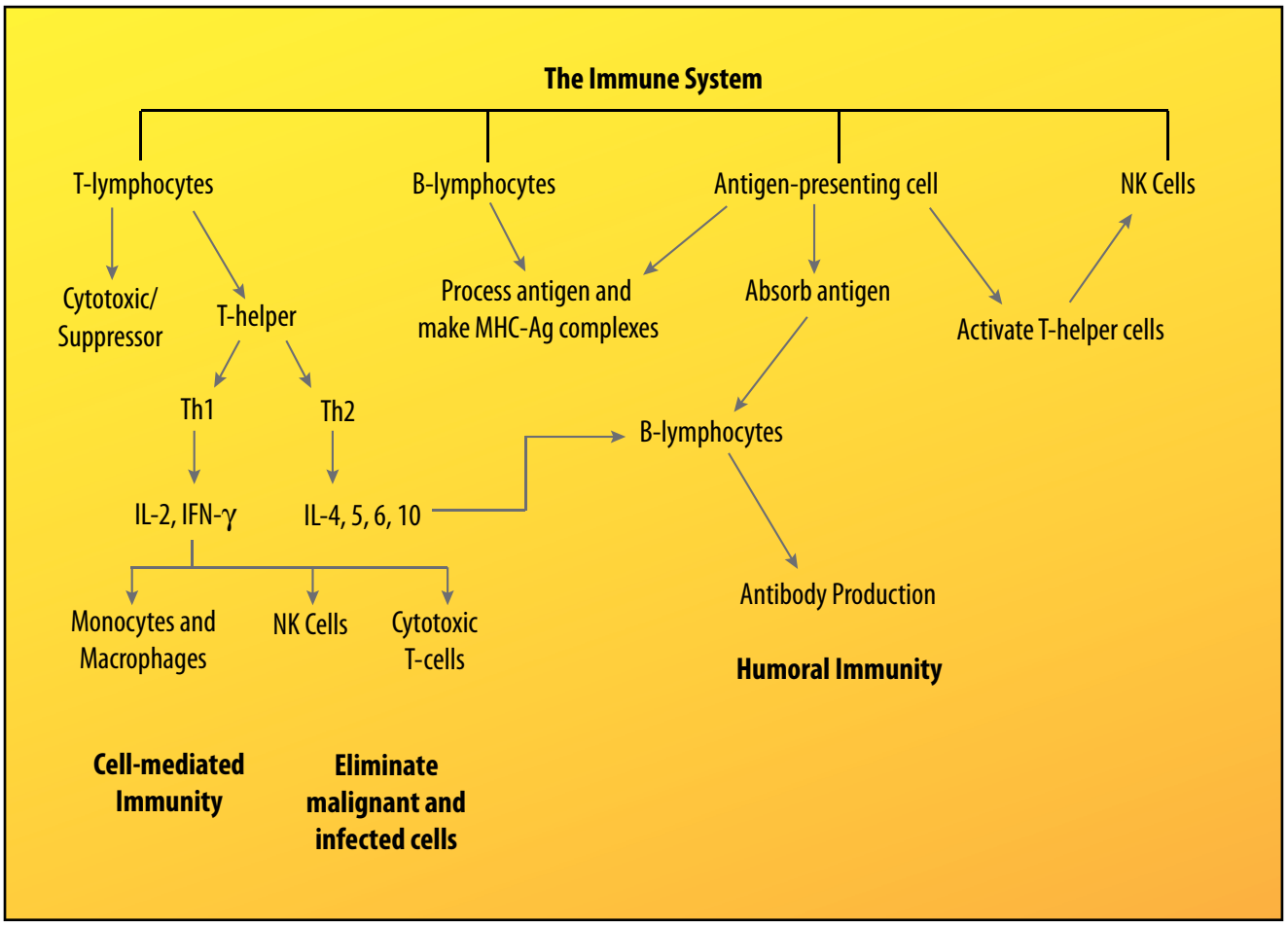
autoimmune hemolytic anemia, Goodpasture's syndrome, and pemphigus), and type 3 hypersensitivity (immune complex hypersensitivity [e.g., reactive arthritis, serum sickness, and systemic lupus erythematosus]). [Note: The numeral designation of hypersensitivity types does not correlate with, and is completely unrelated to, the numerical designations in the Th model.]

