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Pro/Con Debate: Is Occupational Asthma Induced by Isocyanates an IgE-Mediated Disease?

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Abstract

Isocyanates, low-molecular weight chemicals essential to polyurethane production, are one of the most common causes of occupational asthma, yet the mechanisms by which exposure leads to disease remain unclear. While isocyanate asthma closely mirrors other Type I Immune Hypersensitivity ("Allergic") disorders, one important characteristic of hypersensitivity ("allergen"-specific IgE) is reportedly absent in a large portion of affected individuals. This variation from common environmental asthma (which typically is induced by high molecular weight allergens) is important for two reasons. (1) Allergen-specific IgE is an important mediator of many of the symptoms of bronchial hyper-reactivity in "allergic asthma". Lack of allergen-specific IgE in isocyanate hypersensitive individuals suggests differences in pathogenic mechanisms, with potentially unique targets for prevention and therapy. (2) Allergen-specific IgE forms the basis of the most commonly used diagnostic tests for hypersensitivity (skin prick and RAST). Without allergen-specific IgE, isocyanates may go unrecognized as the cause of asthma. In hypersensitive individuals, chronic exposure can lead to bronchial hyperreactivity that persists years after exposure ceases. Thus, the question, of whether or not isocyanate asthma is an IgE mediated disease, has important implications for disease screening/surveillance, diagnosis, treatment and prevention. The present Pro/Con Debate, addresses contemporary, controversial issues regarding IgE in isocyanate asthma.

BACKGROUND

Isocyanate, Asthma, and IgE

Isocyanate-induced asthma is an occupational lung disease with striking similarities to "allergic" asthma, a condition that typifies Type I Immune Hypersensitivity, as defined by Gell and Coombs.[1] A cardinal feature of Type I Immune Hypersensitivity is the presence of allergen specific immunoglobulins that have undergone isotype class switching to the epsilon constant region (i.e. IgE.).[2] Allergen-induced cross-linking of IgE on the surface of mast cells is a "trigger" for asthma, via the release of histamine and other mediators that cause immediate reactions and incite a cascade of ongoing inflammation (including delayed-phase responses).[3–6] Production of IgE (isotype swithching) is largely dependent upon IL-4, a cytokine produced by subset of T cells (Th2-type), whose "helper" activity is critical in orchestrating the inflammatory responses of Type I Immune hypersensitivity.[7–10]

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Absence of Allergen-specific IgE in Isocyanate Asthma?

It has been reported that the majority of individuals with isocyanate-induced asthma do not have allergen-specific IgE (see Table 1)[11–24] findings challenging to reconcile with Gell and Coombs' classic definition of Type I immune hypersensitivity. Without allergen-specific IgE, what mechanisms account for the airway inflammation observed following isocyanate exposure, especially immediate responses? Furthermore, since as described above, isotype switching to IgE generally requires T cell derived IL-4, does the lack of IgE in isocyanate hypersensitive individuals imply fundamental differences in the underlying cellular response to isocyanate compared with common environmental allergens? These same questions extend to asthma caused by certain other low molecular weight compounds (e.g. plicatic acid, persulfates), and other types of idiopathic or "intrinsic" asthma, where "allergen-specific"-IgE is not detectable.

Diagnosis, Surveillance. and Screening

The absence of allergen (isocyanate)-specific IgE in isocyanate asthma creates substantial challenges when evaluating isocyanate-exposed individuals with asthma. Without allergen-specific IgE as a definitive diagnostic, isocyanates may be overlooked or mistakenly exonerated as the cause of disease, and exposure-induced bronchial hyper-reactivity may instead be attributed to other environmental triggers, especially delayed responses, which may occur after the worker leaves the job-site. The lack of allergen-specific IgE also limits pro-active disease screening/surveillance (e.g. routine blood testing/RAST), which might otherwise identify affected workers, including those early in the course of disease, where prompt removal from exposure provides the greatest protection against long-lasting (isocyanate-exposure induced) lung function decline. Thus, uncertainty over the presence and role of (allergen-specific) IgE in isocyanate asthma has a huge impact on efforts towards disease diagnosis, screening and surveillance.

PRO/CON DEBATE

Twelve topics, that support (1–6) or refute (7–12) the role of IgE in isocyanate asthma, were chosen for debate by the authors. The Pro viewpoint supports the hypothesis that isocyanate asthma is an IgE mediated disease, while the Con viewpoint supports the hypothesis that isocyanate asthma is not an IgE mediated disease.

