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Airborne Environmental Injuries and Human Health

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Abstract

The concept that the environment in which we live can have detrimental effects on our health has existed for centuries. Obvious examples of substances that can cause human diseases include infectious agents, poisons, chemicals and other noxious agents, drugs, and physical stimuli such as bright lights and loud sounds. Some less obvious agents can include allergens, nontangible agents such as colorless, odorless gases and aerosolized toxins. In recent decades, humans have developed various new materials and compounds. Additionally, we are now producing known compounds, and even naturally occurring substances, in vastly increased amounts. Many of these substances are generally believed to threaten the health of our environment. However, there is also a considerable amount of hype and exaggeration regarding some of these agents (e.g., mold) that is unsubstantiated. This article extensively reviews the data on a large number of airborne-related illnesses and attempted to place scientific reality in the context of clinical medicine.

Index Entries

Sick Building Syndrome; volatile organic compounds; formaldehyde; phthalates; organophosphate pesticides; organochlorines; particulate matter; biologicals.

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The Sick Building Syndrome

One of the most widespread consequences of the use of new materials in ever more air-tight buildings may be the so-called Sick Building Syndrome (SBS). SBS is a rather poorly defined term referring to a set of nonspecific skin, mucous membrane, neurological, respiratory, and generalized symptoms experienced by people working in nonindustrial environments in the absence of a known causative agent; these symptoms diminish or disappear during absences from these work environments *(1)*. These introductory comments are made with the understanding that the vast majority of so-called SBS outbreaks have been shown secondary to discrimination bias, secondary gain, or both. However, a number of important illnesses can occur in very air-tight buildings. With the recognition that such nonspecific symptoms are reported in almost all office buildings, as well as in schools, libraries, hospitals, homes for the elderly, and apartments, they are increasingly referred to as building-related symptoms. This can be somewhat misleading because the terms "building-related symptoms" and "building-related illness" used to be reserved for symptoms with identified causes *(2,3)*. Confusion can be avoided by distinguishing between nonspecific and specific building-related illnesses. For the sake of simplicity, we use the term SBS for the nonspecific symptomatology experienced by occupants of nonindustrial buildings.

SBS symptoms most commonly are general or neurophysiological or affect mucous membranes, the upper and lower respiratory systems, or the skin. General symptoms include headache, dizziness, nausea, mental fatigue, difficulty in concentrating, and lethargy. Upper respiratory and mucosal symptoms consist of dry, itchy, sore, burning, or otherwise irritated eyes, nose, sinuses, or throat, whereas lower respiratory symptoms include cough, wheeze, difficulty breathing, and chest tightness. Red, dry, or itchy skin is the most common dermatological manifestation.

The prevalence of SBS symptoms ranges between a few percent and 50 to 60%; additionally, with 70% of US workers (or approx 89 million people) employed in nonindustrial indoor settings *(4)*, SBS constitutes one of the most common environmental health issues *(3)*. The economic impact of productivity losses and health care costs has been estimated to amount to $50 to $100 billion, of which $5 to $75 billion is potentially preventable by using the appropriate measures *(4)*.

Appropriate measures are currently difficult to identify because the underlying causes of SBS remain largely unknown, although it has been associated with a large variety of factors, including building, work environment, demographic, and personal characteristics (*see* Table 1). One finding has clearly emerged from the studies analyzing these associations: the etiology of SBS is multifactorial, arising from complex interactions between chemical, physical, biological, and psychosocial factors *(3)*.

The ventilation rate is one of the work environment features most consistently associated with SBS symptoms. From a review of the literature, a multidisciplinary group of European scientists concluded that ventilation rate was strongly associated with perceived air quality, SBS symptoms, and various other health outcomes such as inflammation, infections, asthma, allergy, and short-term sick leave *(5)*. The data also showed that increased ventilation was associated with enhanced productivity. Previous reviews had indicated that there was an increased risk of adverse health effects at outdoor airflow rates lower than 10 L/s and that perceived air quality improved and SBS symptoms decreased with higher ventilation rates in most studies *(6,7)*. The minimum ventilation rate set by the American Society of Heating, Refrigeration, and Air Conditioning Engineers is 10 L/s per person. However, European scientists concluded that the risk of SBS symptoms increased at outdoor air-supply rates lower than 25 L/s per person *(5)*. Note that increasing the outdoor air supply can result in deteriora-

Table 1
Factors Frequently Found to be Associated With Sick Building Syndrome

Building factors	Work environment	Air pollutants	Demographic	Personal
Ventilation system	Insufficient fresh air supply (low ventilation rate, high CO_2 concentrations)	VOCs	Female gender	History of atopy, allergy, or asthma
Number of floors	Excessive air movement	TVOCs	Younger age	History of medical condition (sinus problem, migraine, allergy, or asthma)
Factual building age (years since construction)	Perceived air quality	Microbial TVOCs		Work-related stress and other psychosocial factors
Virtual building age (years since construction or last remodeling)	Olfactory load	"Lost" VOCs		Overtime
Parking garage within the building	Humidity (too low or too high)	NO_2		Personality
	Lighting (too dark or too bright)	O_3		Active smoking
	Crowding	Bio-effluents		
	Dampness	Particulate matter/dust		
	Microbial contamination	ETS		
	Noise, particularly low frequency noise			
	Low thermal comfort (temperature too low, too high, or fluctuating too much)			
	Presence of office machines (copiers, laser printers, visual display terminals)			
	Handling of paper			
	Lack of cleanliness			

tion of indoor air quality if outdoor pollutants are insufficiently filtered by the ventilation system *(8)*.

Indoor carbon dioxide (CO_2) concentrations are often used as a surrogate not only for occupant-generated pollutants but also for ventilation rate per occupant. However, CO_2 concentrations in occupied buildings usually do not reach steady state, and for this and various other reasons, CO_2 concentrations may not accurately reflect ventilation rates *(6)*. Nonetheless, the results of studies investigating the association of CO_2 concentrations with SBS symptoms are generally similar to those obtained with ventilation rates. Analysis of data from 41 of 100 US office buildings studied in the Building Assessment Survey and Evaluation (BASE) undertaken by the US Environmental Protection Agency (EPA) indicated a dose–response relationship between the average workday indoor minus average outdoor CO_2 concentrations (dCO_2) and sore throat, nose or sinus symptoms, tight chest, and wheezing *(9)*. The adjusted odds ratios (ORs) per 100 ppm dCO_2 ranged between 1.2 and 1.5. When the analysis was extended to the whole set of 100 buildings, however, many of the previously reported associations were not evident, and the ORs for sore throat and wheeze were reduced to 1.15 and 1.21, respectively *(10)*.

The rather consistent observation of a significant negative association between ventilation rate or CO_2 levels and SBS symptoms suggests that irritating compounds arising from indoor sources play a causative role in these symptoms and that the removal, or at least dilution, of such chemicals should result in a decrease of reported symptoms. It has long been suspected that volatile organic compounds (VOCs) are important contributors to SBS, but conclusive evidence is lacking. The VOCs may not be responsible for the SBS symptoms; rather, the products of their reaction with ozone and other chemicals may trigger the symptoms. Ultrafine particles, which can act as strong airway irritants, are one example of these reaction products. Particulate matter (PM) from various sources is another possible causative agent of SBS symptoms, especially because it has been associated with respiratory symptoms in healthy and asthmatic subjects.

Two other groups of chemicals known to cause some of the symptoms of SBS, phthalates and pesticides, have received surprisingly little attention in attempts to identify agents involved in SBS. However, they should be an important focus of research, given their large-scale production and use, their known adverse effects in experimental animals, and the growing concern that they, along with other environmental exposures, have contributed to the increasing incidence of certain symptoms and diseases in humans and wildlife. These other exposures include persistent organochlorine compounds that were widely produced and used in the 1960s and 1970s, before researchers realized that they accumulated in the environment and in various biota to the extent that they caused serious adverse effects on wildlife and humans. Their permanence ensures that humans will be exposed to them for generations to come. Therefore, it is important to fully understand their health effects and, above all, their interactions with the myriad of other pollutants we produce and are exposed to in ever-increasing amounts in the air, food, water, dust, soil, and everything we come in contact with.

Volatile Organic Compounds

VOCs are compounds that contain at least one carbon and one hydrogen atom, participate in atmospheric photochemical reactions, and have a low boiling point (50–260°C), which means they readily vaporize at room temperature. Formaldehyde is sometimes designated as a VOC, but it is not truly a VOC because it is a gas at room temperature. Because it also requires different analytical techniques, it is not as routinely measured as VOC.

Occupational exposure to VOCs and formaldehyde are associated with some of the same

symptoms as SBS *(2)*. However, levels of these compounds in office and other buildings are considerably lower than those found in industrial settings. Concentrations of total VOC (TVOC) in office buildings commonly range between less than 100 $\mu g/m^3$ and several thousand micrograms per cubic meter, but maximum values of up to 50,000 $\mu g/m^3$ have been reported *(11,12)*. More than 350 VOCs have been detected at concentrations exceeding 1 ppb in indoor air *(3)*, but generally only about 30 to 70 are routinely measured and even fewer are consistently detected in a majority of office buildings *(12–15)*.

When a group of Nordic scientists reviewed the literature up to early 1996 regarding VOC/TVOC and health, they concluded that neither exposure nor epidemiological studies provided conclusive evidence that TVOC provided a risk index for health and comfort effects in buildings *(11)*. A similar conclusion was reached in a review of studies that examined the association between SBS symptoms and indoor airborne PM, to which VOC can be adsorbed *(16)*. However, the Nordic scientists stated that indoor air pollution, including VOCs, was most likely causally linked to effects on health and comfort. They also emphasized that there were "problems of principle with the concept of TVOC as such" because it is poorly defined—that is, it refers to different mixtures of chemicals with varying biological effects and is used in an unsystematic manner. Additionally, the use of various different sampling and analytical methods constitutes a major source of variability between studies *(17)*.

There are various other problems with the way current assessments of factors related to SBS symptoms are conducted. Measurements are often taken in only a few locations in a building, without accounting for the fact that there are microclimates in buildings resulting from differences in the ventilation rates, in the number of occupants and the amount of bioeffluents they produce, and in the furnishing and equipment and, therefore, in the sources of chemical compounds and their source strength. Additionally, symptoms are generally assessed via questionnaires, and these differ between studies and are not always validated. The period for which symptoms are assessed also varies from the single day on which environmental measurements are taken to as long as the previous year. In several studies, there is a considerable lapse of time between these measurements and the assessment of symptoms. The number and type of factors included as covariates or confounders in the statistical analysis also varies substantially between studies. Additionally, none of the available studies that we reviewed accounted for the fact that people are exposed to a wide variety of chemicals in microenvironments other than the workplace—particularly at home, where they spend the majority of their time.

These considerations may explain the frequent failure to detect an association between VOC/TVOC and SBS. Various other hypotheses have been proposed to explain why VOCs may be an important factor in SBS, although the evidence is inconclusive *(18)*. For example, it is possible that SBS is associated with a subgroup or subgroups of VOCs rather than TVOC and/or with intermediates or products of reactions between certain types of VOCs and ozone (O_3) or various reactive oxygen and nitrogen species.

Principal component analysis (PCA) has become an important tool for identifying groups of chemicals and other factors that could explain the different frequencies of SBS symptoms in different buildings. It condenses a set of highly correlated variables into a smaller number of linearized sums (principal components [PCs]). This works particularly well for VOCs because subsets of them have common sources. Because VOCs can originate from more than one source, they can be associated with more than one PC.

PCA on a total of 39 VOCs measured in 12 California office buildings was used to identify

exposure metrics—that is, mathematical expressions of the potential or actual agent (or combination of agents) that causes an adverse health effect *(19)*. The exposure metric termed irritancy/PC emerged as the most significant predictor of irritant symptoms. It consisted of the two most relevant vectors obtained by PCA, which were identified as representing carpet and building material emissions and emissions from cleaning products and water-based paint; it also accounted for the irritancy of VOCs relative to toluene. When analyzed separately, the cleaning products and water-based paints source vector provided the most important symptom prediction, with statistically significant adjusted ORs ranging from 1.7 to 2.2 for eye, skin, throat, stuffy nose, and overall symptoms.

Other studies that used PCA on VOCs, but without accounting for their irritancy, linked photocopier emissions to mucous membrane symptoms; paint-derived VOCs to sore throat symptoms; construction material emission to dry eyes, mucous membrane symptoms overall, and short breath; and VOCs associated with furniture coating to shortness of breath *(14,20)*.

A combination of PCA and partial least-squares analysis of VOCs desorbed from dust samples from nine office buildings identified a set of compounds that could account for 80% of the variance in the frequency of mucous membrane complaints and another set of compounds that explained 66% of the variance in difficulty concentrating *(21)*. The possibility that oxidative degradation products of α- or β-pinene were among the compounds associated with mucous membrane irritation was particularly intriguing. As discussed later, the oxidation of terpenes produces formaldehyde and other aldehydes, and there are indications that some considerably more irritating substances are also formed.

PCA was also used to identify factors that would be able to distinguish buildings with a high prevalence of SBS symptoms from those with a low prevalence of SBS symptoms *(22)*. The most complex model was able to separate 71% of high-prevalence from low-prevalence buildings, and the most important variable was the higher concentration or more frequent detection of compounds with higher retention times in gas chromatography analysis in buildings with a low prevalence of symptoms.

However, it is unclear whether a comparison between buildings constitutes a meaningful approach to identifying factors that predict SBS symptoms. As Menzies and Bourbeau *(2)* pointed out, three phenomena help explain many of the features of SBS:

1. People vary in their susceptibility to various agents.
2. There is a wide spectrum of responses to a given agent.
3. Exposures vary considerably within large office buildings (i.e., spatial and temporal variations in local pollutant sources and ventilation rates may create many different microenvironments throughout a large building).

In five office buildings with different frequencies of reported SBS symptoms, cluster analysis was used to identify "hot" and "cold" spots—that is, areas with high and low symptom frequencies—in each building *(23)*. Only people working in areas where chemical and other measurements had been taken were included in the analysis. The most striking finding was that the same factors were associated with different symptoms and the same symptoms were associated with different factors in the various buildings. Furthermore, a recent comparison of personal exposures (measured in the breathing zone of individual subjects) to aldehydes, amines, NO_2, O_3, particles, and VOCs in eight office buildings in a town in northern Sweden found that intra-individual differences accounted for the variation of 78% of the 123 measured compounds, whereas differences among buildings were the major source of variability for only 14% of the compounds *(13)*. This highlights the inadequacy of a few stationary measurements in buildings

and underscores the need for personal exposure measurements.

Weschler and Shields *(24)* noted that the inability to identify irritants in an indoor setting does not mean that the setting is free of irritants but may simply reflect the difficulty or even impossibility to detect the relevant compound(s) with the analytical techniques routinely used to monitor indoor air quality. It may not be the VOCs that cause SBS symptoms; rather, it may be reaction products, particularly the reaction of unsaturated VOCs with O_3 and various oxygen and nitrogen radicals *(18)*. The major source of O_3 in indoor air is outdoor-to-indoor transport *(25)*. Additionally, office equipment, such as laser printers and photocopiers, has been shown to emit not only VOC but also O_3 *(26,27)*. Monoterpenes are unsaturated VOCs that contain one or two double bonds that react readily with O_3, OH radicals, and nitrate radicals ($NO_3^{\bullet}$) to yield various aldehydes, ketones, carboxylic acids, and organic nitrates *(28–31)*.

The reaction of terpenes at concentrations below their no observed effect level with O_3 yielded reaction products that acted as strong airway irritants in an established mouse bioassay *(32,33)*. Although known irritants were among the reaction products, they did not fully account for the observed effect, suggesting that one or more highly irritating intermediates (hydroperoxides or radicals) and/or as yet unidentified products were formed. A possible candidate is submicron particles, which have been shown to form when O_3 reacts with terpenes under simulated office conditions *(34)*.

Modeling and experimental measurements demonstrated that the product formation of uni- and bimolecular reactions increased at decreasing ventilation rates, whether or not there was sufficient time for the system to achieve steady state *(35)*. The greatest increase in product formation was seen when the reactants originated indoors. Therefore, the decrease in SBS symptom frequency observed with increasing ventilation rates is likely to reflect not only the removal of pollutants with indoor sources but the restriction of reactions among indoor pollutants.

A study of 29 office buildings in northern Sweden is frequently cited to support the hypothesis that reaction products, rather than VOCs themselves, are associated with SBS symptoms *(36)*. Compared with buildings where TVOCs were higher in the room air than in the intake air, buildings where VOCs were "lost" from intake to room air had an OR of 39 of being SBS buildings *(36)*. The more TVOCs were lost, the higher the concentration of formaldehyde was, providing indirect confirmation of prior experimental data and indicating that VOCs reacted with O_3 to form various aldehydes, including formaldehyde *(28,32,33)*. A major shortcoming of this study is that VOCs were measured up to 6 mo after SBS symptoms had been assessed by questionnaire. Furthermore, PCA of the data from the same 29 office buildings did not confirm the significant association of lost TVOCs with the prevalence of SBS symptoms *(22)*. However, this may have been attributable to the simultaneous "loss" and "gain" of TVOCs in separate rooms within the same building.

It is rather striking that investigations of the possible associations between VOCs and SBS have focused exclusively on VOCs at the workplace, although exposure occurs in almost all microenvironments—particularly at home, but also in cars, public transportation, restaurants, pubs, stores, and movie theaters *(37,38)*. Although rather different half-lives of elimination have been reported for VOCs from blood, there is general agreement that VOCs are rapidly taken up and that their elimination is characterized by a two-exponential, and in some cases a three-exponential, equation *(39)*. This suggests that blood VOCs are distributed to multiple tissues for storage and that the kinetics of elimination vary with the storage site. This is confirmed by measurements of VOCs in breath, which suggest that under steady-state conditions, the residence times for blood

or liver, organs, muscle, and fat are approx 3 min, 30 min, 3 h, and 3 d, respectively *(40)*. From these data, it appears possible that bioaccumulation occurs and, therefore, that not only the kinetics of VOC uptake and elimination but also the threshold for adverse health effects may differ after acute and chronic exposure. It remains to be established whether cumulative exposure to certain groups of VOCs is a better predictor of SBS symptoms than exposure in the work environment alone.

VOCs in Residential Environments

In recent years, several environmental monitoring studies other than those attempting to identify factors involved in SBS symptoms have focused on VOC exposure. A major impetus for such studies was provided by the fact that several VOCs are among the 189 hazardous air pollutants listed in the US Clean Air Act Amendment. These include the known human (Group 1) carcinogens, benzene and 1,3-butadiene, and the probable human (Group 2B) carcinogens, styrene, methylene chloride, and carbon tetrachloride. The International Agency for Research on Cancer (IARC) also recently reclassified formaldehyde from Group 2A (probably carcinogenic to humans) to Group 1 (carcinogenic to humans) *(41)*.

Until recently, the majority of research on VOCs focused on identifying exposures in outdoor air, but data on indoor residential exposure to VOCs are beginning to accumulate (*see* Table 2). In studies measuring personal and residential indoor as well as outdoor concentrations of VOCs, personal exposure of adults and children generally exceeded residential indoor exposure by a substantial margin, and indoor concentrations were considerably higher than outdoor levels *(42–45)*. An analysis of data on personal, residential indoor and outdoor, and work environment indoor concentrations of VOCs in Helsinki, Finland indicated that the geometric means of residential concentrations of VOCs exceeded those of work environments *(46)*. Notably, the sample was representative of the population of Helsinki and included people with occupational exposures to VOCs, as indicated by the high maxima reported for the work environment, which were two orders of magnitude higher than mean residential concentrations. A much smaller study also indicated that many VOCs are present at higher levels in homes than in offices *(37)*. In the absence of exposure to environmental tobacco smoke (ETS), the geometric mean time-weighted microenvironment (residential and work environment indoor) concentrations of many VOCs closely approximated measured personal concentrations of these compounds in subjects from Helsinki *(46)*.

Acceptable lifetime cancer risk benchmarks (i.e., the estimated lifetime excess cancer risk [95th percentile upper-bound] of 1×10^{-5} for an individual exposed to this concentration for a 70-yr lifetime) have been established for various VOCs. In a recent study that monitored VOC exposure of 25 adults in three districts in Minneapolis/St. Paul, only the 90th percentile of outdoor concentrations of benzene and carbon tetrachloride exceeded such benchmark concentrations *(42)*. Conversely, even the median personal and residential indoor concentrations of benzene exceeded the benchmark, and the 90th percentile indoor and personal exposure levels were higher than the risk threshold for three of the other five VOCs for which benchmarks are available. Similarly, in the SHIELDS study of children from two inner-city schools in Minneapolis, researchers found that median indoor residential and personal exposure levels of *p*-dichlorobenzene and benzene were above the acceptable risk thresholds during at least one of the seasons of measurement *(45)*.

Other hazardous air pollutants listed in the Clean Air Act Amendment, such as styrene, benzaldehyde, phenol, 2-butoxyethanol, and hexanal, are mucous membrane irritants, although at far greater concentrations than are generally encountered in indoor environments. 2-Butoxyethanol and oxidation products of D-limonene are skin-contact allergens *(47)*.

Formaldehyde

Formaldehyde is well-established as an irritant of the eye and upper respiratory tract. It was recently reported that formaldehyde at a concentration of 0.1 μg/mL increased the expression of intracellular adhesion molecule (ICAM)-1 and vascular adhesion molecule-1 on human mucosal microvascular endothelial cells to an extent similar to the combination of interleukin (IL)-4 and tumor necrosis factor (TNF)-α *(17a)*. It also promoted adhesion of eosinophils isolated from patients with allergic rhinitis to these cells. No induction of adhesion molecules was observed with the VOCs; 1,2-, 1,3-, or 1,4-benzene; *o*-, *m*-, or *p*-xylene; or toluene at the same concentration. These observations might explain the finding of an increased number and proportion of eosinophils in nasal lavage fluid of healthy volunteers up to 18 h after exposure to 0.5 mg/m^3 of formaldehyde for 2 h *(48)*. In Swedish school personnel, formaldehyde concentrations were significantly associated with decreased nasal patency (measured by acoustic rhinometry) and increased levels of the inflammatory markers eosinophil cationic protein (ECP) and lysozyme, but not myeloperoxidase, in nasal lavage *(49)*.

There are increasing indications that formaldehyde not only affects the upper respiratory tract but that it can also enhance allergic sensitization and, through this and possibly other mechanisms, can cause lower respiratory tract symptoms, including asthma. Formaldehyde has been shown to enhance sensitization in ovalbumin (OVA)-immunized guinea pigs *(50–52)*. Although chronic inhalation of formaldehyde does not appear to induce significant inflammation in the lower respiratory tract of nonsensitized mice *(53)* or guinea pigs *(50)*, it has been shown to increase the number of inflammatory cells in bronchoalveolar lavage fluid of OVA-immunized mice *(53)* and to potentiate allergen-induced bronchoconstriction in OVA-immunized guinea pigs *(50)*.

Occupational or accidental exposure to formaldehyde occasionally has been associated with the development of asthma that can persist even after further exposure to formaldehyde is avoided *(54,55)*. In some of these cases, specific inhalation challenges identified formaldehyde resin dust, but not gaseous formaldehyde, as the cause of asthma symptoms *(55)*. Whereas formaldehyde gas is largely absorbed in the upper respiratory tract, formaldehyde in particulate form could reach the lower respiratory tract, which could explain its greater ability to cause airway responses. Because products made from urea–formaldehyde resins, such as particleboard and medium-density fiberboard, are used extensively in the construction of new houses, formaldehyde resin dust may also be in residential environments. Although wood products are the sources that emit the highest amounts of formaldehyde, a wide variety of other products also contribute to indoor formaldehyde pollution (*see* Table 3; ref. *56*). ETS is another important source of formaldehyde.

Mean or median residential indoor formaldehyde concentrations of 15 to 30 μg/m^3 have been reported in several recent studies from the United States *(57)* and Australia *(58,59)*. Maxima ranged between 139 and 408 μg/m^3, indicating that some homes largely exceed current indoor guidelines (e.g., 120 μg/m^3 in Australia at the time). Notably, with increasing awareness of the adverse health effects of formaldehyde, the guideline values have been steadily decreasing. Currently, the lowest guideline value is the chronic inhalation reference exposure level of 3 μg/m^3 set by the Office of Environmental Health Hazard Assessment of the California EPA. Chronic relevance exposure levels are concentrations or doses at or below which adverse health effects are not likely to occur.

Despite the relatively low concentrations of formaldehyde in homes compared with occupational exposure levels, chronic domestic or other indoor exposure to this chemical can result in sensitization to formaldehyde itself *(60,61)*

Table 2
Residential VOC Levels (in μg/m³)

		71 Homes in three urban neighborhoods in Minneapolis/St. Paul *(42)*	113 Homes in Minneapolis *(45)*[a]	284 Households in Minnesota *(44)*	170 Homes in Arizona *(57)*, but much smaller *n* for many of the VOC
		2-d Charcoal-based passive sampling	2-d Charcoal-based passive sampling	6-d Charcoal-based passive sampling	Integrated 8-h sample over a 24-h sampling period; mixture of active and passive sampling
Benzene	(%)	100	100	100	49
	Median	1.9	2.2	3.3	1.3
	P90	15.3	6.2	12.7[b]	9.5
Carbon tetrachloride	(%)	99.2	99		
	Median	0.5	0.6		
	P90	0.9	0.6		
Chloroform	(%)	75.3	98	98.6	
	Median	0.9	0.8	1.7	
	P90	3.4	2.6	5.7[b]	
p-Dichlorobenzene	(%)	72.6	82.8	88	
	Median	0.2	0.7	0.5	
	P90	1.5	344.6	3.4[b]	
Ethyl benzene	(%)	99.0	100		
	Median	1.4	1.0		
	P90	8.9	2.8		
D-Limonene	(%)	99.6	100		
	Median	9.0	28.6		
	P90	30.7	122.3		
Methylene chloride	(%)	97.9	23.2		
	Median	1.1	0.4		
	P90	11.5	1.3		
α-Pinene	(%)	99.6	100		
	Median	2.5	2.4		
	P90	12.4	6.5		
β-Pinene	(%)	71.0	94.9		
	Median	1.2	2.5		
	P90	5.2	11.7		
Styrene	(%)	74.3	91.9	84.9	
	Median	0.5	0.7	0.9	
	P90	1.4	1.5	2.4[b]	
Tetrachloroethylene	(%)	97.6	98	86.6	
	Median	0.6	0.5	1.4[c]	
	P90	3.8	1.3	4.9[b]	
Toluene	(%)	97.9	100	99.6	86
	Median	12.3	8.2	16.2	10
	P90	53.8	19.2	63.0[b]	49
Trichloroethylene	(%)	83.9	82.8	94.0	1
	Median				
	P90	0.8	0.9	1.4[b]	<1.8
o-Xylene	(%)	99.7	100	100	
	Median	1.6	1.2	2.1	
	P90	11.4	3.2	6.8[b]	
m-/*p*-Xylene	(%)	99.7	100	100	
	Median	4.8	3.7	4.6	
	P90	36.9	10.4	21.6[b]	
Total VOC	(%)				
	Median				
	P90				

GM, geometric mean; DL, detection limit.