Th1 and Th2 cells not only boost the functioning of either the cellular or humoral immune response, but are also capable of inhibiting their rivals. The IFN-γ produced by Th1 cells inhibits Th2-associated functions, while the IL-4 and IL-10 produced by Th2 cells inhibit Th1 functions.[5] Th1 dominance is thought to predispose to organ or tissue-specific autoimmunity (arthritis, diabetes). Th2 dominance appears to lead to increased rates of allergy and systemic autoimmunity (SLE),[6] both of which are commonly seen in persons with chemical overburden. Figure 2 shows the basic flow of the immune system and how the various aspects interact.

Th1/Th2 imbalances have been proposed to play a role in immunotoxicity – adverse effects on the functioning of the immune system resulting from exposure to chemical substances. Immunotoxicity can present as reduced cell-mediated immunity leading to chronic infections (decreased Th1 function), allergies and asthma (increased Th2 function), or chemical sensitivity and autoimmunity (both of which might be a result of either overactive Th1 or Th2 function).[7]

The first manifestation of immunotoxicity often seen in a case history is the development of asthma and/or allergies. Multiple environmental toxicants have been associated with increased incidences of allergic reactivity to the environment and to foods. Exposures with strong correlations to type 1

Figure 2. Flowchart of immune system interrelationships



hypersensitivity reactions include organophosphate and chlorinated pesticides, solvents, and combustion byproducts including tobacco smoke and diesel exhaust. As an example, in a study that looked at the cord blood of 2,050 babies, the levels of chlorinated pesticides were found to be positively associated with allergy. Not only were levels of chlorinated pesticides significantly higher in the cord blood of infants from regions with chemical industry present, but these children also had significantly higher levels of immunoglobulin E (IgE) antibodies. The children with IgE elevations also exhibited a higher incidence of eczema.[8] The remainder of this review will focus on the role of environmental exposures in type 1 hypersensitivity.

The Connection Between Indoor Air Pollutants and Type 1 Hypersensitivity

Indoor-building materials (including carpeting, particle board, and wall coverings), recent painting, and new furniture appear to play a role in childhood allergies and asthma. The highest risk for asthma was having new synthetic carpet installed in the home, while the highest risk for developing allergies of any kind was associated with having new particle board brought into the home.[9] When children are exposed to molds, solvents, and plasticizers in their school air, they also have higher rates of asthma and nighttime breathlessness.[10]

Secondhand Smoke

Environmental tobacco smoke is often thought of as the biggest indoor air pollutant. Combustion byproducts from cigarettes (as well as vehicles) have been shown to lead to higher rates of allergy and asthma.[11] Exposure to cigarette smoke reduces IFN-γ[12] and natural killer (NK) cell activity,[13] both of which are Th1 functions. This decrease in Th1 function has been linked to reduced ability to fight respiratory infections,[12] and has been proposed to play a role in increasing cancer risk.[13] Children exposed to environmental tobacco smoke are also more likely to be plagued by recurrent ear infections than other children without that exposure.[14] While tobacco smoke reduces Th1 response, it also enhances Th2 response through greater production of IL-4, IL-5 and other pro-inflammatory cytokines that lead to increases in allergenicity.[15] Human volunteers who were exposed to ragweed antigen after tobacco smoke exposure produced higher levels of IgE, histamine, IL-4, IL-5, and interleukin-13 (IL-13) than volunteers who were not exposed to tobacco smoke.[16] In animal models, even *in utero* exposure to tobacco smoke has been shown to enhance risk of becoming asthmatic.[17]