1. Clinical presentation of isocyanate asthma is typical of an allergic process.

   Pro: Isocyanate asthmatics generally do not experience asthma symptoms the first time they are exposed to isocyanates, the disease typically takes months to years to develop, and becomes more severe with repeated exposure.[25] A "latent phase" between exposure and the development of asthma is well-described for common environmental asthma and known to reflect the time period during which systemic immune sensitization occurs.[26] The reported immediate and dual phase reactions to isocyanate exposure are typical of "allergic" responses.[27]

   Con: The spectrum of isocyanate asthma is diverse. While some subjects develop clear-cut immediate responses, delayed responses to isocyanate occur more frequently than with high molecular weight allergens.[28] The "latent" phase of isocyanate asthma remains poorly understood and may represent the time necessary for non-immunologic processes, such as repetitive injury-repair cycles or permanent structural changes.[29]

2. Isocyanate-specific IgE may not be detected if the wrong form of "isocyanate antigen" is used in the immunoassay (false negative test).

Pro: The structural form of isocyanates recognized by the human immune system (as an allergen) remains unclear, as isocyanates react rapidly with proteins and water.[30, 31] Different oligomeric formulations, isomers, and phases (vapor/liquid), further impact antigencicity.[17, 22, 23] Most studies of isocyanate-specific IgE to date, have used isocyanate-albumin conjugates, however, such conjugates can differ substantially depending upon the methods used for their production.[22, 23, 30, 32, 33]

Con: Over the last 40 years, a wide-range of experimental methods have been employed to generate and characterize "isocyanate antigens".[17, 22, 23, 32–35] The major carrier protein for isocyanate in vivo has been identified as albumin, and specific sites of conjugation have been identified by mass spectrometry.[23, 36] Despite progress in understanding the antigenicity of isocyanate-albumin conjugates, the most advanced studies to date fall short of accounting for the substantial proportion of isocyanate asthmatics without detectable chemical-specific IgE.[17, 22]

3. Isocyanate specific IgE may be "missed" due to assay detection limits.

Pro: IgE is present at very low concentrations in serum and thus requires highly sensitive reagents for detection, such as radioisotopically labeled anti-human IgE.[37] Many serology studies of isocyanate-specific IgE to date have relied upon enzyme-linked immunosorbant assays (ELISA), often without definition of detection limits.[16, 18, 19, 38]

Con: While the detection limits of most IgE serology tests reported to date, remain unclear, many studies have made use of the same sensitive methods proven reliable for measuring other allergen-specific IgE, including radioisotope and/or fluorescent labels along with high (allergen) density solid phase platforms.[15, 20, 39]

4. Isocyanate specific IgE serum levels may decrease (below detection limits) away from exposure.

Pro: Experimental evidence has shown that isocyanate-specific serum IgE decreases away from exposure, and can become undetectable (by traditional RAST) as quickly as 30 days away exposure.[20] Variable and sometimes long time intervals between an individuals' last exposure and serology testing thus, may contribute to the apparent absence of specific-IgE is patients with the disease (see more below).

Con: Studies that have longitudinally followed serum levels of isocyanate-specific IgE, suggest their 1/2 life is similar to that of IgE specific for common environmental allergens.[20] Antigenic forms of isocyanate (albumin-conjugates) may persist for weeks in the blood stream of exposed individuals.[40, 41]

5. The socio-economics of isocyanate asthma affects the detection of serum specific IgE.

Pro: The socio-economics of isocyanate asthma (and other occupational diseases) may cause workers to postpone medical attention until their condition becomes severe enough to prevent them from working. In the case of isocyanate asthma, this delay could be sufficient time for specific-IgE levels to fall below detection limits, especially if the patient must travel to specialized testing centers for disease diagnosis.

Con: Many occupations that use isocyanates are life-long careers for which workers have invested substantial time and money. Thus, there is self-incentive for workers to remain vigilant about the possibility of hypersensitivity to chemicals in their

workplace, especially isocyanates, which are well-recognized as a cause of occupational asthma.

6. HLA-linkage of isocyanate asthma supports a role for IgE.

Pro: Genetic differences in human leukocyte antigen (HLA) class II alleles have been associated with isocyanate asthma in several different populations. Similar findings have been reported in common environmental asthma, and together with the known role of HLA-class II in antigen presentation to CD4 T-cells, support a role for prototypical TH2-driven/IgE responses.[42–46]

Con: The association between HLA class II and isocyanate asthma has been variable in different studies.[47, 48] Furthermore, the link between HLA class II expression and IgE is indirect via Th2 cells. HLA class II genes are located in region of the genome (Chr 6) that likely contains numerous genes involved in allergic responses.

7. Lack of IL-4 mRNA (a critical factor for epsilon class switching), in situ in the human airway argues against a role for IL-4 in isocyanate asthma.

Pro: While recent studies have highlighted the conspicuous absence of IL-4 in human airway biopsies from isocyanate asthma patients, older studies reported the presence of florid Th2-type airway inflammation using immunohistochemical approaches.[49, 50] The kinetics of IL-4 expression, in relationship to exposure may have contributed to conflicting results, as levels may diminish with increasing time intervals between disease diagnosis and biopsy.