Table 2 (Continued)
Residential VOC Levels (in μg/m^3)

201 Households in Helsinki, Finland *(46)*	796 Households in England *(73)*	40 Households in Oxford, United Kingdom *(373)*	317 Households in Japan *(67)*	Perth, Western Australia *(66)*	
48-h Tenax TA active sampling	4-wk Tenax TA passive sampling	2-d Tenax TA active sampling	1-wk Charcoal-based passive sampling	8-h Active sampling, charcoal sorbent tubes	
				Cases	Controls
71		70		86	
GM 1.57	3.3	GM 2.6		24.8	11.8
4.2	14.6[b]			46.8	31.7
				N/A	
		Mean 26.7	0.01	0.01	
		Max 1029	6.7	5.0	
94		28		N/A	
GM 2.17		GM 1.6	Mean 18.7	1.4	0.8
5.79			Max 278.1	3.6	3.6
99					
GM 11.57	7.1		Mean 25.0		
80.65	51.0[b]		Max 138.8		
100		70			
GM 9.09		GM8.7	Mean 27.5		
38.37			Max 218.9		
50		13		N/A	
GM 0.84		No GM because <20% above DL	Mean 13.1	0.01	0.01
2.17			171.3	1.3	0.8
9		3%			
[c]		No GM because <20% above DL	Mean 5.1		
1.10			Max 46.9		
100		88		99	
GM 14.62	14.9	GM 12.1	Mean 326	11.9	
37.39	74.9[b]		Max 3105	36.9	
3		13			
		No GM because <20% above DL			
0.89					
93		13			
GM 1.88		No GM because <20% above DL			
4.25					
99		63			
GM 6.13	3.7	GM 4.8			
14.82	30.3[b]				
			N/A		
	202	GM 194	Mean 482.6	78.5	36.2
	1010[b]		Max 3278	204.6	101.0

[a]The winter values are listed, which are generally somewhat higher than the measurements obtained in spring.
[b]Values are the 95th percentile rather than the 90th percentile, as in most other studies.
[c]Not reported because the compound was detected in less than 20% of samples
GM, geometric mean; DL, detection limit.

Table 3
Sources of Formaldehyde and VOCs

Compound	Sources	Chronic inhalation Rel (OEHHA) (μg/m³)
Formaldehyde	Most important and highest-emitting sources are particle-board and medium-density fiberboard fabricated with urea–formaldehyde resins; fiberglass insulation, paper products, combustion of gas and solid fuels, ETS, personal computers (PCs), paints, cleaning products, cosmetics	3
VOCs	Combustion products, including traffic emissions and ETS, solvents, floor adhesives, paint, furnishings, photocopiers and PCs, cleaning products, air fresheners, hair spray, moth balls	
Benzaldehyde	Building-related materials such as linoleum; molds and fungi	N/A
Benzene	Combustion products, particularly ETS; paints, wood	60
p-Dichlorobenzene	Moth cakes, air fresheners, toilet bowl deodorizers	800
Ethylbenzene	Combustion products, including ETS; paints or lacquers	2000
Ethylene glycol, propylene glycol	Latex paint	400 (N/A for propylene glycol)
D-Limonene, α- and β-pinene	Cleaning products, air fresheners, waxes, polishes, plywood	N/A
Toluene	Paints, lacquers, printing ink, adhesives, PCs	300
Styrene	Combustion products, including ETS; adhesives, carpeting, PCs	900
m/p-, *o*-xylene	Combustion products, including ETS; printing ink	700
Naphthalene	Combustion products, including ETS; moth balls	9
n-decane, *n*-dodecane, *n*-tridecane, *n*-tetradecane	Sheet vinyl flooring	N/A

OEHHA, Office of Environmental Health Hazard Assessment of the California Environmental Protection Agency.

and can enhance the incidence and severity of atopic sensitization to common allergens *(58,62)*. Importantly, residential formaldehyde exposure has been associated with inflammation of the lower respiratory tract as well as asthma and other lower respiratory tract symptoms in children and adults. Concentrations of exhaled nitric oxide (NO), which is believed to represent a marker of pulmonary inflammation, were found to be significantly higher in healthy children age 6 to 13 yr who were exposed to residential concentrations of formaldehyde of 50 ppb (62 mg/m³) or greater compared to those exposed to levels less than 50 ppb *(63)*. The technique used in this study ensured that the exhaled NO originated from the lower respiratory tract. This suggests that formaldehyde exposure may have induced an inflammatory response, even in children without signs or symptoms of upper or lower respiratory tract disease.

The prevalence of asthma and chronic bronchitis was significantly greater in children, but not adults, from homes with formaldehyde concentrations greater than or equal to 60 ppb (approx 74 μg/m³) compared with those exposed to lower levels *(64)*. A linear decrease in peak expiratory flow rates (PEFRs) was observed with increasing formaldehyde exposure. A study of Swedish adults found significantly higher levels of both VOCs and formaldehyde in connection with indoor painting within the last 12 mo, and, in turn, exposure to recently painted surfaces was associated with increased symptoms related to asthma and current asthma (defined as bronchial hyperresponsiveness) as well as at least one asthma-related symptom in adults *(65)*.

In young children (age <3 yr) who were discharged from the emergency department with asthma as the primary diagnosis, there was a significant association between case status and higher residential formaldehyde exposure compared with age-matched controls *(59)*. In the same group of children, a significant correlation was also detected between total and individual domestic VOC levels and asthma; benzene, ethylbenzene, and toluene were each associated with significantly increased ORs *(66)*. Note that it is difficult to determine whether wheezing illness in such young children truly constitutes asthma. Total VOCs measured in 96 Japanese homes carried significantly elevated ORs for throat and respiratory symptoms in the 317 residents of these buildings *(67)*. Xylene, α-pinene, and nonanal were the three individual VOCs significantly associated with these symptoms. An association between VOC exposure and asthma has further been suggested by the finding that urinary concentrations of muconic acid and 1-hydroxypyrene (metabolites of VOCs and polycyclic aromatic hydrocarbons, respectively) were elevated in children with asthma compared with children without wheezing episodes or atopic diseases *(68)*.

In partial contrast, in a study of 193 children with persistent wheezing illness and 223 controls age 9 to 11 yr, no association was detected between formaldehyde or individual or total VOCs and case status *(69)*. However, the frequency of nocturnal symptoms (wheezing, chest tightness, breathlessness, or cough) was associated with formaldehyde exposure but not with VOC concentrations. In Swedish adults, nocturnal breathlessness was significantly associated with both the formaldehyde and the VOC concentrations in their homes *(70)*.

Residential formaldehyde exposure was not significantly associated with the risk of asthma or respiratory symptoms in a group of 148 Australian children age 7 to 14 yr, although the maximum recorded formaldehyde values of four 4-d samples were associated with atopic sensitization *(58)*. Note that this is one of the few studies in which exposure was measured on several occasions through the year. In most studies, only single measurements of formaldehyde and/or VOCs were taken. Therefore, in our opinion, the associations with allergic sensitization or asthma observed in such studies should be interpreted with considerable caution.

The limited data available indicate that there are substantial day-to-day, daytime vs nighttime, and seasonal fluctuations in VOC exposure resulting not only from changes in the environment over time but also from differences in sources and activities that result in exposure *(46,71)*. Intra-individual variation over multiple monitoring periods was found to span two orders of magnitude for each of the 14 VOCs measured in personal air *(72)*. Additionally, residential indoor VOC concentrations are consistently lower than levels measured in the personal air space of both adults and children *(42–45)*, indicating that they do not fully reflect personal exposure. Furthermore, it is not clear whether peak exposure or chronic low-level exposure constitutes a greater risk for atopy and asthma.

Concentrations of indoor VOCs and formaldehyde generally exceed outdoor concentrations by as much as an order of magnitude *(42–45)*. This clearly shows that they are emitted from indoor sources and are not transported in from the outside. Sources, rather than types and rate of ventilation, were associated with indoor formaldehyde, VOC, CO, and NO_2 levels in homes (ref. *73*; *see* Table 3 for common formaldehyde and VOC sources). This was at least partly confirmed by a Finnish study of VOCs that combined personal exposure assessment with measurements in residential and work environments *(46)*. ETS was found to be a dominant source of personal VOC exposure. In ETS-free homes, variability in VOC exposure stemmed from compounds associated with cleaning products, followed by compounds associated with traffic emissions, long-range

transport of pollutants, and product emissions *(74)*. Together, these data suggest that source control constitutes the most effective way of reducing environmental exposure to formaldehyde and VOCs.

Phthalates

Phthalates are dialkyl- or alkylarylesters of 1,2-benzenedicarboxylic acid. The major representative is di(2-ethylhexyl) phthalate (DEHP), of which the worldwide annual consumption exceeds two million tons *(75)*. Waste that contains DEHP is estimated to emit another 100,000 tons of DEHP annually. Total worldwide phthalate consumption is estimated at 3.25 million tons.

DEHP and other phthalates are used as plasticizers in polyvinyl chloride (PVC) products, which may contain up to 40% DEHP. PVC resins are used to manufacture a wide variety of items, including floor tiles, vinyl upholstery, toys, disposable medical examination and surgical gloves, medical tubing, blood storage bags, components of paper, and paperboard. Additionally, phthalates are used as fixatives, detergents, lubrication oils, and solvents as well as in cosmetics and personal care products. Because phthalates are not covalently bound to PVC-based products, they leach and vaporize from plastic over time.

Exposure Routes

The main exposure route is generally assumed to be ingestion, with fatty foods, such as dairy, fish, meat, and oils containing the highest levels, whereas inhalation and dermal contact make lesser contributions *(76–82)*. However, in the case of diethyl phthalate (DEP) used in personal care products, dermal absorption can probably substantially contribute to total exposure. Recently, the detection of several phthalate metabolites was reported in human breast milk, indicating that oral exposure can begin immediately after birth *(83)*. Additionally, direct intravenous exposure occurs in patients undergoing dialysis or receiving blood transfusions.

Note that there is limited evidence to support the hypothesis that food constitutes the major source of phthalates *(84)*. Rather, a recent study found a significant correlation between the concentrations of di-*n*-butyl (DBP), butyl benzyl (BBzP), and DEP in inhaled air and their urinary monoester metabolites *(85)*. Correlation coefficients ranged from 0.65 for BBzP to 0.42 for DEP. Substantial amounts of various phthalates were also found to be adsorbed to suspended PM and may make even greater contributions to inhalation exposure than phthalates in the vapor phase *(86)*. Together, these results suggest that inhalation may represent an important exposure route for at least some phthalates. Tables 4 and 5 summarize measurements of various phthalates in air and dust of residences, schools, and day care centers.

The ubiquity of phthalates and the resulting high level of contamination of laboratory equipment made it difficult to assess the extent of exposure until measurement of monoester metabolites was introduced *(87)*. After oral ingestion, phthalate diesters are hydrolyzed to their respective monoesters. The relatively polar and low-molecular-weight phthalates are excreted primarily as monoesters. The monoesters of phthalates with higher molecular weights, such as DEHP, di-*n*-octyl phthalate, and di-isononyl phthalate, undergo rather extensive ω-1 and ω-oxidation of their aliphatic side-chains *(88,89)*. In humans, monoesters and the oxidative metabolites are excreted primarily as glucuronides *(89,90)*. Despite their lipophilic nature, phthalates are metabolized and excreted in feces and urine within 3 d; consequently, bioaccumulation is not believed to be a problem.

Studies measuring urinary monoester metabolite concentrations have revealed higher and more widespread phthalate exposure than had previously been suspected (*see* Table 6). Notably, several studies have indicated that

Table 4
Mean Phthalate Concentrations in Dust From Homes and Daycare Centers (in μg/g of Dust)

In dust (mg/g dust)	Phthalate	Sweden $n = 346$ *(109)*		Berlin, Germany $n = 30$ apartments *(624)*		Berlin and 2 villages in the northern part of Germany *(625)*		Cape Cod $n = 120$ *(626)*		Norway $n = 38$ *(86)*		10 day care centers in central North Carolina *(84)* $n = 252$	
		Median	P95	Median	P95	Median	P95	Median	Max	Mean	Max	Mean	Max
	DEHP	770	N/A	703.4	1542	515	1240	340	7700	640	161		
	DBP	150	N/A	47.0	129.6	—		20.1	352	100	1030	18.4	46
	BBzP	135	N/A	29.7	218.5	—		45	1310	110	440	67.7	175
	DEP	0	N/A	6.1	159.6	—		4.98	111	10	110		

Table 5
Median Phthalate Concentrations in Air and Percent Detects (in ng/m^3)

Phthalate	120 Homes on Cape Cod *(626)*		New York *(85)*[a] ($n = 30$)		Krakow, Poland *(85)*[a] ($n = 30$)		Berlin, Germany *(624)* ($n = 59$)		Nine daycare centers in North Carolina *(84)*	
	Median	% Detect	Median	% Detect	Median	% Detect	Median	% Detect	Mean	% Detect
DEHP	77	68	220	100	370	100	156	100		
DBP	220	100	400	100	2300	100	1083	100	239	100
BBzP	less than reporting limit	44	40	100	20	100	18	85	100	100
DEP	590	100	2700	100	840	100	643	100		

[a]Note that these are 48-h personal air samples of pregnant women.

Table 6
50th and 95th Percentile of Urinary Phthalate Metabolite Concentrations (μg/L)

Cohort	*n*	Age range	MEHP		5-OH-MEHP		5oxo-MEHP		MBP		MBzP		MEP		Ref.
			P50	P95	P50	P95	P50	P95	P50	P95	P50	P95	P50	P95	
US subsample of NHANES III	289	N/A	2.7	21.5	—	—	—	—	41.0	294	21.2	137	305	3750	*90*
NHANES 1999–2000	2541	≥6	3.20	23.8	—	—	—	—	26.0	149	17.0	103	164	2840	*92*
Massachusetts	295 men	Mean 36.0	5.0	131	—	—	—	—	14.3	75.4	6.9	37.1	149	1953	*146*
Massachusetts	369 men	5.2	110	13.6	73.1	6.0	34.7	128	1879	*(98)*					
United States	328	6–11	4.90	34.5	—	—	—	—	40.0	163	40.3	214	74.7	756	*92*
United States (Washington, D.C.)	46 women	35–49	7.3	(143.9[a])	—	—	—	—	53.0	(251.3[a])	31.5	(135.2[a])	211.4	(1042.8[a])	*97*
United States	127	Not given	<LOD	20.4	15.6	243	17.4	220	—	—	—	—	—	—	*89*
United States	50	N/A[b]	4.5	(537[a])	35.9	(2417[a])	28.3	(1860[a])							*93*
Erlangen, Germany	85	7–64	10.3	37.9	46.8	224	36.5	156	181	825	21	146	90.2	560	*88*
Germany	254	3–14	7.18	29.7	52.1	188	41.4	139							*625*
Neonates in intensive care unit	6	4–92 d	129	704	2221	13,161	1697	10,413	—	—	—	—	—	—	*102*

[a]These are maximum values because 95th percentile values were not provided.
[b]"Children and adults."

concentrations of most urinary phthalate metabolites are significantly higher in children than in adults *(91,92)*. There is growing evidence that some secondary oxidative metabolites of DEHP, such as mono-(2-ethyl-5-hydroxyhexyl) phthalate (5-OH-MEHP) and mono-(2-ethyl-5-oxohexyl) phthalate (5-oxo-MEHP), are present in urine in considerably higher concentrations than mono-(2-ethylhexyl) phthalate (MEHP) (4.5- and 3.5-fold higher, respectively; refs. *88*,*89*, and *93*; *see also* Table 6). They and other recently identified metabolites may constitute more sensitive biomarkers of exposure to DEHP *(94,95)*.

Extrapolation of daily phthalate intake from urinary excretion of their metabolites is hampered by several factors. Urinary phthalate metabolite levels have been found to vary with the time of sample collection *(92,96)*. Furthermore, substantial within-subject variability has been observed, and researchers have calculated that up to four samples obtained 1 to 3 mo apart may be necessary to classify exposure with a reliability of 80% *(97,98)*. Another difficulty in estimating daily phthalate intakes from urinary excretion of their metabolites is the limited availability of fractional excretion data. This is illustrated by the vast differences (10.3 vs 1.76 μg/kg/d) in the estimates of median daily DEHP intake obtained using the same data but different assumptions of the fractional excretion of MEHP *(99,100)*. Note that if the higher estimate were correct, up to 31% of the metabolite values would yield intake estimates exceeding the reference dose (RfD) of 20 μg/kg of body weight/d set by the US EPA, and 12% of intake estimates would exceed the tolerable daily intake (TDI) value of 37 μg/kg/d set by the corresponding European Union agency. Table 7 summarizes daily intake estimates for DEHP and other common phthalates.

Considerable amounts of phthalates can leach from the bags and tubing used for various medical procedures, such as hemodialysis, and parenteral nutrition *(101)*. The resulting high levels of exposure experienced by neonates in intensive care have long been of particular concern because the rapid growth and development of neonates, combined with the immaturity of their detoxification enzyme systems, makes them particularly vulnerable. A recent small study of six premature neonates in intensive care units *(102)* found 22-fold higher mean urinary MEHP concentrations compared to California toddlers *(91)* and 26-fold higher median MEHP concentrations than were reported for 6- to 11-yr-old children in NHANES III (ref. *92*; *see also* Table 6). Daily intake may exceed 4 mg/kg/d in infants receiving exchange transfusions, whereas patients with adult hemodialysis may be exposed to up to 3 mg/kg/d *(103)*.

It was also feared that mouthing of plastic toys would result in significant phthalate exposure in small children, and many American manufacturers voluntarily discontinued the use of DEHP in plastic toys for small children. However, a recent risk assessment, estimated that exposure of children age 12 to 23 mo by this route was an average of 0.08 μg/kg/d (95% confidence interval 0.04–0.14) and concluded that chewing soft plastic toys was not likely to present a health hazard *(104)*.

Although urinary excretion of phthalate metabolites constitutes a noninvasive method for assessing exposure, the need to correct for dilution and the uncertainty of available fractional excretion data represent serious drawbacks. Serum concentrations of phthalate ester metabolites allow more direct exposure assessment. In serum and breast milk, however, even the measurement of monoester metabolites can yield artificially elevated results because of the presence of lipases capable of mediating the conversion of the parent phthalates into their respective monoesters *(83,105)*. This problem may be circumvented by the use of secondary metabolites arising from the oxidative metabolism of the monoester, such as 5-OH-MEHP and 5-oxo-MEHP in the case of DEHP *(89)*. Unfortunately, conversely to urine, these oxidative metabolites do not constitute the major

Table 7
Estimated Daily Phthalate Intake (in μg/kg/d)

Phthalate	David *(627)* based on NHANES subsample *(90)*		Kohn et al. *(628)* based on NHANES subsample *(90)*		Koch et al. *(99)* data on general German population		German data recalculated by David *(627)*
	GM	P95	Median	P95	Median	P95	Median
DEHP	0.60	3.05	0.71	3.6	10.3[a]	38.3[a]	1.76
DEP	12.34	93.33	12	110	2.32	22.1	
DBP	1.56	6.87	1.5[b]	7.2[b]	5.22[b]	16.2	
BBzP	0.73	3.34	0.88	4.0	0.60	2.52	
DOP (di-*n*-octyl)	0.0096	0.96	<LOD	0.42			
DINP	0.21	1.08	<LOD	1.7			

[a]These values are based on MEHP excretion; they were 13.8 and 52.1, respectively, when using the average of 5-OH-MEHP and 5-oxo-MEHP

[b]Note that Kohn et al. *(628)* and Koch et al. *(99)* used the same fractional excretion values of calculating DBP and BBzP intake. Because values for DBP still differ markedly, there may be true differences in intake in the two populations.

metabolites in serum *(94)* and are not as frequently detectable as MEHP *(89)*.

Inhalation Exposure and Respiratory Symptoms

Animal studies have shown that DEHP, MEHP, and DBP—but not BBzP—have adjuvant properties in terms of IgE and IgG1 production when injected subcutaneously together with OVA *(106–108)*. Findings suggestive of enhanced sensitization have also been reported in humans, but the activity pattern of phthalates was quite distinct. Specifically, results from a Swedish case–control study indicated a significant association between physician-diagnosed rhinitis or eczema and BBzP in dust from the child's bedroom, whereas DEHP was associated with physician-diagnosed asthma, and DEP showed no association with either disease (ref. *109*; *see* Table 4 for phthalate concentrations in dust). The association of individual phthalates with different symptom outcomes may be a reflection of their different physical properties, including vapor pressures, polarities, and octanol/air partition coefficients. Notably, median concentration of DEHP and BBzP were significantly higher in bedrooms with PVC flooring, and a correlation between PVC flooring and case status was also observed in this study, although it was weaker than the associations observed with DEHP and BBzP. This confirms the results of an earlier case–control study that indicated an association of PVC flooring and other plasticizer-containing surfaces with bronchial obstruction in 2-yr-old children in Oslo *(110)*. The association was found to be considerably stronger in children from homes with low air exchange rates compared with those with high air exchange rates, suggesting that chemical compounds in the vapor phase or adsorbed to suspended particles were involved in the observed associations *(111)*. In a previous study by these investigators, DEHP and BBzP concentrations in sedimented dust and suspended PM were highly correlated *(86)*. Dust has been shown to increase the DEHP emission rate from PVC floors and its deposition on internal surfaces *(112)*. In addition to PVC floors, the amount of plastic wall materials was found to be associated with persistent wheezing, cough, and phlegm in a cross-sectional study of children age 1 to 7 yr *(113)*.

An exploratory study examined associations between phthalate exposure as measured by urinary phthalate metabolites and pulmo-

nary function parameters in a subsample of 240 adults who participated in NHANES III *(114)*. There were significant negative associations between mono-*n*-butyl pthalate (MBP) and forced vital capacity (FVC), forced expiratory volume after 1 s (FEV_1), and peak expiratory flow (PEF) in males only. The effect on FVC was essentially confined to nonsmoking males. An association between monoethyl phthalate and lower FVC and FEV_1 was also observed only in males. Conversely, in nonsmoking women, FEV_1 and maximum midexpiratory flow correlated positively with MEHP concentrations.

Under alkaline conditions, DEHP is degraded into MEHP and 2-ethyl-1-hexanol, and the latter is reportedly used in Sweden as an indicator of alkaline degradation of DEHP *(115)*. A geometric mean 2-ethyl-1-hexanol concentration of 2.47 $\mu g/m^3$ was reported in Finnish homes, and the geometric mean personal exposure was only slightly higher (2.63 $\mu g/m^3$; ref. *46*) and similar to the geometric mean of 3.0 $\mu g/m^3$ reported for a German population *(116)*. Findings suggestive of an association between one or both of the DEHP breakdown products, MEHP and 2-ethyl-1-hexanol, with an increased prevalence of self-reported and objective ocular and nasal symptoms have been reported in workers at four Swedish hospitals *(115)*.

Together, these results suggest that phthalate exposure may play a role in SBS symptoms both directly (by causing lower respiratory symptoms) and indirectly (by enhancing atopic sensitization and asthma), both of which are associated with higher frequencies of SBS symptom reporting *(10,14,117)*.

Reproductive Toxicity

Under the auspices of the NTP Center for the Evaluation of Risks to Human Reproduction, a panel of experts assembled comprehensive reviews of the literature published through 2000 concerning the reproductive toxicity of phthalates *(76–82)*. Of this group of compounds, only gestational exposure to DEHP, BBzP, DBP, and, with far lesser potency, di-isononyl phthalate induced defects of the male reproductive organs in rats, mice, rabbits, and—to a far lesser degree—hamsters. The extent and severity of male reproductive toxicity depended greatly on the dose, timing, and duration of exposure and the route and vehicle of administration. Effects on reproductive parameters have also been observed following administration during prepuberty, whereas adult exposure has resulted in adverse effects on the male reproductive system only at very high doses.

Few effects of prenatal or prenatal plus lactational exposure to phthalate esters have been reported in female offspring, but several recent studies indicated that DBP induced isolated instances of reproductive tract malformations *(118)*, significantly delayed vaginal opening and occurrence of first estrous *(119)*, decreased pituitary weights, and increased the incidence of hypoplasia of the alveolar buds of the mammary glands *(120)*. Nonetheless, the male reproductive organs appear to be markedly more sensitive to the effects of phthalates.

Since the aforementioned reviews, the male reproductive toxicity of DEHP, BBzP, and DBP has been confirmed and extended to the demonstration of significant effects, even with markedly lower doses or considerably shorter dosage regimens than had previously been used *(119–124)*. Decreases in sperm count and motility and an increased incidence of morphologically abnormal sperm are among the most sensitive indicators of the male reproductive toxicity of phthalates *(77–79,120,123,125)*. The defects observed in the male reproductive organs include hypospadias, cryptorchidism, testicular atrophy, underdeveloped or absent epididymis, irreversible degeneration and atrophy of seminiferous tubules, reduced anogenital distance, and retained nipples/areolae *(77–79)*. In other words, they involve the testosterone-dependent differentiation of the Wolffian ducts into epididymides, vasa deferentia, seminal

vesicles, and normal development of fetal testes; acquisition of preputial separation and onset of spermatogenesis; and the dihydrotestosterone (DHT)-dependent development of male external genitalia and the prostate, regression of nipples/areolae, and anogenital distance.

Recent studies have indicated that in addition to testosterone- and DHT-dependent processes, insulin-like hormone 3 (Insl3)-dependent processes are also affected by exposure to phthalates that are toxic to the male reproductive organs. Insl3 is produced by Leydig cells and regulates the development of the gubernaculum, which in turn is critical for testicular descent first into the lower abdomen to the inguinal ring and later into the scrotal sacs. A pronounced reduction of Insl3 messenger RNA (mRNA) was observed in testes of male gestation day (GD) 18 fetuses from dams exposed to 1000 mg/kg of DEHP, DBP, or BBzP from GDs 14 to 18; DBP and BBzP were more effective than DEHP *(126)*. Similarly, Insl3 mRNA levels and immunoreactive Insl3 in interstitial cells in testis collected on GD 19 were significantly reduced in fetuses whose dams were exposed to 500 mg/kg/d of DBP, although not at lower doses (100, 10, 1, or 0.1 mg/kg/d) from GD 12 through GD19 *(127)*.

The malformations in androgen-dependent tissues in male rat offspring of mothers treated with DBP or DEHP resemble those induced by well-known anti-androgens, such as vinclozolin or flutamide *(118)*. However, they do not appear to be mediated by the androgen receptor *(77–79,128,129)*. Rather, numerous studies have shown that gestational exposure to DEHP *(126, 128,130)*, DBP *(121,126,127,131,132)*, and BBzP *(126,133)* as well as their common metabolite MBP *(124)* induces a marked decrease in testicular testosterone production and levels of serum testosterone concentrations. In a direct comparison, DBP and BBzP were more effective than DEHP *(126)*. These decreases do not appear to be permanent when exposure is limited to the gestational period *(121,130)*.

Developmentally toxic phthalates not only affect Leydig cells but alter the structure and function of Sertoli cells, which have been proposed to be the actual primary target *(77–79)*. Whereas some recent research have failed to find direct or indirect evidence of alterations in Sertoli structure and function *(118,124,128)*, cell-specific immunohistochemistry has revealed that maturation of Sertoli cells was incomplete in male fetuses exposed to DBP starting at GD 13 *(121)*. During fetal development, Sertoli cells secrete paracrine factors that are essential for the differentiation and testosterone production of Leydig cells. Therefore, the immaturity of Sertoli cells and resulting disturbances in Sertoli-Leydig cell signaling could explain the marked reduction in testosterone synthesis by fetal Leydig cells. Such decreased testosterone production is frequently seen in conjunction with Leydig cell hyperplasia *(121,128,132,134)*. This has been suggested to constitute a compensatory mechanism to maintain testosterone output *(132)*. Alternatively, the reduced testosterone and Insl3 production after gestational exposure to phthalates could delay Leydig cell maturation and differentiation, thereby prolonging their proliferation and resulting in hyperplasia *(126)*.

Several recent studies have used microarray and reverse transcriptase polymerase chain reaction to investigate changes in the gene expression profile in the testes following *in utero* exposure to phthalates. In some cases, this was accompanied by immunohistochemical analysis of changes in protein expression. Interestingly, the phthalates known to be reproductive toxicants all induced very similar alterations in gene expression, whereas no significant changes were observed after exposure to the nondevelopmentally toxic phthalates *(135)*. Consistently with the previously observed decrease in testicular testosterone production, the genes and gene pathways involved in steroidogenesis and cholesterol homeostasis and transport were found to be major targets

and were all downregulated *(127,131,134,135)*. The effects of DBP on the expression of genes involved in cholesterol transport and steroidogenesis were dose-dependent, with significant reductions in mRNA levels of scavenger receptor B type 1 and 3β-hydroxysteroid dehydrogenase observed at doses of 0.1 and 1.0 mg/kg/d, respectively *(127)*.