Perflourocarbons

Perflourooctanesulfonate (PFOS) was the key ingredient of Scotchguard™, which is used as a stain and water repellent and applied to furniture fabrics and carpeting. [Note: In 2003 this product was reformulated and PFOS was replaced with perfluorobutanesulfonic acid (PFBS).] PFOS has been classified as a persistent organic pollutant (POP) by the Stockholm Convention. It was one of the chemicals found ubiquitously in the tested population studied by the Centers for Disease Control and Prevention (CDC) and reported on in the *Fourth National Report on Human Exposure to Environmental Chemicals*. The mean urinary level of PFOS detected was 20.7 ug/L.[18] Exposure to PFOS is thought to occur mostly from indoor air (via inhalation of dust), with the primary source of PFOS being material (carpeting, upholstery, and clothing) in a home that had the PFOS-containing formula of Scotchguard applied. These materials tend to release PFOS (or PFBS, in the reformulated version), which is then carried by dust throughout the home. Exposing mice to PFOS resulted in a reduction of IFN-γ and IL-2 production, while IL-4 and IL-5 production was increased, tipping the immune system toward a Th2 dominance.[19] The effects of prenatal exposure to fluorocarbons on aspects of the immune system was investigated in toddlers. Prenatal exposure to PFOS and perfluorooctanoic acid (PFOA) was positively correlated with cord blood IgE levels; however, atopic dermatitis did not have a statistically significant association with PFOS.[20]

Plasticizers (Phthalates)

Phthalates are compounds added to plastics to make them more flexible. They are not strongly bound to the plastics and are therefore released (or leech) into the surrounding environment quite readily. Anything containing phthalates (shower curtains, raincoats, toys, polyvinyl chloride [PVC] flooring, furniture polishes, plastic food wrap, personal care products, fragrances, etc.) will release these chemicals into the environment, where they will be picked up by the dust and carried throughout the home.[21] Two different phthalates have been associated with higher rates of allergic and respiratory problems. Butyl benzyl phthalate (BBzP) has been associated with rhinitis and eczema, and diethylhexyl phthalate (DEHP) has been associated

with asthma.[22] DEHP is found in all PVC products and BBzP is found in PVC products, carpet tiles, and in some artificial leather products. Phthalates have been shown to induce Th2 cytokine production, shift the Th1/Th2 response in the direction of Th2 cells, and increase IgE and IgG antibodies.[23]

Triclosan

Triclosan is an antimicrobial agent that has been used since 1972 in soaps, deodorants, toothpastes, shaving creams, mouthwashes, and cleaning supplies, and is infused in an increasing number of consumer products, such as kitchen utensils, toys, bedding, socks, and trash bags. It is also one of the two main antimicrobial components in grapefruit seed extracts.[25,25] It has been reported to be present in over half of U.S. streams that were sampled for chemicals, another sign of its widespread use.[26] Triclosan is considered to be a mitochondrial toxin.[27] Urinary levels of triclosan in the National Health and Nutrition Examination Survey (NHANES) 2003-6 were positively associated with allergy and hay fever diagnoses. For those over 18 years of age, higher levels of triclosan were associated with greater odds of having been diagnosed with allergies or hay fever. While urinary triclosan was highest in persons over 20 years of age in the NHANES study, with a mean level of 13.4 ug/g creatinine, it was found in all percentiles (making it ubiquitous), with an overall mean value of 12.7 ug/g creatinine.[28] There is little research on the immune effects of triclosan, but it has been shown to suppress Th1 functioning *in vitro*,[29] as well as to reduce the lytic ability of natural killer cells.[30]

Solvents

Organic solvents are used in many industrial and commercial settings, including dry cleaning, paints and paint thinners, glues, inks, fuels, nail polishes and nail polish removers, furniture finishes, and various building and construction materials. They are commonly found in indoor air samples and in many outdoor air samples as well. When Wistar rats were given water containing small amounts of trichloroethylene (TCE), similar to what homeowners would get by drinking tap water, they produced increased levels of IL-4 (a cytokine contributing to Th2 dominance) and had a time-dependent increase in serum total IgE levels (indicative of development of type 1 hypersensitivity allergic reactivity).[31] Because TCE has contaminated so many ground water sites, the National Exposure Registry (NER) created a Trichloroethylene Subregistry, which is dedicated to the surveillance of general populations exposed long-term to low levels of TCE. Over four thousand individuals living in homes supplied with TCE-contaminated well water were included in this surveillance project, all being near Superfund sites (i.e., uncontrolled or abandoned places where hazardous waste is located, possibly affecting local ecosystems or people). As the cumulative exposure level to TCE increased, individuals exhibited significantly more problems with respiratory allergies, asthma, emphysema, stroke, and hearing impairment.[32]

