Measurement of Offline Exhaled Nitric Oxide in a Study of Community Exposure to Air Pollution

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As part of a large panel study in Seattle, Washington, we measured levels of exhaled nitric oxide (eNO) in children's homes and fixed-site particulate matter with aerodynamic diameters of 2.5 μm or less (PM_{2.5}) outside and inside the homes as well as personal PM_{2.5} during winter and spring sessions of 2000–2001. Nineteen subjects 6–13 years of age participated; 9 of the 19 were on inhaled corticosteroid (ICS) therapy. Exhaled breath measurements were collected offline into a Mylar balloon for up to 10 consecutive days. Mean eNO values were 19.1 (SD ± 11.4) ppb in winter sessions and 12.5 ± 6.6 ppb in spring sessions. Fixed-site PM_{2.5} mean concentrations were 10.1 ± 5.7 μg/m³ outside homes and 13.3 ± 1.4 inside homes; the personal PM_{2.5} mean was 13.4 ± 3.2 μg/m³. We used a linear mixed-effects model with random intercept and an interaction term for medications to test for within-subject–within-session associations between eNO and various PM_{2.5} values. We found a 10 μg/m³ increase in PM_{2.5} from the outdoor, indoor, personal, and central-site measurements that was associated with increases in eNO in all subjects at lag day zero. The effect was 4.3 ppb [95% confidence interval (CI), 1.4–7.29] with the outdoor monitor, 4.2 ppb [95% CI, 1.02–7.4] for the indoor monitor, 4.5 ppb [95% CI, 1.02–7.9] with the personal monitor, and 3.8 ppb [95% CI, 1.2–6.4] for the central monitors. The interaction term for medication category [ICS users vs. nonusers] was significant in all analyses. These findings suggest that eNO can be used as an assessment tool in epidemiologic studies of health effects of air pollution. Key words: airway inflammation, asthma, children, exposure assessment, inhaled corticosteroids, nitric oxide, panel study, personal exposure, PM_{2.5}. Environ Health Perspect 111:1625–1629 (2003).

doi:10.1289/ehp.6160 available via http://dx.doi.org/[Online 12 June 2003]

Epidemiologic studies report consistent adverse health effects of particulate matter (PM) air pollution in population studies (U.S. EPA 2001). However, describing the adverse health effects of fine PM exposure at the individual subject level remains a high priority. Studies designed to provide information concerning these adverse effects include panel studies with subjects followed for several days or longer, clinical exposure studies, and toxicologic studies, including controlled exposures of human subjects. Panel studies are usually designed to combine intensive personal, indoor and/or outdoor air monitoring in conjunction with measures of specific health outcomes. Recent panel studies have concentrated on subjects believed to be susceptible to air pollution, such as those with preexisting respiratory or cardiac disease. As a consequence, the health endpoints commonly measured are lung function, symptoms and medication use, arterial oxygen saturation, blood pressure, and heart rate variability. Recent results from panel studies indicate several adverse health effects associated with exposure to PM with aerodynamic diameters ≤ 2.5 μm (PM_{2.5}). In the United States, decreased heart rate variability was associated with indoor or outdoor PM_{2.5} in 26 elderly subjects in Baltimore, Maryland (Liao et al. 1999), in healthy subjects in Boston, Massachusetts (Magari et al. 2002), in elderly subjects with heart disease in Utah Valley, Utah (Pope et al. 1999), and in elderly subjects in Boston (Gold et al. 2000). Several studies have reported associations between exposure to fine particles and decrements in lung function (Dockery et al. 1989; Koenig et al. 1993) or increases in respiratory symptoms (Yu et al. 2000). Two of these studies were conducted with subjects with asthma in Seattle, Washington. In a recent asthma panel study in Alpine, California, Delfino et al. (2002) found that symptom associations with PM_{10}, nitrogen dioxide, and ozone were notably stronger in 12 asthmatics not taking anti-inflammatory medications compared with 10 subjects who did. Another study by Delfino et al. (1998) which controlled for severity by stratification, found stronger associations between asthma symptoms and both PM_{10} and ozone among seven mild asthmatic subjects not on anti-inflammatory medications compared with seven other mild asthmatic subjects who were on anti-inflammatory medications. These findings are instructive regarding the spectrum of measurements of asthma aggravation. However, few panel studies have investigated associations between exposure to PM and lung inflammation.