Conversely, several genes regulating cell proliferation and survival were upregulated *(127,131,134,136)*, which is consistent with the observed Leydig cell hyperplasia. Other targeted genes and gene pathways included α-inhibin, which is essential for normal Sertoli cell development and insulin signaling *(135)*. Within the Wolffian duct, exposure to DBP from GDs 15 to 19 or 21 altered the expression of genes within the insulin-like growth factor pathway and other developmentally important signaling pathways as well as genes for extracellular matrix components *(137)*. These findings suggest a model in which prenatal DBP exposure disrupts orchestrated molecular responses between epithelia, mesenchyme, and extracellular matrix, thereby altering Wolffian duct morphology. These alterations are likely to be secondary to decreased testosterone synthesis but could also be mediated more directly.

Reduced testicular testosterone production and concentration have also been shown to occur in prepubertal rats *(130,138)*. A comparison of different windows of exposure indicated that DEHP had differential effects during gestation, lactation, prepuberty and young adulthood, with decreasing effects observed with increasing age *(130,136)*. Additionally, different durations of DEHP treatment were associated with either up- or downregulation of Leydig cell testosterone synthesis, whereas serum levels did not necessarily change in the same direction and apparently depended on the differential effects that various durations of DEHP exposure had on enzymes and hormones regulating testosterone synthesis and metabolism *(130,136,138)*.

Relevance to Humans

The proximate developmental toxicants of phthalates in rats and mice are believed to be their respective monoesters. After oral exposure, gut lipases and esterases hydrolyze phthalate esters into their more easily absorbable monoesters. Pronounced interspecies differences exist in lipase activity, with primates exhibiting much lower activity than rats and having correspondingly lower dose-normalized monoester levels *(77)*. Consequently, a default risk assessment, consisting of the lowest observed adverse effect level multiplied by default factors of 10 each for interspecies and interindividual differences, was deemed inappropriate *(139)*. A recent direct comparison confirmed that oral treatment with equal doses of DEHP per unit of body weight resulted in up to 7.5 times lower peak concentrations of MEHP in marmosets than in rats *(140)*. Normalized areas under the curve were up to 16 times lower in the primates. However, a human volunteer who consumed an almost 50-fold-lower dose of DEHP (0.65 mg/kg) than the lowest dose used in the study of marmosets and rats (30 mg/kg) had a similar C_{max} of MEHP (2.5 mg/L compared with 2.7 mg/L in marmosets) *(94)*. Additionally, the dose-normalized area under the curve for this volunteer was at least 15 times higher than in the rats and almost 100 times higher than in the marmosets. Although this is only based on a single individual, it certainly does not suggest that human tissues are exposed to lower concentrations of MEHP than rats after the same dose of DEHP.

It has been proposed that the unconjugated monoesters are the mediators of reproductive toxicity in rats *(141)* because monoesters undergo little glucuronidation in these animals. Conversely, in humans, the majority of phthalate monoesters and even the secondary metabolites are present in urine in the form of glucuronides *(89,90)*. In serum, the metabolites

(at least of MEHP) were reported to be mostly conjugated *(89)*, but this is in marked contrast to the findings from a single human volunteer *(142)*. Note that this volunteer had ingested a high dose of DEHP, and researchers recently showed that, at least in urine, free MEHP made up 3% of total MEHP at the 50th percentile concentration but made up almost 87% at the 95th percentile *(141)*. This correlation was not statistically significant for MEHP, but there was a linear increase in the percentage of free monoethyl phthalate (MEP), MBP, and monobenzyl phthalate (MBzP) in urine with increasing total forms. This could indicate that the difference between the findings in a single volunteer and those of the larger study resulted from the higher dose the volunteer ingested. However, it could also be a reflection of variability in phthalate metabolism, because substantial interindividual variation has been reported in the degree of conjugation *(141)*. Notably, in the investigation of urinary phthalate monoester metabolites in a subsample of NHANES III, 5% of urine samples from 289 subjects had markedly elevated concentrations (67% above the next lowest level) of unconjugated monoesters *(90)*.

In addition to glucuronidation, MEHP undergoes extensive oxidative metabolism in humans *(88,89)*. Nanomolar concentrations of two of the oxidative metabolites of DEHP, 5-oxo-MEHP and 5-OH-MEHP, were recently reported to inhibit DTH-induced androgen receptor (AR) activation in a stably transfected breast cancer cell line by 55 and 60%, respectively, whereas neither DEHP nor MEHP had a significant effect *(129)*. This suggests that these metabolites may contribute to the anti-androgenic effects of this phthalate.

In view of these findings, it is particularly concerning that women of childbearing age had significantly higher urinary concentrations of MBP than women in other age groups *(90)*. However, other studies did not find a significant difference between women of reproductive age (age 20–39 yr) and younger or older females but confirmed that women of all ages had higher urinary concentrations of MBP, MEP, and MBzP compared with men *(88,92)*.

The detection of MEHP and DEHP has been reported in umbilical cord serum, suggesting that human exposure to these chemicals starts *in utero (143)*. A correlation between detectable cord serum MEHP concentrations and lower gestational age, although not with birth weight or Apgar scores, was also suggested. However, the improbably high concentrations of DEHP and its monoester and the finding of higher DEHP than MEHP levels suggest that there may have been considerable contamination of the samples; therefore, the above findings should be considered with caution.

Fisher et al. *(121)* were the first to note the many similarities between the changes on the cellular and tissue level induced by exposure to DBP *in utero* and those observed in the testicular dysgenesis syndrome in humans. This syndrome has its origin in abnormal fetal development of Sertoli and Leydig cells and includes cryptorchidism and hypospadias, testicular germ cell cancers, and disorders of sperm production. These disorders all constitute risk factors for each other, and their incidence is believed to be rising, but the evidence for each is conflicting, with the exception of testicular germ cell cancers *(144)*. Additionally, there is no convincing evidence that if there is a true decline in male reproductive health, phthalates and/or other endocrine-disrupting chemicals are causally related to it.

There are first indications that phthalate exposure is related to semen quality. In adult men, urinary MEP levels were found to be associated with DNA damage in sperm (as measured by the comet assay), whereas MEHP, MBzP, MBP, and monomethyl phthalate were not *(145)*. There was an inverse and dose-dependent relation between urinary MBP concentrations and sperm motility and between MBzP

and MBP levels and sperm concentration *(146)*. None of the other phthalate metabolites detectable in at least 75% of the urine samples, (i.e., MEHP, monoethyl, and monomethyl phthalate) were significantly associated with sperm parameters. Changes in reproductive hormone levels were also observed, but several of them exhibited unexpected patterns and directions *(96)*. For example, inhibin B is secreted by Sertoli cells, and because MBP disrupts Sertoli structure and function, it was surprising that inhibin B increased with higher MBP exposure, whereas follicle-stimulating hormone did not increase. Higher MBzP exposure was associated with a decrease in follicle-stimulating hormone, but there was no change in inhibin B levels.

Note that the attempts to detect associations between phthalate exposure and semen or reproductive hormone parameters were based on single measurements of urinary phthalate metabolite levels. Because of the high within-subject variability—particularly of MEHP levels *(98)*—a single sample may not have accurately reflected average exposure to MEHP and other phthalate monoesters, and this may account for the failure to detect an association between them and semen quality.

DEHP is hepatocarcinogenic in rats and mice *(77,147)*, but the liver tumors arise from the ability of DEHP to act as peroxisome proliferators in rodents, a mechanism that is not believed to be relevant to humans. Accordingly, the IARC reclassified DEHP from "possible carcinogen to humans" to "non-classifiable as to its carcinogenicity to humans" *(148)*. However, the US EPA classified DEHP as a probable human carcinogen. The decision by the IARC has been harshly criticized for allegedly not giving due consideration to all of the available scientific evidence, particularly experimental and epidemiological evidence suggesting that DEHP induces pancreatic tumors in rodents and possibly humans *(149,150)*. A recent addition to that database is a chronic feeding study in Sprague–Dawley rats, in which exposure to DEHP at a dose of 300 mg/kg/d significantly increased the incidence not only of liver tumors but also that of testicular tumors *(147)*. Although lower doses (30 or 95 mg/kg/d) did not significantly increase the incidence of Leydig cell tumors, there was a significant trend for increasing neoplasias with increasing dose.

Organophosphate Pesticides

The term pesticide includes herbicides, insecticides, fungicides, fumigants, rodenticides, and other chemicals designed to destroy or repel pests. According to the US EPA, their use (in terms of active ingredient at user level) exceeded 5 billion pounds worldwide and 1.2 billion pounds in the United States in 2000 and 2001. When chlorine/hypochlorites (2.5 billion pounds), wood preservatives, and specialty biocides were included, total usage in the United States alone was almost five billion pounds. At least 75% of this amount is used in agriculture, and home and garden use and commercial/industrial/government use almost equally share the remaining 20 to 25%. Between 80 and 90% of households have reported indoor use of pesticides *(151,152)*. Of particular concern, 70 and 85% of pregnant women from two New York City cohorts, respectively, reported the indoor use of pesticides during pregnancy *(153,154)*, and 37% employed an exterminator *(154)*. The use of organophosphate (OP) insecticides declined from approx 131 million pounds in 1980 to 73 million pounds in 2001, but its percentage among total insecticides increased from 58 to 70% in the same period. In 1999 and 2001, the two most commonly used OP insecticide active ingredients were malathion and chlorpyrifos, followed by diazinon and terbufos.

Exposure to pesticides can occur via inhalation, dermal absorption, and ingestion. Pharmacokinetics studies in human volunteers

have indicated that OPs are readily absorbed after oral administration and are quickly metabolized to more polar metabolites, which are then eliminated in urine with half-lives ranging from 2 h for orally administered diazinon to up to 27 h for chlorpyrifos *(155–158)*. Limited absorption was observed from occluded dermal doses, and urinary elimination half-lives were longer than after oral administration (9 h for diazinon, 27–30 h for chlorpyrifos) *(155,157,158)*. Approximately 60% of diazinon and 70 to 93% of chlorpyrifos were recovered as urinary metabolites *(155,157,158)*. Only 1 to 3% of the dose was recovered for any of the OP pesticides investigated after dermal application *(155,157,158)*.

Under the Food Quality Protection Act of 1996, an assessment is required for cumulative risks from food, water, and nonoccupational exposure resulting from all uses of OPs and should account for exposure to multiple pesticides that have a common mode of toxicological action and end point of toxicity. The Food Quality Protection Act further requires that infants and children are given particular attention because their higher food and fluid intake per body mass, different diets, and behavior put them at risk of higher exposure. Additionally, the immaturity of the detoxifying enzyme system in small infants and the extensive growth and development that young children undergo renders them more vulnerable to the potential hormonal/endocrine disrupting, neurotoxic, immunotoxic, and/or carcinogenic effects of OP pesticides and other environmental pollutants *(152,159)*.

Simulations incorporating measured transfer efficiencies of pesticides from surfaces to hands and food and observations of children's activities during eating suggest that the frequent hand–food, hand–surface, and surface–food contacts have the potential to contribute 20 to 80% of the total dietary intake of pesticides in children younger than age 4 yr *(160)*.

After broadcast application of chlorpyrifos, air concentrations remained markedly higher in a child's breathing zone (0.25 m above the floor) than in the breathing zone of a sitting adult (1 m), even after ventilation *(161)*. Even on the second day after application, the dose a child was estimated to absorb was 0.038 mg/kg, vastly exceeding the current US EPA RfD for infants and children (0.0003 mg/kg/d).

It has been shown that a semivolatile pesticide such as chlorpyrifos can volatilize days after its indoor application and can be adsorbed to various surfaces *(162)*. Children's felt toys, in particular, and, to a lesser extent, plastic toys accumulated significant levels of chlorpyrifos. For a young child exhibiting typical mouthing and hand-to-mouth behavior, dermal and nondietary oral exposure to such conditions were estimated to constitute a dose of 64 μg/kg/d under the most conservative absorption assumptions and to contribute between 40 and 60% of the total dose. This greatly exceeds the allowable daily intake of 10 μg/kg/d proposed by the US EPA.

Risk assessment of OP pesticides requires knowledge of the magnitude of the exposure. Therefore, either environmental or biological monitoring is used. In recent years, environmental monitoring has yielded information on concentrations of OP pesticides in outdoor, indoor, and personal air; indoor dust; soil; and foods and beverages (*see* Tables 8–10). All of the measured values vary considerably, but it is difficult to determine whether they reflect mostly methodological differences or represent true differences in pesticide concentrations. Note that many of the available studies have focused on chlorpyrifos and diazinon. The US EPA eliminated essentially all indoor residential uses of these pesticides by 2002, but they continue to be used in agriculture.

Several important findings have emerged from these exposure assessment studies. OP pesticides are detectable in essentially all media analyzed, including food, indoor air, dust, and soil near the home. Interestingly, OP pesticides were not detected in duplicate beverage samples in two studies *(163,164)*, whereas

Table 8
Indoor (and Some Personal) Air Concentrations of Pesticides (in ng/m^3)

Pesticide	Indoor air from 60–88 homes in Minnesota (MNCPES) *(163)*			**Personal air** in 48–61 children age 3–12 yr in Minnesota (MNCPES) *(163)*			**Personal air** of 238 African and Dominican women from New York *(154)*			119 Homes in Cape Cod *(626)*			Unspecified number of homes (up to 218 samples) in Arizona *(57)*			80 Homes in Maryland *(172)*			10 Day care centers in North Carolina *(84)*		
	%	P50	P90	%	P50	P90	%	P50	Range	%	P50	Range	%	P50	Range	%	P50	Range	%	Mean	Range
Chlorpyrifos	91	1.74	16.2	95	1.577	11.7	100	7.1	0.7–345	38	<RL	<RL-92	65	8.0	<3.2-(192)-3280[b]	92.5	6.71	0–798	100	9.35	1.26–21.7
Malathion	67	1.18	3.38	54	0.628	2.108	2	ND	ND-11.0												
Diazinon	68	0.29	3.23	65	0.275	2.215	100	22.2	2.0–6010	40	<RL	<RL-550	63	4.6	<2.1-(373)-20,500[b]	100	15.9	3.75–62.4			
Atrazine	22	<LOD/LOQ[a]	20.2	17	<LOD/LOQ[a]	26.97															
Methyl parathion							3	ND	ND-0.9	6	<RL	<RL-92									

[a]Below limit of detection or limit of quantitation.
[b]Values in parentheses are maximum levels over which concentrations are evenly distributed, without significant gaps.
Bold column headings mark outcomes that differ from those presented for other studies.
RL, reporting limit.

Table 9
Pesticide Concentrations in House Dust (in μg/g)

Pesticides	12 Child care centers in central North Carolina *(84)*			Unspecified number of homes (up to 218 samples) in Arizona *(57)*			119 Homes in Cape Cod *(626)*			80 Homes in Maryland as part of the NHEXAS-Maryland investigation *(172)*		
	%	Mean	Range	%	Median	Range	%	Median	Range	%	Median	Range
Chlorpyrifos	100	0.578	0.032–0.05	88	0.16	<0.004–119	18	<RL	<RL-228	79.4	0.355	0–27
Malathion	3	<RL	<RL-1.48	15	0.04	0–1.03	100	0.34	0.01–2.6	100	0.07	0.01–0.29
Diazinon	100	0.223	0.041–0.799	53	0.13	<0.020–66.2	14	<RL	<RL-51.0	4	0.01	0–0.77
Atrazine												
Methylparathion	3	<RL	<RL-0.992	13	0.04	0–1.71						

Pesticides	218 Farm worker homes in Washington State *(168)*			59 Homes in eastern Washington State (26 farming, 22 farm worker, and 11 nonfarming families) *(166)*						76 Homes (49 applicator, 13 farmworker, 14 reference families) in central Washington State *(169,167)*					
				Agricultural			Reference			Agricultural			Reference		
	%	Median	Range	%	Median	Range	%	Median	Range	%	Median	Range	%	Median	Range
Chlorpyrifos	26	0.05	0–2.56	98	0.267	<LOD-3.585	82	0.053	<LOD-0.483						
Malathion	15	0.04	0–1.03				100	0.34	0.01–2.6	100	0.07	0.01–0.29			
Diazinon	4	0.01	0–0.77												
Atrazine															
Methyl parathion	13	0.04	0–1.71												
Ethyl parathion				69	0.154	<LOD-2.786	27	<LOD	<LOD-0.425	48	0	0–0.95	14	0	0–0.02
Phosmet	14	0.02	0–16.9	96	0.519	<LOD-17.10	100	0.185	0.073–0.658	N/A	0.14	0.01–14.6	N/A	0.09	0–0.2
Azinphosmethyl	85	0.53	0–14.9	100	1.100	0.170–11.27	100	2.83	0.134–0.816	N/A	1.0	0.04–9.2	N/A	0.15	0.01–1.1
Dimethyl OP										N/A	1.92	0.2–15.1	N/A	0.27	0.01–1.3
4-Nitrophenol										7	0	0–1500	7	0–6.5	

LOD, limit of detection; LOQ, limit of quantitation; RL, reporting limit

Table 10
Pesticides in Duplicate Diet Samples

Pesticides in food (in μg/kg)	379 4-d Composite duplicate solid food samples from 75 individuals in Maryland *(164)*			96 Duplicate solid food samples Clayton *(163)*		
	%	Mean	P95	%	Median	P90
Chlorpyrifos	38.3	0.7	2.9	57	0.532	1.26
Malathion	75.2	1.8	5.9	46	<LOD/LOQ	10.22
Atrazine	0			8	<LOD/LOQ	<LOD/LOQ
Diazinon				3	<LOD/LOQ	<LOD/LOQ

<LOD/LOQ, below limit of detection or limit of quantification.

others reported their detection in 4 of 21 beverage samples; 4 of 9 (44%) of the samples that included apple juice contained azinphos-methyl *(165)*.

Comparisons of pesticide concentrations in dust, soil, and surface and hand wipes have clearly indicated that exposure of agricultural families is considerably greater than that of nonagricultural reference families *(166–170)*. This higher exposure appears to result from both take-home pathways and proximity of the residence to farmland *(167,169,170)*, although the association with proximity is not a consistent finding *(168)*.

Using food consumption data from the Nurses Health Study and the Health Professionals' Follow-Up Study combined with the data from the Food and Drug Administration Total Diet Study, researchers estimated that mean daily dietary intakes of chlorpyrifos, diazinon, and malathion were 0.8, 0.5, and 5.5 μg/d for women and 0.9, 0.5, and 6.1 μg/d for men, respectively *(171)*.

From duplicate diet samples, adult dietary chlorpyrifos and malathion exposure has been estimated to be 0.5 and 1.3 μg/d, respectively *(164)*, and dietary chlorpyrifos intake in children was estimated to be 0.263 μg/d *(163)*. Mean aggregate chlorpyrifos exposure from a total of six pathways was calculated to be 1.39 μg/d (standard deviation: 2.77 μg/d); inhalation made the greatest contribution (approx 85%), whereas only between 7 and 13% was attributable to pesticide residues in solid food, and the dermal route was negligible *(172,173)*. In two studies of children's pesticide exposure, however, solid food made the greatest contribution to the cumulative intake of chlorpyrifos, malathion, and diazinon *(84,163)*. Interestingly, despite the high contribution that food appeared to make to aggregate chlorpyrifos exposure in the Minnesota Children's Pesticide Exposure Study, there was a much stronger correlation between urinary metabolites of this pesticide and concentrations in personal air than with levels in the ingested solid food *(163)*. Additionally, note that the estimates of dermal absorption neglected to account for the volatilized portion of chlorpyrifos. The finding of a high correlation (correlation coefficient: 0.998) between chlorpyrifos in indoor air and in the corresponding dermal wipes suggests that this route of exposure may be important *(57)*.

The reported dietary pesticide intakes were generally well within the US EPA or similar reference values *(163,165)*. However, it has been noted that dietary intake estimates greatly depend on the assumed value of nondetect samples, with assumption of a zero value underestimating exposure by a factor of 10 to 60 *(171)*.

Biomonitoring of OP pesticide exposure most commonly involves measurement of their urinary metabolites or, much more rarely,

quantification of the pesticides themselves and/or some of their metabolites in plasma *(154,174)*. Whereas urinary dialkylphosphate (DAP) metabolites (Table 11) are nonspecific because they can be derived from a wide variety of OP compounds, certain other urinary metabolites are specific for one or two pesticides (Table 12). Recall that urinary metabolites of OP pesticides can provide only rough estimates of exposure because the amount of absorptionand the fractional excretion of specific metabolites are not really known, nor have all the metabolites been identified. Additionally, it cannot be determined whether and to what extent urinary metabolites represent exposure to one or more parent compounds or direct exposure to their metabolites. Furthermore, urinary metabolite concentrations should be corrected for dilution, but the appropriate method is still under debate *(175)*, particularly because marked seasonal fluctuations in creatinine levels were observed in small children *(176)*.

Biomonitoring of prenatal exposure involves the measurement of pesticides and their metabolites in umbilical cord blood, amniotic fluid, or meconium. A total of eight pesticides were detectable in 45 to 77% of maternal plasma samples obtained at delivery and in a similar percentage of cord plasma samples from 230 mother–infant pairs from New York City *(154)*. Their concentrations in maternal and cord plasma were similar and highly correlated, indicating the occurrence of transplacental transfer and substantial *in utero* exposure *(154)*. A further indication for transplacental transfer comes from the finding that the DAP metabolites DEP, dimethyl phosphate, and dimethylthiophosphate were detected in 10, 10, and 5% of amniotic fluid samples, respectively *(177)*. Meconium consists of fetal bile secretions along with the content of the amniotic fluid that the fetus swallowed, representing exposure from the second trimester through delivery, and is usually not excreted by the fetus until after birth. DEP and diethylthiophosphate (DETP) were present in 95 and 100% of 20 meconium samples from New York newborns, respectively, whereas other OP metabolites were detected in only one or none of the samples *(178)*. Similarly, the detection of diazinon (34.3%), malathion (53%), parathion (32%), and chlorpyrifos (11%), along with various organochlorine (OC) compounds, has been reported in meconium samples from infants in the Philippines *(179)*. Up to six or seven pesticides were detected in 4 and 5% of the samples, respectively.

Some investigators detected an association between reported indoor residential pesticide use and urinary concentrations of specific pesticide metabolites*(180)*, but this association was not detected in several other studies of children and adults *(153,181,182)*. Reported pesticide use in the garden is also not consistently associated with urinary DAP levels *(180,182)*. A significant correlation was reported between levels of chlorpyrifos, diazinon, and the carbamate propoxur in personal air and the concentrations of these insecticides or their metabolites in plasma obtained within a month of the personal monitoring, but there was no correlation in plasma obtained at later time-points *(154)*. Because of the relatively short half-lives of these pesticides, the relevance of these correlations is difficult to evaluate without further information about the regularity or chronicity with which the women were exposed to these pesticides.

Several studies in which urinary pesticide metabolite levels were measured have confirmed the findings of environmental monitoring studies that farm children are exposed to higher levels of OP pesticides compared with children from nonagricultural reference families *(168,169)*, particularly during periods of pesticide application *(183)*. In one of these studies, azinphosmethyl was the pesticide detected with the highest frequency and at the highest concentrations in house dust and was significantly correlated with dimethyl DAP metabolites in urine *(168)*. Only the study that detected

an association between house dust levels of azinphosmethyl and phosmet and proximity to farmland also found higher dimethyl DAP levels in children living near treated orchards compared to those living at a greater distance *(169)*. In the same group of subjects, however, urinary levels of the major chlorpyrifos metabolite, 3,5,6-trichloro-2-pyridinol (TCPy) were not significantly different between children from agricultural and nonagricultural families and did not reflect distance from orchards, although chlorpyrifos was present at higher concentrations in house dust of farming families and was increased with increasing distance from pesticide-treated areas *(167)*.

Although studies of exposure to individual pesticides, even those considering aggregate exposure, have generally found the estimated exposure levels to be well below the RfD *(163)*, there is increasing evidence from biological monitoring studies that exposure to OP pesticides overall may exceed reference doses in a substantial number of subjects from both agricultural and nonagricultural areas.

Calculations of exposure using urinary DAP metabolites are difficult because these metabolites can originate from a large variety of OP pesticides with highly different chronic toxicity and RfD values. In 2- to 5-yr-old children from urban and suburban areas of Seattle, the percentage of exposure estimates exceeding US EPA guidelines ranged between 0 and 100%, depending on which pesticide was assumed to be responsible for the exposure *(184)*. When pesticides commonly applied in an agricultural community in Washington were used to calculate the absorbed daily dose in children age 6 yr or younger, 9 to 56% of children from agricultural families and 0 to 44% of reference children exceeded the EPA RfD for azinphosmethyl and phosmet (3 and 11 μg/kg/d, respectively) during the spray season *(185)*. Similar calculations for the same age groups of children from Yuma County, Arizona, indicated that the highest daily dose values were 61 to 385 times higher than the EPA RfD *(176)*.

In a study of pregnant women in the Salinas Valley in California, the estimated exposure to OP pesticides exceeded the oral benchmark $dose_{10}$ of the US EPA in 0 to 36% of the women, depending on the index chemical on which the estimate was based and exceeded the benchmark dose for 10% response in approx 15% of women regardless of the parent compound *(186)*. The benchmark doses for 10% response are doses expected to result in a 10% reduction in brain cholinesterase activity in rats.

Notably, there is evidence from urinary DAP assessments that suggests that consumption of a predominantly organic diet can greatly reduce dietary exposure to OP pesticides as well as the associated risk *(184)*. However, daily consumption of a single meal prepared with organically grown produce was not sufficient to significantly influence urinary levels of DAP metabolites *(180)*.

Associated Health Problems

OP pesticides and carbamates inhibit acetylcholinesterase (AChE). Because AChE inactivates acetylcholine (ACh) at neuronal junctions, its inhibition results in ACh accumulation and continued neurotransmission. Because the autonomic, the somatic, and the central nervous systems all use ACh, the symptoms of OP-mediated AChE inhibition are manifold and include dizziness, headache, confusion, convulsions, blurred vision, respiratory distress, bradycardia and hypotension, fatigue, weakness, ataxia, muscle cramps, and increased lacrimation and salivation. Although the effects of environmental OP exposure are milder, they can resemble those of acute poisoning and, incidentally, include some well-known SBS symptoms, such as tearing eyes, chest pressure/tightness, and feeling dazed *(187)*.

Numerous animal studies have documented the developmental neurotoxicity of gestational or early postnatal exposure to OP pesticides at relatively low levels that did not result in overt systemic toxicity and inhibited cholinesterase to a minor extent (approx 20%) in the dam

Table 11
Dialkyl Phosphate Urinary Metabolites[a]

Metabolite	Parent compounds	Approx 480 children and 830 adults from NHANES, 1999–2000 *(260)* (μg/L)						446 Pregnant women in the CHAMACOS[b] cohort *(186)* (μg/L)				39 Schoolchildren (18 with predominantly organic diets and 21 with conventional diets) in Seattle, WA *(184)*						
		Adults (age 20–59 yr)			Children (age 6–11 yr)							Conventional diet		Organic diet		Total		Total in **μmol/L**
		GM	P50	P90	GM	P50	P90	%	P50	P90	Max	%	P50	%	P50	%	P50	
Dimethyl DAP	Examples:																	0.06
Dimethylphosphate	Azinphosmethyl, dimethoate, malathion, methidathion, methylparathion, naled, oxydemeton-methyl, phosmet	[c]	0.68	6.5	[c]	1.0	10	62.8	1.7	16.7	2754	43	0.6	22	0.06	33	0.6	
Dimethylthiophosphate		1.59	2.2	38	2.72	4.1	62	83	6.3	52.8	2922	95	14	78	2.8	87	5.8	
Dimethyldithiophosphate		[c]	<LOD	10	[c]	<LOD	16	53.2	0.5	13.2	540	62	2.1	11	0.7	38	0.7	
Diethyl DAP	Examples:																	0.02
Diethylphosphate	Chlorpyrifos, diazinon Disulfoton, parathion, terbufos	0.955	1.0	7.2	1.32	1.4	10	59.9	1.1	9.5	160	14	0.7	17	0.7	15		
Diethylthiophosphate		[b]	0.48	1.3	[b]	0.59	1.7	70.3	0.9	5.8	101	86	3.0	83	2.0	85	2.7	
Diethyldithiophosphate		[b]	0.08	0.45	[b]	0.08	0.43	28.6	0	0.6	44	–	–	–	–	–	–	

[a]These can be derived from most OP pesticides. There are 40 OP pesticides (dimethyl and diethyl OPs), of which 28 are registered with the US EPA.
[b]CHAMACOS Center for the Health Assessment of Mothers and Children of Salinas (The Salinas Valley in California is one of the major agricultural areas of the United States, using an estimated 500,000 pounds of OP pesticides annually.)
[c]Not calculated because of the high proportion or results below LOD.
Boldface units of measure differ from units of measure used in the other studies.
LOD, limit of detection.

