Volatiles organic compounds and pulmonary function in the Third National Health and Nutrition Examination Survey, 1988–1994

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BACKGROUND: Volatile organic compounds (VOCs) are present in much higher concentrations indoors, where people spend most of their time, than outdoors and may have adverse health effects. VOCs have been associated with respiratory symptoms, but few studies address objective respiratory end points such as pulmonary function. Blood levels of VOCs may be more indicative of personal exposures than are air concentrations; no studies have addressed their relationship with respiratory outcomes.

OBJECTIVE: We examined whether concentrations of 11 VOCs that were commonly identified in blood from a sample of the U.S. population were associated with pulmonary function.

METHODS: We used data from 953 adult participants (20–59 years of age) in the Third National Health and Nutrition Examination Survey (1988–1994) who had VOC blood measures as well as pulmonary function measures. Linear regression models were used to evaluate the relationship between 11 VOCs and measures of pulmonary function.

RESULTS: After adjustment for smoking, only 1,4-dichlorobenzene (1,4-DCB) was associated with reduced pulmonary function. Participants in the highest decile of 1,4-DCB concentration had decrements of –153 mL [95% confidence interval (CI), –297 to –8] in forced expiratory volume in 1 sec and –346 mL/sec [95% CI, –667 to –24] in maximum mid-expiratory flow rate, compared with participants in the lowest decile.

CONCLUSIONS: Exposure to 1,4-DCB, a VOC related to the use of air fresheners, toilet bowl deodorants, and mothballs, at levels found in the U.S. general population, may result in reduced pulmonary function. This common exposure may have long-term adverse effects on respiratory health.

KEY WORDS: air fresheners, air pollution (indoor), deodorants, 1,4-dichlorobenzene, exposure, environmental exposure, FEV1, lung function, respiratory function tests, VOC. Environ Health Perspect 114:1210–1214 (2006). doi:10.1289/ehp.9019 available via http://dx.doi.org/ [Online 25 April 2006]

Volatiles organic compounds (VOCs) are a diverse group of chemicals emitted as gases from a variety of commonly used products. The general population is exposed to VOCs from cleaning and degreasing agents, pesticides, air fresheners, toilet bowl deodorants, furniture, tobacco smoke, and building materials such as pressed wood products, adhesives, carpeting, paints, and varnishes. Although VOCs are also released into the outdoor air through automotive exhaust and industrial emissions, indoor VOC concentrations are much higher (Wallace et al. 1987, 1991).

Because people spend most of their time indoors, health effects related to VOCs in the residential setting are a concern, particularly with respect to respiratory illness (Diez et al. 2000; Farrow et al. 2003; Fiedler et al. 2005; Harving et al. 1991; Koren et al. 1992; Norback et al. 1995; Pappas et al. 2000; Wieslander et al. 1997). Several studies have shown that elevated air concentrations of VOCs are associated with respiratory symptoms (Diez et al. 2000; Norback et al. 1995; Pappas et al. 2000; Rumchev et al. 2005; Smedje et al. 1997; Wieslander et al. 1997). Studies of VOC exposures and measures of pulmonary function have mostly been small and have used short-term measurements of VOC air concentrations in a single location to characterize exposures, which may not reflect the chronic exposures to these compounds (Fiedler et al. 2005; Harving et al. 1991; Norback et al. 1995; Pappas et al. 2000; Wieslander et al. 1997). Blood concentrations may better reflect chronic exposures to VOCs because they integrate exposures from all sources and can be used to estimate internal dose (Ashley and Prah 1997; Ashley et al. 1994; Sexton et al. 2005a).

A variety of VOCs were measured in a subset of participants in the Third National Health and Nutrition Examination Survey (1988–1994) (NHANES III) to determine background exposure levels for adults in the general U.S. population (Ashley et al. 1994). Because there is a paucity of information about chronic VOC exposure and pulmonary function, we examined VOC blood concentrations in relation to pulmonary function using data from NHANES III (Ashley et al. 1994).

