Hazardous Air Pollutants and Asthma

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Asthma has a high prevalence in the United States, and persons with asthma may be at added risk from the adverse effects of hazardous air pollutants (HAPs). Complex mixtures (fine particulate matter and tobacco smoke) have been associated with respiratory symptoms and hospital admissions for asthma. The toxic ingredients of these mixtures are HAPs, but whether ambient HAP exposures can induce asthma remains unclear. Certain HAPs are occupational asthmagens, whereas others may act as adjuncts during sensitization. HAPs may exacerbate asthma because, once sensitized, individuals can respond to remarkably low concentrations, and irritants lower the bronchoconstrictive threshold to respiratory antigens. Adverse responses after ambient exposures to complex mixtures often occur at concentrations below those producing effects in controlled human exposures to a single compound. In addition, certain HAPs that have been associated with asthma in occupational settings may interact with criteria pollutants in ambient air to exacerbate asthma. Based on these observations and past experience with 188 HAPs, a list of 19 compounds that could have the highest impact on the induction or exacerbation of asthma was developed. Nine additional compounds were identified that might exacerbate asthma based on their irritancy, respirability, or ability to react with biological macromolecules. Although the ambient levels of these 28 compounds are largely unknown, estimated exposures from emissions inventories and limited air monitoring suggest that aldehydes (especially acrolein and formaldehyde) and metals (especially nickel and chromium compounds) may have possible health risk indices sufficient for additional attention. Recommendations for research are presented regarding exposure monitoring and evaluation of biologic mechanisms controlling how these substances induce and exacerbate asthma. ***Key words:*** **acrolein, aldehydes, asthma, cadmium, chromium, formaldehyde, hazardous air pollutants, metals, nickel, ozone, particulate matter, urban air toxics.** ***Environ Health Perspect*** **110(suppl 4):505–526 (2002).**
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Introduction

Hazardous Air Pollutants

In 1990, Clean Air Act Amendment, Title III, Hazardous Air Pollutants, mandated exposure standards for 189 compounds [referred to as hazardous air pollutants (HAPs) or urban air toxics (UATs)] and emissions control strategies of 30 or more compounds that present the greatest risk to public health. Between 1996 and 2001, one compound was removed from the list and a shorter list of 33 HAPs was developed through consideration of several possible health concerns, with a major emphasis on carcinogenicity, mutagenicity, and teratogenicity. Cancer commonly is used in risk assessment modeling and allows mathematical comparisons of risk estimates among compounds. Noncancer risks also are used in modeling and include reproductive, neurotoxic, and respiratory effects. Other adverse health outcomes, especially asthma, chronic obstructive pulmonary disease, and cardiovascular disease, also are important to exposed populations because of their high prevalence. Yet, much less is currently known about the threshold concentrations and lifetime (chronic) exposures associated with these diseases. This review updates a previous examination of the possible relationship between these compounds and asthma (*1*). Much still remains to be understood about the complex relationship between exposure to these compounds and the development and exacerbation of asthma morbidity.

The ongoing use of over 50,000 commercial chemicals continues to present a major challenge to environmental health scientists because each compound could be considered toxic depending on the magnitude of human exposure, the dose delivered to the target organ, and the biological response. Without complete information on each compound, the systematic evaluation of the toxicology of these chemicals can only be preliminary. Many decades of effort will be required before we understand the relationships between environmental exposure and potential to cause or exacerbate human diseases. In the previous review (*1*), we presented an initial ranking of HAPs based on the likelihood and extent of potential human exposure and the severity of the response. The outcome of that review led to an emphasis on acquisition of additional data on personal exposure assessment. The present review focuses anew on the current gaps in the toxicology literature and recommends research that may help reduce the uncertainty of future evaluations of the health effects of these compounds.

Under the national air toxics program, the U.S. Environmental Protection Agency (U.S. EPA) continues to assess emissions from stationary and mobile sources to improve air quality in urban and rural areas, and the database being generated is extensive (e.g., see website *http://www.epa.gov/triexplorer/reports.htm*). Since 1995 the U.S. EPA also has initiated an Integrated HAP Strategy to address emissions in urban counties. A county is designated "urban" if it contains a metropolitan statistical area (population > 250,000) or if the U.S. Census Bureau designates >50% of the population as urban. An initial outline of actions to reduce HAP emissions and activities to improve the understanding of the health and environmental risks posed by air toxics in urban areas has been presented. The major outcome of this effort was a list of 33 HAPs that pose the greatest potential health threat in urban areas (Table 1) with an accompanying assessment of the area sources responsible for a substantial portion of these emissions. The latter includes 29 area source categories (including 13 new categories not previously subject to standards). Although this review focuses mostly on the short list of 33 compounds, I also discuss additional members of the original 189 HAPs that are still important to asthma.

Persons with Asthma and Increased Susceptibility to Air Pollution

Air quality standards must protect susceptible individuals in the general populations, and persons with asthma clearly are at increased risk from the adverse effects of air pollution. Asthma is a complex respiratory condition operationally defined as a respiratory disease with three primary features (*2–4*). These include *a*) airway inflammation associated with cytokine formation, eosinophilic infiltration, and altered T-cell lymphocytic function; *b*) altered epithelial

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Table 1. Hazardous air pollutants of greatest concern for exposure and health effects.[a]

Acetaldehyde[b]	Formaldehyde[b]
Acrolein[b]	Hexachlorobenzene
Acrylonitrile	Hydrazine[b]
Arsenic compounds	Lead compounds
Benzene[b]	Manganese compounds[b]
Beryllium compounds	Mercury compounds
1,3-Butadiene	Methylene chloride
Cadmium compounds[b]	Nickel compounds[b]
Carbon tetrachloride	Perchloroethylene
Chloroform	Polychlorinated biphenyls
Chromium compounds[b]	Polycyclic organic matter
Coke oven emissions[b]	Propylene dichloride
1,3-Dichloropropene	Quinoline
Dioxin	1,1,2,2-Tetrachloroethane
Ethylene dibromide	Trichloroethylene
Ethylene dichloride	Vinyl chloride
Ethylene oxide[b]	

[a]Data from *http://www.epa.gov/triexplorer/reports.htm.* [b]Compounds suspected of inducing or exacerbating asthma (Table 5).

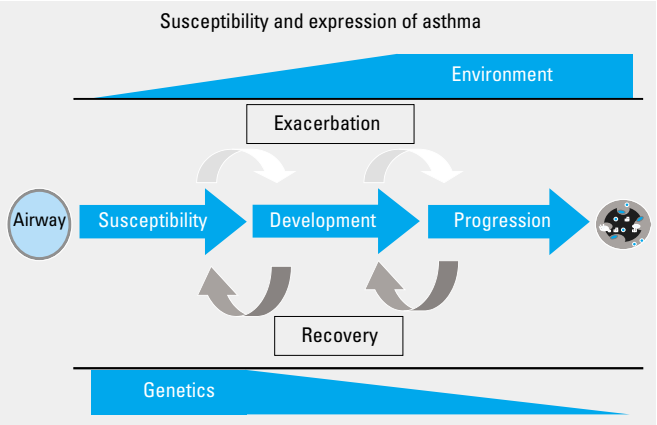

Figure 1. Susceptibility and expression of asthma. Individuals inheriting a certain array of multiple alleles of susceptibility genes are at added risk from birth of developing asthma. This susceptibility may become evident when an initial sensitization and exacerbation occur in early childhood and when immunity (typically mediated by immunoglobin) develops to aeroallergens. Asthma may remit or progress, depending largely on the environmental exposures of each individual. The combination of numerous gene–environment interactions leads to the expression of this complex disease.

Table 2. Candidate genes associated with asthma from linkage analyses of human populations (*364–382*).

Chromosome	Locus	Candidate genes (*35*)[a]
1	p	*IL12RB2*
2	q	*CD28, SCYA20*
5	q31–33	*IL13, IGES, CSF2, IL3, IL4, IL5, IL9*
	q33–35	*CSF1R, ADRB2, NR3C1, LTC4S*
6	p21–23	*HLA, HSP1A1, IER3, LTA (TNFβ), TAP1, TAP2, TNFA, NFYA*
10	q	*ALOX5*
11	q13	*IGR, UGB, FGF3*
12	q14–24	*IFNG, NFYB, IGF1, LTA4H, NOS1,*
13	q21–24	Unknown
14	q11–13	*TCRa/d, NFKBIA*
16	p11–12	*IL4RA*

[a]Gene abbreviations (from Unigene: *http://www.ncbi.nlm.nih.gov/UniGene/*): *IL:* interleukin; *R:* receptor (e.g., *IL12RB2*: interleukin-12 receptor beta-2); *CD28:* antigen CD28 (T-cell antigen CD28 Tp44); *SCYA20*: small inducible cytokine subfamily A, member 20 (Exodus 1, macrophage inflammatory protein 3 alpha); *IGES:* immunoglobulin E concentration, serum; *CSF2:* colony-stimulating factor-2 (granulocyte-macrophage); *CSF1R:* colony-stimulating factor-1 receptor; *ADRB2:* adrenergic receptor beta-2 type; *NR3C1:* nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor); *LTC4S:* leukotriene C_4 synthase; *HLA:* major histocompatibility complex (gene cluster); *HSP1A1:* heat shock protein 70 kDa; *IER3:* immediate-early response 3; *TAP1:* transporter 1, ATP-binding cassette, subfamily B; *TAP2:* transporter 2, ATP-binding cassette, subfamily B *TNFA:* tumor necrosis factor-alpha; *LTA:* lymphotoxin A (formerly tumor necrosis factor-beta); *NYFA:* nuclear transcription factor Y, alpha; *ALOX5:* arachidonate 5-lipoxygenase; *IGR:* IgE responsiveness, atopic (also membrane-spanning 4-domains, subfamily A, member 2 or Fc fragment of IgE, high affinity I, receptor for, beta polypeptide: FCER1B); *UGB:* uterglobin (Clara cell secretory protein or Clara-cell specific 10-kDa protein); *FGF3:* fibroblast growth factor 3; *IFNG*: interferon-gamma; *NFYB:* nuclear transcription factor-Y, beta subunit; *IGF1:* insulin-like growth factor 1; *LTA4H:* leukotriene A4 hydrolase; *NOS1:* nitric oxide synthase 1 (neuronal); *TCRa/d:* T-cell antigen receptor, alpha and T-cell antigen receptor, delta; *NFKBIA:* nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha *IL4R:* interleukin 4 receptor (alpha).

function associated with thickening of the basement membrane, mucin hypersecretion, lost or altered cilia structure, and altered cytokine and other inflammatory mediator production; and *c*) recurrent airflow obstruction often presenting in acute phases as decreased forced expiratory volume and reversible bronchospasm followed by persistent airway hyperreactivity. Although the frequency of asthma is greater among atopic individuals (*5*), not all persons with asthma (e.g., as much as half the adults with occupational asthma) (*6*) exhibit specific antigen–antibody responses. Recently, however, this observation has been debated because 20–40% of the population may be atopic. Atopy is usually assessed by skin provocations with known allergens, but skin tests do not always uncover aeroallergens specific to asthma. Thus, not all airway antigens may be known for each person. Persons with asthma respond to many nonantigenic agents, including dry air, hypo/hypertonic aerosols, acidic aerosols, and sulfur dioxide. Consequently, this latter condition is called nonspecific airway hyperreactivity, which many clinical investigators consider the hallmark of asthma (*3,7*).