Con: A striking absence of epsilon constant region (Cε) and IL-4 mRNA has been observed locally within bronchial mucosa, in patients undergoing inhalation challenge with isocyanate, at a dose sufficient to provoke an asthmatic reaction.[49] The lack of detectable IgE and IL-4 mRNA in patients with isocyanate–induced asthma, represents strong evidence that IgE is not produced in the bronchial mucosa level, following an active challenge with isocyanates. IL-4 is required for B cell switching in favor of IgE and is sufficient to initiate transcription through the heavy chain Cε locus.[51] Thus the lack of both IL-4 and IgE transcripts in the bronchial mucosa, following an isocyanate challenge, suggest that IgE is not crucial to the induction of occupational asthma to isocyanates. Thus, it is likely that non-IgE mediated mechanisms are important, at least in a proportion of patients with isocyanate-induced asthma.

8. Isocyanates do not stimulate vigorous *in vitro* T-cell responses (Th2), which are associated common environmental asthma

Pro: In vitro cellular responses are dependent upon the “antigen”, which as described above, remains unclear for isocyanate chemicals. The antigen presenting cells for isocyanates also remain unclear and may be absent from the in vitro assays reported to date, which commonly utilize peripheral blood mononuclear cells.

Con: The prototypical Th2 responses stimulated by common environmental allergens, and known to induce asthma and IgE in vivo, are not observed when human T-cells from isocyanate asthmatics are cultured with isocyanate (albumin conjugates) in vitro.[52] In contrast, isocyanates stimulate limited proliferation of γδ and CD8 T cells along with production of mainly monocytic cytokines/chemokines (see more below).[53–55] More recently, murine studies suggest that TH-17 cells may be a crucial effector population for isocyanate responsivness.[56]

9. Isocyanate-albumin antigens stimulate predominately the monocytic population of human blood cells, rather than (TH2) cell types known to promote IgE production.

Pro: Any cell-based immunoassay for isocyanates encounters issues with the chemicals cytotoxicity, in addition to uncertainty regarding the “antigenic” form (discussed above). Furthermore, it remains unclear if all of the cells necessary to respond to isocyanate are present in the peripheral blood. Notably limiting in the blood are dendritic cells, γδ T cells, and airway epithelial cell types, which have been shown to respond to isocyanate.[57–59]

Con: Increasing evidence points to an important role for monocytes, and possibly other innate immune cells in the development of isocyanate asthma.[16, 54, 60, 61] In vitro studies from several independent laboratories describe the stimulation of human monocytes and monocyte-like human cell lines, by isocyanate-albumin conjugates, including the production of chemokines associated with asthma, such as MCP-1 and MIF. [16, 54, 60, 62]

10. Histamine releasing factors, such as MCP-1, substitute for IgE, in the asthmatic response triggered by isocyanates.

Pro: While MCP-1 production in vitro (in response to isocyanate albumin antigen) has been shown to be greater by PBMCs from isocyanate asthmatics, vs. exposed controls, mechanisms by which MCP-1 and TH2-like inflammation is selectively induced, without IgE production remain unclear.[16]

Con: Experimental evidence demonstrates high levels of isocyanate-antigen driven MCP-1 production by PBMCs from isocyanate asthmatics (but not controls).[16, 54, 62] MCP-1 is a chemokine with potent histamine releasing activity, equal to or greater than that triggered by IgE receptor cross-linking.[63] A major PBMC cell type that produces MCP-1 is the monocyte, which is innately activated by isocyanate-albumin conjugates.[60, 64, 65] Thus, direct activation of innate immune cells may be a crucial underlying pathological response to isocyanate exposure.[60, 66]

11. Oxidative stress, rather than antigen-driven (e.g. IgE) responses is the pathological mechanism that leads to isocyanate asthma.

Pro: While isocyanates have been shown to induce oxidative stress, evidence that this process participates directly in isocyanate asthma pathogenesis is lacking.[58, 59, 66] Oxidative stress occurs in response to numerous exposures, including many that do not cause asthma.[67, 68]

Con: Isocyanates have been shown to disrupt oxidant homeostasis through several distinct analytic methodologies.[58, 59, 61, 69–72] Evidence linking oxidant stress and allergic responses highlight non-immunologic mechanisms that may modulate isocyanate responsiveness, including the development of asthma.[73–75]

12. Chemical-induced toxicity, rather than antigen-driven (e.g. IgE) responses is the pathological mechanism that leads to isocyanate asthma.

Pro: While isocyanates are highly toxic, occupational exposure limits are set several orders of magnitude below the lowest observable effects dose measured in animal studies.[76, 77]

Con: Repetitive cycles of injury and repair may represent the essential process underlying isocyanate asthma pathogenesis, with immune sensitization and the development of specific IgE as a common secondary phenomenon.[29, 78] With the aid of contemporary molecular techniques, it has been shown that subcytotoxic (occupational) concentrations of isocyanate do have specific effects on airway cells, including oxidative stress as mentioned above.[58, 71] Furthermore genetic studies have shown associations of isocyanate asthma with polymorphisms in

specific enzymes thought to participate is isocyanate metabolism (N-acetyl, and Glutathione-S-Transferases).[79–82]

SUMMARY

Controversy continues to exist over the role of IgE in isocyanate asthma, which has important implications for understanding disease pathogenesis as well as prevention and diagnosis. IgE that specifically binds isocyanate is challenging to define due to isocyanates reactivity with (self) proteins. A better understanding of isocyanates reactivity with self-molecules is essential to understanding their allergenicity, and answering the question, is isocyanate asthma an IgE mediated disease?