Nitric oxide (NO) is a ubiquitous molecule in the body and was named the molecule of the year in 1992 based on its importance in biologic systems (Culotta and Koshland 1992). NO is generated from the oxidation of L-arginine to L-citrulline by nitric oxide synthase (NOS; Redington et al. 2001). It has been shown that type II (inducible) NOS (iNOS) is the form of the enzyme up-regulated during lower airway inflammation (Gaston et al. 1994). iNOS is released by many cells in the lung (macrophages, fibroblasts, neutrophils, and epithelial cells (Lanz et al. 1999). Expression of iNOS is up-regulated by interferon γ, tumor necrosis factor α, and interleukin 1β, all cytokines known to be active in airway inflammation. These cytokines are suspected to be the source of airway NO in subjects with asthma (Yates 2001). Endogenous NO is normally present in the pulmonary airways and in exhaled breath, but it is elevated in subjects with asthma (Redington et al. 2001). In the lung, NO is involved in regulation of vasodilation, in neurotransmission, and as an agent of inflammation and cell-mediated immunity (Yates 2001).

In the clinical setting, measurements of exhaled nitric oxide (eNO) are suggested as a sensitive measurement of airway inflammation (Kharitonov and Barnes 2000; Slutsky et al. 1999) and as a diagnostic tool for identification of asthma (Jones et al. 2001). Jones et al. (2001) report that eNO is as useful as induced sputum or bronchial hyperresponsiveness testing for assessing airway inflammation. Subjects with asthma have elevated levels of eNO compared with nonasthmatic subjects (Jones et al. 2001; Silvestri et al. 2001; Yates 2001). NO plays a prominent role in oxidative stress pathways. Several exogenous factors

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We are very grateful to J. Frost and J. McMillan, Washington State Department of Ecology (Olympia, WA), for assistance with calibration of the NO₂ instrument or for the ambient NO data. We thank M. Budge for assistance in screening the subjects, and T. Hinton for assistance with subject recruitment. We thank the children and their parents for participation in the study.

This research was supported by grants R 827355 (U.S. Environmental Protection Agency (EPA)), R 827177 (U.S. EPA), and PO ES 07033 (National Institutes of Health).

The authors declare they have no conflict of interest. Received 16 December 2002; accepted 12 June 2003.
affect the levels of eNO, such as alcohol consumption, cigarette smoking (Bruce et al. 2002), sex (Tsang et al. 2001), circadian variation (Mattes et al. 2002), and asthma medication (Yates 2001), indicating that careful study design is required. Studies find that eNO does not correlate highly with spirometric measurements (Lanz et al. 1999; Nightingale et al. 1999). A recent study reported good reproducibility of eNO measurements in both healthy and asthmatic adults and children (Kharitonov et al. 2003). These authors also tested the precision of the measurements using one or two samples per session. The difference in the worst case was 0.28 ± 5.8 ppb NO.

Several studies have reported the relationship between inhaled corticosteroid (ICS) therapy in subjects with asthma and eNO values. In one study of childhood respiratory diseases including asthma, no difference in eNO values by ICS use was observed (Narang et al. 2002). However, in a recent review several studies were cited that reported higher eNO values in ICS-naïve subjects and reductions in eNO when subjects are placed on ICS therapy (Yates 2001). In a study of sequential changes in eNO in children with asthma, Beck-Ripp et al. (2002) observed that eNO values were decreased when the children were on steroid treatment. The concentrations of eNO were elevated again after washout. One study reported that montelukast added to ICS therapy further reduced eNO levels in children with asthma (Ghiro et al. 2002). Another study came to the opposite conclusion and reported a significant decrease in eNO with ICS treatment but not with montelukast alone (Kannaess et al. 2002).

As suggested above, eNO may be an important indicator of asthma aggravation in children with asthma. Mechanisms of adverse effects of air pollutants such as ozone and PM often involve oxidative stress and subsequent tissue inflammation and injury. NO appears to be involved in tissue injury (Moncada et al. 1991; Nathan 1992). Therefore, we decided to explore the association between daily changes in eNO and daily changes in fine particle levels in a panel of children with asthma in a planned exposure assessment and health effects study in Seattle. Our hypotheses were that we would observe an association between eNO and PM$_{10}$ and that the association would be modified by the use of ICS therapy.