Gene–Environment Interaction in Asthma

The molecular basis of asthma is currently under extensive study in many laboratories. Briefly, the development and expression of asthma involve three stages (Figure 1). The first stage is an initial inherited susceptibility to atopy and asthma. This susceptibility involves host factors that include inherited polymorphisms. Individuals with these polymorphisms may be at added risk of developing asthma, yet the overt symptoms may never develop. Exactly which genes control an asthma phenotype(s) is unclear, but it is clear that asthma is likely to be controlled by multiple genes (Table 2). Several likely candidate genes have been identified. For example, one chromosomal region harbors a leading candidate gene, immunoglobulin E (IgE), and the IgE molecule is a critical antibody in acquired immunity. In allergic asthma, specific immunologic responses (e.g., proteins carried on airborne particulates) are mediated by (and will not occur without) a preliminary sensitization step that involves generating IgE or occasionally immunoglobulin G (IgG) antibodies. This process confers a high degree of specificity (e.g., individuals allergic to one laboratory species, e.g., rats, often will not develop asthma exacerbations when exposed to a similar species, e.g., mice). Sensitization leads to an exquisite responsiveness that induces disease responses to airborne exposures in the range of nanograms to picograms per cubic meter. In addition, the penetrance of an asthma phenotype depends on environmental exposures; therefore, asthma is clearly a complex disease. Thus, as defined here, the first stage could be considered latent asthma

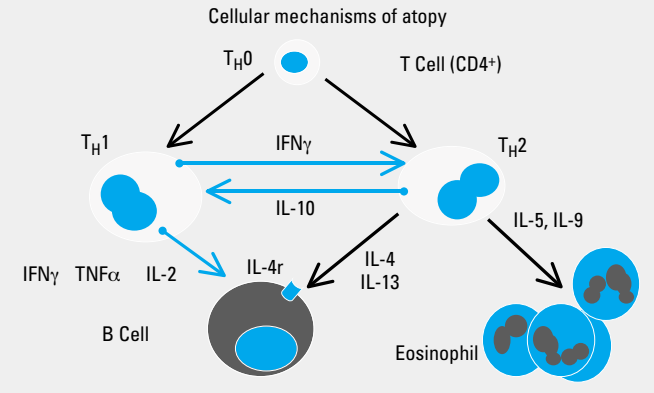

Figure 2. Cellular mechanisms of atopy. In the development of atopy (or systemic allergy), subpopulations of helper T-cells (a subtype of lymphocytes that stains positively with the surface marker $CD4^+$) vary and alter the expression of cytokines. These cytokines in turn alter effector cells by influencing proliferation and function of B-cells (lymphocytes that produce antibody, IgE, or IgG) and eosinophils. When the precursory helper T-cells (T_H0) mature, they will become T_H1 or T_H2 subtypes, which suppress or augment effector cell function, respectively, by releasing differing arrays of cytokines. The T_H1 cell release interferon-γ (IFNγ), tumor necrosis factor-α (TNFα), and IL-2γ, which inhibit (cyan arrow) T_H2 differentiation and B-cell antibody formation. In contrast, T_H2 cells release IL-4, IL-5, IL-9, IL-10, and IL-13, which inhibit T_H1 differentiation and augment eosinophil proliferation and B-cell antibody formation (mainly through binding to the IL-4 receptor).

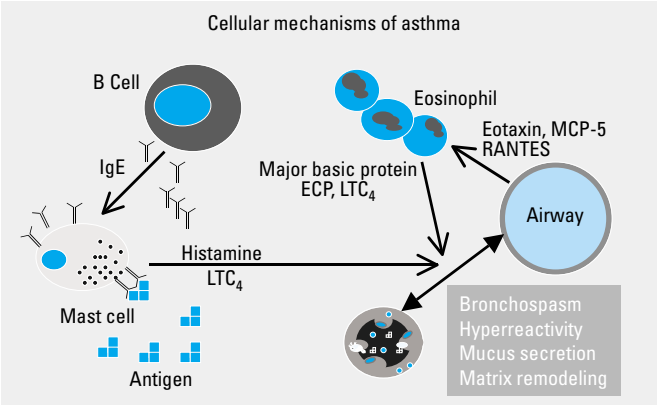

Figure 3. Cellular mechanisms of asthma. The B cells that are activated to produce antibody (IgE) that specifically binds aeroallergens such as house dust mite or pollens. When dimers of IgE–antibody complex bind to the IgE receptor, the mast cells become activated to release mediators [e.g., histamine and leukotriene (LT) C_4), which alter airway function. In addition, the local migration of eosinophils into and maintenance of eosinophils in airway epithelium is induced by local production of chemotactic cytokines (chemokines), including small inducible cytokine 12 [SCYA12; also known as monocyte chemotactic protein-5 (MCP-5)], eotaxin, and RANTES (regulated upon activation, normally T-expressed, and presumably secreted; also known as SCYA5). These mediators also activate eosinophils to release preformed major basic protein, eosinophil cationic protein (ECP), and LTC_4. The combination of all these events with the direct damage air pollutants can do to the epithelium leads to the develop and progression of the cardinal features of asthma: reversible bronchospasm, airway smooth muscle hyperreactivity, increased mucus production and secretion, and extracellular matrix remodeling.

in individuals with increased risk due to inherited susceptibility (asthma genotypes).

The second stage is the development of clinically discernable asthma. This often occurs during the first 3–6 years of life in persons with allergic asthma. Susceptible individuals become sensitized via specific IgE antibody formation. In addition, the condition is expressed fully (development of heightened sensitivity) upon repetitive exposure to environmental triggers (antigens) such as house dust mite allergens. Persons who inherit susceptibility genes (asthma genotypes) begin to develop symptoms (phenotype) upon exposure (environmental penetrance).

The initial process of sensitization, a key event that precedes the development of asthma, can be enhanced by coexposures to adjuvant. In immunization methodology, an adjuvant serves two functions: acting as a vehicle that permits delivery without rapid clearance and having irritancy that activates cells critical to innate immunity (e.g., tissue macrophage or dendritic cells), which sequester and present antigen to T-type lymphocytes (T-cells). To enhance antigenicity, adjuvant consists of a vehicle in which antigen is absorbed (e.g., suspension of minerals including aluminum hydroxide or phosphate), water–mineral oil emulsion (i.e., Freund's incomplete), or water–mineral oil with killed mycobacteria (i.e., Freund's complete). Several environmental chemicals, including diesel particles, may share the attributes of adjuvants. Presentation of antigen to T-cells causes clonal expansion of a subtype of T-cells [T-helper cells, type 2 (T_H2)], induction of IgE (or IgG) antibody formation by B-type lymphocytes, and release eosinophil growth factors and chemoattractants. This process is accomplished through mediators that are released upon stimulation of subpopulations of immune cells (Figure 2).

The third stage of asthma involves progression, in which chronic inflammation, epithelial cell and matrix remodeling, and airway smooth muscle effects predominate. Cellular changes in the airways include persistent eosinophilia, mast cell activation, and mucus cell proliferation (Figure 3). Re-exposure to antigen induces bronchospasm and may produce irreversible remodeling of the airways and only partial recovery. This stage is accelerated by repetitive exacerbations that worsen the condition incrementally. Recovery is mainly influenced by avoidance of antigen stimuli and treatment with corticoid steroids and other anti-inflammatory and epithelial cell growth enhancers that modulate recovery (Figure 1).

A complex disease, asthma is recognized to be oligogenetic, that is, a phenotype under the control of multiple genes. In addition, environmental exposure is critical for many of these genes to be expressed or phenotypes to be observed, i.e., variable penetrance due to environmental factors. Examination of a single gene (or the role of a single polymorphisms) in complex diseases such as asthma is likely to inform us only about a portion of the phenotype. Alternatively, interactions of multiple chromosomal regions can be uncovered by genomewide scans. These scans involve assessment of linkage of the phenotype with polymorphic genetic markers distributed at selected intervals on each chromosome (i.e., linkage analysis). This has been done in human populations, and multiple candidate genes present in these chromosomal regions have been identified (Table 2).

In addition, various phenotypes important to asthma (e.g., bronchial hyperreactivity) have been examined using genomewide scans in laboratory animals. For example many recent studies have used offspring from polar inbred mouse strains to identify chromosomal regions [quantitative trait loci (QTLs)] containing possible candidate genes with linkage to atopy (e.g., high levels of inducible immunoglobulin) or physiological responses consistent with asthma (e.g., resting airway reactivity) (Table 3). Transgenic mice can then be used to functionally analyze genes suspected of contributing to quantitative traits. This approach enables examination of the role a single gene may play, but it can be impractical for surveying the large genomic intervals containing many genes that are typically associated with QTLs. To screen for genes contained in an asthma-linked QTL mapping to human chromosome 5q31, Symula et al. (*8*) generated a set of transgenic mice containing large inserts of human DNA

(yeast artificial chromosomes) that together covered over a 1-Mb interval of 5q31. This region contains 6 cytokine genes and 17 partially characterized genes. Mice were screened for altered IgE response to antigen treatment. The transgenic lines that were highly responsive shared a 180-kb region containing five genes, including interleukin-4 (IL-4; 147780) and IL-13 (147683), that can induce IgE class switching in B-cells. Further analysis of these mice and other mice transgenic for mouse Il-4, Il-5, Il-9, and Il-13 demonstrated asthma-associated phenotypes *in vivo* (*9–12*). The causative and interactive role of the human and suspected (from inbred mouse genotyping) candidate genes is under further investigation, but a preliminary presentation of the role of these genes in the natural history of asthma can be envisioned (Figure 4).

Asthma can be transient (developing and remitting during childhood) or persist for many years, with respiratory signs and symptoms that are erratic in frequency and severity. Recovery is difficult to predict and may lead to an intrinsic, sporadic nature that contributes to a major concern for this disease. With adequate medication, persons with asthma may become symptom free for many years. Nonetheless, severe, life-threatening asthmatic attacks can arise rapidly. Sometimes these attacks are initially presented as mild symptoms to which the victim has long become accustomed. Therefore, patients and physicians may depend solely on self-administered bronchodilators for therapy, assuming relief is shortly in hand, only to be faced with a rapidly mounting array of irreversible changes (e.g., airway obstruction by mucus inspissations). Indeed, this lack of appreciation for this condition by patients and general practitioners along with inappropriate bronchodilator therapy has been considered to contribute to increases in asthma mortality (*13–17*). Without recognition of the inflammatory and epithelial components of this disease, early therapies directed solely at preventions of bronchospasms can leave the persistent inflammatory condition unchecked. In addition, patients relieved of symptoms may be less likely to avoid environmental exposures that increase epithelial injury and may hasten acute attacks.

Effects of Irritants in Persons with Asthma

One consequence for persons with asthma is an increased susceptibility to lower doses of inhaled irritants. Controlled exposures of asthma patients note responses at lower concentrations of inhaled compounds than do healthy control subjects (*18*). Studies have found effects with a broad range of irritants, including several criteria air pollutants: SO_2 (*19,20*), NO_2 (*21–24*), and acidic sulfates (*25–29*). Thus, the standard concentrations of these compounds have been lowered to protect these individuals, as mandated by the Clean Air Act. Recently, several studies have found that diesel exhaust particles (DEPs) may have a role as a mucosal adjunct in the induction of sensitization to antigen and can enhance total antibody (IgE) formation (*30–32*). Persons with asthma may be at increased risk of airway responses to inhaled acetaldehyde (*33*). Evidence also suggests that DEPs can augment T_H2 while inhibiting T_H1 (interferon-gamma) formation *in vitro* (*34,35*) and *in vivo* (*36–38*). DEPs are of special relevance to HAPs because they consist of numerous organics, aldehydes, and metals that are HAPs or share toxic properties with HAPs. For example, phenanthrene, an aromatic hydrocarbon contained in DEPs, produces many of the effects noted with complete DEPs (including enhanced antigen-specific IgE production) (*39,40*).

Table 3. Candidate genes associated with asthma from linkage analyses of inbred mice (*383–388*).