Persons occupationally exposed to household cleaners had a risk that is 1.7 times higher for asthma compared to persons not regularly exposed to household cleaning compounds.[33] Persons who are not professional cleaners, but who use spray-cleaning compounds at least once weekly at home, are 49 percent more likely to have asthma and 39 percent more likely to experience wheezing. For people who used cleaning sprays four times a week, the risk jumped to a 2.11-fold increased likelihood of being diagnosed with asthma.[34] Xylene is a common ingredient in household cleaners: It has demonstrated a powerful ability to induce Th2 dominance in animals.[35]

Painters are exposed to solvent-based paints daily. When compared to carpenters, the associations between outdoor painters and respiratory disorders were as follows: asthma (OR = 4.7), rhinitis (OR = 2.4), asthma-like symptoms (OR = 2.7), and chronic bronchitis (OR = 2.9). In this study, outdoor painters had higher rates of these respiratory problems than indoor painters.[36] This finding could be due to water-based paints (i.e., non-solvent containing paints) being used more frequently indoors. It might also suggest that when working outdoors, people might not take the same precautions. In other words, they might think that respirators do not need to be used. One of the main solvents in paints is toluene, which has demonstrated the ability at low doses to enhance Th2 dominance and increase IgG production in an allergic mouse model.[37]

The Leipzig Allergy Risk Children Study (LARS) measured exposure to a variety of solvents in premature infants and infants with allergic risk factors during the first year of life. When these children were 3 years old, specific IgE antibodies to food and indoor and outdoor allergens were measured. In a subset of these children, cytokine secretion profiles of peripheral T cells were assessed. The children exposed to higher amounts of indoor solvents (from cleaning supplies, building materials, paints and environmental tobacco

smoke) had an enhanced Th2 immune response and were much more likely to have become reactive to milk and egg whites. The solvents leading to this pro-allergic state included toluene, o-xylene, meta- and paraxylene (xylenes are found in cleaning compounds), ethyl toluene, ethyl benzene and chlorobenzene. Benzene, ethylbenzene and chlorobenzene led to the highest levels of IL-4 production and lowest IFN-γ levels.[38] It should be noted that benzene and ethylbenzene are common chemical compounds in emissions from gas-powered engines, and might account for some of the increased risk for allergic reactivity previously mentioned that has been observed in persons living in high-traffic urban environments.

Heavy Metals

Several studies have reported associations between the heavy metals lead (Pb) and mercury (Hg) and risk for type 1 hypersensitivity. Children from Springfield-Green County in Missouri had blood Pb levels ranging from 1-45 mcg/dl, which were positively associated with their serum IgE levels.[39] A study conducted thirteen years later of 318 children from the same area confirmed the findings, and reported that the children with the clearest increases in IL-4 and IgE were those with Pb toxicity and exposure to cigarette smoke. In this study, the higher the Pb levels in the blood, the higher the serum IgE.[40] Mice exposed to Pb exhibit a clear Th2 response, with a reduction of IFN-γ and increases in the levels of IgE and IgG.[41] This Th2 response of the murine immune system to Pb was far stronger than that for Hg in the same study. Mercuric chloride (HgCl2) has demonstrated an ability to induce higher IgE production, increase levels of IL-4, and promote a shift to Th2 dominance from human basophils.[42] A study in Brazil confirmed that methylmercury (MeHg) exposure caused an increased production of IL-6 and IL-4, resulting in Th2 dominance.[43] However, a study of 656 Faroese children revealed only a slight tendency towards increased IgE production for prenatal exposure to MeHg, with postnatal exposure showing no association at all.[44]