**Materials and Methods**

The research was part of an intensive exposure assessment and health effects panel study of susceptible subpopulations in Seattle from 1999 through 2002 (Liu et al. 2003). That study was a 2-year comprehensive exposure assessment study that examined PM exposures in 108 individuals with and without chronic obstructive respiratory disease, coronary artery disease, and asthma. The health outcome measurements collected were lung function, symptoms, medication use, and exhaled NO. In this article, we report eNO results. eNO was collected only in children with asthma.

Nineteen children, 6–13 years old, were recruited from a local asthma and allergy clinic. All had physician-diagnosed asthma and were prescribed asthma medications daily or regularly. Each child in the panel was asked to participate for a 10-day monitoring session in the winter of 2000–2001 and the spring of 2001. Fourteen children participated in the eNO study during the winter heating season, and 15 children participated during spring. Ten participated in both seasons. Clinical characteristics of the children are given in Table 1. Approximately half of the children were prescribed ICS therapy. Four subjects were on other anti-inflammatory medications (three on montelukast and one on cromolyn). Two subjects were prescribed both ICS and montelukast. The remainder of the subjects were prescribed only inhaled albuterol as needed. However, our analysis was designed to test the hypothesis that ICS therapy would be associated with weaker associations between PM$_{10}$ and eNO, and our medication interaction term used only ICS medication. As mentioned above, it is not clear whether montelukast treatment affects airway eNO concentrations.

Exhaled breath measurements were collected offline daily in the children’s homes into an NO-inert and impermeable Mylar balloon for up to 10 consecutive days. Jobsis et al. (1999) found satisfactory agreement between end expiratory plateau values of NO during exhalation at 20% of vital capacity and NO values from collection by exhaling into a balloon. Samples were collected in the afternoon or early evening at the child’s residence. Children were asked to forgo food intake for 1 hr before collection of exhaled breath. Exhaled breath was collected before lung function measurements, because deep inspirations affect NO concentration (Deykin et al. 1998). The children were instructed to inhale nearly to total lung capacity and exhale through a Teflon straw with an inner diameter of 3.5 mm and length of 35 cm until the 18-inch-diameter Mylar bag was filled halfway (Jobsis et al. 1999). Reports show that exhalation through a small-diameter straw creates sufficient pressure (at least 6 cm H$_2$O) to close the epiglottis and prevent contamination of the airway NO sample by nasal NO. Although we did not measure flow directly, exhaled eNO values from individuals in our laboratory using the straw technique used in the field showed good comparison with those collected from the same subject using a manometer to verify flow rate (16.1 vs. 14 ppb in one test and 8.2 vs. 9.2 ppb in another). Children were coached to maintain an even flow rate. Deykin et al. (2002) recently published data showing that flow rate variations do not affect eNO values significantly within the range of 50–500 L/sec. Because we did not measure NO levels in the homes or scrub the inhaled air, we controlled for ambient NO by adding outdoor central-site ambient NO values for the time of eNO collection to our regression model. Further, we discarded data collected on days with high outdoor NO (> 100 ppb).

NO was measured within 24 hr of collection using a chemiluminescent nitrogen oxide (NO$_x$) monitor (model 200A; API, San Diego, CA). We tested the stability of NO in