Chromosome	Locus (cM)	Homologue	Candidate genes (*22*)[a]	Phenotype[b]	Agonist[c]
2	73	2q13–21	*Il1b, Bhr1*	R_L	Mch
6	47	3p24–26	*Il5ra, Ly36, Ly49*	APTI	Ach
9	18	11q23	*Il10r*	Penh	Ova/Mch
10	44	12q22–24	*Ifng*	Penh	Mch
11	29	5q27–31	*Il4, Il5, Il13, Csf2*	Eos	Ova
				R_L	Mch
	52	17q12–22	*Nos2, Scya11*	Penh	Ova/Mch
15	50	22q12–13	*Il2rb, Csfrb1, Csfrb2, Pdgf, Bhr2*	R_L	Mch
17	18	6p21	*Tnf, Mcpt6, Mcpt7*	Penh	Ova/Mch
			Bhr3	R_L	Mch

[a]Gene abbreviations (from Unigene: *http://www.ncbi.nlm.nih.gov/UniGene/*): *Il1b:* interleukin 1 beta; *Bhr1:* bronchial hyperresponsiveness 1; *Il5ra*: interleukin 5 receptor, alpha: *Ly36* Lymphocyte antigen 36, *Ly49:* lymphocyte antigen 49; *IL10:* interleukin 10 receptor; *Ifng*: interferon gamma; *Il*: interleukin; *Csf2:* colony stimulating factor 2 (granulocyte-macrophage); Igf1: insulin-like growth factor 1; *Nos2:* nitric oxide synthase 2, inducible, macrophage; *Scya11* small inducible cytokine A11 (eotaxin); *Il2rb:* interleukin 2 receptor, beta chain*; Csf2rb1:* colony stimulating factor 2 receptor, beta 1, low-affinity (granulocyte-macrophage)*; Pdgf:* platelet derived growth factor, B polypeptide; *Bhr2:* bronchial hyperresponsiveness 2*; Tnf:* tumor necrosis factor*; Mcpt6,* mast cell protease 6; *Mcpt7:* mast cell protease 7. *Bhr3*: Bronchial hyperresponsiveness 3. [b]Phenotype abbreviations: R_L: lung resistance; APTI: airway pressure-time index; Penh: enhanced pause (airflow/rate change); Eos: eosinophils in bronchoalveolar lavage. [c]Agonist abbreviations: Mch: methacholine; Ach: acetylcholine; Ova/Mch: methacholine after ovalbumin challenge; Ova: ovalbumin challenge.

Although irritants alone may have mixed effects, interactions between irritants and inhaled antigens may contribute to asthma exacerbations. For example, clinical studies of ozone's effects among persons with asthma have been controversial, and whether these individuals respond to lower concentrations than do control subjects remains unclear (*41–43*). However, ozone exposures can increase bronchial reactivity to subsequent antigen challenges among asthma patients (*44–46*). A similar effect has been found with exposures to NO_2 (*47,48*), particulate matter (*49*), and DEPs (*50*). The mechanisms for these interactions are unclear, are likely to be complex, and may include altered deposition or reduction of epithelial barrier functions. Recent evidence suggests that DEPs may augment exposure to inhaled antigens by carrying antigens through the upper respiratory tract and increasing deposition in the conducting airways (*51*). Such effects, although indirect, may make persons more responsive to an allergen to which they are sensitized. Seasonal increases in asthma symptoms during periods of increased air pollution and antigen exposure may partially be explained by this interaction.

Much has been learned from irritant exposure studies, yet the results from studies with persons with asthma have to be viewed with caution. Qualitatively, these studies can be useful in assessing whether specific pollutants affect persons with asthma to a greater extent than healthy subjects and possibly giving valuable insights into mechanisms controlling responses. However, clinical findings have been quantitatively different from epidemiologic findings: in clinical studies, the lowest effective concentration that produces bronchoconstriction is often higher than that found to produce adverse pulmonary effects when subjects are exposed in free-roving environments. Because asthma varies in its severity, a selection bias of subjects with milder forms of the disease could be responsible for the difference noted between clinical and epidemiologic studies. Typically, studies of asthma are conducted when persons are without symptoms and currently not using medication. Persons with severe asthma rarely are symptom free and will often develop difficulty in breathing (reduced lung function) without continually using corticosteriods. Obviously, this selection basis makes results only partially representative of all persons with asthma in the general population.

Epidemiologic Studies of Persons with Asthma

In epidemiologic studies, associations between air pollution (mainly focusing on criteria pollutants) and the prevalence of respiratory symptoms characteristic of asthma

have been noted throughout the world. These studies have found that current levels of criteria air pollutants [particularly particulate matter with a mass median aerodynamic diameter ≤10 μm (PM_{10}) or ≤2.5 μm ($PM_{2.5}$)] are associated with increases in prevalence of respiratory symptoms (wheezing, cough, and chest tightness) (*52–62*) and in emergency department visits or hospital admissions for asthma (*63–81*). When the data from atopic and nonatopic patients were separated, the association with air pollution was unaffected (*54,56,69*), suggesting that both are affected by air pollution. This supports findings of clinical studies that suggest that irritants interact with inhaled antigens. Air pollution has also been associated with augmented respiratory signs, including decreases in pulmonary function, demonstrated by depressed forced expiratory volume in l sec ($FEV_{1.0}$) or peak expiratory flow rate (PEFR) (*71,76*).

The criteria air pollutant with the strongest statistical association differs among studies, but often $PM_{2.5}$ and sulfate are implicated. Sulfur dioxide has been associated with respiratory responses in some studies (*54,67,68*) but not others (*63*). Although weather, pollen, and environmental tobacco smoke (ETS) are important risk factors for asthma, each has been found to act independently of air pollution, and thus they do not explain the association between air pollution and asthma (*55,66,74,81–85*).

Because these associations were identified while criteria pollutant concentrations either decreased or maintained levels noted in previous years (*83–110*), scientists have argued against the role of criteria pollutant concentrations in inducing asthma. However, because the relationship between current exposure to these pollutants and asthma exacerbation remains, further examination of the role of and possible further reductions of HAP exposure remain reasonable. In addition, the cross-sectional studies that found associations were conducted over short periods, so any recent changes in diagnostic criteria for asthma are not likely to explain these associations (*94–95,107–110*). Together, these studies provide evidence that air pollution can act as a complex mixture and at current exposure levels can affect the exacerbation and possibly the development of asthma. Relevant to this assessment of HAPs are the associations between stationary sources and adverse health outcomes (*54,65,75,86–92*). Along with the observation that different pollutants often lead to a similar array of responses, these findings suggest that the specific compounds measured may be serving as indicators of a wider array of air pollutants (including UATs) generated from stationary sources.

Exposure Assessment

HAP Entry and Fate in the Environment

The quantification of human exposure remains a primary issue in assessing the culpability of HAPs in exacerbating asthma because existing air sampling networks do not quantify the ambient concentrations of these compounds on a hourly, daily, or yearly basis. Currently, data collection efforts have focused on emission inventories that may have value in understanding this problem.

HAPs can enter the environment by a number of pathways, including release into the air (e.g., vaporization of gases), soil, or water. The most relevant route of entry into the environment is total air release, which often is the largest source of release (Figure 5). Exposure also depends on the intrinsic physical/chemical properties of each compound, including vapor pressure and solubility in various media (i.e., water or organic solvents, etc.). In addition, certain attributes of the manufacturing and generating procedures (e.g., the temperature of the effluent) can influence chemical speciation of stack releases. Highly volatile substances can more

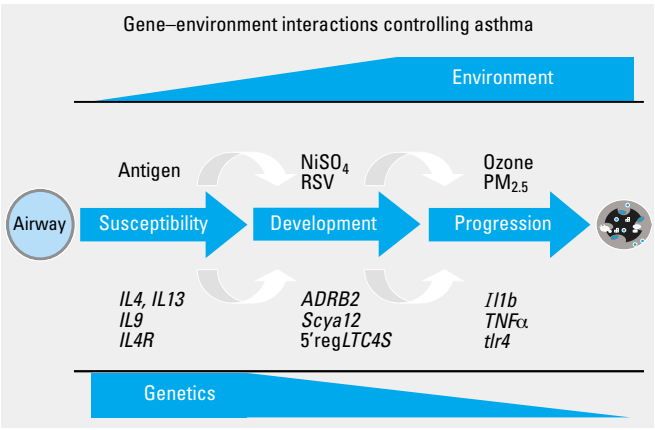

Figure 4. Gene–environment interactions in asthma. (*Top*) Susceptibility to asthma can progress with the exposure to antigen and development of immunity, with the exposure to additional antigenic and irritating compounds such as nickel sulfate ($NiSO_4$), or during respiratory [e.g., respiratory syncytial viral (RSV)] infections or exacerbated by irritants (acrolein and $PM_{2.5}$). (*Bottom*) Candidate genes have been identified through linkage analysis conducted with isolated human populations and with inbred mouse studies that are likely to influence the progression of asthma. These include interleukins (e.g., IL4, IL9, IL13) and their receptors [e.g., the IL4 receptor (IL4R)], which influence the initiation of sensitization and immunoglobulin production. Following this, the development of asthma may be influenced by polymorphisms in the β-adrenergic receptor (subtype B2, ADRB2), small inducible cytokine 12 (Scya12, or MCP-5), and the 5′ regulator region of leukotriene C4 synthase (5′regLTC4S). Last, polymorphic genes such as IL-1β (Il1b), tumor necrosis factor-α (TNFα), and the toll-like receptor-4 (tlr4) may go on to influence exacerbations that lead to progression of the disease.

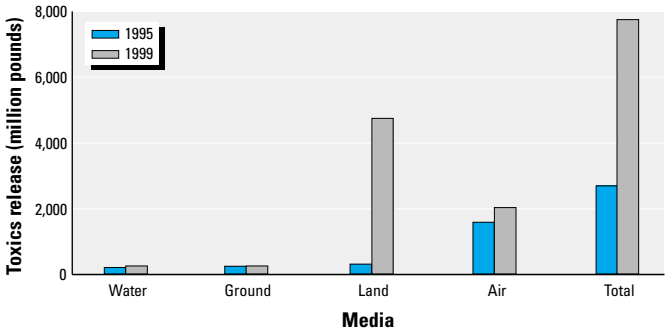

Figure 5. Hazardous air pollutants release into various media from the U.S. EPA 1995 and 1999 Toxic Release Inventories (*341*). Air emissions (which include fugitive air emissions and release into stacks) were a major source of release in 1995, making up more than 70% of the total. In 1999, release of hazardous air pollutants into land increased mainly because of additional reporting from landfills and onsite mining; release into the air remained a large source of release. *Water* is material discharged to streams, rivers, lakes, oceans, and other bodies of water, including releases from contained sources, such as industrial process outflow pipes or open trenches and storm water runoff. *Ground* is material placed by underground injection or the subsurface emplacement of fluids through wells, most often associated with manufacturing, petroleum, mining, commercial, and service industries and federal and municipal government activities. *Land* is material disposed to onsite (within the boundaries of the reporting facility) landfills (buried waste), land treatment/application farming (applied to or incorporated into soil), surface impoundments (uncovered holding areas used to volatilize and/or settle materials), other disposal methods (such as waste piles), or releases to land (such as spills or leaks). *Air* (total air emissions) is the sum of fugitive and stack air material release. Fugitive air emissions are releases not released through a confined air stream and equipment leaks, evaporative losses from surface impoundments and spills, and releases from building ventilation systems. Stack air (point) source emissions occur through placement into confined air streams such as stacks, vents, ducts, or pipes.

readily escape into the ambient air and thus cause added concern.

Emission inventories for HAPs indicate that release into the air is the principal route by which these materials enter the environment. Total air emissions from stationary sources include fugitive emissions (e.g., loses due to vaporization) and emissions through stacks, which are the greatest source of release (Figure 6). Note that many states that produce the largest amounts of HAP emission, such as Ohio and North Carolina, are not as populated as are larger states, such as New York and California, suggesting that controls could have significant impact. Many of the HAP compounds persist in the air by processes that dominate the formation of the urban aerosol. Urban aerosols have been chemically characterized only to a limited extent in the past (*99–106*). However, the standard for PM_{10} overlaps with specific HAPs because particles in this size range and smaller often derive from anthropogenic sources, whereas larger particles (≥10 μm) arise from natural sources (e.g., sea salt, soil, etc.).

