

Review

Chemical pollution, respiratory allergy and asthma: a perspective

Gareth S. Evans,¹ David Cadogan,² Andreas Flueckiger,³ Christa Hennes^{4,*} and Ian Kimber⁵

¹ Health and Safety Laboratory, Buxton, Derbyshire SH17 9JN, UK

² ECPI, Cefic B-1160 Brussels, Belgium

³ F. Hoffmann-La Roche Ltd, CH-4070 Basel, Switzerland

⁴ ECETOC, B-1160 Brussels, Belgium

⁵ Syngenta Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire SK10 4TJ, UK

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ABSTRACT: The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) convened a workshop in June 2005 to address the speculation that exposure to specific chemicals, and/or chemical pollutants in general, may play an important role in the increased prevalence of allergy and asthma in 'westernised' societies. This paper summarises one perspective arrived at during this workshop. It was acknowledged that certain chemicals and certain types of pollution might trigger or exacerbate asthmatic reactions in sensitised subjects. However, overall levels of pollution appear not to have had a major impact upon the prevalence of atopic allergy. Epidemiological studies suggest that pollution may in some circumstances protect from acquisition of sensitisation. Increasing exposure to household chemicals may enhance pre-existing allergies, but evidence for their causation of allergy is lacking. Other risk factors considered included societal dietary changes and exposure to endotoxins.

Future research needs were identified which included epidemiological studies employing exposure and biomonitoring data, studies on domestic exposure to chemicals and their association with the incidence of allergy and asthma, and prospective birth cohort studies employing well-defined aspects of lifestyle, diet, chemical and endotoxin exposure as factors that may drive susceptibility to allergy and asthma. Copyright © 2007 John Wiley & Sons, Ltd.

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Do Specific Chemicals and Chemical Pollutants in General Play an Important Role in The Development of Allergy and Asthma?

There continues to be significant interest in the observation that in more modernised societies there has been a substantial increase in the prevalence of atopic allergy and asthma during the past four decades (Anderson *et al.*, 2004; Burney *et al.*, 1990; Latvala *et al.*, 2005; von Mutius *et al.*, 1992). The observed changes have been too rapid to be accounted for by modifications to the gene pool and there is a general acknowledgement that alterations in lifestyle, alone or in concert with changing environmental factors, are likely to have driven the increases in prevalence (Strachan, 1996; Kimber, 1998; Ring, 1997).

There has been speculation that exposure to some specific chemicals in particular, and/or chemical pollution in general, may play important pathogenetic roles, and possible mechanisms through which this might occur have been proposed. However, there is in addition a variety of other factors that have also been implicated as important predisposing factors, including exposure to tobacco smoke during prenatal development (Lux *et al.*, 2000); diet (both quantity and quality) (Devereux and Seaton, 2005); reduced exposure neonatally and during infancy to infectious microorganisms; and alterations in indoor air quality. At the same time, the levels of 'classical' outdoor air pollutants (sulphur dioxide, nitrogen oxides, particulate matter like PM₁₀, i.e. of 10 µm or smaller diameter, volatile organic compounds) have decreased (Peterson and Saxon, 1996).

Against this background a Workshop was convened in 2005 to address specifically whether and to what extent chemicals have played a role in the increased burden of allergy and asthma in 'westernised' societies (ECETOC, 2005). The purpose of this short commentary is not to summarise, or to review, the presentations made, but rather to provide one perspective, based upon discussions

* Correspondence to: Christa Hennes, European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), 4, avenue E. Van Nieuwenhuysse, 1160 Brussels, Belgium.
E-mail: christa.hennes@ecetoc.org

provoked by the Workshop, on the impact of chemical exposure on the development of allergy and asthma.

