Evaluation of a Possible Association of Urban Air Toxics and Asthma

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The prevalence of asthma, measured either as the frequency of hospital admissions or number of deaths attributed to asthma, has increased over the last 15 to 20 years. Rapid increases in disease prevalence are more likely to be attributable to environmental than genetic factors. Inferring from past associations between air pollution and asthma, it is feasible that changes in the ambient environment could contribute to this increase in morbidity and mortality. Scientific evaluation of the links between air pollution and the exacerbation of asthma is incomplete, however. Currently, criteria pollutants [SO_x, NO_x, O_3, CO, Pb, particulate matter (PM_{10})] and other risk factors (exposure to environmental tobacco smoke, volatile organic compounds, etc.) are constantly being evaluated as to their possible contributions to this situation. Data from these studies suggest that increases in respiratory disease are associated with exposures to ambient concentrations of particulate and gaseous pollutants. Similarly, exposure to environmental tobacco smoke, also a mixture of particulate and gaseous air toxics, has been associated with an increase in asthma among children. In addition, current associations of adverse health effects with existing pollution measurements are often noted at concentrations below those that produce effects in controlled animal and human exposures to each pollutant alone. These findings imply that adverse responses are augmented when persons are exposed to irritant mixtures of particles and gases and that current measurements of air pollution are, in part, indirect in that the concentrations of criteria pollutants are acting as surrogates of our exposure to a complex mixture. Other irritant air pollutants, including certain urban air toxics, are associated with asthma in occupational settings and may interact with criteria pollutants in ambient air to exacerbate asthma. An evaluation of dose–response information for urban air toxics and biological feasibility as possible contributors to asthma is therefore needed. However, this evaluation is compounded by a lack of information on the concentrations of these compounds in the ambient air and their effects on asthma morbidity and mortality. Through an initial review of the current toxicological literature, we propose a tentative list of 30 compounds that could have the highest impact on asthma and respiratory health. These compounds were selected based on their ability to induce or exacerbate asthma in occupational and nonoccupational settings, their allergic potential and ability to react with biological macromolecules, and lastly, their ability to irritate the respiratory passages. We recommend better documentation of exposure to these compounds through routine air sampling and evaluation of total exposure and further evaluation of biological mechanisms through laboratory and epidemiological studies directed specifically at the role these substances play in the induction and exacerbation of asthma. — Environ Health Perspect 103(Suppl 6):253–271 (1995)

Key words: asthma, hazardous air pollutants, volatile organic compounds, aldehydes, environmental, tobacco smoke, ambient aerosols, chronic obstructive pulmonary disease.

Introduction

Urban Air Toxics

The Title III—Hazardous Air Pollutants portion of the 1990 Clean Air Act Amendment mandates the preparation of exposure standards for an initial list of 189 compounds within 6 years and a comprehensive strategy to control emissions from sources in urban areas within 5 years. The latter requires an identification of not less than 30 hazardous air pollutants that present the greatest threat to public health in the largest number of urban areas. Several health concerns are to be considered, with emphasis on carcinogenicity, mutagenicity, and teratogenicity. In the review that follows, we consider the possible relationship between these compounds and an additional disease, asthma. Asthma morbidity (emergency room visits, etc.) and mortality have steadily increased since the mid-1970s, a situation that will require a better understanding of environmental risk factors.

Clean air is essential for life. Human commerce and recreation have led to the purification, development, and macroscale use of over 50,000 chemicals. Each can be considered toxic depending on the magnitude of exposure, the dose to target organ, and the biological response. Systematic evaluation and reevaluation of the toxicology of these chemicals is ongoing and may require many decades of effort to understand the relationships between environmental exposure and potential to cause or exacerbate human diseases. Faced with the immediate need to protect human health by providing recommendations for over 180 compounds (Table 1), referred to here as urban air toxics (UATs), we attempt to rank this substantial list of compounds (and groups of compounds). Any prioritization should be based on the likelihood and extent of human exposure and the severity of the response. Unfortunately, adequate scientific details are lacking for

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Table 1. Urban air toxics, the 189 substances listed in the 1990 Amendment to the Clean Air Act as hazardous air pollutants.

ACETALDEHYDE
ACETAMIDE
ACETONITRILE
ACETOPHENONE
2-ACETYLAMINOFLUORENE
ACROLEIN
ACRYLAMIDE
ACRYLIC ACID
ACRYLONITRILE
ALLYL CHLORIDE
4-AMINOBIPHENYL
ANILINE
o-ANISIDINE
ASBESTOS
BENZENE
BENZIDINE
BENZOTRICHLORIDE
BENZYL CHLORIDE
BIPHENYL
bis(2-ETHYLHEXYL) PHTHALATE
bis(CHLOROMETHYL) ETHER
BROMOFORM
1,3-BUTADIENE
CALCIUM CYANAMIDE
CAPROLACTAM
CAPTAN
CARBARYL
CARBON DISULFIDE
CARBON TETRACHLORIDE
CARBONYL SULFIDE
CATECHOL
CHLORAMBEN
CHLORDANE
CHLORINE
CHLOROACETIC ACID
2-CHLOROACETOPHENONE
CHLOROBENZENE
CHLOROBENZILATE
CHLOROFORM
CHLOROMETHYL METHYL ETHER
CHLOROPRENE
CRESOLS/CRESYLIC ACID
o-, *m*-, *p*-CRESOL
CUMENE
2,4-D, SALTS AND ESTERS
DICHLORODIPHENYLDICHLOROETHYLENE
DIAZOMETHANE
DIBENZOFURANS
1,2-DIBROMO-3-CHLOROPROPANE
DIBUTYLPHTHALATE
1,4-DICHLOROBENZENE (*p*)
3,3-DICHLOROBENZIDENE
DICHLOROETHYL ETHER
(or) *bis*(2-CHLOROETHYL) ETHER
1,3-DICHLOROPROPENE
DICHLOROVOS
DIETHANOLAMINE
N,N-DIETHYL ANILINE
(or) *N,N*-DIMETHYLANILINE
DIETHYL SULFATE
3,3-DIMETHOXYBENZIDINE
DIMETHYL AMINOAZO-BENZENE
3,3'-DIMETHYL BENZIDINE
DIMETHYL CARBAMOYL CHLORIDE
DIMETHYL FORMAMIDE
1,1-DIMETHYL HYDRAZINE
DIMETHYL PHTHALATE
DIMETHYL SULFATE
4,6-DINITRO-*o*-CRESOL AND SALTS
2,4-DINITROPHENOL
2,4-DINITROTOLUENE
1,4-DIOXANE
(or) 1,4-DIETHYLENEOXIDE
1,2-DIPHENYLHYDRAZINE
EPICHLOROHYDRIN
(or) 1-CHLORO-2,3-EPOXYPROPANE
1,2-EPOXYBUTANE
ETHYL ACRYLATE
ETHYL BENZENE
ETHYL CARBAMATE (URETHANE)
ETHYL CHLORIDE (CHLOROETHANE)
ETHYLENE DIBROMIDE
ETHYLENE DICHLORIDE
ETHYLENE GLYCOL
ETHYLENE IMINE (AZIRIDINE)
ETHYLENE OXIDE
ETHYLENE THIOUREA
ETHYLIDENE DICHLORIDE
(or) 1,1-DICHLOROETHANE
FORMALDEHYDE
HEPTACHLOR
HEXACHLOROBENZENE
HEXACHLOROBUTADIENE
HEXACHLOROCYCLOPENTADIENE
HEXACHLOROETHANE
HEXAMETHYLENE-1,6-DIISOCYANATE
HEXAMETHYLPHOSPHORAMIDE
HEXANE
HYDRAZINE
HYDROCHLORIC ACID
HYDROGEN FLUORIDE
HYDROGEN SULFIDE
HYDROQUINONE
ISOPHORONE
LINDANE
MALEIC ANHYDRIDE
METHANOL
METHOXYCHLOR
METHYL BROMIDE (BROMOMETHANE)
METHYL CHLORIDE (CHLOROMETHANE)
METHYL CHLOROFORM
(or) 1,1,1-TRICHLOROETHANE
METHYL ETHYL KETONE (2-BUTANONE)
METHYL HYDRAZINE
METHYL IODIDE (IODOMETHANE)
METHYL ISOBUTYL KETONE (HEXONE)
METHYL ISOCYANATE
METHYL METHACRYLATE
METHYLENE-*tert*-BUTYL ETHER
4,4-METHYLENE BIS(2-CHLOROANILINE)
METHYLENE CHLORIDE
METHYLENE DIPHENYL DIISOCYANATE
4,4'-METHYLENEDIANILINE
NAPHTHALENE
NITROBENZENE
4-NITROBIPHENYL
4-NITROPHENOL
2-NITROPROPANE
N-NITROSO-*N*-METHYLUREA
N-NITROSODIMETHYLAMINE
N-NITROSOMORPHOLINE
PARATHION
PENTACHLORONITROBENZENE
(or) QUINTOBENZENE
PENTACHLOROPHENOL
PHENOL
p-PHENYLENEDIAMINE
PHOSGENE
PHOSPHINE
PHOSPHORUS
PTHALIC ANHYDRIDE
POLYCHLORINATED BIPHENYLS (PCB)
1,3-PROPANE SULTONE
β-PROPIONALDEHYDE
PROPIONALDEHYDE
PROPOXUR (BAYGON)
PROPYLENE DICHLORIDE
PROPYLENE OXIDE
1,2-PROPYLENIMINE
(or) 2-METHYL AZIRIDINE
QUINOLINE
QUINONE
STYRENE
STYRENE OXIDE
2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN (TCDD)
1,1,2,2-TETRACHLOROETHANE
TETRACHLOROETHYLENE
TITANIUM TETRACHLORIDE
TOLUENE
2,4-TOLUENE DIAMINE
2,4-TOLUENE DIISOCYANATE
o-TOLUIDINE
TOXAPHENE
1,2,4-TRICHLOROBENZENE
1,1,2-TRICHLOROETHANE
TRICHLOROETHYLENE
2,4,5-TRICHLOROPHENOL
2,4,6-TRICHLOROPHENOL
TRIETHYLAMINE
TRIFLURALIN
2,2,4-TRIMETHYLPENTANE
VINYL ACETATE
VINYL BROMIDE
VINYL CHLORIDE
VINYLIDENE CHLORIDE
(or) 1,1-DICHLOROETHYLENE
XYLENES (ISOMERS AND MIXTURES)
o-, *m*-, *p*-XYLENES
ANTIMONY COMPOUNDS
ARSENIC COMPOUNDS (INORGANIC INCLUDING ARSINE)
BERYLLIUM COMPOUNDS
CADMIUM COMPOUNDS
CHROMIUM COMPOUNDS
COBALT COMPOUNDS
COKE OVEN EMISSIONS
CYANIDE COMPOUNDS
GLYCOL ETHERS
LEAD COMPOUNDS
MANGANESE COMPOUNDS
MERCURY COMPOUNDS
FINE MINERAL FIBERS
NICKEL COMPOUNDS
POLYCYCLIC ORGANIC MATTER
RADIONUCLIDES (INCLUDING RADON)
SELENIUM COMPOUNDS

many of these compounds; therefore, we also present information on the current gaps in the toxicology literature and recommend research needs that may be useful in reducing the uncertainty of future evaluations of the health effects of these compounds.