Table 11 (Continued)

Metabolite	Parent compounds	213 Adults (farm workers) and a child age 2–6 yr (n = 211) from each household *(168)*						110 Children (age 2–5 yr) from Seattle, WA *(182)*		44 Children (age 2–5 yr) from Washington State *(183)*	
		Adults			Children						
		%[b]	P50 in **µmol/L**	P95 in **µmol/L**	%	Median in **µmol/L**	P95 in **µmol/L**	P50 in **µmol/L**	P90 in **µmol/L**	P50 in **µmol/L**	P95 in **µmol/L**
Dimethyl DAP	Examples:		0.09	3.02		0.08	0.52	0.11	0.93	0.06	0.51
Dimethylphosphate	Azinphosmethyl, dimethoate, malathion, methidathion, methylparathion, naled, oxydemeton-methyl, phosmet	20			19						
Dimethylthiophosphate		92			88						
Dimethyldithiophosphate		54			54						
Diethyl DAP	Examples:		0.06	0.12		0.06	0.11	0.0	0.31	0.04	0.1
Diethylphosphate	Chlorpyrifos, diazinon Disulfoton, parathion, terbufos										
Diethylthiophosphate		0			0.9						
Diethyldithiophosphate											

[a]These can be derived from most OP pesticides. There are 40 OP pesticides (dimethyl and diethyl OPs), of which 28 are registered with the US EPA.

[b]CHAMACOS Center for the Health Assessment of Mothers and Children of Salinas (The Salinas Valley in California is one of the major agricultural areas of the United States, using an estimated 500,000 pounds of OP pesticides annually.)

[c]Not calculated because of the high proportion or results below LOD.

Boldface unit of measure differ from units of measure used in the other studies.

LOD, limit of detection.

Table 12
Urinary Concentrations of Specific Metabolites of OP and Non-OP Pesticides

Metabolite (in μg/L, unless otherwise stated)	Parent compounds	Approx 480 children and 830 adults from NHANES, 1999–2000 *(260)*						Approx 1000 adults (age 20–59 yr) from NHANES III *(629)*			50 Adults in Germany *(630)*			MNCPES[a] 90 children (age 3–13 yr), up to three samples per child *(181)*			Younger than age 6 yr (61 from agricultural and 14 from reference families) in a central Washington State agricultural community *(167)*			
		Adults (age 20–59 yr)			Children (age 6–11 yr)												Agri.-cultural		Ref.	
		GM	P50	P95	GM	P50	P95	%	P50	P95	%	P50	P95	%	P50	P95	%	P50	%	P50
3,5,6-Trichloro-2-pyridinol (TCPy)	Chlorpyrifos	1.53	1.50	8.6	2.88	2.70	16.0	82	3.0	13	100	1.4	11.3	93	7.2	26	23	0[c]	29	0[c]
Malathion dicarboxylic acid	Malathion	[b]	<LOD	<LOD	[b]	<LOD	2.8							37	<1.0	8.7				
4-Nitrophenol	Parathion, methyl parathion; nitrobenzene	[b]	<LOD	4.29	[b]	<LOD	4.2	41	ND	5.2							7	0[c]	7	0[c]
2-Isopropyl-4methyl-6-hydroxypyrimidine	Diazinon	[b]	<LOD	<LOD	[b]	>LOD	<LOD													
1-Naphthol	Naphthalene, carbaryl	1.79	1.40	14.0	[b]	1.11	5.6	86	4.4	43			45	1.0	14					

[a]Minnesota Children's Pesticide Exposure Study

[b]Not calculated because of the high proportion or results below the detection limit (which was 0.4 μg/L for TCPy, 0.29 μg/L for malathion dicarboxylic acid, and 1.0 μg/L for 1-naphthol). Comparatively, the LODs were 8 and 9 μg/L for TCPy and 4-nitrophenol, respectively, in the Washington State study *(167)* and 1.4 for TCPy in the MNCPES *(181)*.

[c]The mean values for chlorpyrifos were 4.9 and 4.6 for agricultural and reference children, respectively; the mean values for 4-nitrophenol were 121 and 25, respectively.

LOD, limit of detection.

(159). Such exposure resulted in impairments in maze performance, locomotion, coordination and balance, righting reflexes, and cliff avoidance. The molecular and cellular changes in the fetal or newborn brain that could account for these effects include inhibition of brain AChE and choline acetyltransferase activity *(188–190)*, alteration of muscarinic receptor function via inhibition of ligand binding and permanent reduction in the density of muscarinic cholinergic receptors *(188,189,191,192)*, altered synaptic development and function that can persist into adulthood *(193)*, decreased expression and activity of multiple components of the adenylyl cyclase cascade *(194)*, impaired DNA *(195)* and RNA synthesis *(196)*, and reduced cellularity and brain weight in offspring. Most of these studies were performed using chlorpyrifos, but similar effects and mechanisms were observed with other OP pesticides *(159)* as well as two different pyrethroids *(191)*.

Few studies have addressed possible neurodevelopmental effects of prenatal OP exposure in humans. Recently, the association between prenatal OP pesticide exposure and neonatal neurodevelopment as assessed by the Brazelton Neonatal Behavioral Assessment Scale was investigated in 381 full-term infants in the CHAMACOS project. Table 11 includes maternal DAP metabolite levels during pregnancy in this cohort of women, which contained a substantial portion of agricultural workers from the Salinas Valley and other women with rather high environmental exposure to pesticides because of their heavy use in this agricultural center. Total, dimethyl, and diethyl DAP in urine were all significantly associated with an increased number of abnormal reflexes (failure to respond or hypoactive response) and the proportion of neonates with more than three abnormal reflexes *(197)*. Interestingly, the association differed depending on the age at which the Brazelton Neonatal Behavioral Assessment Scale was administered. The association was negative in neonates examined after age 3 d but was unexpectedly positive in infants assessed within the first 3 d of life (n = 197).

An ecological study of 4- to 5-yr-old Yaqui children in Mexico demonstrated decreases in stamina, hand–eye coordination, and recall and an almost complete inability to draw a person in children living in an agricultural valley who were exposed to multiple pesticides compared to children from families living in the foothills who were employed in ranching *(198)*. Notably, the two groups shared genetic, cultural, and social traits and differed mostly in type of parental employment and the use of pesticides and chemical fertilizers.

Several other cohorts have been established for the investigation of the effects of *in utero* OP pesticide exposure on pregnancy and neurodevelopmental outcomes. Only pregnancy outcomes have been reported for these cohorts as well as for women of the CHAMACOS project. In the CHAMACOS cohort, DAP metabolites were associated with a significant increase in head circumference and a marginally significant increase in birth length *(199)*. Only dimethyl phosphate, and not DEP, metabolites and cord cholinesterase activity were significantly associated with decreased length of gestational duration. In marked contrast, in a cohort of African-American and Dominican women from New York, cord blood concentrations of chlorpyrifos were a significant independent predictor of decreased birth weight and birth length *(200)*. Ethnic-specific regressions indicated that the effect on birth weight was statistically significant only among African-American women, whereas the effect on birth length was significant only in Dominican women. An extension of this study confirmed the significant association between cord plasma chlorpyrifos and diazinon levels and decreased birth weight and length in a somewhat larger cohort, but it was unable to detect an association with insecticide concentrations in maternal personal air during pregnancy *(201)*. Notably, although the associations between cord plasma

concentrations of chlorpyrifos and diazinon were highly significant in children born before the US EPA started to phase out residential use of these pesticides, they were no longer detected in children born after. However, only cord plasma chlorpyrifos, but not diazinon, levels were significantly decreased in the relevant period.

In a different cohort of pregnant women in New York, no association was detected between self-reported pesticide use during pregnancy, urinary levels of TCPy, or pyrethroid metabolites obtained during the third trimester and birth weight, length, head circumference, or gestational age *(202)*. However, when maternal activity of the phase-II detoxifying enzyme paraoxonase 1 activity was accounted for, maternal urinary chlorpyrifos metabolite levels were associated with a small, but significant, decrease in head circumference. Most of the enzymes involved in the metabolism, activation, and detoxification of OP pesticides and other chemicals discussed here exhibit polymorphisms that greatly influence enzyme activity. This study represents one of the rare examples where at least one of these polymorphisms was accounted for.

Notably, urinary levels of pesticide metabolites are highly variable, and measurements obtained at three different time-points show significant within-person variability *(163,186)*. Therefore, one or two spot-urine samples are unlikely to provide a reliable measure of pesticide exposure throughout pregnancy. This may partially explain the inconsistent findings regarding birth outcomes in the aforementioned studies. Whether cord plasma or meconium concentrations constitute a more reliable measure remains to be established.

Other Health Effects of OP Pesticides

Chronic exposure of rats to the pesticide rotenone has been found to constitute an animal model of Parkinson's disease that reproduces the typical biochemical, molecular, anatomical, and behavioral findings in Parkinson's disease *(203)*. These include binding to complex I in the brain, selective nigrostriatal dopaminergic degeneration with relative sparing of the dopaminergic fibers in medial aspects of striatum, cytoplasmic inclusions containing ubiquitin and α-synuclein resembling the Lewy bodies associated with Parkinson's disease, and hypokinesia and rigidity. Notably, rotenone is a "natural" plant-derived compound that even organic farmers use on vegetable crops.

Several epidemiological studies have suggested an association between agricultural work, which usually includes pesticide exposure, or pesticide exposure *per se* and idiopathic Parkinson's disease *(204–208)*, although others have found only suggestive evidence for such an association *(209)* or have found no association *(210)*.

There is increasing evidence that occupational exposure to certain pesticides increases the risk of several cancers, including cancers of the brain *(211)* and lungs *(211–213)*, acute myeloid leukemia *(211)*, and possibly multiple myeloma *(214)*. Children may be particularly sensitive to the carcinogenic effects of pesticides, as suggested by numerous reports of associations between residential pesticide exposure and childhood cancers—particularly brain cancer and leukemia but also Wilm's tumor, Ewing's sarcoma, and germ cell tumors *(215, 216)*.

Because cholinergic nerves in the vagi provide the major neural control of airway tone and reactivity, it seems plausible that OPs could induce airway hyperreactivity and asthma *(159)*. Seven days after a single subcutaneous injection of 70 mg/kg of chlorpyrifos, vagally induced bronchoconstriction was found to be potentiated in guinea pigs in the absence of AChE inhibition *(217)*. This effect was accompanied by decreased M2 muscarinic receptor function, whereas M3 receptor function was not affected. Similar results were obtained 24 h after

administration of 1 or 10 mg/kg of parathion and 0.75 or 75 mg/kg of diazinon, although only the higher doses inhibited AChE *(218)*. Intraperitoneal administration of parathion to guinea pigs increased lung resistance and mucus secretion and induced pulmonary edema *(219)*. These broncho-obstructive effects were demonstrated to depend on the biotransformation of parathion by P450 enzymes. Even doses that did not increase lung resistance were able to induce airway hyperresponsiveness not only to ACh but also to histamine. The latter was prevented by atropine, suggesting the involvement of a cholinergic mechanism.

In the Agricultural Health Study, data collected on more than 20,000 farmers indicated that use of the OPs malathion and chlorpyrifos dose-dependently increased the risk of wheeze, and parathion also carried an elevated OR *(220)*. It remains to be established whether OP pesticides at environmental exposure levels increase the risk of asthma and asthma-like symptoms.

Organochlorines

OCs comprise a diverse group of synthetic chemicals that include not only pesticides but polychlorinated biphenyls (PCBs), polybrominated biphenyls, polychlorinated dibenzofurans (PCDFs), and polychlorinated dibenzodioxins (PCDDs). OC pesticides include 1,1,1-trichloro-2,2-*bis*(*p*-chlorophenyl)ethane (DDT); lindane and other hexachlorocyclohexanes; cyclodienes such as dieldrin, chlordane, and heptachlor; and hexachlorobenzene. Many OCs—particularly the more heavily chlorinated ones—resist biotic and abiotic degradation and are lipophilic; therefore, they not only bioaccumulate in all parts of the environment, but are bioconcentrated from one trophic level to the next.

PCDDs and PCDFs are tricyclic aromatic compounds. Because they can be substituted with between one and eight chlorine atoms, there are potentially 75 different PCDD and 135 PCDF congeners (isomers with similar halogen substitution patterns). However, the actual number present in biotic samples is much lower, and mainly 2,3,7,8-substituted congeners are detected. The most toxic congener is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), often referred to simply as "dioxin," whereas the PCDDs are called dioxins.

There are 209 possible PCB congeners, which differ in the degree of chlorination and the position of the chlorine atom; however, depending on the species and its trophic level, only between 50 and 150 congeners are detectable in biotic samples *(221)*. Whereas PCDDs and PCDFs have rigid planar structures, the two rings of PCB molecules are joined by a single carbon–carbon bond, thus allowing axial rotation of the benzene rings. This freedom is restricted by the number and positions of the chlorine substituents and decreases from non-ortho via mono-ortho to di-, tri-, and tetra-ortho PCBs. Planar PCBs exhibit the greatest resemblance to the dioxins.

Whereas PCBs and polybrominated biphenyls were purposely produced for use as dielectric fluid in transformers and capacitors, hydraulic fluid, plasticizers, and fire retardants, PCDD/Fs arise as byproducts of thermal and industrial processes, particularly via incineration of municipal and hazardous waste. PCBs were produced in the United States from the 1920s until they were banned in 1977, with peak production occurring during the 1960s and 1970s. Historical global production of PCBs is conservatively estimated at 1.3 million tons, which were used almost exclusively in the Northern hemisphere *(222)*. Emissions (i.e., releases into the environment) of PCBs were estimated to be in the range of 440 and 92,000 tons *(223)*, and other data strongly have suggested that actual emissions were closer to the upper estimate *(224,225)*. The environmental residence times of two of the major PCB congeners, PCBs 153 and 180, were recently estimated to be 110 and 70 yr, respectively *(225)*,

suggesting that although the production of PCBs was halted approx 30 yr ago, exposure will continue for decades, if not centuries.

Exposure Routes

Because persistent OCs are lipophilic, resist metabolism and biodegradation, and bioaccumulate to similar extents in various biota, humans are simultaneously exposed to complex mixtures of these compounds. However, the precise nature of the mixture depends on various factors such as solubility, volatility, and rates of degradation as well as dietary and other lifestyle factors and geographic location. For the purposes of risk assessment and regulatory action, the concept of toxic equivalency factors (TEFs; i.e., potency factors relative to TCDD) has been developed *(226)*. It is based on evidence that PCDDs, PCDFs, and certain PCBs exert their toxicity via binding to the aryl hydrocarbon receptor and subsequent induction of gene expression, particularly of various cytochrome P450 isozymes. The TEF concept assumes that the combined effects of these OCs can be predicted by a model of concentration addition. TEF values can then be used to calculate toxic equivalent (TEQ) concentrations by multiplying the concentrations of each PCDD, PCDF, or PCB by its TEF. Commonly, either the World Health Organization (WHO) TEQs or the international TEQs (I-TEQs) developed by the NATO are used.

Inhalation of airborne OCs, stemming mostly from municipal and industrial incinerators and open burning of household trash, and dermal exposure make comparatively minor contributions to exposure. More than 90% of current exposure to background levels of PCBs (dioxins and dibenzofurans) and DDT and its metabolite dichlorophenyl dichloroethylene (DDE) is believed to come from the dietary intake of contaminated foods—particularly dairy products, meat, and fish *(227,228)*. Fish can contribute 75% or more of total PCDD/F and PCB TEQ ingestion in countries with high fish consumption *(229)*, and in several studies, intake of fish—particularly from highly contaminated waters like the Great Lakes or the Baltic sea—has shown a significant association with serum concentrations of PCBs and their metabolites and PCDD/Fs *(228,230–234)*.

Notably, the traditional diet of many Arctic populations includes substantial amounts of marine foods, including sea mammals. Although OCs have been produced and used primarily in the lower and middle latitudes of the Northern hemisphere, long-range transport via the predominantly northward flow of rivers and ocean and atmospheric currents results in high exposure levels in the Arctic *(235)*. Because of their lipophilicity and resistance to biodegradation, many OCs bioaccumulate in fatty tissues and are biomagnified in the aquatic food webs. Sea mammals are predators at the top of their food chains and contain very high levels of OCs. Their consumption is associated with concentrations of PCBs and other OCs in serum, breast milk, and adipose tissue samples obtained from various Inuit populations that are up to fivefold higher than in other North American or European populations *(236–238)*.

In the United States, daily dietary intake of dioxin TEQs in the early 1990s was estimated to be 0.3 to 3.0 pg/kg body weight TEQs for an adult who weighed 65 kg *(239)*. Estimates in eight European countries during the 1990s (assessed by various methods) varied between 65 pg I-TEQ/d in the Netherlands and 210 pg I-TEQ/d in Spain, which is equivalent to 1 to 3 pg I-TEQ/kg body weight/d assuming a body weight of 70 kg *(240)*. A more recent market basket study conducted in Finland on almost 4000 samples representing 228 food items, combined with results of a 1997 dietary survey, produced a similar estimate of 115 pg WHO-TEQ/d, or 1.5 pg WHO-TEQ/kg body weight using an average weight of 76 kg *(229)*. Up to threefold higher values for mean daily PCB and dioxin intake estimates have been reported for children *(241,242)*. In most of the countries,

the contributions of dioxins and dioxin-like PCBs to total TEQs were roughly equal, varying between approx 40 and 60%. Together, these data indicate that the daily intake of dioxin TEQs of many Europeans exceeded and probably still exceeds the TDI of 1 to 4 pg/kg/d recommended by the WHO *(243)*. TDI or acceptable daily intake values indicate the amount of a chemical a person can be exposed to on a daily basis over his or her lifetime without suffering deleterious effects.

There are numerous indications from studies of adipose, serum, and breast milk levels showing that exposure to OCs has been generally declining in North America and Europe since their peak production in the late 1960s and early 1970s *(244–250)*. The most consistent decline is observed in the concentrations of DDT and its metabolites, whereas the temporal development of PCB and PCDD/F levels is somewhat more erratic. In Europe, concentrations of PCDD/Fs and PCBs have been decreasing in many food stuffs, and there are indications that changes in consumer dietary patterns—particularly reduced fat consumption—have also contributed to a decrease in OC intake *(240)*. Note that DDT is still utilized for vector control, and the use of many OC compounds continued for much longer periods in many other countries around the world than in the United States and Europe. Therefore, the body burden of certain OCs is still very high in numerous populations *(251,252)*. Additionally, major contamination incidents continue to occur because of inappropriate waste disposal, and these add considerably to the body burden of the affected populations in countries where OC levels are generally declining *(253)*.

Although levels of OCs in breast milk have been decreasing since the earliest measurements in the 1980s *(248,254,255)*, they still frequently result in infant exposures that are up to two orders of magnitude higher than TDI values. Such values are based on lifetime intakes and are not intended to apply to the relatively short nursing period. On the other hand, as previously discussed, infants are likely to be considerably more susceptible to the various toxic effects of environmental pollutants, including OC compounds.

It has been estimated that nursing contributes 6 to 12% of cumulative TEQ intake until the age of 25 yr *(241)*. For children and adolescents up to age 17 yr, duration of breastfeeding alone or in combination with PCB concentrations in breast milk or maternal plasma lipids predicted serum PCB concentrations *(227,244, 256–258)*. Inclusion of an index of body fat mass was found to further improve the predictive ability of this model *(259)*.

For almost 2000 participants of NHANES III, serum concentrations were determined for 25 PCB congeners *(260)*. For all congeners, including some of the most commonly detected, the 50th percentile was lower than the limit of detection (LOD). For a surprising number of congeners, even the 95th percentile was lower than the LOD. For PCBs 118, 138, 153, and 180, the 75th percentile values were 13.1, lower than LOD, lower than LOD, and 37.4 ng/g of lipid, respectively. Similar data from other studies are not directly comparable because they were not population-based, were obtained by different analytical methods, and were not always on blood lipid base. Nonetheless, it is striking that some of these studies detected PCBs 138 and 153 in a high percentage of subjects. For example, despite similar detection limits as those reported in the Centers for Disease Control study, PCBs 138 and 153 were detected in 93 and 97%, respectively, of umbilical cord plasma samples obtained from neonates born to Canadian women living in southern Québec and exposed to background levels of PCB *(261)*. The geometric mean values were 12.7 and 16.9 ng/g of plasma lipids, respectively. In blood samples from German schoolchildren obtained between 1996 and 2003, all 5th percentile values for PCBs 138, 153, and 180 were above the detection limit *(244)*. Median concentrations in the most recent

samples (2002/2003) were 0.01, 0.03, and 0.01 μg/L for PCBs 138, 153, and 180, respectively.

Significant correlations between maternal and cord serum concentrations of PCBs and other OC compounds suggest the occurrence of transplacental transfer *(261–263)*, and neonatal levels of PCBs have been found to increase with length of gestation in full-term neonates born after 38 to 42 wk of gestation *(264)*. The detection of OCs in amniotic fluid and meconium samples has also been reported *(179,265)*, further confirming that OC exposure starts *in utero*.

Absorption and Elimination

The limited human data available indicate almost complete absorption of lower chlorinated PCB and PCDD/F congeners and somewhat lesser, but still substantial, absorption of the higher chlorinated congeners *(266–268)*. There is still uncertainty about the extent of dermal absorption, which appears to depend not only on the degree of chlorination *(269)* but also on the matrix in which PCBs are applied *(270)* and on the method used to estimate absorption *(271)*. One of the most common methods, fecal and/or urinary excretion of label, may considerably underestimate dermal absorption, as indicated by the finding that when tissue distribution was accounted for in a mass balance study in pigs, absolute dermal absorption of a single PCB congener was found to be 22%, whereas the urinary and fecal excretion methods would have indicated absorption of only 8 to 10% *(271)*.

After initial distribution to highly perfused tissues such as liver and muscle, PCBs are then redistributed to adipose tissue and skin, which serve as long-term storage sites *(272)*. The primary sites to which more than 95% of the body burden of PCDD/Fs distributes are the liver and adipose tissues, including blood lipids and the adipose tissue of muscles and skin *(273,274)*.

The major metabolites of PCBs are methyl sulfones and polychlorobiphenylols (OH-PCBs). Although the hydroxylation of lipophilic substances renders them more hydrophilic and generally facilitates their excretion, there are indications that some OH-PCBs are selectively retained, mainly by binding to plasma proteins such as albumin and the thyroid hormone transport protein, transthyretin *(275)*. In vitro, the affinity of certain OH-PCBs for transthyretin has been shown to be up to four times stronger than that of thyroxine (T4) *(276)*. Although at least 38 OH-PCBs have been identified in human blood plasma *(277)*, five hydroxylated metabolites constitute the vast majority of OH-PCBs in plasma *(231,275,278–280)*. The ratio of total OH-PCBs to total PCBs is generally in the range of 0.1 to 0.3, with declining ratios at higher total PCB concentrations *(278–280)*.

Estimated half-lives range from a few years to 30 yr or more for the more persistent PCBs *(281)*, from 7 to 8 yr for TCDD *(282,283)*, from 3 to more than 15 yr for other PCDDs, and from 3 to almost 20 yr for PCDFs *(282)*; half-lives are approx 7 yr for DDT *(284)* and approx 10 yr for DDE *(285)*. Notably, elimination rates for TCDD appear to depend on age *(286)* and body fat *(283)* and are believed to slow with decreasing body burden *(287–289)*. OCs are primarily excreted in the bile *(272,290)*. Lactation can also represent a major route of excretion. The high levels of OCs found in breast milk indicate that OCs are mobilized from adipose tissue during lactation, and significant decreases in the maternal body burden of PCDD/Fs and PCBs with simultaneous accumulation in their infants has been observed, particularly following the first delivery *(291,292)*.

Health Effects of OC Compounds

Much of the knowledge of the health effects of OCs comes from highly exposed occupational cohorts and from Air Force personnel involved in the spraying of Agent Orange in Vietnam. Additionally, there are three cohorts that experienced high levels of environmental exposure. Because of an industrial accident in Seveso, Italy, the air and soil from surrounding areas were contaminated mostly with TCDD. Two industrial accidents in Japan and Taiwan

resulted in the contamination of cooking oil, primarily with PCBs and PCDFs. The resulting symptoms were referred to as Yusho in Japan and Yu-Cheng in Taiwan (meaning "oil disease"). Table 13 provides brief descriptions of these cohorts.

There should be a note of caution in interpreting epidemiological studies that analyze associations between exposures to OC compounds and various health effects. Generally, either PCBs or PCDD/Fs, but not both groups of compounds, have been measured in these studies. However, humans are invariably exposed to mixtures of these and other OC compounds, and the contributions of the individual components of the mixture to the effect under investigation are unknown. Additionally, several studies of OC tissue levels in North America and Europe found modest-to-strong correlations not only between total PCBs and PCDD/Fs but also among and between individual PCBs and PCDD/Fs *(254,259,293–297)*. Together, these factors can result in not only considerable confounding but in misclassifications of the observed effects *(294)*. This is most clearly illustrated by the fact that some PCB congeners are dioxin-like and, similar to dioxins, exert most of their effects through the Ah receptor, whereas others act as Ah receptor antagonists. Developmental neurotoxicities represent an example of an effect to which both Ah receptor-mediated mechanisms and mechanisms that are not Ah receptor-mediated are likely to contribute.

On the other hand, the strong correlation ($r > 0.9$) between some individual PCB congeners, such as PCB 153 or PCB 138, and total PCBs allows use of only a few PCB congeners as a measure of total PCB exposure. In many recent epidemiological studies, PCBs 138, 153, 180, and, frequently, PCB 118 were used to estimate total PCB burden *(298,299)*.

In 1997, the IARC classified TCDD as a group 1 human carcinogen but considered other PCDDs and PCDFs as not classifiable regarding their carcinogenicity in humans *(300,301)*. DDE and certain PCBs have estrogenic activity in vitro and in vivo, and an association between higher blood levels of DDE and PCBs and breast cancer has been suggested in some case–control studies, but this has not been confirmed in most of the recent studies *(302)*.

There is increasing, although not entirely consistent, evidence from occupationally and otherwise highly exposed cohorts that TCDD and possibly other PCDD/Fs are associated with increased mortality from ischemic heart disease *(303–305)*. Even at background levels of exposure, TCDD was found to increase the risk of type 2 diabetes *(303,306,307)*, and this increase was not associated with the TCDD elimination rate *(308)*. Again, the data are not entirely consistent *(309,310)*. An association has also been suggested between PCB exposure and diabetes (mostly type 1) *(311)*.