Materials and Methods

Study population. We used data from NHANES III and its component Priority Toxicant Reference Range Study, designed to assess the levels of common pesticides and VOCs in a representative sample of the U.S. adult population. The studies were conducted from 1988 through 1994. Detailed information about NHANES III and the Priority Toxicant Reference Range Study may be found elsewhere [National Center for Health Statistics (NCHS) 1996, 2000]. Briefly, NHANES III is the seventh in a series of periodic surveys conducted by the NCHS of the Centers for Disease Control and Prevention designed to provide national estimates of the health and nutritional status of noninstitutionalized U.S. civilians ≥2 months of age. The Priority Toxicant Reference Range Study included a sample of 1,338 men and women from NHANES III, 20–59 years of age, selected on the basis of age, race, sex, and region of residence. Among these 1,338 participants, 1,018 provided an additional blood sample for measurement of VOCs and completed a questionnaire about exposure to various chemical products.

Pulmonary function. In NHANES III, spirometry was conducted according to the 1987 American Thoracic Society recommendations (NCHS 2001). The National Institute of Occupational Safety and Health (NIOSH) served as the quality control center for the results. Technicians received formal training and satisfactorily completed an NIOSH-approved course on spirometry.

Our analyses included forced expiratory volume at 1 sec (FEV1; milliliters), forced vital capacity (FVC; milliliters), peak expiratory flow rate (PEFR; milliliters per second), and maximum mid-expiratory flow rate (MMEFR; milliliters per second). We adjusted all models for race/ethnicity group (indicator variables for African American, Mexican American, and other), age (continuous), age squared (continuous), standing height (continuous), body mass index (continuous), and sex, to account for differences in pulmonary function based on these characteristics.

We included participants in analyses if they had at least two successful pulmonary function maneuvers and if their results were...
coded as reliable and reproducible. A reliable maneuver was a maximal exhalation without cough, excessive hesitation, leak, obstructed mouthpiece, variable effort, or early termination (NCHS 1996). Reproducible maneuvers were recorded for FVC and FEV1 and were defined as the largest FVC and second largest FVC within 5%, and the largest FEV1 and second largest FEV1 within 5%. Of 1,018 participants with VOC measures, 953 met our pulmonary function inclusion criteria.

**VOCs.** In the Priority Toxicant Reference Range Study, 32 VOCS were measured in blood, using purge and trap gas chromatography/mass spectrometry as previously described (Ashley et al. 1992, 1994). We analyzed the 11 VOCS with median values above the limit of detection [1,1,1-trichloroethane (1,1,1-TCE), 1,4-dichlorobenzene (1,4-DCB), 2-butanone, acetone, benzene, ethylbenzene, m,p-xylene, o-xylene, styrene, tetrachloroethene, toluene]. Of the 953 participants who had a value for at least 1 of 11 VOCS and who had acceptable pulmonary function data, sample sizes varied across VOCS (range, 513–953), because results for some VOCS were not available for all participants (NCHS 2001). Although the reasons for different sample sizes are not given in the NHANES III documentation, it is possible that some blood samples failed to meet acceptability standards or were invalid due to clotting, or that the laboratory experienced problems with instruments or quality control parameters (Sexton et al. 2005a).

**Statistical analyses.** We used ordinary least-squares regression models to evaluate the association between each VOC and each pulmonary function outcome. For samples with VOC measures below the limit of detection, a value equal to the detection limit divided by the square root of 2 was assigned (NCHS 2000). We used natural log transformations of VOC concentrations to reduce the influence of out adjustment for smoking. However, because smoking and environmental tobacco smoke are sources of VOCS and also affect pulmonary function, we then added terms for smoking status (current, quit within the previous 12 months, quit more than 12 months previously, never), number of cigarettes smoked per day (continuous), years smoked (continuous), and serum cotinine level (continuous). Smoking was a confounder for most VOCS.