Another route involves formation through secondary reactions in the atmosphere. For example, several reactive hydrocarbons are formed during combustion and can accumulate in the atmosphere (*111–115*). These compounds are contained in urban photo-oxidant plumes and contribute to ozone formation. Because ozone formation depends on reactive hydrocarbon species (e.g., aldehydes), the continuous measurement of ozone concentrations could be useful in estimating the ambient concentrations of precursors that include HAPs. Interestingly, once inhaled, ozone is likely to react with unsaturated fatty acids in the airway lining fluid or the cell membranes to form aldehydes, hydroxyhydroperoxides, and hydrogen peroxide (*116,117*). These intermediates are HAPs and can activate mediator release from human airway epithelial cells, thereby linking the biochemical outcomes of ozone with these compounds (*118,119*). The source of these types of HAPs is mixed. Urban activities including automotive transit, power generation, manufacturing, solvent use, and wood burning affect the formation and release of these compounds. Limiting ozone precursors (hydrocarbons and nitrogen oxides) could limit indirectly the entry of certain HAP compounds into the atmosphere in the future.

Besides direct release into the air and secondary formation, volatile HAPs can enter the atmosphere through intermediate transport. Even though a chemical is released initially into water, soil, sediment, or biota, if volatile it will enter the atmosphere eventually through evaporation from water or soil. For example, organic compounds with low or modest solubility in water will partition to the air–liquid interface after an initial dispersion as an emulsion in a factory effluent stream; thus, continuous and sole discharge into water can unexpectedly generate significant air concentration, as revealed in fugacity models (*120,121*). Movement from the air into other media and back again suggests equilibrium can be achieved or predicted. However, uniform dispersion is unlikely in any compartment in real-world situations and further adds uncertainty in estimating degradation rates in each compartment. This unpredicted routing could partially explain why airshed models that depend solely or heavily on air emission inventories have underestimated ambient concentrations.

Dominated by proximity to point sources, intermittent exposure to HAPs in high concentrations can depend on regional meteorology, atmospheric dispersion, transport, and removal. This type of exposure is difficult to monitor or model. Source–receptor analysis is therefore valuable. One element in source–receptor analysis is the identification of sensitive receptors in the population downwind from a point source. Because persons with asthma constitute approximately 4–10% of the residents of urban areas (*122,123*), this group remains one of the largest target populations and needs further consideration in evaluation of risks associated with exposures that could enter the neighborhoods near emissions sources.

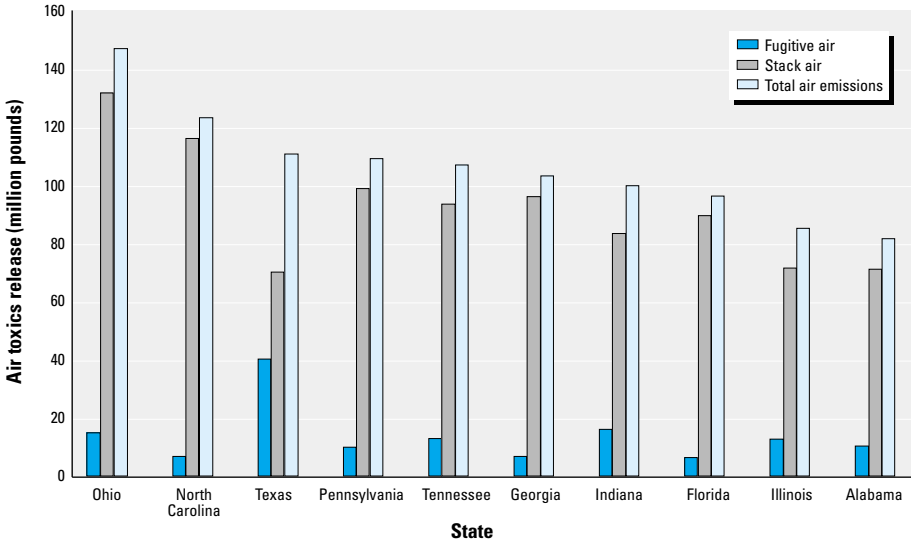

Figure 6. The 10 leading states in air emissions of hazardous air pollutants in 1999. Total air emissions are the sum of fugitive and stack air material release. Fugitive air emissions are material not released through a confined air stream but released through equipment leaks, through evaporative losses from surface impoundments and spills, and from building ventilation systems. Stack air (point) source emissions occur through placement into confined air streams such as stacks, vents, ducts, or pipes. In most states the stack effluent greatly exceeds the fugitive air release (*341*).

Threshold Concentrations That Induce Asthma

Unlike many environmental agents that have been tested only in laboratory animals (e.g., compounds associated with lung cancer), human health effects of many of the chemicals that produce asthma have been readily identified. Many HAPs are known to produce asthma in industrial settings, and much has been learned about these chemicals (asthmagens) from the occupational experience. In these settings, exposures can still be difficult to quantify; nonetheless, causal associations can be demonstrated more easily because removal from the occupational setting can lead to improvement of symptoms.

For example, polyisocyanate-induced asthma clearly has been attributed to exposure in the workplace. Historically, approximately 5–10% of all workers exposed to toluene diisocyanate, other polyisocyanates, or their monomeric precursors develop occupational asthma (*6*). This condition typically develops after several years of occupational exposure, which indicates a latency period when exposures are occurring while subjects are asymptomatic.

In occupational settings, control strategies are designed to reduce exposure concentrations below threshold limit values (TLVs) and thereby prevent adverse health effects. Presently, we often have little quantitative information for chemicals that have been associated qualitatively with occupational asthma. We do not yet have mathematical models that predict the relationship between overt signs and the dose, concentration, and duration of exposure. Past experience indicates that levels of exposure that induce asthma vary among individuals. Nonetheless, current occupational

standards assume that a threshold dose can be established at which no additional cases of asthma will develop. However, this assumption may be flawed because initiation of occupational asthma has been noted among workers wearing respiratory protective equipment and when exposures met existing TLVs (*6*).

Investigations of airway hyperreactivity in laboratory animals might provide some insights into the issue of threshold dose. The temporal aspects of this relationship seem to be quite complex, for instance, the induction of hyperreactivity in guinea pigs exposed to formaldehyde and acrolein (*124*). In these studies, hyperreactivity initially was assessed by measurement of the dose of acetylcholine necessary to double pulmonary resistance after a 2-hr exposure. However, by extending exposure to 8 hr, an effect greater than predicted by a dose based on the concentration × time results from the 2-hr data was observed, suggesting that low-level exposure of prolonged duration may have greater consequences than predicted by acute exposure data. This would explain why some clinical studies with exposures of short duration (<4 hr) do not uncover effects at levels that are associated with pulmonary effects in epidemiologic studies.

Many of the HAPs are respiratory irritants. Irritants can uncover asthma (possibly among susceptible individuals) by a nonimmunospecific process. Several case histories have been reported, and have been termed reactive airways dysfunction syndrome (RADS) (*125*). The pathogenesis of this syndrome is speculative because exposures are examined retrospectively. Typically, patients without pre-existing respiratory complaints develop airway hyperreactivity shortly after an accidental exposure or an exposure in an area with no or poor ventilation. After this single high-level exposure, hyperreactivity and abnormal bronchial epithelial biopsies can persist for a year or longer (up to 12 years). Causative agents have varied greatly, but all are respiratory irritants and include chlorine (*126–128*), toluene diisocyanate (*129–131*), hydrazine (*125*), sulfur dioxide (*132,133*), acetic acid (*134*), and ammonia (*135,136*).

One attribute of RADS that differs from typical occupational asthma is the lack of a preceding latency period, because it is often initiated by a single exposure. Evidence suggests that atopy or asthma can predispose individuals to this syndrome (*137*). Therefore, it appears that hidden (symptom-free) asthma may be uncovered by environmental exposure to irritants. Persons with this syndrome often develop severe, progressive airway disease and subsequently develop responses to a wide range of agents (nonspecific airway hyperreactivity). Workers also report that symptoms are equivalent at home and at work (*137–142*). Because of a lack of exposure measurements during the initiating events, is it difficult to establish a threshold for this type of response; nonetheless, very high exposure levels are assumed to be responsible for these cases.

Threshold Concentrations That Might Exacerbate Pre-Existing Asthma

The concentration necessary to produce a multiphasic diminution of lung function in persons sensitive to an inhaled compound can be exquisitely low. A definitive feature of antigen-induced hypersensitivity is that effects are observed after exposure below the concentration that will cause bronchoconstriction in nonsensitized persons exposed in an identical manner (e.g., during clinical experiments). In dermal sensitization, an allergen is often effective at concentrations well below those that are irritating to nonsensitized subjects. This situation is well known among occupational physicians, but epidemiologic data of dose–response relationships in occupational settings are lacking and limited to anecdotal case histories. For instance, an individual with hypersensitivity to an antibiotic reportedly developed asthmatic bronchospasm the night after (delayed allergic response) a visit to the town where it was produced, although this individual never entered the manufacturing facility. Similarly, a toluene diisocyanate–sensitive patient was so reactive that he responded when walking in the neighborhood of a factory (*143*). Another rosin-sensitive worker became reactive to pine trees and even unheated rosins or turpentine (*144*). In addition, bronchoprovocation tests have been positive in previously sensitized workers after exposure to concentrations as low as the current limit of chemical detection (i.e., 7 pg/m^3 toluene diisocyanate) (*145–148*). Thus, once hypersensitivity has been initiated, the dose necessary to elicit subsequent response can be extremely low. In such cases any level of environmental exposure can be considered hazardous for these individuals. Thus, it is currently very difficult to attempt to set threshold doses [no observed effect levels (NOELs) useful in determining reference concentrations (Rfcs)] for this susceptible population.

Exposure Assessment Using Probability-Based Sampling Procedures

Exposure assessment for HAPs is currently incomplete, but several strategies have been developed to reduce uncertainty. One approach is probability-based survey sampling procedures that combine questionnaires with multimedia and multipathway monitoring to estimate total personal exposure (*149–153*). An initial study by Whitmore et al. (*149*) assessed nonoccupational exposure to 32 pesticides by monitoring air outside and inside each home and analyzing drinking water, food, and dermal routes of exposure. Ten of the pesticides monitored are on the HAP listing, and other studies have found associations between the use of pesticides and asthma (*154–156*). In the study, four HAPs (chlordane, dichlorovos, heptachlor, propoxur) had greater inhalation than dietary exposure, with the air concentrations up to 20 times higher indoors than outdoors. Based on these estimates of personal exposure, Whitmore et al. (*149*) presented risk assessments for air exposure assuming a constant exposure over a 70-year lifetime and reference doses from the Integrated Risk Information System (IRIS) (*http://www.epa.gov/iris*) and other sources. The estimated inhalation risks were negligible (i.e., no-cancer-risk estimate was >1 × 10^{-6}) for all compounds except chlordane, although the chlorane risk estimate may be high because of the diminished use of this pesticide. Because indoor exposure may be due to past use in the home, considering the possible risk due solely to outside exposure is also important. Chlordane levels have been measured in Jacksonville, Florida, where the estimated outside air exposure levels equaled about 22 ng/m^3 (compared with 197 ng/m^3 indoors), or about 10% of that used in the above risk assessment estimate (*1*). Thus, because exposure to other HAPs also may be greater indoors than outdoors, accurate exposure assessment requires detailed analyses that involve total exposure evaluations. In addition, the Whitmore et al. study analyzed only two locations, and these findings may not be readily generalized to other regions and climates.

