

COMMENTARY

Household chemicals, immune function, and allergy: A commentary

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Abstract

In recent decades, in the US and in Western and Northern Europe, there has been a significant increase in the prevalence of atopic allergic disease. Although that increase may now be slowing, or have already reached a plateau, there remains considerable interest in the factor or factors that may have caused this increased susceptibility to allergy and asthma. Certainly, the changes recorded have been too rapid to implicate a change in the gene pool, and for that reason attention has focused on the possible impact of environmental, dietary, and lifestyle factors. Although the hygiene hypothesis proposes that increased susceptibility to allergic sensitization is associated with changes in childhood exposure pathogenic microorganisms, other factors have been considered also. Among these is exposure to chemicals and atmospheric pollutants. There is some evidence that exposure to certain chemicals may elicit or exacerbate respiratory reactions in those who are already sensitized, or who already have existing airway disease. However, a recent article has proposed that exposure to specific household cleaning products may be one factor that is able to affect susceptibility to allergic sensitization. In the light of that article it is timely now to consider again the ability of chemical exposure to influence sensitization to common antigens.

Keywords: Immune function, allergic disease, household chemicals, volatile organic compounds, propylene glycol, glycol ethers

Introduction: The prevalence of allergy and atopy

Allergy describes the adverse health effects that may be provoked by the stimulation of a specific immune response. Both proteins and chemicals can induce allergic sensitization in susceptible subjects. When those sensitized individuals encounter the same inducing allergen on a second or subsequent occasion then a more accelerated and more aggressive immune response may be elicited resulting in inflammation that is described clinically as an allergic reaction. Allergic responses are different from autoimmune responses (immune reactions to self) or anti-infectious responses, but use similar cellular and molecular mechanisms.

Some forms of allergy, such as hay fever, most types of food allergy, and allergic asthma, are associated with immunoglobulin E (IgE) antibody responses. Here sensitization results from the elaboration of allergen-specific

IgE antibody responses. These antibodies bind, via plasma membrane receptors, to mast cells, and are cross-linked following subsequent exposure to the inducing allergen. This results in mast cell activation and degranulation and the release of both pre-formed and newly synthesized mediators that together elicit inflammation and the signs and symptoms of allergic disease.

Atopy describes a pre-disposition to mount IgE antibody responses, and is in large part heritable. However, it is clear that environmental factors and conditions also play important roles in influencing susceptibility to allergic disease, including IgE-mediated allergies. Perhaps the most vivid reflection of this is the fact that, in the US and Western and Northern Europe, there has been a substantial increase in the prevalence of atopic allergy and asthma since the end of the Second World War (Burney et al., 1990; Anderson et al., 2004; Latvala et al., 2005). These increases have clearly been too

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rapid to reflect a change in the gene pool and, although it may be that the upward trend in the prevalence of allergic disease is slowing or has plateaued (Patel et al., 2008), the nature of the environmental factors that have triggered the changes remain of considerable interest (Strachan, 1989, 1996; Ring, 1997; Kimber, 1998; Holgate, 1998; Peden, 2000; Yazdanbakhsh et al., 2002; Platts-Mills et al., 2005; von Mutius, 2007; Devereux, 2006; Pearce and Douwes, 2006).

There have been proposed a number of reasons why atopic allergy should have become more prevalent. Arguably the most interesting suggestion has become known as the hygiene hypothesis. This is predicated on the view that, in the absence of sufficient exposure to microbial antigens during infancy, the developing immune system fails to realign from a T-helper (T_H)2-type bias that apparently pertains at birth. The argument is that, with the increasingly sterile domestic environments in which children are raised, the immune system of infants maintains, or maintains for longer, a T_H 2 selectivity that pre-disposes to the development of IgE antibody responses and the acquisition of allergic sensitization. Although there is intriguing circumstantial evidence to support the hygiene hypothesis, it has not been formally proven, and there are reasons to suspect that it might not provide a complete explanation (Strachan, 1989, 1996; Ring, 1997; Howarth, 1998; Prescott et al., 1998; Erb, 1999; Folkerts et al., 2000; Peden, 2000; Yazdanbakhsh et al., 2002).