Persons with Asthma and Increased Susceptibility to Air Pollution

Air quality standards are designed to protect susceptible populations, and persons with asthma are clearly at increased risk from the adverse health effects of air pollution. Because asthma is a complex respiratory condition with varied definitions (*1–3*), it is helpful to develop an operational definition of this disease. Asthma is defined here as a respiratory disease with three primary features. The first is airway inflammation (associated with eosinophilic infiltration and altered T-cell lymphocytic function). A second feature is altered epithelial function (associated with thickening of the basement membrane, mucin hypersecretion, loss or altered ciliary structure, and altered cytokine and other inflammatory mediator production). The third and most predominate feature is recurrent airflow obstruction (presented in dual phases as decreased forced expiratory volume, bronchospasm, or airway hyperreactivity). Although the frequency of asthma is greater among atopic individuals (*4*), not all persons with asthma (e.g., more than half the adults with occupational asthma) (*5*) exhibit specific antigen–antibody responses. Instead, these individuals respond to many agents including dry air, hypo/hypertonic aerosols, acidic aerosols, and sulfur dioxide. Consequently, this condition is called nonspecific airway hyperreactivity, which many clinical investigators consider the hallmark of asthma (*2,6*).

Although asthma may persist for many years, the signs and symptoms are markedly erratic both in frequency and severity. In some ways, this intrinsic, sporadic nature contributes to the licentiousness of this disease. Severe, life-threatening asthmatic attacks can arise rapidly even after presentation of mild symptoms to which the victim is accustomed. Thus, 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 inspissation). Indeed, this lack of appreciation for this condition by patients and general practitioners has been cited as contributing to the recent increases in asthma mortality (*7,8*).

One factor that has been considered as having a possible role in the recent increases in asthma mortality is the use of bronchodilator therapy (*9–11*). Without recognition of the inflammatory and epithelial components of this disease, therapies directed solely at preventions of bronchospasm can leave a persistent inflammatory condition unchecked. In addition, patients relieved of symptoms may be more likely to put themselves in harm's way by not avoiding environmental exposures that increase epithelial injury and may hasten acute attacks. In addition, bronchodilation will alter the deposition pattern of subsequently inhaled irritant particles increasing their penetration to distal, small diameter airways and lengthening clearance times.

In the past, controlled human exposures of persons with asthma indicate that these patients respond to bronchoconstrictive substances at lower concentrations than do healthy control subjects (*12*). Of the current criteria pollutants, SO_2 (*13,14*), NO_2 (*15–18*), and acidic sulfates (*19–23*) can produce bronchoconstriction (or increase bronchial reactivity) at lower concentrations among asthmatic subjects. Clinical studies with ozone are more controversial (*24–26*), although a recent study by Molfino (*27*) suggests that O_3 exposures can increase bronchial reactivity to subsequent antigen challenges in persons with airway hypersensitivity. Results from these studies qualitatively indicate that specific pollutants affect persons with asthma to a greater extent than healthy subjects. However, clinical findings are quantitatively disparate from epidemiological findings in that in clinical studies, the lowest effective concentration that produces bronchoconstriction is often higher than that noted 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 epidemiological studies.

In several recent epidemiological studies, associations between air pollution and the prevalence of respiratory symptoms characteristic of asthma have been noted throughout the world (Table 2). When atopic and nonatopic patients were handled separately, the association with air pollution was unaffected (*31,33,34*). This suggests that both asthma subpopulations are affected equally by air pollution. Besides increases in symptoms, air pollution has been associated with decreases in pulmonary function, e.g., depressed forced expiratory volume-1 second (FEV_1) or peak expiratory flowrate (PEF) (*35,36*).

Emergency department visits and hospital admissions for asthma have also been consistently associated with the amount of exposure to air pollution (Table 3). The implicated air pollution variable differs among studies, with the most frequent being particulate, sulfate, and sulfur dioxide. In contrast, earlier studies failed to find similar associations with SO_2 and hospital admissions for asthma (*47*).

Several additional observations have been noted by the investigators of these studies. Although weather, pollen, and environmental tobacco smoke are important risk factors in asthma, each has been found to act independently of air pollution and thus do not explain the association between air pollution and asthma (*32,41,44,48–50*). Local stationary sources are often associated with effects (*31,38,45,51–57*). This observation, along with the observation that a variety of pollutants are associated with the same responses (Tables 2,3), suggests that the specific compounds measured may serve as indicators of a wider array of air pollutants (including UATs). By focusing on selected epidemiological studies that have been conducted in the last 5 years, emphasis is placed on the current effects of air pollution. All the reported associations have been noted during a period when criteria pollutants are either decreasing or maintaining levels noted in previous years (*50,58*). Last, because some recent studies are cross-sectional over short periods, it is unlikely that any recent changes in diagnostic criteria for asthma could explain these associations (*59–62*). Together these studies indicate that air pollution is a complex mixture that can produce effects at current levels of exposure that are important to the etiology of asthma.

Table 2. Recent epidemiologic studies associating air pollution with increased prevalence of respiratory symptoms (wheezing, chest tightness, cough) in persons with asthma.

Study population	Implicated pollutant(s)	Location	Investigator
Children	PM_{10}	Utah Valley, Utah	Pope (*28*)
Children and adults	Particulate, NO_x, O_3	Helsinki, Finland	Pönkä (*29*)
Adults	Particulate, H^+	Denver, Colorado	Ostro (*30*)
Children	SO_2	New So. Wales, Australia	Henry (*31*)
Children and adults	Particulate	Piteå, Sweden	Forsberg (*32*)
Children	Particulate, SO_2	Rome, Italy	Corbo (*33*)

[a]Particulate ≤ 10 μm.

Table 3. Recent epidemiologic studies associating air pollution with increases in hospital admissions or emergency room visits for asthma.

Study population	Implicated pollutant(s)	Location	Investigator
Children and adults	SO_4, SO_2, O_3	Ontario, Canada	Bates (*37*)
Children	O_3	Six U.S. cities	Dockery (*38*)
Children	SO_2	Oporto, Portugal	Queirós (*39*)
Children	SO_2	Hong Kong	Tseng (*40*)
Adults	SO_4, SO_2	Vancouver, Canada	Bates (*41*)
Children	PM_{10}[a]	Utah Valley, Utah	Pope (*28*)
Children and adults	O_3	Northern New Jersey	Cody (*42*)
Children	Particulate	Melbourne, Australia	Rennick (*43*)
Severe adults	Particulate, NO_2, SO_2, H_2S	Oulu, Finland	Rossi (*44*)
Children and adults	PM_{10}[a]	Seattle, Washington	Schwartz (*45*)
Children and adults	O_3	Central New Jersey	Weisel (*46*)

[a]Particulate ≤ 10 μm.

Exposure Assessment

Entry and Fate in the Environment

Exposure is a primary issue regarding the culpability of UATs in the exacerbation of asthma. This is an extremely complex issue for this group of compounds. Ideally, existing air sampling networks could quantify hourly, daily, or yearly the ambient concentrations of all these 189 compounds. Evaluation of a massive data collection effort and its effectiveness in control–design strategies is well beyond the limited scale of this review. Nonetheless, appreciation for the magnitude of this problem and a preliminary understanding of exposure assessment is necessary to begin to evaluate whether such a future undertaking would have merit.

UATs can enter the environment by a complex array of pathways. Vaporization of gases is the primary route of entry and is often a consequence of fugitive emissions from stationary sources. This process depends on the intrinsic physical/chemical properties of each compound including vapor pressure and solubilities in various media (i.e., water, organic solvents, etc.) as well as certain attributes of the manufacturing and generating procedures (e.g., the temperature of the effluent). Highly volatile substances can more readily escape into the ambient air and thus have added concern. Emission inventories for UATs indicate that release into the air is the principal route through which these materials enter the environment (Figure 1).

In addition to direct entry from stationary sources by volatilization, specific compounds can enter the urban air by mechanical dispersion or condensation, processes that dominate the formation of the urban aerosol. Urban aerosols have been chemically characterized to a limited extent in the past (*64–71*). However, the past and current criteria pollutants, total suspended particulate (TSP), and particulate material ≤ 10 μm (PM_{10}) overlap with specific UATs because particles in this size range and smaller are derived from anthropogenic sources, whereas larger particles (>10 μm) arise from natural sources (e.g., sea salt, soil, etc.). More details of the implication of the ambient levels of particulate matter to asthma are presented below.

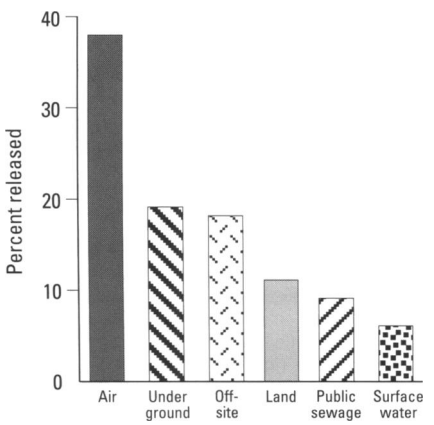

Figure 1. Distribution of toxic chemicals into the environment by route of release or transfer estimated from release inventories in 1989. Data from U.S. EPA (*63*).