Birth Outcomes

In women who gave birth between 1959 and 1966, the OR of preterm birth was significantly increased, with increasing concentrations of DDE in maternal serum *(284,312)*. A less consistent, but significant, increase in the OR of being small for gestational age was also observed *(312)*. The reduction in birth weight of children born to mothers who frequently consumed more Great Lakes sport-caught fish compared to children of mothers who rarely consumed contaminated fish was also associated with higher maternal serum DDE levels but not PCB levels *(313)*. However, such effects of DDE have not been observed in studies of more recent cohorts, suggesting that they may no longer occur at current exposure levels *(238,314,315)*.

There were signs of intrauterine growth retardation in children of Yusho and Yu-Cheng mothers *(316,317)*, but it is unclear whether this resulted from the PCBs, PCDFs, and/or the thermal degradation products of PCBs. An association between exposure to background levels of PCBs and birth weight or gestational age has

Table 13
Description of Cohorts With High Environmental Exposure to Dioxins

Cohort	Year	Description of exposure	Serum/plasma levels[a]	References
Yusho, Japan	1968	Approx 1700 victims ate contaminated rice oil with similar characteristics as that in the Yu-Cheng cohort described below	Mean whole blood levels of a penta- and a hexa-CDF of 10 and 30 ppb/lipid in 1980; mean TEQ levels in 1995 of 156 ppt lipid (range: 86–1016)	*288,631*
Yu-cheng, Taiwan	1979	Approx 2000 victims ate rice oil accidentally contaminated with PCBs, PCDFs, and poly-chlorinated terphenyls and quaterphenyls, which are thermal degradation products of PCBs. They were estimated to have consumed an average of approx 1 g of PCBs and 3.8 mg of PCDFs	40–60 ppb PCB; 2.7 ppt penta-CDF; 10.8 ppt hexa-CDF[b]	*284,329*
Seveso, Italy	1976	An industrial accident at a trichlorophenol plant released a chemical cloud containing an estimated multiple-kilogram amount of TCDD. The most heavily contaminated area, according to measurements mostly of soil and of some plasma samples, was designated as zone A; the area adjacent in the fallout path was called zone B; zone R was slightly and patchily contaminated	Medians: Zone A 443 ppt Zone B: 87 ppt Zone R: 15 ppt 828–56,000 ppt in children with chloracne	*632*

[a]Serum samples were analyzed after the necessary methods were developed in the 1980s.
[b]These concentrations were estimated to be 10 to 20 times higher than background for PCB and 100,000 times higher for penta-CDF, whereas hexa-CDF was not normally detected.
CDF, chlorinated dibenzofuran.

not been seen consistently *(238,284,318–321)*. There is also no strong evidence for a negative effect of PCDDs and PCDFs on birth outcomes *(321,322)*.

In the Seveso cohort, the sex ratio (male-to-female) in the children born after the accident became lower with increasing paternal exposure to TCDD, as assessed in serum samples collected in 1976 and 1977 *(323,324)*. This was particularly obvious in fathers exposed before the age of 19 yr (sex ratio: 0.38). The exposure levels of the mothers were not associated with any changes in sex ratio. Almost identical results were recently reported in workers from a Russian pesticide-producing plant exposed to high levels of dioxin *(325)*. Conversely, no significant differences in the sex ratio were observed in the Yusho and Yu-Cheng incidents in Japan and Taiwan *(326,327)* or in children born to veterans of Operation Ranch Hand who were exposed to Agent Orange *(328)*.

Neurodevelopmental Effects

The possible neurodevelopmental toxicities of PCBs and PCDD/Fs are one of the major concerns regarding environmental background exposure to OCs and are the focus of much ongoing research. Gestational exposure of rodents and monkeys to PCBs is consistently found to have negative effects on learning as well as locomotor activity and function *(221)*. In the Taiwanese Yu-Cheng incident, exposed mothers reported a delay in 32 of 33 developmental milestones in their children who were born up to 7 yr following the poisoning *(317)*. The exposed children also scored consistently lower than controls on several formal cognitive and behavioral tests, with the exception of the verbal IQ on the Wechsler Intelligence Scale for Children *(317,329)*. Similar levels of exposure to PCBs that were not contaminated by PCDFs were associated with markedly less toxicity, thus implicating the PCDFs or other thermal breakdown products present in the contaminated cooking oil in the observed neurodevelopmental effects *(317)*. Children in the Japanese rice oil poisoning were not formally tested but were reported to exhibit hypotony, hyperactivity, and altered latencies and amplitudes of auditory evoked potentials and were reported to have lower mean intelligence quotients *(221)*.

Table 14 summarizes the associations of neurodevelopmental outcomes in infants and children with the PCB exposure levels of their mothers. Several methodological aspects greatly hamper comparison of the results. One of the difficulties is that different specimens (maternal serum or plasma, maternal milk, cord serum plasma) were used for exposure assessment, and the results were expressed per wet-weight or per gram lipid of the respective tissues. Additionally, the earlier studies measured PCBs by the packed column gas chromatography method and did not quantitate individual congeners, whereas in more recent studies, various combinations of individual congeners were measured. Longnecker et al. *(330)* used a variety of approaches to re-express the reported PCB concentrations as median PCB 153 levels in nanogram per gram of lipid in maternal serum for six of these cohorts *(257,299,314,331,332)* as well as for four other cohorts for which data on neurological testing are not yet available. These calculated PCB 153 concentrations are included in Table 14. The use of PCB 153 for this purpose is appropriate because PCB 153 is highly correlated with total PCBs. Although substantial uncertainty arises from the assumptions that were made to convert packed-column into high-resolution results and milk into serum levels, the authors felt that the primary findings were not be substantially altered. These primary findings demonstrated substantial overlap in the distribution of exposure in the majority of studies, but the median exposure in the Faroe Islands was fourfold higher than the overall median.

As summarized in Table 14, the overall results of these studies indicate that prenatal PCB exposure is associated with subtle, but significant, delays in the neurodevelopment of

Table 14
Neurodevelopmental Outcomes Associated With Prenatal PCB Exposure

Cohort period of enrollment	*n*[a]	Age	PCBs analyzed	Median PCB concentration	Estimated median PCB 153 concentrations in MS (ng/g lipid)[b]	Tests used	Significant associations with prenatal PCB exposure	Comments	Reference
North Carolina (1978–1982)	912	1–3 wk	Scaled average PCB levels of CS, MS, and several BM samples; total PCBs by packed column method	9.06 ppb in MS and 1.77 ppm per gram lipid in BM at birth	80	BNBAS	Hypotonicity and hyporeflexia		*292,314*
	676	18 mo				BSID	None (but *see* comment)	Nonsignificant inverse association with psychomotor scores	*335*
	670	24 mo				BSID	Significant inverse association with psychomotor scores		*335*
	645	3 yr				MCSCA	None		*342*
	628	4 yr							
	636	5 yr							
Lake Michigan (1980–1981)[d]	123		CB Total PCBs by packed column method	2.5 ng/mL	120	BNBAS	None	A significant association was observed; however, with maternal fish consumption, and almost identical findings were reported in the Oswego cohort	*339,336*
	123	7 mo				Fagan test	Dose-dependent decrease in preference for novelty	Weaker, but significant, association with maternal fish consumption	*333*
	219	4 yr				MCSCA	Lower performance on verbal and memory scales		*338*
	212	11 yr	[c]			WISC, Wide Range Achievement Test	Lower full-scale and verbal IQ scores; poorer verbal comprehension (particularly vocabulary, information, and similarities subtests) and freedom from distractibility.		*331*
Lake Ontario/ Oswego project[d] (1991–1994)	293	12–14 h and 25–48 h	69 PCB congeners and coeluters in CB	0.525 ng/g wet weight[e]	40	BNBAS	Significant dose-dependent association between cord a blood concentration of highly chlorinated (C17–C19) PCBs and NBAS scores 25–48 h after birth but not 12–14 h after birth. Habituation and autonomic scores were the NBAS clusters showing significant negative associations after controlling for all relevant covariates.	A previous study in the same cohort showed a significant negative association between fish consumption and NBAS scores *(339)* (*see* the results from the Lake Michigan cohort above).	*340*

	230	6 mo				Fagan II	Significant dose-dependent association between total cord PCBs and declining performance	Conversely to the NBAS in neonates, performance on Fagan II was not significantly associated with highly chlorinated PCBs	*334*
	219	12 mo				Fagan II	Significant dose-dependent association between total cord PCBs as well as highly chlorinated PCBs and declining performance		*334*
	194	38 mo				MCSCA General Cognitive Index (GCI)	Significant dose-dependent decline in GCI performance with increasing concentrations of highly chlorinated PCBs in cord blood. Of the GCI subscales, Perceptual Scale and Quantitative Scale were significantly negatively associated	Significant interaction with maternal hair mercury; negative association between maternal hair mercury and McCarthy performance was evident in children with higher prenatal PCB exposure	*341*
	197	54 mo				MCSCA GCI	No significant association between cord blood PCBs and the McCarthy GCI or any of its subscales		*341*
Groningen and Rotterdam, Netherlands (1990–1992)	418	2 wk	118, 138, 153, 180 in CB[f]	0.38 ng/mL	100	Prechtl	None	Lower neurological optimality scores were significantly associated with the concentrations of a variety of individual PCDD, PCDF, and PCB congeners and with total PCB/dioxin TEQ values in the breast milk samples obtained during the second week, even after adjustment for cord blood concentrations; higher planar PCB TEQ values in breast milk were also associated with hypotonia.	*344*
Rotterdam only	207	3, 7, 18 mo				BSID	None with CB PCB levels ($n = 175$), but decreased psychomotor development index score with increasing maternal plasma PCB concentrations		*263*
	418	18 mo				Hempel, Prechtl	A small, but significant, negative effect on neurological optimality score in children of fathers who did not smoke	Conversely to the analysis in neonates, there now was an association with prenatal, but not postnatal, exposure	*345*
	394	42 mo				Touwen/ Hempel	None		*346*

(continued)

Table 14 (Continued)
Neurodevelopmental Outcomes Associated With Prenatal PCB Exposure

Cohort period of enrollment	n[a]	Age	PCBs analyzed	Median PCB concentration	Estimated median PCB 153 concentrations in MS (ng/g lipid)[b]	Tests used	Significant associations with prenatal PCB exposure	Comments	Reference
	395	42 mo				Dutch version of KABC	Lower scores on the overall cognitive and sequential and simultaneous processing scales, the association being significant in the formula-fed (but not in the breast-fed) group		*332*
Rotterdam cohort only	193	42 mo				Dutch version of the RDS	Lower scores on the verbal comprehension scales, the association being significant in the formula-fed (but not in the breast-fed) group		*332*
	397	6.5 yr				MCSCA	Lower scores on the GCI and memory subscales only in the subgroup of children with less optimal parental and home characteristics		*343*
Düsseldorf, Germany (1993–1995)	171	7 mo	Sum of 138, 153, 180 in CB	Mean 0.55 ng/mL	140	Bailey II and Fagan	None	Significant negative association between PCB levels (mean 427 ng/g fat) in early milk samples and the Bailey II mental developmental index	*298*
	116	7, 30, and 42 mo				BSID; KABC	None	Negative association between mental and motor development and PCB levels in early milk samples, which was significant at 30 mo (BSID) and 42 mo (KABC)	*257*
Faroe Islands (1986–1987)	435 (full cohort 1022)	7 yr	118, 138, 153, 170, 180 in cord tissue	1.88 ng/g wet weight; 1.02 mg/g lipid[g]	N/A[h]	Neuro-behavioral Evaluation System; BNT; WISC Revised; CVL; Bender Visual Motor Gestalt Test	Lower performance on Boston Naming Test, Continuous Performance Test reaction time, but significance was lost after adjustment for mercury exposure.	The effects of PCB were more apparent in children with the highest tertile of mercury exposure, suggesting a significant interaction.	*352*

Faroe Islands (1994–1995)	182	Approx 2 wk	Two times the sum of 138, 153, 180 in MS	GM 1.12 mg/g lipid	450	Prechtl	None	*299*
United States, 12 sites (Collaborative Perinatal Project) (1959–1965)	1207	8 mo	MS taken during pregnancy	2.7 ng/mL		BSID	None	*633*

[a]*n* is the number of children remaining in the cohort; the actual number of children completing the tests was often somewhat lower.

[b]From Longnecker et al. *(330)*, who used a combination of published and unpublished data from original investigators, laboratory re-analyses, conversion factors based on published data, and expert opinion to express the exposure level as median PCB 153 concentration (ng/g lipid) in maternal serum.

[c]Because of methodological limitations, maternal serum and milk PCB concentrations, rather than cord blood concentrations, were used to assess prenatal exposure.

[d]Includes mothers with elevated PCB levels because of consumption of sport-caught fish.

[e]Note that the statistical analysis in this study was restricted to highly chlorinated congeners, but quartile values were only provided for total PCBs in cord blood.

[f]Note that in this study, breast milk samples obtained in the second and sixth weeks and, if possible, 3 mo after delivery were analyzed for the 17 2,3,7,8-substituted PCDDs and PCDFs, 3 planar PCBs, and 23 nonplanar PCB congeners.

[g]PCB concentrations in cord tissue correlated well with cord blood levels when measured in a subsample ($r = 0.90$ and 0.87 for wet weight and lipid-adjusted values).

[h]Most likely very similar to the 450 ng/g lipid found in the other Faroe Islands cohort listed next in the Table.

BM, breast milk; CB, cord blood; CP, cord plasma; CS, cord serum; MS, maternal serum; MP, maternal plasma; BNBAS, Brazelton Neonatal Behavioral Assessment Scale; BNT, Boston Naming Test; BSID, Bailey Scales of Infant Development; CVL, California Verbal Learning; KABC, Kaufman assessment battery for children; MCSCA, McCarthy Scales of Children's Abilities; RDS, Reynell developmental scales; WISC, Wechsler Intelligence Scales for Children.

infants and children. Despite the much greater transfer of OCs from the mother to the infant via breast milk, most studies have not revealed any significant associations between postnatal exposure via breastfeeding and neurodevelopmental outcomes *(331,333–335)*. The exceptions are discussed here.

The strongest and most persistent adverse effects were observed in the Michigan cohort, which included mothers who frequently consumed PCB-contaminated sports-caught fish from Lake Michigan *(331,333,336–338)*. Notably, the early developmental findings in the Michigan cohort have essentially been replicated in the Oswego cohort, which also included mothers who had consumed substantial amounts of sport-caught fish from Lake Ontario *(334,339–341)*. The only difference was that studies of the Michigan cohort indicated a weak, but statistically significant, association between maternal fish consumption and performance on the Fagan test (preference for novelty), whereas such an association was not found in the Oswego cohort *(334)*. However, the effect size in the Oswego cohort was considerably smaller than reported for the Lake Michigan cohort (2.1 and 1.4% at 6 and 12 mo, respectively, vs 10.4% at 7 mo), which might be attributable to the lower levels of PCB and other contaminants in the Lake Ontario mothers compared with the Oswego mothers. However, note that the estimated PCB 153 concentrations in the Michigan cohort were similar to those observed in the Dutch cohort and were somewhat lower compared with the German cohort *(330)*. In the German cohort, no effect of prenatal PCB exposure was found using either the Fagan test or Bayley Scales of Infant Development (BSID) *(257,298)*. However, early postnatal PCB exposure (PCBs in early breast milk samples) showed a significant negative association with the Bayley II mental, but not psychomotor, developmental index at age 7 mo *(298)*. Negative associations between the PCB concentration in milk and mental and motor development (as assessed with the BSID) were only of borderline significance at age 7 and 18 mo but became highly significant in 30-mo-old children in that cohort *(257)*. Mental development continued to be negatively affected by lactational PCB exposure at age 42 mo (as assessed by the Kaufmann Assessment Battery for Children). In the Rotterdam cohort, postnatal PCB and dioxin exposure via breastfeeding was also negatively correlated with BSID scores at age 7 mo *(263)*. Conversely to the German findings, this study also demonstrated an effect from prenatal exposure. In further contrast to the results from the German cohort, it was the psychomotor, but not the mental, development index that was significantly decreased, and the associations were no longer significant at age 18 mo.

Lower full-scale and verbal IQ scores were still associated with a composite measure of prenatal PCB exposure in 11-yr-old children from the Lake Michigan cohort *(331)*. No other cohort has been followed for such an extended period, but in another study, significant effects of prenatal PCB exposure were no longer apparent in children past age 3 yr *(342)*. Others found that the children with the highest prenatal exposure caught up to the performance level of the least exposed children by age 54 mo *(341)* or that *in utero* PCB and dioxin exposure continued to significantly affect cognitive and motor abilities past age 6 yr only in those with suboptimal home environments *(343)*. The latter finding suggests that more optimal intellectual stimulation can counteract the effects of prenatal PCB exposure. Other investigations confirmed that the home environment (HOME score) had a positive influence on mental development that was greater overall than the negative effect of neonatal PCB exposure *(257)*.

There are also indications that breastfeeding has a positive influence on mental and psychomotor development and can counteract some of the negative effects of PCB exposure *(263)*. Because the majority of studies indicated that prenatal rather than postnatal exposure was

associated with neurodevelopmental parameters, a WHO working group did not find the evidence sufficient to change the WHO recommendation to support breastfeeding *(221)*.

In the Dutch cohort from Rotterdam and Groningen (*see also* Table 14), exposure to both PCBs and dioxins was assessed *(344)*. Because of the requirement for rather large sample volumes, PCDD/Fs could not be measured in cord blood, but they were determined in a 24-h breast milk sample obtained during the second week after birth. Their concentrations were not associated with any measure of neurological condition up to age 42 mo *(318,344–346)*. In another brief publication on this cohort, it was reported that the mean sum of all TEQs from dioxins and dioxin-like PCBs (total PCB-dioxin TEQ) was actually higher in neurologically normal newborns compared with the 24 children classified as neurologically slightly or definitely abnormal *(347)*. However, at age 3 mo, total PCB–dioxin TEQs tended to be associated with a reduction in the psychomotor developmental index *(263)*. Additionally, postnatal total PCB–dioxin TEQ exposure (accounting for the duration of breastfeeding) was associated with significantly lower psychomotor developmental index scores in 7-mo-old infants *(263)*.

Studies on a small sample of infants (n = 38) from the Netherlands focused exclusively on developmental outcomes associated with perinatal PCDD/F exposure, as determined by measuring 7 PCDD and 10 PCDF congeners in breast milk samples obtained within 3 wk after birth *(348,349)*. At age 5 to 7 d and 26 wk, the Prechtl neurological optimality score did not show an association with exposure level *(348)* nor did the BSID scores show an association at age 2 yr *(349)*. The Hempel test of neuromotor functioning revealed significantly enhanced maturation in the high-exposure group, as evidenced by significantly fewer suboptimal scores. The authors hypothesized that dioxins may have acted as thyroxine agonists because they found that thyroid function in this cohort was rather elevated in the high-exposure group in the first 11 wk after birth *(350,351)*.

Together, these data indicate that prenatal or perinatal exposure to PCBs and possibly PCDD/Fs adversely affects neurodevelopment. However, we emphasize that the various neurodevelopmental parameters were in the normal range, even at the highest exposure levels. It is highly unfortunate that differences in study design, in the reporting of quantitative exposure data and the outcomes associated with them, and in the number and types of confounders considered in the statistical analyses, as well as inconsistencies in some of the results, seriously hamper comparison of the results. Additionally, the differences in the reported outcomes make an evaluation of the effect size difficult. Ultimately, however, the fact that there is any effect at all is of paramount concern.

Effect of OCs on Thyroid Hormone Status

In vitro and animal studies have shown that PCBs and their hydroxylated metabolites can induce various enzymes involved in the metabolism of thyroid hormones and can displace thyroid hormones from their binding proteins *(276)*. Both of these mechanisms are likely to contribute to the decreased plasma levels and reduced availability of T4 and T3 observed in experimental animals. Reductions in brain T4 concentrations have also been reported, but brain T3 levels are frequently unaffected, suggesting the existence of effective compensatory mechanisms. *In utero* exposure to single PCB congeners was associated with reduced plasma T4 levels in rat pups, and reduced T4 levels were also observed in wildlife species. Results of thyroid-stimulating hormone (TSH) levels are inconsistent. Learning and behavioral deficits as well as reductions in auditory evoked potentials have been observed in rodents and monkeys perinatally exposed to PCBs. These manifestations resemble

those induced by fetal hypothyroidism, but a causal link between the neurodevelopmental and the thyroid effects of PCB exposure cannot be established using the available data.

High levels of environmental exposure to OCs (as experienced by Inuit and other coastal populations in which the traditional diet includes fish and the meat and blubber of sea mammals) have also been reported to affect neonatal thyroid hormone status. In a comparison of various populations in the Québec province, concentrations of total PCBs (49 congeners) and total OH-PCBs (15 congeners) in cord blood both showed significant negative correlations with TSH concentrations but were not associated with levels of T3 or free T4 *(279)*. Notably, in those cord plasma samples, the major chlorinated phenolic compound was pentachlorophenol, and it was negatively correlated with T3, free T4, and thyroxine-binding globulin.

In the Faroese birth cohort, more frequent maternal fish consumption during pregnancy was significantly associated with decreased TSH concentration, but not T4 levels, in neonatal blood samples obtained 4 to 7 d after birth *(352)*. A slight tendency for TSH and T4 to decrease with increasing PCB concentrations in umbilical cord tissue was no longer evident after adjustment for the frequency of maternal fish consumption during pregnancy.

When stored cord-blood samples form 160 of the children from the North Carolina cohort were assayed for free and total T4 and TSH, their levels were not found to be associated with the originally measured average PCB concentrations in mother's milk and serum that had been scaled to be comparable with the level in milk at birth *(353)*.

In the Dutch cohort, higher values for the sum of all TEQs from dioxins or planar or nonplanar PCBs in a 24-h representative breast milk sample obtained during the second week after delivery were significantly correlated with decreased maternal plasma levels of total T3 and T4 *(354)*. The TEQ sum of dioxins (dioxin TEQ), dioxins and dioxin-like PCBs (total PCB-dioxin TEQ), and PCBs (PCB TEQ) were all positively correlated with plasma TSH levels in the infants at ages 2 wk and 3 mo. Infants exposed to dioxin levels greater than the median exhibited significantly decreased mean plasma total T4 and increased plasma TSH levels in the second week after birth, whereas only TSH levels were increased in umbilical cord plasma and plasma obtained 3 mo after birth.

In marked contrast, in 38 Dutch neonates, T4 concentrations were increased at birth (in cord blood) and at ages 1 and 11 wk in the group in which mothers' breast milk contained high levels of dioxin (29.2–82.7 TEQ/kg milk fat) compared with the group with low exposure *(351)*. Thyroxine-binding globulin was not significantly different at birth and at age 1 wk but was significantly higher in the group with high exposure at age 11 wk. Notably, the more highly exposed children in this cohort had significantly fewer suboptimal scores on the Hempel test of neuromotor functioning, suggesting enhanced maturation *(349)*. The authors hypothesized that this could result from the thyroxine agonist activity of dioxins. Elevated serum T3 and T4 concentrations, but normal TSH levels, have been reported in Yusho patients compared with unexposed controls; however, they do not correlate with PCB levels, suggesting that the effect is mediated by PCDFs or other thermal breakdown products of PCB *(355)*.

Particulate Matter

PM consists of a complex mixture of organic and inorganic liquids and solids in the form of particles of different sizes and structures. The precise mixture varies by region and season. For example, PM in the northeastern United States has a high sulfate content (approx 40% by mass), whereas nitrates and organic compounds comprise approx 30% of the mass of PM in parts of the western United States *(356)*.

Table 15
Ambient Air Quality Standards

Agency	PM_{10}	Averaging time PM_{10}	$PM_{2.5}$	Averaging time $PM_{2.5}$
US EPA	50 mg/m^3	Annual	15.0 mg/m^3	Annual
US EPA	150 mg/m^3	24 h	65 mg/m^3	24 h
EU (Europe)	40 mg/m^3	Annual		
EU (Europe)	50 mg/m^3, not to be exceeded more than 35 times a calendar year	24 h		
	TSP[a]			
Canada	70 mg/m^3	Annual		
	120 mg/m^3	24 h		

[a]Total suspended particles (TSP) are the only category of PM for which standards are set in Canada.

Within a given area, there can be substantial differences between winter and summer particulate air pollution concentrations; some areas show peak levels in the summer because of photochemical reactions, whereas other areas are more polluted in the winter because of increased emissions resulting from heating, and yet others show little seasonal variation *(356–359)*.

Particles with a 50% cut-off aerodynamic diameter of 10 μm (PM_{10}) can be inhaled into the lungs and, therefore, are referred to as thoracic, respirable, or inhalable particles. Since 1987, mass concentration of PM_{10} has been used in setting the US National Ambient Air Quality Standard for particulate air pollution (for comparison, *see* Table 15, which also shows values from Canada and the European Union). PM_{10} consists of fine particles with an aerodynamic diameter of 2.5 μm ($PM_{2.5}$) and coarse particles ($PM_{2.5–10}$), and the contribution of $PM_{2.5}$ to PM_{10} was relatively constant in a given area but varied between 35 and 80% by region *(356)*. In 1997, the EPA proposed standards for $PM_{2.5}$ (*see also* Table 15). $PM_{2.5}$ can be further divided into nucleation mode or ultrafine particles (UFPs) with an aerodynamic diameter less than 0.1 μm and accumulation mode particles (approx 0.1–1 μm). Whereas measurements of larger particles are commonly based on their mass concentration, UFPs have very little mass but comprise the vast majority of the total number of particles. Therefore, they are measured as number concentration.

In Europe, there is a rather longstanding tradition of assessing levels of black smoke, which consists of black particles with an aerodynamic diameter less than 4.5 μm and measures elemental carbon (EC). Based on the once valid assumption that black smoke originated mostly from burning coal, the OECD defined a standard of converting reflectance of these black soot particles into mass concentration. These standards are no longer appropriate because coal burning has decreased considerably in most industrialized countries over recent decades. Today, an estimated 60 to 90% of the atmospheric EC content is produced by diesel-powered vehicles. It is estimated that more than 80% of diesel exhaust particles have an aerodynamic diameter of 1 μm or less *(360)*. Nonetheless, compared with purely gravimetric methods, measuring reflectance has the major advantage of providing some important information on the composition of particles.

Particle Sources

Coarse particles are generated from soil and other crustal materials mostly by the mechanical processes of agriculture, mining, construction, and road traffic, but they also include particles of biological origin, such as pollen and fungal spores. The most important sources

of fine particles are incomplete combustion processes, formation of secondary particles via gas-to-particle reactions, and coagulation processes in the atmosphere. To varying degrees, ambient urban PM levels depend on both primary regional emissions and long-range transport.

Indoor particle concentrations are determined by the concentration of particles outside and the generation of particles indoors. The contribution of outdoor $PM_{2.5}$ to indoor levels has been estimated to average between 30 and 80% for homes from different geographical areas of the United States and Europe but can vary from 0 to 100% between individual buildings within these areas *(361–365)*. This large variability results from the fact that the fraction of indoor PM derived from outdoor sources depends on various factors. These factors include particle penetration efficiency, particle deposition rate, air exchange rate, and the extent of particle generation during indoor activities of the residents, which, in turn, are subject to circadian and seasonal variation *(363,366–368)*. The penetration efficiency of outdoor particles has been found to be close to one independent of particle size, indicating that building shells essentially do not filter particles nor do they provide protection from inhalation exposure to ambient PM *(363,366,367)*. However, the effective penetration efficiency or infiltration efficiency (defined as the equilibrium fraction of ambient PM that penetrates indoors and remains suspended) depends on particle size because larger particles have higher deposition rates, whereas resuspension involves almost exclusively particles greater than 1 μm *(366–368)*.