We then used a change-in-estimate method to evaluate additional variables as confounders for the VOCS still related to pulmonary function after adjustment for smoking (Greenland 1989). Our cutoff criterion was a 10% change in the VOC β-coefficient in relation to pulmonary function. In this manner, we assessed the following potential confounders: socioeconomic status (education, poverty:income ratio, use of food stamps within the previous 12 months), self-reported doctor diagnosis of emphysema, use of fireplace within the previous 12 months or wood or gas stove for heating or cooking, age of the house (construction year before 1946, 1946–1973, 1974 to present), presence of furry pets at home, and occupational exposure. Occupational exposure (yes, no) was indicated by a variable denoting occupations associated with chronic obstructive pulmonary disease (COPD) in this population (Hnizdo et al. 2002). The only factor that met the criterion for confounding was self-reported doctor diagnosis of asthma, and this was included in the final models. We repeated analyses excluding people with self-reported doctor diagnosis of asthma, and the results were not changed appreciably.

**Results.** Characteristics of the study population are shown in Table 1. The mean age was 36.6 years (range, 20–59), 43.1% were female, and 26.3% were current smokers.

Table 2 shows distributions of the 11 VOCS with median values above the limit of detection [1,1,1-trichloroethane (1,1,1-TCE), 1,4-dichlorobenzene (1,4-DCB), 2-butanone, acetone, benzene, ethylbenzene, m,p-xylene, o-xylene, styrene, tetrachloroethene, toluene]. VOCS were selected if median values were above the limit of detection. VOCs not meeting inclusion criterion: current smokers 29.5 22.1 26.3

Table 1. Selected characteristics of participants in NHANES III Priority Toxicant Reference Range Study (1988–1994).

| Race/ethnicity (%) | Males (n = 542) | Females (n = 411) | Totala (n = 953) |
|--------------------|----------------|------------------|-----------------|
| Non-Hispanic white | 39.9 ± 39.1 | 38.2 ± 39.1 | 39.1 ± 39.1 |
| African American   | 32.3 ± 31.1 | 31.1 ± 30.8 | 31.8 ± 31.5 |
| Mexican American   | 25.3 ± 24.8 | 26.3 ± 25.7 | 25.7 ± 25.7 |
| Other              | 2.6 ± 2.3   | 4.4 ± 4.1   | 3.4 ± 3.0   |
| Smoking status (%) |                |                |                |
| Current smokers    | 29.5 ± 29.1 | 22.1 ± 21.6 | 26.3 ± 25.9 |
| Former smokers     | 1.3 ± 1.1   | 1.3 ± 1.2   | 1.3 ± 1.2   |
| Former smokersc    | 15.3 ± 15.0 | 9.3 ± 9.1  | 12.7 ± 12.2 |
| Never smokers      | 53.9 ± 53.9 | 67.4 ± 66.9 | 59.7 ± 59.7 |
| Potential confounders (%) | 7.0 ± 7.0 | 9.0 ± 9.0 | 7.9 ± 7.9 |
| Diagnosed asthma   | 7.0 ± 7.0   | 9.0 ± 9.0   | 7.9 ± 7.9   |
| Diagnosed emphysema | 1.1 ± 1.1   | 0.7 ± 0.7   | 0.9 ± 0.9   |
| Presence of furry pets | 34.3 ± 34.3 | 35.8 ± 35.8 | 34.9 ± 34.9 |
| Occupation with COPD risk | 31.5 ± 31.5 | 12.2 ± 12.2 | 22.3 ± 22.3 |

Table 2. Values of selected VOCS (µg/L) measured in participants in NHANES III Priority Toxicant Reference Range Study, 1988–1994, limited to participants with pulmonary function data.