The hygiene hypothesis is one that has sought to provide a more holistic explanation for the dramatic increases in the prevalence of atopic allergy and asthma first articulated in a coherent fashion by Strachan (1989). From a mechanistic/immunological perspective this hypothesis, and modified versions of it, suggests that in evolutionary terms exposure of the developing infant to microbial challenges has served to guide the maturing immune system to elaborate preferential type 1 responses, and to move away from a proallergic Th2 phenotype that may predominate earlier during development. The argument is that in the absence of such challenges, or with reduced microbial exposure, such realignment of the immune system fails to occur, or to occur sufficiently, such that it results in predisposition to allergy and asthma (Peden, 2000; Howarth, 1998; Prescott *et al.*, 1998; Erb, 1999; Folkerts *et al.*, 2000; Yazdanbakhsh *et al.*, 2002; Umetsu *et al.*, 2002). There are available intriguing circumstantial data that suggest increased protection from microbial challenge in early life predisposes to allergic sensitisation, and are therefore consistent with this hypothesis. Thus, for instance, there has been found a positive association of allergy with family affluence in Western societies, and a negative correlation with family size (Strachan, 1996). With regard to the latter, it has been reported that skin prick test reactivity to common allergens declines with increasing numbers of siblings, and that the number of older siblings appears to be more influential than the number of younger siblings (Strachan, 1989; von Mutius *et al.*, 1994; Strachan, 1995; Strachan *et al.*, 1994).

Given that a variety of environmental and domestic factors and lifestyle circumstances may impact on susceptibility to allergy and asthma, the question addressed here is to what extent specific chemicals, or general chemical pollution, may also contribute to this. Particular types of pollution may exacerbate asthmatic reactions in individuals that already have a hyperreactive bronchial system. Furthermore, there is good evidence that some chemicals may cause asthma amongst specific groups, for example amongst workers occupationally exposed to diisocyanates. However, the question here is whether (in general) exposure to chemicals and pollutants can explain the high numbers of newly induced cases of atopic allergy and allergic asthma that are being reported.

It is probably fair to say that overall levels of pollution appear not to have had a major impact upon the prevalence of atopic allergy, and in fact may even be protective with respect to the acquisition of sensitisation (von Mutius *et al.*, 1992; Wichmann and Heinrich, 1995; Braback *et al.*, 1994). Nevertheless, it is possible that certain specific forms of pollution may be relevant, and that which has attracted considerable attention is diesel exhaust.

Diesel Exhaust Particles (DEP)

Diesel exhaust is a major contributor to particulate matter pollution in urban areas and high-level exposure has been implicated as one stimulator of allergic sensitisation (Ishizaki *et al.*, 1987; Salvi *et al.*, 1999). There is substantial evidence from experimental systems that DEP can act as immunological adjuvants (serving to promote selectively type 2 immune responses), and enhance responses to inhaled allergens, possibly via generation of reactive oxygen species (Muranaka *et al.*, 1986; Diaz-Sanchez *et al.*, 1994; Terada *et al.*, 1997; Nel *et al.*, 1998; Diaz-Sanchez *et al.*, 2000; Gilliland *et al.*, 2004). Although a plausible case can be made it is difficult in practice to identify the extent to which diesel exhaust has impacted on the prevalence of allergic sensitisation.

Another area of growing interest is possible health consequences of the indoor air environment, of specific relevance to this article being household cleaning products.

Household Cleaning Products

Cleaning products used in the home (that may involve exposure to a variety of preservatives, disinfectants, perfumes, chlorine-releasing compounds and volatile organic chemicals) have been associated with asthma, the relative risk among professional cleaners being approximately 1.5 compared with relevant controls (Zock *et al.*, 2001; Karjalainen *et al.*, 2002; Medina-Ramon *et al.*, 2003; Medina-Ramon *et al.*, 2005; Rumchev *et al.*, 2004). However, collectively these investigations provide little or no indication that household cleaning is associated with a consistent increase in the incidence of allergic sensitisation. Although it would appear that some household agents might be able to elicit or exacerbate asthmatic reactions, it seems unlikely that the increased variety of cleaning materials available in the domestic setting, or the availability in recent years of aerosol delivery systems have had a significant impact on atopic allergy. A study (Sherriff *et al.*, 2005) has concluded that there may be a link between maternal exposure to cleaning products and persistent wheezing in infants. However, this should be interpreted with caution because it was not possible to determine with certainty whether the effect reported in this study was related to pre- or postnatal exposure.

The case for chemicals playing a role in enhanced susceptibility to asthma and atopic allergy must be viewed in the context of a variety of other factors for which evidence is growing of their causal role in the

increased prevalence of these conditions. Among these factors are the following.