The most important indoor source of particles is ETS *(361,366,369–373)*. Considerable generation of particles also occurs during cooking and certain cleaning activities; vacuuming and the overall movement of people resuspend particles and contribute to indoor concentrations *(363,366,374,375)*. Notably, one of these studies has provided evidence that terpene-ozone reactions can result in pronounced elevations in fine particles and UFPs *(375)*. As previously discussed, the products of terpene-O_3 reactions have been shown to act as strong airway irritants *(32,33)*. ETS results in elevated particle counts in all size ranges, but appears to more strongly affect the size fraction smaller than 1.0 μm *(376)*. Cooking is one of the major indoor sources of UFP, with frying, toasting, baking, and barbecuing generating particles mostly in the ranges of 0.02 to 0.1 μm and 0.1 to 0.5 μm *(357,370,375)*. Sautéing produces particles both in the ultrafine and coarse modes (2.5–10 μm). Although dusting, vacuuming, and walking constitute important sources of $PM_{2.5}$, they predominantly raise the concentrations of coarse particles *(357,375)*. Note that indoor particle events are brief and intermittent and not only have a pronounced effect on the size distribution of particles but can also raise particle number concentrations up to 100-fold and can result in peak mass concentrations that are several orders of magnitude higher than the values obtained from time-integrated samples *(375)*.

Exposure

Tables 16 and 17 summarize the results of recent studies that measured indoor, outdoor, and personal exposure levels to PM_{10} and $PM_{2.5}$. These data highlight that there are considerable regional differences in ambient concentrations of particulate air pollution not only worldwide but also within the United States. They further show that for both PM_{10} and $PM_{2.5}$, personal exposure frequently exceeds residential indoor and residential and/or ambient outdoor concentrations, and in many of these studies, residential indoor levels are also elevated compared with those measured outdoors. Consequently, personal exposure can exceed Ambient Air Quality Standards in a substantial portion of the population, even if outdoor concentrations meet the standards *(366)*. The excess personal PM exposure compared with indoor and outdoor PM concentrations is referred to as the "personal cloud."

Table 16
Mean Personal, Residential Indoor and Outdoor, and Ambient PM_{10} Mass Concentrations

Location	Number of subjects	Type of samplers	Integration period	Measurement period	P (range)	I	O	Ambient	Reference
Riverside, CA	171[a]	PEM and stationary indoor and ambient monitors	12 h	12 h daytime	**149.8** (35.1–454.8)	**94.7** (16.6–512.8)	**94.9** (16.2–506.6)	**91.0** (18.2–221.2)	*382*
Fresno, CA	16 elderly	PEM for all measurements	24 h	12 d	**37.3**	**16.7**	**28.7**		*634*
Boston, MA	18 patients with COPD (nonsmokers)	PEM for personal, HI for in/outdoors	12 h	6–12 d in winter and summer	**37.2** (9.3–210.9)	**31.9** (2.4–328.5)	**22.2** (2.7–76.0)		*385*
Detroit, MI	20 children with asthma	PEM and cyclone samplers	24 h	1 wk in each season (annual averages reported)	**68.4**	**52.2**	**25.8**		*372*
Toronto, Canada	141 adults	Personal impactor		3 d	**67.9**	**29.8**		**24.3**	*369*
Amsterdam, Netherlands	37 adults	Personal impactor and HI	24 h	24 h	**61.7** (38.0–112.8)	**34.4** (18.6–65.3)	—	**41.5** (31.9–50.2)	*380*
Amsterdam and Wageningen, Netherlands	45 children	Both personal and ambient with a personal impactor (which did not differ significantly from colocated HI)	24 h	24 h	**105.2** (56.9–195.4)	**38.5** (24.5–55.8)			*386*
Banská Bystrica, Slovakia	49 adults (students, office workers, industrial workers)	PEM and HI	24 h	24 h in summer[b]	**122**	**79**		**35**	*635*
Santiago, Chile	20 children	PEM and HI	24 h	5 d in winter	**146.3** (25.9–574.3)	**103.8** (27.1–208.2)	**115.5** (16.9–281.0)		*388*

[a]This study provides population means because it was based on a probability-based sample.
[b]In the winter, mean personal, indoor, and outdoor concentrations were about the same (120 μg/m^3), lower (66 μg/m^3), and higher (45 μg/m^3), respectively.
Boldface units used to distinguish concentration means from concentration ranges.
P, personal; I, residential indoors; O, residential outdoors.

Table 17
Mean Personal, Residential Indoor and Outdoor, and Ambient $PM_{2.5}$ Mass Concentrations

Location	Number of subjects	Type of samplers	Integration period	Measurement period	P	I	O	Ambient	References
Riverside, CA	171	PEM	12 h	12 h daytime	— (2.8–238.3)	**48.2** (7.4–187.8)	**48.9** (1.4–151.4)	**46.7**	*382*
Los Angeles, CA	106 samples (some subjects were sampled twice)	PEM and HI	48 h	48 h	**29.3**	**16.2**	**19.2**		*365*
Alpine, CA	19 children with asthma	pDR (nephelometer) for personal, and HI	24	2 wk	**37.9**	**30.3**	—	**23.6**	*463*
Houston, TX	101				**37.2**	**17.2**	**14.7**		
Elizabeth, NJ	100				**46.9**	**20.1**	**20.4**		
Seattle, WA	28 elderly healthy	Harvard PEM and HI	24 h	10 d	**9.3** (0.8–96.2)	**7.4** (0.4–38.0)	**9.0** (0.7–24.5)	**10.1** (1–29.5)	*383*
	34 elderly patients with COPD				**10.5** (0.8–45.6)	**8.5** (1.0–49.9)	**9.2** (–0.2–28.9)		
	27 elderly patients with CHD				**10.8** (1.4–66.6)	**9.5** (1.6–65.3)	**12.6** (1.3–41.5)		
	19 children with asthma				**13.3** (1.0–49.4)	**9.2** (2.2–36.3)	**11.3** (2.8–40.4)		
Boston, MA	19 patients with COPD (nonsmokers)	PEM for personal, HI for in/outdoors	12 h	6–12 d in summer and winter	**21.6** (0.6–127.7)	**17.5** (1.6–73.2)	**14.2** (0.9–56.9)		*385*
Towson (Baltimore), MD	15 (from a pool of 21)	PEM	24 h	up to 23 d	**13.0** (2.4–47.8)	**10.0**	**22.0**	**22.0**	*636*
Fresno, CA	16 elderly patients in retirement community	PEM for all measurements	24 h	12 d	**11.1**	**8.0**	**10.1**		*634*
Toronto, Canada	922 (but only 185 and 187 outdoor and indoor samples, respectively)	Personal impactor	3 d	3 d	**28.4**	**21.1**	**15.1**		*369*
Amsterdam, Netherlands	37 elderly patients	Cyclone PEM and HI	24 h	biweekly for 6 mo	**24.3** (8.5–133.7)	**28.6** (9.1–238.8)	—	**20.6** (12.8–31.1)	*387*
Helsinki, Finland	47 elderly patients				**10.8** (3.8–32.7)	**11.0** (3.2–26.6)	—	**12.6** (10.4–18.0)	*387*
Helsinki, Finland	137 non-ETS exposed[a]	Cyclone PEM and impactor MEM (microenvironmental monitors)	48 h	48 h	**9.9**	**8.2**	**9.5**		*371*

Oxford, UK	30–42	Cyclone PEM and impactor MEM	48 h	48 h	**17.4**	**17.3**	**9.1**		*373*
Banská Bystrica, Slovakia	49 adults	PEM and HI	24 h	24 h in summer[c]	**88**	**55**		**22**	*635*
Athens, Greece	117 students	Cyclone PEM	24 h	24 h in winter[b]	**46.4** (7.5–140.4)	—	—		*637*
Halkida, Greece	77 students				**66.0** (9.8–259.8)	—	—		
Santiago, Chile	20 children	PEM and HI	24 h	5 d in winter	**69.5** (19.9–201.5)	**68.5** (13.7–204.3)	**68.1** (17.2–189.6)		*388*

[a]Note that personal exposures were significantly higher for active smokers and people who were exposed to ETS (31.0, and 16.6, respectively), as were residential indoor concentrations in the presence of ETS (20.8 μg/m^3).

[b]Mean personal exposures in the summer were 35.8 μg/m^3 (range: 4.9–125.0) in Athens and 37.9 μg/m^3 (range: 10.6–233.4) in Halkida.

[c]In winter, mean personal, indoor, and ambient concentrations were lower (69 μg/m^3), similar (53 μg/m^3), and higher (32 μg/m^3), respectively.

Boldface units used to distinguish concentration means from concentration ranges.

P, personal; I, residential indoors; O, residential outdoors.

There is still uncertainty regarding the factors that contribute to this excess, but ETS, cooking, cleaning, and other indoor activities are all important *(377,378)*. Other microenvironmental exposures—particularly traveling in vehicles—also significantly contribute *(376,378,379)*. Personal exposure overall is predicted by ETS and, in its absence, by residential indoor concentrations, followed by work environment concentrations and traffic density in the nearest street from home *(371,380,381)*. Outdoor $PM_{2.5}$ levels only predicted personal exposure in models that excluded residential and workplace indoor concentrations *(371)*. This is consistent with the results of most cross-sectional studies, which indicate that the correlation between personal and outdoor PM levels is weak to moderate *(365,369,382)*. Considerably stronger correlations have been reported from most longitudinal studies—especially in the absence of ETS exposure *(380,383–386)*—even in elderly subjects who spend an even greater percentage of their time indoors and at home *(387)*. Correlations between personal and indoor particulate levels are frequently stronger, even in cross-sectional studies *(369,382,388)*. However, note that the strength, magnitude, and even direction of the associations vary considerably among individuals *(384,385)*.

Lung Deposition, Clearance, and Changes in Airways

Inhalation is the major pathway of exposure to airborne particles, and adverse health effects can occur when particles are deposited in the lung or enter the systemic circulation via the lung. The fractional deposition of fine particles and UFPs is fairly high, generally ranging from approx 0.4 to 0.7 for UFPs, depending on the nature and size of the test aerosol and the breathing pattern *(389–392)*. Total lung as well as peak deposition within certain regions of the lung depend on particle size, becoming greater with decreasing particle size for particles less than 0.5 μm and with increasing particle size for particles greater than 0.5 μm *(389–394)*. The site of peak deposition also depends on particle size, with the site of maximal deposition shifting proximally with decreasing particle size for particles less than 0.1 μm and with increasing particle size for particles greater than 1 μm *(393,394)*. This entails that local deposition dose can greatly exceed the average dose of the entire lung. Whereas fine and coarse particles deposit by gravitational sedimentation and inertial impaction, diffusion is the predominant mechanism of deposition of particles for the UFP range and up to a diameter of approx 0.3 to 0.5 μm. Peak deposition of UFP was observed in a volumetric lung region corresponding to the transition zone between the conducting airways and alveolar regions *(394)*. Similarly, autopsy studies of lung tissue from subjects who had lived in areas with high particulate air pollution have indicated that tissue retention of fine particles is mostly observed in this transition zone *(395)*. There is some evidence that UFPs are not necessarily retained in the lung but can diffuse directly into the systemic circulation *(396)*.

In healthy subjects, the magnitude of the total deposition fraction for fine particles and UFPs mainly depends on tidal volume and respiratory time and does not differ significantly between young and elderly subjects using the same controlled breathing patterns *(391, 397,398)*. Consistent with these observations, deposition of UFPs (<100 nm) increases markedly with exercise as a result of both increased minute ventilation and an increase in the depositional fraction *(389,390)*. The influence of lung function parameters (functional residual capacity, FEV_1, and specific airway conductance) on the deposition fraction appears to be essentially negligible in healthy subjects *(391,398)*. However, this is not applicable to patients with obstructive airway disease. Results from several recent studies indicate that deposition of fine particles as well as UFPs is greater in patients with asthma or chronic obstructive pulmonary disease (COPD) than in healthy subjects *(389,*

399,400), whereas clearance does not differ significantly *(400)*.

Examination of autopsy lungs indicates that particles are retained in lung parenchyma from residents of areas with low-to-moderate air pollution *(401)* and that particle burden is significantly higher in lungs from residents of more highly polluted areas *(402)*. A vast majority of these particles have aerodynamic diameters smaller than 2.5 μm, but UFPs constitute only a small fraction of the total *(401)*. Such studies further show that retention of fine particles occurs primarily in terminal and respiratory bronchioles and is associated with inflammatory changes and small airway remodeling that may contribute to chronic airflow obstruction *(395,403,404)*.

Epidemiological Studies of Health Effects

In an ever-growing number of time series studies from around the world, short-term increases in PM_{10} (or black smoke) are statistically associated with increased cardiopulmonary morbidity and mortality *(405–407)*. Conversely, there are indications that reduction of particulate air pollution is associated with a significant decrease in daily mortality *(408)*. Fewer studies have addressed the effects of fine particles, but studies that have analyzed both PM_{10} and $PM_{2.5}$ have provided evidence of much stronger associations of morbidity and mortality with the fine fraction *(409–411)*. High correlations between PM and other air pollutants have been reported in some locations, and other criteria pollutants have also been linked to increased morbidity and mortality *(407)*. However, at least part of the effect of PM appears to be independent of other air pollutants, and it remains a matter of debate whether gaseous pollutants are confounders, effect modifiers, or actual surrogates for PM exposure *(359,412,413)*.

Effect estimates for the increase in overall mortality associated with a 10 $\mu g/m^3$ increase in PM_{10} range from approx 0.2 to approx 0.7% *(359,414,415,416)*. Corresponding estimates for cardiorespiratory mortality are usually considerably higher, and there is a markedly greater increase in respiratory compared with cardiovascular mortality *(415,417)*. However, because cardiovascular disease affects far more people, the absolute number of cardiovascular deaths associated with particulate air pollution is substantially greater than that of respiratory deaths.

Cross-sectional time series suffer from the inability to control for confounding factors such as smoking, alcohol consumption, diet and nutrition, body mass index, occupational exposure, and socioeconomic factors. However, the results from several large prospective cohort studies, in which such corrections are possible, have not only confirmed that higher ambient particulate pollution levels are associated with significant increases in deaths from lung cancer and cardiopulmonary disease but have yielded much larger effect estimates *(409,418)*. The results of the Harvard Six Cities Study *(409)* were independently validated *(419)*. In a recent extended follow-up of one of the American Cancer Society cohorts, an increase in annual mean $PM_{2.5}$ concentration was found to correlate with increases in all-cause, cardiopulmonary, and lung cancer mortality of at least 4, 6, and 8% of subjects, respectively; the estimate depended on the time period during which $PM_{2.5}$ levels were measured *(410)*. All other causes of mortality were not associated with particulate air pollution. In partial contrast, in a cohort of nonsmoking Seventh-Day Adventists, ambient concentrations of PM_{10} were significantly associated with all-cause mortality in both genders and with lung cancer deaths in males only but were not associated with cardiopulmonary mortality *(420)*. However, there was a significant association with deaths for which the death certificate made any mention of nonmalignant respiratory disease as an underlying or contributing cause of death.

There are indications that the elderly and people with underlying heart disease, respira-

tory disease, or diabetes are more susceptible to the adverse effects of particulate and other air pollution *(421–423)*. Nonetheless, the increase in daily mortality associated with particulate air pollution does not appear to be simply " premature harvesting"—that is, the advancement of death by a few days in individuals with severe illness. Instead, some recent analyses have suggested that particulate air pollution shortens life expectancy by at least several months *(424,425)*. Additionally, consistent with the results of prospective studies, the effect size estimates become considerably larger when longer lag periods are considered *(417,425)*.

We emphasize that although the effects of acute PM exposure on mortality are very small, a vast majority of the world population is exposed to this type of pollution, making the number of premature deaths associated with this exposure substantial. A recent estimate stated that 800,000 deaths worldwide are attributable to particulate pollution alone, of which approx 65% occur in Asia *(426)*. Note that adverse effects associated with particulate air pollution are evident at levels below the standards set by various governmental and supragovernmental agencies. Furthermore, the relationship between PM concentrations and adverse health effects is essentially linear, and there does not appear to be a threshold below which exposure can be considered safe *(405,406)*.

The biological plausibility of a causal association between particulate air pollution and adverse cardiovascular and respiratory health effects is supported by the fact that adverse effects of particulate and other air pollution on mortality and morbidity have rather consistently been reported from numerous areas worldwide with widely differing mixtures of air pollutants, absolute levels of PM, particle sources, and, therefore, particle composition. However, there are considerable differences in the size of the effect estimates. This is most likely attributable to differences in absolute exposure levels, particle sources, and their size distribution and composition, but may also include differences in the subjects and in the definitions of outcome measures. Further evidence of plausibility comes from the finding that PM-associated adverse health effects cover a continuous spectrum of severity *(406)*. In addition to increased mortality, this spectrum includes increased hospitalizations for cardiovascular and respiratory diseases *(412,427,428)*, emergency department and other health care visits for asthma and other respiratory symptoms *(407,429–431)*, prevalence of atherosclerosis *(432)*, decreased lung function and lung function growth *(433–439)*, and increased respiratory infections and respiratory symptoms *(440,441)*.

Associations of PM_{10} With Lung Function, Symptoms, and Medication Use

In addition to cross-sectional and prospective cohort studies, panel studies have become an important tool for assessing the effects of particulate pollution on respiratory and other health outcomes. Such studies use repeated measurements of the outcome of interest in a fairly small group of subjects and correlate them with daily changes in ambient concentrations of PM and other air pollutants, which are generally obtained from central monitoring sites.

A significant association between particulate pollution and declines in PEFRs as well as increased prevalence of cough and lower respiratory symptoms has been reported in some panels of unselected children *(442,443)* but not in others *(444)*. In other studies, only children with asthma or asthmatic symptoms appeared to be susceptible to the effects of particulate air pollution *(445,446)*. Similarly, in panels of unselected adults, associations of PM and other air pollutants with increases in the prevalence of decrements in PEFR greater than 20 or in respiratory symptoms were only observed in those with chronic respiratory symptoms or increased airway lability but not in those without *(447,448)*.

Such findings suggest that patients with obstructive airway disease are more susceptible to the adverse effects of particulate air pollution. Therefore, most panel studies have focused on children and adults with asthma or, more rarely, COPD. Significant negative associations between daily fluctuations in PM_{10} and PEF deviation or prevalence of PEF decrements greater than 10 and 20% have been reported in asthmatic children *(406,445,449–454)*. An association of borderline significance was also noted in one panel of patients with COPD *(455)*. These are not entirely consistent findings *(456–459)*. Notably, no effect of PM_{10} on PEFR were observed in the Pollution Effects on Asthmatic Children in Europe (PEACE) study, one of the largest panel studies on air pollution and respiratory health in children with chronic respiratory symptoms, involving more than 2000 children in 14 European centers *(460)*. Even stratification into more sensitive subgroups did not yield any significant findings *(461,462)*.

The association between exposure to PM_{10} and other lung function measures, such as FEV_1 or FVC, has been investigated more rarely. Significant negative associations between residential outdoor and, to a lesser extent, central site PM_{10} values and FEV_1 were observed in children with asthma from southern California *(463)*. In a panel of 86 children with asthma from Detroit, PM_{10} and 8-h peak O_3 levels with a 2-d lag showed a significant negative correlation with diurnal variability in FEV_1 and lowest daily FEV_1 value *(450)*. However, others were unable to detect an effect of PM_{10} on FEV_1 or FVC *(464)*.

In numerous panel studies of children and adults with asthma, a significant association has been detected between elevations in PM_{10} concentrations and increased incidence and prevalence of cough, phlegm, specific respiratory symptoms, or symptom scores *(406,448, 449,456,465–467)*. Similar associations have been reported in patients with COPD *(455,458)*. Again, there have been studies that have not confirmed these findings, including the large PEACE study *(457,459,460)*.

Some panel studies with asthmatic children and adults have indicated that the prevalence of asthma medication use rises during, or shortly after, periods of elevated PM pollution *(453,468–472)*. Associations have been reported between both bronchodilator and maintenance medication use and various PM size fractions, including PM_{10} and $PM_{2.5}$ as well as UFPs. However, others failed to observe a significant effect of PM on the prevalence of asthma medication intake or the daily dose *(457,466,473)*.

Several studies have analyzed potential interactions between the effects of anti-inflammatory medication use and exposure to ambient PM on asthma symptoms and lung function *(449,450,457,461,463,465,470,474–478)*. In some investigations, associations between PM and increased symptoms and/or decreased lung function were only noted, or were stronger, in those subjects who were taking anti-inflammatory medication *(449,450)*. This was even reported from panels whose prevalence of asthma medication use increased in association with elevated particulate pollution *(470,474)*. Note that this increased overall medication use did not necessarily affect the associations of PM with lung function in the same way it influenced the association with symptoms *(470,474)*. Others were unable to detect a significant interaction between the effects of anti-inflammatory medication use at baseline and PM_{10} exposure on asthma symptoms *(466)* or lung function (FEV_1) *(463)*. Finally, there have also been studies in which particulate air pollution significantly affected lung function, exhaled NO *(476,477)*, or symptoms *(457,475)* to a much greater extent, or exclusively in children who did not take inhaled corticosteroids.

Some of these discrepancies may have resulted from the fact that some studies assessed medication use only at baseline, whereas others assessed medication use during the entire follow-up period. Additionally, the effects of

particulate pollution on lung function and symptoms were observed at different lag and averaging times in the various studies. The averaging time for particulate concentrations, symptom severity of the subjects, and medication use were all found to have a major impact on the association between PM pollution and increased symptom scores in a study of 25 children and adolescents with asthma in southern California *(465)*. The largest effect of 24-h mean PM_{10} concentrations was noted in less symptomatic children who did not take anti-inflammatory medications, whereas more symptomatic asthmatics showed the greatest increase in symptoms in association with short-term PM_{10} excursion (1-h means). No association between PM_{10} at any averaging or lag time could be detected in subjects who took anti-inflammatory medications, whereas nonmedicated subjects exhibited large and significant increases in symptom scores in association with same-day 8-h maximum and 24-h mean PM_{10} levels as well as with their 5-d moving averages. Overall, the available data suggest that anti-inflammatory medication and possibly bronchodilator use provide some protection from the effects of particulate pollution on lung function and symptoms in patients with asthma. Protection may be incomplete if the type or dose of medication is inadequate. In some patient groups, however, medication use appears to be a marker of asthma severity, which confounds the protective effects of anti-inflammatory therapy.

Interactions have been observed not only with medication use but also with respiratory infections. In a panel of 86 children with asthma living in Detroit, both $PM_{2.5}$ and PM_{10} were significantly associated with decreased lung function in children with upper respiratory infections with a 3- to 5-d lag, whereas $PM_{2.5}$ did not show significant effects in the absence of upper respiratory infections *(450)*. Others did not detect a significant interaction between the effects of respiratory infections and concentrations of particulate air pollution on percent predicted FEV_1 *(463)*. When symptom severity was the outcome of interest, however, the same investigators found significantly stronger associations with various averaging times of PM_{10}, O_3, and NO_2 during respiratory infections, with some of the ORs increasing up to fivefold *(475)*.

Associations of $PM_{2.5}$ With Lung Function, Symptoms, and Medication Use

Routine monitoring of $PM_{2.5}$ began in the United States only after standards for this size fraction were proposed in 1997, and it is still not performed in most European countries. Therefore, fewer studies have investigated the effects of fine PM on respiratory health. Re-analysis of data from three large panel studies revealed a significant association between $PM_{2.5}$ and increased prevalence of lower respiratory symptoms as well as decreased evening PEF, with the strongest association noted with sulfate fine particles *(443)*. Conversely, in several panels of children and adults with asthma or asthmatic symptoms, exposure to varying concentrations of $PM_{2.5}$ essentially did not correlate with PEF *(464,473,479)*. Ambient fine particulate concentrations were significantly associated with decreased FEV_1 in asthmatic children both in an area where residential wood burning heavily influenced PM concentrations *(446)* and in an area affected by long-range transport of mostly traffic-related combustion products *(463)*. Additionally, fine particles derived predominantly from wood burning showed a significant association with decreases in FVC *(446)*. Conversely, FEV_1 and lowest daily FEV_1 values did not correlate with $PM_{2.5}$ in asthmatic children from Detroit, although in combination with O_3, $PM_{2.5}$ had highly significant effects on both variability and lowest daily values of FEV_1 *(450)*. The risk of lower respiratory symptoms and cough was also found to increase with elevated levels of ambient $PM_{2.5}$ *(466,479)*, as was medication use *(468,469)*.

Associations With Personal PM

One of the few studies to monitor personal PM_{10} and $PM_{2.5}$ exposures in children with asthma found that their associations with FEV_1 were significantly stronger than those of any of the stationary site measurements, which included indoor home, outdoor home, and central site monitoring *(463)*. The strongest association was demonstrated with an interquartile increase in mean 12-h daytime 5-d moving average of personal PM exposure, which was associated with a 22% decrease in FEV_1. In another panel study of subjects with asthma from Toronto, Canada, FVC, FEV_1, and forced expiratory $flow_{25–75}$ ($FEF_{25–75}$) were not significantly associated with personal particulate exposure, but there was considerable confounding by increased use of asthma medication *(480)*.

Re-analysis of data from three large panel studies indicated that fine particles—particularly fine sulfate particles—were more strongly associated with increased lower respiratory symptoms and decreased evening PEF than the coarse fraction *(443)*. However, other studies have provided little indication that the effects of fine particulate matter ($PM_{2.5}$) are stronger than those of PM_{10}. Rather, in the few available direct comparisons, PM_{10} actually was found to have slightly stronger independent effects on FEV_1 *(450,463)* and symptoms in children with asthma *(466)* and on PEFR in unselected children *(442)*. As we later discuss, in the context of possible mechanisms, there are some indications that the ultrafine size fraction of PM may affect respiratory outcomes more strongly than fine or inhalable particles, but the available data are inconclusive.

Confounders and Effect Sizes

Note that PM can correlate moderately to highly with other air pollutants—in particular, O_3, NO_2, and SO_2. When one or more of these pollutants were analyzed with PM, they frequently had similar or stronger effects on respiratory outcomes *(445,456,457,465–467,472, 475)*. Two-pollutant models indicate that the effects of PM often are at least partly independent of those of other pollutants *(442,450,465)*, but there are also instances where inclusion of gaseous pollutants in the model abrogates the significance of the PM effects *(475,478)*. Conversely, abrogation of the effects of other pollutants by PM has also been described *(442,463)*, suggesting that the effects of air pollution most likely result from complex mixtures rather than a single agent.

It has been estimated that a 10-$\mu g/m^3$ increase in the concentration of ambient PM_{10} is associated with an increase of approx 3% in the prevalence of lower respiratory symptoms *(406,407)*. Effect size estimates for decrements in lung function are considerably lower, with an estimated decrease of 0.15% in FEV_1 and a decrease of 0.08% in PEF in association with a 10-$\mu g/m^3$ increase in PM_{10}. The prevalence of decrements in PEF greater than 10 and 20% may constitute a more clinically relevant outcome measure *(454)*. Re-analysis of five panel studies indicated that a 10-$\mu g/m^3$ increment in PM_{10} on the same or the previous day was associated with increases of 2.7 and 2.4%, respectively, in the prevalence of decrement in PEF greater than 10%. The increases in the prevalence of PEF decrements greater than 20% were somewhat larger.

Lag Times

Panel studies generally investigate the effects of PM exposure on the same day (lag 0) as the assessment of the outcome in question, on 1 to 4 d prior, or averaged over a few days. Although associations have been detected between same-day PM_{10} concentrations and the prevalence of decrements in PEF greater than 20% *(454,470)*, other results have indicated that the highest effect estimate was obtained with 5-d mean levels *(454)*. The largest effect of PM_{10} levels on PEF deviation was also noted very consistently with 4- or 5-d averages in ambient PM_{10} con-

centrations *(445,451,470,473)*. This contrasts with the results of a study in healthy children, who exhibited the greatest PM_{10}-asscoiated decrease in PEF immediately following the 24-h monitoring period, whereas no association was observed with 5-d moving average concentrations *(442)*. This may suggest that the effects of particulate pollution on lung function in healthy and asthmatic children are mediated by different mechanisms.