Herbicides and Pesticides

Herbicides and pesticides have strong associations with asthma and allergies. Mice exposed to low levels of malathion, an organophosphate (OP) pesticide, showed significantly higher levels of degranulated mast cells than mice without exposure to this pesticide. This response indicates increased type 1 allergic reactivity.[45] Children raised in agricultural areas would potentially be exposed to higher levels of OP pesticides. Evidence suggests that children from these areas are prone to Th2 dominance and higher rates of asthma and wheezing.[46] *In vitro* assays of eight children exposed to four carbamate- and four organophosphate pesticides showed that all eight had inhibited IL-2 production, leading to diminished cell-mediated immune response and enhanced Th2 activity.[47] A study of over 4,000 Southern Californian children showed that exposure to herbicides during the first year of life increased risk for asthma 4.5-fold. This association between herbicide exposure and asthma was far higher than the association found between either indoor smoke exposure or cockroaches and asthma. The second-highest risk factor for developing asthma was home pesticide use (OR = 2.39).[48] Twelve persons with chlorpyrifos (an OP pesticide) exposure were checked for immune function from 1-4.5 years after pesticide application. Seven of them were exposed from home application by licensed pesticide applicators. The majority of these individuals had a history of atopy prior to exposure, but five developed reactivity after exposure, with one developing multiple allergies and the other four developing antibiotic sensitivity.[49]

In a study that looked at the cord blood of 2,050 babies, the level of organochlorine (OC) compounds, including OC pesticides, was associated with allergy. Levels of OC compounds in cord blood were also significantly higher in the infants born in regions with chemical industry present. Those children also had significantly higher levels of IgE and exhibited a higher incidence of eczema.[50] In children, serum levels of the OC insecticide, dichlorodiphenyldichlorethylene (DDE), and the fungicide, hexachlorobenzene (HCB), were positively associated with higher IgE levels and asthma incidence.[51]

Veterans, exposed to the broad-leaf herbicide/pesticide combination, 2,4-Dichlorophenoxyacetic acid (2,4-D), and the herbicide, 2,4,5-Trichlorophenoxyacetic acid (2,4,5-T), better known as Agent Orange, were studied to detect whether exposure to these compounds had an effect on immune response. Exposure to these chlorophenoxy acid herbicides resulted in Th2 dominance, with increased IL-4 and IgE, and reduced IFN-γ.[52] The herbicide, atrazine, has also demonstrated the ability to dramatically reduce NK cell activity, reflecting a reduction of Th1 action.[53]

The Connection Between Outdoor Air Pollutants and Type 1 Hypersensitivity

On days with higher ambient air pollution, emergency rooms see more cases of asthma in the pediatric and elderly populations.[54] Studies from around the globe have repeatedly shown that persons living in areas of higher traffic are far more likely to visit the emergency department to receive treatment for their asthma than those living in areas with less traffic.[55-61] In these studies, it is typically noted that high truck traffic and diesel "soot" lead to greater rates of emergency department visits. The main pollutant associated with these acute respiratory exacerbations is particulate matter (PM) that is less than 2.5 microns in diameter ($PM_{2.5}$), although nitrogen dioxide (NO_2)[62] and ozone[63] have also been associated.

Diesel Exhaust Particles

Diesel vehicles comprised 70 percent of all new vehicle sales in France, and 50 percent in the rest of Europe, in 2010.[64] In the United States, the sale of diesel vehicles increased by almost 40 percent in 2010. While diesel engines used to be mainly found in large trucks, earth-moving equipment, ships, buses, locomotives, and power generators, they are now commonly found in passenger vehicles on every roadway in the world. The increased use of diesel engines, along with the existing experimental evidence, suggests the possibility that diesel exhaust could be a significant contributor to the worldwide increase in asthma and other type 1 hypersensitivity disorders.

Animal evidence indicates that diesel exhaust particle (DEP) exposure leads to increased rates of allergic reactivity and asthma, along with elevated production of antigen-specific IgE and histamine. When mice were exposed to egg albumin *after* DEP exposure, they produced more IgE to ovalbumin than mice who were not exposed to DEP.[65]

In humans exposed to DEP, the levels of mRNA for cytokine production (IL-4, IL-5, IL-6, IL-10, and IL-13) were increased after DEP exposure. Elevated levels of IL-4 were also detected in the nasal lavage fluid after DEP exposure.[66] In this study, the overall changes in the mucosal immune response were suggestive of an elevated Th2 response. In another group of human volunteers, exposure to DEP caused a reduction in IFN-γ production after exposure.[67] Other studies have confirmed the increase in Th2 cytokine production after DEP exposure, and have reported that this exposure leads to increased reactivity to ragweed,[68] cedar,[69] birch pollen,[70] and egg protein.[71,72]