In addition to the hygiene hypothesis, a number of other potentially important factors have been proposed and these include changes in dietary habits, altered indoor air quality, and exposure to atmospheric pollution and diesel exhaust particles (Peterson and Saxon, 1996; Salvi et al., 1999; Lux et al., 2000; Peden, 2000; Chen et al., 2004; Devereux and Seaton, 2005; Devereux, 2006; Kim et al., 2007). The other candidate that has been suggested is chemical exposure, i.e., that exposure to specific chemicals or to chemicals in general is able to cause an increased susceptibility to allergic sensitization (Evans et al., 2008). It is that theme that will be explored in the following section.

Chemical exposure and a generalized increase in susceptibility to allergy

It is now well established that the acquisition of sensitization to a chemical or protein requires both recognition of the inducing allergen, and the availability locally of relevant pro-inflammatory signals. The latter are often described as 'danger signals' that are required to alert the adaptive immune system to the fact that antigen exposure is associated with cellular and tissue events that may indicate a threat (Matzinger, 1998). Such signals may be supplied as a result of cell damage or cell trauma resulting from incursion by antigen itself, or they may be supplied by other parallel events. One illustrative example is provided by skin sensitization that is

acquired following topical exposure to contact allergens such as 2,4-dinitrochlorobenzene (DNCB). This chemical could be considered to be a complete antigen since, at many concentrations, DNCB supplies not only the specific antigenic signal, but is also able to cause skin irritation and thereby supply the local danger signals required for effective immune activation. In this case, it has been shown that when lower concentrations of DNCB are used for sensitization in mice, i.e., concentrations that are non-irritating or only poorly irritating, then sensitization can be enhanced by co-administration of a skin irritant that provides an independent source of danger signals (Cumberbatch et al., 1993). Another possible example is provided by the observation that air pollutants and nanoparticles are able to enhance in mice immune responses to inhaled ovalbumin (de Haar et al., 2005); the available data suggest that this augmentation of responses is similarly a reflection of the provision of appropriate danger and co-stimulatory signals.

The point is that the necessary co-stimulatory danger signals need not be supplied directly by the inducing antigen or allergen itself. Within temporal and spatial constraints it is possible, therefore, that adaptive immune responses can be supported and enhanced by provision of independently derived 'danger signals.' The implication in the context of this commentary is that exposure via an appropriate route to chemicals that are not themselves antigenic or allergenic could, in theory, impact on adaptive immune and allergic responses to third party antigens. If the argument is that exposure to chemicals is able to encourage the development of allergic sensitization secondary to promotion of IgE antibody production, then the implication is that certain chemicals are able not only to enhance the vigor of immune responses, but also to impact on the quality of responses such as to encourage selective T_H 2 cell development. Considering chemicals as being able to cause danger and increase co-stimulatory help in an antigen non-specific fashion implies that they act as adjuvants; that is, substances that increase and/or alter the immunogenicity of unrelated antigens. Precedents exist insofar as certain adjuvants, such as alum (aluminium salts) for instance, are considered to favor T_H 2-type immune responses and IgE antibody production (De Gregorio et al., 2008).

In a recent review, it was concluded that at that time (Evans et al., 2008) there was little reason to suppose that exposure to chemicals *per se* had caused an increased susceptibility to allergic sensitization. Nevertheless, we have been prompted here to reconsider this conclusion in the light of a recent article published by Choi et al. (2010b).

A case in point: Propylene glycol and the glycol ethers

The investigations reported by Choi et al. (2010b) formed part of a larger study, the Dampness in Buildings and Health (DBH) study that was initiated in 2000. Choi et al.