References

1. Gell, P.; Coombs, R. Clinical Aspects of Immunology. 1. Blackwell; 1963.
2. Ishizaka K, Ishizaka T, Hornbrook MM. Physicochemical properties of reaginic antibody. V. Correlation of reaginic activity wth gamma-E-globulin antibody. J Immunol. 1966; 97:840–53. [PubMed: 4163008]
3. Parish WE. Release of histamine and slow reacting substance with mast cell changes after challenge of human lung sensitized passively with reagin in vitro. Nature. 1967; 215:738–9. [PubMed: 4168447]
4. Ishizaka K, Ishizaka T, Hornbrook MM. Physico-chemical properties of human reaginic antibody. IV. Presence of a unique immunoglobulin as a carrier of reaginic activity. J Immunol. 1966; 97:75–85. [PubMed: 4162440]
5. Johansson SG, Bennich H. Serum immunoglobulin (IgE) levels in asthma. Thorax. 1969; 24:510. [PubMed: 4183632]
6. Johansson SG. IgE in allergic diseases. Proc R Soc Med. 1969; 62:975–6. [PubMed: 4186871]
7. Ueda A, Chandswang N, Ovary Z. The action of interleukin-4 on antigen-specific IgG1 and IgE production by interaction of in vivo primed B cells and carrier-specific cloned Th2 cells. Cell Immunol. 1990; 128:31–40. [PubMed: 2140534]
8. Steinke JW, Borish L. Th2 cytokines and asthma. Interleukin-4: its role in the pathogenesis of asthma, and targeting it for asthma treatment with interleukin-4 receptor antagonists. Respir Res. 2001; 2:66–70. [PubMed: 11686867]
9. Ansel KM, Djuretic I, Tanasa B, Rao A. Regulation of Th2 differentiation and Il4 locus accessibility. Annu Rev Immunol. 2006; 24:607–56. [PubMed: 16551261]
10. Oettgen HC. Regulation of the IgE isotype switch: new insights on cytokine signals and the functions of epsilon germline transcripts. Curr Opin Immunol. 2000; 12:618–23. [PubMed: 11102763]
11. Gallagher JS, Tse CS, Brooks SM, Bernstein IL. Diverse profiles of immunoreactivity in toluene diisocyanate (TDI) asthma. J Occup Med. 1981; 23:610–6. [PubMed: 6268767]
12. Karol MH, Tollerud DJ, Campbell TP, Fabbri L, Maestrelli P, Saetta M, Mapp CE. Predictive value of airways hyperresponsiveness and circulating IgE for identifying types of responses to toluene diisocyanate inhalation challenge. Am J Respir Crit Care Med. 1994; 149:611–5. [PubMed: 8118626]
13. Baur X, Dewair M, Fruhmann G. Detection of immunologically sensitized isocyanate workers by RAST and intracutaneous skin tests. J Allergy Clin Immunol. 1984; 73:610–8. [PubMed: 6609183]
14. Butcher BT, O'Neil CE, Reed MA, Salvaggio JE. Radioallergosorbent testing of toluene diisocyanate-reactive individuals using p-tolyl isocyanate antigen. Journal of Allergy & Clinical Immunology. 1980; 66:213–6. [PubMed: 6251126]
15. Keskinen H, Tupasela O, Tiikkainen U, Nordman H. Experiences of specific IgE in asthma due to diisocyanates. Clin Allergy. 1988; 18:597–604. [PubMed: 2854010]
16. Bernstein DI, Cartier A, Côté J, Malo JL, Boulet LP, Wanner M, Milot J, L'Archevéque J, Trudeau C, Lummus Z. Diisocyanate antigen-stimulated monocyte chemoattractant protein-1 synthesis has

greater test efficiency than specific antibodies for identification of diisocyanate asthma. Am J Respir Crit Care Med. 2002; 166:445–50. [PubMed: 12186818]

