Airborne Environmental Injuries and Human Health

Andrea T. Borchers,¹ Christopher Chang,¹,³ Carl L. Keen,² and M. Eric Gershwin¹,*

¹Division of Rheumatology, Allergy and Clinical Immunology, ²Department of Nutrition, University of California at Davis, Davis, CA, ³AirMD, Sacramento, CA

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.

*Author to whom correspondence and reprint requests should be addressed. E-mail: megershwin@ucdavis.edu
The Sick Building Syndrome

One of the most widespread consequences of the use of new materials in ever more airtight 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 CO₂ 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) | Offactory load | “Lost” VOCs |  | Overtime |
| Parking garage within the building | Humidity (too low or too high) | NO₂ |  | Personality |
|  | Lighting (too dark or too bright) | O₃ |  | Active smoking |
|  | Crowding | Bio-effluents |  |  |
|  | Dampness | Particulate matter/dust |  |  |
|  | Microbial contamination |  |  |  |
|  | 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 (CO₂) concentrations are often used as a surrogate not only for occupant-generated pollutants but also for ventilation rate per occupant. However, CO₂ concentrations in occupied buildings usually do not reach steady state, and for this and various other reasons, CO₂ concentrations may not accurately reflect ventilation rates (6). Nonetheless, the results of studies investigating the association of CO₂ 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 CO₂ concentrations (dCO₂) and sore throat, nose or sinus symptoms, tight chest, and wheezing (9). The adjusted odds ratios (ORs) per 100 ppm dCO₂ 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 CO₂ 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 µg/m³ and several thousand micrograms per cubic meter, but maximum values of up to 50,000 µg/m³ 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 bio-effluents 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 (O₃) 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, NO₂, O₃, 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.
Airborne Environmental Injuries and Human Health

Clinical Reviews in Allergy & Immunology Volume 31, 2006

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 O₃ and various oxygen and nitrogen radicals (18). The major source of O₃ 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 O₃ (26,27). Monoterpenes are unsaturated VOCs that contain one or two double bonds that react readily with O₃, OH radicals, and nitrate radicals (NO₃•) 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 O₃ 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 O₃ reacts with terpenes under simulated office conditions (34).

Modeling and experimental measurements demonstrated that the product formation of unimolecular 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 O₃ 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 $1 \times 10^{-5}$ 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 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/m³ 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/m³ have been reported in several recent studies from the United States (57) and Australia (58,59). Maxima ranged between 139 and 408 µg/m³, indicating that some homes largely exceed current indoor guidelines (e.g., 120 µg/m³ 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/m³ 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)

| VOC                      | Residential VOC Levels | Integrated 8-h sample over a 24-h sampling period; mixture of active and passive sampling |
|--------------------------|------------------------|------------------------------------------------------------------------------------------|
|                          | 71 Homes in three urban neighborhoods in Minneapolis/St. Paul (42) | 113 Homes in Minneapolis (45) |
|                          | 284 Households in but much smaller n for many of the VOC | Arizona (57), |
|                          | 2-d Charcoal-based passive sampling | 2-d Charcoal-based passive sampling | 6-d Charcoal-based passive sampling |
| Benzene (%)              | 100                    | 100                                      | 100                                      | 49 |
| Median                   | 1.9                    | 2.2                                      | 3.3                                      | 1.3 |
| P90                      | 15.3                   | 6.2                                      | 12.7                                     | 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                                      |    |
| p-Dichlorobenzene (%)    | 72.6                   | 82.8                                     | 88                                       |    |
| Median                   | 0.2                    | 0.7                                      | 0.5                                      |    |
| P90                      | 1.5                    | 344.6                                    | 3.4                                      |    |
| Ethyl benzene (%)        | 99.0                   | 100                                      |                                           |    |
| Median                   | 1.4                    | 1.0                                      |                                           |    |
| P90                      | 8.9                    | 2.8                                      |                                           |    |
| γ-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                                      |                                           |    |
| 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                                      |    |
| Tetrachloroethylene (%)  | 97.6                   | 98                                       | 86.6                                     |    |
| Median                   | 0.6                    | 0.5                                      | 1.4                                      |    |
| P90                      | 3.8                    | 1.3                                      | 4.9                                      |    |
| Toluene (%)              | 97.9                   | 100                                      | 99.6                                     | 86 |
| Median                   | 12.3                   | 8.2                                      | 16.2                                     | 10 |
| P90                      | 53.8                   | 19.2                                     | 63.0                                     | 49 |
| Trichloroethylene (%)    | 83.9                   | 82.8                                     | 94.0                                     | 1  |
| Median                   |                         |                                           |                                           |    |
| o-Xylene (%)             | 99.7                   | 100                                      | 100                                      |    |
| Median                   | 1.6                    | 1.2                                      | 2.1                                      |    |
| m- / p-Xylene (%)        | 99.7                   | 100                                      | 100                                      |    |
| Median                   | 4.8                    | 3.7                                      | 4.6                                      |    |
| P90                      | 36.9                   | 10.4                                     | 21.6                                     |    |
| Total VOC (%)            |                         |                                           |                                           |    |
| Median                   |                         |                                           |                                           |    |
| P90                      |                         |                                           |                                           |    |

GM, geometric mean; DL, detection limit.
### Table 2 (Continued)
Residential VOC Levels (in µg/m³)

| 201 Households in Helsinki, Finland (46) | 7% Households in England (73) | 40 Households in Oxford, United Kingdom (373) | 317 Households in Japan (67) | 317 Households in England (73) | 40 Households in Helsinki, Finland (46) | 201 Households in Helsinki, Finland (46) |
|-----------------------------------------|--------------------------------|-----------------------------------------------|----------------------------|-------------------------------|-----------------------------------------|-----------------------------------------|
| 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                       | Cases                                         | Controls                   | Cases                          | Controls                       | Cases                          |

|               | GM 15.7 | GM 2.6 | GM 2.6 | GM 11.57 | GM 9.09 | GM 19.4 |
|---------------|---------|--------|--------|----------|---------|---------|
| Mean          | 2.6     | 2.6    | 2.6    | 2.6      | 2.6     | 2.6     |
| Max           | 1029    | 1029   | 1029   | 1029     | 1029    | 1029    |
| N/A           |         |        |        |          |         |         |

Note: The winter values are listed, which are generally somewhat higher than the measurements obtained in spring.

Note: Values are the 95th percentile rather than the 90th percentile, as in most other studies.

Note: 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                                   |
| 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 NO₂ 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)

| Phthalate | Sweden (n = 346) | Berlin, Germany (n = 30) | Berlin and 2 villages in the northern part of Germany (n = 624) | Cape Cod (n = 120) | Norway (n = 38) | 10 day care centers in central North Carolina (n = 252) |
|-----------|------------------|--------------------------|---------------------------------------------------------------|-------------------|----------------|------------------------------------------------------|
| DEHP      | 770 N/A          | 703.4 1542               | 515 1240                                                      | 340 7700          | 640 161        | 18.4 46                                               |
| 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/m³)

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

*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. |
|-------------------------------|-----|-----------|------|-----------|-----------|-----|------|-----|------|
| US subsample of NHANES III    | 289 | N/A       | 2.7  | 21.5      | —         | —   | —    | 41.0| 294  |
| NHANES 1999–2000              | 2541| ≥6        | 3.20 | 23.8      | —         | —   | —    | 26.0| 149  |
| Massachusetts                 | 295 | men       | 5.0  | 131       | —         | —   | —    | 14.3| 75.4 |
| Massachusetts                 | 369 | men       | 5.2  | 110       | 13.6      | 73.1| 6.0  | 34.7| 128  |
| United States                 | 328 | 6–11      | 4.90 | 34.5      | —         | —   | —    | 40.0| 163  |
| United States (Washington, D.C.) | 46  | women     | 7.3  | (143.9)   | —         | —   | —    | 53.0| (251.3) |
| United States                 | 127 | Not given | <LOD | 20.4      | 15.6      | 243 | 17.4 | 220 | —    |
| United States                 | 50  | N/A       | 4.5  | (537)     | 35.9      | (2417)| 28.3 | (1860)| —    |
| Erlangen, Germany             | 85  | 7–64      | 10.3 | 37.9      | 46.8      | 224 | 36.5 | 181 | 825  |
| Germany                       | 254 | 3–14      | 7.18 | 29.7      | 52.1      | 188 | 41.4 | 139 | —    |
| Neonates in intensive care unit | 6   | 4–92 d    | 129  | 704       | 2221      | 13,161| 1697 | 10,413| —    |

*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
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 phthalate (MBP) and forced vital capacity (FVC), forced expiratory volume after 1 s (FEV <sub>1</sub>), 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<sub>1</sub> was also observed only in males. Conversely, in nonsmoking women, FEV<sub>1</sub> 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 µg/m<sup>3</sup> was reported in Finnish homes, and the geometric mean personal exposure was only slightly higher (2.63 µg/m<sup>3</sup>; ref. 46) and similar to the geometric mean of 3.0 µg/m<sup>3</sup> 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/m³)

| Pesticide       | Indoor air from 60–88 homes in Minnesota (MNCPES) (163) | Personal air in 48–61 children of 238 African and Dominican women from New York (154) | Personal air from 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 % P50 Range % P50 Range % Mean Range | % P50 Range % P50 Range % P50 Range % P50 Range % P50 Range % P50 Range % P50 Range % P50 Range % P50 Range % P50 Range % P50 Range % P50 Range % P50 Range % P50 Range % P50 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< 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< 100 15.9 3.75–62.4 | | | | | |
| Atrazine        | 22 <LOD/LOQ 20.2 17 <LOD/LOQ 26.97 | | | | | |
| Methyl parathion| 3 ND ND-0.9 6 <RL <RL-92 | | | | | |

aBelow limit of detection or limit of quantitation.
bValues 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   | %     | Mean   | Range   | Median  | Range   | %     | Mean   | 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                       | 3     | <RL    | <RL-0.992 | 13      | 0.04    | 0–1.71 |
| Methylparathion                | 3     | <RL    | <RL-0.992 | 13      | 0.04    | 0–1.71 |

| Pesticides                      | 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) |
|--------------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
|                                | %     | 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 | 100   | 0.34   | 0.01–2.6 |
| 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  | 69    | 0.154  | <LOD-2.786 | 27    | <LOD   | <LOD-425 | 48    | 0.07   | 0–0.95 |
| Atrazine                       | 13    | 0.04   | 0–1.71  | 96    | 0.519  | <LOD-17.10 | 100   | 0.185  | 0.073–0.658 | N/A   | 0.14   | 0.01–14.6 |
| Ethyl parathion                | 14    | 0.02   | 0–16.9  | 100   | 1.100  | 0.170–11.27 | 100   | 2.83   | 0.134–0.816 | N/A   | 1.0    | 0.04–9.2 |
| Phosmet                        | 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 |
| Azinphosmethyl                 | 14    | 0.02   | 0–16.9  | 69    | 0.154  | <LOD-2.786 | 27    | <LOD   | <LOD-425 | 48    | 0.07   | 0–0.95 |
| Dimethyl OP                    | 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 |
| 4-Nitrophenol                  | 7     | 0.53   | 0–6.5   | 7     | 1.92   | 0.2–15.1  | 7     | 0.65   |

LOD, limit of detection; LOQ, limit of quantitation; RL, reporting limit
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   | <LOD/LOQ | <LOD/LOQ | 8 | <LOD/LOQ | <LOD/LOQ |
| Diazinon                    | 3   | <LOD/LOQ | <LOD/LOQ | 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 under-estimating 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 absorption and 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

Clinical Reviews in Allergy & Immunology
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 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

| Metabolite       | Parent compounds                                                                 | Adults (age 20–59 yr) | Children (age 6–11 yr) | Conventional diet | Organic diet | Total | Total |
|------------------|----------------------------------------------------------------------------------|-----------------------|------------------------|-------------------|--------------|-------|-------|
|                  |                                                                                  | GM P50 P90 | GM P50 P90 | % P50 | P50 | P90 | Max | % P50 | % P50 | % P50 |
| Dimethyl DAP     |                                                                                  | 0.68 6.5 | 1.0 10 | 62.8 | 17 | 16.7 | 2754 | 43 | 0.6 | 22 | 0.06 | 33 | 0.6 |
| Dimethylthiophosphate | Examples: Azinphosmethyl, dimethoate, malathion, methidathion, methyliparathion, naled, oxydemeton-methyl, phosmet | 1.59 2.2 | 38 | 2.72 | 4.1 | 62 | 83 | 63 | 52.8 | 2922 | 95 | 14 | 78 | 2.8 | 87 | 5.8 |
| Diethyl DAP      |                                                                                  | 0.48 1.3 | 0.59 | 1.7 | 70.3 | 0.9 | 5.8 | 101 | 86 | 3.0 | 83 | 2.0 | 85 | 2.7 |
| Diethylthiophosphate | Examples: Chlorpyrifos, diazinon, Disulfoton, parathion, terbufos | 0.955 1.0 | 7.2 | 1.32 | 1.4 | 10 | 59.9 | 11 | 9.5 | 160 | 14 | 0.7 | 17 | 0.7 | 15 |

*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.*

**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.)*

*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                                                                 | Adults | Children |
|------------------|----------------------------------------------------------------------------------|--------|----------|
|                  |                                                                                  | P50    | P95      | Median   | P95 | P50 | P95 | P50 | P95 |
|                  |                                                                                  | µmol/L | µmol/L   | µmol/L   | µmol/L | µmol/L | µmol/L | µmol/L | µmol/L |
| Dimethyl DAP     | Examples: Azinphosmethyl, dimethoate, malathion, methidathion, methylparathion, naled, oxydimenton-methyl, phosmet |       |         |         |       |       |       |       |       |
| Dimethylphosphate|                                                                                  | 0.09   | 3.02     | 0.08     | 0.52 | 0.11  | 0.93  | 0.06  | 0.51  |
| Dimethylthiophosphate |                                                                                  | 20     | 19       | 92       | 88   | 54    | 54    | 0     | 0.9   |
| Dimethyldithiophosphate |                                                                                  | 0      | 0.9      | 0        | 0.1  | 0.0   | 0.31  | 0.04  | 0.1   |
| Diethyl DAP      | Examples: Chlorpyrifos, diazinon, Disulfoton, parathion, terbufos               | 0.06   | 0.12     | 0.06     | 0.11 | 0.0   | 0.31  | 0.04  | 0.1   |
| Diethylphosphate |                                                                                  | 0      | 0.9      | 0        | 0.1  | 0.0   | 0.31  | 0.04  | 0.1   |
| Diethylthiophosphate |                                                                                  | 0      | 0.9      | 0        | 0.1  | 0.0   | 0.31  | 0.04  | 0.1   |
| Diethyldithiophosphate |                                                                                  | 0      | 0.9      | 0        | 0.1  | 0.0   | 0.31  | 0.04  | 0.1   |

*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.

^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.)

^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 | Adults (age 20–59 yr) | Children (age 6–11 yr) | Agricultural Ref. |
|---------------------------------------------|------------------|-----------------------|------------------------|-------------------|
|                                             | GM P50 P95       | GM P50 P95            | % P50 P95              | % P50 % P50       |
| 3,5,6-Trichloro-2-pyridinol (TCPy)          | Chlorpyrifos     | 1.53 1.50 8.6 2.88    | 16.0 82 3.0 13         | 100 1.4 11.3 93 7.2 26 |
| Malathion dicarboxylic acid                 | Malathion        | <LOD <LOD            | 2.8                     | 37 <1.0 8.7       |
| 4-Nitrophenol                               | Parathion, methyl parathion; nitrobenzene | <LOD <LOD | 4.2 | 41 ND 5.2 | 7 0c 7 0c |
| 2-Isopropyl-4methyl-6-hydroxypyrimidine    | Diazinon         | <LOD <LOD            | >LOD <LOD              |                   |
| 1-Naphthol                                  | Naphthalene, carbaryl | 1.79 1.40 14.0 1.11 | 5.6 86 4.4 43         | 45 1.0 14       |

*Minnesota Children's Pesticide Exposure Study
bNot 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 MNCPEES (181).

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.
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 adenyl 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-year-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 Wilms’ 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),

Clinical Reviews in Allergy & Immunology

Volume 31, 2006
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.
Airborne Environmental Injuries and Human Health 41

Clinical Reviews in Allergy & Immunology Volume 31, 2006

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
| Cohort period of enrollment | n | Age | PCBs analyzed | Median PCB concentration | 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 | BNBAS | Hypotonicity and hyporeflexia | None | 292,314 |
|                             | 676 | 18 mo |                          |                          | BSID      | None (but see comment)                              | Non-sig. | 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)   | 123 |       | CB Total PCBs by packed column method | 2.5 ng/mL | 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 | 333 |
|                             | 219 | 4 yr   |                          |                          | MCSCA     | Lower performance on verbal and memory scales | 338 |
|                             | 212 | 11 yr  |                          |                          | 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 (1991–1994) | 293 | 12–14 h and 25–48 h | 69 PCB congeners and coeluters in CB | 0.525 ng/g wet weight | BNBAS | Significant dose-dependent association between cord blood concentration of highly chlorinated (C17–C19) PCBs and NBAS scores 25–48 h after birth but not 12–14 h after birth. Habitation 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 |
| Study | Age | Measure | Results |
|-------|-----|---------|---------|
| Fagan II | 6 mo | 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 |
| Fagan II | 12 mo | Significant dose-dependent association between total cord PCBs and declining performance | |
| MCSCA GCI | 38 mo | 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 |
| MCSCA GCI | 54 mo | No significant association between cord blood PCBs and the McCarthy GCI or any of its subscales | |

Groningen and Rotterdam, Netherlands (1990–1992)

| Study | Age | Measure | Results |
|-------|-----|---------|---------|
| 0.38 ng/mL | 2 wk | 118, 138, 153, 180 in CB | 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. |
| BSID | None with CB PCB levels (n = 175), but decreased psychomotor development index score with increasing maternal plasma PCB concentrations | |
| 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 was now an association with prenatal, but not postnatal, exposure |
| TOUWEN | None | |

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

| Cohort period of enrollment | Study Location | Age | PCBs analyzed | Median PCB concentration | Estimated median PCB 153 concentrations in MS (ng/g lipid) | Tests used | Significant associations with prenatal PCB exposure | Comments | Reference |
|-----------------------------|----------------|-----|---------------|--------------------------|----------------------------------------------------------|------------|---------------------------------------------------|----------|-----------|
| 395                         | Dutch version of Rotterdam 193 | 42 mo | Lower scores on the overall cognitive and sequential processing scales, the association being significant in the formula-fed (but not in the breast-fed) group | 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 | Lower scores on the GCI and memory subscales only in the subgroup of children with less optimal parental and home characteristics | 332 |
| 193                         | Düsseldorf, Germany (1993–1995) | 42 mo | Sum of 138, 153, 180 in CB | Mean 0.55 ng/mL | 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                         | Faroe Islands (1986–1987) | 7, 30, and 42 mo | 118, 138, 153, 170, 180 in cord tissue | 1.88 ng/g wet weight; 1.02 ng/g lipid | Neuro-behavioral Evaluation System; BNT; WISC Revised; CVL; Bender Visual Motor Gestalt Test | Lower performance on the 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 |
| Location            | n     | Age       | Summary of PCBs | GM | Age at Measurement | Test | Notes                                                                 |
|---------------------|-------|-----------|-----------------|----|--------------------|------|----------------------------------------------------------------------|
| Faroe Islands       | 182   | 2 wk      | Two times the sum of 138, 153, 180 in MS | 450| Prechtl            | None |                                                                     |
| United States       | 1207  | 8 mo      | MS taken during pregnancy | 2.7 ng/mL | BSID | None |                                                                       |

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

* 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.

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

* Includes mothers with elevated PCB levels because of consumption of sport-caught fish.