A third source of atmospheric pollutants arises from secondary reactions in the atmosphere. Many reactive hydrocarbons (often with very short half-lives) can be formed and can accumulate in the atmosphere (*72–76*). This is particularly important for urban photo-oxidant plumes most often associated with ozone formation. Because ozone formation is dependent upon reactive hydrocarbon species (e.g., aldehydes), the continuous measurement of ozone concentrations could be useful in estimating the ambient concentrations of these compounds. Once inhaled, ozone is likely to react with unsaturated fatty acid in the airway lining fluid or the cell membrane to form aldehydes, hydroxyhydroperoxides, and hydrogen peroxide (*77,78*). These intermediates have recently been shown to activate mediator release from human airway epithelial cells in culture, thereby linking the biochemical outcomes of ozone with these compounds (*79*). Reductions in the emissions of ozone precursors (hydrocarbons and nitrogen oxides) are likely to limit indirectly the entry of certain UAT compounds into the atmosphere in the future. Urban activities of automobile transit, power generation, manufacturing, solvent use, wood burning, and even barbecuing have impact on the formation and release of these compounds.

Besides direct entry into the air and secondary formation, other chemicals can gain significant entry into the atmosphere through intermediate transport. In this case, chemicals that partition into water, soil, sediment, or biota can enter the atmosphere through evaporation from water or soil. For example, organic compounds with low or moderate solubility in water will partition to the air–liquid interface following an initial dispersion as an emulsion in a factory effluent stream. Thus, continuous and sole discharge into water can unexpectedly generate significant atmospheric concentrations. For example, recent fugacity models, e.g., Level III models by Mackay (*80*), predict that as much as 5% of naphthalene (a water-insoluble chemical with moderate volatility) will be distributed into the air when 100% is discharged into water. Although such a percentage seems low, the impact can be considerable. For example, dispersion of naphthalene solely into water at an emission rate of 1000 kg/hr (distributed throughout 100,000 km^2 or about the area of Ohio) can yield atmospheric concentrations of 50 ng/m^3. This is approximately one quarter of the value achieved by 100% emission of the same amount directly into the air (210 ng/m^3) when fugacity into other media is considered. This is somewhat remarkable and may partially explain why concentration estimates produced by airshed models that depend heavily on air emission inventories underpredict measurements made in the ambient air downwind from a point source (MA Marty, personal communication).

The movement of toxics from the air into other media and back again suggests an equilibrium can be achieved or predicted. However, uniform dispersion is unlikely in any compartment in real world situations. Furthermore, such models have uncertainty in estimating degradation rates in each compartment.

Degradation in the air itself can be appreciable and can even be sufficient to limit exposure. Naphthalene, the chemical used in the example above, is rapidly photolyzed. Based on the quantum yield for sunlight photolysis at latitude 40°N at midday in the summer, the half-life of naphthalene can vary markedly from 71 to 550 days (*81*). In addition, photooxidation through reactions with hydroxyl radicals (often produced in urban plumes) can dramatically reduce the half-life of naphthalene to between 3 and 30 hr. Such variance in the environmental degradation rates can widely influence air concentrations.

This latter situation presents another dilemma facing attempts to assess human exposure to UATs. Exposure to many of these compounds is likely to be dominated by proximity to point sources that produce intermittent, high concentrations as well as regional meterology, atmospheric dispersion, transport, and removal. Source–receptor analysis is therefore important. This attribute places significance on the identification of sensitive receptors in the population downwind from a point source. Because persons with asthma constitute approximately 3.8 to 8.7% of the residents

of urban areas (*82,83*), this group represents an important target population and should be considered as such in evaluation of possible risks associated with exposure that could enter the neighborhoods of emission sources.

Exposure Assessment, Threshold Concentrations, and the Induction of Asthma

We have learned a great deal about the induction of chemically induced asthma from occupational experience. In this setting, exposure can still be difficult to quantify, but causal association can more readily be demonstrated. For example, polyisocyanate-induced asthma has clearly been ascribed to exposure in the workplace. Historically, approximately 5 to 10% of all workers exposed to toluene diisocyanate, other polyisocyanates, and their monomeric precursors develop occupational asthma (*5*). Although host determinants (genetic factors) can modulate asthma, exposure to specific, identifiable agents is clearly associated with the development of asthma. This condition typically develops after several years of occupational exposure, indicative of a latency period when exposures are occurring while subjects are asymptomatic. Several of these compounds are included in the UAT list, and this selection of compounds of concern in the ambient environment draws from the experience in the occupational environment.

Current control strategies are designed to reduce occupational exposure concentrations below threshold limit values (TLVs). Exposures at these levels should ideally result in few or no adverse health effects. This approach from the occupational experience impinges directly on the method of application of risk assessment for noncancer health effects. However, although exposures have qualitatively been associated with occupational asthma, quantification of human exposure to a specific compound has been limited. Mathematical models of the relationship between dose (the concentration and duration of exposure) and occupational asthma have yet to be firmly established. 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. For example, initiation of occupational asthma has been noted among workers wearing respiratory protective equipment and when exposures met current TLVs (*5*).

Induction of airway hyperreactivity in animals provides some insight into the issue of threshold dose. For example, we recently examined the induction of hyperreactivity in guinea pigs exposed to formaldehyde and acrolein (*84*). In these studies, the dose of acetylcholine necessary to double pulmonary resistance (ED_{200}) was measured after 2- and 8-hr exposures. Figure 2 shows that exposures extended to 8 hr produced an effect greater than that predicted by the common estimates of dose. After 8 hr of exposure to 1.1 ppm formaldehyde, the percentage change in ED_{200} equaled 67 ± 4%. This is equivalent to the maximal effect produced by 2 hr of exposure to either ≥ 30 ppm formaldehyde or ≥ 1.0 ppm acrolein. Thus the estimated dose–response relationship for aldehyde-induced hyperreactivity after prolonged exposure did not follow a simple concentration × time relationship (i.e., an equivalent response occurred after 1.1 ppm × 8 hr = 8.8 ppm × hr that is nearly 7 times less than what would be predicted by 31 ppm × 2 hours = 62 ppm × hr). These findings suggest that low-level exposure of prolonged duration may be of greater consequence than would be predicted by acute exposure. 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 epidemiological studies.

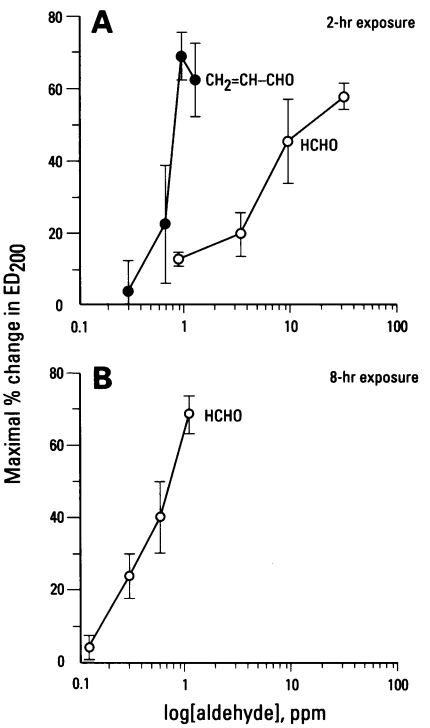

Figure 2. Dose-response effects of acrolein (CH_2=CH–CHO) or formaldehyde (HCHO) on airway hyperreactivity in guinea pig. (*A*) Two-hour exposures to acrolein or formaldehyde produced a maximal decrease in the effective dose of intravenous acetylcholine necessary to double specific pulmonary resistance (ED_{200}) at concentrations of > 0.9 and 30 ppm, respectively. (*B*) When exposures were extended to 8 hr, a dose of 1.0 ppm formaldehyde produced an effect equivalent to that following 30 ppm × 2 hr. Values are means ± SE of groups of five to seven guinea pigs. Data from Swiechichowski (*84*).

Induction of irritant-induced asthma without a latency period has also been reported extensively in the medical literature and has been termed reactive airways dysfunction syndrome (RADS) (*85*). The pathogenesis of this syndrome is speculative because reports are retrospective in nature. 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. Following this single exposure, hyperreactivity and abnormal bronchial epithelial biopsies persist for a year or longer (up to 12 years). Causative agents have varied greatly, but all are respiratory irritants and include chlorine (*86–88*), toluene diisocyanate (*89–91*), hydrazine (*85*), sulfur dioxide (*92,93*), acetic acid (*94*), and ammonia (*95,96*). This condition differs from typical occupational asthma because it lacks a preceding latent period and can be initiated by a single exposure. Persons with this syndrome often experience subsequent responses to a wide range of agents (nonspecific airway hyperreactivity) and workers report that symptoms are equivalent either at home or at work (*97–100*). Because of a lack of exposure measurements during the initiating events, is it difficult to establish a threshold for this type of response; nonetheless, it is assumed that very high exposure levels are responsible for these cases.

Exposure Assessment and the Exacerbation of Asthma

In addition to scientific uncertainties associated with the establishment of threshold doses for chemicals that induce asthma, the levels of occupational exposure necessary to cause the persistence of sensitization or to elicit responses upon reexposure have yet to be established. Often the exposure concentration necessary to produce a multi-phasic response of diminished lung function in persons already sensitive to a compound can be exquisitely low, well below the concentration that will cause bronchoconstriction in nonsensitized persons exposed in clinical

experiments. However, epidemiological data of dose– response relationships in occupational settings are lacking and limited to anecdotal case histories. For example, one worker sensitive to ampicillin reportedly developed asthmatic bronchospasm the night after (delayed allergic response) a visit to the town where the factory that produces ampicillin is located. In another case, a toluene diisocyanate-sensitive patient was so reactive that he responded when walking in the neighborhood of a factory (*101*). Another cololphony (rosin)-sensitive worker became reactant to pine trees and even unheated colophony or turpentine (*102*). In addition, broncoprovocation tests have been positive in previously sensitized workers after exposure at concentrations as low as the current limit of chemical detection, i.e., 7 μg/m^3 toluene diisocyanate (*103,104*). These histories indicate that once initiation of hypersensitivity has occurred, elicitation of response can be evoked upon minimal reexposure at extremely low concentrations. Thus, for these individuals any environmental exposure should be considered hazardous, and any attempt to set threshold doses for this susceptible population (that could provide a margin of safety) must be regarded as extremely tenuous.