17. Campo P, Wisnewski AV, Lummus Z, Cartier A, Malo JL, Boulet LP, Bernstein DI. Diisocyanate conjugate and immunoassay characteristics influence detection of specific antibodies in HDI-exposed workers. Clin Exp Allergy. 2007; 37:1095–102. [PubMed: 17581205]
18. Grammer LC, Harris KE, Malo JL, Cartier A, Patterson R. The use of an immunoassay index for antibodies against isocyanate human protein conjugates and application to human isocyanate disease. J Allergy Clin Immunol. 1990; 86:94–8. [PubMed: 2164544]
19. Cartier A, Grammer L, Malo JL, Lagier F, Ghezzo H, Harris K, Patterson R. Specific serum antibodies against isocyanates: association with occupational asthma. J Allergy Clin Immunol. 1989; 84:507–14. [PubMed: 2794294]
20. Tee RD, Cullinan P, Welch J, Burge PS, Newman-Taylor AJ. Specific IgE to isocyanates: a useful diagnostic role in occupational asthma. J Allergy Clin Immunol. 1998; 101:709–15. [PubMed: 9600510]
21. Kim H, Kim YD, Choi J. Seroimmunological characteristics of Korean workers exposed to toluene diisocyanate. Environ Res. 1997; 75:1–6. [PubMed: 9356188]
22. Ye YM, Kim CW, Kim HR, Kim HM, Suh CH, Nahm DH, Park HS, Redlich CA, Wisnewski AV. Biophysical determinants of toluene diisocyanate antigenicity associated with exposure and asthma. J Allergy Clin Immunol. 2006; 118:885–91. [PubMed: 17030242]
23. Wisnewski AV, Stowe MH, Cartier A, Liu Q, Liu J, Chen L, Redlich CA. Isocyanate vapor-induced antigenicity of human albumin. J Allergy Clin Immunol. 2004; 113:1178–84. [PubMed: 15208602]
24. Karol MH. Study of guinea pig and human antibodies to toluene diisocyanate. Am Rev Respir Dis. 1980; 122:965–70. [PubMed: 6161573]
25. Malo JL, Chan-Yeung M. Agents causing occupational asthma. J Allergy Clin Immunol. 2009; 123:545–50. [PubMed: 18951622]
26. Maestrelli P, Boschetto P, Fabbri LM, Mapp CE. Mechanisms of occupational asthma. J Allergy Clin Immunol. 2009; 123:531–42. quiz 43–4. [PubMed: 19281901]
27. Redlich, CA.; Bello, D.; Wisnewski, AV. Health Effects of Isocyanates. In: Rom, WN., editor. Environmental and Occupational Medicine. 2007. p. 502-15.
28. Dufour MH, Lemiere C, Prince P, Boulet LP. Comparative airway response to high-versus low-molecular weight agents in occupational asthma. Eur Respir J. 2009; 33:734–9. [PubMed: 19129274]
29. Holgate ST, Davies DE. Rethinking the pathogenesis of asthma. Immunity. 2009; 31:362–7. [PubMed: 19766079]
30. Wisnewski AV, Liu J, Redlich CA. Antigenic changes in human albumin caused by reactivity with the occupational allergen, diphenyl methane diisocyanate (MDI). Anal Biochem. (in press).
31. Hettick JM, Ruwona TB, Siegel PD. Structural elucidation of isocyanate-peptide adducts using tandem mass spectrometry. J Am Soc Mass Spectrom. 2009; 20:1567–75. [PubMed: 19477659]
32. Tse CS, Pesce AJ. Chemical characterization of isocyanate-protein conjugates. Toxicol Appl Pharmacol. 1979; 51:39–46. [PubMed: 230615]
33. Scheel LD, Killens R, Josephson A. Immunochemical Aspects of Toluene Diisocyanate (TDI) Toxicity. Am Ind Hyg Assoc J. 1964; 25:179–84. [PubMed: 14125870]
34. Karol MH, Ioset HH, Alarie YC. Tolyl-specific IgE antibodies in workers with hypersensitivity to toluene diisocyanate. Am Ind Hyg Assoc J. 1978; 39:454–8. [PubMed: 210646]
35. Karol MH, Alarie Y. Antigens which detect IgE antibodies in workers sensitive to toluene diisocyanate. Clin Allergy. 1980; 10:101–9. [PubMed: 6244907]
36. Wisnewski AV, Srivastava R, Herick C, Xu L, Lemus R, Cain H, Magoski NM, Karol MH, Bottomly K, Redlich CA. Identification of human lung and skin proteins conjugated with hexamethylene diisocyanate in vitro and in vivo. Am J Respir Crit Care Med. 2000; 162:2330–6. [PubMed: 11112159]
37. Wide L, Bennich H, Johansson SG. Diagnosis of allergy by an in-vitro test for allergen antibodies. Lancet. 1967; 2:1105–7. [PubMed: 4168552]