Evidence also indicates that simultaneous exposure to DEP and a food- or airborne allergen will lead to more rapid development of allergic reactivity to the allergen than would be seen from allergen exposure, alone, without DEP.[73] An *in vitro* study found that DEP produced suppression of IFN-γ, while not affecting IL-4 and IL-5, suggesting a reduction in Th1 function. DEP exposure also reduced Th1 function by inhibiting IFN-γ mRNA expression and protein production more potently than dexamethasone or cyclosporine A.[74] This reduction of Th1 function and cell-mediated immunity has been proposed as the likely mechanism for DEP exposure being associated with respiratory infections.[75-78]

Glutathione Connections to the Th1/Th2 Model and to Type 1 Hypersensitivity Disorders

Glutathione is a tripeptide made up of glycine, cysteine, and glutamate, and contains a sulfhydryl group bonded to a carbon-containing group. It is the most abundant non-protein thiol (thiol groups being reducing agents) in mammalian cells. Glutathione exists in reduced (GSH) and oxidized (GSSG) states. GSH acts as a reducing agent within cells by maintaining a tight control of the reduction/oxidation (redox) status. GSH is also a powerful antioxidant with a special affinity for lipid peroxides, an action that is facilitated by the enzyme glutathione peroxidase (GPx). GSH is 85–90 percent freely distributed in the cytosol of the cell, but is also found in the mitochondria, the peroxisomes, the nuclear matrix, and the endoplasmic reticulum (ER).[79] In the mitochondria, it is found mostly in the inner mitochondrial membrane, where it protects the membrane against depolarization from xenobiotic toxicants.[80] GSH production is dependent upon adequate cysteine levels and the functioning of the enzymes glutamate-cysteine ligase (GCL) and glutathione synthase (GS).[81] GSH is involved in many distinct physiological reactions including cellular signaling, biotransformation of xenobiotics (through the activity of the glutathione-S-transferase [GST] enzyme family), and thiol disulfide exchange reactions. It is also an important reservoir of cysteine. GSH is necessary for the proper functioning of the immune system.

In vivo and *in vitro* testing have shown that the GSH content in antigen-producing cells determines whether the immune response will be primarily Th1 or Th2 dominant.[82] Low GSH levels lead to an increase in Th2 dominance. Several chemical

toxicants, including many linked to increased type 1 hypersensitivity activity – mercury,[42] lead,[83] PFOS,[84] phthalates,[85] toluene,[86] benzene,[86] endosulfan (a chlorinated pesticide),[87] chlorpyrifos,[87] and diesel exhaust[88] – have been shown to deplete GSH stores.

Supplementation with N-acetylcysteine (NAC) – a stabilized form of the amino acid L-cysteine with antioxidant properties – can increase levels of GSH in a variety of tissues including the blood, lungs and liver.[89,90] Administration of NAC has increased GSH in animals exposed to DEP.[87] The imbalances in Th1/Th2 response caused by exposure to DEP, specifically the DEP-induced reduction of IFN-γ, can be prevented by administration of NAC.[87] Prior to this experiment, NAC had been shown to help to prevent the allergic reactivity caused by DEP exposure, although the mechanism had not been identified.[91]

GSTs are considered to be phase II biotransformation enzymes. GSH can be bonded to a phase I xenobiotic metabolite through the action of one of the GST enzymes. The addition of a GSH molecule makes the xenobiotic more water-soluble (now in the form of a mercapturic acid) and hence ready for excretion from the body in the urine. The three most common GST enzymes are glutathione-S-transferase Mu 1, Pi 1 and Tau 1 (GSTM1, GSTP1, GSTT1, respectively).