Exposure Assessment from Probability-Based Sampling Procedures

Because exposure assessment for UATs is currently incomplete, several strategies must be developed to reduce uncertainty. One approach is to use probability-based survey sampling procedures that combine questionnaires with multimedia and multipathway monitoring to estimate total personal exposure. A recent example is a study by Whitmore et al. (*105*) in which nonoccupational exposure to 32 pesticides was assessed (Table 4). Air monitoring was performed outside and inside each home, and drinking water, food, and dermal routes of exposure were analyzed. Ten of these pesticides are on the UAT listing, and other studies have found associations between the use of pesticides and asthma (*106*). Inhalation exposure exceeded dietary exposure for four of these substances (chlordane, dichlorovos, heptachlor, and propoxur) with the concentrations being approximately 7 to 20 times greater indoors than outdoors. Dietary exposures were greater for five other UAT/pesticides (captan, carbaryl, DDT and related compounds, hexachlorobenzene, and methoxychlor), and the relative level of exposure for one substance (γ-BHC) was undeterminable.

Table 4. Weighted estimates of average daily air concentrations and cancer risk assessment for eight urban air toxics for Jacksonville, Florida, and Springfield/Chicopee, Massachusetts.[a]

Air toxic	Average daily concentration, ng/m^3 [b]	Excess lifetime cancer risk × 10^{-6} [c]	Reference dose, ng/kg-day[d]	Hazard index[e]
Jacksonville				
Chlordane	197.0	70.0	0.06	1.0
Heptachlor	115.0	200.0	0.5	0.07
Dichlorvos	62.0	–	0.8	0.02
Propoxur	185.0	0.4	4.0	0.01
γ-BHC	11.0	-	0.3	0.01
DDE, etc.	0.6	0.06	0.5	0.0003
Carbaryl	7.5	–	100.0	2×10^{-5}
Methoxychlor	0.3	–	50.0	2×10^{-6}
Springfield/Chicopee				
Chlordane	198.0	70.0	0.06	1.0
Heptachlor	27.0	–	0.5	0.02
Dichlorvos	3.3	–	0.8	0.001
Propoxur	15.0	0.03	4.0	0.001
γ-BHC	1.9	–	0.3	0.002
DDE, etc.	3.8	0.4	0.5	0.0005
Carbaryl	0.1	–	100.0	3×10^{-7}
Methoxychlor	7.0	–	50.0	$<5\times10^{-5}$

[a]Adapted from Whitmore (*105*). [b]Average daily concentration measured using personal air exposures. [c]Cancer risk ≤ 1E–06 is generally considered negligible by U.S. EPA. [d]See Whitmore (*105*) for sources. [e]A hazard index value of ≤ 1 is generally considered negligible by the U.S. EPA.

Based on these estimates of personal exposure, risk assessments for air exposure were presented assuming a constant exposure over a 70-year lifetime and reference doses from the Integrated Risk Information System (IRIS) and other sources. The inhalation risks were estimated to be negligible ($<1\times10^{-6}$) for all compounds except chlordane (Table 4). However, these authors noted that these estimates are potentially high because of the discontinuation of use of these compounds and variable degradation in the environment. The data were considered insufficient to support risk assessment for food, dermal contact, or house dust exposure. Because indoor exposure may be due to past use in the home, it is also important to consider the possible risk due solely to outside exposure. For chlordane in Jacksonville, Florida, the estimated outside air exposure levels equaled about 22 ng/m^3 (compared to 197 ng/m^3 indoors), or about 10% of that used in the above risk assessment estimate. Thus, because exposure to other UATs also may be greater indoors than outdoors, accurate exposure assessment requires detailed analyses that involve total exposure evaluations. In addition, the above study is limited to only two locations, and these findings may not be readily generalized to other regions and climates.

Possible Exposure Concentrations of UATs Indoors

Assessment of possible human exposure for these compounds clearly requires consideration of exposure in the indoor environment.

Table 5. Estimates of indoor air concentrations[a] and odor threshold[b] for the 10 most reported volatile organic compounds/air toxics.

Air toxic	Indoor air concentrations,[a] μg/m^3			Lowest odor threshold, [b] μg/m^3
	Minimum	Maximum	Mean	
Formaldehyde	8.0	634	98.0	60
Toluene	9.0	2252	56.0	8030
Trichloroethane	<1.0	880	19.0	2×10^6
Ethylbenzene	1.5	800	11.0	400
1,4-Dichlorobenzene	<0.6	1006	9.7	9×10^4
Acetaldehyde	2.1	48	9.6	1980
Tetrachloroethylene	1.0	617	9.5	3×10^4
Trichloroethylene	<1.0	$>5\times10^4$	6.0	1×10^6
Benzene	<1.0	6338	5.1	4600
Xylenes	1.2	2076	3.8	348

[a]Concentrations from Samfield (*107*). [b]Odor thresholds are lowest value reported.

Table 6. Estimates of indoor air concentrations[a] and odor threshold[b] for 13 frequently reported volatile organic compounds/air toxics.

Air toxic	Indoor air concentrations,[a] µg/m^3			Lowest odor threshold,[b] µg/m^3
	Minimum	Maximum	Mean	
Methylene chloride	ND	5000	342.0	5×10^6
Carbon tetrachloride	0.4	33	12.0	1×10^6
Naphthalene	<1.0	676	11.0	–
n-Hexanes	2.0	590	9.3	–
Chloroform	0.07	210	5.8	3×10^6
2-Butanone	<1.0	41	5.3	800
Pentachlorobenzene	ND	39	3.1	–
Styrene	<1.0	54	1.8	200
Chlorobenzene	<0.4	27	<1.7	1060
Trichlorobenzene	ND	33	<0.8	–
N-Nitrosodimethylamine	ND	33	0.17	–
Quindone	0.0013	0.031	0.03	4×10^4
Hexachlorobenzene	ND	0.021	0.001	–

ND, not detected or below the lower detection limit. [a]Concentrations from Samfield (*107*). [b]Odor thresholds are lowest value reported.

Recently, the U.S. EPA compiled a database of concentrations of volatile organic compounds (VOC) measured indoors (*107*). Based on reports from 1979 through 1990, information on over 220 compounds ranging from 30 to 446 Daltons molecular weight was recorded. Table 5 lists the 10 most frequently reported compounds. Concentrations are presented as the minimum and maximum values to present a range (these values are the lowest and highest value obtained from all recorded values), mean values (estimated as a mean of the mean values reported), and lowest odor threshold. The concentrations of 13 other UATs frequently measured indoors are presented in Table 6. The odor threshold for each compound (except formaldehyde) is typically orders of magnitude higher than measured values, even when the lowest odor threshold value is considered. This suggests that human exposures can frequently occur when the odor is imperceptible. Complementary to this observation is the likelihood that olfactory detection indicates high exposure. The odor threshold for many of these compounds (Tables 5,6) is well above its recent reference exposure guideline (Tables 7,8). Because complaints of malodorous emissions are common outdoors near point sources, this comparison suggests that local exposures can be significant.

An earlier total exposure assessment methodology (TEAM) study had measured many of the same compounds (*108*), determining the concentrations of 20 VOCs in personal air, outdoor air, expired breath, and drinking water. The median concentrations in air and breath of 10 of the more prevalent compounds are presented in Table 7. Each is included on the list of urban air toxics (Table 1). Personal concentrations often exceeded outdoor concentrations by a factor of 2 or greater in New Jersey, and by a factor of 5 to 10 in North Carolina and North Dakota. This suggests that indoor VOC sources are likely to be 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 to 1000. 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.

In similar investigations of indoor air quality, Molhave and associates (*109–112*) measured the concentrations of several VOCs in Denmark. Using these data, the authors presented the concept of total VOC exposure in which the concentration of a mixture of 22 compounds is weighted by their relative concentrations in the environment. This group of compounds excludes carcinogens and includes 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 (Table 8). Because of the exclusion of carcinogens, this list differs from the lists in Tables 5 through 7. The relative amount of each compound is in proportion to a single concentration as measured by a flame ionization detector calibrated with a single reference compound, toluene. The concentrations of total VOCs measured in older dwellings (200–1700 µg/m^3) were typically lower than in new homes (500–19,000 µg/m^3), with complaints

Table 7. Weighted median concentrations (µg/m^3) for air and breath samples obtained in the total exposure assessment methodolgy (TEAM) study.[a]

Compound	New Jersey			North Carolina			North Dakota		
	Personal air	Outdoor air	Breath	Personal air	Outdoor air	Breath	Personal air	Outdoor air	Breath
Trichloroethane	17.0	4.6	6.6	32.0	60.0	–	25.0	>0.1	9.3
Benzene	16.0	7.2	12.0	9.8	0.4	15.0	–	–	56.0
m,p-Xylene	16.0	9.0	6.4	6.9	1.5	3.8	6.2	>0.1	4.5
Tetrachloroethylene	7.4	3.1	6.8	3.3	0.7	3.9	5.0	0.7	8.0
Ethylbenzene	7.1	3.0	2.9	2.5	0.3	1.5	2.1	>0.1	1.4
o-Xylene	5.4	3.0	2.2	3.6	0.6	1.2	2.7	>0.1	2.7
p-Dichlorobenzene	3.6	1.0	1.3	2.6	0.4	1.2	1.7	>0.1	0.8
Chloroform	3.2	0.6	1.8	1.7	0.1	0.7	0.4	>0.1	2.9
Trichloroethylene	2.4	1.4	0.9	1.5	0.2	0.5	0.5	>0.1	0.9
Styrene	1.9	0.7	0.8	1.4	0.1	0.4	–	–	–
Carbon tetrachloride	1.5	0.9	0.7	–	–	–	–	–	–

[a]Data adapted from Wallace (*108*).