Estimates of Indoor Concentrations

In the past the U.S. EPA compiled a database of concentrations of volatile organic compounds (VOCs) measured indoors (*157*). Based on reports from 1979 through 1990, information was recorded on more than 220 compounds ranging in molecular weight from 30 to 446 Da. The 10 compounds most frequently found in reports of poor indoor air quality included formaldehyde, toluene, trichlorobenzene, ethylbenzene, 1,4-dichlorobenzene, acetaldehyde, tetrachloroethylene, trichloroethylene, benzene, and xylenes. Thirteen other HAPs most frequently measured indoors include methylene chloride, carbon tetrachloride, naphthalene, *n*-hexanes, chloroform, 2-butanone, pentachlorobenzene, styrene, chlorobenzene, trichlorobenzene, *N*-nitrosodimethylamine, quinolone, and hexachlorobenzene. In most incidences, the odor threshold for each compound (except formaldehyde) was typically orders of

magnitude higher than measured values, even when the lowest odor threshold value is considered, indicating that human exposure and complaints frequently occur when the odor is imperceptible. Complementary to this observation is the likelihood that olfactory detection indicates high exposures, because odor thresholds for many of these compounds are well above reference exposure guidelines. Because complaints of malodorous emissions are common outdoors near point sources, this comparison suggests that local exposures can be significant.

An earlier study used a total exposure assessment methodology (TEAM) (*158,159*) to examine numerous compounds, including 20 VOCs in personal air, outdoor air, expired breath, and drinking water. The median concentrations in the breath of 10 of the more prevalent compounds ranged from 0.4 (styrene) to 56.0 (benzene) μg/m^3. This list also included other HAPs (trichloroethane, xylenes, tetrachloroethylene, ethylbenzene, dichlorobenzene, chloroform, trichloroethylene, and carbon tetrachloride). Personal concentrations vary more among individuals and often exceed outdoor concentrations by a factor of 2 or more in New Jersey, and by a factor of 5–10 in North Carolina and North Dakota (*1*). This suggests that indoor sources or personal activities are of greater significance than outdoor sources. In addition, the distributions of the measurements were skewed, with geometric standard deviations ranging from 2.5 to 3.5, which means the range of the concentrations usually exceeded a factor of 100–1,000. Proximity to point sources (defined as 1.5 km from a suspected source) was stratified and had little influence on air or breath measurements. In contrast, personal activities, including occupation, smoking or living with a smoker (increasing expired benzene, styrene, ethylbenzene, and other aromatic hydrocarbons), filling a gas tank (doubling expired benzene), and visiting a dry cleaner or wearing dry-cleaned clothing (increasing expired trichloroethylene with a half-life of 20 hr), significantly contributed to the levels of certain compounds measured in expired breath. An assessment of the source of irritant VOCs in New Jersey resembled that found for automobile exhaust, gasoline vapor, or ETS for personal exposures, and automobile exhaust or gasoline vapors for outdoor concentrations (*159*).

Recently, the Centers for Disease Control and Prevention's National Center for Environmental Health presented an estimate of the U.S. population's exposure to 27 chemicals (determined by measuring compounds or their metabolites in blood or urine) (*160*). Analyses were conducted on data from a portion of the population from the National Health and Nutrition Examination Survey (NHANES) for 1999, conducted in 12 locations across the country. The chemicals measured included 13 metals (antimony, barium, beryllium, cadmium, cesium, cobalt, lead, mercury, molybdenum, platinum, thallium, tungsten, and uranium), cotinine (a marker of tobacco smoke exposure), and organophosphate pesticide and phthalate metabolites. Urine metabolites of pesticides measured included chlorpyrifos, diazinon, fenthion, malathion, parathion, disulfoton, phosmet, phorate, temephos, methyl parathion, and dimethyl-, dimethylthio-, diethyl-, diethylthio-, and diethyldithiophosphate. Urine metabolites of seven monophthalates included benzyl, butyl, cyclohexyl, ethyl, 2-ethylhexyl, isononyl, and *n*-octyl phthalate. Although this is only an initial database for future comparison, 1999 serum cotinine levels for nonsmokers decreased by about 75% from the levels measured in 1991, indicating a reduction in exposure of the U.S. population to ETS. In addition, more than half of youths in the NHANES study continue to have measurable cotinine levels. Likewise, the population's exposure to lead decreased in 1999. These decreases have been observed for many years dating back to the 1976 NHANES surveys.

In previous investigations of indoor air quality, Molhave and colleagues (*161–165*) measured the concentrations of total VOCs in older dwellings (200–1,700 μg/m^3), which were typically lower than that in new homes (500–19,000 μg/m^3); complaints were more frequent when levels exceeded 1,700 μg/m^3. Excluding carcinogens, a mixture of 22 compounds was prepared that included 10 substances most frequently present in the atmosphere in new homes and 10 substances in greatest concentrations in nonindustrial buildings in which complaints had been recorded about quality of the indoor air. The relative amount of each compound was prepared in proportion to a single concentration as measured by a flame ionization detector calibrated with a single reference compound, toluene. To investigate whether these compounds influenced pulmonary functions among persons with asthma, subjects were exposed for 1.5 hr to concentrations of 2.5 and 25 mg/m^3 total VOCs (*165*). The higher concentration, 25 mg/m^3, produced mild to moderate bronchoconstriction (10% decrease in $FEV_{1.0}$). Individual responses varied, with bronchoconstriction more pronounced in individuals with the greatest baseline airway hyperreactivity. The effect of 2.5 mg/m^3 was not distinguishable from control. Subjective measures of discomfort (odor and eye, nose, or throat irritation) first increased and then diminished during exposure, suggesting acclimatization, and these responses were similar in magnitude to those noted in previous studies with healthy subjects (*163*). Using a similar VOCs mixture, Koren and Delvin (*166*) also noted an increase in nasal inflammatory cells in lavage fluid immediately and 18 hr after a 4-hr exposure to 25 mg/m^3. More recently, persons with asthma were found to have decreases in forced expiratory flow rates after a 4-hr exposure to 50 mg/m^3, although this concentration was without effect in control subjects (*167*). These findings are consistent with reports of symptoms among persons exposed to VOCs in indoor environments (*168–171*). From these studies (*161–165*), Molhave has suggested the following guidelines in nonindustrial settings: At total VOC levels of <200 μg/m^3, no discomfort from odor, eye, nose, or throat irritation or headache is likely, whereas at >3,000 μg/m^3, complaints have occurred in most investigated buildings; at >5,000 μg/m^3, objective measures of upper respiratory tract irritation increase markedly.

Epidemiologic information on the respiratory effects of environmental VOCs exposure is limited (*172,173*). A study of Kanawha Valley, West Virginia, found an association between exposure and respiratory symptoms among schoolchildren (third and fifth graders) (*173*). The Kanawha Valley was selected because it contains several chemical-manufacturing plants within a valley topography that can confine atmospheric mixing. Exposures were categorized by school location (in or out of the valley and near or far from an industrial site) and by the sum of the concentrations of 5 petroleum-related chemicals (i.e., benzene, toluene, *m,p*-xylene, *o*-xylene, and decane) or 10 manufacturing process–related chemicals (i.e., butanol, carbon tetrachloride, chloroform, 1,2-dichloroethane, 2-ethoxyethyl acetate, methyl isobutyl ketone, mesityl oxide, perchloroethylene, styrene, and 1,1,1-trichloroethane) measured at 74 elementary schools. The concentrations of petroleum-related compounds (mean ± SD, 19 ± 22 μg/m^3; maximum, 154 μg/m^3, with about half that contributed by toluene) were higher than the concentrations of manufacturing process–related compounds (mean ± SD, 4.6 ± 1.7 μg/m^3; maximum, 13 μg/m^3, with about half that contributed by a mixture of trichloroethane and chloroform).

Exposure (measured as concentrations or proximity to source) was associated with increased incidence of chronic lower respiratory symptoms, and children enrolled in schools within the valley had higher rates of doctor-diagnosed asthma. Other potential confounders (e.g., parental smoking and familial socioeconomic status) associated

weakly with health outcomes and proximity to sites. Adjusting for these variables, the association of chronic airway responses important to asthma and exposure was still evident. Although the Kanawha Valley is somewhat unusual in that it has several chemical manufacturing sources, the levels of air pollutants in this area are not very different from those at other sites in the United States (*105,174*).

Several differences exist between the findings from VOCs exposure in the controlled human experiments and those in the epidemiologic Kanawha Valley Health Study. The most obvious difference is in the concentrations producing responses. In the controlled exposure study, no response was observed at 2,500 μg/m^3, whereas lung function decreased at 25,000 μg/m^3. In contrast, total VOCs concentrations in the Kanawha Valley were about 25 μg/m^3. However, the populations (adults vs. children), the nature of the response (acute bronchoconstriction vs. chronic symptoms and diagnosed asthma), and the length of exposure (1.5 hr vs. continuous) are different. These findings suggest that threshold concentrations (lowest concentration at which measurable effects occur) observed in epidemiologic studies are below those in clinical studies.

Community exposure to another HAP, toluene diisocyanate, also has been investigated among individuals living near a polyurethane foam manufacturing facility (*175*). Ambient air sampling near the plant indicated the presence of toluene diisocyanate. Ten (9%) of 113 residents examined also had elevated serum levels of diisocyanate-specific antibodies (IgE or IgG). Exposure histories of antibody-positive individuals ruled out occupational exposure or the use of diisocyanate-containing consumer products, suggesting that ambient air exposure may be responsible for the positive antibody responses detected in some residents of the community. [These findings are relevant to case reports of individuals developing symptoms to toluene diisocyanate after brief exposures (*147*).]

Health Effects Assessment

Criteria Pollutants and Mortality/Morbidity

Mounting epidemiologic evidence continues to associate air pollution with numerous adverse health effects, including mortality (cardiopulmonary disease and possibly cancer) and morbidity (*53,64,66,72,83,95, 172,174,176–190*). Altered respiratory symptoms (e.g., chest tightness, coughing, shortness of breath, wheezing), altered pulmonary function (e.g., $FEV_{1.0}$ or PEFR diminutions), bronchodilator usage, school or work absence, and hospital admissions for asthma increase in association with exposures to air pollution. Although local sources are difficult to evaluate rigorously, and long-range transport is recognized to influence ambient concentrations, local sources can augment adverse effects. For example, the Harvard Six-Cities study found higher mortality in Steubenville, Ohio, and St. Louis, Missouri, locations where the air quality is influenced more by regional stationary sources mixed with long-range transport processes, than in Watertown, Massachusetts, or Kingston/Harriman, Tennessee, locations influenced almost solely by long-range transport processes (*83,183*). These and several other epidemiologic studies have focused on criteria pollutants, with the strongest associations often observed with fine particulate matter.

Because air pollution is a complex mixture, several investigators have postulated that any single exposure variable cannot be solely responsible for observed adverse effects (*83,104,178–181*). Thus, measurements of criteria pollutants also may serve as exposure surrogates for a complex mixture of criteria pollutants mixed with regional HAPs. Detailed chemical analyses of particulate matter vary significantly from location to location, and data are limited (*100,104, 191,192*). Typical analyses of particles in the 2.5- to 10-μm fraction are dominated by reentrained road dust (containing soil particles, engine oil, metals, tire particles, sulfates and nitrates) and construction and wind-blown dusts (mostly soil particles). At or below 2.5 μm, the chemical signatures are primarily generated by products from combustion, condensation, and coagulation of gases and ultrafine particles produced by traffic, coal combustion, and metal, oil, and chemical manufacturing (*70,95*).

ETS, HAPs, and Asthma

Children with mothers who smoke experience increased severity and frequency (additional episodes) of asthma episodes and diminished lung function, even at low doses (*193–205*). ETS is a mixture of exhaled mainstream and sidestream smoke consisting of over 4,000 chemicals. ETS contains several human respiratory carcinogens (including benzo[*a*]pyrene, benz[*a*]anthracene, other polycyclic aromatic hydrocarbons, 4-aminobiphenyl, and nitrosadimethylamine and irritants (including formaldehyde, acrolein, other aldehydes, cadmium, and other metals) (*196*). Twenty-nine of the 49 major components in ETS are HAPs (*1*).