* 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.

* 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 172,3,7,8-substituted PCDDs and PCDFs, 3 planar PCBs, and 23 nonplanar PCB congeners.

* 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).

* 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, Bayley Scales of Infant Development; CVL, California Verbal Learning; KAIC, Kaufman assessment battery for children; MCSCA, McCarthy Scales of Children’s Abilities; BCS, 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 (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).
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 (PM₁₀) can be inhaled into the lungs and, therefore, are referred to as thoracic, respirable, or inhalable particles. Since 1987, mass concentration of PM₁₀ 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). PM₁₀ consists of fine particles with an aerodynamic diameter of 2.5 µm (PM₂.₅) and coarse particles (PM₂.₅–₁₀), and the contribution of PM₂.₅ to PM₁₀ was relatively constant in a given area but varied between 35 and 80% by region (356). In 1997, the EPA proposed standards for PM₂.₅ (see also Table 15). PM₂.₅ 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. 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.

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. 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 \(\mu\)m.

The most important indoor source of particles is ETS. 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. Notably, one of these studies has provided evidence that terpene-ozone reactions can result in pronounced elevations in fine particles and UFPs. As previously discussed, the products of terpene-\(O_3\) reactions have been shown to act as strong airway irritants. ETS results in elevated particle counts in all size ranges, but appears to more strongly affect the size fraction smaller than 1.0 \(\mu\)m. 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 \(\mu\)m and 0.1 to 0.5 \(\mu\)m. Sautéing produces particles both in the ultrafine and coarse modes (2.5–10 \(\mu\)m). Although dusting, vacuuming, and walking constitute important sources of PM\(_{2.5}\), they predominantly raise the concentrations of coarse particles. 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.

**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. 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$^c$            | 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 (9.3–210.9)  | 16.7 (2.4–328.5) | 28.7 (2.7–76.0)  |                | 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 (38.0–112.8) | 52.2 (18.6–65.3) | 25.8 (31.9–50.2) |                | 372       |
| Toronto, Canada        | 141 adults         | Personal impactor                             | 3 d                |                   | 67.9 (38.0–112.8) | 29.8 (18.6–65.3) | 24.3 (31.9–50.2) |                | 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) | —              (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          | PEM and HI                                    | 24 h               | 24 h in summer$^e$ | 122 (25.9–574.3)  | 79 (27.1–208.2)  | 35 (16.9–281.0)  |                | 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       |

$^c$This study provides population means because it was based on a probability-based sample.

$^e$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       | 48.2          | 48.9          | 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 h               | 2 wk               | 37.9          | 30.3          | —             | 23.6    | 463        |
| Houston, TX    | 101                | PEM              | 48 h               | 48 h               | 37.2          | 17.2          | 14.7          |         |            |
| Elizabeth, NJ  | 100                | PEM              | 48 h               | 48 h               | 46.9          | 20.1          | 20.4          |         |            |
| Seattle, WA    | 28 elderly healthy | Harvard PEM and HI | 24 h               | 10 d               | 9.3           | 7.4           | 9.0           | 10.1    | 383        |
|                | 34 elderly patients with COPD |              |                    |                    | (0.8–96.2)    | (0.4–38.0)    | (0.7–24.5)    | (1–29.5) |            |
|                | 27 elderly patients with CHD |              |                    |                    | (0.8–45.6)    | (1.0–49.9)    | (–0.2–28.9)   |         |            |
|                | 19 children with asthma |              |                    |                    | 10.8          | 9.5           | 12.6          |         |            |
|                |                    |                  |                    |                    | (1.4–66.6)    | (1.6–65.3)    | (1.3–41.5)    |         |            |
|                |                    |                  |                    |                    | 13.3          | 9.2           | 11.3          |         |            |
|                |                    |                  |                    |                    | (1.0–49.4)    | (2.2–36.3)    | (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 up to 23 d | 21.6          | 17.5          | 14.2          | 385     |            |
|                |                    |                  |                    |                    | (0.6–127.7)   | (1.6–73.2)    | (0.9–56.9)    |         |            |
| Towson (Baltimore, MD) | 15 (from a pool of 21) | PEM              | 24 h               | 12 d               | 13.0          | 10.0          | 22.0          | 22.0    | 636        |
|                |                    |                  |                    |                    | (2.4–47.8)    |               |               |         |            |
| 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          | 28.6          | —             | 20.6    | 387        |
|                |                    |                  |                    |                    | (8.5–133.7)   | (9.1–238.8)   |               | (12.8–31.1) |            |
| Helsinki, Finland | 47 elderly patients |              |                    |                    | 10.8          | 11.0          | —             | 12.6    | 387        |
|                |                    |                  |                    |                    | (3.8–32.7)    | (3.2–26.6)    |               | (10.4–18.0) |            |
| Helsinki, Finland | 137 non-ETS exposed* | Cyclone PEM and impactor MEM (microenvironmental monitors) | 48 h               | 48 h               | 9.9           | 8.2           | 9.5           | 371     |            |
| Location          | Population | Method                                      | Exposure Time | Personal Concentration (µg/m³) | Residential Indoor Concentration (µg/m³) | Residential Outdoor Concentration (µg/m³) |
|-------------------|------------|---------------------------------------------|---------------|-------------------------------|----------------------------------------|-----------------------------------------|
| Oxford, UK        | 30–42      | Cyclone PEM and impactor MEM                | 48 h          | 17.4                          | 17.3                                   | 9.1                                     | 373                                     |
| Banska Bystrica,  | 49 adults  | PEM and HI                                  | 24 h          | 88                            | 55                                     | 22                                      | 635                                     |
| Slovakia          |            |                                             | 24 h in summer |                                |                                        |                                         |                                         |
| Athens, Greece    | 117 students | Cyclone PEM                               | 24 h          | 46.4                          | (7.5–140.4)                            | (9.8–259.8)                             | 637                                     |
| Halkida, Greece   | 77 students |                                             | 24 h          | 66.0                          |                                        |                                         |                                         |
| Santiago, Chile   | 20 children | PEM and HI                                 | 24 h          | 69.5                          | 68.5                                   | 68.1                                    | 388                                     |

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/m³).

Mean personal exposures in the summer were 35.8 µg/m³ (range: 4.9–125.0) in Athens and 37.9 µg/m³ (range: 10.6–233.4) in Halkida.

In winter, mean personal, indoor, and ambient concentrations were lower (69 µg/m³), similar (53 µg/m³), and higher (32 µg/m³), 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,
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 \( \mu \text{m} \), 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 \( \mu \text{g/m}^3 \) 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 non-smoking 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 PM₁₀ 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 decreases in 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\textsubscript{10} and PM\textsubscript{2.5} exposures in children with asthma found that their associations with FEV\textsubscript{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\textsubscript{1}. In another panel study of subjects with asthma from Toronto, Canada, FVC, FEV\textsubscript{1}, and forced expiratory flow\textsubscript{25-75} (FEF\textsubscript{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\textsubscript{2.5}) are stronger than those of PM\textsubscript{10}. Rather, in the few available direct comparisons, PM\textsubscript{10} actually was found to have slightly stronger independent effects on FEV\textsubscript{1} and symptoms in children with asthma and on PEFR in unselected children (466) and on PEF 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\textsubscript{3}, NO\textsubscript{2}, and SO\textsubscript{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-µg/m\textsuperscript{3} increase in the concentration of ambient PM\textsubscript{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\textsubscript{1}, and a decrease of 0.08% in PEF in association with a 10-µg/m\textsuperscript{3} increase in PM\textsubscript{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-µg/m\textsuperscript{3} increment in PM\textsubscript{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\textsubscript{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\textsubscript{10} levels on PEF deviation was also noted very consistently with 4- or 5-d averages in ambient PM\textsubscript{10} con-
centrations (445,451,470,473). This contrasts with the results of a study in healthy children, who exhibited the greatest PM$_{10}$-associated 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 sub-micrometer 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, PM10 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 PM2.5 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 non-significantly associated with PM2.5 (492). Finally, exposure to ambient PM2.5 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 PM10, black smoke, NO, and NO2 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 PM2.5 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 µg/m3 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/m²) than in Chapel Hill (25 L/min/m²). 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 FEV₁, FVC, FEF₂⁵–⁷⁵ and FEF₂⁰–⁷⁰) 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-
Airborne Environmental Injuries and Human Health

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).
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\textsubscript{10} and PM\textsubscript{2.5} in children with asthma along with residential indoor and outdoor as well as central-site PM concentrations, FEV\textsubscript{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\textsubscript{2.5} and PM\textsubscript{10} showed stronger associations with FEV\textsubscript{1} than residential outdoor or central-site concentrations. Assessment of indoor and outdoor PM\textsubscript{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\textsubscript{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\textsubscript{1.5} 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\textsubscript{1}. Ambient exposures (as determined from ambient concentrations and time-activity data) were associated with decreased FEV\textsubscript{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\textsubscript{2.5} were associated with FEV\textsubscript{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\textsubscript{2.5} exposure. Interestingly, lag 0 indoor home PM\textsubscript{2.5} and PM\textsubscript{10} concentrations...
were significantly associated with decreases in FEV₁, whereas residential outdoor and central site measurements showed some significant associations with FEV₁ 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. pneumoni*a; 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/m³ in outdoor air and to more than 10,000 CFU/m³ in indoor air samples (547). Median indoor and outdoor concentrations were 80 and approx 500 CFU/m³, 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/m³ in indoor air samples from buildings with visible mold growth (548). With one notable exception (450,000 CFU/m³), 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/m³) than in the home environment (4700 spores/m³), and concentrations of fungi in the home environment were similar to personal exposure levels (5700 spores/m³). The geometric mean concentrations of viable fungi were 2 to 3, 5 to 6, and 12 CFU/m³ 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-
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

### Table 18

| Genus        | Size of spores (µ) | Substrates and other characteristics                                                                 |
|--------------|--------------------|------------------------------------------------------------------------------------------------------|
| *Alternaria* | 8–75               | Multicell, multisepate 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. Plant debris, soil.                                            |
| *Dreschlera* |                    | Dark to golden brown; multisepate spores.                                                              |
| *Epicoccum*  | 20                 | Soils, saprophytic on plants, important producer of trichothecenes.                                    |
| *Fusarium*   | 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* |             | Found on spoiling food, decaying fruits, and vegetables.                                               |
| *Rhizopus*   |                    | Found on organic matter, dung, and soils. Colorless spores.                                            |
| *Mucor*      |                    | Saprophytic, grows on cellulic material, including livestock feed, ceiling tiles, paper, and cotton cloth. It is a diurnal sporulator. |
| *Stemphyllium*| 23–75              | Soil, dung, decaying plant matter, fibers, wood, grasses, textiles, and paper; may be confused with *Alternaria*. |
| *Ulocladium* |                    | Teardrop shape spores, saprophytic and parasitic; part of the *Dreschlera* group.                     |
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/m³. Brazil sets the threshold for hazardous exposure at 750 spores/m³, whereas the standard in the Netherlands is 10⁴ spores/m³ (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 non-industrial 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*.
Short-term exposure to high doses of *P. chrysogenum* 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/m³ 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/m³), medium (500–999 CFU/m³), or high levels (>1000 CFU/m³). 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 Cladosporium 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 trichotheccenes (ref. 590; see Table 19 for the various categories of mycotoxins and the types of trichotheccenes). Trichotheccenes are a group of structurally similar sesquiterpene molecules, characterized by a 12, 13-epoxytrichothec-9-ene ring system. Trichotheccenes generally are extremely stable and are degraded only by heating at high temperatures for a prolonged period. Metabolites of trichotheccenes 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. 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 *Stachybotrys 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 trichotheccenes. 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 × 10⁵ spores per instillation) and not at the lower dose (1 × 10³).
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 $1 \times 10^5$ intact, autoclaved, and ethanol-extracted spores of *S. chartarum* in 7-d-old rats. 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-$\alpha$, IL-1$\beta$, 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 intratracheal 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*. 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-$\alpha$ 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-1$\beta$ 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. 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 glucuronimidated 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 \( \beta \)-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 vitellogenin 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.

References

1. Tsai YJ, Gershwin ME. The sick building syndrome: what is it when it is? Compr Ther 2002;28(2):140–144.
2. Menzies D, Bourbeau J. Building-related illnesses. N Engl J Med 1997;337(21):1524–1531.
3. Jones AP. Indoor air quality and health. Atmospher Environ 1999;33:4535–4564.
4. Mendell MJ, Fisk WJ, Kreiss K, et al. Improving the health of workers in indoor environments: priority research needs for a national occupational research agenda. Am J Public Health 2002;92(9):1430–1440.
5. Wargocki P, Sundell J, Bischof W, et al. Ventilation and health in non-industrial indoor environments: report from a European multidisciplinary scientific consensus meeting (EUROVEN). Indoor Air 2002;12(2):113–128.
6. Seppänen OA, Fisk WJ, Mendell MJ. Association of ventilation rates and CO2 concentrations with health and other responses in commercial and institutional buildings. Indoor Air 1999;9(4):226–252.
7. Mendell MJ. Non-specific symptoms in office workers: a review and summary of the literature. Indoor Air 1993;3:227–236.
8. Menzies D, Tamblyn RM, Nunes F, Hanley J, Tamblyn RT. Exposure to varying levels of contaminants and symptoms among workers in two office buildings. Am J Public Health 1996;86(11):1629–1633.
9. Apte MG, Fisk WJ, Daisey JM. Associations between indoor CO2 concentrations and sick building syndrome symptoms in U.S. office buildings: an analysis of the 1994–1996 BASE study data. Indoor Air 2000;10(4):246–257.
10. Erdmann CA, Apte MG. Mucous membrane and lower respiratory building related symptoms in relation to indoor carbon dioxide concentrations in the 100-building BASE dataset. Indoor Air 2004;14(Suppl 8):127–134.
11. Andersson K, Bakke JV, Bjørseth O, et al. TVOC and health in non-industrial indoor environments. Report from a Nordic Scientific Consensus Meeting at Långholm in Stockholm, 1996. Indoor Air 1997;7:78–91.
12. Reynolds SJ, Black DW, Borin SS, et al. Indoor environmental quality in six commercial office buildings in the midwest United States. Appl Occup Environ Hyg 2001;16(11):1065–1077.
13. Glas B, Levin JO, Stenberg B, Stenlund H, Sunesson AL. Variability of personal chemical exposure in eight office buildings in Sweden. J Expo Anal Environ Epidemiol 2004;14 (Suppl 1):S49–S57.
14. Apte MG, Erdmann CA. Associations of indoor carbon dioxide concentrations, VOCs, environmental susceptibilities with mucous membrane and lower respiratory sick building syndrome symptoms in the BASE study: Analyses of the 100 building dataset. Lawrence Berkeley National Laboratory
15. Bluyssen PM, de Oliveira Fernandes E, Groes L, et al. European indoor air quality audit project in 56 office buildings. Indoor Air 1996;6:221–238.

16. Schneider T, Sundell J, Bischof W, et al. ‘EUROPART’. Airborne particles in the indoor environment. A European interdisciplinary review of scientific evidence on associations between exposure to particles in buildings and health effects. Indoor Air 2003;13(1):38–48.

17. Jurvelin J, Edwards R, Saarella K, et al. Evaluation of VOC measurements in the EXPOLIS study. Air Pollution Exposure Distributions within Adult Urban Populations in Europe. J Environ Monit 2001;3(1):159–165.

18. Wolkoff P, Clausen PA, Jensen B, Nielsen GD, Wilkins CK. Are we measuring the relevant indoor pollutants? Indoor Air 1997;7:92–106.

19. Ten Brinke J, Selvin S, Hodgson AT, et al. Development of new volatile organic compound (VOC) exposure metrics and their relationship to “sick building syndrome” symptoms. Indoor Air 1998;8:140–52.

20. Apte MG, Daisey JM. VOCs and “Sick Building Syndrome”: Application of a new statistical approach for SBS research to U.S. EPA BASE study data. In: Proceedings of Indoor Air 99, The 8th International Conference on Indoor Air Quality and Climate; 1999 August 8–13; Edinburgh, Scotland; 1999. pp. 117–22.

21. Wilkins CK, Wolkoff P, Gyntelberg F, Skov P, Valbjørn O. Characterization of office dust by VOCs and TVOC release – Identification of potential irritant VOCs by partial least squares analysis. Indoor Air 1993;3:283–290.

22. Pommer L, Fick J, Sundell J, et al. Class separation of buildings with high and low prevalence of SBS by principal component analysis. Indoor Air 2004;14(1):16–23.

23. Niven RM, Fletcher AM, Pickering CA, et al. Building sickness syndrome in healthy and unhealthy buildings: an epidemiological and environmental assessment with cluster analysis. Occup Environ Med 2000;57(9):627–634.

24. Weschler CJ, Shields HC. Potential reactions among indoor pollutants. Atmospheric Environment 1997;31(21):3487–3495.

25. Weschler CJ. Ozone in indoor environments: concentration and chemistry. Indoor Air 2000;10(4):269–288.

26. Brown SK. Assessment of pollutant emissions from dry-process copiers. Indoor Air 1999;9(4):259–267.

27. Tuomi T, Engström B, Niemelä R, Svinhufvud J, Reijula K. Emission of ozone and organic volatiles from a selection of laser printers and copiers. Appl Occup Environ Hyg 2000;15(8):629–634.

28. Grosjean D, Williams EL, Seinfeld JH. Atmospheric oxidation of selected terpenes and related carbonyls: gas-phase carbonyl products. Environ Sci Technol 1992;26(8):1526–1532.

29. Wängberg I, Barnes I, Becker KH. Product and mechanistic study of the reaction of NO, radials with α-pinene. Environ Sci Technol 1997;31:2130–2135.

30. Pommer L, Fick J, Andersson B, Nilsson C. The influence of $O_3$ relative humidity, NO and NO$_2$ on the oxidation of α-pinene and Δ3-carene. J Atmospheric Chem 2004;48:173–189.

31. Pommer L, Fick J, Nilsson C, Andersson B. An experimental comparison of a kinetic model for the reaction of α-pinene and Δ3-carene with ozone and nitrogen oxides. Indoor Air 2004;14(Suppl 8):75–83.

32. Wolkoff P, Clausen PA, Wilkins CK, Nielsen GD. Formation of strong airway irritants in terpene/ozone mixtures. Indoor Air 2000;10:82–91.

33. Wolkoff P, Clausen PA, Wilkins CK, Hougaard KS, Nielsen GD. Formation of strong airway irritants in a model mixture of (+)-α-pinene/ozone. Atmospheric Environment 1999;33:693–698.

34. Wainman T, Zhang J, Weschler CJ, Lioy PJ. Ozone and limonene in indoor air: a source of submicron particle exposure. Environ Health Perspect 2000;108(12):1139–1145.

35. Weschler CJ, Shields HC. The influence of ventilation on reactions among indoor pollutants: modeling and experimental observations. Indoor Air 2000;10(2):92–100.

36. Sundell J, Andersson B, Andersson K, Lindvall T. Volatile organic compounds in ventilating air in buildings at different sampling points in the buildings and their relationship with the prevalence of occupant symptoms. Indoor Air 1993;3:82–93.

37. Kim YM, Harrad S, Harrison RM. Concentrations and sources of VOCs in urban domestic and public microenvironments. Environ Sci Technol 2001;35(6):997–1004.

38. Schupp T, Bolt HM, Hengstler JG. Maximum exposure levels for xylene, formaldehyde and acetaldehyde in cars. Toxicology 2005;206(3):461–470.

39. Ashley DL, Prah JD. Time dependence of blood concentrations during and after exposure to a mixture of volatile organic compounds. Arch Environ Health 1997;52(1):26–33.

40. Wallace DG, Buckley T, Pellizzari E, Gordon S. Breath measurements as volatile organic compound biomarkers. Environ Health Perspect 1996;104(Suppl 5):861–869.

41. IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. http://www-ciericfr/htdocs/announcements/vol88htm 2004; Accessed April 15, 2005.
Airborne Environmental Injuries and Human Health

42. Sexton K, Adgate JL, Ramachandran G, et al. Comparison of personal, indoor, and outdoor exposures to hazardous air pollutants in three urban communities. Environ Sci Technol 2004;38(2):423–430.

43. Payne-Sturges DC, Burke TA, Breyssie P, Diener-West M, Buckley TJ. Personal exposure meets risk assessment: a comparison of measured and modeled exposures and risks in an urban community. Environ Health Perspect 2004;112(5):589–598.

44. Adgate JL, Eberly LE, Stroebel C, Pellizzari ED, Sexton K. Personal, indoor, and outdoor VOC exposures in a probability sample of children. J Expo Anal Environ Epidemiol 2004;14(5):54–513.

45. Adgate JL, Church TR, Ryan AD, et al. Outdoor, indoor, and personal exposure to VOCs in children. Environ Health Perspect 2004;112(14):1386–1392.

46. Edwards RD, Jurvelin J, Saarela K, Jantunen M. VOC concentrations measured in personal samples and residential indoor, outdoor and workplace microenvironments in EXPOLIS-Helsinki, Finland. Atmosphere Environ 2001;35:4531–4543.

47. Matura M, Goossens A, Bordalo O, et al. Oxidized citrus oil (R-limone): a frequent skin sensitizer in Europe. J Am Acad Dermatol 2004;46(2):239–244.

48. Pazdruk K, Gorski P, Krakowiak A, Ruta U. Changes in nasal lavage fluid due to formaldehyde inhalation. Int Arch Occup Environ Health 1993;64(7):515–519.

49. Norbäck D, Wålinder R, Wieslander G, Smedje G. Inhalative allergic sensitization in the guinea pig. Int Arch Allergy Immunol 1995;106(4):422–424.

50. Fujimaki H, Kurokawa Y, Kunugita N, Kikuchi M, Sato F, Arashidani K. Differential immunogenic and neurogenic inflammatory responses in an allergic mouse model exposed to low levels of formaldehyde. Toxicology 2004;197(1):1–13.

51. Riedel F, Hasenauer E, Barth PJ, Koziorowski A, Kita T, Fujimura M, Myou S, et al. Potentiation of allergic bronchoconstriction by repeated exposure to formaldehyde in guinea-pigs in vivo. Clin Exp Allergy 2003;33(12):1747–1753.

52. Tarkowski M, Gorski P. Increased IgE antiovalbumin level in mice exposed to formaldehyde. Int Arch Allergy Immunol 1995;106(4):422–424.

53. Fujimaki H, Kurokawa Y, Kunugita N, Kikuchi M, Sato F, Arashidani K. Differential immunogenic and neurogenic inflammatory responses in an allergic mouse model exposed to low levels of formaldehyde. Toxicology 2004;197(1):1–13.

54. Vandenplas O, Fievez P, Delwiche JP, Boulanger J, Thimpoint J. Persistent asthma following accidental exposure to formaldehyde. Allergy 2004;59(1):115,116.

55. Lemière C, Desjardins A, Cloutier Y, et al. Occupational asthma due to formaldehyde resin dust with and without reaction to formaldehyde gas. Eur Respir J 1995;8(5):861–865.

56. Sherman MH, Hodgson AT. Formaldehyde as a basis for residential ventilation rates. Indoor Air 2004;14(1):2–8.

57. Gordon SM, Callahan PJ, Nishioka MG, et al. Residential environmental measurements in the national human exposure assessment survey (NHEXAS) pilot study in Arizona: preliminary results for pesticides and VOCs. J Expo Anal Environ Epidemiol 1999;9(5):456–470.

58. Garrett MH, Hooper MA, Hooper BM, Raymond PR, Abramson MJ. Increased risk of allergy in children due to formaldehyde exposure in homes. Allergy 1999;54(4):330–337.

59. Rumchev KB, Spickett JT, Bulsara MK, Phillips MR, Stick SM. Domestic exposure to formaldehyde significantly increases the risk of asthma in young children. Eur Respir J 2002;20(2):403–408.

60. Pratt MD, Belsito DV, DeLeo VA, et al. North American contact dermatitis group patch test results, 2001-2002 study period. Dermatitis 2004;15(4):176–183.

61. Wantke F, Demmer CM, Tappler P, Gotz M, Jarisch R. Exposure to gaseous formaldehyde induces IgE-mediated sensitization to formaldehyde in school children. Clin Exp Allergy 1996;26(3):276–280.

62. Lehmann I, Rehwagen M, Diez U, et al. Enhanced in vivo IgE production and T cell polarization toward the type 2 phenotype in association with indoor exposure to VOC: results of the LARS study. Int J Hyg Environ Health 2001;204(4):211–221.

63. Franklin P, Dingle P, Stick S. Raised exhaled nitric oxide in healthy children is associated with domestic formaldehyde levels. Am J Respir Crit Care Med 2000;161(5):1757–1759.

64. Krzyzanowski M, Quackenboss JJ, Lebowitz MD. Chronic respiratory effects of indoor formaldehyde exposure. Environ Res 1990;52(2):117–125.

65. Wieslander G, Norbäck D, Björnsson E, Janson C, Boman G. Asthma and the indoor environment: the significance of emission of formaldehyde and other organic compounds from newly painted indoor surfaces. Int Arch Occup Environ Health 1997;69(2):115–124.

66. Rumchev K, Spickett J, Bulsara M, Phillips M, Stick S. Association of domestic exposure to volatile organic compounds with asthma in young children. Thorax 2004;59(9):746–751.

67. Saijo Y, Kishi R, Sata F, et al. Symptoms in relation to chemicals and dampness in newly built dwellings. Int Arch Occup Environ Health 2004;77(7):461–470.

68. Kim JH, Kim JK, Son BK, et al. Effects of air pollutants on childhood asthma. Yonsei Med J 2005;46(2):239–244.
69. Venn AJ, Cooper M, Antoniak M, Laughlin C, Britton J, Lewis SA. Effects of volatile organic compounds, damp, and other environmental exposures in the home on wheezing illness in children. Thorax 2003;58(11):955–960.

70. Norbäck D, Björnsson E, Janson C, Widstrom J, Boman G. Asthmatic symptoms and volatile organic compounds, formaldehyde, and carbon dioxide in dwellings. Occup Environ Med 1995;52(6):388–95.

71. Kim YM, Harrad S, Harrison RM. Levels and sources of personal inhalation exposure to volatile organic compounds. Environ Sci Technol 2002;36:5405–5410.

72. Sexton K, Adgate JL, Mongin SJ, et al. Evaluating differences between measured personal exposures to volatile organic compounds and concentrations in outdoor and indoor air. Environ Sci Technol 2004;38(9):2593–2602.

73. Raw GJ, Coward SK, Brown VM, Crump DR. Exposure to air pollutants in English homes. J Expo Anal Environ Epidemiol 2004;14(Suppl 1):S85–S94.

74. Edwards RD, Jurvelin J, Koistinen K, Saarela K, Jantunen M. VOC source identification from personal and residential indoor, outdoor and workplace microenvironment samples in EXPOLIS-Helsinki, Finland. Atmospher Environ 2001;35:4829–4841.

75. Lorz PM, Towae FK, Enke W, Jäckh R, Bhargava N. Phthalic acid and derivatives. In: Ullmann’s Encyclopedia of Industrial Chemistry Release 2003. Weinheim: Wiley-VCH, 2002.

76. Kavlock R, Boekelheide K, Chapin R, et al. NTP Center for the Evaluation of Risks to Human Reproduction: phthalates expert panel report on the reproductive and developmental toxicity of di-n-octyl phthalate. Reprod Toxicol 2002;16(5):721–734.

77. Kavlock R, Boekelheide K, Chapin R, et al. NTP Center for the Evaluation of Risks to Human Reproduction: phthalates expert panel report on the reproductive and developmental toxicity of di(2-ethylhexyl) phthalate. Reprod Toxicol 2002;16(5):529–653.

78. Kavlock R, Boekelheide K, Chapin R, et al. NTP Center for the Evaluation of Risks to Human Reproduction: phthalates expert panel report on the reproductive and developmental toxicity of di-n-butyl phthalate. Reprod Toxicol 2002;16(5):489–527.

79. Kavlock R, Boekelheide K, Chapin R, et al. NTP Center for the Evaluation of Risks to Human Reproduction: phthalates expert panel report on the reproductive and developmental toxicity of butyl benzyl phthalate. Reprod Toxicol 2002;16(5):453–487.

80. Kavlock R, Boekelheide K, Chapin R, et al. NTP Center for the Evaluation of Risks to Human Reproduction: phthalates expert panel report on the reproductive and developmental toxicity of di-n-hexyl phthalate. Reprod Toxicol 2002;16(5):709–719.

81. Kavlock R, Boekelheide K, Chapin R, et al. NTP Center for the Evaluation of Risks to Human Reproduction: phthalates expert panel report on the reproductive and developmental toxicity of diisononyl phthalate. Reprod Toxicol 2002;16(5):679–708.

82. Kavlock R, Boekelheide K, Chapin R, et al. NTP Center for the Evaluation of Risks to Human Reproduction: phthalates expert panel report on the reproductive and developmental toxicity of di-isodecyl phthalate. Reprod Toxicol 2002;16(5):655–678.

83. Calafat AM, Slakman AR, Silva MJ, Herbert AR, Needham LL. Automated solid phase extraction and quantitative analysis of human milk for 13 phthalate metabolites. J Chromatogr B Analyt Technol Biomed Life Sci 2004;805(1):49–56.

84. Wilson NK, Chuang JC, Lyu C. Levels of persistent organic pollutants in several child day care centers. J Expo Anal Environ Epidemiol 2001;11(6):449–458.

85. Adibi JJ, Perera FP, Jedrychowski W, et al. Prenatal exposures to phthalates among women in New York City and Krakow, Poland. Environ Health Perspect 2003;111(14):1719–1722.

86. Øie L, Hersoug LG, Madsen JØ. Residential exposure to plasticizers and its possible role in the pathogenesis of asthma. Environ Health Perspect 1997;105(9):972–978.

87. Blount BC, Milgram KE, Silva MJ, et al. Quantitative detection of eight phthalate metabolites in human urine using HPLC-APCI-MS/MS. Anal Chem 2000;72(17):4127–4134.

88. Koch HM, Rossbach B, Drexler H, Angerer J. Internal exposure of the general population to DEHP and other phthalates—determination of secondary and primary phthalate monoester metabolites in urine. Environ Res 2003;93(2):177–185.

89. Kato K, Silva MJ, Reidy JA, et al. Mono(2-ethyl-5-hydroxyhexyl) phthalate and mono(2-ethyl-5-oxohexyl) phthalate as biomarkers for human exposure assessment to di(2-ethylhexyl) phthalate. Environ Health Perspect 2004;112(3):327–330.

90. Blount BC, Silva MJ, Caudill SP, et al. Levels of seven urinary phthalate metabolites in a human reference population. Environ Health Perspect 2000;108(10):979–982.

91. Brock JW, Caudill SP, Silva MJ, Needham LL, Hilborn ED. Phthalate monoesters levels in the urine of young children. Bull Environ Contam Toxicol 2002;68(3):309–314.

92. Silva MJ, Barr DB, Reidy JA, et al. Urinary levels of seven phthalate metabolites in the U.S. population from the National Health and Nutrition Examina-
Airborne Environmental Injuries and Human Health

93. Barr DB, Silva MJ, Kato K, et al. Assessing human exposure to phthalates using monoesters and their oxidized metabolites as biomarkers. Environ Health Perspect 2004;112(3):331–338.

94. Koch HM, Bolt HM, Preuss R, Angerer J. New metabolites of di(2-ethylhexyl)phthalate (DEHP) in human urine and serum after single oral doses of deuterium-labelled DEHP. Arch Toxicol 2005;79:367–376.

95. Preuss R, Koch HM, Angerer J. Biological monitoring of the five major metabolites of di-(2-ethylhexyl)phthalate (DEHP) in human urine using column-switching liquid chromatography-tandem mass spectrometry. J Chromatogr B Analyst Technol Biomed Life Sci 2005;816(1–2):269–280.

96. Duty SM, Calafat AM, Silva MJ, Ryan L, Hauser R. Phthalate exposure and reproductive hormones in adult men. Hum Reprod 2005;20(3):604–610.

97. Hoppin JA, Brock JW, Davis BJ, Baird DD. Reproducibility of urinary phthalate metabolites in first morning urine samples. Environ Health Perspect 2002;110(5):515–518.

98. Hauser R, Meeker JD, Park S, Silva MJ, Calafat AM. Temporal variability of urinary phthalate metabolite levels in men of reproductive age. Environ Health Perspect 2004;112:1734–1740.

99. Koch HM, Drexler H, Angerer J. An estimation of the daily intake of di(2-ethylhexyl)phthalate (DEHP) and other phthalates in the general population. Int J Hyg Environ Health 2003;206(2):77–83.

100. David RM. Commentary regarding the article by Koch et al. An estimation of the daily intake of di(2-ethylhexyl)phthalate (DEHP) and other phthalates in the general population. Int J Hyg Environ Health 2003;206:77–83; Int J Hyg Environ Health 2004;207:75,76.

101. Kambia K, Dine T, Gressier B, et al. Evaluation of childhood exposure to di(2-ethylhexyl) phthalate from perfusion kits during long-term parenteral nutrition. Int J Pharm 2003;262(1–2):83–91.

102. Calafat AM, Needham LL, Silva MJ, Lambert G. Exposure to di-(2-ethylhexyl) phthalate among premature neonates in a neonatal intensive care unit. Pediatrics 2004;113(5):e429–e434.

103. NTP. Report on Carcinogens 11th edition, di(2-ethylhexyl) phthalate CAS No. 117-81-7: National Toxicology Program.

104. Babich MA, Chen SB, Greene MA, et al. Risk assessment of oral exposure to diisononyl phthalate from children’s products. Regul Toxicol Pharmacol 2004;40(2):151–167.

105. Kato K, Silva MJ, Brock JW, et al. Quantitative detection of nine phthalate metabolites in human serum using reversed-phase high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry. J Anal Toxicol 2003;27(5):284–289.

106. Larsen ST, Hansen JS, Thygesen P, Begtrup M, Poulsen OM, Nielsen GD. Adjuvant and immunosuppressive effect of six monophthalates in a subcutaneous injection model with BALB/c mice. Toxicology 2001;169(1):37–51.

107. Larsen ST, Lund RM, Nielsen GD, Thygesen P, Poulsen OM. Adjuvant effect of di-2-butyl-, di-n-octyl-, di-iso-nonyl- and di-iso-decyl phthalate in a subcutaneous injection model using BALB/c mice. Pharmacol Toxicol 2002;91(5):264–272.

108. Larsen ST, Lund RM, Thygesen P, Poulsen OM, Nielsen GD. Investigation of the adjuvant and immuno-suppressive effects of benzyl butyl phthalate, phthalic acid and benzyl alcohol in a murine injection model. Food Chem Toxicol 2003;41(3):439–446.

109. Bornhag CG, Sundell J, Weschler CJ, et al. The association between asthma and allergic symptoms in children and phthalates in house dust: a nested case-control study. Environ Health Perspect 2004;112:1393–1397.

110. Jaakkola JJ, Öie L, Naftsd P, Botten G, Samuels SO, Magnus P. Interior surface materials in the home and the development of bronchial obstruction in young children in Oslo, Norway. Am J Public Health 1999;89(2):188–192.

111. Øie L, Naftsd P, Botten G, Magnus P, Jaakkola JK. Ventilation in homes and bronchial obstruction in young children. Epidemiology 1999;10(3):294–299.

112. Clausen PA, Hansen V, Gunnarsen L, Afshari A, Wolkoff P. Emission of di-2-ethylhexyl phthalate from PVC flooring into air and uptake in dust: emission and sorption experiments in FLEC and CLIMPAQ. Environ Sci Technol 2004;38(9):2531–2537.

113. Jaakkola JJ, Verkasalo PK, Jaakkola N. Plastic wall materials in the home and respiratory health in young children. Am J Public Health 2000;90(5):797–799.

114. Hoppin JA, Ulmer R, London SJ. Phthalate exposure and pulmonary function. Environ Health Perspect 2004;112(5):571–574.

115. Wieslander G, Norbäck D, Nordstrom K, Wålinder P. Emission of di-2-ethylhexyl phthalate from building materials. Environ Health Perspect 2004;112(5):797–799.

116. Hoffmann K, Krause C, Seifert B, Ullrich D. The German Environmental Survey 1990/92 (GerES II): sources of personal exposure to volatile organic compounds. J Expo Anal Environ Epidemiol 2000;10(2):115–125.

117. Ooi PL, Goh KT, Phoon MH, Foo SC, Yap HM. Epidemiology of sick building syndrome and its asso-
118. Mylchreest E, Cattley RC, Foster PM. Male reproductive tract malformations in rats following gestational and lactational exposure to Di(n-butyl) phthalate: an antiandrogenic mechanism? Toxicol Sci 1998;43(1):47–60.

119. Salazar V, Castillo C, Ariznavarreta C, Campón R, Tresguerres JA. Effect of oral intake of dibutyl phthalate on reproductive parameters of Long Évans rats and pre-pubertal development of their offspring. Toxicology 2004;205(1-2):131–137.

120. Lee KY, Shibutani M, Takagi H, et al. Diverse developmental toxicity of di-n-butyl phthalate in both sexes of rat offspring after maternal exposure during the period from late gestation through lactation. Toxicology 2004;203(1-3):221–238.

121. Fisher JS, Macpherson S, Marchetti N, Sharpe RM. Human ‘testicular dysgenesis syndrome’: a possible model using in-utero exposure of the rat to dibutyl phthalate. Hum Reprod 2003;18(7):1383–1394.

122. Tył RW, Myers CB, Marr MC, et al. Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. Reprod Toxicol 2004;18(2):241–264.

123. Zhang Y, Jiang X, Chen B. Reproductive and developmental toxicity in F1 Sprague-Dawley male rats exposed to di-n-butyl phthalate in utero and during lactation and determination of its NOAEL. Reprod Toxicol 2004;18(5):669–676.

124. Kai H, Shono T, Tajiri T, Suita S. Long-term effects of intrauterine exposure to mono-n-butyl phthalate on the reproductive function of postnatal rats. J Pediatr Surg 2005;40(2):429–433.

125. Higuchi TT, Palmer JS, Gray LE Jr, Veeramachaneni DN. Effects of dibutyl phthalate in male rabbits following in utero, adolescent, or postpubertal exposure. Toxicol Sci 2003;72(2):301–313.

126. Wilson VS, Lambright C, Furr J, et al. Phthalate ester-induced gubernacular lesions are associated with reduced insl3 gene expression in the fetal rat testis. Toxicol Lett 2004;146(3):207–215.

127. Lehmann KP, Phillips S, Sar M, Foster PM, Gaido KW. Dose-dependent alterations in gene expression and testosterone synthesis in the fetal testes of male rats exposed to di (n-butyl) phthalate. Toxicol Sci 2004;81(1):60–68.

128. Parks LG, Olsby JS, Lambright CR, et al. The plasticizer diethylhexyl phthalate induces malformations by decreasing fetal testosterone synthesis during sexual differentiation in the male rat. Toxicol Sci 2000;58(2):339–349.

129. Stroheker T, Cabaton N, Nourdin G, Régnier JF, Lhuguenot JC, Chagnon MC. Evaluation of antiandrogenic activity of di-(2-ethylhexyl)phthalate. Toxicology 2005;208(1):115–121.