38. Park HS, Kim HY, Nahm DH, Son JW, Kim YY. Specific IgG, but not specific IgE, antibodies to toluene diisocyanate-human serum albumin conjugate are associated with toluene diisocyanate bronchoprovocation test results. J Allergy Clin Immunol. 1999; 104:847–51. [PubMed: 10518831]
39. Baur X, Chen Z, Flagge A, Posch A, Raulf-Heimsoth M. EAST and CAP specificity for the evaluation of IgE and IgG antibodies to diisocyanate-HSA conjugates. Int Arch Allergy Immunol. 1996; 110:332–8. [PubMed: 8768800]
40. Johannesson G, Sennbro CJ, Willix P, Lindh CH, Jonsson BA. Identification and characterisation of adducts between serum albumin and 4,4′-methylenediphenyl diisocyanate (MDI) in human plasma. Arch Toxicol. 2004; 78:378–83. [PubMed: 15007542]
41. Sepai O, Henschler D, Sabbioni G. Albumin adducts, hemoglobin adducts and urinary metabolites in workers exposed to 4,4′-methylenediphenyl diisocyanate. Carcinogenesis. 1995; 16:2583–7. [PubMed: 7586170]
42. Fabbri LM, Mapp CE, Balboni A, Baricordi R. HLA class II molecules and asthma induced by toluene diisocyanate. Int Arch Allergy Immunol. 1995; 107:400–1. [PubMed: 7613190]
43. Bignon JS, Aron Y, Ju LY, Kopferschmitt MC, Garnier R, Mapp C, Fabbri LM, Pauli G, Lockhart A, Charron D, et al. HLA class II alleles in isocyanate-induced asthma. Am J Respir Crit Care Med. 1994; 149:71–5. [PubMed: 8111601]
44. Kim SH, Oh HB, Lee KW, Shin ES, Kim CW, Hong CS, Nahm DH, Park HS. HLA DRB1*15-DPB1*05 haplotype: a susceptible gene marker for isocyanate-induced occupational asthma? Allergy. 2006; 61:891–4. [PubMed: 16792590]
45. Choi JH, Lee KW, Kim CW, Park CS, Lee HY, Hur GY, Kim SH, Hong CS, Jang AS, Park HS. The HLA DRB1*1501-DQB1*0602-DPB1*0501 haplotype is a risk factor for toluene diisocyanate-induced occupational asthma. Int Arch Allergy Immunol. 2009; 150:156–63. [PubMed: 19439981]
46. Mapp CE, Beghe B, Balboni A, Zamorani G, Padoan M, Jovine L, Baricordi OR, Fabbri LM. Association between HLA genes and susceptibility to toluene diisocyanate-induced asthma. Clin Exp Allergy. 2000; 30:651–6. [PubMed: 10792356]
47. Beghe B, Padoan M, Moss CT, Barton SJ, Holloway JW, Holgate ST, Howell WM, Mapp CE. Lack of association of HLA class I genes and TNF alpha-308 polymorphism in toluene diisocyanate-induced asthma. Allergy. 2004; 59:61–4. [PubMed: 14674935]
48. Rihs HP, Barbalho-Krolls T, Huber H, Baur X. No evidence for the influence of HLA class II in alleles in isocyanate-induced asthma. Am J Ind Med. 1997; 32:522–7. [PubMed: 9327077]
49. Jones MG, Floyd A, Nouri-Aria KT, Jacobson MR, Durham SR, Taylor AN, Cullinan P. Is occupational asthma to diisocyanates a non-IgE-mediated disease? J Allergy Clin Immunol. 2006; 117:663–9. [PubMed: 16522468]
50. Maestrelli P, Occari P, Turato G, Papiris SA, Di Stefano A, Mapp CE, Milani GF, Fabbri LM, Saetta M. Expression of interleukin (IL)-4 and IL-5 proteins in asthma induced by toluene diisocyanate. Clin Exp Allergy. 1997; 27:1292–8. [PubMed: 9420133]
51. Vercelli D, Geha RS. Regulation of isotype switching. Curr Opin Immunol. 1992; 4:794–7. [PubMed: 1466804]
52. Bernstein JA, Munson J, Lummus ZL, Balakrishnan K, Leikauf G. T-cell receptor V beta gene segment expression in diisocyanate-induced occupational asthma. J Allergy Clin Immunol. 1997; 99:245–50. [PubMed: 9042053]
53. Maestrelli P, Del Prete GF, De Carli M, D'Elios MM, Saetta M, Di Stefano A, Mapp CE, Romagnani S, Fabbri LM. CD8 T-cell clones producing interleukin-5 and interferon-gamma in bronchial mucosa of patients with asthma induced by toluene diisocyanate. Scand J Work Environ Health. 1994; 20:376–81. [PubMed: 7863302]
54. Lummus ZL, Alam R, Bernstein JA, Bernstein DI. Diisocyanate antigen-enhanced production of monocyte chemoattractant protein-1, IL-8, and tumor necrosis factor-alpha by peripheral mononuclear cells of workers with occupational asthma. J Allergy Clin Immunol. 1998; 102:265–74. [PubMed: 9723671]
55. Wisnewski AV, Herrick CA, Liu Q, Chen L, Bottomly K, Redlich CA. Human gamma/delta T-cell proliferation and IFN-gamma production induced by hexamethylene diisocyanate. J Allergy Clin Immunol. 2003; 112:538–46. [PubMed: 13679813]