Indoor $PM_{2.5}$ levels are typically elevated by 2–5 μg/m^3 per cigarette smoked (*194–196*). Background indoor $PM_{2.5}$ levels vary depending on other indoor aerosol sources and the amount of penetration of the ambient aerosol [often substantial (50–80%) for particles in this size range], and typically are 15 μg/m^3 (*1,100*). Smoking can produce $PM_{2.5}$ levels of about 40 μg/m^3 (ranging from 18 to 95 μg/m^3) (*196,206,207*). Asthma among children has been noted when mothers smoke 10 or more cigarettes per day (*208,209*). Applying the relationship between cigarettes smoked and $PM_{2.5}$ developed by Leaderer et al. (*196*), 10 cigarettes could generate an atmosphere containing 20–50 μg/m^3 $PM_{2.5}$ above background and result in total exposures of approximately 35–65 μg/m^3. Exposures in this range have been estimated to induce 8,000–26,000 new cases of asthma annually (based on estimates of maternal smoking). Exposures to HAPs when mixed with particulate load in this range could adversely affect persons with asthma.

Another study supporting the relationship between ETS generated by mothers and respiratory symptoms (wheeze, etc.) associated with childhood asthma indicated that symptoms increase with the amount of maternal smoking (*210*). Again, the threshold level of smoking for adverse responses was at relatively low exposures of 1–4 or 5–14 cigarettes per day. Applying the estimates of $PM_{2.5}$ produced by this level of smoking (*196*), an additional 2–20 μg/m^3 or 17–35 μg/m^3, respectively, would be added to background levels. A study of higher levels of smoking reported that exposures to >20 cigarettes/day (or 40–100 μg/m^3) produces 3.6 times more bronchial hyperreactivity, a characteristic sign of asthma (*211*).

Because maternal smoking has a greater effect than paternal smoking, it also may influence asthma *in utero* by limiting lung development (*197–205,212–214*). In addition, average concentrations of room air samples may underpredict the levels in a child's breathing zone because mothers often hold their small children. This proximity could result in complex exposure patterns of intermittent high-level exposures of short duration. Conversely, older children spend less time at home or in a room with a parent who smokes. Exposure patterns to HAPs also may be intermittent, with wide variances in concentration. Time–activity information would be useful in predicting individual exposures by combining microenvironmental concentration information with duration of exposure obtained from time–activity analyses.

Although combustion is a major source of compounds in both ETS and HAP, the physical and chemical properties of ETS differ from those of the ambient mixture of gaseous and particulate HAPs. HAPs account for most of the toxicity of ETS because most respiratory irritants that are contained in ETS are HAPs (Table 4). The levels of HAPs present in ETS are greater than in urban air, however. The particle size also may differ: particles in freshly

Table 4. Concentration of hazardous air pollutants found in mainstream cigarette smoke (*195*).

>100 µg/cigarette in mainstream smoke	
Acetaldehyde[a]	Methyl chloride
Catechol	Phenol
Hydroquinone	Toluene
100 > *x* > 10 µg/cigarette	
Acrolein[a]	Formaldehyde[a]
Benzene[a]	Propionaldehyde
1,3-Butadiene[a]	Quinoline[a]
Carbonyl sulfide	Styrene
Cresols	
<10 µg/cigarette	
4-Aminobiphenyl	*N*-Nitrosodiethanolamine
Aniline	*N*-Nitrosodimethylamine
Cadmium[a]	Polonium-210
Chromium[a]	Polycylic aromatic hydrocarbons[a]
Dioxins[a]	Benz[*a*]anthracene
Hydrazine[a]	Benzo[*a*]pyrene
Nickel[a]	2-Toluidine

[a]Compounds listed as hazardous air pollutants.

generated ETS are <1.0 µm [sidestream smoke particles are typically 0.001–1.0 µm, and mainstream smoke particles are 0.1–1.0 µm in diameter (*215*)], whereas the cutoff diameter of ambient aerosol containing HAPs is 2.5 µm ($PM_{2.5}$). Besides mass concentration (i.e., µg/m^3), certain aspects of particulate toxicity depend on the particle number and surface area (*216–218*). Because mass depends on particle volume, small increases in diameter in this range can have large influences on the reduction in number of particles. Thus, particles between 1.0 and 2.5 µm add greatly to the mass estimates of HAPs in air. Nonetheless, ambient $PM_{2.5}$ concentrations of 11 and 30 µg/m^3 and PM_{10} of 18 and 47 µg/m^3 have been associated with increases in cardiovascular and respiratory disease (*83–85,219–222*).

Evaluating Human Exposure and Its Relationship to Asthma

Induced airflow obstruction (decreased expiratory flow and reversed by adrenergic therapy) after direct exposure in a clinical setting is an operational method to detect occupational asthma (*6,143,223*). Common asthmagens identifiable by this method include metals such as cadmium (*224,225*), chromium (*226,229*), cobalt (*230–233*), and nickel (*234–239*) compounds. This method is aided by knowledge of the chemicals present in the workplace and the reversal of symptoms upon removal from the workplace. However, this approach is impractical to completely evaluate 189 compounds.

An asthmagen can be defined as a compound that evokes asthma symptoms through immunologic mechanisms and has documented case reports in the medical literature associating exposure with asthma (an inducer of asthma). Table 5 lists HAPs that fit this definition, including several anhydrides, isocyanates, metals, and inorganic and organic compounds. The threshold concentration needed to produce bronchospasms can be below that necessary to induce (nonimmunospecific) irritation, and thus immunologic mechanisms are suspected. This often involves the development of specific immunoglobulins (e.g., specific IgE) that can be confirmed by skin prick tests or lymphocyte expansion assays.

Table 5. Hazardous air pollutants that can exacerbate or induce asthma.

Chemical class	Compound[a]	Reference
Aldehydes	Acetaldehyde[b]	(*33,343,344*)
	Acrolein[b]	(*124,343,389–394*)
	Formaldehyde[b]	(*124,169,343,395–403*)
	Propionaldehyde	(*395,398*)
Anhydrides	*Maleic anhydride*	(*404,405*)
	Phthalic anhydride	(*405–408*)
Isocyanates	*Hexamethylene-1,6-diisocyanate*	(*146,409–411*)
	Methylene diphenyl diisocyanate	(*277,412–415*)
	Methyl isocyanate	(*146,416–421*)
	Toluene diisocyanate	(*129–131,143,145–148,175,306,307,422*)
Metals	Cadmium compounds[b]	(*217,224,225,346*)
	Chromium compounds[b]	(*226–229,235,239,350*)
	Cobalt compounds	(*230–233,350*)
	Manganese compounds[b]	(*223,423–425*)
	Nickel compounds[b]	(*234–239,337,426–433*)
Other compounds	Carbaryl	(*434–436*)
	Chlorine	(*126–128,437–448*)
	Coke oven emissions[b]	(*449–451*)
	Diazomethane	(*452*)
	Diethanolamine	(*453,454*)
	Ethylene imine (aziridine)	(*455,456*)
	Ethylene oxide[b]	(*457–459*)
	Hydrochloric acid	(*460–465*)
	Methyl methylacrylate	(*466–468*)
	Styrene	(*334–336*)

[a]Compounds in italics have case reports of occupational asthma resulting from exposure (inducers); nonitalic compounds are irritants that can augment symptoms in persons with asthma (exacerbators). [b]Compounds on list of 33 hazardous air pollutants of greatest concern (Table 1).

Although several occupational asthmagens have been identified through their immunologic mechanism, this is not always the case. Therefore, compounds that do not produce full antibody-mediated responses should be excluded cautiously. For this reason, Table 5 also includes several compounds that lack clear evidence of a specific immunologic response (i.e., identification of specific IgE) but have been associated with occupational asthma. These compounds can be considered exacerbators of asthma. Other members of this list are substances (acting like sulfur dioxide and perhaps ozone) that may not produce antigenic responses but still provoke bronchoconstriction in persons with asthma at concentrations that are lower than those that are bronchoconstrictive in healthy subjects. These chemicals act as irritants and induce airway epithelial injury and inflammation, effects that can be barely perceived at doses in the range occurring in ambient environments. Released from stationary sources, such HAPs can mix with other toxic chemicals in the urban air or may add to the irritant load indirectly through photochemical processes to contribute to the total irritant load of ambient air.

Insufficient scientific data exist to evaluate the immunologic potential of many of the compounds of interest. In addition, limiting the definition of asthma to antigenic responses is difficult, and several chemicals have not been clinically tested to determine whether they can cause or exacerbate asthma (*240–245*). Therefore, an assessment of the toxicity of these compounds must also include consideration of the chemical properties of HAPs. Properties important to this question included those chemical and physical attributes that influence airway dosimetry (respirability), irritancy, and reactivity with biological macromolecules. Based on these attributes, several additional compounds contained on the list of 189 HAPs could be suspected of exacerbating asthma, but it is unclear whether they can induce persistent asthma (Table 6). Respiratory irritants with wide-scale usage in this list include hydrogen fluoride, hydrogen sulfide, phosgene, and phosphene. These compounds are known irritants to the respiratory tract and in some cases have been responsible for community air pollution episodes involving accidental emissions (e.g., rail car derailments).

Adding to the difficulty of this evaluation are the uncertainties created by the gaps in the literature regarding the human toxicity of each compound. Nonetheless, the limited human experience must be considered

Table 6. Other hazardous air pollutants suspected of being respiratory tract irritants that may exacerbate asthma.

Compound	Reference
Benzene	(*158,159,469–473*)
Caprolactam	(*474–476*)
bis-Chloromethyl methyl ether	(*477–479*)
1,2-Dibromo-3-chloropropane	(*480*)
Dibutyl phthalate	(*481–484*)
Dimethyl sulfate	(*485–487*)
Hydrazine[a]	(*488–490*)
Hydrogen fluoride	(*463,491–493*)
Hydrogen sulfide	(*494–499*)
Mercury and compounds[a]	(*500–508*)
Phosgene	(*509–511*)
Phosphine	(*512,513*)
Trichlorophenol	(*514*)

[a]Compounds on list of 33 hazardous air pollutants of greatest concern (Table 1).

Table 7. Release inventory of Hazardous air pollutants that induce asthma. Compounds are listed in order of release into air, from 1999 toxics release inventory.[a]

Compound	No. of Facilities	Total release (thousand pounds)	Total air release (thousand pounds)	Change since 1995
Styrene	1,637	57,516	54,744	Increase
Chlorine	1,234	50,037	49,371	Decrease
Methyl methylacrylate	309	5,016	4,367	New
Nickel compounds[b]	1,373	70,334	1,191	Increase
Chromium compounds[b]	1,774	174,487	748	Increase
Ethylene oxide[b]	148	558	483	New
Maleic anhydride	374	451	379	Decrease
Diethanolamine	414	1,116	374	New
Diisocyanate	1,373	2,280	355	New
Phthalic anhydride	159	3,245	277	Decrease
Cobalt compounds	440	16,427	79	Increase
Toluene diisocyanate	183	74	35	Decrease
Ethylene imine (aziridine)	3	163	10	New
Diazomethane	—	> 1	> 1	New
Methyl isocyanate	5	> 1	> 1	Decrease
Coke oven emissions[b]	—	—	—	New
Subtotal (listed compounds)	3,295	245,379	2,422	—
Total	9,426	381,705	112,414	—

[a]Data from U.S. EPA (*341*). [b]Compounds on list of 33 hazardous air pollutants of greatest concern (Table 1).

in developing logical strategies to assess possible links between environmental exposure to these compounds and asthma. This second group of compounds suspected of exacerbating asthma includes skin allergens (compounds producing allergic contact dermatitis) with chemical properties that suggest inhalation as a route of exposure (*246,247*).