130. Akingbemi BT, Youker RT, Sottas CM, et al. Modulation of rat Leydig cell steroidogenic function by di(2-ethylhexyl)phthalate. Biol Reprod 2001;65(4):1252–1259.

131. Shultz VD, Phillips S, Sar M, Foster PM, Gaido KW. Altered gene profiles in fetal rat testes after in utero exposure to di(n-butyl) phthalate. Toxicol Sci 2001;64(2):233–242.

132. Mylchreest E, Sar M, Wallace DG, Foster PM. Fetal testosterone insufficiency and abnormal proliferation of Leydig cells and gonocytes in rats exposed to di(n-butyl) phthalate. Reprod Toxicol 2002;16(1):19–28.

133. Nagao T, Ohta R, Marumo H, Shindo T, Yoshimura S, Ono H. Effect of butyl benzyl phthalate in Sprague-Dawley rats after gavage administration: a two-generation reproductive study. Reprod Toxicol 2000;14(6):513–532.

134. Barlow NJ, Phillips SL, Wallace DG, Sar M, Gaido KW, Foster PM. Quantitative changes in gene expression in fetal rat testes following exposure to di(n-butyl) phthalate. Toxicol Sci 2003;73(2):431–441.

135. Liu K, Lehmann KP, Sar M, Young SS, Gaido KW. Gene expression profiling following in utero exposure to phthalate esters reveals new gene targets in the etiology of testicular dysgenesis. Biol Reprod 2005;73(1):180–192.

136. Akingbemi BT, Ge R, Klinefelter GR, Zirkin BR, Hardy MP. Phthalate-induced Leydig cell hyperplasia is associated with multiple endocrine disturbances. Proc Natl Acad Sci USA 2004;101(3):775–780.

137. Bowman CJ, Turner KJ, Sar M, Barlow NJ, Gaido KW, Foster PM. Altered gene expression during rat Wolffian duct development following di(n-butyl) phthalate exposure. Toxicol Sci 2005;86(1):161–174.

138. Kim HS, Saito K, Ishizuka M, Kazusaka A, Fujita S. Short period exposure to di-(2-ethylhexyl) phthalate regulates testosterone metabolism in testis of prepubertal rats. Arch Toxicol 2003;77(8):446–451.

139. Foster PM, Cattley RC, Mylchreest E. Effects of di-n-butyl phthalate (DBP) on male reproductive development in the rat: implications for human risk assessment. Food Chem Toxicol 2000;38(1 Suppl):S97–S99.

140. Kessler W, Numtip W, Grote K, Csanády GA, Chahoud I, Filser JG. Blood burden of di(2-ethylhexyl) phthalate and its primary metabolite mono(2-ethylhexyl) phthalate in pregnant and nonpregnant rats and marmosets. Toxicol Appl Pharmacol 2004;195:142–153.

141. Silva MJ, Barr DB, Reidy JA, et al. Glucuronidation patterns of common urinary and serum monoester phthalate metabolites. Arch Toxicol 2003;77(10):561–567.

142. Koch HM, Bolt HM, Angerer J. Di(2-ethylhexyl) phthalate (DEHP) metabolites in human urine...
and serum after a single oral dose of deuterium-labelled DEHP. Arch Toxicol 2004;78(3):123–130.

143. Latini G, De Felice C, Presta G, et al. In utero exposure to di-(2-ethylhexyl)phthalate and duration of human pregnancy. Environ Health Perspect 2003;111(14):1783–1785.

144. Fisher JS. Environmental anti-androgens and male reproductive health: focus on phthalates and testicular dysgenesis syndrome. Reproduction 2004;127(3):305–315.

145. Duty SM, Singh NP, Silva MJ, et al. The relationship between environmental exposures to phthalates and DNA damage in human sperm using the neutral comet assay. Environ Health Perspect 2003;111(9):1164–1169.

146. Duty SM, Silva MJ, Barr DB, et al. Phthalate exposure and human semen parameters. Epidemiology 2003;14(3):269–277.

147. Voss C, Zerban H, Bannasch P, Berger MR. Lifelong exposure to di-(2-ethylhexyl)-phthalate induces tumors in liver and testes of Sprague-Dawley rats. Toxicology 2005;206(3):359–371.

148. International Agency for Research on Cancer (IARC). IARC monographs on the Evaluation of Carcinogenic Risks to Humans. Some Industrial Chemicals. World Health Organization, Lyon 2000;77. Available from: www.monographs.iarc.fr/ENG/Monographs/vol177/volume177.pdf. Last accessed: June 15, 2005.

149. Brody C, DiGangi J, Easthope T, Rossi M, Schettler T. [IARC downgrading of DEHP. Health Care Without Harm letter]. Int J Occup Environ Health 2003;9:399–400.

150. Melnick RL, Brody C, Huff J. The IARC evaluation of DEHP excludes key papers demonstrating carcinogenic effects. Int J Occup Environ Health 2003;9(4):400–402.

151. Davis JR, Brownson RC, Garcia R. Family pesticide use in the home, garden, orchard, and yard. Arch Environ Contam Toxicol 1992;22(3):260–266.

152. Landrigan PJ, Claudio L, Markowitz SB, et al. Pesticides and inner-city children: exposures, risks, and prevention. Environ Health Perspect 1999;107(Suppl 3):431–437.

153. Berkowitz GS, Obel J, Deych E, et al. Exposure to indoor pesticides during pregnancy in a multiethnic urban cohort. Environ Health Perspect 2003;111(1):79–84.

154. Whyatt RM, Barr DB, Camann DE, et al. Contemporary-use pesticides in personal air samples during pregnancy and blood samples at delivery among urban minority mothers and newborns. Environ Health Perspect 2003;111(5):749–756.

155. Garfitt SJ, Jones K, Mason HJ, Cocker J. Exposure to the organophosphate diazinon: data from a human volunteer study with oral and dermal doses. Toxicol Lett 2002;134(1-3):105–113.

156. Garfitt SJ, Jones K, Mason HJ, Cocker J. Development of a urinary biomarker for exposure to the organophosphate propetamphos: data from an oral and dermal human volunteer study. Biomarkers 2002;7(2):113–122.

157. Griffin P, Mason H, Heywood K, Cocker J. Oral and dermal absorption of chlorpyrifos: a human volunteer study. Occup Environ Med 1999;56(1):10–13.

158. Nolan RJ, Rick DL, Freshour NL, Saunders JH. Chlorpyrifos: pharmacokinetics in human volunteers. Toxicol Appl Pharmacol 1984;73(1):8–15.

159. Eskenazi B, Bradman A, Castorina R. Exposures of urban cohort. Environ Health Perspect 2003;111(1):74–79.

160. Akland GG, Pellizzari ED, Hu Y, et al. Factors influencing total dietary exposures of young children. J Expo Anal Environ Epidemiol 2000;10(6 Pt 2):710–722.

161. Fenske RA, Black KG, Elkner KP, Lee C-L, Methner MM, Soto R. Potential exposure and health risks of infants following indoor residential pesticide applications. Am J Public Health 1990;80(6):689–693.

162. Gurunathan S, Robson M, Freeman N, et al. Accumulation of chlorpyrifos on residential surfaces and toys accessible to children. Environ Health Perspect 1998;106(1):9–16.

163. Clayton CA, Pellizzari ED, Whitmore RW, Quackenboss JJ, Adgate J, Selton K. Distributions, associations, and partial aggregate exposure of pesticides and polynuclear aromatic hydrocarbons in the Minnesota Children’s Pesticide Exposure Study (MNCPES). J Expo Anal Environ Epidemiol 2003;13(2):100–111.

164. MacIntosh DL, Kabiru CW, Ryan PB. Longitudinal investigation of dietary exposure to selected pesticides. Environ Health Perspect 2001;109(2):145–150.

165. Fenske RA, Kedan G, Lu C, Fisker-Andersen J, Curl CL. Assessment of organophosphorous pesticide exposures in the diets of preschool children in Washington State. J Expo Anal Environ Epidemiol 2002;12(1):21–28.

166. Simcox NJ, Fenske RA, Wolz SA, Lee IC, Kalman DA. Pesticides in household dust and soil: exposure pathways for children of agricultural families. Environ Health Perspect 1995;103(12):1126–1134.

167. Fenske RA, Lu C, Barr D, Needham L. Children’s exposure to chlorpyrifos and parathion in an agricultural community in central Washington State. Environ Health Perspect 2002;110(5):549–553.

168. Curl CL, Fenske RA, Kissel JC, et al. Evaluation of take-home organophosphorus pesticide exposure among agricultural workers and their children. Environ Health Perspect 2002;110(12):A787–A792.

169. Lu C, Fenske RA, Simcox NJ, Kalman D. Pesticide exposure of children in an agricultural community: evidence of household proximity to farmland and take home exposure pathways. Environ Res 2000;84(3):290–302.
170. McCauley LA, Lasarev MR, Higgins G, et al. Work characteristics and pesticide exposures among migrant agricultural families: a community-based research approach. Environ Health Perspect 2001;109(5):533–538.

171. MacIntosh DL, Kabiru C, Echols SL, Ryan PB. Dietary exposure to chlorpyrifos and levels of 3,5,6-trichloro-2-pyridinol in urine. J Expo Anal Environ Epidemiol 2001;11(4):279–285.

172. Pang Y, MacIntosh DL, Camann DE, Ryan PB. Analysis of aggregate exposure to chlorpyrifos in the NHEXAS-Maryland investigation. Environ Health Perspect 2002;110(3):235–240.

173. MacIntosh DL, Spengler JD, Özkaynak H, Tsai L, Ryan PB. Dietary exposures to selected metals and pesticides. Environ Health Perspect 1996;104(2):202–209.

174. Barr DB, Barr JR, Maggio VL, et al. A multi-analyte method for the quantification of contemporary pesticides in human serum and plasma using high-resolution mass spectrometry. J Chromatogr A 2002;778(1–2):99–111.

175. Meeker JD, Ryan L, Barr DB, et al. The relationship of urinary metabolites of carbaryl, napthalene and chlorpyrifos with human semen quality. Environ Health Perspect 2004;112(17):1665–1670.

176. O’Rourke MK, Lizardi PS, Rogan SP, Freeman NC, Aguirre A, Saint CG. Pesticide exposure and creatinine variation among young children. J Expo Anal Environ Epidemiol 2000;10(6 Pt 2):672–681.

177. Bradman A, Barr DB, Clauss Henn BG, Drumheller T, Curry C, Eskenazi B. Measurement of pesticides and other toxicants in amniotic fluid as a potential biomarker of prenatal exposure: a validation study. Environ Health Perspect 2003;111(14):1779–1782.

178. Whyatt RM, Barr DB. Measurement of organophosphate metabolites in postpartum meconium as a potential biomarker of prenatal exposure: a validation study. Environ Health Perspect 2001;109(4):417–420.

179. Ostrea EM, Jr., Morales V, Ngoumgna E, et al. Prevalence of fetal exposure to environmental toxins as determined by meconium analysis. Neurotoxicology 2002;23(3):329–339.

180. Aprea C, Strambi M, Novelli MT, Lunghini L, Bozzi N. Biologic monitoring of exposure to organophosphorus pesticides in 195 Italian children. Environ Health Perspect 2000;108(6):521–525.

181. Adgate JL, Barr DB, Clayton CA, et al. Measurement of children’s exposure to pesticides: analysis of urinary metabolite levels in a probability-based sample. Environ Health Perspect 2001;109(6):583–590.

182. Lu C, Knutson DE, Fisker-Andersen J, Fenske RA. Biological monitoring survey of organophosphorus pesticide exposure among pre-school children in the Seattle metropolitan area. Environ Health Perspect 2001;109(3):299–303.

183. Koch DJ, Lu C, Fisker-Andersen J, Jolley L, Fenske RA. Temporal association of children’s pesticide exposure and agricultural spraying: report of a longitudinal biological monitoring study. Environ Health Perspect 2002;110(8):829–833.

184. Curl CL, Fenske RA, Elgethun K. Organophosphorus pesticide exposure of urban and suburban pre-school children with organic and conventional diets. Environ Health Perspect 2003;111(3):377–382.

185. Fenske RA, Kissel JC, Lu C, et al. Biologically based pesticide dose estimates for children in an agricultural community. Environ Health Perspect 2000;108(6):515–520.

186. Castorina R, Bradman A, McKone TE, Barr DB, Harrny ME, Eskenazi B. Cumulative organophosphate pesticide exposure and risk assessment among pregnant women living in an agricultural community: a case study from the CHAMACOS cohort. Environ Health Perspect 2003;111(13):1640–1648.

187. Azaroff LS, Neas LM. Acute health effects associated with nonoccupational pesticide exposure in rural El Salvador. Environ Res 1999;80(2 Pt 1):158–164.

188. Chanda SM, Pope CN. Neurochemical and neurobehavioral effects of repeated gestational exposure to chlorpyrifos in maternal and developing rats. Pharmacol Biochem Behav 1996;53(4):771–776.

189. Ahlbom J, Fredriksson A, Eriksson P. Exposure to an organophosphate (DFP) during a defined period in neonatal life induces permanent changes in brain muscarinic receptors and behaviour in adult mice. Brain Res 1995;677(1):13–19.

190. Slotkin TA, Cousmins MM, Tate CA, Seidler FJ. Persistent cholinergic presynaptic deficits after neonatal chlorpyrifos exposure. Brain Res 2001;902(2):229–243.

191. Eriksson P, Fredriksson A. Neurotoxic effects of two different pyrethroids, bioallethrin and deltamethrin, on immature and adult mice: changes in behavioral and muscarinic receptor variables. Toxicol Appl Pharmacol 1991;108(1):78–85.

192. Gupta RC, Rech RH, Lovell KL, Welsch F, Thornburg JE. Brain cholinergic, behavioral, and morphological development in rats exposed in utero to methylparathion. Toxicol Appl Pharmacol 1985;77(3):405–413.

193. Dam K, Garcia SJ, Seidler FJ, Slotkin TA. Neonatal chlorpyrifos exposure alters synaptic development and neuronal activity in cholinergic and catecholaminergic pathways. Brain Res Dev Brain Res 1999;116(1):9–20.

194. Song X, Seidler FJ, Saleh JL, Zhang J, Padilla S, Slotkin TA. Cellular mechanisms for developmental toxicity of chlorpyrifos: targeting the adenylyl...
Airborne Environmental Injuries and Human Health

200. Perera FP, Rauh V, Tsai WY, et al. Effects of trans-

208. Fall PA, Fredrikson M, Axelson O, Granérus AK.

206. Menegon A, Board PG, Blackburn AC, Mellick GD,

205. Gorell JM, Johnson CC, Rybicki BA, Peterson EL,

204. Butterfield PG, Valanis BG, Spencer PS, Lindeman

203. Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna

202. Berkowitz GS, Wetmur JG, Birman-Deych E, et al.

201. Whyatt RM, Rauh V, Barr DB, et al. Association be-

200. Johnson DE, Seidler FJ, Slotkin TA. Early biochemi-

203. Dam K, Seidler FJ, Slotkin TA. Developmental neu-

204. Johansen NC, Racette S, Saugstad OD, et al. Pesti-

205. Wieland S, Bergman B, Moawad AH, et al. Pesti-

206. Johnson DE, Seidler FJ, Slotkin TA. Early biochemi-

207. Hoppin JA, Umbach DM, London SJ, Alavanja MC,

Clinical Reviews in Allergy & Immunology Volume 31, 2006

Volume 31, 2006

study in southeastern Sweden. Mov Disord 1999;

209. Firestone JA, Smith-Weller T, Franklin G, Swanson

P, Longstreth WT, Jr., Checkoway H. Pesticides and risk of Parkinson disease: a population-based

case-control study. Arch Neurol 2005;62(1):91–95.

210. Nuti A, Ceravolo R, Dell’Agnello G, et al. Environ-

mental factors and Parkinson’s disease: a case-

control study in the Tuscany region of Italy. Parkinsonism Relat Disord 2004;10(8):481–485.

211. Blair A, Grauman DJ, Lubin JH, Fraumeni JF, Jr. Lung cancer and other causes of death among li-

ensed pesticide applicators. J Natl Cancer Inst 1983;71(1):31–37.

212. Alavanja MC, Dosemeci M, Samanic C, et al. Pesti-

cides and lung cancer risk in the agricultural health study cohort. Am J Epidemiol 2004;160(9):

876–885.

213. Lee WJ, Blair A, Hoppin JA, et al. Cancer incidence

among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. J Natl Cancer Inst 2004;96(23):1781–1789.

214. De Roos AJ, Blair A, Rusiecki JA, et al. Cancer inci-

dence among glyphosate-exposed pesticide applic-

ators in the agricultural health study. Environ Health Perspect 2005;113(1):49–54.

215. Zahm SH, Ward MH. Pesticides and childhood can-

cer. Environ Health Perspect 1998;106 (Suppl 3):893–908.

216. Daniels JL, Olshan AF, Savitz DA. Pesticides and

childhood cancers. Environ Health Perspect 1997;

105(10):1068–1077.

217. Fryer AD, Lein PJ, Howard AS, Yost BL, Beckles

RA, Jett DA. Mechanisms of organophosphate inse-

cicide exposure reproduces features of Parkinson’s
disease. Nat Neurosci 2000;3(12):1301–1306.

218. Lein PJ, Fryer AD. Organophosphorus insecticides

induce airway hyperreactivity by decreasing neu-

ronal M2 muscarinic receptor function independent

dent of acetylcholinesterase inhibition. Toxicol Sci

2005;83(1):166–176.

219. Segura P, Chávez J, Montaño LM, et al. Identifica-

tion of mechanisms involved in the acute airway toxicity

induced by parathion. Naunyn Schmiedebergs Arch

Pharmacol 1999;360(6):699–710.

220. Hoppin JA, Umbach DM, London SJ, Alavanja MC,

Sandler DP. Chemical predictors of wheeze among

farmer pesticide applicators in the Agricultural Health Study. Am J Respir Crit Care Med 2002;

165(5):683–689.

221. Brouwer A, Ahlborg UG, van Leeuwen FX, Feeley

MM. Report of the WHO working group on the

assessment of health risks for human infants from

exposure to PCDDs, PCDFs and PCBs. Chemo-
sphere 1998;37(9-12):1627–1643.

222. Breivik K, Sweetman A, Pacyna JM, Jones KC. To-

wards a global historical emission inventory for se-
lected PCB congeners—a mass balance approach. 1. Global production and consumption. Sci Total Environ 2002;290(1-3):181–198.

223. Breivik K, Sweetman A, Pajunen J, Jones KC. Towards a global historical emission inventory for selected PCB congeners—a mass balance approach. 2. Emissions. Sci Total Environ 2002;290(1-3):199–224.

224. Meijer SN, Ockenden WA, Sweetman A, Breivik K, Grimalt JO, Jones KC. Global distribution and budget of PCBs and HCB in background surface soils: implications for sources and environmental processes. Environ Sci Technol 2003;37(4):667–672.

225. Jönsson A, Gustafsson Ö, Axelman J, Sundberg H. Global accounting of PCBs in the continental shelf sediments. Environ Sci Technol 2003;37(2):245–255.

226. Van den Berg M, Birnbaum L, Bosveld AT, et al. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. Environ Health Perspect 1998;106(12):775–792.

227. Nawrot TS, Staessen JA, Den Hond EM, et al. Host and environmental determinants of polychlorinated aromatic hydrocarbons in serum of adolescents. Environ Health Perspect 2002;110(6):583–589.

228. DeVoto E, Kohlmeier L, Heeschen W. Some dietary predictors of plasma organochlorine concentrations in an elderly German population. Arch Environ Health 1998;53(2):147–155.

229. Kiviranta H, Ovaskainen ML, Vartiainen T. Market basket study on dietary intake of PCDD/Fs, PCBs, and PBDEs in Finland. Environ Int 2004;30(7):923–932.