Some of the effects of PM_{10} and $PM_{2.5}$ on FEV_1 and FVC appear to be more immediate because significant correlations with same-day ambient concentrations were reported in at least one study *(446)*, and associations with same-day indoor and personal 12-h daytime exposures were noted in another *(463)*. Considerations of 2- and 4-d lags did not significantly alter the observed associations in one case *(446)*; in the other study, the strongest effects were observed for 5-d moving averages of $PM_{2.5}$ and PM_{10} concentrations *(463)*. Diurnal variability of FEV_1 and lowest daily FEV values were found to be affected most strongly 2 d after exposure to PM_{10}, whereas the average daily exposure of 3 to 5 d before the FEV_1 measurement was not significantly associated with these outcomes *(450)*. Note that unlike the preceding study, exposure was not averaged over all five preceding days. However, both $PM_{2.5}$ and PM_{10} concentrations with a 3- to 5-d lag significantly correlated with both FEV_1 measures in children with upper respiratory infections.

Although symptoms were exclusively associated with same-day exposure to PM_{10} in some studies *(449,467)*, other investigators found effects only after lags of at least 2 d *(466)*, and 2- to 5-d mean PM_{10} concentrations exhibited the strongest associations with symptoms in several other panels *(455,456,470)*. Medication use is quite consistently found to be associated most strongly with 5-d mean PM_{10} concentrations *(469–471)*, and strong effects have also been reported with 14-d cumulative exposure *(469)*.

Notably, it has been reported that symptom scores in children with asthma were more strongly associated with 1- and 8-h maximum PM_{10} than with 24-h PM_{10} levels *(465,475)*. Others have also described an association of symptoms with 1-h peak PM_{10} concentrations *(466)*. This suggests that brief excursions may have a more pronounced effect on asthma symptoms, and possibly lung function, than the 24-h integrated concentrations on which most epidemiological studies are based.

Overall, exposure to particulate air pollution appears to have both acute and somewhat more chronic and cumulative effects. This suggests that several different mechanisms are involved. Whereas the acute effects could result from irritant effects of particulate air pollution, effects noted after considerable lag periods may involve inflammatory processes that take several days to fully develop. It is also possible that exposure to particulate and other air pollutants primes the immune system for increased responses to subsequent allergen exposure.

Mechanisms

The underlying mechanisms through which particulate pollution may contribute to increased cardiopulmonary morbidity and mortality are incompletely understood. It has been hypothesized that UFPs are primarily responsible for the observed health effects because they make up a vast majority of the overall number of particles and are more likely than larger particles to reach the alveoli *(481)*. According to this hypothesis, UFPs deposited in the alveoli would trigger an inflammatory response with subsequent release of inflammatory mediators that could not only exacerbate lung disease but could induce systemic inflammation and prothrombotic changes in the blood *(481)*. This hypothesis is partly based on the finding that UFPs can cause pulmonary inflammation in rats, whereas larger particles with the same composition cannot *(482,483)*. Particle compo-

sition, rather than mass, has been shown to be associated with pulmonary inflammation *(484)*, and small particles have larger surface areas and contain higher concentrations of soluble transition metals, organic compounds, sulfates, and nitrates. All of these constituents have been implicated in the induction of oxidative stress and inflammatory changes in vitro and in experimental animals *(485–490)*.

Consistent with the hypothesis that submicrometer particles are mainly responsible for the adverse health effects of particulate air pollution, PEF was more strongly associated with the 5-d mean number of UFP particles than with the mass concentration of fine particles in a panel of adult asthmatics from Erfurt, Germany *(491)*. The effects of number concentrations of various size fractions of UFPs and mass concentrations of PM were also compared in adult patients with asthma from Helsinki *(464,473)*. In these studies, number concentrations of UFPs, but not particle mass in any size range, were negatively associated with PEF deviations but not with respiratory symptoms or medication use.

Conversely, in a study involving children with asthmatic symptoms from a smaller town in eastern Finland, PM_{10} and black smoke were significantly associated with decreased morning PEF, whereas particle number concentrations were not *(451)*. Only nonsignificant inverse associations were observed with some of the six measured size ranges (0.01–0.032 to 3.2–10). Similar findings were reported in patients with COPD *(455)*.

Others found $PM_{2.5}$ and UFPs to be similarly associated with symptoms in adult patients with asthma *(469)*. In a panel of elderly subjects with coronary heart disease from three European countries, elevated levels of ambient fine particles increased the risk of shortness of breath, whereas avoidance of activities was significantly associated with UFPs and was nonsignificantly associated with $PM_{2.5}$ *(492)*. Finally, exposure to ambient $PM_{2.5}$ and UFPs independently increased the risk of ST-segment depression during exercise, which is an indicator of myocardial ischemia *(493)*.

These results do not confirm the hypothesis that UFPs are responsible for most of the adverse health outcomes associated with particulate pollution. Instead, they indicate that the contribution of fine, and possibly coarse, particles should not be neglected. However, evidence is accumulating to support the hypothesis that pulmonary and systemic inflammation and prothrombotic changes play important roles in the health effects of particulate air pollution.

Evidence of Inflammation

Exhaled NO is generally considered a marker of inflammation in the lung. In unselected cohorts of Dutch schoolchildren, elevations in PM_{10}, black smoke, NO, and NO_2 were significantly associated with exhaled NO *(444,452)*. Additionally, there was an increase in NO metabolites, IL-8, and uric acid in nasal lavage in response to some of these pollutants *(452)*. Generally, greater effects were noted in urban compared to suburban children. A panel study of 19 children with asthma in Seattle, Washington, also found that elevations in personal, residential indoor, residential outdoor, and central site monitoring $PM_{2.5}$ levels were significantly associated with increases in exhaled NO *(476)*. The effect was restricted to children not taking inhaled corticosteroids.

Young healthy volunteers from the Chapel Hill, North Carolina, area were submitted to controlled exposure to concentrated ambient air particles (CAPS) at concentrations between 23.1 and 311.1 $\mu g/m^3$ for 2 h with intermittent exercise; this exposure induced mild pulmonary inflammation in the subjects with the highest exposure compared with those exposed to filtered air *(494)*. This was evident in a significant increase in the percentage and absolute numbers of neutrophils in bronchial and bronchoalveolar lavage fluid (BALF) obtained

18 h later, although total cell count increased only in BALF. However, BALF concentrations of inflammatory cytokines and other mediators, such as IL-6, IL-8, prostaglandin E2, α1-antitrypsin, and fibronectin, did not change *(494)*, nor did expression of activation markers on bronchoalveolar lavage or peripheral blood lymphocytes or alveolar macrophages *(495)*. Blood fibrinogen increased after exposure to CAPS, but the change was not statistically significant.

Somewhat different results were obtained in healthy and asthmatic adults from the Los Angeles area who were exposed to CAPS *(496)*. Analysis of induced sputum obtained approx 22 h after exposure did not provide evidence of pulmonary inflammation, because the white blood cell count, differential cell counts, IL-6, and IL-8 did not change significantly after CAPS exposure compared with filtered air exposure. Lung function and respiratory symptoms were also not affected. However, there were some indications of systemic inflammation because plasma-soluble ICAM-1 concentrations were increased following CAPS exposure in both groups. Additionally, plasma IL-6 increased during exposure to filtered air and to CAPS in both healthy subjects and asthmatics, but the increase was greater after exposure to CAPS than after air exposure in asthmatics, whereas the healthy subjects showed smaller increases after exposure to CAPS than after air exposure. There were no significant CAPS-induced changes in serum amyloid, fibrinogen, von Willebrandt factor, and factor VII. A notable difference between the studies was that the targeted ventilation rate was considerably lower in Los Angeles (15–20 $L/min/m^2$) than in Chapel Hill (25 $L/min/m^2$). The resulting lower exposure from decreased deposition fraction together with the use of induced sputum rather than BALF in the Los Angeles group might partly explain why the results of the two studies differed. Differences in particle composition may also have contributed to the discrepant results.

There have also been several studies in which healthy volunteers were exposed to whole diesel exhaust *(497–499)* or diesel exhaust particles *(500)*. No significant changes in lung function (as assessed by FEV_1, FVC, FEF_{50}, and $FEF_{25—75}$) were noted in healthy volunteers exposed to whole diesel exhaust *(497,498)*. However, when the more sensitive method of whole-body plethysmography was used, significant increases in airway resistance and specific airway resistance became evident after diesel exhaust exposure compared with exposure to air, although it could not be established whether this resulted from the particulate fraction or other constituents of diesel exhaust *(497)*.

Indicators of pulmonary inflammation included increased numbers of neutrophils and B-cells and raised levels of histamine and fibronectin, but not IL-8 and soluble ICAM-1, in BALF obtained 6 h after exposure to diesel exhaust *(498)*. Bronchial biopsy samples also exhibited elevated numbers of neutrophils, mast cells, and total T-cells in submucosa and epithelium along with enhanced expression of adhesion molecules and their ligands in bronchial tissue *(498)*. A marked rise in neutrophils and platelets in peripheral blood suggested a systemic inflammatory response. BALF obtained 24 h after exposure to diesel exhaust still contained increased numbers of neutrophils and also showed a significant rise in the number of alveolar macrophages and particularly of lysozyme-positive macrophages *(501)*. Unlike the result observed in 6-h samples, neither fibronectin nor tryptase or ECP were elevated.

Similar findings have been reported after healthy volunteers have been exposed to diesel exhaust particles *(500)*. Specifically, airway inflammation was evident in a small, but consistent and significant, increase in neutrophils and myeloperoxidase in induced sputum but was not evident in IL-8 and TNF-α. In this study, plasma IL-6, TNF-α, and P-selectin were measured as markers of systemic inflammation and were found not to change signifi-

cantly after exposure to diesel exhaust particles compared with exposure to air.

Nonetheless, indications of systemic inflammation in response to PM exposure have also been reported from cross-sectional and panel studies. Increased white blood cell and platelet counts were significantly associated with PM_{10} concentrations in a subsample of NHANES III participants *(502)*, although there was no association with $PM_{2.5}$ levels in a panel of elderly subjects *(503)* or in young healthy subjects *(504)*. An increase in the percentage of neutrophils was reported in highway patrol troopers *(505)*. Additionally, elevated levels of C-reactive protein were found in association with $PM_{2.5}$ *(503,505)*, PM_{10} *(506)*, and total suspended particles *(507)*. Several authors also reported that fibrinogen concentrations rose after exposure to elevated concentrations of PM_{10} *(502,508)*, although this was not noted in young healthy adults *(504)*. Others detected a significant positive association between fibrinogen and O_3 but not PM_{10} *(509)*. Fibrinogen is not only an acute phase protein but is also a marker of hemostasis because it plays a central role in coagulation. Other hemostatic markers have also been reported to be associated with $PM_{2.5}$ exposure in cars of highway patrol troopers *(505)* and with PM_{10} and other ambient air pollutants *(509)*. Increases in plasma viscosity were found during an air pollution episode in Germany *(510)*, but no association was detected between blood viscosity and $PM_{2.5}$ concentrations in a panel of elderly subjects from Utah *(503)*.

Decreased Autonomic Control

Numerous panel and some cross-sectional population-based studies *(511,512)* have investigated the association of PM_{10} and $PM_{2.5}$ with time- and frequency-domain parameters of heart rate variability (HRV). In panel studies, small, but significant, decreases in time domains, such as the standard deviation of all normal-to-normal intervals (SDNN) and the square root of the mean of the sum of the squares of differences between adjacent NN intervals (r-MSSD) were observed in association with daily fluctuations in centrally monitored $PM_{2.5}$ and PM_{10} concentrations *(503,513,514)* as well as in association with personal exposure to UFPs *(515)*. Frequency domains of HRV, such as high- and low-frequency power, also showed small but significant inverse associations with daily changes in outdoor and indoor $PM_{2.5}$ concentrations *(516,517)* or the time-weighted total exposure derived from them *(518)*. They also decreased significantly in association with fluctuation in personal exposure to submicrometer particles *(515)*. The inability to detect significant effects of $PM_{2.5}$ and PM_{10} on HRV in some other panel studies *(519,520)* likely results from the small sample sizes, low absolute pollution levels in both of the locations, low variability of $PM_{2.5}$ measurements for most subjects, and, possibly, differences in the composition of particles from these cities compared with other metropolitan areas.

Most of these panel studies were conducted in elderly subjects, and there are indications that the elderly are more susceptible to the effects of particulate pollution on HRV than younger adults *(515)*. Susceptibility appears to be further enhanced in subjects with underlying cardiovascular disease (CVD) and hypertension *(516,517)*, although others did not observe a significant effect modification by CVD *(518)*. However, some effects on HRV have also been reported in young subjects in association with personal $PM_{2.5}$ and UFP exposure *(515,521)*, with the effects of UFPs being smaller in young subjects than in older subjects studied simultaneously *(515)*. Additionally, brief occupational and environmental exposures to $PM_{2.5}$ were significantly associated with decreased SDNN in relatively young cohorts of boilermakers (mean age: approx 40 yr) *(522,523)*.

In striking contrast to the fairly consistent finding of decreased HRV, in nine North Carolina State Highway Patrol troopers, $PM_{2.5}$ exposure inside their vehicles was associated with increased HRV and other changes suggestive of increased vagal tone *(505)*. Principal factor

analysis of components of $PM_{2.5}$ and associated pollutants indicated that these changes were associated most strongly with PM resulting from brake wear and engine emissions *(524)*. This type of PM may exert different effects than ambient particles from other sources. The results of controlled exposure studies are also not entirely consistent with these findings *(496, 525)*. Note that particle concentrators used to generate CAPS concentrate fine particles but not UFPs. This could account for some of the differences between the results of controlled exposure studies with CAPS compared with those of panel studies because UFPs were shown to exert significant effects on HRV *(515)*.

Overall, however, there is rather consistent evidence that exposure to PM results in changes in cardiac autonomic control, and the decreases in SDNN in r-MSSD suggest reduced parasympathetic tone. Exposure to particulate air pollution is also associated with a decrease in heart rate *(511,513,526–528)*, which is consistent with an increase in sympathetic tone; however, an association has not been evident in all studies *(503,514)*.

Types of Particles and Particle Constituents Responsible for the Observed Effects

Specific rotation factor analysis of the elemental composition of fine and course PM measured in six US cities indicated that $PM_{2.5}$ from mobile sources (i.e., motor vehicle exhaust) showed the strongest association with overall daily mortality, followed by particles from coal combustion sources *(529)*. Fine particles from crustal sources were not associated with mortality. Interestingly, a 10-$\mu g/m^3$ increase in particles from mobile sources was associated with a 2% increase in deaths from ischemic heart disease, but this was not statistically significant. An adverse effect of traffic-related particles on respiratory deaths was not evident. Conversely, deaths from COPD and pneumonia increased with increased exposure to particles from coal combustion sources, whereas this factor did not affect deaths from ischemic heart disease.

Similarly, analysis of data from 14 US cities regarding PM_{10} emissions by source category indicated that hospital admissions for CVD were most strongly correlated with increasing percentage of PM_{10} from highway vehicles and highway diesels *(428)*. A correlation between percentage of PM_{10} from highway vehicles/diesels and hospitalization for COPD was not observed for the entire data set but became significant after exclusion of two cities (Boulder, Colorado, and Provo-Orem, Utah).

These findings are consistent with reports of increased mortality and morbidity in association with indicators of traffic *(530)* and traffic-related air pollution, such as black smoke and NO_2 *(531)*. Additionally, in several studies, *(532,533)*, including some analyses of the effects of air pollution on respiratory health *(448,453,457)*, some investigators found black smoke to be more strongly associated with adverse health effects compared with PM_{10} or $PM_{2.5}$. EC and organic carbon are also likely to be derived largely from traffic emissions. In Hispanic children living in an area of Los Angeles with high traffic density, an asthma symptom score was more strongly associated with EC and OC than with PM_{10} *(449)*. In two-pollutant models that included EC and OC along with PM_{10}, the OR for PM_{10} was reduced to 1.0, whereas the ORs of EC and OC remained unchanged.

The composition of PM does not vary only by emission source; even ambient particles used for CAPS studies show considerable day-to-day variation in their OC, EC, and elemental composition *(484,534)*. Huang et al. *(534)* applied principal component analysis to data from their study, which showed that controlled exposure to CAPS from the Chapel Hill area induced an increase in neutrophils in the bronchial and alveolar fraction and increased blood fibrinogen levels in young healthy adults *(494)*. The results of this analysis indicated that among

the water-soluble fraction of CAPS, a sulfate/Fe/Se factor was associated with an increase in the percentage of neutrophils in BALF and a Cu/Zn/V factor was associated with increased blood fibrinogen. This suggests that soluble constituents of PM differentially affect target organs and systems, which is consistent with the findings of in vitro and animal studies suggesting that particle-associated metals differ in their ability to affect different cell types within the lung and in the mechanisms by which they operate (e.g., induction of oxidative stress or of inflammatory cytokine production by lung epithelial cells and alveolar macrophages) *(486, 488,535)*.

These analyses were restricted to outdoor particles. It has been suggested that ambient stationary site measurements, as used in time series and most panel studies, do not accurately reflect personal exposures because people spend approx 90% of their time indoors and the contribution of outdoor particles to indoor concentrations varies widely between homes. Ambient sampling has been shown to overestimate the exposures resulting from traffic-related and long-range transport sources and to underestimate some significant indoor sources (of residential and indoor work environments) *(536)*. Additionally, the chemical composition of indoor and outdoor particles can differ markedly *(537, 538)*. Notably, some indoor and outdoor particles exhibited similar trace element composition, but scanning electron microscopy revealed that spherical particles, usually indicative of combustion or other high temperature industrial processes, were present almost exclusively in outdoor and ambient samples *(537)*. Furthermore, indoor particles can have greater toxicity than outdoor particles *(539)*. Then, the issue arises regarding whether indoor or outdoor exposures are more relevant to the observed health outcomes.

In a study that assessed personal exposure to PM_{10} and $PM_{2.5}$ in children with asthma along with residential indoor and outdoor as well as central-site PM concentrations, FEV_1 was associated with the 5-d average of all measurements but was most strongly associated with personal exposure *(463)*. Residential indoor levels of $PM_{2.5}$ and PM_{10} showed stronger associations with FEV_1 than residential outdoor or central-site concentrations. Assessment of indoor and outdoor $PM_{2.5}$ levels in some of the HRV studies also indicated somewhat greater effects associated with indoor concentrations *(517,518)*. Biomarkers of oxidative stress in blood were associated with personal exposure to $PM_{2.5}$ and black smoke but not with ambient background concentrations *(504)*.

These studies do not clarify whether indoor or outdoor sources are most relevant to the observed health effects. In recent studies, different modeling approaches have been used to determine ambient and nonambient exposures to then correlate them with observed health effects *(526)*. In one of these studies *(526)*, personal $PM_{2.5}$ exposure was found to be composed mostly of nonambient particle exposure, and neither total personal nor nonambient exposure was associated with any of the investigated health outcomes, with the exception of an unexpected increase in FEV_1. Ambient exposures (as determined from ambient concentrations and time-activity data) were associated with decreased FEV_1 and systolic blood pressure and increased heart rate and supraventricular ectopic heartbeats. In most cases, ambient exposures provided better effect estimates than ambient concentrations. In another study, increases in exhaled NO were more strongly associated with the ambient-generated component of personal exposure *(477)*. Conversely, and also differing from the previously discussed results *(526)*, indoor-generated $PM_{2.5}$ were associated with FEV_1 and FVC but not midexpiratory flow *(477)*. Note that this association was somewhat dependent on the model used for estimating the indoor-generated component of $PM_{2.5}$ exposure. Interestingly, lag 0 indoor home $PM_{2.5}$ and PM_{10} concentrations

were significantly associated with decreases in FEV_1, whereas residential outdoor and central site measurements showed some significant associations with FEV_1 only at longer averaging periods in another panel of children with asthma *(463)*. This also suggests that indoor and outdoor particles differ in the mechanisms through which they induce adverse effects on respiratory health. Although somewhat preliminary in nature, these results suggest that ambient and nonambient particles are differentially associated with various health outcomes.

Biologicals

Microbes

The first report of a cluster of people in the same building becoming ill at the same time occurred in 1976, when 182 attendees of a convention of the American Legion in Philadelphia developed a disease characterized by respiratory symptoms that proved fatal in 29 of the cases. The disease was named Legionnaires' disease, and the organism responsible was eventually called *Legionella pneumonia*. *Legionella* species are found naturally in warm and humid environments. In buildings, they grow in air conditioning cooling towers, hot water tanks, other parts of the plumbing systems, and hot tubs. The disease is contracted by the inhalation of aerosolized droplets of water that are contaminated with the bacteria, but it is not spread by person-to-person contact. The incubation period is 2 to 14 d. Every year, 8000 to 10,000 people are hospitalized with Legionnaires' disease. Individuals over age 65 yr, those with chronic lung diseases, those who are immunosuppressed, and patients with chronic illness (such as diabetes or cancer) are more susceptible. The mortality rate ranges from 5 to 30%. A less severe, nonrespiratory form of Legionnaires' disease was named Pontiac fever because it was first described in 144 health department facility workers in Pontiac, Michigan *(540)*. The illness is caused by a bacterium with characteristics similar to that of *L. pneumonia*; it is self-limiting, and the symptoms include headache, fever, malaise, and myalgias.

Although the etiology of these disease outbreaks associated with specific buildings was initially unknown, causative agents were eventually identified, making Legionnaires' disease and Pontiac fever examples of specific building-related illnesses. Other microbial agents have also been reported to cause outbreaks of disease that are confined to a particular building. Examples include influenza virus infections in nursing homes *(541–544)* and, more recently, clusters of severe acute respiratory syndrome cases in a hospital *(545)* and an apartment complex *(546)*. However, in these cases, the buildings were not reservoirs of the infectious agents. Rather, transmission from human to human within the building caused the outbreaks.

Fungi and Molds

Fungi are ubiquitous. They require moisture for growth and survival but can grow on various substrates, including dead or living plant and animal tissue, paint, paper products, and building materials. During reproduction, they become airborne as mold spores. Fungal spore concentrations in indoor environments are measured in either air or dust, and the results are reported either as viable (culturable) spore concentrations in colony-forming units (CFU) per cubic meter or per gram of dust or as total (viable and nonviable) spore counts expressed in spores per cubic meter. The total spore count can be up to two orders of magnitude higher than the number of viable microbes.

Viable fungal spore concentrations in more than 12,000 samples from more than 1700 buildings in the United States ranged from below the detection limit to more than 8200 CFU/m^3 in outdoor air and to more than 10,000 CFU/m^3 in indoor air samples *(547)*. Median indoor and outdoor concentrations were 80 and approx 500 CFU/m^3, respectively. Similarly, in 19

studies from North America, Europe, Asia, and Australia, total viable spore counts varied between below the detection limit and 23,000 CFU/m^3 in indoor air samples from buildings with visible mold growth *(548)*. With one notable exception (450,000 CFU/m^3), the maxima in indoor air samples from buildings without signs of mold growth were lower. There is seasonal as well as regional variability in the number of airborne mold spores and in the ratio of outdoor to indoor concentrations *(547,548)*. This applies not only to concentrations of total fungi but also to specific genera and species *(549)*. Outdoor viable as well as total spore counts are generally higher than, but show a positive correlation with, indoor levels *(548,549)*. Indoor mold spore concentrations can exceed those found outdoors in buildings with obvious water damage or signs of mold growth; however, several studies have reported similar mold spore counts in buildings with and without dampness and mold problems *(548,550)*. The profile of indoor fungi also differs from that found outdoors, and the diversity of fungal species is frequently greater in damp buildings *(551)*.

Worldwide, the most common genera in indoor and outdoor air are *Penicillium*, *Cladosporium*, and *Aspergillus (547–549)*. Species that require high water activity, such as *Stachybotrys* and *Trichoderma*, are reported much less frequently because of their more infrequent occurrence and because they are difficult to culture with the standard culture methods *(547)*. (Table 18 provides a list of common airborne spores and their characteristics.)

Fungal spore release is irregular and depends on various environmental conditions. Additionally, fungal spores in settled dust can be resuspended by human activities. Consequently, there can be substantial temporal variation in airborne spore counts. Measurements of airborne fungal spores fail to capture this variability and poorly reflect actual exposure because they are usually based on very short sampling periods (10–30 min). There are few reports of longer term (24-h) measurements *(549,552)*. In one study, personal exposure of 81 Finnish schoolteachers to total as well as viable microbes was determined by 24-h sampling with a personal button particle sampler and was compared with residential and workplace indoor concentrations *(552)*. Geometric mean concentrations of total fungi were higher in the work environment (9000 spores/m^3) than in the home environment (4700 spores/m^3), and concentrations of fungi in the home environment were similar to personal exposure levels (5700 spores/m^3). The geometric mean concentrations of viable fungi were 2 to 3, 5 to 6, and 12 CFU/m^3 in work, home, and personal samples, respectively.

Fungal spores settle with floor dust, which can be resuspended during walking and other human activities; therefore, fungal concentrations in floor dust are believed to be a surrogate for cumulative exposure. More recently, fungal components such as extracellular polysaccharides (EPS), β-(1→3)-D-glucans, and ergosterol have been measured in house dust *(553,554)* and air *(555)*. The results suggest that they may represent acceptable markers of fungal exposure. Statistically significant, although not very strong, correlations were detected between EPS of *Aspergillus/Penicillium* (EPS-Asp/Pen) and β-glucan levels in house dust and total culturable fungi *(553,554)*. The weakness of the association may reflect that both markers represent total fungal biomass rather than only culturable species. In one of the studies, EPS-Asp/Pen levels in floor dust were found to correlate positively with occupant-reported, but not investigator-observed, mold and dampness problems in the living room *(554)*. For bedrooms, the association was inverted, possibly because of allergen avoidance measures. In 110 homes in Canada, airborne β-glucan and ergosterol concentrations obtained via long-term active sampling (5–7 d) were highly correlated not only with each other but also with area covered by visible mold growth (as care-

Table 18
Fungi in Air: Common Airborne Spores

Genus	Size of spores (μ)	Substrates and other characteristics
Alternaria	8–75	Multicell, multiseptate spores; grows on plant material and rotting vegetation, found indoors in damp areas.
Aspergillus	2–10	Stored cereal grains, dead vegetation, found indoors, found outdoors in compost heaps; spores look similar to *Penicillium*; speciation can be done by culture.
Curvularia	18–43	Light brown mold with distinct septae.
Dreschlera		Plant debris, soil.
Epicoccum	20	Dark to golden brown; multiseptate spores.
Fusarium		Soils, saprophytic on plants, important producer of trichothecenes.
Cladosporium	4–20	Dead vegetation, textiles.
Acremonium		Dead organic debris, foodstuffs, soils; small one-cell colorless spores.
Stachybotrys		Soils, decaying leaf litter, cellulose, seeds, and decaying plant substrates.
Trichoderma	2–10	Soils, decaying wood, grains, citrus, damp wood, paper, textiles.
Penicillium	3–5	Used in the manufacture of blue cheese, common indoors, grows on stored foods, fruit, cheeses, bread.
Periconia	16–18	Soil, grasses, dead leaves, rarely found indoors.
Cephalosporium		
Rhizopus		Found on spoiling food, decaying fruits, and vegetables.
Mucor		Found on organic matter, dung, and soils. Colorless spores.
Stemphyllium	23–75	Saprophytic, grows on cellusic material, including livestock feed, ceiling tiles, paper, and cotton cloth. It is a diurnal sporulator.
Ulocladium		Soil, dung, decaying plant matter, fibers, wood, grasses, textiles, and paper; may be confused with *Alternaria.*
Botrytis		Teardrop shape spores, saprophytic and parasitic; part of the *Dreschlera* group.

fully documented by trained inspectors) *(555)*. The correlation between glucans and total spore counts was markedly weaker, although highly significant.