Table 8. Volatile organic compounds (VOC) and relative ratios approximated from sampling indoor environments and used in controlled exposures.

Compound	Ratio	Compound	Ratio
n-Butylacetate	1.0	α-Pinene	0.1
p-Xylene[a]	1.0	Methylethyl ketone (2-butanone)[a]	0.01
n-Butanol	0.1	Cyclohexane	0.01
n-Decane	0.1	Isopropanol	0.01
1-Decene	0.1	3-Methyl-3-butanone	0.01
1,2-Dichloroethane[a]	0.1	4-Methyl-2-pentanone	0.01
Ethoxyethylacetate	0.1	1-Octene	0.01
Ethylbenzene[a]	0.1	*n*-Pentanal	0.01
n-Hexanal	0.1	*n*-Propylbenzene	0.01
n-Hexane[a]	0.1	1,2,4-Trimethylbenzene	0.01
n-Nonane	0.1	*n*-Undecane	0.01

[a] Compounds included in Title III—Hazardous Air Pollutants of the Clean Air Act 1990 (see Table 1).

Table 9. Atmospheric concentrations (μg/m^3) of 15 volatile organic compounds measured at 74 elementary schools in Kanawha Valley, West Virginia.[a]

	Mean (SD)	Median	Maximum
Petroleum-related compounds			
Toluene	9.7 (17.2)	4.8	117.4
m,p-Xylene	4.1 (3.8)	3.1	25.1
Benzene	3.2 (1.2)	3.0	6.9
o-Xylene	1.5 (1.1)	1.1	7.5
Decane	0.8 (0.4)	0.7	1.9
Total	19.2 (22.3)	13.1	154.4
Process-related compounds			
1,1,1-Trichloroethane	1.0 (0.2)	1.0	2.0
Carbon tetrachloride	0.6 (0.2)	0.6	1.5
1-Butanol	0.6 (0.4)	0.6	2.6
Chloroform	0.9 (1.1)	0.6	7.9
Perchloroethylene	0.6 (0.4)	0.5	2.2
Methyl isobutyl ketone	0.4 (0.2)	0.4	0.9
1,2-Dichloroethane	0.3 (0.1)	0.3	0.6
Styrene	0.1 (>0.1)	0.1	0.2
Mesityl oxide	0.1 (0.1)	>0.1	0.5
2-Ethoxyethyl acetate	>0.1 (0.1)	>0.1	0.6
Total	4.6 (1.7)	4.2	13.0

[a] Data from Ware (*115*).

being more frequent when levels exceed 1700 μg/m^3.

To investigate whether these compounds influenced pulmonary functions among persons with asthma, controlled 1.5 hr exposures were performed at concentration of total VOC of 2.5 and 25 mg/m^3 (*113*). At the end of the 25 mg/m^3 exposure, subjects developed bronchoconstriction, with the FEV_1 decreasing about 10% from pre-exposure control. 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 (*111*). Using a similar VOC mixture, Koren and Delvin (*114*) 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. From these studies, Molhave has offered tentative guidelines for exposure to these compounds 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 above 3000 μg/m^3, complaints have occurred in most investigated buildings; above 5000 μg/m^3 objective measures of upper respiratory tract irritation increase markedly.

Epidemiologic information on the respiratory effects of environmental VOC exposure is limited. One recent study, conducted in Kanawha Valley, West Virginia, found an association between exposure and respiratory symptoms among schoolchildren (third and fifth graders) (*115*). 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 or 10 manufacturing process-related chemicals. The concentrations of these chemicals were measured at the elementary schools and are presented in Table 9. When exposure was characterized by either proximity to sources or by concentrations, a positive association with the incidence of chronic lower respiratory symptoms was noted. Moreover, children enrolled in schools within the valley had higher rates of doctor-diagnosed asthma. Importantly, other potentially confounding variables including parental smoking and familial socioeconomic status had weak associations with health outcomes and proximity to sites. Nevertheless, these analyses adjusted for these variables and 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 extremely different from those in other sites in the United States. Table 10 presents the mean and maximum concentration of 10 VOCs (5 petroleum-related and 5 process-related compounds) as measured in the Kanawha Valley and four other locations. At each location, the mean values are typically 0.1 to 0.5 of the maximal values. This suggests that the concentrations of each substance vary greatly within a location. The between-location variability is also large. For example, mean benzene concentrations in Kanawha, Houston, and San Jose have been 3.2, 19.6, and 39.6 μg/m^3, respectively. Similarly, mean toluene concentrations have been measured to be 9.7, 27.3, and 79.5 μg/m^3, respectively, in these three locations. It is important to consider that each measurement can be influenced by differences in sampling and analytical procedures and sampling times. These parameters varied between these studies, making direct comparisons more qualitative than strictly quantitative. Nonetheless, because the values in Kanawha Valley do not exceed the values in other locations, it is possible that exposures like those of the Kanawha Valley can occur elsewhere throughout the United States.

In addition, several differences exist between the findings from VOC exposure in the controlled human experiments and those in the epidemiologic Kanawha Valley Health Study. First, and most obvious, is the difference in the concentrations at which responses were noted. In the controlled exposure study, no acute responses were noted at 2500 μg/m^3, whereas 25,000 μg/m^3 decreased lung function. The total VOC concentration in the Kanawha Valley was about 25 μg/m^3 (petroleum-related mean VOC subtotal = 19.2 and process-related mean VOC subtotal = 4.6 μg/m^3) (Table 9). However, the populations (adult vs children), the nature of the response (acute bronchoconstriction vs chronic

Table 10. Ambient concentrations (μg/m^3) of volatile organic comounds at selected sites in the United States.[a]

	Kanawha Valley, WV	San Jose, CA	Downey, CA	Denver, CO	Houston, TX
	Mean concentrations				
Petroleum-related compounds					
Toluene	9.7 (17.2)	80.0	64	13.0	27.0
m,p-Xylene	4.1 (3.8)	57.0	44	8.2	15.0
Benzene	3.2 (1.2)	40.0	28	7.1	20.0
o-Xylene	1.5 (1.1)	25.0	18	2.7	5.9
Decane	0.8 (0.4)	–	–	–	–
Process-related compounds					
1,1,1-Trichloroethane	1.0 (0.2)	6.7	6.3	3.5	2.0
Carbon tetrachloride	0.6 (0.2)	0.9	1.2	1.6	1.8
Chloroform	0.9 (1.1)	0.5	0.7	0.6	1.2
Perchloroethylene	0.6 (0.4)	13.0	25.0	2.9	1.1
1,2-Dichloroethane	0.3 (0.1)	–	0.4	>0.1	1.8
		Maximum concentrations			
Petroleum-related compounds					
Toluene	117.0	173.0	241.0	97.0	294.0
m,p-Xylene	25.0	110.0	163.0	64.0	78.0
Benzene	6.9	75.0	92.0	43.0	129.0
o-Xylene	7.5	48.0	69.0	18.0	31.0
Decane	1.9	–	–	–	–
Process-related compounds					
1,1,1-Trichloroethane	14.0	17.0	15.0	10.0	6.7
Carbon tetrachloride	22.0	1.6	2.4	2.3	7.2
Chloroform	95.0	1.0	1.9	1.3	7.8
Perchloroethylene	3.7	45.0	25.0	17.0	11.0
1,2-Dichloroethane	17.0	–	2.5	0.5	9.8

[a]Mean and petroleum-related maximum values for Kanawha Valley were measured at 74 elementary schools in November and December 1988. Adapted from Ware (*115*). Process-related maximum values for Kanawha Valley were measured between April 1987 and March 1988. Adapted from Cohen (*70*). Values for other locations were measured as follows: San Jose, April 1985; Downey, February 1984; Denver, April 1984; Houston, March 1984. Adapted from Singh (*116*). SD is shown in parentheses.

symptoms and diagnosed asthma), and the length of exposure (90 min vs continuous) are all different. In addition, the composition of the mixture (by a necessity that the controlled exposure excluded carcinogens) and the relative ratios varied in the total mixture. It also should be noted that the VOC compounds used in the controlled exposure studies (e.g., alkanes, xylene, benzene, or toluene) are not particularly irritating to the respiratory mucosa. Nonetheless, the clinical study supports the biological feasibility of the associations noted in the epidemiological study.

Health Effects Assessment

Criteria Pollutants and Mortality

Air pollution has been linked to adverse health effects. Increased mortality from cardiopulmonary disease and cancer has been noted in areas with elevated air pollution concentrations. Similarly, increased morbidity has been associated with environmental exposure (*117,118*). The latter includes increases in respiratory symptoms (e.g., shortness of breath, wheezing, coughing, chest tightness), decreased pulmonary function (e.g., depressed FEV_1 or PEF, increased use of bronchodilators, absence from school or work, and increased hospital admissions). As noted above, most previous analyses of these associations have focussed on criteria pollutants because much less has been reported for other pollutants. Because air pollution is a complex mixture, several investigators have postulated that any single exposure variable cannot solely be responsible for observed adverse effects (*50,69, 119–121*). Thus, measurements of criteria pollutants also may serve as exposure surrogates for a complex mixture of criteria pollutants and UATs.

In the past, epidemiologic studies in several cities throughout the United States have examined the relationship between mortality and the current criteria air pollutants. Observations from these studies have relevance to this assessment of the role of UAT in asthma. As mentioned above, one constant finding is the presence of covariables that might explain the observed associations. Weather, cigarette smoking, migration, and ethnic/socioeconomic variables impact mortality; however, these variables act independently of specific pollutants in these analyses. Numerous studies have consistently observed associations between air pollution and mortality in different populations, in different areas, and at different times of the year (*37,42,50,60,122,123*).

A second constant finding is the influence of local sources on mortality. Although this question has not been evaluated rigorously and long-range transport is recognized to influence ambient concentration, local sources can have strong influences on the association of air pollutants with mortality. A good example is the Harvard Six Cities study in which local, stationary sources in Steubenville, Ohio, and St. Louis, Missouri, dominate air pollution concentrations (*50,124*). Importantly, these cities have higher mortality than Watertown, Massachusetts, and Kingston/Harriman, Tennessee. The latter cities have moderate air pollution levels that are attributable largely to long-range transport processes of pollutants into these airsheds from other regions upwind of these communities rather than from local sources.