230. Moysich KB, Ambrosone CB, Mendola P, et al. Exposures associated with serum organochlorine levels among postmenopausal women from western New York State. Am J Ind Med 2002;41(2):102–110.

231. Sjödin A, Hagmar L, Klasson-Wehler E, Björk J, Bergman A. Influence of the consumption of fatty Baltic Sea fish on plasma levels of halogenated environmental contaminants in Latvian and Swedish men. Environ Health Perspect 2000;108(11):1035–1041.

232. Laden F, Neas LM, Spiegelman D, et al. Predictors of plasma concentrations of DDE and PCBs in a group of U.S. women. Environ Health Perspect 1999;107(1):75–81.

233. Hanrahan LP, Falk C, Anderson HA, et al. Serum PCB and DDE levels of frequent Great Lakes sport fish consumers—a first look. Environ Res 1999;80(2 Pt 2):S26–S37.

234. Svensson BG, Nilsson A, Hansson M, Rappe C, Akesson B, Skerfving S. Exposure to dioxins and dibenzofurans through the consumption of fish. N Engl J Med 1991;324(4):69–81.

235. Macdonal RW, Barrie LA, Bidleman TF, et al. Contaminants in the Canadian Arctic: 5 years of progress in understanding sources, occurrence and pathways. Sci Total Environ 2000;254(2-3):93–234.

236. Mulvad G, Pedersen HS, Hansen JC, et al. Exposure of Greenlandic Inuit to organochlorines and heavy metals through the marine food-chain: an international study. Sci Total Environ 1996;186(1-2):137–139.

237. Bjerregaard P, Dewailly E, Ayotte P, Pars T, Ferron L, Mulvad G. Exposure of Inuit in Greenland to organochlorines through the marine diet. J Toxicol Environ Health A 2001;62(2):69–81.

238. Bjerregaard P, Hansen JC. Organochlorines and heavy metals in pregnant women from the Disko Bay area in Greenland. Sci Total Environ 2000;245(1-3):195–202.

239. Scheckter A, Startin J, Wright C, et al. Congener-specific levels of dioxins and dibenzofurans in U.S. food and estimated daily dioxin toxic equivalent intake. Environ Health Perspect 1994;102(11):962–966.

240. Buckley-Golder D, King K, Brown K. Compilation of EU Dioxin Exposure and Health Data. Summary Report: European Commission DG Environment, UK Department of the Environment Transport and the Regions (DETR), 1999.

241. Patandin S, Dagnelie PC, Mulder PG, et al. Dietary exposure to polychlorinated biphenyls and dioxins from infancy until adulthood: A comparison between breast-feeding, toddler, and long-term exposure. Environ Health Perspect 1999;107(1):45–51.

242. Wittsiepe J, Schrey P, Wilhelm M. Dietary intake of PCDD/F by small children with different food consumption measured by the duplicate method. Chemosphere 2001;43(4-7):881–887.

243. van Leeuwen FX, Feeley M, Schrenk D, Larsen JC, Farland W, Younes M. Dioxins: WHO’s tolerable daily intake (TDI) revisited. Chemosphere 2000;40(9-11):1095–1101.

244. Link B, Gabrio T, Zoellner I, et al. Biomonitoring of persistent organochlorine pesticides, PCDD/PCDFs and dioxin-like PCBs in blood of children from South West Germany (Baden-Wuerttemberg) from 1993 to 2003. Chemosphere 2005;58(9):1185–1201.

245. Mes J. Trends in the levels of some chlorinated hydrocarbon residues in adipose tissue of Canadians. Environ Pollut 1990;65(3):269–278.

246. Mes J. Temporal changes in some chlorinated hydrocarbon residue levels of Canadian breast milk and infant exposure. Environ Pollut 1994;84(3):261–268.

247. Loganathan BG, Tanabe S, Hidaka Y, Kawano M, Aoki A. Temporal trends of perfluorinated compounds (PFCs) and PCBs in milk of adults from Japan, 1928-1985. Environ Health Perspect 1994;102(11):962–966.

248. Lundén Å, Norén K. Polychlorinated naphthalenes in blood of children from South West Germany (Baden-Wuerttemberg) from 1993 to 2003. Chemosphere 2005;58(9):1185–1201.

249. Jackson WG, Jr., Michalek JE. Temporal changes in TCDD levels in 1419 Air Force Vietnam-era veterans not occupationally exposed to herbicides. J Expo Anal Environ Epidemiol 2001;11(1):50–55.
250. Aylward LL, Hays SM. Temporal trends in human TCDD body burden: decreases over three decades and implications for exposure levels. J Expo Anal Environ Epidemiol 2002;12(5):319–328.

251. Minh NH, Someya M, Minh TB, et al. Persistent organochlorine residues in human breast milk from Hanoi and Hochiminh City, Vietnam: contamination, accumulation kinetics and risk assessment for infants. Environ Pollut 2004;129(3):431–441.

252. Revich B, Aksel E, Ushakova T, et al. Dioxin exposure and public health in Chapaevsk, Russia. Chemosphere 2001;43(4-7):951–966.

253. van Larebeke N, Hens L, Schepens P, et al. The Belgian PCB and dioxin incident of January-June 1999: exposure data and potential impact on health. Environ Health Perspect 2001;109(3):265–273.

254. Fürst P, Fürst C, Wilmers K. Human milk as a bioindicator for body burden of PCDDs, PCDFs, organochlorine pesticides and PCBs. Environ Health Perspect 1994;102 Suppl 1:187–193.

255. van Leeuwen FX, Malisch R. Results of the third round of the WHO-coordinated exposure study on the levels of PCBs, PCDDs and PCDFs in human milk. Organohalogens Compd 2002;56:311–316.

256. Karmaus W, DeKoning EP, Kruse H, Witten J, Osius N. Early childhood determinants of organochlorine concentrations in school-aged children. Pediatr Res 2001;50(3):331–336.

257. Walkowiak J, Wiener JA, Fastabend A, et al. Environmental exposure to polychlorinated biphenyls and quality of the home environment: effects on psychodevelopment in early childhood. Lancet 2001;358(9293):1602–1607.

258. Lanting CI, Fidler V, Huisman M, Boersma ER. Determinants of polychlorinated biphenyl levels in plasma from 42-month-old children. Arch Environ Contam Toxicol 1998;35(1):135–139.

259. Ayotte P, Muckle G, Jacobson JL, Jacobson SW, Dewailly É. Assessment of pre- and postnatal exposure to polychlorinated biphenyls: lessons from the Inuit Cohort Study. Environ Health Perspect 2003;111(9):1253–1258.

260. CDC (Centers for Disease Control and Prevention), Department of Health and Human Services. Second National Report on Human Exposure to Environmental Chemicals. Atlanta, GA: National Center for Environmental Health, Division of Laboratory Sciences; 2003.

261. Pereg D, Dewailly É, Poirier GG, Ayotte P. Environmental exposure to polychlorinated biphenyls and placental CYP1A1 activity in Inuit women from northern Québec. Environ Health Perspect 2002;110(6):607–612.

262. Jacobson JL, Fein GG, Jacobson SW, Schwartz PM, Dowler JK. The transfer of polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs) across the human placenta and into maternal milk. Am J Public Health 1984;74(4):378,379.

263. Koopman-Esseboom C, Weisglas-Kuperus N, de Ridder MA, Van der Pauw CG, Tuinstra LG, Sauer PJ. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. Pediatrics 1996;97(5):700–706.

264. Lackmann GM, Angerer J, Salzberger U, Töllner U. Influence of maternal age and duration of pregnancy on serum concentrations of polychlorinated biphenyls and hexachlorobenzene in full-term neonates. Biol Neonate 1999;76(4):214–219.

265. Foster W, Chan S, Platt L, Hughes C. Detection of endocrine disrupting chemicals in samples of second trimester human amniotic fluid. J Clin Endocrinol Metab 2000;85(8):2954–2957.

266. Dahl P, Lindström G, Wiberg K, Rappe C. Absorption of polychlorinated biphenyls, dibenzo-p-dioxins and dibenzofurans by breast-fed infants. Chemosphere 1995;30(12):2297–2306.

267. Abraham K, Hille A, Ende M, Helge H. Intake and fecal excretion of PCDDs, PCDFs, HCB and PCBs (138, 153, 180) in a breast-fed and a formula-fed infant. Chemosphere 1994;29(9–11):2279–2286.

268. Abraham K, Knoll A, Ende M, Päpke O, Helge H. Intake, fecal excretion, and body burden of polychlorinated dibenzo-p-dioxins and dibenzofurans in breast-fed and formula-fed infants. Pediatr Res 1996;40(5):671–679.

269. Garner CE, Matthews HB. The effect of chlorine substitution on the dermal absorption of polychlorinated biphenyls. Toxicol Appl Pharmacol 1998;149(2):150–158.

270. Mayes BA, Brown GL, Mondello FJ, Holtzclaw KW, Hamilton SB, Ramsey AA. Dermal absorption in rhesus monkeys of polychlorinated biphenyls from soil contaminated with Aroclor 1260. Regul Toxicol Pharmacol 2002;35(3):289–295.

271. Qiao GL, Riviere JE. Enhanced systemic tissue distribution after dermal versus intravenous 3,3’,4,4’-tetrachlorobiphenyl exposure: limited utility of radiolabel blood area under the curve and excretion data in dermal absorption calculations and tissue exposure assessment. Toxicol Appl Pharmacol 2001;177(1):26–37.

272. Matthews HB, Anderson MW. The distribution and excretion of 2,4,5,2’,5’-pentachlorobiphenyl in the rat. Drug Metab Dispos 1975;3(3):211–219.

273. Leung HW, Paustenbach DJ, Murray FJ, Andersen ME. A physiological pharmacokinetic description of the tissue distribution and enzyme-inducing properties of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. Toxicol Appl Pharmacol 1990;103(3):399–410.

274. Carrier G, Brunet RC, Brodeur J. Modeling of the toxicokinetics of polychlorinated dibenzo-p-dioxins and dibenzofurans in mammalians, including humans. I. Nonlinear distribution of PCDD/PCDF body burden between liver and adipose tissues. Toxicol Appl Pharmacol 1995;131(2):253–266.

Clinical Reviews in Allergy & Immunology Volume 31, 2006
Clinical Reviews in Allergy & Immunology Volume 31, 2006

275. Bergman A, Klasson-Wehler E, Kuroki H. Selective retention of hydroxylated PCB metabolites in blood. Environ Health Perspect 1994;102(5):464–469.

276. Brouwer A, Longnecker MP, Birnbaum LS, et al. Characterization of potential endocrine-related health effects at low-dose levels of exposure to PCBs. Environ Health Perspect 1999;107(Suppl 4):639–649.

277. Hovander L, Malmberg T, Athanasiadou M, et al. Identification of hydroxylated PCB metabolites and other phenolic halogenated pollutants in human blood plasma. Arch Environ Contam Toxicol 2002;42(1):105–117.

278. Fängström B, Athanasiadou M, Grandjean P, Weihe P, Bergman A. Hydroxylated PCB metabolites and PCBs in serum from pregnant Faroese women. Environ Health Perspect 2002;110(9):895–899.

279. Sandau CD, Ayotte P, Dewailly É, Duffe J, Norstrom RJ. Pentachlorophenol and hydroxylated polychlorinated biphenyl metabolites in umbilical cord plasma of neonates from coastal populations in Quebec. Environ Health Perspect 2002;110(4):411–417.

280. Sandau CD, Ayotte P, Dewailly É, Duffe J, Norstrom RJ. Analysis of hydroxylated metabolites of PCBs (OH-PCBs) and other chlorinated phenolic compounds in whole blood from Canadian Inuit. Environ Health Perspect 2000;108(7):611–616.

281. Phillips DL, Smith AB, Burse VW, Steele GK, Needham LL, Hannon WH. Half-life of polychlorinated biphenyls in occupationally exposed workers. Arch Environ Health 1989;44(6):351–354.

282. Flesch-Janys D, Becher H, Gurn P, et al. Elimination of polychlorinated dibenzo-p-dioxins and dibenzofurans in occupationally exposed persons. J Toxicol Environ Health 1996;47(4):363–378.

283. Michalek JE, Tripathi RC. Pharmacokinetics of TCDD in veterans of Operation Ranch Hand: 15-year follow-up. J Toxicol Environ Health A 1999;57(6):369–378.

284. Longnecker MP, Ragan WJ, Lucier G. The human health effects of DDT (dichlorodiphenyltrichloroethane) and PCBs (polychlorinated biphenyls) and an overview of organochlorines in public health. Annu Rev Public Health 1997;18:211–244.

285. Wolff MS, Zeleniuch-Jacquotte A, Dubin N, Tontiolo P. Risk of breast cancer and organochlorine exposure. Cancer Epidemiol Biomarkers Prev 2000;9(3):271–277.

286. van der Molen GW, Kooijman SA, Michalek JE, Slob W. The estimation of elimination rates of persistent compounds: a re-analysis of 2,3,7,8-tetrachlorodibenzo-p-dioxin levels in Vietnam veterans. Chemosphere 1998;37(9-12):1833–1844.

287. Michalek JE, Pirkle JL, Needham LL, et al. Pharmacokinetics of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Seveso adults and veterans of operation Ranch Hand. J Expo Anal Environ Epidemiol 2002;12(1):44–53.

288. Masuda Y. Fate of PCDF/PCB congeners and change of clinical symptoms in patients with Yusho PCB poisoning for 30 years. Chemosphere 2001;43(4-7):925–930.

289. Carrier G, Brunet RC, Brodeur J. Modeling of the toxicokinetics of polychlorinated dibenzo-p-dioxins and dibenzofurans in mammalian, including humans. II. Kinetics of absorption and disposition of PCDDs/PCDFs. Toxicol Appl Pharmacol 1995;131(2):267–276.

290. Minh TB, Watanabe M, Tanabe S, Yamada T, Hata J, Watanabe S. Specific accumulation and elimination kinetics of tris(4-chlorophenyl)methane, tris(4-chlorophenyl)methanol, and other persistent organochlorines in humans from Japan. Environ Health Perspect 2001;109(9):927–935.

291. Abraham K, Pärké O, Gross A, et al. Time course of PCDD/PCDF/PCB concentrations in breastfeeding mothers and their infants. Chemosphere 1998;37(9-12):1731–1741.

292. Rogan WJ, Gladen BC, McKinney JD, et al. Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: effects of maternal factors and previous lactation. Am J Public Health 1986;76(2):172–177.

293. Hauser R, Chen Z, Pothier L, Ryan L, Altshul L. The relationship between human semen parameters and environmental exposure to polychlorinated biphenyls and p,p’-DDE. Environ Health Perspect 2003;111(12):1505–1511.

294. Longnecker MP, Ryan JJ, Gladen BC, Schecter AJ. Correlations among human plasma levels of dioxin-like compounds and polychlorinated biphenyls (PCBs) and implications for epidemiologic studies. Arch Environ Health 2000;55(3):195–200.

295. Gladen BC, Longnecker MP, Schecter AJ. Correlations among polychlorinated biphenyls, dioxins, and furans in humans. Am J Ind Med 1999;35(1):15–20.

296. Ayotte P, Dewailly É, Ryan JJ, Bruneau S, Lebel G. PCBs and dioxin-like compounds in plasma of adult Inuit living in Nunavik (Arctic Quebec). Chemosphere 1997;34(5–7):1459–1468.

297. Koopman-Esseboom C, Huisman M, Weisglas-Kuperus N, et al. PCB and dioxin levels in plasma of 418 Dutch women and their infants. Predictive value of PCB congener levels in maternal plasma for fetal and infant’s exposure to PCBs and dichlorodiphenyl dichloroethanes (DDT). Chemosphere 1999;38(5–7):1459–1468.

298. Steuerwald U, Weihe P, Jorgensen PJ, et al. Maternal seafood diet, methylmercury exposure, and neonatal neurologic function. J Pediatr 2000;136(5):599–605.
300. International Agency for Research on Cancer (IARC). IARC monographs on the Evaluation of Carcinogenic Risks to Humans. Polychlorinated dibenzo-furans. World Health Organization, Lyon 1997; http://www-cie.iarc.fr/htdocs/monographs/ vol69/dibfuran.html. Last accessed on April 24, 2006.

301. International Agency for Research on Cancer (IARC). IARC monographs on the Evaluation of Carcinogenic Risks to Humans. Polychlorinated dibenzo-para-dioxins. World Health Organization, Lyon 1997; http://www-cie.iarc.fr/htdocs/monographs/ vol69/dibfuran.html. Last accessed on April 24, 2006.

302. Snedeker SM. Pesticides and breast cancer risk: a review of DDT, DDE, and dieldrin. Environ Health Perspect 2001;109 (Suppl 1):35–47.

303. Pesatori AC, Zocchetti C, Guercilena S, Consonni D, Turrini D, Bertazzi PA. Dioxin exposure and non-neoplastic health effects: a mortality study. Occup Environ Med 1998;55(2):126–131.

304. Flesch-Janys D, Berger J, Gurn P, et al. Exposure to polychlorinated dioxins and furans (PCDD/F) and mortality in a cohort of workers from a herbicide-producing plant in Hamburg, Federal Republic of Germany. Am J Epidemiol 1995;142(11):1165–1175.

305. Vena J, Boffetta P, Becher H, et al. Exposure to dioxin and nonneoplastic mortality in the expanded IARC international cohort study of phenoxyherbicide and chlorophenol production workers and sprayers. Environ Health Perspect 1998;106 (Suppl 2):645–653.

306. Henriksen GL, Ketchum NS, Michalek JE, Swaby JA. Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand. Epidemiology 1997; 8(3):252–258.

307. Longnecker MP, Michalek JE. Serum dioxin level in relation to diabetes mellitus among Air Force veterans with background levels of exposure. Epidemiology 2000;11(1):44–48.

308. Michalek JE, Ketchum NS, Tripathi RC. Diabetes mellitus and 2,3,7,8-tetrachlorodibenzo-p-dioxin elimination in veterans of Operation Ranch Hand. J Toxicol Environ Health A 2003;66(3):211–221.

309. Bertazzi PA, Consonni D, Bachetti S, et al. Health effects of dioxin exposure: a 20-year mortality study. Am J Epidemiol 2001;153(11):1031–1044.

310. Steenland K, Flocielli L, Deddens J, Fingerhut M, Chang LI. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzop-p-dioxin. J Natl Cancer Inst 1999;91(9):779–786.

311. Longnecker MP, Klebanoff MA, Brock JW, Zhou H. Polychlorinated biphenyl serum levels in pregnant subjects with diabetes. Diabetes Care 2001;24(6):1099–1101.

312. Longnecker MP, Klebanoff MA, Zhou H, Brock JW. Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth. Lancet 2001;358(9276):110–114.

313. Weisskopf MG, Anderson HA, Hanrahan LP, et al. Maternal exposure to Great Lakes sport-caught fish and dichlorodiphenyl dichloroethylene, but not polychlorinated biphenyls, is associated with reduced birth weight. Environ Res 2005;97(2):149–162.

314. Rogan WJ, Gladen BC, McKinney JD, et al. Neonatal effects of transplacental exposure to PCBs and DDE. J Pediatr 1986;109(2):335–341.

315. Berkowitz GS, Lapinski RH, Wolff MS. The role of DDE and polychlorinated biphenyl levels in preterm birth. Arch Environ Contam Toxicol 1996;30(1):139–141.

316. Rogan WJ. PCBs and cola-colored babies: Japan, 1968, and Taiwan, 1979. Teratology 1982;26:259–261.

317. Rogan WJ, Gladen BC, Hung KL, et al. Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. Science 1988;241(4863):334–336.

318. Patandin S, Koopman-Esseboom C, de Ridder MA, Weisglas-Kuperus N, Sauer PJ. Effects of environmental exposure to polychlorinated biphenyls and dioxins on birth size and growth in Dutch children. Pediatr Res 1998;44(4):538–545.