| VOC | LOD | No. < LOD | No. | Median | 10th | 90th | No. | Median | 10th | 90th |
|-----|-----|-----------|-----|--------|------|------|-----|--------|------|------|
| 1,1,1-TCE | 0.09 | 513 | 122 | 292 | 0.14 | 0.08 | 0.54 | 221 | 0.13 | 0.06 | 0.41 |
| 1,4-DCB | 0.07 | 854 | 38 | 491 | 0.33 | 0.11 | 3.89 | 363 | 0.30 | 0.10 | 4.83 |
| 2-Butanone | 0.50 | 908 | 0 | 515 | 5.59 | 2.41 | 13.72 | 393 | 5.36 | 2.26 | 11.28 |
| Acetone | 200 | 852 | 0 | 479 | 1,945 | 801 | 7,187 | 373 | 7,188 | 769 | 1,109 |
| Benzene | 0.03 | 743 | 113 | 292 | 0.14 | 0.06 | 0.42 | 322 | 0.06 | 0.26 | 0.41 |
| Ethylbenzene | 0.02 | 570 | 33 | 325 | 0.07 | 0.03 | 0.22 | 245 | 0.05 | 0.02 | 0.16 |
| m,p-Xylene | 0.03 | 953 | 362 | 542 | 0.13 | 0.02 | 0.47 | 411 | 0.11 | 0.02 | 0.34 |
| o-Xylene | 0.04 | 593 | 24 | 343 | 0.11 | 0.06 | 0.21 | 250 | 0.10 | 0.06 | 0.17 |
| Styrene | 0.02 | 589 | 74 | 336 | 0.05 | 0.01 | 0.16 | 253 | 0.04 | 0.01 | 0.10 |
| Tetrachloroethene | 0.03 | 539 | 133 | 306 | 0.07 | 0.02 | 0.38 | 233 | 0.06 | 0.02 | 0.32 |
| Toluene | 0.09 | 540 | 4 | 308 | 0.33 | 0.14 | 1.32 | 232 | 0.25 | 0.13 | 0.88 |

LOD, limit of detection. 10th and 90th are percentiles.

Subjects with at least one analysis of VOC blood concentration and pulmonary function. a Former smokers who quit smoking within the previous 12 months. b Former smokers who quit smoking > 12 months previously. c Self-reported doctor's diagnosis of asthma or emphysema.
Among all participants, 1,4-DCB was inversely related to all four pulmonary function measures within each of the six subgroups. The results were strongest and statistically significant for non-Hispanic white females (FEV1, β = –266, p = 0.02) and African-American males (FEV1, β = –282, p = 0.01), although we did not find significant evidence of effect modification by race/sex combinations (multiple partial F-test, p > 0.10 for all pulmonary function outcomes).

Higher levels of 1,4-DCB were related to reduced pulmonary function in never-smokers as well as smokers (Table 4). Results for never-smokers were similar when we defined nonsmokers in a more stringent manner as having serum cotinine < 0.62 ng/mL, the 75th percentile among nonsmokers (n = 299, data not shown).

To further examine the relationship between 1,4-DCB and pulmonary function, we conducted additional analyses using urinary concentrations of 2,5-dichlorophenol (2,5-DCP), the major metabolite of 1,4-DCB (Hisinsk et al. 1997). 2,5-DCP was one of 12 pesticide metabolites measured in the urine of NHANES III participants, using capillary gas chromatography and tandem mass spectrometry (Hill et al. 1995b). Although 2,5-DCP measurements were available only on 534 of the 846 subjects included in the analysis of 1,4-DCB, the β-coefficients for both compounds were inversely related to all pulmonary function measures, and the result for FEV1 was more statistically precise. For example, the expected change in FEV1 with each increase in exposure from the 10th to 90th percentile (3.76 µg/L for 1,4-DCB and 4.67 µg/L for 2,5-DCP) was –96 mL (p = 0.03) for 1,4-DCB and –134 mL (p = 0.02) for 2,5-DCP.