The third constant finding is the order of the relative strengths of the associations between mortality and specific criteria pollutants. Although controversial, these pollutants can be ranked from strongest to weakest as follows: $PM_{2.5} \geq PM_{10} > SO_x \geq H^+ \geq O_3 > NO_x$ (*30,37,41,50,115,121, 125–128*). In most recent studies, particulate matter, a complex mixture containing several UATs, is the dominant pollutant (*50,68,120,129*). The strength of this relationship is remarkably consistent across studies (*128,130*). In addition, association with mortality has been reported for exposures at concentrations well below the current PM_{10} standard (150 μg/m^3). A recent estimate of the total population exposed to ambient PM_{10} levels in counties and cities not in attainment with this standard is over 41 million, of which approximately 1 million adults and 625,000 children have asthma (*131*). Because of the extent of human exposure and the strength of PM_{10} (a complex mixture) as an associated risk factor, it is important to consider the chemical composition of this pollutant.

Detailed chemical analyses of PM_{10} vary significantly from location to location and data are limited (*65,69,132,133*). Although apportionment of PM_{10} may be site specific, typically particles in the 2.5- to 10-μm size range consist of re-entrained road dust [soil particles, engine oil including metals, tire particles, sulfate (6% of <10 μm), and nitrate (7% of <10 μm)],

and construction and wind-blown dust (mostly soil particles). Fine particles less than 2.5 μm are derived primarily from combustion, condensation, and coagulation of gases and ultrafine particles; thus, particles in this smaller size range are derived predominantly from anthropogenic sources. Preliminary and tentative analyses of the effect of including particle source on mortality estimates suggest that the least significant indicator is soil, whereas auto and oil sources are intermediate and metal industry and coal combustion sources are more significant contributors to mortality (*28,60*).

Environmental Tobacco Smoke, UATs, and Asthma

Environmental tobacco smoke (ETS) has recently been associated with an increase of asthma in children (*134–136*). Maternal smoking is associated with an increase in severity and frequency (additional episodes) of asthma in children with the disease. Importantly, this exacerbation of asthma and symptoms related to asthma may occur at low doses.

ETS is a complex mixture of over 4000 chemicals from exhaled mainstream and sidestream smoke. ETS contains several human respiratory carcinogens (including benzo[*a*]pyrene, benz[*a*]anthracene, other polycyclic aromatic hydrocarbons, 4-aminobiphenyl, and nitrosadi-methylamine) and irritants (including formaldehyde, acrolein, other aldehydes, cadmium, and other metals) (*136,137*) (Table 11). Twenty-nine of the 49 major components in ETS are UATs (compare Table 1 with Table 11). Each is a complex mixture of chemicals in both gas and particle phase. Because of these similarities, it is relevant to compare and contrast ETS and UATs in asthma.

ETS exposure has been assessed by measurement of a number of its constituents in air. Nicotine, respirable suspended particulate (RSP = PM < 2.5 μm), benz[*a*]pyrene, benzene, formaldehyde, toluene, carbon monoxide, 4-aminobiphenyl, and other chemicals have been used to assess ETS exposure. Of these, nicotine and RSP have the widest application, and these two variables correlate reasonably (RSP = 17.9 ± 10.8 nicotine; each in $\mu g/m^3$) (*138*). Either measure has been used as ETS exposure surrogates, and when measured together can accurately represent the frequency, duration, and magnitude of ETS exposure (*136*).

Because nicotine is not suspected of inducing asthma and is not a UAT, and because RSP contains many compounds that affect asthma and are UATs, a preliminary evaluation of the magnitude of RSP exposure associated with increased asthma is worthwhile. The amount of RSP produced in the breathing zone of a child will vary with the number of smokers, proximity to the smokers, ventilation, and other variables. Nonetheless, average room RSP concentrations (obtained from ≥ 4 hr samples) are typically elevated by 2 to 5 $\mu g/m^3$ per cigarette smoked in an average size room (*138*). Background indoor RSP levels vary depending on other indoor aerosol sources and the amount of penetration of the ambient aerosol [this can be substantial (50–80%) for particles in this size range], and typically are 15 $\mu g/m^3$ [Table 12; (*65*)]. Smoking typically can bring RSP levels up to 45 $\mu g/m^3$ (with a range of 18–95 $\mu g/m^3$) (*138–140*).

Increases in the incidence and prevalence of asthma among children have been noted when mothers smoke 10 or more cigarettes per day (*141,142*). Applying the findings of Leaderer et al. (*138*), we calculate that 10 cigarettes would generate an atmosphere containing 20 to 50 $\mu g/m^3$ RSP above background and result in total exposure to approximately 35 to 65 $\mu g/m^3$ RSP. Exposures in this range have been estimated to induce 8000 to 26,000 new cases of asthma annually (based on estimates of maternal smoking). It is feasible that UAT exposures, when mixed with the respirable particulate load in this range, also could adversely impact persons with asthma. This level of particulate exposure is

Table 11. Major chemicals in environmental tobacco smoke.

Vapor phase	Particulate phase
>1000 μg/cigarette in mainstream smoke	
Carbon monoxide	Nicotine
1000 > × > 100 μg/cigarette in mainstream smoke	
Toluene[a]	Phenol[a]
Acetaldehyde[a]	Catechol[a]
Methyl chloride[a]	Hydroquinone[a]
Nitrogen oxides	
Acetic acid	
Hydrogen cyanide	
Formic acid	
100 > × > 1.0 μg/cigarette in mainstream smoke	
Formaldehyde[a]	Quinoline[a]
Benzene[a]	Cresols[a]
Acrolein[a]	Anatabine
Propionaldehyde[a]	γ-Butyrolacetone
1,3-Butadiene[a]	
Styrene[a]	
Carbonyl sulfide[a]	
3-Vinylpyridine	
3-Methylpyridine	
Methylamine	
Dimethylamine	
Ammonia	
>1.0 μg/cigarette in mainstream smoke	
Hydrazine[a]	4-Aminobiphenyl[a]
N-Nitrosodimethylamine[a]	2-Toluidine[a]
N-Nitrosodiethylamine	*N*-Nitrosodiethanolamine[a]
N-Nitrosopyrrolidine	Cadmium[a]
	Nickel[a]
	Chromium[a]
	Polycyclic aromatic hydrocarbons[a]
	Benz[*a*]anthracene[a]
	Benz[*a*]pyrene[a]
	Aniline[a]
	Polonium-210[a]
	Dioxins[a]
	Zinc
	2-Naphthylamine
	4-(*N*-Methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone
	N-Nitrosonornicotine
	1-Methyl-9H-pyrido[3,4-*b*]-indole

[a]Compounds included in Title III—Hazardous Air Pollutants of the Clean Air Act 1990. Concentrations are from IARC (*137*) and U.S. EPA (*136*).

Table 12. Average ambient aerosol concentrations (μg/m^3) in six cities in the United States.[a]

City	Total suspended particulate	PM_{10}	$PM_{2.5}$	$PM_{2.5}/PM_{10}$
Portage, WI	34	18	11	0.61
Topeka, KS	57	26	13	0.50
Watertown, MA	49	24	15	0.63
Harrison, TN	49	33	21	0.64
St Louis, MO	73	31	19	0.61
Steubenville, OH	90	47	30	0.64

[a]Values for total suspended particulate are from 1977 to 1985; PM_{10} and $PM_{2.5}$ from 1979 to1985. From Dockery (*50*).

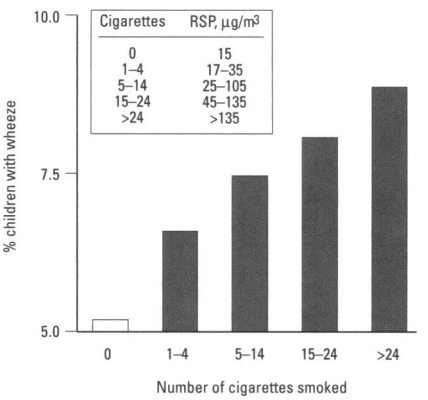

Figure 3. Increase in the percentage of children with the respiratory symptom of wheeze associated with maternal smoking. From Newspiel (*143*). Table (insert) includes estimated values of respirable suspended particulate calculated from data presented by Leaderer (*138*).

well below the current PM_{10} ambient air standard of 150 μg/m^3.

Other studies have examining the relationship between ETS generated by mothers and respiratory symptoms (wheeze, etc.) associated with asthma in children. The data in Figure 3 suggest an association with an increase in symptoms with an increase in maternal smoking (*143*). Again, an adverse response was noted at relatively low levels of exposure of 1 to 4 and 5 to 14 cigarettes per day smoked by the mother. Applying the estimates of RSP produced by these exposures yields estimated concentrations of added particulate of 2 to 20 μg/m^3 and 17 to 35 μg/m^3 above background. Similarity, Lebowitz and Quakenboss (*144*) 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.

Several factors are uncertain in these comparisons, however. First, because maternal smoking has a greater effect than paternal smoking, it also may influence the development of asthma *in utero* by limiting lung development (*145–147*). In addition, average concentrations of room air samples may underpredict the levels in a child's breathing zone because small children are often held by their mothers. 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 UATs also may be intermittent, with wide variances in concentration. Thus, it is important to obtain time–activity information to predict personal exposures by combining microenvironmental concentration information with duration of exposure obtained from time–activity analyses.

Second, the physical and chemical properties of ETS differ from those of the ambient mixture of gaseous and particulate UATs. Although several main irritants are contained in both, the levels of most are greater in ETS than in urban air. The particle size also may differ in that ETS is ≤ 1.0 μm [sidestream smoke is typically 0.001–1.0 μm and mainstream smoke is 0.1–1.0 μm in diameter (*148*)], whereas the cutoff diameter of PM_{10} in the ambient aerosol containing UATs is 10 μm. Besides mass concentration (i.e., μg/m^3), certain aspects of particulate toxicity depend on the number of particles (*149–151*). Because mass depends on particle volume, small increases in diameter in this range can have large influences on the reduction number of particles. Thus, particles between 1.0 to 10 μm add greatly to the mass estimates of UATs in air. Nonetheless, ambient fine (< 2.5 μm) particulate between 11 and 30 μg/m^3 and inhalable (< 10 μm) particulate between 18 and 47 μg/m^3 has been associated with increase in cardiovascular and respiratory disease (*50*).