319. Grandjean P, Bjerve KS, Weihe P, Steuerwald U. Birthweight in a fishing community: significance of essential fatty acids and marine food contaminants. Int J Epidemiol 2001;30(6):1272–1278.

320. Gladen BC, Shkirya-Nyshnyk ZA, Chyslavskova N, Zadorozhnaia TD, Little RE. Persistent organochlorine compounds and birth weight. Ann Epidemiol 2003;13(3):151–157.

321. Vartiainen T, Jaakkola JJ, Saarikoski S, Tuomisto J. Birth weight and sex of children and the correlation to the body burden of PCDDs/PCDFs and PCBs of the mother. Environ Health Perspect 1998;106(2):61–66.

322. Eskenazi B, Mocarelli P, Warner M, et al. Maternal serum dioxin levels and birth outcomes in women of Seveso, Italy. Environ Health Perspect 2003;111(7):947–953.

323. Mocarelli P, Brambilla P, Gerthoux PM, Patterson DG, Jr., Needham LL. Change in sex ratio with exposure to dioxin. Lancet 1996;348(9024):409.

324. Mocarelli P, Gerthoux PM, Ferrari E, et al. Paternal dioxin and nonneoplastic mortality in a cohort of workers from a herbicide-producing plant in Hamburg, Federal Republic of Germany. Am J Epidemiol 1995;142(11):1165–1175.

325. Ryan JJ, Amirova Z, Carrier G. Sex ratios of children of Russian pesticide producers exposed to dioxin. Environ Health Perspect 2003;111(7):947–953.

326. Yoshimura T, Kaneko S, Hayabuchi H. Sex ratio in offspring of those affected by dioxin and dioxin-like compounds: the Yusho, Seveso, and Yucheng incidents. Occup Environ Med 2001;58(8):540, 541.

327. Rogan WJ, Gladen BC, Guo YL, Hsu CC. Sex ratio after exposure to dioxin-like chemicals in Taiwan. Lancet 1999;353(9148):206, 207.

328. Michalek JE, Rahe AJ, Boyle CA. Paternal dioxin and the sex of children fathered by veterans of Operation Ranch Hand. Epidemiology 1999;9(4):474, 475.
329. Chen YC, Guo YL, Hsu CC, Rogan WJ. Cognitive development of Yu-Cheng (‘Oil Disease’) children prenatally exposed to heat-degraded PCBs. Jama 1992;268(22):3123–3128.

330. Longnecker MP, Wolff MS, Gladen BC, et al. Comparison of polychlorinated biphenyl levels across studies of human neurodevelopment. Environ Health Perspect 2003;111(1):65–70.

331. Jacobson JL, Jacobson SW. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N Engl J Med 1996;335(11):783–789.

332. Patandin S, Lanting CI, Mulder PG, Boersma ER, Sauer PJ, Weisglas-Kuperus N. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. J Pediatr 1999;134(1):33–41.

333. Jacobson SW, Fein GG, Jacobson JL, Schwartz PM, Dowler JK. The effect of intrauterine PCB exposure on visual recognition memory. Child Dev 1985;56(4):853–860.

334. Darvill T, Lonky E, Reihman J, Stewart P, Pagano J. Prenatal exposure to PCBs and infant performance on the Fagan test of infant intelligence. Neurotoxicology 2000;21(6):1029–1038.

335. Rogan WJ, Gladen BC. PCBs, DDE, and child development at 18 and 24 months. Ann Epidemiol 1991;1(5):407–413.

336. Jacobson JL, Jacobson SW, Humphrey HE. Effects of exposure to PCBs and related compounds on growth and activity in children. Neurotoxicol Teratol 1990;12(4):319–326.

337. Jacobson JL, Jacobson SW, Humphrey HE. Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. J Pediatr 1990;116(1):38–45.

338. Lonky E, Reihman J, Darvill T, Mather JS, Daly H. Neonatal Behavioral Assessment Scale performance in humans influenced by maternal consumption of environmentally contaminated Lake Ontario fish. J Great Lakes Res 1996;22(2):198–212.

339. Stewart PW, Reihman J, Lonky EJ, Darvill TJ, Pagano J. Prenatal PCB exposure and neonatal behavioral assessment scale (NBAS) performance. Neurotoxicol Teratol 2000;22(1):21–29.

340. Stewart PW, Reihman J, Lonky EJ, Darvill TJ, Pagano J. Cognitive development in preschool children prenatally exposed to PCBs and MeHg. Neurotoxicol Teratol 2003;25(1):11–22.

341. Gladen BC, Rogan WJ. Effects of perinatal polychlorinated biphenyls and dichlorodiphenyl dichloroethene on later development. J Pediatr 1991;119(1 (Pt 1)):58–63.

342. Vreugdenhil HJ, Lanting CI, Mulder PG, Boersma ER, Weisglas-Kuperus N. Effects of prenatal PCB and dioxin background exposure on cognitive and motor abilities in Dutch children at school age. J Pediatr 2002;140(1):48–56.

343. Huisman M, Koopman-Desbeoom C, Fidler V, et al. Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development. Early Hum Dev 1995;41(2):111–127.

344. Huisman M, Koopman-Desbeoom C, Lanting CI, et al. Neurological condition in 18-month-old children perinatally exposed to polychlorinated biphenyls and dioxins. Early Hum Dev 1995;43(2):165–176.

345. Pluim HJ, van der Goot M, Olie K, van der Slikke JW, Koppe JG. Missing effects of background dioxin exposure on development of breast-fed infants during the first half year of life. Chemosphere 1996;33(7):1307–1315.

346. Ilsern A, Briët JM, Koppe JG, Pluim HJ, Oosting J. Signs of enhanced neuromotor maturation in children due to perinatal load with background levels of dioxins. Follow-up until age 2 years and 7 months. Chemosphere 1996;33(7):1317–1326.

347. Koopman-Desbeoom C, Huisman M, Touwen BC, et al. Newborn infants diagnosed as neurologically abnormal with relation to PCB and dioxin exposure and their thyroid-hormone status. Dev Med Child Neurol 1997;39(11):785.

348. Pluim HJ, van der Goot M, Olie K, van der Slikke JW, Koppe JG. Missing effects of background dioxin exposure on development of breast-fed infants during the first half year of life. Chemosphere 1996;33(7):1307–1315.

349. Pluim HJ, van der Goot M, Olie K, van der Slikke JW, Koppe JG. Missing effects of background dioxin exposure on development of breast-fed infants during the first half year of life. Chemosphere 1996;33(7):1307–1315.

350. Pluim HJ, de Vijlder JJ, Olie K, et al. Effects of pre- and postnatal exposure to chlorinated dioxins and furans on human neonatal thyroid hormone concentrations. Environ Health Perspect 1993;101(6):504–508.

351. Pluim HJ, Koppe JG, Olie K, et al. Effects of dioxins on thyroid function in newborn babies. Lancet 1992;339(8804):1303.

352. Grandjean P, Weihe P, Burse VW, et al. Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxics. Neurotoxicol Teratol 2001;23(4):305–317.

353. Longnecker MP, Gladen BC, Patterson DG, Jr., Rogan WJ. Polychlorinated biphenyl (PCB) exposure in relation to thyroid hormone levels in neonates. Epidemiology 2000;11(3):249–254.

354. Koopman-Desbeoom C, Morse DC, Weisglas-Kuperus N, et al. Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. Pediatr Res 1994;36(4):468–473.

355. Murai K, Okamura K, Tsuji H, et al. Thyroid function in “yusho” patients exposed to polychlorinated biphenyls (PCB). Environ Res 1987;44(2):179–187.

356. Spengler JD, Koutrakis P, Dockery DW, Raizenne M, Speizer FE. Health effects of acid aerosols on
North American children: air pollution exposures. Environ Health Perspect 1996;104(5):492–499.

357. Abt E, Suh HH, Allen G, Koutrakis P. Characterization of indoor particle sources: A study conducted in the metropolitan Boston area. Environ Health Perspect 2000;108(1):35–44.

358. Sørensen M, Loft S, Andersen HV, et al. Personal exposure to PM_{2.5}, black smoke and NO in Copenhagen: relationship to bedroom and outdoor concentrations covering seasonal variation. J Expo Anal Environ Epidemiol 2005;15:1–10.

359. Abt E, Suh HH, Allen G, Koutrakis P. Characterization of indoor particle sources: A study conducted in the metropolitan Boston area. Environ Health Perspect 2000;108(1):35–44.

360. Sydbom A, Blomberg A, Parnia S, Stenfors N, Sandström T, Dahlén SE. Health effects of diesel exhaust emissions. Eur Respir J 2001;17(4):733–746.

361. Koutrakis P, Briggs SLK, Leaderer BP. Source apportionment of indoor aerosols in Suffolk and Onondaga counties, New York. Environ Sci Technol 1992;26:521–527.

362. Götschi T, Oglesby L, Mathys P, et al. Comparison of black smoke and PM_{2.5} levels in indoor and outdoor environments of four European cities. Environ Sci Technol 2002;36(6):1191–1197.

363. Allen R, Larson T, Sheppard L, Wallace L, Liu L-JS. Use of real-time light scattering data to estimate the contribution of infiltrated and indoor-generated particles to indoor air. Environ Sci Technol 2003;37(16):3484–3492.

364. Cyrys J, Pitz M, Bischof W, Wichmann HE, Heinrich J. Relationship between indoor and outdoor levels of fine particle mass, particle number concentrations and black smoke under different ventilation conditions. J Expo Anal Environ Epidemiol 2004;14:275–283.

365. Meng QY, Turpin BJ, Korn L, et al. Influence of ambient (outdoor) sources on residential indoor and personal PM_{2.5} concentrations: analyses of RIOPA data. J Expo Anal Environ Epidemiol 2005;15(1):17–28.

366. Ozkaynak H, Xue J, Spengler J, Wallace L, Pellizzari E, Jenkins P. Personal exposure to airborne particles and metals: results from the Particle TEAM study in Riverside, California. J Expo Anal Environ Epidemiol 1996;6(1):57–78.

367. Thatcher TL, Layton DW. Deposition, resuspension, and penetration of particles within a residence. Atmospheric Environ 1999;29(13):1487–1497.

368. Long CM, Suh HH, Catalano PJ, Koutrakis P. Using time- and size-resolved particulate data to quantify indoor penetration and deposition behavior. Environ Sci Technol 2001;35(10):2089–2099.

369. Pellizzari ED, Clayton CA, Rodes CE, et al. Particulate matter and manganese exposures in Toronto, Canada. Atmospheric Environ 1999;33:721–734.

370. Brauer M, Hirtle R, Lang B, Ott W. Assessment of indoor fine aerosol contributions from environmental tobacco smoke and cooking with a portable nephelometer. J Expo Anal Environ Epidemiol 2000;10(2):136–144.

371. Koistinen KJ, Hänninen O, Rotko T, Edwards RD, Moschandreas D, Jantunen MJ. Behavioral and environmental determinants of personal exposures to PM_{2.5} in EXPOLIS - Helsinki, Finland. Atmospheric Environ 2001;35:2473–2481.

372. Keeler GJ, Dvonch T, Yip FY, et al. Assessment of personal and community-level exposures to particulate matter among children with asthma in Detroit, Michigan, as part of Community Action Against Asthma (CAAA). Environ Health Perspect 2002;110 (Suppl 2):173–181.

373. Lai HK, Kendall M, Ferrier H, et al. Personal exposures and microenvironment concentrations of PM_{2.5}, VOC, NO_{x} and CO in Oxford, UK. Atmospheric Environ 2004;38:6399–6410.

374. Kamens R, Lee C-T, Wiener R, Leith D. A study to characterize indoor particles in three non-smoking homes. Atmospheric Environ A 1991;25A(5/6):939–948.

375. Long CM, Suh HH, Koutrakis P. Characterization of indoor particle sources using continuous mass and size monitors. J Air Waste Manag Assoc 2000;50(7):1236–1250.

376. Brauer M, Hirtle RD, Hall AC, Yip TR. Monitoring personal fine particle exposure with a particle counter. J Expo Anal Environ Epidemiol 1999;9:228–236.

377. Howard-Reed C, Rea AW, Zufall MJ, et al. Use of a continuous nephelometer to measure personal exposure to particles during the U.S. Environmental Protection Agency Baltimore and Fresno Panel studies. J Air Waste Manag Assoc 2000;50(7):1125–1132.

378. Rea AW, Zufall MJ, Williams RW, Sheldon L, Howard-Reed C. The influence of human activity patterns on personal PM exposure: a comparative analysis of filter-based and continuous particle measurements. J Air Waste Manag Assoc 2001;51(9):1271–1279.

379. Levy JJ, Houseman EA, Ryan L, Richardson D. Students from the 1998 Summer Program in Biostatistics, Spengler JD. Particle concentrations in urban microenvironments. Environ Health Perspect 2000;108(11):1051–1057.

380. Janssen NA, Hoek G, Brunekreef B, Harssema H, Mensink I, Zuidhof A. Personal sampling of particulate matter and manganese exposures in Toronto, Canada. Atmospheric Environ 1999;33:721–734.
390. Daigle CC, Chalupa DC, Gibb FR, et al. Exposure of chronic obstructive pulmonary disease patients to particulate matter: relationships between personal and ambient air concentrations. J Air Waste Manag Assoc 2000;50(7):1081–1094.

391. Kim CS, Jaques PA. Total lung deposition of ultrafine particles in healthy adults. Phil Trans R Soc Lond A 2000;358:2693–2705.

392. Wilson FJ, Jr., Hiller FC, Wilson JD, Bone RC. Quantitative deposition of ultrafine stable particles in human lungs for susceptible populations in Seattle. Environ Health Perspect 2003;111(7):909–918.

393. Kim CS, Hu SC, DeWitt P, Gerrity TR. Assessment of regional deposition of inhaled particles in human lungs by serial bolus delivery method. J Appl Physiol 1996;81(5):2203–2213.

394. Kim CS, LaQuey PA. Respiratory dose of inhaled ultrafine particles in healthy adults. Phil Trans R Soc Lond A 2000;358:2693–2705.

395. Pinkerton KE, Green FH, Saiki C, et al. Distribution of particulate matter and tissue remodeling in the human lung. Environ Health Perspect 2000;108(11):1063–1069.

396. Nemmar A, Heat PH, Vanquickenborne B, et al. Passage of inhaled particles into the blood circulation in humans. Circulation 2002;105(4):411–414.

397. Kim CS, Lewars GA, Sackner MA. Measurement of total lung aerosol deposition as an index of lung abnormality. J Appl Physiol 1988;64(4):1527–1536.

398. Kim CS, Jaques PA. Analysis of total respiratory deposition of inhaled ultrafine particles in adult subjects at various breathing patterns. Aerosol Sci Technol 2004;38:525–540.

399. Kim CS, Kang TC. Comparative measurement of lung deposition of inhaled fine particles in normal subjects and patients with obstructive airway disease. Am J Respir Crit Care Med 1997;155(3):899–905.

400. Brown JS, Zeman KL, Bennett WD. Ultrafine particle deposition and clearance in the healthy and obstructed lung. Am J Respir Crit Care Med 2002;166(9):1240–1247.

401. Churg A, Brauer M. Human lung parenchyma retains PM2.5. Am J Respir Crit Care Med 1997;155(6):2109–2111.

402. Brauer M, Avila-Casado C, Fortoul TI, Vedal S, Stevens B, Churg A. Air pollution and retained particles in the lung. Environ Health Perspect 2001;109(10):1039–1043.

403. Churg A, Brauer M, del Carmen Avila-Casado M, Fortoul TI, Wright JL. Chronic exposure to high levels of particulate air pollution and small airway remodeling. Environ Health Perspect 2003;111(5):714–718.

404. Souza MB, Saldiva PH, Pope CA, 3rd, Capelozzi VL. Respiratory changes due to long-term exposure to urban levels of air pollution: a histopathologic study in humans. Chest 1998;113(5):1312–1318.

405. Brook RD, Franklin B, Casco W, et al. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation 2004;109(21):2655–2671.

406. Pope CA, 3rd. Epidemiology of fine particulate air pollution and human health: biologic mechanisms and who’s at risk? Environ Health Perspect 2000;108(Suppl 4):713–723.

407. Health effects of outdoor air pollution. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. Am J Respir Crit Care Med 1996;153(1):3–50.

408. Clancy L, Goodman P, Sinclair H, Dockery DW. Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study. Lancet 2002;360(9341):1210–1214.

409. Dockery DW, Pope CA, 3rd, Xu X, et al. An association between air pollution and mortality in six U.S. cities. N Engl J Med 1993;329(24):1753–1759.
410. Pope CA, 3rd, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 2002;287(9):1132–1141.

411. Schwartz J, Dockery DW, Neas LM. Is daily mortality associated specifically with fine particles? J Air Waste Manag Assoc 1996;46(10):927–939.

412. Atkinson RW, Anderson HR, Sunyer J, et al. Acute effects of particulate air pollution on respiratory admissions: results from APHEA 2 project. Air Pollution and Health: a European Approach. Am J Respir Crit Care Med 2001;164(10 Pt 1):1860–1866.

413. Samet JM, Schwartz J, Catalano PJ, Suh HH. Gaseous pollutants in particulate matter epidemiology: confounders or surrogates? Environ Health Perspect 2001;109(10):1053–1061.

414. Peng RD, Dominici F, Pastor-Barriuso R, Zeger SL, Samet JM, Dominici F, Pastor-Barriuso R, Zeger SL, Samet JM. Seasonal analyses of air pollution and mortality in 100 U.S. cities. Johns Hopkins University, Department of Biostatistics Working Papers 2004;Paper 41.

415. Pope CA, 3rd, Burnett RT, Thun MJ, et al. Particulate air pollution and mortality in 20 U.S. cities, 1987-1994. N Engl J Med 2000;343(24):1742–1749.

416. Levy JI, Hammitt JK, Spengler JD. Estimating the mortality impacts of particulate matter: what can be learned from between-study variability? Environ Health Perspect 2000;108(2):109–117.

417. Zanobetti A, Schwartz J, Samoli E, et al. The temporal pattern of respiratory and heart disease mortality in response to air pollution. Environ Health Perspect 2003;111(9):1188–1193.

418. Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. N Engl J Med 2000;343(24):1742–1749.

419. Zanobetti A, Schwartz J, Samoli E, et al. Temporal patterns of respiratory and mortality in response to air pollution. Environ Health Perspect 2003;111(9):1188–1193.

420. Pope CA, 3rd, Burnett RT, Thun MJ, et al. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 1995;151(3 Pt 1):669–674.

421. Levy JI, Hammitt JK, Spengler JD. Estimating the mortality impacts of particulate matter: what can be learned from between-study variability? Environ Health Perspect 2000;108(2):109–117.

422. Abbey DE, Nishino N, McDonnell WF, et al. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am J Respir Crit Care Med 1999;159(2):373–382.

423. Krewski D, Burnett RT, Goldberg M, et al. Reanalysis of the Harvard Six Cities Study, part I: validation and replication. Inhal Toxicol 2005;17(7–8):335–342.

424. Zeger SL, Dominici F, Samet J. Harvesting-resistant estimates of air pollution effects on mortality. Epidemiology 1999;10(2):171–175.

425. Schwartz J. Harvesting and long term exposure effects in the relation between air pollution and mortality. Am J Epidemiol 2000;151(5):440–448.

426. Cohen AJ, Ross Anderson H, Ostro B, et al. The global burden of disease due to outdoor air pollution. J Toxicol Environ Health A 2005;68(13-14):1301–1307.

427. Peters A, Dockery DW, Muller JE, Mittleman MA. Increased particulate air pollution and the triggering of myocardial infarction. Circulation 2001;103(23):2810–2815.