Diet

There is no doubt that the period during which an increased prevalence of asthma has been observed in 'westernised' cultures has witnessed significant changes in diet, including a reduced intake of green vegetables and of certain antioxidants, vitamins and micronutrients. On this basis a case has been made that these changes may be causally linked, at least with respect to diet and asthma (Devereux and Seaton, 2005; Chen *et al.*, 2004; Martindale *et al.*, 2005).

Bacterial Endotoxin

There has in recent years been considerable interest in the mechanisms by which bacterial lipopolysaccharide (LPS) may impact on immune and inflammatory responses. This has been mirrored by investigations of occupational exposure, for example agriculture (Eduard *et al.*, 2004a; Portengen *et al.*, 2005; Eduard *et al.*, 2004b) and exposure in the domestic environment (Thorne *et al.*, 2005; Abraham *et al.*, 2005) regarding the possible influence of endotoxin exposure on susceptibility to allergy and asthma. The situation is, however, complicated insofar as the available evidence from these studies indicates that although endotoxin may protect against allergic disease including atopic asthma, the converse is true for airway hyper-responsiveness, lung function and non-atopic asthma (Eduard *et al.*, 2004a; Portengen *et al.*, 2005; Eduard *et al.*, 2004b; Thorne *et al.*, 2005; Abraham *et al.*, 2005). Such complexity may be attributable at least in part, to the fact that the impact of endotoxin on relative susceptibility to asthma and allergy may be dependent upon relevant gene–environment interactions. That is, the nature of resulting biological effects will be influenced by both the conditions, timing and extent of exposure to endotoxin, and by polymorphisms in genes encoding toll-like receptors (TLR) with which LPS interacts (William *et al.*, 2005; Marks, 2006). It is probably worth making the point here that polymorphisms of genes other than those coding for TLR may also be relevant to considerations of environmental impacts on allergy and asthma (Vercelli, 2004; Kleeberger and Peden, 2005; Ober and Thompson, 2005).

Drugs

Whilst certain drugs, e.g. beta-lactams, are known to induce allergies directly, and others are designed to suppress the symptoms of allergy, there is debate about the

capability of 'non-allergenic' and 'non-anti-allergenic' drugs to modulate the susceptibility of an individual to allergy. In this context perhaps the best example of a drug that has been found to be associated with an increased risk of asthma and allergy is paracetamol (acetaminophen). Although the underlying biological mechanisms are uncertain, the impact of paracetamol has been observed in a number of independent studies and appears not to be associated simply with aspirin avoidance (Shaheen *et al.*, 2000; Newson *et al.*, 2000; Davey *et al.*, 2005).

While there is little reason to suppose that exposure to chemicals *per se* has had an important influence on the increasing prevalence of asthma and allergy during the past four decades, the data available remain incomplete. A significant challenge for future epidemiological studies is to obtain relevant and accurate exposure data, either by environmental measurements or by suitable biomonitoring. Clinical-epidemiological studies, and experimental studies, also need accurate definitions of the asthma phenotype and in this context it needs to be recognised that a high proportion of asthma does not appear to be caused by allergy. A more searching evaluation of the extent to which chemical exposure is able to impact on susceptibility to atopic allergy and asthma is required, and we propose that this in turn will require investment in two main areas of research.

Exposure to Chemicals in the Home Environment

It would be of great value to have more detailed information on associations between increases in the incidence of allergy and asthma and altered patterns of exposure to chemicals in the domestic environment. Of relevance here are a number of parameters including the extent, duration, timing and route(s) of exposure, and these metrics will be influenced by the introduction of new products, product formulations and practices, changing ventilation patterns and the use of air conditioning, and the introduction of energy saving measures. Overlying these considerations is the fact that it may prove that exposure to mixtures of chemicals, rather than to individual compounds, is of greater relevance for assessment of health effects and this adds another level of complexity. Despite these difficulties such analyses are of importance if the relevance of indoor chemicals is to be elucidated adequately.

Prospective Studies

There is a need for well-designed prospective birth cohort studies (probably multicentre and/or multinational in nature) that could embrace effectively consideration of well-defined aspects of lifestyle and other factors in driving

susceptibility to allergy and asthma. This also is a major undertaking, but probably represents the most certain route to evaluating the relationships between lifestyle, environmental factors, chemical exposure and acquired susceptibility to allergy and asthma. Study populations of particular interest in this context are those currently with comparatively low incidence rates of asthma who are in the process of undergoing a rapid 'westernisation' of their lifestyle (such as, for example, populations in Eastern Europe and certain developing countries in Asia).

