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Dear Requestor:

The comment period for public review of the *External Review Draft of Air Quality Criteria for Oxides of Nitrogen* has been extended. The revised deadline for submitting comments on the document is March 30, 1992. Because of your specified interest in the document, we have enclosed a copy of the paper, *Synthesis of Environmental Evidence: Nitrogen Dioxide Epidemiology Studies*, authored by Vic Hasselblad, Dennis J. Kotchmar, and David M. Eddy. The paper presents the information and analysis contained in Chapter 14 of the document, Epidemiology Studies of Oxides of Nitrogen. The paper has been accepted for publication by the Journal of the Air and Waste Management Association.

Sincerely yours,

Lester D. Grant

Lester D. Grant, Ph.D.
Director, Environmental Criteria and Assessment Office

Enclosure

EPA/600/8-91/049A
Journal Supplement

Synthesis of Environmental Evidence: Nitrogen Dioxide Epidemiology Studies

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Practical Implications—
"Synthesis of Environmental Evidence: Nitrogen Dioxide Epidemiology Studies"

The assessment methodology discussed in the paper, meta-analysis, provides an alternative approach for assessing environmental data bases. Meta-analysis has the potential to increase the ability to estimate a small but meaningful change in the risk of a health outcome measure by analyzing the total evidence from all studies simultaneously. The specific example of the relationship of lower respiratory illness and nitrogen dioxide (NO_2) exposure is a case in point. The evidence of the individual studies was inconclusive. When taken as a whole, the results of the meta-analysis suggest an increase of at least 20% in the odds of respiratory illness in children exposed to an increase of 30 $\mu g/m^3$ NO_2. This analysis can be considered along with other evidence in assessing health effects of exposure to NO_2.

Abstract

The use of meta-analysis is becoming more common in the medical literature, but it is not common in the environmental literature. Although meta-analysis cannot combine a group of poorly executed, conflicting studies to get an unequivocal answer, there are certain situations where it can be helpful. The inability of studies to produce similar results may be a function of the power of the studies rather than a reflection of their quality. The literature on the effects of nitrogen dioxide on the odds of respiratory illness in children is such an example. Three quantitative methods for the synthesis of this evidence are presented. Although the methods produce slighlty different results, the conclusion from all three methods is that the increase in the odds of respiratory illness in children exposed to a long-term increase of 30 $\mu g/m^3$ (comparable to the increase resulting from exposure to a gas stove) is about 20%. This estimated increase is not sensitive to the method of analysis.

Introduction

The United States Environmental Protection Agency (U.S. EPA) is directed by the Clean Air Act[1] to promulgate standards that protect the public health from air pollutants and are based on air quality criteria. Such criteria are to reflect the latest scientific information useful in indicating the kind and extent of all identifiable public health effects that may be expected from the presence of ambient air pollutants. Air Quality Criteria Documents (AQCDs) for these pollutants attempt to integrate and synthesize key information from several disciplines to provide a coherent framework from which interpretation and judgments can be made concerning the risk to human health. Reducing the uncertainties inherent in such information strengthens the conclusions that can be drawn.

Over the past decade, quantitative approaches have been developed to synthesize evidence from multiple studies. Making use of such approaches in evaluating and synthesizing epidemiologic evidence as part of AQCD preparation requires that the methods be able to handle the results of a variety of analyses, including multiple logistic regression analyses, and provide combined estimates of the probability of a given type of health effect occurring at a specified exposure level. This eliminated many meta-analysis methods often used with clinical trials, as well as the method of effect sizes. In preparing a revised AQCD for nitrogen oxides, three methods were found to be useful. These methods are described below, and comparisons are then made between the results of the three methods as applied to the evaluation and synthesis of epidemiologic evidence concerning the effects of nitrogen dioxide on respiratory disease symptoms in children.

The purpose of this paper is to (1) demonstrate that there are situations where the synthesis of environmental evidence is feasible, (2) describe some of the models used for this synthesis, and (3) apply these models to a specific data set of interest.