| Table 1. Characteristics of pediatric subjects. |
|-----------------|----------|----------|-------------|----------|--------|
| Subject no., session | Age (years) | Sex | Baseline FEV$_1$(L) | Percent predicted | eNO H/SD Medication |
| 1 W,S | 10 | F | 2.49 | 100 | 10.4 | 4.0 C A |
| 2 W,S | 9 | M | 1.42 | 67 | 22.3 | 20.6 C A |
| 3 W,S | 9 | M | 1.96 | 94 | 15.7 | 4.5 C A |
| 4 W | 6 | M | 0.42 | 43 | 23.3 | 11.0 A |
| 5 W,S | 7 | M | NA | NA | 34.0 | 20.8 C A |
| 6 W | 6 | M | 0.88 | 58 | 25.8 | 11.8 A |
| 7 W,S | 10 | M | 1.86 | 92 | 16.3 | 7.1 C A |
| 8 W,S | 7 | M | 1.41 | 83 | 12.9 | 7.5 C A |
| 9 W | 11 | M | 2.00 | 79 | 14.9 | 3.9 C |
| 10 W,S | 12 | F | 2.95 | 87 | 20.3 | 11.5 A M |
| 11 W,S | 9 | M | 1.82 | 97 | 20.0 | 11.5 C A |
| 12 W | 13 | F | 3.00 | 100 | 15.1 | 3.3 A |
| 13 W,S | 6 | M | 1.34 | 83 | 25.2 | 11.5 A M |
| 14 S | 7 | M | 1.65 | 98 | 15.1 | 5.9 C A |
| 15 W,S | 10 | F | 2.13 | 78 | 9.6 | 12 C A |
| 16 S | 10 | M | 2.23 | 97 | 13.8 | 4.7 C |
| 17 S | 9 | M | 1.45 | 86 | 14.2 | 6.9 C |
| 18 S | 11 | F | 1.71 | 72 | 14.1 | 5.0 A |
| 19 S | 9 | M | 2.38 | 97 | 8.0 | 2.0 C A |

Abbreviations: A, albuterol; C, corticosteroid; Cr, cromolyn; M, montelukast; NA, not available; S, spring sessions; W, winter sessions.

*Predicted FEV$_1$. 

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PM2.5 concentrations also were monitored in the study. Central-site NO values were correlated with ambient relative humidity. The zero air was scrubbed of NO with potassium permanganate and charcoal. The sample from the balloon was fed directly into the NO analyzer through a Nafion dryer (Perma Pure, Inc., Toms River, NJ), which equilibrated the sample with ambient relative humidity.

PM2.5 measurements were taken inside and outside subjects’ residences using Harvard impactors. Our research group evaluated the performance of continuous PM monitors (nephelometers) and Harvard impactors and found that the performance of continuous PM monitors was consistent with that found by Jobsis et al. (2001). The NOi instrument was calibrated by the Washington State Department of Ecology (Olympia, WA) using a programmable multigas calibrator (AMKO, Richmond Hill, Ontario, Canada). During the eNO analysis, the sample from the balloon was 500 cc/min (±10%) for 10 minutes until eNO values stabilized (6.5–78 ppb). The zero air was scrubbed of NO with potassium permanganate and charcoal. The sample from the balloon was fed directly into the NO analyzer through a Nafion dryer (Perma Pure, Inc., Toms River, NJ), which equilibrated the sample with ambient relative humidity.

PM2.5 concentrations also were monitored continuously at three central sites (Beacon Hill, Lake Forest Park, and Kent) with tapered element oscillating microbalance (TEOM) monitors, operated by the Puget Sound Clean Air Agency. In addition, daily NO concentrations were monitored continuously at the Beacon Hill central site using a chemiluminescence monitor operated by the Washington State Department of Ecology.

We used a linear mixed-effects model with random intercept and interaction term for medication to test for within-subject association between PM2.5 and eNO. The model included terms for within-subject, within-session effects of PM2.5. Analyses were performed on the raw data, controlling for confounding variables including ambient relative humidity.

Results

During the winter, eight children had data for all 10 days of each session, two had data for 9 days, and four had data for 8 days, for a total of 130 person-days. None of the children had fewer than 8 days of valid eNO values. During the spring, three children had data for all 10 days, three for 9 days, five for 8 days, and two for 7 days, for a total of 111 person-days.

Exposure assessment. The mean PM2.5 values from the monitors outside the residence over the 10 days of study for the subjects reported here was 13.3 ± 1.4 µg/m3; the mean PM2.5 from the indoor monitors was 11.1 ± 4.9 µg/m3, and that from personal monitors was 13.4 ± 3.2 µg/m3. The mean PM2.5 average value from the three central-site monitors was 10.1 ± 5.7 µg/m3. The maximum PM2.5 values for outdoor, indoor, and personal monitors were 40.4, 36.3, and 49.4 µg/m3, respectively. During the study period, based on the time-activity diary records, the children with asthma spent an average of 66% of their time indoors at home and 21% indoors away from home (primarily at school). They spent 4.6% of their time in transit and 4.6% outdoors. The interquartile range of PM2.5 for the monitors outside the homes was 9.8 µg/m3 during the winter sessions and 5.3 µg/m3 during the spring sessions.

eNO assessment. Inhaled NO may affect concentrations of airway NO. Therefore, we included central-site NO values (supplied by the Washington State Department of Ecology) in our linear mixed-effects model. Hourly NO values from a central-site monitor were available for each day of NO collection in this study. Central-site NO values were correlated with the daily outdoor PM2.5 (r = 0.50) and with daily eNO values (r = 0.43). However, the correlation between central-site NO and daily outdoor PM2.5 was reduced substantially for NO values less than 100 ppb (r = 0.04).