An Evaluation of Human Exposure and Its Relationship to Asthma

Identification Criteria for UATs Likely to Impact Asthma

Reversible, acute airflow obstruction (indicated by diminished expiratory flow that can be reversed by adrenergic therapy) produced by direct exposure in a clinical setting has become a useful operational definition for the evaluation of chemically induced asthma (*5,101*). Through direct bronchoprovocation with a series of compounds, certain chemicals have been identified to produce marked responses. Common asthmagens identifiable by this method include metals (chromium trioxide, chromates, nickel sulfate, and platinum compounds). Such an approach is particularly useful in diagnosis of occupational asthma and is aided by knowledge of the chemicals present in the workplace and the reversal of symptoms upon their removal from the workplace. Although much can be learned by this diagnostic strategy, it may be impractical to apply this approach to future evaluations of the toxicity of over 189 compounds.

Further, certain known occupational asthmagens act by an immunologic mechanism in some persons, but not in others. These compounds include polyisocyanates, acid anhydrides, and aldehydes. In these cases, the threshold concentration needed to produce bronchospasm is likely to below that necessary to induce nonimmunospecific irritation. Other substances (acting like sulfur dioxide and perhaps ozone) do not produce antigenic responses but can provoke bronchoconstriction in persons with asthma at concentrations that are lower than those that are bronchoconstrictive in healthy subjects. These chemicals may act as an irritant and have an ability to induce airway epithelial injury and inflammation, effects that can be barely perceptible at doses in the range occurring in the environment. Released from stationary sources, such UATs can mix with other toxic chemicals in the urban air and add to the irritant load presented to persons with asthma in the general population.

Many UATs have insufficient scientific data to evaluate their immunologic potential, however. Because of this situation, because it is difficult to limit the definition of asthma to antigenic responses, and because of difficulties in ascertaining whether each chemical by itself causes or

Table 13. Estimates of environmental concentrations of air toxics suspected of being human asthmagens.

Compound	Past exposure levels, μg/m³		
	Occupational	Nonoccupational	Fugitive emissions
Aldehydes			
Acrolein	130–7200	32	320–640
Formaldehyde	>370	0.05–70.1	–
Propionaldehyde	–	–	–
Acetaldehyde	1200–3400	0.4–124	–
Polyisocyanates/Isocyanates			
Toluene diisocyanate	14–1050	0–150	100–17,700
Hexamethyl diisocyanate	1000–3780	–	–
Methylene diphenyl diisocyanate	102–204	–	–
Methyl isocyanate	–	–	–
Acidic anhydrides			
Maleic anhydride	–	–	–
Phthalic anhydride	3000–13,000	–	–
Metals			
Cadmium	15–5000	3–50	–
Chromium	>1300	0.009–0.300	>1000
Chromate (VI)	38–1000	–	–
Cobalt	70–500	0.01	–
Nickel	500–900	0.005–0.035	0.124–0.328
Others			
Hydrazine	350–1100	–	4000
p-Phenylenediamine	–	–	–

exacerbates asthma through clinical experimentation (*152*), the broader chemical properties of UATs need to be considered. Properties that are important to this question include respirability, irritancy, and skin antigenicity.

Several compounds identified as UATs share these properties and can clearly be classified as suspected human asthmagens. These compounds are listed in Table 13. These compounds have had documented reports in the medical literature associating human exposure with asthma (either as inducers or exacerbaters). This includes polyisocyanates, aldehydes, anhydrides, and metals–compounds with wide acceptance among the scientific community as to their effects in occupational settings.

Other UATs share a portion of these properties, but it is unclear whether they can induce persistent asthma. Adding to the difficulty of this situation are the uncertainties created by the gaps in the literature regarding the human toxicity of each compound. Nonetheless, to develop logical strategies to assess possible links between environmental exposure to these compounds and asthma, the limited human experience must be considered. This second group of compounds (Table 14) includes skin allergens (compounds producing allergic contract dermatitis) with chemical properties that suggest inhalation as a route of exposure (*153,154*). This includes hydrazine, *p*-phenylenediamine, nickel, and chromium compounds. In addition, other compounds known to react covalently with proteins or DNA include polycylic aromatics/aryl epoxides, *bis*-chloromethyl 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 (*155–158*). Carcinogenic compounds can cause irritation and inflammation at sites of exposure and are often antigenic (*159–164*).

Last, potent respiratory irritants with wide-scale usage are included in this list. Substances such as cadmium compounds, chlorine, hydrochloric acid, hydrogen fluoride, phosgene, phosphine, and hydrogen sulfide 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).

Noticeably not included on these lists are UATs that are also VOC compounds listed in Tables 5 through 8. As noted above, these compounds have been associated with increased asthma symptoms in controlled human studies (*111,113,114*) and epidemiologic studies (*165*). 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. Investigations of human exposures to these compounds separately and as mixtures are likely to yield additional insights into their possible role in inducing asthma and therefore will be worthwhile.

Our literature review of other UATs listed in Table 1 suggests that they may be of lesser concern. It is appreciated that these compounds also may contribute (particularly as mixtures) to other serious health outcomes, and therefore inclusion of compounds with high enough priorities for more immediate consideration should be based on these effects. (Examples include benzene and 1,3-butadiene.)

Table 14. Concentrations of air toxics suspected of being respiratory irritants (exacerbators) in asthma.

Compound	Past exposure levels, μg/m³		
	Occupational	Nonoccupational	Fugitive emissions
bis-Chlormethyl ether	0–14,100	–	–
Dimethyl carbamyl chloride	300–7000	–	–
Dimethyl sulfate	42–5290	–	–
Phosgene	520–4000	–	–
Phosphine	60–370	–	–
Chlorine	1000–2900	30	–
Coke oven emission	0.06–0.56	0.03–0.14	–
β-Propiolactone	–	–	–
Chlorine	1000–2900	30	>3000
Hydrogen fluoride	890	0.16–1.9	–
Dioctyl phthalate	8000–53,000	0.026–0132	–
Dibutyl phthalate	–	0.033–0.006	–
Dimethyl phthalate	–	–	–
Hydrochloric acid	500–15,000	–	–
Hydrogen sulfate	>140,000	–	–

Estimates of the Magnitude of Exposure to Asthmagens

The extent of human exposure must be considered in the evaluation of the role of UAT in asthma. Because air sampling is

not routinely performed on each of these compounds, the lack of scientific information requires caution. One approach is to consider the extent of occupational exposure as an indication of possible sources of emissions. Recently, Seta and coworkers (*166*) 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.) At a minimum, this suggests that several point sources exist that can potentially contribute to community air pollution. Historic levels reported in occupational settings are presented in Tables 13 and 14. Information on the level of current exposures is limited and requires additional study.

Table 15. Estimated release of asthmagens into the air, 1990.[a]

Compound	Facilities	Pounds, × 1000
Styrene	1,398	31,817
Formaldehyde	871	12,309
Acetaldehyde	80	7,179
Propionaldehyde	18	989
Nickel and compounds	2,111	923
Phthalic anhydrides	188	689
Methylene diphenyl diisocyanate	589	665
Maleic anhydride	226	493
Chromium and compounds	201	150
Toluene diisocyanate	172	113
Cadmium and compounds	254	104
Cobalt and compounds	201	37
Hydrazine	54	27
Acrolein	16	22
Methyl isocyanate	8	14
p-Phenylenediamine	12	1
Total	6,399[b]	55,532[b]

[a]Values are estimates from U. S. EPA (*167*). [b]Assumes no overlap in usage (may be an overestimate if more than one compound is used).

Table 16. Estimated release into the air of urban air toxics suspected of exacerbating asthmagens, 1990.[a]

Compound	Facilities	Pounds, × 1000
Respiratory carcinogens		
bis-Chlormethyl ether	3	5
Polycylic aromatics	–	–
β-Propiolactone	–	–
Dimethyl carbonyl chloride	–	–
Respiratory irritants		
Chlorine	1747	105,072,589
Dibutyl phthalate	152	130,027
Dimethyl phthalate	62	333,555
Dimethyl sulfate	31	9,739
Dioctyl phthalate	353	1,344,752
Hydrochloric acid	3347	77,389,964
Hydrogen sulfide	–	–
Hydrogen fluoride	531	8,736,302
Phosgene	35	4,854
Phosphine	–	–

[a]Values are estimates from U.S. EPA (*167*).

Another approach to estimate the extent of exposure is to consider the emission inventories recently compiled by the U.S. EPA. Table 15 lists UAT compounds that are known or suspected asthmagens and presents the number of facilities and the total amounts estimated to be released into the air. These values are for the amounts released directly into the air and do not include estimates of intermedia transport or other pathways that might result in inhalation exposures in the ambient air. Styrene (*168–170*), formaldehyde (*171*), and acetaldehyde (*172*) are the three chemicals with the greatest number of reporting sources and with the greatest amount of release. In 1990, the total estimated release into the air of these 16 asthmagens was over 55 million pounds.

Release inventories for other UATs that might influence the respiratory health of persons with asthma are listed in Table 16. The highest levels of release are reported for chlorine and hydrochloric acid, two respiratory tract irritants. The estimated release of respiratory carcinogens is low. Estimates of the release of polycyclic aromatic hydrocarbons, however, are unlikely to be accurate because this value does not include amount produced by combustion. In addition, 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. Furthermore, recent studies in California suggest that models of air toxic exposures using inventories often underestimate the actual measured concentrations downwind from stationary sources (MA Marty, personal communication). Nonetheless, the large number of possible point sources indicates that extensive human exposure is possible.

In addition, predictions of ambient concentrations require applications of air quality dispersion models of chemical-specific data. It is unclear whether inventory data have enough fidelity for such applications. Another important gap in the literature is whether cumulative effects result from multiple acute exposures at high levels. Release inventories only present estimates of annual averages and therefore lack detail for modeling elevated acute exposures.