In addition, other compounds known to react covalently with proteins or DNA include polycyclic aromatics/aryl epoxides, *bis*-chloromethyl methyl ether, dimethyl carbonyl chloride, dimethyl sulfate, and β-propiolactone. These compounds can act directly by forming specific immunoglobulin complexes or indirectly by forming haptens or other antigenic determinants to produce adverse responses in the airways (*248–250*). Carcinogenic compounds can cause irritation and inflammation at sites of exposure and are often antigenic (*251–259*). Respiratory carcinogens (or suspected carcinogens) include antimony compounds (*260–263*), arsenic compounds (*263–268*), hexamethylphosphoramide (*269,270*), 4,4′-methylene-bis(2-chloroaniline) (*271,272*), bromoform (*273,274*), methylene chloride (*275*), 4,4′-methylenedianiline (*276,277*), nitrobenzene (mice) (*278–280*), 4-nitrobiphenyl (*281*), 2-nitropropane (*282–285*), *N*-nitroso-*N*-methylurea (*286*), *N*-nitrosodimethylamine (*287–290*), *N*-nitrosomorpholine (*291–293*), pentachlorophenol (mice) (*294,295*), polycyclic aromatic hydrocarbons (*250,254,255*), 1,3-propane sultone (*296,297*), propylene oxide (*298–300*), 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (*301–305*), 2,4-toluene diamine (*306,307*), vinyl acetate (*308,309*), vinyl chloride (*310–317*), and vinylidene chloride (*311,318–321*). Unlike the compounds in Table 5 that are known to induce asthma in occupational settings, several of these suspected carcinogens (e.g., bromoform, 4,4′-methylenedianiline, pentachlorophenol propylene oxide, vinyl acetate) only have evidence in laboratory animal studies. Interestingly, some of these compounds induce skin irritation or sensitization (e.g., dimethylbenz[*a*]anthracene, 4,4′-methylenedianiline, and TCDD). Relevant to this relationship are the associations of DEPs with augmented sensitization and airway responsiveness (*32,34–40*) and possibly lung tumors, noted only in rats (*322–332*). In addition, toluene diamine is a metabolite of toluene diisocyanate (*307*), a potent asthmagen, and thereby links, in principal, reactive intermediates of carcinogens with asthma. However, carcinogens may also be immune suppressive (*254,333*), so this relationship is likely to be complex (specific for dose and compound) and must be viewed with caution.

The VOCs listed in Tables 5 and 6 are limited to aldehydes, benzene, and styrene (*334–336*). Benzene is included because it has been associated with asthma exacerbation (although the major concern with this compound is carcinogenesis). In the ambient atmosphere, benzene levels may indicate proximity to traffic and thereby indicate exposure to mobile source emissions. As noted above, VOCs have been associated with increased asthma symptoms in controlled human studies (*157–168*) and epidemiologic studies (*169–171,173*). However, because these studies measured exposures to mixtures and because many of the compounds listed have not been associated with asthma or other respiratory effects, these compounds have not been included in this tentative list. Additional investigations of human exposures to these compounds separately and as mixtures are needed and are likely to yield additional insights into their possible role in inducing asthma. The literature review of other HAPs listed in Table 1 suggests that they may be of lesser concern. These compounds also may contribute (particularly as mixtures) to other serious health outcomes, and therefore including compounds for more immediate consideration should be based on these effects (e.g., 1,3-butadiene).

Estimates of the Magnitude of Asthmagens Release

Human exposure must be considered in evaluating the role of HAPs in asthma. Because air sampling is not routinely performed on each of these compounds, the lack of scientific information suggests caution. One approach is to consider the extent of occupational exposure as an indication of possible sources of emissions. Recently, Seta and co-workers (*337*) estimated that over 6 million workers are potentially exposed to chemical or metal asthmagens at industrial settings throughout the United States. (Potential exposure to polyisocyanates alone exceeded 110,000 workers.) These estimates have been supported by additional studies (*338,339*). Similarly, an estimated 720,000 people live near (<12.5 miles) primary nickel-emitting sources producing median ambient concentrations of 0.2 μg Ni/m^3, and 160 million people residing near nickel sources are estimated to receive median concentrations of 0.05 μg Ni/m^3 (*340*). At a minimum, this suggests that several emission sources can potentially contribute to community air pollution. Information on the level of current individual exposures of persons with asthma or the potential to develop asthma is limited and requires additional studies.

Another approach to estimate possible exposures is to consider the toxic (emissions) release inventories compiled annually by the U.S. EPA (*341,342*). Table 7 lists release inventories of compounds thought to have a role of inducing asthma.

Table 8. Release inventory of hazardous air pollutants suspected of exacerbating asthma.[a]

Compound	No. of facilities	Total release (thousand pounds)	Total air release (thousand pounds)	Change since 1995
Hydrochloric acid	1,497	668,696	666,193	New
Formaldehyde[b]	849	24142	12,409	Increase
Acetaldehyde[b]	283	12,942	11,944	Increase
Manganese compounds[b]	1,662	523,514	2,459	New
Propionaldehyde	27	542	426	Decrease
Acrolein[b]	29	377	204	Increase
Cadmium compounds[b]	127	12,086	49	Decrease
Hydrazine[b]	62	143	10	Decrease
Carbaryl	18	67	5	
Subtotal (listed compounds)	3,012	573,204	27,075	—
Total	4,544	1,242,509	693,699	—

[a]Data from U.S. EPA (*341*). [b]Compounds on list of 33 hazardous air pollutants of greatest concern (Table 1).

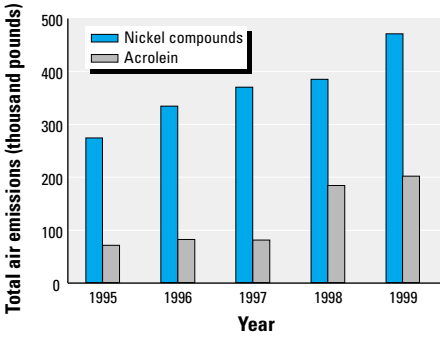

Figure 7. Trends in annual total air emissions release of nickel compounds and acrolein, which can either induce or exacerbate asthma and have been associated with estimated noncancer risks in the general population (*341*).

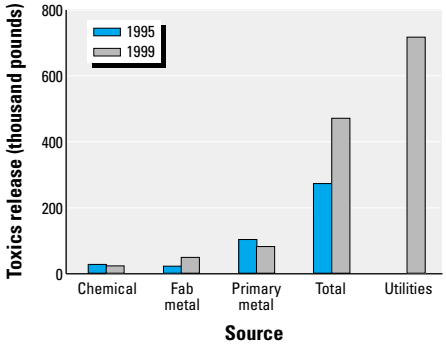

Figure 8. Trends in annual total air emissions release of nickel compounds for various industries. The total air emissions are the sum of fugitive and stack air emissions. In 1995, the larger sources included chemical, fabricating (Fab) metal, and primary metal industries (these industries combined = Total). The inventory total increased for 1999, using the same industry reporting as for 1995. In addition, starting in 1998, the emissions from electrical utilities were also included in nickel compound air releases, and in 1999 they exceeded the total of all other sources combined.

Each value listed under "total air release" is the sum of fugitive air and stack air releases. It does not include estimates of transport across media or other pathways that might result in inhalation exposures in the ambient air. Styrene, chlorine, methyl methylacrylate, and nickel and chromium compounds are among the chemicals with the greatest number of reporting sources and with the greatest amount of release.

Table 8 lists air release inventories for other HAPs that are mostly likely to exacerbate rather than induce asthma. The highest levels of release are reported for hydrochloric acid, formaldehyde, acetaldehyde, and manganese compounds—and to a lesser extent, acrolein. Acrolein is a potent respiratory tract irritant and, as for nickel compounds, emission inventories have increased slightly over time (Figure 7). In addition, the estimated release of most respiratory carcinogens that are suspected of influencing asthma is low. An exception is the release of polycyclic aromatic hydrocarbons that has been included since 1995 and from 1995 to 1999 increased from 434 to 1,339 thousand pounds (total air emissions). Accurately assessing the amount of polycyclic aromatic hydrocarbon is also difficult because a large portion is produced by combustion from mobile sources.

Emission inventories are, at best, only qualitative and may serve as indications of the magnitude of point sources. These estimates have not been validated by air sampling near point sources, and some airshed models using release inventories may underestimate the actual measured concentrations downwind from stationary sources. Any estimate of temporal increases or decreases has uncertainty because the number of reporting industries, the covered industry groups, and reporting requirements are not constant from year to year. For example, electrical utilities did not report total air emissions for nickel compounds before 1998. In 1999, electric utilities are a substantial source of nickel compound and released 718 thousand pounds, which is 1.5 times that of other sources combined (including chemical, 24; fabricated metal, 50; and primary metals, 82 thousand pounds) (Figure 8). Nonetheless, the large number of possible point sources indicates that extensive human exposure is possible.

In addition, predictions of ambient release and resulting exposure concentrations require applications of air quality dispersion models to chemical-specific data. Whether inventory data have enough fidelity for such applications is unclear. Nonetheless, models can be developed and estimates of noncancer risk using Rfcs can be determined. An important gap in the literature is whether cumulative effects result from multiple acute exposures at high levels, not reflected by these inventories. Release inventories present only estimates of annual averages and therefore lack detail for modeling elevated acute exposures.

Estimated Exposure Guidelines

Concentration guidelines for occupational and nonoccupational exposure have been developed by a number of agencies, including the American Conference of Governmental Industrial Hygienists (ACGIH), the U.S. EPA, and the California Environmental Protection Agency. Often, the assessment of nonoccupational exposure uses the current ACGIH TLVs for time-weighted averages for occupational exposures for a normal 8-hr workday and a 40-hr work week, to which nearly all workers can be repeatedly exposed day after day without adverse effects (*345*). Bronchoprovocation challenges typically start at these concentrations, and occupational asthma is often defined by a decrease in lung function occurring at or below these values. Robinson and Paxman (*346*) estimated that cancer risks at the median TLV-based ambient air guidelines exceed 1,000 cases per million exposed persons for cadmium (1,040), nickel and compounds (1,420), propylene oxide (1,550), coke oven emissions (1,860), benzene (2,500), and arsenic and its compounds (7,300). These investigators noted that TLVs are not designed to represent NOELs for regulatory purposes. Consequently, TLVs are unlikely to provide an adequate margin of safety for the general population.

Other attempts to design standards include the ambient air level goals developed by Calabrese and Kenyon (*347*). They calculated levels using NOELs or lowest observed effect levels corrected for lifetime exposure and divided by appropriate multiplicative uncertainty factors (as much as 1,000 over the NOEL). Using animal toxicity data, adjustments were made for the equivalent human breaching rates using species-specific equations and absorption factors.