Conclusions

Despite a popular belief that the increased burden of allergic diseases (and in particular asthma) that has been observed in 'westernised' societies can be attributed (at least in part) to exposure to specific chemicals and/or pollution in general, the available evidence suggests that a more complex relationship exists in which environmental and lifestyle factors play important roles in this trend. There are good reasons to accept that exposure to specific chemicals and chemical pollutants may have the ability to enhance or exacerbate allergic reactions in those subjects already sensitised. However suggestions of a causative role for these agents in the development of allergy are at odds with evidence obtained in studies that have compared the prevalence of allergic disease and asthma in heavily polluted *versus* less polluted European countries. These studies having demonstrated a positive relationship between the prevalence of infectious and irritant airway diseases and the concentration of sulphur dioxide and total suspended particles, but no clear association between levels of these pollutants and the prevalence of asthma and allergies.

Attractive explanations for a unifying immunological mechanism behind this trend, for example the hygiene hypothesis, have failed to explain consistently the association between environmental factors and the risks of developing allergic disease. Indeed, data are emerging that some environmental and lifestyle factors may contribute to the increased burden, and may do so by influencing development of the respiratory tract and immune system *in utero*, or during infancy. In this context changing patterns of diet, urbanisation and the use of some pharmaceuticals require further consideration. Future research should be directed to epidemiological studies that are supported by relevant and accurate exposure and biomonitoring data. The possible associations between the incidence of allergy and asthma and patterns of exposure to chemicals in the domestic environment, as well as lifestyle and dietary factors, need to be investigated. Prospective birth cohort studies that include well-defined aspects of lifestyle and other environmental factors (e.g. diet, chemical and endotoxin exposure) should be considered.