Current Exposure Guidelines

Tables 17 and 18 present concentration guidelines for occupational and nonoccupational exposure. Included in these tables are the current ACGIH-TLVs (threshold limit values from the American Conference of Governmental Industrial Hygienists) for time-weighted averages for occupational exposures for a normal 8-hr workday and a 40-hr workweek, to which nearly all workers can be repeatedly exposed, day after day, without adverse effects. Importantly, 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. Consequently, these values are unlikely to provide an adequate margin of safety for the general population. In addition, a comparison of the lowest odor threshold presented in Tables 5 and 6 and the TLVs presented in Tables 17 and 18 indicates that odor thresholds are often above recommended exposure limits, suggesting that when odor is detected, significant exposure can occur.

Also presented in Tables 17 and 18 are guidelines for exposure in the ambient air. Ambient air level goals (AALG) were obtained from a monograph by Calabrese and Kenyon (*174*). These guidelines are based on calculation from no observed effects level (NOEL) or lowest observed effects level (LOEL) corrected for lifetime exposure and divided by appropriate multiplicative uncertainty factors (as much as 1000 over the NOEL). When animal toxicity data are used, adjustments are made for the equivalent human breathing rates using species-specific equations and absorption factors.

Also presented in Tables 17 and 18 are the current reference exposure levels (RELs) developed for California (*175*). Exposure to each substance independently at or below these values is not expected to result in adverse (noncancer) health effects following 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 $\mu g/m^3$) equal to the cancer unit risk. For example, if a community of one million is exposed to 2.7 $\mu g/m^3$

Table 17. Air exposure limits/guidelines and cancer unit risks for asthmagens.

Compound	ACGIH-TLV,[a] µg/m^3	ALG,[b] µg/m^3	California reference exposure levels[c] Acute, µg/m^3	Chronic, µg/m^3	Cancer unit risk,[d] (µg/m^3 × 10^6)$^{-1}$
Acid anhydrides					
Maleic anhydride	1,000	20.0	10.0	2.4	–
Phthalic anhydride	6,000	300.0	{7000}	–	–
Aldehydes					
Acetaldehyde	45,000	–	–	9.0	2.7
Acrolein	230	0.037	2.5	0.02	–
Formaldehyde	370	0.062	370.0	3.6	6.0
Metals					
Cadmium and compounds	10	0.00011	–	{3.5}	4,200.0
Chromium and compounds	50	0.00002	–	0.002	14,000.0
Cobalt and compounds	50	0.24	–	–	–
Nickel and compounds	100	0.00036	1.0	0.24	260.0
Polyisocyanates					
Methylene diphenyl Diisocyanate	51	0.6	–	–	–
Toluene diisocyanate	36	–	–	0.095	11.0
Other compounds					
Hydrazine	100	0.0001	–	0.24	4,900.0
Methyl isocyanate	47	–	–	0.36	–
p-Phenylenediamine	100	–	–	–	–
Styrene	213	26.0	–	{700}	0.57

[a]Values are threshold limit values (TLV) for time-weighted averages for occupational exposures for a normal 8-hr workday and a 40-hr workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. Data from American Conference of Governmental Industrial Hygienists (*173*). [b]Ambient air level goal (AALG) as presented by Calabrese and Kenyon (*174*). [c]Reference exposure levels as presented by California Air Pollution Control Officers Association (*175*). Exposures to a single substance at or below this level is not expected to result in adverse (noncancer) health effects following estimated annual average for inhalation (chronic) or estimated 1-hr maximum concentrations (acute). Values in brackets {} are based on oral acceptable exposure levels. [d]Cancer unit risks are cancer potency values or preliminary potency values from California Air Pollution Control Officers Association (*175*). Exposure estimates multiplied by these values equal individual cancer risk for exposure to a single compound.

Table 18. Air exposure limits/guidelines and cancer unit risks for compounds suspected of exacerbating asthma.

Compound	ACGIH-TLV,[a] µg/m^3	ALG,[b] µg/m^3	California reference exposure levels[c] Acute, µg/m^3	Chronic, µg/m^3	Cancer unit risk, (µg/m^3 × 10^6)$^{-1}$
Respiratory carcinogens					
bis-Chloromethyl ether	4.7 (A1)[e]	2.0×10^{-7}	–	–	13,000
Polycyclic aromatics	(A2)	–	–	–	1,700
β-Propiolactone	1,500.0 (A2)	–	–	–	–
Dimethyl carbonyl chloride	(A2)	–	–	–	–
Respiratory irritants					
Chlorine	1,500.0	17.0	23	7.1	–
Dibutyl phthalate	5,000.0	44.0	–	–	–
Dimethyl phthalate	5,000.0	700.0	–	–	–
Dimethyl sulfate	520.0 (A2)	–	–	–	–
Dioctyl phthalate	–	–	–	–	–
Hydrochloric acid	7,500.0	150.0	3,000	7.0	–
Hydrogen sulfide	14,000.0	–	42	42.0	–
Hydrogen fluoride	2,600.0	–	580	5.9	–
Phosgene	400.0	–	12	–	–
Phosphine	4,200.0	–	–	{10}	–

[a]Values are threshold limit values (TLV) for time-weighted averages for occupational exposures for a normal 8-hr workday and a 40-hr workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. Data from American Conference of Governmental Industrial Hygienists (*173*). [b]Ambient air level goal (AALG) as presented by Calabrese and Kenyon (*174*). [c]Reference exposure levels as presented by California Air Pollution Control Officers Association (*175*). Exposures to a single substance at or below this level is not expected to result in adverse (noncancer) health effects following estimated annual average for inhalation (chronic) or estimated 1-hr maximum concentrations (acute). Values in brackets {} are based on oral acceptable exposure levels. [d]Cancer unit risks are cancer potency values or preliminary potency values from California Air Pollution Control Officers Association (*175*). Exposure estimates multiplied by these values equal individual cancer risk for exposure to a single compound. [e]Designations of A1 and A2 are given by the ACGIH for confirmed and suspected human carcinogens, respectively.

acetaldehyde, control actions are recommended based on a cancer risk (rather than based on the chronic REL that is 9.0 µg/m^3). Similarly, styrene exposures are limited more by the estimates for cancer risk than by the chronic REL. For the remainder of compounds in Table 17 that have both a cancer unit risk and chronic REL value (formaldehyde, cadmium, chromium, nickel, toluene diisocyanate, and hydrazine), exposure is to be limited based more on the chronic noncancer effects.

It is noteworthy that IRIS or other documentation of these values does not consider the possibility of induction or exacerbation of asthma specifically as a basis for chronic noncancer effects. NOEL for these compounds are primarily selected by the estimates of respiratory irritation. For example, formaldehyde's ACGIH-TLV and IRIS values are based on the data obtained on irritation, and not on potential to induce asthma or animal carcinogenesis data (*173*). 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 of more relevance when considering safeguarding a heterogeneous general population compared to 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.

Future Research Priorities

Exposure Assessment

Future scientific investigations are needed to evaluate the possible links between UATs and asthma. Currently, little information exists on human exposure to these compounds. In particular, emission release inventories have yet to be validated by environmental sampling. Another unsettled issue specific to 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 and release from building materials, personal care products, and clothing (*171*). Initially, field investigations could assess total exposures to aldehyde and metal asthmagens

using probability-based sampling. One exposure aspect that is important in the induction of asthma is that the magnitude of peak concentrations and ambient air samples should include variant sample times if possible. Last, this group of compounds is ideal for future investigation of fugacity models and it would be helpful to know the amount of intermedia transport for these compounds, particularly the less volatile organic compounds.

Health Effects Assessment

Because these compounds are highly toxic and in some cases carcinogenic, further human clinical testing is unlikely. Consequently, *in vitro* toxicology testing with human cell culture systems may be an acceptable alternative. End points important to airway inflammation, for example cytokine and eicosanoid production, should be examined to establish dose–response information. 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 molecular end points (e.g., detection of mRNA for key cytokine by *in situ* hybridization), these species are often less responsive than humans and make tests of lung functions difficult. 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 in evaluation of airway bronchoconstriction and hyperreactivity. The effects of chronic inhalation exposure to the UATs and the induction of persistent hyperreactivity is 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 UATs, UATs with particulate matter, or UATs 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 dioxide and metal aerosols (*176*). Currently, ambient air quality standards are based largely on data obtained when each criteria pollutant is tested independently. Indeed, concerns about exceedances are based on the expected adverse effects of the pollutant in highest concentration (often ozone) without concern about coexposure to other irritant pollution present in the typical oxidant urban plume. For example, urban concentrations of aldehydes and other volatile organic compounds follow diurnal patterns and have peaks above 50 $\mu g/m^3$ (*171*). These exposures can occur with subsequent high ozone exposures (>250 $\mu g/m^3$), and recent epidemiological 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 17.)

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. It would be useful to estimate the extent of exposure to these identifiable asthmagens. Such data could be useful in assessments of health care costs (*178*).

Last, the current epidemiological information on the possible associations between UATs and asthma is inadequate. Recent studies with criteria pollutants suggest that animal and clinical exposure data can underestimate respiratory health effects. One epidemiological study of formaldehyde suggests that children exposed in homes with concentrations of >150 $\mu g/m^3$ had a higher frequency of asthma and bronchitis than children with residential exposure <50 $\mu g/m^3$ (*179*). Decrements in PEF were also correlated 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 UAT exposure on persistent pulmonary function is thus warranted.

Conclusions

In summary, asthma is a serious illness with a high prevalence among the general population. Over the last 15 years, the incidence and severity of asthma have continued to increase. In the past, exposure to air pollution has been associated with an increase in respiratory symptoms and hospital admissions for asthma. The role of UATs 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 etiological factors in asthma.

Several UATs are known comounds or are related to compounds that are occupational asthmagens. Environmental agents associated with asthma include ambient particulate matter and environmental tobacco smoke; both are complex mixtures containing many compounds that are UATs. Last, several UATs 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 UAT compounds have antigenic potential and can be 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 UATs in asthma.

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