The most commonly used values for noncancer risk assessment are the current U.S. EPA Rfcs (*http://www.epa.gov/ttn/atw/*). These values do not consider the possibility of induction or exacerbation of asthma specifically as a basis for chronic (noncancer) NOEL. Instead, each Rfc for most of these

Table 9. California Environmental Protection Agency chronic inhalation REL.[a]

Compound	REL (μg/m^3)
Acetaldehyde	9.0
Acrolein	0.02
Benzene	60
Chlorine	0.2
Dioxins	0.00004
Formaldehyde	3.0
Hydrogen chloride	9.0
Mercury compounds	0.09
Nickel compounds	0.05
Styrene	700
Toluene diisocyanate	0.095

[a]Data from *http://www.oehha.ca.gov/air/chronic_rels/pdf/relsP32k.pdf.*

Table 10. Chemicals contributing to noncancer hazard index derived from the Environmental Defense Fund National Scorecard.[a]

Compounds	Chemical hazard index	Cumulative hazard index	Population in areas
Acrolein	1.800	61%	175,358,109
Formaldehyde	0.410	14%	11,896,327
Diesel emissions	0.400	13%	11,635,229
Acetaldehyde	0.082	3%	311,276
Nickel	0.040	1%	231,063
Beryllium	0.036	1%	985,448
Chromium	0.029	1%	190,869
Benzene	0.023	1%	21

[a]Data from *http://www.scorecard.org/env-releases/def/hap_background.html.*
Definitions: chemical hazard index = the estimated concentration of a compound divided by its Reference Concentration based on a noncancer risk estimate model (may be useful for ranking purposes but are not necessarily predictive of any actual individual's risk of a specific outcome). Cumulative hazard index = the hazard index obtained by summing all UATs with noncancer effects in an area. Each UAT contributes its single chemical hazard index to the total. Environmental Defense's Scorecard calculates a cumulative index across all health effects, and also effect-specific hazard indices (for respiratory, immuno-, neurotoxicity, etc.). Population in areas = the number of people living in census tracts where compound's estimated concentration exceeds its reference concentration (hazard index is greater than one). This is an estimate of number of people exposed to levels of HAPs that exceed the Clean Air Act's noncancer risk goal.

compounds is selected primarily by the estimates of respiratory irritation. For example, formaldehyde's values are based on the data obtained on irritation, and not on the potential to induce asthma (*http://www.epa.gov/ttnatw01/urban/natpapp.pdf*). Because the diagnosis of occupational asthma involves pulmonary responses that are reported at or below the TLV, exacerbation of asthma can occur at doses of these compounds below those that induce irritation. Therefore, the TLV and NOEL do not always account for the exacerbation of existing asthma. Inasmuch as sensitization is more relevant when considering safeguarding a heterogeneous general population compared with an occupational population, these exposure guidelines should be considered tentative until further information can be obtained on the relationship between levels that produce irritation and asthma in industrial settings, and asthma in the nonoccupational settings.

Table 9 presents the current reference exposure levels (RELs) developed for California for certain HAPs (*348,349*). Exposure to each substance independently at or below these values is not expected to result in adverse (noncancer) health effects after estimated 1-hr maximum concentrations (acute) or annual average (chronic) for inhalation. To compare these values with the cancer unit risk, the latter must be multiplied by an exposure estimate (concentration × number of persons exposed). A major difference between these two values is that cancer unit risks are derived by linear extrapolation, assuming no threshold. In contrast, RELs assume a threshold (based on the NOEL presented by IRIS and other sources). One way to compare these values is to assume lifetime exposure of one million people to a concentration (in μg/m^3) equal to the cancer unit risk. For example, if a community of one million is exposed to 2.7 μg/m^3 acetaldehyde, control actions are recommended based on a cancer risk (rather than based on the chronic REL, which is 9.0 μg/m^3). Similarly, styrene exposures are limited more by the estimates for cancer risk than by the chronic REL. For many HAPs that have both a cancer unit risk and a chronic REL value (including acrolein, formaldehyde, nickel, and toluene diisocyanate), exposure is to be limited based more on the chronic noncancer effects.

Recently, Morello-Frosch and colleagues (*350*) modeled outdoor concentration estimates from the U.S. EPA's 1990 release inventories to characterize air toxics in California. Concentration estimates were used with chronic toxicity data to estimate cancer and noncancer hazards for individual compounds. Morello-Frosch et al. estimated 8,600 excess lifetime cancer cases, 70% of which were attributable to four pollutants: polycyclic organic matter, 1,3-butadiene, formaldehyde, and benzene. For noncancer effects, they estimated a total hazard index across census tracts and found that the greatest effects were primarily due to acrolein and chromium concentration estimates. However, the 1990 data are lower than the 1999 release inventories for these compounds. In addition, formaldehyde, methylene diphenyl diisocyanate, magnesium, cobalt, acetaldehyde, and hydrochloric acid contributed to the noncancer risk. Most of the estimated risk involved releases from area and mobile source emissions, although several locations in the state have point sources that account for a large portion of estimated concentrations and health risks. In addition, a similar estimate of a noncancer hazard index was derived for the Environmental Defense Fund National Scorecard (Table 10). Many of the same compounds, including acrolein, formaldehyde, and nickel and chromium compounds, were identified, and estimates of the number of individuals possibly exposed at or above these levels were obtained.

Future Research Priorities

Exposure Assessment Research Needs

Since our initial review of these issues in 1995 (*1*), a number of studies have begun to estimate the levels of human exposure. A recent Gaussian air dispersion modeling study conducted by Rosenbaum et al. (*351*) used the Assessment System for Population Exposure Nationwide database to assess the spatial distribution of concentrations of HAPs. Ratios of median concentrations based on 1990 emission source estimates for 148 compounds suggest that emission totals that do not consider emission source type could be misleading, and model performance suggested a tendency to underpredict observed concentrations. Overall, Rosenbaum et al. concluded that emissions estimates for HAPs have a high degree of uncertainty and contribute to discrepancies between modeled and monitored concentration estimates. Similarly, Kyle et al. (*352*) compared the air release inventories with monitoring data in California. They also concluded that release inventories tend to underestimate exposure and that current monitoring methods do not have sufficient sensitivity to fully assess the health significance of exposure to HAPs and made several useful recommendations to fill current data gaps.

Release inventories still need further validation by additional environmental sampling (*351–357*). Better monitoring methods and models are needed to estimate the risk these compounds may pose. In addition, future scientific investigations are needed to evaluate the indoor and personal exposure levels of HAPs because an unsettled issue specific for these compounds is the relative extent of indoor exposure. Because these compounds are in ETS, involuntary exposures are likely to be frequent. Aldehydes have several other indoor sources, including wood fires, cigarette smoke, and release from building materials,

personal care products, and clothing (*343,358*). Initially, field investigations could assess outdoor, indoor, and personal exposures to aldehyde and metal asthmagens using probability-based sampling. Measurements of the magnitude of peak concentrations and collection of ambient air samples should, if possible, include various sample times, an exposure aspect that is important in the induction of asthma. Last, this group of compounds is ideal for future investigation of fugacity models, and knowing the amount of transport across media for these compounds, particularly the less volatile organic compounds, would be helpful (*359–361*).

Health Effects Assessment Research Needs

Because these compounds are highly toxic and in some cases carcinogenic, further human clinical testing is unlikely. Consequently, tests with laboratory animals and *in vitro* toxicology testing with human cell culture systems may be acceptable alternatives. End points important to airway inflammation (e.g., cytokine and eicosanoid production) should be examined to gather dose–response information. Currently, the development of cDNA microarrays for global assessment of gene expression is very promising and may enable signature response patterns to be evaluated (*429*). These end points can readily be investigated in laboratory animals. Unfortunately, animal models of asthma have limitations, with most previous investigations focusing on acute, reversible airway hyperreactivity instead of persistent chemically induced asthma. Although small rodents (mice in particular) have advantages for measurement of genetic and molecular end points (e.g., genomewide scans and microarray detection of mRNA), these species are often less responsive than humans and tests of lung functions are difficult to perform in mice. Larger laboratory species (e.g., guinea pigs), in contrast, have disadvantages in that molecular end points are harder to measure (requiring gene cloning to generate riboprobes for this species) but are useful for evaluation of airway bronchoconstriction and hyperreactivity. Nonetheless, the effects of chronic inhalation exposure to the HAPs and the induction of persistent hyperreactivity are worthy of future investigations. In addition, information is needed on the dose related to continuation of a persistent syndrome in animals that already have hyperreactivity. Animal data on the effects of complex mixtures, including exposure to two or more HAPs, HAPs with particulate matter, or HAPs with criteria pollutants also could be investigated with animals.

Dose–response data would be helpful to evaluate a current assumption made in risk assessment that the effect of each substance is additive for a given organ system. This assumption is contradicted by studies with respiratory irritants that suggest synergy can occur (e.g., acid sulfates and sulfur dioxide with metal aerosols) (*362,363*). Currently, ambient air quality standards are based largely on data obtained when each criteria pollutant is tested independently. Indeed, concerns about exceedences are based on the expected adverse effects of the pollutant in highest concentration (often ozone) without concern about co-exposure to other irritant pollutants present in the typical oxidant urban plume. For example, urban concentrations of aldehydes and other VOCs follow diurnal patterns and have peaks about 50 μg/m^3 (*171*). These exposures can occur with subsequent high ozone exposures (>250 μg/m^3), and recent epidemiologic studies tentatively suggest that pollution interactions may potentiate respiratory responses (*177*). (Note that formaldehyde, acetaldehyde, and acrolein exposures often occur together in concentrations that exceed the REL values presented in Table 9.)

The number of persons living near emitting point sources is unknown but could be derived from census data and information on the location of point sources throughout the United States. Furthermore, the percentage of persons in these populations that have asthma can be estimated based on NHANES survey data. Estimating the extent of exposure to these identifiable asthmagens could be useful, particularly in assessments of healthcare costs (*178*).

Benchmark concentrations are based on standard toxicologic references and represent HAP toxic levels above which health risks may occur. Outdoor concentrations of HAPs need to be compared with defined benchmark concentrations for noncancer health effects that include asthma. In addition, continuous air sampling needs to be conducted on a few HAPs that have exceeded health benchmark values at one or more sites by modeling, monitoring, or both (including acrolein, arsenic, benzene, 1,3-butadiene, carbon tetrachloride, chromium, chloroform, ethylene dibromide, formaldehyde, and nickel). Noncancer risk estimate should also be apportioned by source, with emphasis on mobile, area, and point sources and background.

The current epidemiologic information on the possible associations between HAPs and asthma is inadequate. Recent studies with criteria pollutants suggest that animal and clinical exposure data can underestimate respiratory health effects. One epidemiologic study of formaldehyde suggests that children exposed in homes with concentrations of >150 μg/m^3 had a higher frequency of asthma and bronchitis than children with residential exposure of <50 μg/m^3 (*179*). Decrements in lung function (i.e., peak expiratory flow) were also associated with formaldehyde exposure. Clinical studies with formaldehyde, in contrast, require much higher concentrations to produce transient increases in airway resistance (*171*). This suggests that persistent respiratory effects can result from indoor formaldehyde exposures and that environmental exposures produce effects not observed in clinical studies with short-term exposures. Confirmation through additional investigation of the effects of environmental aldehyde and other HAP exposures on persistent pulmonary function is thus warranted. The contribution of HAPs as constituents of $PM_{2.5}$ is extremely important and will require detailed speciation of the chemical constituents of ambient samples.

Conclusions

Asthma is a serious illness with a high prevalence among the general population. Since the last review in 1995, the incidence and severity of asthma have remained high. Exposure to current levels of air pollution has been associated with an increase in respiratory symptoms and hospital admissions for asthma. Environmental agents associated with asthma include ambient particulate matter and ETS; both are complex mixtures containing many HAPs.

The role of HAPs in this condition (with and relative to other known hazardous compounds in air pollution) has yet to be explored thoroughly. Nonetheless, there is good reason to think that certain compounds may be etiologic factors in the induction and exacerbation of asthma. This review presents 25 compounds of the 188 original HAPs that should be further evaluated for their role in asthma (Table 5). Several estimates of possible human exposures based on assessment of release inventories suggest that among these compounds, aldehydes (especially acrolein and formaldehyde) and metals (especially nickel and chromium compounds) may be of particular concern for persons with asthma. These and several other HAPs are known to be or are related to compounds that are occupational asthmagens.

Last, several HAPs that have not been reported to produce asthma directly may be particularly hazardous to persons with asthma because they can exacerbate asthma through repetitive irritation of airway epithelium. Other HAP compounds can potentiate airway responses to inhaled antigens or are irritating when inhaled. The latter includes respiratory carcinogens that can form antigenic determinants through alkylation reactions with cellular macromolecules. Further research is needed to clarify the issues surrounding the extent of human exposure and the potential role of HAPs in asthma.

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