Quantitative Methods for Synthesizing Evidence

The three quantitative approaches employed in evaluating the nitrogen dioxide (NO_2) health effects evidence are (1) the variance-weighted method, (2) random-effects models as described by DerSimonian and Laird,[2] and (3) the Confidence Profile Method as described by Eddy[3] and Eddy et al.[4,5]

Variance-Weighted Method

One of the oldest methods for combining estimates of a parameter is the variance-weighted method, which is described by Hald.[6] Assume that there are *n* studies, each giving estimates, $\hat{\theta}_i$, of a parameter θ, where $i = 1,2,\ldots,n$. The method assumes that each study is independent of the other studies and that each study is estimating exactly the same parameter. We shall refer to this as the fixed-effects model. The minimum variance estimate for any estimate, which is a linear combination of the $\hat{\theta}_i$'s, is:

$$\hat{\theta} = \left[\sum_{i=1}^{n} w_i \times \hat{\theta}_i\right] \Big/ \left[\sum_{i=1}^{n} w_i\right], \qquad (1)$$

where $w_i = 1 / \text{variance}(\hat{\theta}_i)$. The statistic for testing the null hypothesis that all $\hat{\theta}_i$'s are estimating the same parameter is

$$X^2 = \sum_{i=1}^{n} w_i \, (\hat{\theta}_i - \hat{\theta})^2, \qquad (2)$$

which is approximately distributed as a chi-square distribution with (n − 1) degrees of freedom.

Combining Using Random-Effects Models

Random-effects models have been used for many years, although they are sometimes called two-stage or hierarchical models. Random-effects models arise when the parameter or parameters of "mother nature" do not remain constant from study to study. Instead, they vary randomly and are in fact assumed to be random variables from some distribution. The problem then becomes to estimate (or derive a posterior distribution for) some function of these parameters.

One such random-effects model is the so-called "normal-normal" model. In this model we assume that each estimate, $\hat{\theta}_i$, of the parameter θ is sampled from a normal distribution with mean μ_i and variance σ_i^2. For now, we assume that σ_i^2 is known and that μ_i is a random value from another normal distribution with mean θ and variance τ^2. The likelihood for the estimates from n different studies is

$$L \propto \exp\left[-\sum_{i=1}^{n}\left[(\hat{\theta}_i - \theta)^2 / (\tau^2 + \sigma_i^2) + 1n(\tau^2 + \sigma_i^2)\right] / 2\right]. \tag{3}$$

The parameter θ can be estimated, or a posterior for θ and τ^2 can be calculated if prior distributions (priors) are specified for θ and τ^2. A flat prior $[p(\tau^2) \equiv 1]$ will work for τ^2, but the natural noninformative prior $1/\tau$, leads to problems. The integrals do not converge for τ^2 near zero, and the intergrals do not converge as τ^2 approaches infinity unless n is at least 4. A safer prior for τ^2 is

$$p(\tau^2) = e^{-\tau^2} / (\tau\sqrt{\pi}). \tag{4}$$

Usually, the actual variances of the estimates, σ_i^2, are not known and are replaced by their sample values.

Often the study parameter that varies is an effect measure, such as an odds ratio. This parameter then has two sources of variation: (1) the variation resulting from "mother nature" choosing different parameter values for each study and (2) the sampling variation from the study itself given a particular value from "mother nature". DerSimonian and Laird[2] give formulas for partitioning the variation in a random-effects model without making any particular distributional assumptions about the parameters. Let $\hat{\theta}_i$ be the estimate of the parameter, as before, and let w_i be the inverse of the sampling variance of $\hat{\theta}_i$. Define $\hat{\theta}_w$ as

$$\hat{\theta}_w = \sum_{i=1}^{n} w_i \, \hat{\theta}_i \Big/ \sum_{i=1}^{n} w_i. \tag{5}$$

Estimate τ^2 by

$$\hat{\tau}^2 = \max \left\{ 0, \ [\hat{\theta}_w - (n - 1)] \Big/ \left[\sum_{i=1}^{n} w_i - \left[\sum_{i=1}^{n} w_i^2 \Big/ \sum_{i=1}^{n} w_i \right] \right] \right\}. \tag{6}$$