428. Janssen NA, Schwartz J, Zanobetti A, Suh HH. Air conditioning and source-specific particles as modifiers of the effect of PM10 on hospital admissions for heart and lung disease. Environ Health Perspect 2002;110(1):43–49.

429. Atkinson RW, Anderson HR, Strachan DP, Bland JM, Brenner SA, Ponce de Leon A. Short-term associations between outdoor air pollution and visits to accident and emergency departments in London for respiratory complaints. Eur Respir J 1999;13(2):257–265.

430. Norris G, YoungPong SN, Koenig QJ, Larson TV, Sheppard L, Stout JW. An association between fine particles and asthma emergency department visits for children in Seattle. Environ Health Perspect 1999;107(6):489–493.

431. Sinclair AH, Toltsd M. Associations and lags between air pollution and acute respiratory visits in an ambulatory care setting: 25-month results from the aerosol research and inhalation epidemiological study. J Air Waste Manag Assoc 2004;54(9):1212–1218.

432. Künzli N, Jerrett M, Mack WJ, et al. Ambient air pollution and atherosclerosis in Los Angeles. Environ Health Perspect 2005;113(2):201–206.

433. Horak F, Jr., Studnicka M, Gartner C, et al. Particulate matter and lung function growth in southern California children: results from a second cohort. Am J Respir Crit Care Med 1999;159(2):373–382.

434. Bobak M, Stafoggia M, La Montagna W, et al. Association between air pollution and lung function growth in southern California children: results from a second cohort. Am J Respir Crit Care Med 2002;166(1):76–84.

435. Jwedychowski W, Flak E, Mróz E. The adverse effect of low levels of ambient air pollutants on lung function growth in preadolescent children. Environ Health Perspect 1999;107(8):669–674.

436. Raizenne M, Neas LM, Damokosh AI, et al. Health effects of acid aerosols on North American children: pulmonary function. Environ Health Perspect 1996;104(5):506–514.
438. Abbey DE, Burchette RJ, Knutsen SF, McDonnell WF, Lebowitz MD, Enright PL. Long-term particulate and other air pollutants and lung function in nonsmokers. Am J Respir Crit Care Med 1998; 158(1):289–298.

439. Ackermann-Liebrich U, Leuenberger P, Schwartz J, et al. Lung function and long-term exposure to air pollutants in Switzerland. Am J Respir Crit Care Med 1997;155:122–129.

440. Abbey DE, Ostro BE, Petersen F, Burchette RJ. Chronic respiratory symptoms associated with estimated long-term ambient concentrations of fine particulates less than 2.5 microns in aerodynamic diameter (PM2.5) and other air pollutants. J Expo Anal Environ Epidemiol 1995;5(2):137–159.

441. Zemp E, Elsasser S, Schindler C, et al. Long-term ambient air pollution and respiratory symptoms in adults (SAPALDIA study). Am J Respir Crit Care Med 1999;159:1257–1266.

442. Neas LM, Dockery DW, Koutrakis P, Speizer FE. Fine particles and peak flow in children: acidity versus mass. Epidemiology 1999;10(5):550–553.

443. Schwartz J, Neas L. Fine particles are more strongly associated than coarse particles with acute respiratory health effects in schoolchildren. Epidemiology 2000;11(1):6–10.

444. Fischer PH, Steerenberg PA, Snelder JD, van Loveren H, van Amsterdam JG. Association between exhaled nitric oxide, ambient air pollution and respiratory health in school children. Int Arch Occup Environ Health 2002;75(5):348–353.

445. Timonen KL, Pekkanen J. Air pollution and respiratory health among children with asthma or cough symptoms. Am J Respir Crit Care Med 1999;159(6):1227–1266.

446. Roemer W, Clench-Aas J, Englert N, et al. Inhomogeneity in response to air pollution in European children (PEACE project). Occup Environ Med 1999;56(2):86–92.

447. Lewis TC, Robins TG, Dvonch JT, et al. Air pollution-associated changes in lung function among asthmatic children in Detroit. Environ Health Perspect 2003;111(4):647–656.

448. Lewis TC, Robins TG, Dvonch JT, et al. Air pollution-associated changes in lung function among asthmatic children in Detroit. Environ Health Perspect 2003;111(4):647–656.

449. Timonen KL, Pekkanen J, Ruuskanen J, Reponen A, Mirme A. Effects of ultrafine and fine particles in urban air on peak expiratory flow among children with asthmatic symptoms. Environ Res 1997;74(1):24–33.

450. Steerenberg PA, Nierkens S, Fischer PH, et al. Traffic-related air pollution affects peak expiratory flow, exhaled nitric oxide, and inflammatory nasal markers. Arch Environ Health 2001;56(2):167–174.

451. Gielen MH, van der Zee SC, van Wijnen JH, van Steen CJ, Brunekreef B. Acute effects of summer air pollution on respiratory health of asthmatic children. Am J Respir Crit Care Med 1997;155(6):2105–2108.

452. Steerenberg PA, Nierkens S, Fischer PH, et al. Traffic-related air pollution affects peak expiratory flow, exhaled nitric oxide, and inflammatory nasal markers. Arch Environ Health 2001;56(2):167–174.
Airborne Environmental Injuries and Human Health

477. Koenig JQ, Mar TF, Allen RW, et al. Pulmonary effects of indoor- and outdoor-generated particles in children with asthma. Environ Health Perspect 2005;113(4):499–503.

478. Gent JF, Triche EW, Holford TR, et al. Association of low-level ozone and fine particles with respiratory symptoms in children with asthma. Jama 2003;290(14):1859–1867.

479. Tiittanen P, Timonen KL, Ruuskanen J, Mirme A, Pekkanen J. Fine particulate air pollution, resuspended road dust and respiratory health among symptomatic children. Eur Respir J 1999;13(2):266–273.

480. Silverman F, Hosein HR, Corey P, Holton S, Tarlo SM. Effects of particulate matter exposure and medication use on asthma. Arch Environ Health 1992;47(1):51–56.

481. Seaton A, MacNee W, Donaldson K, Godden D. Particulate air pollution and acute health effects. Lancet 1995;345(8937):176–178.

482. Gilmour PS, Ziesenis A, Morrison ER, et al. Pulmonary and systemic effects of short-term inhalation exposure to ultrafine carbon black particles. Toxicol Appl Pharmacol 2004;195:35–44.

483. Oberdörster G, Ferin J, Gelein R, Soderholm SC, Finkelstein J. Role of the alveolar macrophage in lung injury: studies with ultrafine particles. Environ Health Perspect 1992;97:193–199.

484. Saldiva PH, Clarke RW, Coull BA, et al. Lung inflammation induced by concentrated ambient air particles is related to particle composition. Am J Respir Crit Care Med 2002;165(12):1610–1617.

485. Xia T, Korge P, Weiss JN, et al. Quinones and aromatic chemical compounds in particulate matter induce mitochondrial dysfunction: implications for ultrafine particle toxicity. Environ Health Perspect 2004;112(14):1347–1358.

486. Carter JD, Ghio AJ, Samet JM, Devlin RB. Cytokine production by human airway epithelial cells after exposure to an air pollution particle is metal-dependent. Toxicol Appl Pharmacol 1997;146:180–188.

487. Molinelli AR, Madden MC, McGee JK, Stonehuerner JG, Ghio AJ. Effect of metal removal on the toxicity of airborne particulate matter from the Utah Valley. Inhal Toxicol 2002;14(10):1069–1086.

488. Campen MJ, Nolan JP, Schladweiler MC, et al. Cardiovascular and thermoregulatory effects of inhaled PM-associated transition metals: a potential interaction between nickel and vanadium sulfate. Toxicol Sci 2001;64(2):243–252.

489. Costa DL, Dreher KL. Bioavailable transition metals in particulate matter mediate cardiopulmonary injury in healthy and compromised animal models. Environ Health Perspect 1997;105 (Suppl 5): A188.

490. Dreher K, Jaskot R, Kodavanti U, Lehmann J, Winsett D, Costa D. Soluble transition metals mediate the acute pulmonary injury and airway hyperreactivity induced by residual oil fly ash particles. Chest 1996;109(Suppl 5): 335S, 343S.
96. Borchers et al.

491. Peters A, Wichmann HE, Tuch T, Heinrich J, Heyder J. Respiratory effects are associated with the number of ultrafine particles. Am J Respir Crit Care Med 1997;155(4):1376–1383.

492. de Hartog JJ, Hoek G, Peters A, et al. Effects of fine and ultrafine particles on cardiorespiratory symptoms in elderly subjects with coronary heart disease: the ULTRA study. Am J Epidemiol 2003;157(7):613–623.

493. Pekkanen J, Peters A, Hoek G, et al. Particulate air pollution and risk of ST-segment depression during repeated submaximal exercise tests among subjects with coronary heart disease: the Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study. Circulation 2002;106(8):933–938.

494. Ghio AJ, Kim C, Devlin RB. Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. Am J Respir Crit Care Med 2000;162(3 Pt 1):981–988.

495. Harder SD, Soukup JM, Ghio AJ, Devlin RB, Becker S. Inhalation of PM_{2.5} does not modulate host defense or immune parameters in blood or lung of normal human subjects. Environ Health Perspect 2001;109 (Suppl 4):599–604.

496. Gong H, Jr., Linn WS, Sioutas C, et al. Controlled exposures of healthy and asthmatic volunteers to concentrated ambient fine particles in Los Angeles. Inhal Toxicol 2003;15(4):305–325.

497. Rudell B, Ledin MC, Hammarström U, Stjernberg N, Lundbäck B, Sandström T. Effects on symptoms and lung function in humans experimentally exposed to diesel exhaust. Occup Environ Med 1996;53(10):658–662.

498. Salvi S, Blomberg A, Rudell B, et al. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. Am J Respir Crit Care Med 1999;159(3):702–709.

499. Rudell B, Wass U, Hörstedt P, et al. Efficiency of automotive cabin air filters to reduce acute health effects of diesel exhaust in human subjects. Occup Environ Med 1999;56(4):222–231.

500. Nightingale JA, Maggs R, Cullinan P, et al. Airway inflammation after controlled exposure to diesel exhaust particulates. Am J Respir Crit Care Med 2000;162(1):161–166.

501. Rudell B, Blomberg A, Helleday R, et al. Bronchoalveolar inflammation after exposure to diesel exhaust: comparison between unfiltered and particle trap filtered exhaust. Occup Environ Med 1999;56(8):527–534.

502. Schwartz J. Air pollution and blood markers of cardiovascular risk. Environ Health Perspect 2001;109 Suppl 3:405–409.

503. Pope CA, 3rd, Hansen ML, Long RW, et al. Ambient particulate air pollution, heart rate variability, and blood markers of inflammation in a panel of elderly subjects. Environ Health Perspect 2004;112(3):339–345.

504. Sørensen M, Daneshvar B, Hansen M, et al. Personal PM_{2.5} exposure and markers of oxidative stress in blood. Environ Health Perspect 2003;111(2):161–166.

505. Riediker M, Cascio WE, Griggs TR, et al. Particulate matter exposure in cars is associated with cardiovascular effects in healthy young men. Am J Respir Crit Care Med 2004;169(8):934–940.

506. Seaton A, Soutar A, Crawford V, et al. Particulate air pollution and the blood. Thorax 1999;54(11):1027–1032.

507. Peters A, Fröhlich M, Döring A, et al. Particulate air pollution is associated with an acute phase response in men; results from the MONICA-Augsburg Study. Eur Heart J 2001;22(14):1198–1204.

508. Pekkanen J, Brunner EJ, Anderson HR, Tiittanen P, Atkinson RW. Daily concentrations of air pollution and plasma fibrinogen in London. Occup Environ Med 2000;57(12):818–822.

509. Liao D, Heiss G, Chinchilli VM, et al. Association of criteria pollutants with plasma hemostatic/inflammatory markers: a population-based study. J Expo Anal Environ Epidemiol 2005;15:319–328.

510. Peters A, Döring A, Wichmann HE, Koenig W. Increased plasma viscosity during an air pollution episode: a link to mortality? Lancet 1997;349(9065):1582–1587.

511. Liao D, Duan Y, Whitsett EA, et al. Association of higher levels of ambient criteria pollutants with impaired cardiac autonomic control: a population-based study. Am J Epidemiol 2004;159(8):768–777.

512. Park SK, O’Neill MS, Vokonas PS, Sparrow D, Schwartz J. Effects of air pollution on heart rate variability: the VA normative aging study. Environ Health Perspect 2005;113(3):304–309.

513. Pope CA, 3rd, Verrier RL, Lovett EG, et al. Heart rate variability associated with particulate air pollution. Am Heart J 1999;138(5 Pt 1):890–899.

514. Gold DR, Litonjua A, Schwartz J, et al. Ambient pollution and heart rate variability. Circulation 2000;101(11):1267–1273.

515. Chan CC, Chuang KJ, Shiao GM, Lin LY. Personal exposure to submicrometer particles and heart rate variability in human subjects, Environ Health Perspect 2004;112(10):1063–1067.

516. Liao D, Creason J, Shy C, Williams R, Watts R, Zweidinger R. Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. Environ Health Perspect 1999;107(7):521–525.

517. Holguin F, Téllez-Rojo MM, Hernández M, et al. Air pollution and heart rate variability among the elderly in Mexico City. Epidemiology 2003;14(5):521–527.

518. Creason J, Neas L, Walsh D, et al. Particulate matter and heart rate variability among elderly retirees: the
Baltimore 1998 PM study. J Expo Anal Environ Epidemiol 2001;11:116–122.

519. Brauer M, Ebel ST, Fisher TV, Brumm J, Petkau AJ, Vedal S. Exposure of chronic obstructive pulmonary disease patients to particles: respiratory and cardiovascular health effects. J Expo Anal Environ Epidemiol 2001;11(6):490–500.

520. Sullivan JH, Schreuder AB, Trenga CA, et al. Association between short term exposure to fine particulate matter and heart rate variability in older subjects with and without heart disease. Thorax 2005;60(6):462–466.

521. Vallejo M, Ruiz S, Hermosillo AG, Borja-Aburto VH, Cárdenas M. Ambient fine particles modify heart rate variability in young healthy adults. J Expo Anal Environ Epidemiol 2005;15:1–6.

522. Magari SR, Hauser R, Schwartz J, Williams PL, Smith TJ, Christiani DC. Association of heart rate variability with occupational and environmental exposure to particulate air pollution. Circulation 2001;104(9):986–991.

523. Magari SR, Schwartz J, Williams PL, Hauser R, Smith TJ, Christiani DC. The association between personal measurements of environmental exposure to particulates and heart rate variability. Epidemiology 2002;13(3):305–310.

524. Riediker M, Devlin RB, Griggs TR, et al. Cardiovascular effects in patrol officers are associated with fine particulate matter from brake wear and engine emissions. Part Fibre Toxicol 2004;1(1):2.

525. Devlin RB, Ghio AJ, Kehrl H, Sanders G, Cascio W. Elderly humans exposed to concentrated air pollution particles have decreased heart rate variability. Eur Respir J Suppl 2003;40:76s–80s.

526. Ebel ST, Wilson WE, Brauer M. Exposure to ambient and nonambient components of particulate matter: a comparison of health effects. Epidemiology 2005;16(3):396–405.

527. Peters A, Perz S, Döring A, Stieber J, Koenig W, Wichmann HE. Increases in heart rate during an air pollution episode. Am J Epidemiol 1999;150(10):1094–1098.

528. Dockery DW, Pope CA, 3rd, Kanner RE, Martin Villegas G, Schwartz J. Daily changes in oxygen saturation and pulse rate associated with particulate air pollution and barometric pressure. Res Rep Health Eff Inst 1999(83):1–19; discussion 21–28.

529. Laden F, Neas LM, Dockery DW, Schwartz J. Association of fine particulate matter from different sources with daily mortality in six U.S. cities. Environ Health Perspect 2000;108(10):941–947.

530. Janssen NA, Brunekreef B, van Vliet P, et al. The relationship between air pollution from heavy traffic and allergic sensitization, bronchial hyperresponsiveness, and respiratory symptoms in Dutch schoolchildren. Environ Health Perspect 2003;111(12):1512–1518.

531. Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. Lancet 2002;360(9341):1203–1209.

532. Bremer SA, Anderson HR, Atkinson RW, et al. Short-term associations between outdoor air pollution and mortality in London 1992-4. Occup Environ Med 1999;56(4):237–244.

533. Schwartz J, Litonjua A, Suh H, et al. Traffic related pollution and heart rate variability in a panel of elderly subjects. Thorax 2005;60(6):455–461.

534. Huang YC, Ghio AJ, Stonehauer J, et al. The role of soluble components in ambient fine particles-induced changes in human lungs and blood. Inhal Toxicol 2003;15(4):327–342.

535. Gavett SH, Madison SL, Dreher KL, Winsett DW, McGee JK, Costa DL. Metal and sulfate composition of residual oil fly ash determines airway hyperreactivity and lung injury in rats. Environ Res 1997;72(2):162–172.

536. Koistinen KJ, Edwards RD, Mathys P, Ruuskainen J, Künzli N, Jantunen MJ. Sources of fine particulate matter in personal exposures and residential indoor, residual outdoor and workplace microenvironments in the Helsinki phase of the EXPOLIS study. Scand J Work Environ Health 2004;30 Suppl 2:36–46.

537. Conner TL, Norris GA, Landis MS, Williams RW. Individual particle analysis of indoor, outdoor, and community samples from the 1998 Baltimore particulate matter study. Atmospher Environ 2001;35:3935–3946.

538. Reff A, Turpin BJ, Porcja RJ, et al. Functional group characterization of indoor, outdoor, and personal PM_{2.5} results from RIOPA. Indoor Air 2005;15(1):53–61.

539. Long CM, Suh HH, Kobzik L, Catalano PJ, Ning YY, Koutrakis P. A pilot investigation of the relative toxicity of indoor and outdoor fine particles: in vitro effects of endotoxin and other particulate properties. Environ Health Perspect 2001;109(10):1019–1026.

540. Glick TH, Gregg MB, Berman B, Mallison G, Rhodes WW, Jr., Kassanoiff I. Pontiac fever. An epidemic of unknown etiology in a health department: I. Clinical and epidemiologic aspects. Am J Epidemiol 1978;107(2):149–160.

541. Arroyo JC, Postic B, Brown A, Harrison K, Birgenheier R, Dowda H. Influenza A/Philippines/2/82 outbreak in a nursing home: limitations of influenza vaccination in the aged. Am J Infect Control 1984;12(6):329–334.

542. Goodman RA, Orenstein WA, Munro TF, Smith SC, Sikes RK. Impact of influenza A in a nursing home. Jama 1982;247(10):1451–1453.