GSTM1 is active in the conjugation of epoxides, such as benzo(a)pyrene, most other aromatic hydrocarbons formed during combustion, and aflatoxin B1. Epoxides are metabolites of phase I biotransformation by cytochrome P450, family 1, subfamily A, polypeptide 1 (CYP1A1). Biotransformation of epoxides by CYP1A1 results in the formation of a more toxic epoxide compound. An inability to further biotransform epoxide intermediates, because of a reduced functioning of GSTM1, would, in theory, increase the toxicity caused by exposure to epoxides. Expression of GSTM1 is influenced by genetics. Genetic polymorphisms of GSTM1 are found in up to 50 percent of populations who have been tested for it.[91] Individuals with the single-nucleotide polymorphism (SNP) resulting in the GSTM1 null genotypes (lack of GSTM1 function) are much more likely to develop airborne/environmental allergies after exposure to DEP.[92] Individuals with this SNP had greater IgE responses to ragweed than those without it (102.5 vs. 45 U/ml), and had higher histamine levels (14.0 vs. 7.4 nmol/L). Persons with the GSTP1 null genotype also had higher total IgE (120.3 vs. 27.7 U/ml) and histamine levels (13.8 vs. 5.2 nmol/L). Individuals with either a GSTM1- or GSTP1 null genotype also show an increased IgE production with exposure to cigarette smoke compared to persons with a functioning GSTM1 enzyme.[93]

While evidence is strongly suggestive of reduced functional activity of at least certain GST enzymes contributing to increased Th2 dominance and enhanced allergic reactivity after exposure to combustion byproducts (DEP and environmental tobacco smoke), enhancing GST function might reduce allergic tendency. Sulforaphanes, found in Brassica family vegetables (e.g. broccoli, Brussels sprouts, cauliflower), have demonstrated the ability to enhance the functioning of GST.[94] Even among individuals with a GSTM1 null genotype, consumption of Brassica family vegetables will increase serum GST level and activity.[95] Sulforaphanes have shown the ability to increase levels of GSTM1, GSTP1 and other phase II enzymes in the respiratory tract, providing better protection in those tissues.[96] Sulforaphanes have been shown to reduce the pro-allergic effects of DEP in B lymphocytes.[97] Pretreatment of human bronchial epithelial cells with sulforaphanes prior to DEP exposure was also effective at preventing the allergenicity of diesel exhaust.[98]

While more research is required, existing evidence indicates that strategies aimed at either increasing GSH levels, enhancing GST activity, or both, might help to reduce the tendency to type 1 hypersensitivity caused by exposure to certain compounds.