Now define v_i as $1/(1/w_i + \hat{\tau}^2)$. The estimate of θ is

$$\hat{\theta} = \sum_{i=1}^{n} v_i \, \hat{\theta}_i \Big/ \sum_{i=1}^{n} v_i, \tag{7}$$

and the variance of $\hat{\theta}$ is approximately

$$Var(\hat{\theta}) \cong 1 \Big/ \sum_{i=1}^{n} v_i. \tag{8}$$

Confidence Profile Method

The Confidence Profile Method is a very general method for combining virtually any kind of evidence about various parameters, as long as those parameters can be described in a model. The Confidence Profile Method can be used in either a Bayesian mode, to estimate a joint posterior distribution for the parameters of interest, or in a non-Bayesian mode, to estimate a joint likelihood function for the parameters of interest. The method will be applied to the special case where each study is estimating the same endpoint. The Confidence Profile Method uses a model that consists of three elements: (1) basic parameters, (2) functional parameters, and (3) likelihood functions relating evidence to basic or functional parameters. The description of these elements follows.

Basic Parameters. Basic parameters are those parameters that appear in the model that are not functions of any other parameters. For example, the respiratory disease rate in children living in homes with electric stoves in a particular study could be a basic parameter. For convenience, we will denote the basic parameters as $\theta_1, \theta_2, \ldots, \theta_k$. If a Bayesian analysis is to be used, then all basic parameters must have prior distributions. Noninformative priors for these parameters can be derived in a variety of ways. One standard method is to use a Jeffreys' prior.[7]

Functional Parameters. Each functional parameter, θ_j, is defined as a function of the basic parameters $\theta_1, \theta_2, \ldots, \theta_k$, and all previously defined functional parameters $\theta_{k+1}, \ldots, \theta_{j-1}$:

$$\theta = f_j(\theta_1, \theta_2, \ldots, \theta_{j-1}),\ j = k + 1, \ldots, m. \quad (9)$$

Although the functions can be any mathematical expression, certain functions are very common. For example, the multiple logistic model is often used:

$$\theta_i = 1 \Big/ \left[1 + \exp\left(-\sum_{j=1}^{k} \beta_j \, x_{ij} \right) \right], \tag{10}$$

where the β_j's are logistic regression coefficients, the x_{ij}'s are known constants and θ_i represents the probability that the i^{th} response is positive.

Likelihood Functions. Likelihood functions connect observed evidence to basic and functional parameters. For example, the likelihood function for a multiple logistic regression problem could be:

$$L(y \mid \beta_1, \beta_2, \ldots, \beta_k) \propto \prod_{i=1}^{n} \theta_i^{y_i} (1 - \theta_i)^{1-y_i}, \tag{11}$$

where θ_i is defined in equation (10) and where y_i equals 1 if the response is positive and equals zero otherwise. For a more complete discussion of likelihood functions, see Barnard and Sprout.[8]

The Model. Once the basic parameters, functional parameters, and likelihoods are defined, the model has been formulated. The general log-likelihood for the model (assuming independence of experiments) is:

$$LL = \sum_{s=1}^{S} \sum_{i=1}^{n_s} \ln L_{si}(Y_i \mid \theta_1, \ldots, \theta_m), \tag{12}$$

where i indexes the observations of an individual study, s indexes the S different experiments, n_s is the number of observations in experiments S, and Y_i is the observed data for the i^{th} study. If priors have been defined, then the m dimensional posterior is defined as:

$$\pi(\theta_1,\ldots,\theta_{k+m}) = \left[\prod_{s=1}^{S}\prod_{i=1}^{n_S} L_{si}(Y_i|\theta_1,\ldots,\theta_m)\right]\left[\prod_{j=1}^{k}\pi_j(\theta_j)\right]. \qquad (13)$$

Methods of Model Solution. There are five different methods for solving the model once it has been defined: (1) maximum likelihood estimation, (2) maximum likelihood methods for determining the posterior model, (3) exact solutions in certain special cases, (4) approximate solutions using moments, and (5) Monte Carlo simulation. The choice depends on the complexity of the model, the accuracy required, and the amount of computational power and time available. For additional discussion of these, see Eddy et al.[5] The Confidence Profile Method can be used for both fixed and random effects models.