(2010b) sought to examine whether exposure to volatile organic compounds (VOC) influences allergic airway disease in children. In a case-control study of 400 young Swedish children the authors considered the potential impact on allergic disease of exposure in bedroom air to a number of classes of compounds. These included alkanes, aldehydes, aromatic hydrocarbons, methylalkanes, dimethylalkanes, texanols, organic acids, and a mixture of propylene glycol and glycol ethers (PGEs). Only PGEs were reported to show a significant association with the allergic phenotype. Among cases then there was an association also of PGEs with IgE sensitization. It is relevant to explore this reported relationship, notwithstanding considerations of study design, and the legitimacy for instance of examining associations with a variety of chemical species (PGEs) rather than with single chemicals.

The conclusion drawn by Choi et al. (2010b) was that exposure of pre-school children (aged 1–5 years) to low levels of PGEs (median exposure levels of $<10 \mu\text{g}/\text{m}^3$) in the bedroom air environment is associated with an increased risk of allergic symptoms and IgE sensitization. Although there is no suggestion that PGEs are themselves allergenic, the implications are that exposure of young children in an appropriate environment to PGEs, resulting from the use of household cleaning materials (Choi et al., 2010a), can enhance susceptibility to the development of IgE-mediated allergic sensitization, and that such PGEs are possibly acting as adjuvants.

It has previously been reported by others that cleaning products used in household environments, including those with VOC, are associated with an increased risk of asthma (Zock et al., 2001; Karjalainen et al., 2002; Medina-Ramon et al., 2003; Rumchev et al., 2004). However, although these investigations appeared to reveal a clear correlation between household cleaning materials and clinical disease, it was argued that this was a reflection of the ability of such materials to elicit or exacerbate reactions in those with pre-existing airway disease (Evans et al., 2008). There was no reason, on the basis of those investigations, to implicate domestic cleaning materials as a cause of increased susceptibility to allergic sensitization. The conclusions drawn in the report by Choi et al. (2010b) provide for the first time therefore reason to consider whether in general household cleaning products containing chemicals, and in particular PGEs, are able to influence and augment the process of allergic sensitization.

As PGEs have no significant allergenic properties themselves, and are generally regarded as being unable to cause allergic sensitization (Basketter et al., 1998; Lessmann et al., 2005; Anzai et al., 2010), the implication is that in certain circumstances these materials are able to display adjuvant-like properties. One possibility suggested in the paper by Choi et al. (2010b) is that PGEs may act as endocrine disruptors, and in turn affect immune or allergic response through such a mechanism. However, currently there is little or no evidence available

to implicate PGEs as endocrine disruptors, and the link between endocrine disruption and immune perturbation remains speculative (Chalubinski and Kowalski, 2006).

Although the Choi et al. (2010b) study describes an interesting observation, there is a need for further investigations before exposure to PGEs can be implicated as an important risk factor for allergic sensitization. Most important of all is the need for experimental studies that would provide a plausible and persuasive mechanistic basis for the ability of PGEs, when experienced at very low levels of exposure, to interact with the immune system and to deliver adjuvant like signals that would augment IgE antibody responses. In advance of those supplementary investigations it is premature to conclude that exposure to PGEs encourages allergic sensitization, or has contributed to the increased prevalence of allergy and asthma.

Conclusions

The nature of environmental and lifestyle factors that influence the development of allergic sensitization, and that may have caused a recent increase in the prevalence of atopic allergic disease, remain unclear. Among the candidate factors that have attracted interest are chemicals that are encountered in the workplace or in domestic environments. There has been a recent observation that one such group of chemicals might be PGEs. The argument is that, although PGEs are themselves unable to cause sensitization, they can encourage the IgE antibody responses and the development of allergy.