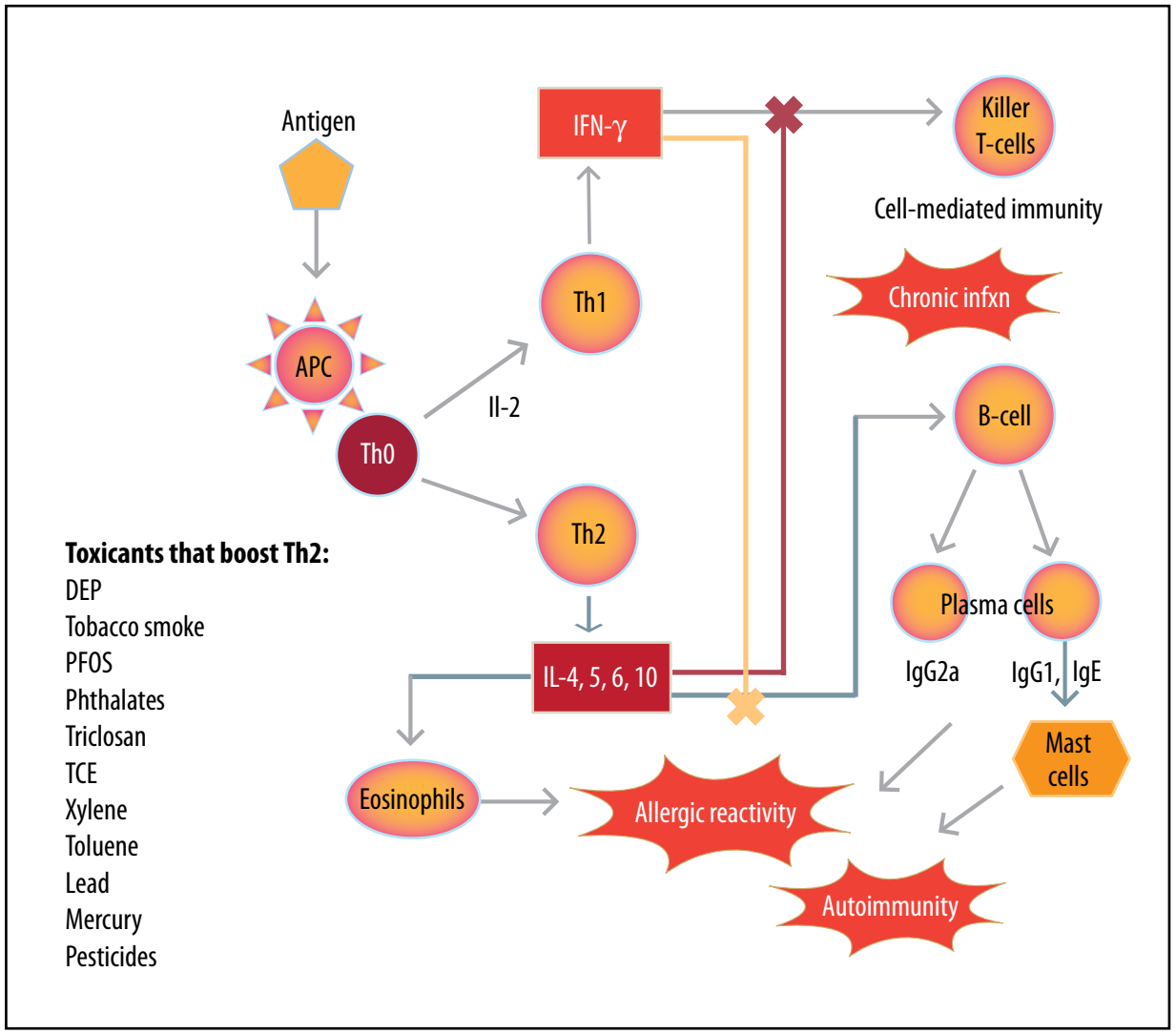
Conclusion

Multiple commonly encountered environmental toxicants have been associated with the worldwide increase of asthma and allergies. One underlying mechanism for this increased allergic tendency secondary to exposure appears to be an imbalance in T-helper function caused by exposure to the toxicant. Many of the studies mentioned in this review used very low levels of the compounds, consistent with what the average non-occupationally exposed person would encounter in daily life. Exposure to even these low levels can result in dramatic changes in cytokine production, activity of the immune system, overall Th1 and Th2 balance, and mediators of type 1 hypersensitivity mediators such as IgE. The environmental toxicants identified to date that are capable of producing these responses are ubiquitous, being found in food,

indoor air, and outdoor air. Persons living in an urban area, or close to roadways with high traffic and high diesel exhaust, would be expected to have the greatest exposure to at least some of the environmental compounds, with the strongest links to type 1 hypersensitivity disorders. This is consistent with epidemiological research that has consistently detected increased incidence of allergies and asthma in persons living in these conditions.

Figure 3 provides a list of some of the environmental exposures that might produce Th2 dominance and lead to type 1 hypersensitivity, and displays the mechanism by which they have been proposed to produce this shift in the immune response. Reducing exposure to the suspected environmental toxicants is an obvious and excellent means of prevention, as individuals with lower exposure levels have fewer problems, according to the existing literature. There are also supplemental and dietary actions that might significantly help to reduce the adverse effects of these toxicants on the immune system. Current evidence supports a dietary recommendation to consume, on a daily

Figure 3. Th2 dominance occurring because of environmental toxicant exposure



This figure (adapted from Inoue and Takano[99]) illustrates the effects that environmental toxicants have on the immune system Th1/Th2 balance, acting to reduce Th1 and enhance Th2, and producing an overall dominance of the Th2 response.

basis, vegetables from the sulforaphane-rich Brassica family (e.g., broccoli, cabbage, cauliflower, kale, Brussels sprouts). Based on the existing studies, which have reported that NAC administration helps counteract the immune imbalances caused by DEP, dietary supplementation with NAC might also be beneficial.

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