References

- Abraham JH, Finn PW, Milton DK, Ryan LK, Perkins DL, Gold DR. 2005. Infant home endotoxin is associated with reduced allergen-stimulated lymphocyte proliferation and IL-13 production. *J. Allergy Clin. Immunol.* **116**: 431–437.
- Anderson HR, Ruggles R, Strachan DP, Austin BR, Burr M, Jeffs D, Standring P, Steriu A, 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.
- Braback L, Breborowicz A, Dreborg S, Knutsson A, Pieklik H, Björkstén B. 1994. Atopic sensitisation and respiratory symptoms among Polish and Swedish school children. *Clin. Exp. Allergy* **24**: 826–835.
- Burney PGJ, Chinn S, Roma RJ. 1990. Has the prevalence of asthma changed? Evidence from the national study of health and growth 1973–1986. *Br. Med. J.* **300**: 1306–1310.
- Chen R, Hu Z, Seaton A. 2004. Eating more vegetables might explain reduced asthma symptoms. *Br. Med. J.* **328**: 1052–1053.
- Davey G, Berhane Y, Duncan P, Aref-Adib G, Britton J, Venn A. 2005. Use of acetaminophen and the risk of self-reported allergic symptoms and skin sensitization in Butajira, Ethiopia. *J. Allergy Clin. Immunol.* **116**: 859–862.
- Devereux G, Seaton A. 2005. Diet as a risk factor for atopy and asthma. *J. Allergy Clin. Immunol.* **115**: 1109–1117.
- Diaz-Sanchez D, Dotson AR, Takenaka H, Saxon A. 1994. Diesel exhaust particle induce local IgE production *in vivo* and alter the pattern of IgE messenger RNA isoforms. *J. Clin. Invest.* **94**: 1417–1425.
- Diaz-Sanchez D, Penichet-Garcia M, Saxon A. 2000. Diesel exhaust particles directly induce activated mast cells to degranulate and increase histamine levels and symptom severity. *J. Allergy Clin. Immunol.* **106**: 1140–1146.
- Eduard W, Douwes J, Omenaas E, Heederik D. 2004a. Do farming exposures cause or prevent asthma? Results from a study of adult Norwegian farmers. *Thorax* **59**: 381–386.
- Eduard W, Omenaas E, Bakke PS, Douwes J, Heederik D. 2004b. Atopic and non-atopic asthma in a farming and a general population. *Am. J. Ind. Med.* **46**: 396–399.
- Erb KJ. 1999. Atopic disorders: a default pathway in the absence of infection? *Immunol. Today* **20**: 317–322.
- European Centre for Ecotoxicology and Toxicology of Chemicals. 2005. *Workshop on Chemical Pollution, Respiratory Allergy and Asthma. Workshop Report No. 6.* ECETOC: Brussels.
- Folkerts G, Walzl G, Openshaw PJM. 2000. Do common childhood infections 'teach' the immune system not to be allergic? *Immunol. Today* **21**: 118–122.
- Gilliland FD, Li YF, Saxon A, Diaz-Sanchez D. 2004. Effect of glutathione-S-transferase M1 and P1 genotypes on xenobiotic enhancement of allergic responses: randomised, placebo-controlled crossover study. *Lancet* **363**: 119–125.
- Howarth PH. 1998. Is allergy increasing? — early life influences. *Clin. Exp. Allergy* **28**(Suppl 6): 2–7.
- Ishizaki T, Koizumi K, Ikemori R, Ishiyama Y, Kushibiki E. 1987. Studies of prevalence of Japanese cedar pollinosis among residents in a densely cultivated area. *Ann. Allergy* **58**: 265–270.
- Karjalainen A, Martikainen R, Karjalainen J, Klaukka T, Kurppa K. 2002. Excess incidence of asthma among Finnish cleaners employed in different industries. *Eur. Respir. J.* **19**: 90–95.
- Kimber I. 1998. Allergy, asthma and the environment: an introduction. *Toxicol. Lett.* **102–103**: 301–306.
- Kleeberger SR, Peden D. 2005. Gene-environment interactions in asthma and other respiratory diseases. *Annu. Rev. Med.* **56**: 383–400.
- Latvala J, von Hertzen L, Lindholm H, Haahela T. 2005. Trends in prevalence of asthma and allergy in Finnish young men: nationwide study, 1996–2003. *Br. Med. J.* **330**: 1186–1187.
- Lux AL, Henderson AJ, Pocock SJ. 2000. Wheeze associated with prenatal tobacco smoke exposure: a prospective, longitudinal study. ALSPAC Study Team. *Arch. Dis. Child.* **83**: 307–312.
- Marks GB. 2006. Environmental factors and gene-environment interactions in the aetiology of asthma. *Clin. Exp. Pharmacol. Physiol.* **33**: 285–289.
- Martindale S, McNeill G, Devereux G, Campbell D, Russell G,