Intriguing as this proposal is there is clearly a need for supplementary investigations to corroborate these observations, and to provide a mechanistic basis for the ability of PGEs to influence immune and allergic responses. In advance of that additional information it is premature to draw any conclusions.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

- Anderson, H. R., Ruggles, R., Strachan, D. P., Austin, B. R., Burr, M., Jeffs, D., Standring, P., Steriu, A., and Goulding, R. 2004. Trends in the prevalence of symptoms of asthma, hay fever and eczema in 12–14 year olds in the British Isles, 1995–2002: Questionnaire survey. *Br. Med. J.* 328:1052–1053.
- Anzai, T., Ullmann, L. G., Hayashi, D., Satoh, T., Kumazawa, T., and Sato, K. 2010. Effects of strain differences and vehicles on results of local lymph node assays. *Exp. Anim.* 59:245–249.
- Basketter, D. A., Gerberick, G. F., and Kimber, I. 1998. Strategies for identifying false positive responses in predictive skin sensitization tests. *Food Chem. Toxicol.* 36:327–333.
- Burney, P. G., Chinn, S., and Roma, R. J. 1990. Has the prevalence of asthma changed? Evidence from the national study of health and growth 1973–1986. *Br. Med. J.* 300:1306–1310.

- Chalubinski, M., and Kowalski, M. L. 2006. Endocrine disrupters - potential modulators of the immune system and allergic response. *Allergy* 61:1326-1335.
- Chen, R., Hu, Z., and Seaton, A. 2004. Eating more vegetables might explain reduced asthma symptoms. *Br. Med. J.* 328:1052-1053.
- Choi, H., Schmidbauer, N., Spengler, J., and Bornehag, C. G. 2010a. Sources of propylene glycol and glycol ethers in air at home. *Int. J. Environ. Res. Public Health* 7:4213-4237.
- Choi, H., Schmidbauer, N., Sundell, J., Hasselgren, M., Spengler, J., and Bornehag, C. G. 2010b. Common household chemicals and the allergy risks in pre-school age children. *PloS One* 5:e13423.
- Cumberbatch, M., Scott, R. C., Basketter, D. A., Scholes, E. W., Hilton, J., Dearman, R. J., and Kimber, I. 1993. Influence of sodium lauryl sulphate on 2,4-dinitrochlorobenzene-induced lymph node activation. *Toxicology* 77:181-191.
- de Gregorio, E., Tritto, E., and Rappuoli, R. 2008. Alum adjuvanticity: Unravelling a century old mystery. *Eur. J. Immunol.* 38:2068-2071.
- de Haar, C., Hassing, I., Bol, M., Bleumink, R., and Pieters, R. 2005. Ultrafine carbon black particles cause early airway inflammation and have adjuvant activity in a mouse allergic airway model. *Toxicol. Sci.* 87:409-418.
- Devereux, G. 2006. The increase in the prevalence of asthma and allergy: Food for thought. *Nat. Rev. Immunol.* 6:869-874.
- Devereaux, G., and Seaton, A. 2005. Diet as a risk factor for atopy and asthma. *J. Allergy Clin. Immunol.* 115:1109-1117.
- Erb, K. J. 1999. Atopic disorders: A default pathway in the absence of infection. *Immunol. Today* 20:317-322.
- Evans, G. S., Cadogan, D., Flueckiger, A., Hennes, C., and Kimber, I. 2008. Chemical pollution, respiratory allergy and asthma: A perspective. *J. Appl. Toxicol.* 28:1-5.
- Folkerts, G., Walzl, G., and Openshaw, P. J. 2000. Do common childhood infections 'teach' the immune system not to be allergic. *Immunol. Today* 21:118-122.
- Holgate, S. T. 1998. Asthma and allergy - disorders of civilization? *Quart. J. Med.* 91:171-184.
- Howarth, P. H. 1998. Is allergy increasing - early life influences. *Clin. Exp. Allergy* 28:2-7.
- Karjalainen, A., Martikainen, R., Karjalainen, J., Klaukka, T., and Kurppa, K. 2002. Excess incidence of asthma among Finnish cleaners employed in different industries. *Eur. Respir. J.* 19:90-95.