Safe vs Hazardous Mold Levels

There is no consensus regarding what constitutes safe or hazardous levels of mold. However, there is clearly an enormous variation in mold levels between cities, depending on their temperature and humidity. It should also be obvious that mold has been in the air and in the environment since long before people existed. The mere presence of mold even at elevated counts does not imply disease, despite an enormous hype in the media over the so-called mold-related syndromes. Indeed, certain environments, such as greenhouses or situations following floods, have consistently failed to disclose an epidemic or any disease cluster. The only exception to this is exacerbation of asthma in individuals who have IgE directed against mold allergens. The National Allergy Bureau of the American Academy of Allergy, Asthma and Immunology interprets outdoor fungal levels (in counts per cubic meter) as follows: 0 = absent, 1 to 6499 = low, 6500 to 12,999 = medium, 13,000 to 49,999 = high, and 50,000 or greater = very high. The American Academy of Allergy, Asthma and Immunology also certifies and reports mold spore data from nearly 80 certified pollen and mold spore counting centers throughout the United States and Canada. The measures that constitute a safe indoor mold spore level are even less well-defined. Several states and

countries have attempted to set standards for hazardous indoor mold levels. A consensus has proved elusive, and these standards are not supported by clinical data or other scientific evidence. The New York City Department of Health recommends evacuation if the indoor/outdoor ratio is greater than 1 and if indoor concentrations exceed 1000 spores/m^3. Brazil sets the threshold for hazardous exposure at 750 spores/m^3, whereas the standard in the Netherlands is 10^4 spores/m^3 (http://www.inspect-ny.com/sickhouse/moldlevels.htm). Ironically, these recommendations were not developed by vigorous scientific panels: they were arbitrary. In fact, mold counts higher than this value are normally found outdoors!

Biomonitoring

There are currently no generally accepted biomarkers of fungal exposure. Although elevated fungal-specific IgG and IgA concentrations have been reported with higher frequency in an exposed population compared with a control population *(556)*, researchers have not distinguished between the two groups. Other investigators failed to detect significant differences in the prevalence of IgG antibodies against *S. chartarum* between a group of subjects with confirmed exposure to high concentration of this fungus and a control group *(557,558)*. In our own experience, and that of others, the use of IgG antibodies has no clinical value in the so-called mold-related illnesses. The only important and unusual exceptions to this are the well-described precipitating IgG antibodies in hypersensitivity pneumonitis.

Health Effects

Reviews performed by a committee of European scientists regarding the literature on health effects associated with building dampness have concluded that dampness in nonindustrial work and residential environments is associated with a variety of health effects *(559,560)*. Such health effects *(67,109,561–563)* include increased prevalence of self-reported and physician-diagnosed asthma, decreased lung function, increased prevalence and severity of asthmatic and allergic symptoms, allergic sensitization, and inflammatory markers in nasal lavage. There is also evidence for associations with other typical SBS symptoms, although it is weaker than evidence for respiratory symptoms. However, the agents responsible for the increased risk of health effects associated with exposure to dampness remain unclear. There is some evidence that house dust mites are involved but do not fully account for the observed effects. Additionally, it is possible that organic chemicals given off by degrading building materials mediate some of the health effects associated with building dampness. However, microbiological agents and/or some of their products are prime candidates.

There have been numerous reports of significant associations of SBS symptoms and other health effects not only with self-reported visible mold growth, but also with viable fungal spore counts in air and dust *(548)*. Similarly to building dampness, the associations are with respiratory symptoms, lung function, and asthma prevalence. Inconsistent results were reported for nasal, throat, eye, skin, and general symptoms. Recently, however, significant and dose-dependent associations were detected between levels of culturable fungi in floor dust and mucous membrane and general symptoms in female—but not in male—teachers from 15 Danish public schools *(550)*. Specifically, the risk of experiencing difficulties in concentrating was increased more than 10-fold at the highest exposure levels. Otherwise, however, the strongest associations with symptoms were detected for recent airway infections, hay fever, psychosocial factors, and current smoking status. None of the objective measures of health effects (lung function parameters, IL-8, and ECP in nasal lavage) were associated with mold exposure or symptoms. Subsequently, a controlled exposure study was conducted with eight school employees who had shown increased histamine release to *P. chrysogenum*

(564). Short-term exposure to high doses of *P. chrosygenum* and *Trichoderma harzianum* spores did not result in more mucous membrane or general symptoms than placebo. However, exposure to a high concentration of fungal spores for a short period may not accurately capture the effects of long-term exposure to low or moderate doses. One should emphasize that clinical data have only demonstrated a value of IgE antibodies against allergens as a predictor of whether health effects are observed. Although several studies have claimed that fungi are involved in sinus disease, such data do not clearly indicate environmental molds and suggest that recovered mold in cultures is primarily secondary to overgrowth from the use of broad-spectrum antibiotics. Often, such claims of sinus disease and mold are not even accompanied by appropriate sinus imaging.

Interestingly, studies of children attending the same schools indicated that levels of culturable fungi in floor dust were significantly associated with symptoms in boys only *(565)*. Specifically, mold exposure increased the risk of eye irritation, headache, concentration problems, and dizziness. Similarly to the adult population, the strongest associations with symptoms were observed for factors other than mold exposure—particularly recent airway infection, hay fever, and psychosocial factors.

As part of the BASE study funded by the US EPA, repeated measurements of culturable fungi in air, floor dust, and chair dust were obtained over a period of 1 yr in 21 offices in four office buildings in Boston *(566)*. In addition to work environment and personal factors, a group of unidentifiable fungi in chair dust was significantly associated with nonspecific symptoms in a multivariate analysis. Fungal concentrations in chair dust also predicted upper respiratory symptoms as well as work environment and personal factors.

Few studies have examined the association between SBS symptoms and aero-allergens by measuring exposure directly at the workstation of each participant rather than at a single site or a few sites within a building. One such study found that symptoms of the upper and lower respiratory system were not associated with total culturable fungi, but they correlated significantly with detectable airborne *Alternaria* and house dust mite concentrations *(567)*. Notably, *Alternaria* spore counts were low, with mean levels of 7 and 6 CFU/m^3 in the offices and the HVAC supply systems, respectively.

Results from another study involving 48 schools with a high incidence of SBS symptoms suggested that *Penicillium* and *Stachybotrys* were the main genera associated with these symptoms *(568)*. In 20 of these schools, *Penicillium* levels in areas whose occupants reported a high frequency of SBS symptoms significantly exceeded those of areas with a low frequency of complaints as well as *Penicillium* levels from outdoor air samples. In the other schools, airborne *Penicillium* concentrations were not elevated, but heavy to very heavy growth of either *Penicillium* and *Cladosporium* or *Stachybotrys* species was found in swab samples from water-damaged areas. Remedial actions taken by many of the schools reportedly resulted in indoor air fungal profiles similar to those found outdoors and were associated with a marked decrease in the frequency of symptom reports. However, a causal relationship could not be established, because significant bias was inherent in the methodology used to evaluate subject complaints and because other possible causes of the complaints were not investigated. Interestingly, in another building with a high frequency of indoor air quality complaints and visible fungal growth in many rooms, the outdoor fungal profile changed considerably during a 6-h observation period, whereas the indoor fungal profile underwent little alteration *(569)*. Similarly to the study of school buildings, *Penicillium* was the dominant species in indoor air at all time-points, whereas it was the dominant species in outdoor air in only two of the six samples.

Other studies have confirmed that remedial action can result in a significant decrease in the total airborne viable mold concentration and a decrease in the microbial diversity along with a decrease in most of the symptoms assessed *(570)*. Notably, the concentration of airborne bacteria also declined after the repair of moisture damage, making it difficult to determine whether bacterial or fungal exposure were mainly responsible for the observed symptoms. Similarly, renovation plus thorough cleaning of buildings containing a public swimming pool resulted in a marked decrease in the number of viable molds, led to a change in the species composition of the molds, and was associated with a decrease in the symptom frequency from 66% before the renovation to 4% after completion of the intervention *(571)*. However, as emphasized earlier, these data are confounded by discrimination bias and the lack of controls and often include issues of secondary gain.

Numerous studies, including several longitudinal studies, have addressed the association between residential dampness and/or mold and wheezing and persistent cough in infants and small children. Although wheezing in infancy does not necessarily develop into asthma later in life, it is an acknowledged risk factor. In a case–control study of 251 pairs of small children, those who were diagnosed with bronchial obstruction were significantly more likely to live in homes with dampness problems in the 2 yr preceding (as confirmed by independent trained investigators or professional builders) *(572)*. In a prospective birth cohort study of more than 4000 children from Stockholm, Sweden, home dampness was significantly associated with the occurrence of asthma or recurrent wheeze in children followed for the first 2 yr of their lives *(573)*. Mold odor reported at baseline, but not water damage or presence of visible molds, predicted asthma incidence in a 6-yr prospective cohort study involving children age 1 to 6 yr at baseline *(574)*. This association remained significant after adjusting for parental atopy and various other known risk factors for the development of asthma, although there was no adjustment for the presence of specific allergens.

In infants at high risk of developing asthma (i.e., those with a mother and an older sibling with physician-diagnosed asthma), there was a significant association between frequent wheezing and persistent cough and mothers' reports of visible signs of molds and mildew *(575)*. The number of airborne viable mold spores was also significantly associated with wheeze, even after adjusting for several common aero-allergens, environmental exposures, and other known risk factors.

The same outcomes were assessed in another study involving 880 infants of mothers who had at least one older child with physician-diagnosed asthma *(576)*. In this study, airborne levels of fungi were categorized into undetectable, low (1–499 CFU/m^3), medium (500–999 CFU/m^3), or high levels ($\geq$1000 CFU/m^3). Infants exposed to high *Penicillium* concentrations were at significantly increased risk of developing wheeze and persistent cough during their first year of life. Although the level of *Cladosporium* spores in indoor air correlated with occupant-reported mold and water leaks, *Cladosporium* concentrations were not significantly associated with either of these symptoms, whereas reported mold was associated with persistent cough.

A prospective study of a birth cohort involving 499 children of atopic parents demonstrated that those who were exposed to high levels of certain fungal spores had a higher incidence of developing lower respiratory tract illnesses (including bronchiolitis, croup, pneumonia, and bronchitis) in the first year of life *(577)*. Specifically, significant associations were detected between lower respiratory tract illness and airborne (but not dust-borne) *Penicillium* and dust-borne (but not airborne) *Cladosporium*, *Zygomycetes*, and *Alternaria*. Notably, these

associations were observed after controlling for markers of moisture damage, which independently predicted lower respiratory tract illness. In all three studies that measured fungal concentrations *(575–577)*, exposure to mold was assessed on only one occasion early in each infant's life, few other environmental exposures were accounted for, and only one investigation examined the simultaneous effects of molds and other aero-allergens (particularly house dust mites, cats, dogs, and cockroaches) *(575)*. Therefore, substantial misclassification of fungal exposure cannot be ruled out, and a causal relationship cannot be definitively established.

Results of time series studies have indicated that increased concentrations of outdoor fungal spores are associated with decreases in PEFR in unselected children *(578)* and in children with asthma *(459,579)* and with increases in asthma symptom severity and inhaler use *(459, 580)* and in the number of emergency hospital visits for asthma in children *(581)*; however, this association was not observed in another study *(582)*. Fungal spore levels have also been reported to be associated with increased mortality from asthma in persons ages 5 to 34 yr *(583)*.

Mechanisms

The mechanisms by which exposure to airborne fungi may induce SBS symptoms and related health effects appear secondary to IgE-mediated disease. Sensitization to fungal allergens has been reported to be significantly associated with asthma, although considerable regional variation in the rates of sensitization was noted *(584)*. For example, among children with bronchial hyperreactivity, 56% had elevated IgE antibodies (CAP scores ≥2) against *Alternaria* allergens in Los Alamos, New Mexico, compared with only 19% in Albemarle, Virginia *(584)*. Control patients had a significantly lower prevalence of scores greater than 2. The overall sensitization rate was 20% for *Alternaria* allergens compared with only 8% to *Cladosporium* allergens. Similarly, rates of sensitization to *Cladosproium* in more than 11,200 subjects from various European countries ranged between 1 and 7% *(585)*. Sensitization to *Cladosporium* was associated with increased bronchial hyperresponsiveness to metacholine in some countries, but there was no association in other countries or in the group overall. Additionally, spore extracts of *Basidiomycetes*, *Cladosporium*, and *Penicillium* can induce early and late asthmatic reactions in sensitized subjects *(586,587)*.

β-(1→3)-D-glucans are glucose polymers that are cell wall components of most fungi and of some bacteria and many plants. A large variety of β-(1→3)-D-glucans exists, with varying molecular weights, solubility characteristics, conformations (triple helix, single helix, random coil), and degrees of branching (frequency of attachment of β-[1→6]-glucan side branches). Each one of these characteristics affects the type and extent of biological activity, which is predominantly immunostimulatory. The number of different β-glucans that have been investigated in experimental studies is very limited. β-(1→3)-D-glucans have been used as markers of fungal exposure, but it remains unclear to what extent they contribute to the health effects attributed to such exposure. One researcher recently reviewed epidemiological and controlled exposure studies along with data from animal experiments investigating the effects of fungal β-glucans on respiratory health *(588)*. The author concluded that the epidemiological data suggested an association between β-glucan exposure and airway inflammation and respiratory symptoms. However, the available evidence was inconsistent and suffered from insufficient statistical power, lack of control for other potential causal agents, and potentially from considerable exposure misclassification. The results of animal studies suggest that high concentrations of β-glucans have the potential to induce airway inflammation and to enhance specific IgE sensitization, although neither were consistent findings.

Notably, extracts of *Cladosporium herbarum* and *P. chrysogenum*, both molds that colonize damp building walls, were reported to enhanced OVA-specific IgE and IgG1 response in mice when administered subcutaneously *(589)*. The β-glucan concentrations of the extracts were very low, suggesting that other fungal components were primarily responsible for this adjuvant effect.

Certain molds are able to produce toxic metabolites known as mycotoxins. They have been studied most extensively in the context of fungal contaminants of foods such as wheat, grapes, rice, maize, oilseeds, and so forth. The fungi that contaminate these grains and foods are also common household fungi, and it is believed that humans can be exposed to mycotoxins in indoor air. Examples of fungi that can produce mycotoxins include *Fusarium, Aspergillus, Alternaria, Penicillium,* and *Stachybotrys*. The most common mycotoxins belong to a class of molecules called trichothecenes (ref. *590*; *see* Table 19 for the various categories of mycotoxins and the types of trichothecenes). Trichothecenes are a group of structurally similar sesquiterpene molecules, characterized by a 12, 13-epoxytrichothec-9-ene ring system. Trichothecenes generally are extremely stable and are degraded only by heating at high temperatures for a prolonged period. Metabolites of trichothecenes may be less toxic than the parent compound *(591)*. Interestingly, however, mycotoxins do not appear to be airborne, and even in contaminated air environments, the quantities that humans are exposed to are extraordinarily small and require an enormous exposure for a clinical effect. Therefore, again, the presence of molds containing mycotoxins on a wall or on a carpet should not be interpreted as indicative of ill health any more than the likely presence of such mold on the soles of shoes should be interpreted in the same manner.

The main focus of research on the toxic effects of mycotoxins in experimental animals has been on their ingestion as part of the diet.

Table 19
Mycotoxins

Aflatoxins
Zearalenone
Secalonic D
Trichothecenes
Satratoxins
Trichoverols
Verrucarol
Verrucarins
Trichoverrins
T-2 toxin
Nivalenol
Deoxynivalenol
Diaceroxyserpenol
Isosatratoxin F
Ochratoxin A

Such studies have shown that several different mycotoxins can induce decreased feed efficiency and anorexia *(592–594)*, various effects on the immune system (predominantly immunosuppression; refs. *592,595,* and *596*), carcinogenicity *(597,598)*, and nephrotoxicity. Major mechanisms of toxicity include the inhibition of protein synthesis, mitochondrial toxicity, cytotoxicity, and the induction of apoptosis *(599–601)*.

Animal studies also indicate that intratracheal instillation of mycotoxin-producing fungi—particularly *Stachybotris chartarum*—can induce considerable pulmonary inflammation in rats and mice *(602,603)*. Some of these studies have suggested that the inflammatory response is mediated mainly by trichothecenes. However, more recent investigations have provided evidence that other fungal components also contribute to the lung pathology induced by exposure to *S. chartarum*. Repeated intranasal instillation of *S. chartarum* spores was found to cause an influx of monocytes, neutrophils, and lymphocytes into BALF and to increase mRNA expression of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and several chemokines *(604)*. These effects were only observed at the higher dose (1×10^5 spores per instillation) and not at the lower dose (1×10^3

spores per instillation). Neither T-helper 1 or T-helper 2 cytokines nor total or specific IgE, IgG1, and IgG2a levels were significantly increased by *S. chartarum* instillation. Notably, a strain of *S. chartarum* that produced satratoxin and a strain that did not produce satratoxin were used in the experiments. The inflammatory effects of the two strains were almost identical, indicating that satratoxin was not required for the induction of pulmonary inflammation.

Similar results were reported from an investigation of the effects of intratracheal administration of 1×10^5 intact, autoclaved, and ethanol-extracted spores of *S. chartarum* in 7-d-old rats *(605)*. During the 72 h following exposure to all three types of fungal spores, there was a significant reduction in alveolar space with simultaneous elevation of TNF-α, IL-1β, and neutrophils in BALF. Intact spores had the greatest effect, followed by autoclaved and ethanol-extracted spores. Differences in the time-course of the response indicated that the trichothecenes were the main contributors to the early inflammation, which peaked 24 h after exposure, although proteins already participated. Peak release of proteins and/or other fungal compounds occurred later in the inflammatory response and appeared to be mainly responsible for prolonging it.

In another study, mice received intratrachel instillations of 30, 300, or 3000 spores/g body weight (or 7500–750,000 spores per instillation) of a trichothecene- or atranone-producing strain of *S. chartarum* or of *Cladosporium cladosporioides (606)*. Both of the *S. chartarum* strains, but not *C. cladosporioides*, caused marked vascular leakage in the lung, although they had very different time-courses. Significant increases in BALF TNF-α concentrations were noted after treatment with all three fungi but did not show a linear dose–response in the case of the two *S. chartarum* strains. Conversely, IL-6 levels in BALF rose with increasing spore dose, with only the highest dose of all three fungi producing statistically significant increases. Only the highest dose of the atranone-producing *S. chartarum* strain significantly raised IL-1β concentrations. However, note that the lowest dose of the other strain induced similar levels, but they were not statistically significantly different from controls. Together, these results clearly suggest that substances other than trichothenes and atranones contributed to lung inflammation and pathology. This confirms the findings of the other studies, which also indicate that mycotoxins play an important role in lung inflammation and pathology but do not support the hypothesis that mycotoxins are solely responsible for these effects. Note that these results cannot be directly translated to humans because they were obtained with very high doses of spores corresponding to between 21 million to more than 1 billion spores for an average 70-kg human.

The potential health effects of exposure to *Stachybotrys* and its associated mycotoxins (satratoxins) were examined in 53 occupants of a water-damaged building *(557)*. There was an association detected between the presence of satratoxin H and spirocyclic lactones and lower respiratory, dermatological, eye, constitutional, and chronic fatigue symptoms. Additionally, occupants of the water-damaged building exhibited a lower proportion of mature T-lymphocytes compared with controls without any contact to the test site. This was not a double-blind study, and there was no effort to rule out other causes of the occupants' symptoms. Therefore, no conclusion can be made from this study regarding a causal effect of trichothecenes on human health.

Specific Sinopulmonary Diseases Caused by Mold and Other Microbial Agents

Aspergillus fumigatus and related species have been found to play a role in numerous pulmonary and upper airway diseases. These diseases include allergic bronchopulmonary aspergillosis (ABPA), allergic fungal sinusitis, and hypersensitivity pneumonitis.

ABPA is an allergic reaction to a fungus that mimics pneumonia; it is characterized clinically by asthma and airway inflammation and serologically by increased titers of *Aspergillus*-specific IgE in the blood. Increased eosinophils are present in lung tissue. The usual culprit is *A. fumigatus*, a fungus that grows in soil, decaying vegetation, food, water, and/or dust. Other fungi, including *Penicillium, Helminthosporium, Curvularia*, and *Candida*, may cause a similar disease. Sensitization to the fungus leads to an inflammatory response in the lungs and airways, which includes eosinophil infiltration and increased mucus production. Eventually, bronchiectasis and pulmonary fibrosis can occur. Symptoms include wheezing, shortness of breath, cough productive of brownish mucus, fever, and malaise. Changes observed in chest radiographs are consistent with pneumonia. Laboratory studies have revealed high levels of *Aspergillus*-specific IgE and elevated peripheral blood eosinophils. *Aspergillus* skin testing reveals sensitization, but the test is also positive in patients with a simple allergy to *Aspergillus*. Treatment for ABPA includes corticosteroids and antifungal agents.

Allergic fungal sinusitis (AFS) is a disease that is pathologically similar to ABPA, but the sites of inflammation are the paranasal sinuses. Other features include nasal polyposis, nasal and sinus accumulation of fungal debris and allergic mucin, and crust formation *(607)*. Cultures from the sinuses yield *Aspergillus*, although this is not pathognomonic, nor is the lack of positive *Aspergillus* cultures enough to rule out AFS. It is estimated that approx 5% of all patients with chronic rhinosinusitis have AFS. It is more common in atopic patients who have a diagnosis of allergic rhinitis and who test positive to one or more fungal allergens. AFS primarily affects young adults, and most cases are geographically distributed in temperate areas with high humidity. Aside from *Aspergillus*, AFS can be caused by dematiaceous fungi, including *Bipolaris, Curvularia, Exserohilum, Drechslera, Alternaria, Helminthosporium*, and *Fusarium*. There is controversy regarding whether AFS is an infectious or allergic disease. The fact that most patients with AFS have positive skin test and radioallergosorbent test to fungal allergens, as well as the prominent incidence of atopy in patients with AFS, support an allergic component to this disease. Eosinophils also play a significant role in AFS, and ECP levels were significantly higher in the mucin of patients with AFS compared with control patients *(608)*. Criteria for diagnosis of AFS include radiographical evidence of sinusitis, positive fungal stain or culture from the sinus at time of surgery, presence of allergic mucin, absence of fungal invasion, and absence of contributory factors such as immunodeficiencies or diabetes mellitus *(609)*. Differential diagnoses of AFS include saprophytic fungal growth, fungus balls of the sinuses, eosinophilic mucin sinusitis, and invasive fungal sinusitis. Hypersensitivity pneumonitis is another respiratory disease that is probably caused by microbes, but it is primarily an allergic disease. Hypersensitivity pneumonitis frequently occurs as occupational asthma, and several etiological agents have been cited. Examples of hypersensitivity pneumonitis and their suspected source include Farmer's lung (moldy hay), bird fancier's lung (parakeet droppings), pigeon breeder's disease (pigeon droppings), hen worker's lung (chicken droppings), bagassosis (sugar cane), mushroom worker's lung (mushroom compost), air conditioner lung (contaminated humidifiers or air conditioners), cork worker's lung (mold cork), malt worker's lung (moldy malt or barley), sequoiosis (moldy bark from redwoods), and woodworker's lung (wood dust). Symptoms include fever, chills, cough, and respiratory distress occurring 4 to 8 h after re-exposure to the inciting agent. If prolonged exposure is present, then the disease progresses into a chronic form and fibrosis develops, eventually leading to respiratory failure. Diagnosis is primarily based on clini-

cal features, but it is supported by identification of the source agent, presence of specific antibodies in blood, chest radiography, pulmonary function tests, and lung biopsy. Treatment is based on avoidance and the use of corticosteroids. Therefore, it is important that individual patients be examined, including vigorous review of medical histories, physical examinations, and appropriate diagnostic testing to confirm and establish diagnosis and begin appropriate therapy.

Discussion and Conclusions

We are continuously exposed to a wide variety of environmental pollutants, and many of them individually have been shown to have detrimental effects on health and development in experimental animals. Fewer studies exist for humans, and the results are not always consistent. This is not unexpected, however, because almost all current research neglects that humans are exposed to a myriad of environmental pollutants and that interactions between compounds may be responsible for the various symptoms and diseases that have reportedly increased in incidence in recent decades.

Certain VOCs, formaldehyde, phthalates, and possibly OPs and carbamate pesticides have all been linked to lower respiratory symptoms in humans. Not only OCs, but also OP compounds, may induce subtle neurodevelopmental defects. Similarly to certain phthalates, the major DDT metabolite, *p,p'*-DDE, has been shown to be a potent anti-androgen in vitro and in vivo *(610)*. Gestational exposure to *p,p'*-DDE resulted in reduced anogenital distance at birth and retention of thoracic nipples on postnatal day 13, but it did not decrease testosterone levels. Similarly, exposure to TCDD and certain PCBs can cause developmental toxicity that is manifest particularly in the male reproductive system *(276)*. Conversely, *o,p'*-DDT, a minor component of technical grade DDT, and some DDT metabolites exhibit estrogenic activity, as do some hydroxylated PCB metabolites, whereas other PCBs and their metabolites act as anti-estrogens *(276,610–614)*. This indicates a substantial potential for interactions among this large variety of compounds.

Associations with decreased semen quality have been suggested not only for certain phthalates *(145,146)* but also for PCBs overall and/or individual PCB congeners and their metabolites *(293,615,616)*, *p,p'*-DDE *(293)*, and OP pesticides *(175,617,618)*. Results from an exploratory analysis suggest a greater than additive interaction between MBzP and MBP and PCB-153 and CYP450-inducing PCBs *(619)*. It was proposed that this interaction could result from the inhibition of UDP-glucuronosyl transferase by hydroxylated PCBs, which results in greater amounts of free phthalate monoesters, believed to be the main biologically active metabolites. Unfortunately, neither OH-PCBs nor the ratio of free vs glucuronidated phthalate monoesters was determined.

There have been few attempts to address the interaction of mixtures of compounds at physiologically relevant concentrations. A notable exception is the pioneering work by Kortenkamp and colleagues. For example, they showed that a mixture of the OCs, *o,p'*-DDT, *p,p'*-DDT, *p,p'*-DDE, and β-hexachlorocyclohexane exhibited combination effects on MCF-7 human breast cancer cell proliferation (E-SCREEN) when each of the components was used at concentrations at or below their respective no-observed effect concentrations *(620)*. Similar results were obtained with combinations of up to 12 estrogenic chemicals in the yeast estrogen screen assays *(612,621,622)*. Generally, the concentration addition model provided excellent predictions of the observed effects, whereas the independent action model, for the most part, did not. However, there were indications that cytotoxic or growth inhibitory effects of compounds included in mixtures might compromise the ability of the model to predict combination effects *(622)*. The model of

concentration addition was also found to accurately predict the effects of certain binary mixtures of environmental estrogens in vivo, using juvenile rainbow trout as the animal model and vitellogin induction as the measured end point *(623)*.

These findings "put into sharp relief the limitations of the traditional focus on single agent effects during hazard and risk assessments" *(612)*, not only of the endocrine-disrupting chemicals this comment referenced but of many other environmental toxicants.

Organic matter, such as proteins derived from living organisms, or toxins emitted by living organisms can also be associated with respiratory diseases. Combinations of aero-allergens can result in chronic allergic illnesses, including allergic rhinoconjunctivitis, sinusitis, and asthma. Mycotoxins released from fungi have not been demonstrated to cause human illness, although in vitro studies have demonstrated numerous cellular effects. Further research needs to be performed to characterize whether or not clinical effects of mycotoxins exist.

SBS has been described since 1982, but there are no consistent data showing a common cause for the myriad of symptoms described. We do know that the symptoms are nonspecific and occur in more than one person in the same building and that multiple agents, as described earlier, have been cited as etiological factors. In addition to toxins, chemicals, and bioaerosols, there may be a major psychological component to SBS.

We need the concerted effort of scientists from many different disciplines—particularly from informatics—for the identification of biological and nonbiological toxicants and the unraveling of their contribution to health effects in humans and wildlife. This should finally bring the power of computers to bear on the inordinate complexity of interactions among environmental pollutants as well as the interactions between pollutants and the organisms they affect.

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