Table 2. Association between eNO (ppb) and PM2.5 (µg/m3), winter and spring sessions, controlling for ambient NO and removing high outdoor NO days (> 100 ppb; n = 19).

| Monitor     | ICS nonuser (n = 10) | ICS user (n = 9) |
|-------------|----------------------|------------------|
| Change in eNO (95% CI) per 10 µg/m³ increase in PM2.5 |
| Personal    | 4.48 [1.02–7.93]     | 0.09 [−2.39 to 2.21] |
| Indoor      | 4.28 [1.38–7.17]     | 0.74 [−2.28 to 3.78] |
| Central site| 3.82 [2.22–6.43]     | 1.28 [−1.23 to 3.79] |

Discussion

In this study we found a consistent relationship between daily eNO values in children with asthma and daily PM2.5 measured at fixed sites and on subjects. As hypothesized, we found that the use of ICS therapy modified the association between eNO and PM2.5. Including ambient NO values for the hour of the home visit from a central site in our model and discarding high NO days (> 100 ppb) attenuated the magnitude but did not alter the association between PM2.5 and eNO in all analyses. Same-day outdoor, indoor, personal, and central PM2.5 levels were associated with eNO in either analysis.

At the time we collected these data, we were not using a system that scrubbed ambient NO. There is a possibility that elevated levels of inspired NO affected the levels of eNO. The levels of inspired NO are due to both indoor-generated NO as well as NO that has infiltrated from outdoors. We do not think that indoor-generated NO affected the association found here, for three reasons: a) There is no...
obvious reason why indoor NO would vary with subject’s medication use; b) although five of the homes had gas cooking stoves, which could increase indoor NO levels, there was no correlation between eNO values and the presence of a gas stove; c) because outdoor NO can potentially affect inhaled indoor NO and thus eNO, we eliminated those days with outdoor NO > 100 ppb in our analysis, and the significance of the association was unchanged (p < 0.004). At the present time, the relationships between indoor, outdoor, and personal air pollution and health outcomes are being studied vigorously by several investigators. The role of confounding variables is one concern. We present our data as a contribution to this ongoing literature.

The use of exhaled NO as a novel biomarker of adverse respiratory health effects was suggested by van Amstel et al. (2000), who had previously found an association between exhaled NO values and high levels of outdoor air pollution in the Netherlands in healthy, nonsmoking subjects (van Amsterdam et al. 1999). Ambient carbon monoxide and NO were highly correlated with the collected eNO. More recently, eNO levels were associated with exposure to PM$_{10}$, black smoke, nitrogen dioxide, and ambient NO in a panel study of children in the Netherlands (Steerenberg et al. 2001). Adamkiewicz et al. (2002) presented preliminary data showing an association between measures of air pollution and eNO values in a panel of elderly nonsmoking subjects in Steubenville, Ohio. Their analysis found a 1.46 (95% CI, 0.29–2.63) ppb increase in eNO for a mean interquartile range increase in PM$_{2.5}$. The effect found in the present study was stronger, which is not surprising because children with asthma are known to be at risk for airway inflammation.

Exhaled NO has been measured in controlled studies of air pollution exposures to 0.2 ppm ozone in healthy subjects; no significant changes in exhaled NO were found either at 6 or 24 hr after exposure (Olin et al. 2001). Newson et al. (2000) also found that eNO values did not change after exposure of subjects with mild atopic disease to 0.2 ppm ozone for 2 hr. A similar study was reported by Nightingale et al. (1999), who found no change in eNO after exposure of subjects with asthma to 0.2 ppm ozone for 2 hr, even though forced expiratory volume in 1 sec (FEV$_1$) decreased 9%. On the other hand, exposure to active cigarette smoke is associated with an increase in NO metabolites in breath condensate in current smokers (Balint et al. 2001).