- Seaton A. 2005. Antioxidant intake in pregnancy in relation to wheeze and eczema in the first two years of life. *Am. J. Respir. Crit. Care Med.* **171**: 121–128.
- Medina-Ramon M, Zock JP, Kogevinas M, Sunyer J, Anto JM. 2003. Asthma symptoms in women employed in domestic cleaning: a community based study. *Thorax* **58**: 950–954.
- Medina-Ramon M, Zock JP, Kogevinas M, Sunyer J, Torralba Y, Borrell A, Burgos F, Anto JM. 2005. Asthma, chronic bronchitis, and exposure to irritant agents in occupational domestic cleaning: a nested case–control study. *Occup. Environ. Med.* **62**: 598–606.
- Muranaka M, Suzuki S, Koizumi K, Takafuji S, Miyamoto T, Ikemori R, Tokiwa H. 1986. Adjuvant activity of diesel-exhaust particulates for the production of IgE antibody in mice. *J. Allergy Clin. Immunol.* **77**: 616–623.
- Nel AE, Diaz-Sanchez D, Ng D, Hiura T, Saxon A. 1998. Enhancement of allergic inflammation by the interaction between diesel exhaust particles and the immune system. *J. Allergy Clin. Immunol.* **102**: 539–554.
- Newson RB, Shaheen SO, Chinn S, Burney PG. 2000. Paracetamol sales and atopic disease in children and adults: an ecological analysis. *Eur. Respir. J.* **16**: 817–823.
- Ober C, Thompson EE. 2005. Rethinking genetic models of asthma: the role of environmental modifiers. *Curr. Opin. Immunol.* **17**: 670–678.
- Peden DB. 2000. Development of atopy and asthma: candidate environmental influences and important periods of exposure. *Environ. Health Perspect.* **108**: 475–482.
- Peterson B, Saxon A. 1996. Global increases in allergic respiratory disease: the possible role of diesel exhaust particles. *Ann. Allergy Asthma Immunol.* **77**: 263–270.
- Portengen L, Preller L, Tielen M, Dockes G, Heederik D. 2005. Endotoxin exposure and atopic sensitization in adult pig farmers. *J. Allergy Clin. Immunol.* **115**: 797–802.
- Prescott SL, Macaubas C, Holt BJ, Smallacombe TB, Loh R, Sly PD, Holt PG. 1998. Transplacental priming of the human immune system to environmental allergens: universal skewing of initial T cell responses toward the Th2 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, Stick S. 2004. Association of domestic exposure to volatile organic compounds with asthma in young children. *Thorax* **59**: 746–751.
- Salvi SS, Frew A, Holgate S. 1999. Is diesel exhaust a cause for increasing allergies? *Clin. Exp. Allergy* **29**: 4–8.
- Shaheen SO, Sterne JA, Songhurst CE, Burney PG. 2000. Frequent paracetamol use and asthma in adults. *Thorax* **55**: 266–270.
- Sherriff A, Farrow A, Golding J, Henderson J. 2005. Frequent use of chemical household products is associated with persistent wheezing in pre-school age children. *Thorax* **60**: 45–49.
- Strachan DP. 1989. Hay fever, hygiene, and household size. *Br. Med. J.* **299**: 1259–1260.
- Strachan DP. 1995. Epidemiology of hay fever: towards a community diagnosis. *Clin. Exp. Allergy* **25**: 296–303.
- Strachan D. 1996. Socioeconomic factors and the development of allergy. *Toxicol. Lett.* **86**: 199–203.
- Strachan DP, Griffiths JM, Anderson HR, Johnston IDA. 1994. Allergic sensitisation and position in the sibship: a national study of young British adults. *Thorax* **49**: 1053P.
- Terada N, Maesako K-I, Hiruma K, Hamano N, Houki G, Konno A, Ikeda T, Sai M. 1997. Diesel exhaust particulates enhance eosinophil adhesion to nasal epithelial cells and cause degranulation. *Int. Arch. Allergy Immunol.* **114**: 167–174.
- Thorne P, Kulhankova K, Yin M, Cohn R, Arbes SJ Jr, Zeldin DC. 2005. Endotoxin exposure is a risk factor for asthma: the national survey of endotoxin in United States housing. *Am. J. Respir. Crit. Care Med.* **172**: 1371–1377.
- Umetsu DT, McIntire JJ, Okbari O, Macaubas C, DeKruyff RH. 2002. Asthma: an epidemic of dysregulated immunity. *Nature Immunol.* **3**: 715–720.
- Vercelli D. 2004. Genetics, epigenetics, and the environment: switching, buffering, releasing. *J. Allergy Clin. Immunol.* **113**: 381–386.
- von Mutius E, Fritzsche C, Weiland SK, Roll G, Magnussen H. 1992. Prevalence of asthma and allergic disorders among children in united Germany: a descriptive comparison. *Br. Med. J.* **305**: 1395–1399.
- von Mutius E, Martinez FD, Fritzsche C, Nicolai T, Reitmar P, Thiemann HH. 1994. Skin test reactivity and number of siblings. *Br. Med. J.* **308**: 692–695.
- Wichmann HE, Heinrich J. 1995. Health effects of high level exposure to traditional pollutants in East Germany: review and ongoing research. *Environ. Health Perspect.* **103**(Suppl 2): 29–35.
- William LK, Ownby DR, Maliarik MJ, Johnson CC. 2005. The role of endotoxin and its receptors in allergic disease. *Ann. Allergy Asthma Immunol.* **94**: 323–332.
- Yazdanbakhsh M, Kremsner PG, van Ree R. 2002. Allergy, parasites, and the hygiene hypothesis. *Science* **296**: 490–494.
- Zock JP, Kogevinas M, Sunyer J, Almar E, Muniozguren N, Payo F, Sanchez JL, Anto JM. 2001. Asthma risk, cleaning activities and use of specific cleaning products among Spanish indoor cleaners. *Scand. J. Work Environ. Health* **27**: 76–81.