543. Gross PA, Rodstein M, LaMontagne JR, et al. Epidemiology of acute respiratory illness during an
influenza outbreak in a nursing home. A prospective study. Arch Intern Med 1988;148(3):559–561.
544. Horman JT, Stetler HC, Israel E, Sorley D, Schipper MT, Joseph JM. An outbreak of influenza A in a nursing home. Am J Public Health 1986;76(5):501–504.
545. Wong TW, Lee CK, Tam W, et al. Cluster of SARS among medical students exposed to single patient, Hong Kong. Emerg Infect Dis 2004;10(2):269–276.
546. Yu IT, Sung JJ. The epidemiology of the outbreak of severe acute respiratory syndrome (SARS) in Hong Kong—what we do know and what we don’t. Epidemiol Infect 2004;132(5):781–786.
547. Shelton BG, Kirkland KH, Flanders WD, Morris GK. Profiles of airborne fungi in buildings and outdoor environments in the United States. Appl Environ Microbiol 2002;68(4):1743–1753.
548. Kolstad HA, Brauer C, Iversen M, Sigsgaard T, Mikkelsen S. Do indoor molds in nonindustrial environments threaten workers’ health? A review of the epidemiologic evidence. Epidemiol Rev 2002;24(2):203–217.
549. Lee T, Grinshpun SA, Martuzevicius D, et al. Relationship between indoor and outdoor bioaerosols collected with a button inhalable aerosol sampler in urban homes. Indoor Air 2006;16(1):37–47.
550. Ebbehøj NE, Meyer HW, Würtz H, et al. Molds in floor dust, building-related symptoms, and lung function among male and female schoolteachers. Indoor Air 2005;15 Suppl 10:7–16.
551. Nilsson A, Kihlström E, Lagesson V, et al. Microorganisms and volatile organic compounds in airborne dust from damp residences. Indoor Air 2004;14(2):74–82.
552. Toivola M, Alm S, Reponen T, Kolari S, Nevalainen M, Dales RE. A comparison of airborne ergosterol, glucan and Air-O-Cell data in relation to physical parameters. Indoor Air 2005;15(4):257–266.
553. Chew GL, Douwes J, Doekes G, et al. Fungal extracellular polysaccharides, β(1→3)-glucans and cultural fungi in repeated sampling of house dust. Indoor Air 2001;11(3):171–178.
554. Douwes J, van der Sluis B, Doekes G, et al. Fungal extracellular polysaccharides in house dust as a marker for exposure to fungi: relations with cultural fungi, reported home dampness, and respiratory symptoms. J Allergy Clin Immunol 1999;103(3 Pt 1):494–500.
555. Foto M, Vrijmoed LL, Miller JD, Ruest K, Lawton M, Dales RE. A comparison of airborne ergosterol, glucan and Air-O-Cell data in relation to physical assessments of mold damage and some other parameters. Indoor Air 2005;15(4):257–266.
556. Vojdani A, Thrasher JD, Madison RA, Gray MR, Heuser G, Campbell AW. Antibodies to molds and satratoxin in individuals exposed in water-damaged buildings. Arch Environ Health 2003;58(7):421–432.
557. Johanning E, Biagini R, Hull D, Morey P, Jarvis B, Landsbergis P. Health and immunology study following exposure to toxigenic fungi (Stachybotrys chartarum) in a water-damaged office environment. Int Arch Occup Environ Health 1996;68(4):207–218.
558. Johanning E, Landsbergis P, Gareis M, Yang CS, Olmsted E. Clinical experience and results of a Sentinel Health Investigation related to indoor fungal exposure. Environ Health Perspect 1999;107 Suppl 3:489–494.
559. Bornehag CG, Sundell J, Bonini S, et al. Dampness in buildings as a risk factor for health effects, EUROEXPO: a multidisciplinary review of the literature (1998-2000) on dampness and mite exposure in buildings and health effects. Indoor Air 2004;14(4):243–257.
560. Bornehag CG, Blomquist G, Gyntelberg F, et al. Dampness in buildings and health. Nordic interdisciplinary review of the scientific evidence on associations between exposure to ‘dampness’ and health effects, NORDDAMP. Indoor Air 2001;11:72–86.
561. Engvall K, Norrby C, Norbäck D. Sick building syndrome in relation to building dampness in multifamily residential buildings in Stockholm. Int Arch Occup Environ Health 2001;74(4):270–278.
562. Park JH, Schleiff PL, Attfield MD, Cox-Ganser JM, Kreiss K. Building-related respiratory symptoms can be predicted with semi-quantitative indices of exposure to dampness and mold. Indoor Air 2004;14(6):425–433.
563. Bornehag CG, Sundell J, Hagerhed-Engman L, Sigsgaard T, Janson S, Aberg N. ‘Dampness’ at home and its association with airway, nose, and skin symptoms among 10,851 preschool children in Sweden: a cross-sectional study. Indoor Air 2005;15 Suppl 10:48–55.
564. Meyer HW, Jensen KA, Nielsen KF, et al. Double blind placebo controlled exposure to molds: exposure system and clinical results. Indoor Air 2005;15 Suppl 10:73–80.
565. Meyer HW, Würtz H, Suadicani P, Valbjørn O, Sigsgaard T, Gyntelberg F. Molds in floor dust and building-related symptoms among adolescent school children: a problem for boys only? Indoor Air 2005;15 Suppl 10:17–24.
566. Chao HJ, Schwartz J, Milton DK, Burge HA. The work environment and workers’ health in four large office buildings. Environ Health Perspect 2003;111(9):1242–1248.
567. Menzies D, Comtois P, Pasztor J, Nunes F, Hanley JA. Aeroallergens and work-related respiratory symptoms among office workers. J Allergy Clin Immunol 1998;101(1 Pt 1):38–44.
568. Cooley JD, Wong WC, Jumper CA, Straus DC. Correlation between the prevalence of certain fungi

Clinical Reviews in Allergy & Immunology Volume 31, 2006
and sick building syndrome. Occup Environ Med 1998;55(9):579–584.
569. McGrath JJ, Wong WC, Cooley JD, Straus DC. Continuously measured fungal profiles in sick building syndrome. Curr Microbiol 1999;38(1):33–36.
568. Meklin T, Potus T, Pekkanen J, Hyvärinen A, Hirvonen MR, Nevalainen A. Effects of moisture-damage repairs on microbial exposure and symptoms in schoolchildren. Indoor Air 2005;15 Suppl 10:40–47.
567. Ebbehøj NE, Hansen MØ, Sigsgaard T, Larsen L. Building-related symptoms and molds: a two-step intervention study. Indoor Air 2002;12(4):273–277.
566. Naftstad P, Øie L, Mehl R, et al. Residential dampness problems and symptoms and signs of bronchial obstruction in young Norwegian children. Am J Respir Crit Care Med 1998;157(2):410–414.
565. Wickman M, Melên E, Berglind N, et al. Strategies for preventing wheezing and asthma in small children. Allergy 2003;58(8):742–747.
564. Jaakkola JJ, Hwang BF, Jaakkola N. Home dampness and molds, parental atopy, and asthma in childhood: a six-year population-based cohort study. Environ Health Perspect 2005;113(3):357–361.
563. Belanger K, Beckett W, Triche E, et al. Symptoms of wheeze and persistent cough in the first year of life: associations with indoor allergens, air contaminants, and maternal history of asthma. Am J Epidemiol 2003;158(3):195–202.
562. Gent JF, Ren P, Belanger K, et al. Levels of household mold associated with respiratory symptoms in the first year of life in a cohort at risk for asthma. Environ Health Perspect 2002;110(12):A781–A786.
561. Stark PC, Burge HA, Ryan LM, Milton DK, Gold DR. Fungal levels in the home and lower respiratory tract illnesses in the first year of life. Am J Respir Crit Care Med 2003;168(2):232–237.
560. Neas LM, Dockery DW, Burge H, Koutrakis P, Speizer FE. Fungus spores, air pollutants, and other determinants of peak expiratory flow rate in children. Am J Epidemiol 1996;143(8):797–807.
559. Higgins BG, Francis HC, Yates C, et al. Environmental exposure to air pollution and allergens and peak flow changes. Eur Respir J 2000;16(1):61–66.
558. Delfino RJ, Coate BD, Zeiger RS, Seltzer JM, Street DH, Koutrakis P. Daily asthma severity in relation to personal ozone exposure and outdoor fungal spores. Am J Respir Crit Care Med 1996;154(3 Pt 1):633–41.
557. Dales RE, Cakmak S, Burnett RT, Judek S, Coates F, Brook JR. Influence of ambient fungal spores on emergency visits for asthma to a regional children’s hospital. Am J Respir Crit Care Med 2000;162(6):2087–2090.
556. Lierl MB, Hornung RW. Relationship of outdoor air quality to pediatric asthma exacerbations. Ann Allergy Asthma Immunol 2003;90(1):28–33.
555. Targonski PV, Persky VW, Ramekrishnan V. Effect of environmental molds on risk of death from asthma during the pollen season. J Allergy Clin Immunol 1995;95(5 Pt 1):955–961.
554. Perzanowski MS, Sporik R, Squillace SP, et al. Association of sensitization to Alternaria allergens with asthma among school-age children. J Allergy Clin Immunol 1998;101(5):626–632.
553. Chin, S, Burney P, Sunyer J, Jarvis D, Lutchynska C. Sensitization to individual allergens and bronchial responsiveness in the ECRHS. European Community Respiratory Health Survey. Eur Respir J 1999;14(4):876–884.
552. Lopez M, Voigtlander JR, Lehrer SB, Salvaggio JE. Bronchoprovocation studies in basidiospore-sensitive allergic subjects with asthma. J Allergy Clin Immunol 1989;84(2):242–246.
551. Licorich K, Novey HS, Kozak P, Fairshter RD, Wilson AF. Role of Alternaria and Penicillium spores in the pathogenesis of asthma. J Allergy Clin Immunol 1985;76(6):819–825.
550. Douwes J, (1→3)-β-D-glucans and respiratory health: a review of the scientific evidence. Indoor Air 2005;15(3):160–169.
549. Instanes C, Ormstad H, Rydjord B, Wiker HG, Hetland G. Mould extracts increase the allergic response to ovalbumin in mice. Clin Exp Allergy 2004;34(10):1634–1641.
548. Assoulin-Daya Y, Leong A, Shoenfeld Y, Gershwin ME. Studies of sick building syndrome. IV. Mycotoxicosis. J Asthma 2002;39(3):191–201.
547. Bretz M, Knecht A, Gockler S, Humph F. Structural elucidation and analysis of thermal degradation products of the Fusarium mycotoxin nivalenol. Mol Nutr Food Res 2005;49(4):309–316.
546. Marin DE, Taranu I, Bunciu RP, et al. Changes in performance, blood parameters, humoral and cellular immune responses in weanling piglets exposed to low doses of aflatoxin. J Anim Sci 2002;80(5):1250–1257.
545. Rotter BA, Prelusky DB, Pestka JJ. Toxicology of deoxynivalenol (vomitoxin). J Toxicol Environ Health 1996;48(1):1–34.
544. Tryphonas H, Iversen F, So Y, et al. Effects of deoxynivalene (vomitoxin) on the humoral and cellular immunity of mice. Toxicol Lett 1986;30(2):137–150.
543. Kurz RS, Czuprnsky C. Effect of aflatoxin B1 on in vitro production of interleukin-1 by bovine mononuclear phagocytes. Vet Immunol Immunopathol 1992;34(1-2):149–158.
542. Lorenzana RM, Beasley VR, Buck WB, Ghent AW. Experimental T-2 toxocolisn in swine. II. Effect of intravascular T-2 toxin on serum enzymes and biochemistry, blood coagulation, and hematoloy. Fundam Appl Toxicol 1985;5(5):893–901.
541. Iversen F, Armstrong C, Nera E, et al. Chronic feeding study of deoxynivalenol in B6C3F1 male and
female mice. Teratog Carcinog Mutagen 1995; 15(6):283–306.

598. Schiefer HB, Rousseaux CG, Hancock DS, Blakley BR. Effects of low-level long-term oral exposure to T-2 toxin in CD-1 mice. Food Chem Toxicol 1987; 25(8):593–601.

599. Poapolathep A, Ohtsuka R, Kiatipattanasakul W, Ishigami N, Nakayama H, Doi K. Nivalenol—induced apoptosis in thymus, spleen and Peyer’s patches of mice. Exp Toxicol Pathol 2002;53(6): 441–446.

600. Yang GH, Jarvis BB, Chung YJ, Pestka JJ. Apoptosis induction by the satratoxins and other trichothecene mycotoxins: relationship to ERK, p38 MAPK, and SAPK/JNK activation. Toxicol Appl Pharmacol 2000;164(2):149–160.

601. Ihara T, Sugamata M, Sekijima M, Okumura H, Yoshino N, Ueno Y. Apoptotic cellular damage in mice after T-2 toxin-induced acute toxicity. Nat Toxins 1997;5(4):141–145.

602. Rao CY, Brain JD, Burge HA. Reduction of pulmonary toxicity of Stachybotrys chartarum spores by methanol extraction of mycotoxins. Appl Environ Microbiol 2000;66:2817–2821.

603. Yike I, Miller MJ, Tomashefski J, Walenga R, Dearborn DG. Infant rat model of Stachybotrys chartarum induced mycotoxicosis. Mycopathologia 2001;154:139–152.

604. Leino M, Mäkelä M, Reijula K, et al. Intranasal exposure to spores of two Stachybotrys chartarum strains. Toxicol Sci 2005;84(2):408–417.

605. Yike I, Richthoff J, Rylander L, Jönsson BA, et al. Serum levels of 2,2’,4,4’,5,5’-hexachlorobiphenyl (CB-153) in relation to markers of reproductive function in young males from the general Swedish population. Environ Health Perspect 2003;111(4):409–413.

606. Feger TA, Rupp NT, Kuhn FA, Ford JL, Dolen WK. Local and systemic eosinophil activation in allergic fungal sinusitis. Ann Allergy Asthma Immunol 1997;79(3):221–225.

607. Feger TA, Rupp NT, Kuhn FA, Ford JL, Dolen WK. Local and systemic eosinophil activation in allergic fungal sinusitis. Ann Allergy Asthma Immunol 1997;79(3):221–225.

608. Collins M, Nair S, Smith W, Kette F, Gillis D, Wormald PJ. Role of local immunoglobulin E production in the pathophysiology of noninvasive fungal sinusitis. Laryngoscope 2004;114(7):1242–1246.

609. deShazo RD, Swain RE. Diagnostic criteria for allergic fungal sinusitis. J Allergy Clin Immunol 1995; 96(1):24–35.

610. Kelce WR, Stone CR, Laws SC, Gray LE, Kemppainen JA, Wilson EM. Persistent DDT metabolite p,p’-DDE is a potent androgen receptor antagonist. Nature 1995;379(6532):581–585.

611. Meerts IA, Hoving S, van den Berg JH, et al. Effects of in utero exposure to 4-hydroxy-2,3,3’4,4’,5-pentachlorobiphenyl (4-OH-CB107) on developmental landmarks, steroid hormone levels, and female estrous cyclicity in rats. Toxicol Sci 2004;82(1):259–267.

612. Silva E, Rajapakse N, Kortenkamp A. Something from “nothing” – eight weak estrogenic chemicals combined at concentrations below NOECs produce significant mixture effects. Environ Sci Technol 2002;36(8):1751–1756.

613. Garner CE, Jefferson WN, Burka LT, Matthews HB, Newbold RR. In vitro estrogenicity of the catechol metabolites of selected polychlorinated biphenyls. Toxicol Appl Pharmacol 1999;154(2):188–197.

614. Fielden MR, Chen I, Chittim B, Safe SH, Zacharewski TR. Examination of the estrogenicity of 2,4,6,2’-pentachlorobiphenyl (PCB 104), its hydroxylated metabolite 2,4,6,2’-pentachloro-4-biphenylol (HO-PCB 104), and a further chlorinated derivative, 2,4,6,2’,4’,6’-hexachlorobiphenyl (PCB 155). Environ Health Perspect 1997;105(11):1238–1248.

615. Dallinga JW, Moonen EJ, Dumoulin JC, Evers JL, Geraedts JP, Kleinjans JC. Decreased human semen quality and organochlorine compounds in blood. Hum Reprod 2002;17(8):1973–1979.

616. Abell A, Ernst E, Bonde JP. Semen quality and sexual hormones in greenhouse workers. Scand J Work Environ Health 2000;26(6):492–500.

617. Kamijima M, Hibi H, Gotoh M, et al. A survey of semen indices in insecticide sprayers. J Occup Health 2004;46(2):109–118.

618. Hauser R, Williams P, Alshul L, Calafat AM. Evidence of interaction between polychlorinated biphenyls and phthalates in relation to human sperm motility. Environ Health Perspect 2005;113(4):425–430.

619. Payne J, Scholze M, Kortenkamp A. Mixtures of four organochlorines enhance human breast cancer cell proliferation. Environ Health Perspect 2001;109(4):391–397.

620. Rajapakse N, Silva E, Kortenkamp A. Combining xenoestrogens at levels below individual no-observed-effect concentrations dramatically enhances steroid hormone action. Environ Health Perspect 2002;110(9):917–921.

621. Rajapakse N, Silva E, Scholze M, Kortenkamp A. Deviation from additivity with estrogenic mixtures containing 4-nonylphenol and 4-tert-octylphenol detected in the E-SCREEN assay. Environ Sci Technol 2004;38(23):6343–6352.

622. Thorpe KL, Hutchinson TH, Hetheridge MJ, Scholze M, Sumpter JP, Tyler CR. Assessing the biological...
potency of binary mixtures of environmental estrogens using vitellogenin induction in juvenile rainbow trout (*Oncorhynchus mykiss*). Environ Sci Technol 2001;35(12):2476–2481.

624. Fromme H, Lahrz T, Piloty M, Gebhart H, Oddoy A, Rüden H. Occurrence of phthalates and musk fragrances in indoor air and dust from apartments and kindergartens in Berlin (Germany). Indoor Air 2004;14(3):188–195.

625. Becker K, Seiwert M, Angerer J, et al. DEHP metabolites in urine of children and DEHP in house dust. Int J Hyg Environ Health 2004;207(5):409–417.

626. Rudel RA, Camann DE, Spengler JD, Korn LR, Brody JG. Phthalates, alkylphenols, pesticides, polybrominated diphenyl ethers, and other endocrine-disrupting compounds in indoor air and dust. Environ Sci Technol 2003;37(20):4543–4553.

627. David RM. Exposure to phthalate esters. Environ Health Perspect 2000;108(10):A440.

628. Kohn MC, Parham F, Masten SA, et al. Human exposure estimates for phthalates. Environ Health Perspect 2000;108(10):A440–A442.

629. Hill RH, Jr., Head SL, Baker S, et al. Pesticide residues in urine of adults living in the United States: reference range concentrations. Environ Res 1995;71(2):99–108.

630. Koch HM, Hardt J, Angerer J. Biological monitoring of exposure of the general population to the organophosphorous pesticides chlorpyrifos and chlorpyrifos-methyl by determination of their specific metabolite 3,5,6-trichloro-2-pyridinol. Int J Hyg Environ Health 2001;204(2-3):175–180.

631. Ryan JJ, Hsu CC, Boyle MJ, Guo YL. Blood serum levels of PCDFs and PCBs in Yu-Cheng children peri-natally exposed to a toxic rice oil. Chemosphere 1994;29(6):1263–1278.

632. Bertazzi PA, Bernucci I, Brambilla G, Consonni D, Pesatori AC. The Seveso studies on early and long-term effects of dioxin exposure: a review. Environ Health Perspect 1998;106 Suppl 2:625–633.

633. Daniels JL, Longnecker MP, Klebanoff MA, et al. Prenatal exposure to low-level polychlorinated biphenyls in relation to mental and motor development at 8 months. Am J Epidemiol 2003;157(6):485–492.

634. Rodes CE, Lawless PA, Evans GF, et al. The relationships between personal PM exposures for elderly populations and indoor and outdoor concentrations for three retirement center scenarios. J Expo Anal Environ Epidemiol 2001;11:103–115.

635. Brauer M, Hruba F, Mihalikova E, et al. Personal exposure to particles in Banska Bystrica, Slovakia. J Expo Anal Environ Epidemiol 2000;10:478–487.

636. Williams R, Suggs J, Creason J, et al. The 1998 Baltimore Particulate Matter Epidemiology-Exposure Study: part 2. Personal exposure assessment associated with an elderly study population. J Expo Anal Environ Epidemiol 2000;10(6 Pt 1):533–543.

637. Georgiadis P, Stoikidou M, Topinka J, et al. Personal exposures to PM_{2.5} and polycyclic aromatic hydrocarbons and their relationship to environmental tobacco smoke at two locations in Greece. J Expo Anal Environ Epidemiol 2001;11(3):169–183.