Because many epidemiologic studies rely on central-site monitors for evaluations of health outcomes, there is concern about whether central-site data are representative of residences. One of the goals of our large intensive indoor/outdoor and personal PM monitoring study was to evaluate the relationship between central-site and residential PM monitors (Liu et al. 2003). Our data indicate that eNO effects estimated from central fixed-site monitors are similar to effects estimated from monitors outside and inside homes and personal monitors.

The mean eNO values in our study (19 and 12 ppb, winter and spring sessions, respectively) agree with values seen in subjects with asthma in several other studies. Beck-Ripp et al. (2002) report an average value of 14.9 ± 1.9 ppb in a group of 34 children with asthma not treated with corticosteroids. The average decreased to 7.6 ± 0.8 ppb after 4 weeks on ICS therapy. Another study of eNO found an average 15.9 ± 14.9 ppb in atopic children versus 7.6 ± 1.6 ppb in nonatopic children (Silvestri et al. 2001). However, there are reports of much higher eNO values in similar populations. For instance, Lanz et al. (1999) reported an average of 48 ± 8 ppb in a group of children with asthma before ICS treatment. These children were experiencing acute exacerbations of asthma. Because the field of eNO measurements is emerging, standard operating protocols for breath collection and analysis are still evolving, and normative population values of lung NO in subjects with or without asthma are not known with certainty.

Outdoor sources of PM$_{2.5}$ in Seattle are wood smoke from residential wood stoves, diesel exhaust particles from trucks and buses, and automotive traffic. Seattle is one of the most traffic-congested cities in the United States. One source-apportionment study evaluated speciated data from the Beacon Hill site in Seattle using positive matrix factorization (Maykut et al. Unpublished data). The authors estimated the major sources contributing to PM$_{2.5}$ in Seattle to be vegetative burning (35%), mobile sources (22%), and sulfate (20%), with road dust, nitrate, and marine aerosol making up the balance. The present study found consistent associations between PM$_{2.5}$ and eNO from children studied during both winter and spring; there was no significant

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**Figure 1.** Relationships between eNO and PM$_{2.5}$ from the monitor outside the home for each of the 19 children in the study (1–19). Ten of the children participated in both the winter (W) and spring (S) sessions. Table 1 gives characteristics of the individual children.
season effect. However, PM$_{2.5}$ values were considerably higher during winter (inter quartile range = 9.8 g/m$^3$ in winter vs. 5.3 g/m$^3$ in spring). Winter is the time of year when fine particles from wood stoves predominate.

Interestingly, personal exposure as well as outdoor exposure to PM was associated with eNO. Very few data address health effects in studies reporting personal exposure values. Personal monitor values are affected by both outdoor and indoor sources. The children in this study spent approximately 93% of their time indoors. The associations between eNO values and personal PM$_{2.5}$ are biologically plausible. A large number of studies document indoor sources of environmental agents that can aggravate asthma (e.g., Carter et al., 2001; Eggleston and Bush 2000; Shapiro et al. 1999).

These sources include cat dander, environmental tobacco smoke, molds, and dust mites. Homes with smokers were excluded from our panel study, but the other indoor asthma triggers are ubiquitous. Along with these asthma triggers, personal exposures include PM from many personal activities such as cooking or vacuuming, as well as vehicle exhaust because of close proximity to these sources.

We conclude that these data suggest ambient PM$_{2.5}$ exposure in Seattle is associated with an increase in eNO in children with asthma. Because eNO is a marker of airway inflammation, and PM has been shown to cause inflammation in animal studies, our result is biologically plausible. This finding also agrees with previous asthma research in Seattle that showed associations between PM$_{2.5}$ and lung function decrements in children (Koenig et al., 1993), visits to emergency departments for asthma (Norriss et al., 1999), hospitalizations for asthma (Sheppard et al., 2000), and increases in asthma symptoms in children (Yu et al., 2000). Finally, we suggest that collection of eNO in a field-panel study can be used to assess the effects of ambient air pollution. These findings confirm that eNO may be an effective, noninvasive tool for epidemiological studies of health effects of air pollution.

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