- Kim, J. L., Elfman, L., Mi, G., Wislander, G., Smedje, G., and Norback, D. 2007. Indoor molds, bacteria, microbial volatile organic compounds and plasticizers in schools - associations with asthma and respiratory symptoms in pupils. *Indoor Air* 17:153-163.
- Kimber, I. 1998. Allergy, asthma and the environment: An introduction. *Toxicol. Lett.* 102-103:301-306.
- Latvala, J., von Hertzen, L., Lindholm, H., and Haahtela, T. 2005. Trends in prevalence of asthma and allergy in Finnish young men: Nationwide survey, 1996-2003. *Br. Med. J.* 330:1186-1187.
- Lessmann, H., Schnuch, A., Geier, J., and Uter, W. 2005. Skin-sensitizing and irritant properties of propylene glycol. *Contact Dermatitis* 53:247-259.
- Lux, A. L., Henderson, A. J., and Pocock, S. J. 2000. Wheeze associated with prenatal tobacco smoke exposure: A prospective longitudinal study. ALSPAC Study Team. *Arch. Dis. Child.* 83:307-312.
- Matzinger, P. 1998. An innate sense of danger. *Semin. Immunol.* 10:399-415.
- Medina-Ramon, M., Zock, J. P., Kogevinas, M., Sunyer, J., and Anto, J. M. 2003. Asthma symptoms in women employed in domestic cleaning: A community based study. *Thorax* 58:950-954.
- Patel, S. P., Jarvelin, M. R., and Little, M. P. 2008. Systematic review of worldwide variations of the prevalence of wheezing symptoms in children. *Environ. Health* 7:57.
- Pearce, N., and Douwes, J. 2006. The global epidemiology of asthma in children. *Int. J. Tuberc. Lung Dis.* 10:125-132.
- Peden, D. B. 2000. Development of atopy and asthma: Candidate environmental influences and important periods of exposure. *Environ. Health Perspect.* 108:475-482.
- Peterson, B., and Saxon, A. 1996. Global increases in allergic respiratory disease: The possible role of diesel exhaust particles. *Ann. Allergy Asthma Immunol.* 77:263-270.
- Platts-Mills, T. A., Erwin, E., and Woodfolk, J. A. 2005. Is the hygiene hypothesis still a viable explanation for the increased prevalence of asthma? *Chem. Immunol. Allergy* 91: 3-15.
- Prescott, S. L., Macaubas, C., Holt, B. J., Smallacombe, T. B., Loh, R., Sly, P. D., and Holt, P. G. 1998. Transplacental priming of the human immune system to environmental allergens: Universal skewing of initial T-cell responses toward the T_H2 cytokine profile. *J. Immunol.* 160:4730-4737.
- Ring, J. 1997. Allergy and modern society: Does 'Western life style' promote the development of allergies? *Int. Arch. Allergy Immunol.* 113:7-10.
- Rumchev, K., Spickett, J., Bulsara, M., Phillips, M., and Stick, S. 2004. Association of domestic exposure to volatile organic compounds with asthma in young children. *Thorax* 59:746-751.
- Salvi, S. S., Frew, A., and Holgate, S. T. 1999. Is diesel exhaust a cause for increasing allergies? *Clin. Exp. Allergy* 29:4-8.
- Strachan, D. P. 1989. Hay fever, hygiene, and household size. *Br. Med. J.* 299:1259-1260.
- Strachan, D. P. 1996. Socioeconomic factors and the development of allergy. *Toxicol. Lett.* 86:199-203.
- von Mutius, E. 2007. Allergies, infections and the hygiene hypothesis - the epidemiological evidence. *Immunobiology* 212:433-439.
- Yazdanbakhsh, M., Kremsner, P. G., and van Ree, R. 2002. Allergy, parasites, and the hygiene hypothesis. *Science* 296:323-332.
- Zock, J. P., Kogevinas, M., Sunyer, J., Almar, E., Muniozgueren, N., Payo, E., Sanchez, J. L., and Anto, J. M. 2001. Asthma risk, cleaning activities and use of specific cleaning products among Spanish indoor cleaners. *Scand. J. Work Environ. Health* 27:76-81.

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