56. Kim SR, Lee KS, Park SJ, Min KH, Lee KY, Choe YH, Lee YR, Kim JS, Hong SJ, Lee YC. PTEN down-regulates IL-17 expression in a murine model of toluene diisocyanate-induced airway disease. J Immunol. 2007; 179:6820–9. [PubMed: 17982072]
57. Lee YM, Kim HA, Park HS, Lee SK, Nahm DH. Exposure to toluene diisocyanate (TDI) induces IL-8 production from bronchial epithelial cells: effect of pro-inflammatory cytokines. J Korean Med Sci. 2003; 18:809–12. [PubMed: 14676436]
58. Wisnewski AV, Liu Q, Miller JJ, Magoski N, Redlich CA. Effects of hexamethylene diisocyanate exposure on human airway epithelial cells: in vitro cellular and molecular studies. Environ Health Perspect. 2002; 110:901–7. [PubMed: 12204825]
59. Lantz RC, Lemus R, Lange RW, Karol MH. Rapid reduction of intracellular glutathione in human bronchial epithelial cells exposed to occupational levels of toluene diisocyanate. Toxicol Sci. 2001; 60:348–55. [PubMed: 11248147]
60. Wisnewski AV, Liu Q, Liu J, Redlich CA. Human innate immune responses to hexamethylene diisocyanate (HDI) and HDI-albumin conjugates. Clin Exp Allergy. 2008; 38:957–67. [PubMed: 18498542]
61. Verstraelen S, Wens B, Hooyberghs J, Nelissen I, Witters H, Schoeters G, Cauwenberge PV, Heuvel RV. Gene expression profiling of in vitro cultured macrophages after exposure to the respiratory sensitizer hexamethylene diisocyanate. Toxicol In Vitro. 2008; 22:1107–14. [PubMed: 18395406]
62. Lummus ZL, Alam R, Bernstein JA, Bernstein DI. Characterization of histamine releasing factors in diisocyanate-induced occupational asthma. Toxicology. 1996; 111:191–206. [PubMed: 8711735]
63. Kuna P, Reddigari SR, Rucinski D, Oppenheim JJ, Kaplan AP. Monocyte chemotactic and activating factor is a potent histamine-releasing factor for human basophils. J Exp Med. 1992; 175:489–93. [PubMed: 1370686]
64. Colotta F, Borre A, Wang JM, Tattanelli M, Maddalena F, Polentarutti N, Peri G, Mantovani A. Expression of a monocyte chemotactic cytokine by human mononuclear phagocytes. J Immunol. 1992; 148:760–5. [PubMed: 1370516]
65. Cushing SD, Fogelman AM. Monocytes may amplify their recruitment into inflammatory lesions by inducing monocyte chemotactic protein. Arterioscler Thromb. 1992; 12:78–82. [PubMed: 1731861]
66. Matheson LA, Santerre JP, Labow RS. Changes in macrophage function and morphology due to biomedical polyurethane surfaces undergoing biodegradation. J Cell Physiol. 2004; 199:8–19. [PubMed: 14978730]
67. Cantin AM, North SL, Hubbard RC, Crystal RG. Normal alveolar epithelial lining fluid contains high levels of glutathione. J Appl Physiol. 1987; 63:152–7. [PubMed: 3040659]
68. Cantin AM, Paquette B, Richter M, Larivee P. Albumin-mediated regulation of cellular glutathione and nuclear factor kappa B activation. Am J Respir Crit Care Med. 2000; 162:1539–46. [PubMed: 11029374]
69. Mishra PK, Raghuram GV, Panwar H, Jain D, Pandey H, Maudar KK. Mitochondrial oxidative stress elicits chromosomal instability after exposure to isocyanates in human kidney epithelial cells. Free Radic Res. 2009; 43:718–28. [PubMed: 19513903]
70. Mishra PK, Khan S, Bhargava A, Panwar H, Banerjee S, Jain SK, Maudar KK. Regulation of isocyanate-induced apoptosis, oxidative stress, and inflammation in cultured human neutrophils: Isocyanate-induced neutrophils apoptosis. Cell Biol Toxicol. 2009
71. Lee CT, Ylostalo J, Friedman M, Hoyle GW. Gene expression profiling in mouse lung following polymeric hexamethylene diisocyanate exposure. Toxicol Appl Pharmacol. 2005; 205:53–64. [PubMed: 15885264]
72. Elms J, Beckett PN, Griffin P, Curran AD. Mechanisms of isocyanate sensitisation. An in vitro approach. Toxicol In Vitro. 2001; 15:631–4. [PubMed: 11698162]
73. Bowler RP, Crapo JD. Oxidative stress in allergic respiratory diseases. J Allergy Clin Immunol. 2002; 110:349–56. [PubMed: 12209079]
74. Rahman I, MacNee W. Oxidative stress and adaptive response of glutathione in bronchial epithelial cells. Clin Exp Allergy. 2002; 32:486–8. [PubMed: 11972591]