To facilitate interpretation of the association between 1,4-DCB and pulmonary function that we observed in these data using logit transformation, we categorized nontransformed values of 1,4-DCB into deciles. Figure 1 shows the changes in FEV1 (milliliters) and MMEFR (milliliters per second) for each decile of 1,4-DCB exposure, compared with participants in the lowest decile. Tests for linear trend across deciles were statistically significant (FEV1, p = 0.02; MMEFR, p = 0.02). Subjects in the highest decile of exposure had FEV1 decrements of –153 mL (95% confidence interval [CI], –297 to –8) and MMEFR decrements of –346 mL/sec (95% CI, –667 to –24), compared with participants in the lowest decile.

**Discussion**

We examined the relationship between blood concentrations of 11 VOCs with median values above the limit of detection and pulmonary function outcomes in participants of NHANES III and found that 1,4-DCB was the only VOC associated with reduced pulmonary function after adjustment for smoking. Participants in the highest decile of 1,4-DCB concentration had FEV1 and MMEFR decrements of –153 mL (95% CI, –297 to –8) and
It is possible that 1,4-DCB blood concentrations may reflect exposure better than do blood concentrations of other VOCs, because air and blood concentrations are better correlated for 1,4-DCB (Sexton et al. 2005a). In the School Health Initiative: Environment, Learning, Disease (SHIELD) study, 2-day integrated personal air samples of indoor VOCs were taken immediately before taking VOC blood measurements from 143 children among 846 participants in the NHANES III (Eisner 2002). Personal air samples and VOC blood concentrations were taken four times over 2 years. VOC blood measurements from 143 children reaching statistical significance, despite the smaller sample size.

Figure 1. Changes in FEV₁ (A) and MMEFR (B) (with 95% CIs) for each decile of 1,4-DCB concentration among 846 participants in the NHANES III (1988–1994).
FEV₁ is a sentinel event for adverse health permanent effects. Thus, chronic reduction in pulmonary function can be transient and do not necessarily reflect permanent adverse health effects (ATS 2000), they generally precede permanent effects. Thus, chronic reduction in FEV₁ is a sentinel event for adverse health effects from inhaled exposures, such as air pollution (ATS 2000). In particular, FEV₁ has been identified as a risk factor in cardiovascular disease, stroke, and lung cancer, as well as an important predictor of all-cause mortality (Hole et al. 1996).

It is probable that most exposures to 1,4-DCB are chronic, rather than acute and sporadic, because 1,4-DCB is a component of household products used for prolonged periods. For example, air fresheners, toilet bowl deodorants, and mothballs are used until their emissions cease, and then they are replaced. Staff interviewers in the SHIELD study, where blood concentrations of 1,4-DCB were high, noted that many children's homes had pervasive scents of air fresheners (Sexton et al. 2005a).

Because NHANES III is a cross-sectional study, measurements of exposure and outcome were made at the same time, and it is not possible to determine if 1,4-DCB exposure preceded pulmonary function decline. A longitudinal study measuring pulmonary function and exposure to 1,4-DCB at various time points would be necessary to evaluate the temporality of this relationship. Although it is possible that people who are exposed to toilet bowl air or freshener emissions and other room deodorizers might also be exposed to cleaning products that impair pulmonary function, we had no data to address this.

The inverse association between 1,4-DCB concentration and pulmonary function may have been affected by unmeasured confounders. We assessed the influence of other factors that may be related to pulmonary function and to 1,4-DCB exposure, such as type of heating, use of wood fires, age of house, presence of furred pets, occupation, socioeconomic status, presence of environmental tobacco smoke, smoking history, and diagnosis of asthma or emphysema. Only emphysema confounded the relationship between 1,4-DCB and pulmonary function deficits. The ability to carefully adjust for smoking with several variables, including the objective measure of environmental tobacco smoke exposure, serum cotinine, was a considerable strength of our analyses.

The size and diversity of this NHANES III sample make it possible to examine the relationships between VOCs and pulmonary function in more detail than has been possible in smaller studies. Our findings suggest that 1,4-DCB exposure at levels found in the U.S. general population may result in decreases in pulmonary function. Larger and longitudinal studies would be necessary to properly evaluate the effects on respiratory symptoms and disease.

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