75. Janssen-Heininger YM, Poynter ME, Aesif SW, Pantano C, Ather JL, Reynaert NL, Ckless K, Anathy V, van der Velden J, Irvin CG, van der Vliet A. Nuclear factor kappaB, airway epithelium, and asthma: avenues for redox control. Proc Am Thorac Soc. 2009; 6:249–55. [PubMed: 19387025]

76. Pauluhn J. Acute inhalation toxicity of polymeric diphenyl-methane 4,4′-diisocyanate in rats: time course of changes in bronchoalveolar lavage. Arch Toxicol. 2000; 74:257–69. [PubMed: 10959801]

77. Pauluhn J. Brown Norway rat asthma model of diphenylmethane-4,4′-diisocyanate (MDI): analysis of the elicitation dose-response relationship. Toxicol Sci. 2008; 104:320–31. [PubMed: 18495671]

78. Holgate ST. Pathogenesis of asthma. Clin Exp Allergy. 2008; 38:872–97. [PubMed: 18498538]

79. Wikman H, Piirila P, Rosenberg C, Luukkonen R, Kaaria K, Nordman H, Norppa H, Vainio H, Hirvonen A. N-Acetyltransferase genotypes as modifiers of diisocyanate exposure-associated asthma risk. Pharmacogenetics. 2002; 12:227–33. [PubMed: 11927838]

80. Mapp CE, Fryer AA, De Marzo N, Pozzato V, Padoan M, Boschetto P, Strange RC, Hemmingsen A, Spiteri MA. Glutathione S-transferase GSTP1 is a susceptibility gene for occupational asthma induced by isocyanates. J Allergy Clin Immunol. 2002; 109:867–72. [PubMed: 11994713]

81. Piirila P, Wikman H, Luukkonen R, Kaaria K, Rosenberg C, Nordman H, Norppa H, Vainio H, Hirvonen A. Glutathione S-transferase genotypes and allergic responses to diisocyanate exposure. Pharmacogenetics. 2001; 11:437–45. [PubMed: 11470996]

82. Broberg KE, Warholm M, Tinnerberg H, Axmon A, Jonsson BA, Sennbro CJ, Littorin M, Rannug A. The GSTP1 Ile105 Val polymorphism modifies the metabolism of toluene di-isocyanate. Pharmacogenet Genomics. 20:104–11. [PubMed: 20032816]

Table 1

Studies of Isocyanate-Specific IgE in Isocyanate Asthma

% IgE+	# Subjects	Patient source	Diagnosis	Isocyanate	Antigen Preparation & Characterization	"Substitution"***	Assay	Ref.
0%	11	Manufacturing Plant	Symptoms	TDI	Liquid phase, Guttman Assay	13:1	RAST	11
3%	34	Various Industries	SIC*	TDI	Liquid phase, UV spectroscopy	34:1	RAST	12
14%	247	Multiple Isocyanate Industries/Clinics	Physician	TDI, TMI*, MDI, MMI*	Liquid phase, Derivatization w/Azo dye	26:1, 13:1, 15:1, 10:1	RAST	13
19%	26	Cotton Seed Processing Industry	SIC	TMI	Liquid phase, UV spectroscopy	16:1	RAST	14
20%	35	Finland Health Registry	SIC	TDI, MDI, HDI	-	-	RAST	15
21%	19	Pulmonary Disease Clinics Montreal/Quebec	SIC	TDI, MDI, HDI	Liquid phase, Mass spectrometry	3:1 to 10:1	ELISA	16
22%	23	Pulmonary Disease Clinics Montreal/Quebec	SIC	HDI and oligomer	Vapor & Liquid phases, Mass Spectrometry	6:1, 23:1 2:1	RAST	17
23%	26	Hôpital du Sacré Coeur, Montreal, Canada	SIC	TDI, MDI, HDI	Liquid phase, chemical (TNBS)	10:1, 7:1, 24:1	ELISA	18
31%	29	Hôpital du Sacré Coeur, Montreal, Canada	SIC	TDI, MDI, HDI	Liquid phase, chemical (TNBS) and immunoelectrophoresis	-	ELISA	19
34%	58	Royal Brompton Hospital United Kingdom	SIC or Physician	TDI, MDI, HDI	-	-	RAST	20
38%	8	Musical Instrument and Motor Vehicle Industries	Expiratory (Peak) Flow	TDI, MDI, HDI	Liquid phase, UV spectroscopy	-	RAST	21
44%	66	Furniture/Musical Instrument Industries	SIC	TDI	Vapor phase, Chemical (TNBS) and MALDI-MS	12:1	ELISA	22
55%	11	Hôpital du Sacré Coeur & Yale Medical Clinic	SIC	HDI	Vapor phase, Chemical (TNBS) and MALDI-MS	3:1	RAST	23
**91%	12	Multiple Worsites	Physician Records	TDI	Liquid Phase UV spectroscopy	30:1	RAST	24

*Specific inhalation challenge (SIC)

**Selection criteria was physician-verified work-related immediate-type asthma attack

***Substitution = molar ratio of isocyanate to albumin (isocyanate:albumin)

- Not reported