An Application to Studies of Nitrogen Dioxide Effects on Respiratory Illness Symptoms

Lower respiratory tract illness (LRI) is one of the major causes of childhood morbidity in the United States.[9] This is of public health importance because childhood respiratory illness is extremely common and the potential for exposure to NO_2 is great.[10] Lower respiratory illness takes on added importance since recurrent childhood respiratory illness may be a risk factor for later susceptibility to lung damage.[10-13] Various studies of LRI have reported rates ranging from about 20 to 30 illnesses per 100 children in the first year of life.[9,14,15] The rate of LRI in children is affected by several factors that include age, immunologic status, prior viral infections, level of health, socioeconomic status, day care attendance,[16] environmental tobacco smoke (ETS), and exposure to NO_2 and other pollutants.

Bacteria are not thought to be common causes of LRI in nonhospitalized infants in the United States.[15] Seventy-five percent of the isolated microbes were one of four types: respiratory syncytial virus, parainfluenza virus Types 1 and 3, and M. pneumonia.[9,14] Early insult from virus infection in the lower respiratory tract is an essential element of the development of chronic and persistent impairment.[11-13] It is now recognized that infections, reactive airways, ETS, and other inhaled pollutants, are the most important risk factors in the development of chronic lung disease.[17] Thus, factors such as NO_2, which increase the risk for LRI, are important because of the associated public health concern and the potential for increase in the development of chronic lung disease.

Epidemiological studies of the relationship between NO_2 exposure and a health outcome such as LRI in children provide the majority of the evidence for examination of such relationships. Several factors arise in the interpretation of epidemiological studies of the health effects of NO_2: (1) measurement error in exposure, (2) misclassification of the health outcome, (3) selection bias, (4) adjustment for covariates, (5) publication bias, (6) internal consistency, and (7) plausibility of the effect based on other evidence.

The effect of measurement error on estimation has been studied by several authors, including Shy et al.,[18] Gladen and Rogan,[19] Stephanski and Carroll,[20] Fuller,[21] Schafer,[22] and Whittemore and Keller.[23] In general, measurement error that is independent of the health outcome will result in estimated effects biased towards the null. Whittemore and Keller[23] specifically consider the data of Melia et al.[29] as described by Florey et al.[34] and show that a 20% misclassification rate of the exposure category will result in an underestimate of the logistic regression coefficient by as much as 50%. Stefanski and Carroll[20] have shown that, even without the independence of error related to outcome, the bias is towards the null in situations where the risks are not extremely close to 0 or 1. The use of the presence of a gas stove as a surrogate for actual NO_2 exposure introduces misclassification.

Most studies of respiratory disease and NO_2 exposures measured the important covariates of age, gender, socio-economic level of the parents, and parental smoking habits. The estimated effect (regression coefficient of disease on NO_2 exposure) will be an overestimate when a missing covariate is either positively or negatively correlated with both the exposure variable and the health outcome. The estimated effect will be an underestimate when a missing covariate is positively correlated with the exposure variable and negatively correlated with the health outcome, or vice versa. Ware et al.[24] found that parents with some college education were more likely to report respiratory symptoms and were less likely to use a gas stove, leading to an underestimate of the health effect if education were left out of the analysis.

Studies that examine NO_2 relationships to respiratory illness, when reviewed independently, produce somewhat mixed results.[25] The use of quantitative methods of synthesizing evidence presents the opportunity to examine the consistency between these studies and the strength of the total data base. Selected studies are discussed, followed by a combined analysis.

British Studies

Results of British studies have been reported by Melia et al.,[26-31] Goldstein et al.,[32,33] and Florey et al.[34,35] The initial study, reported by Melia et al.,[26] was based on a survey of 5,658 children (excludes asthmatics, thus 100 less than the number reported), aged 6 to 11 years, with sufficient information in 28 randomly selected areas of England and Scotland. The study included a self-administered, parent-completed questionnaire that obtained information on the presence of morning cough, day or night cough, colds going to chest, chest sounds of wheezing or whistling, and attacks of bronchitis. The questionnaire was distributed in 1973 and asked about symptoms during the previous 12 months. Colds going to chest accounted for the majority of the symptoms reported. Information about cooking fuel (gas or electric), age, gender, and social class (manual or nonmanual labor) was obtained, but information on parental smoking was not. No measurements of NO_2, either indoors or outdoors, were given. The authors presented their results in the form of a contingency table with complete covariate information for nonasthmatic children under age eight. The authors indicated that there was a trend for increased symptoms in homes with gas stoves, but that the increase was only significant for girls in urban areas; however, they did not report odds ratios or other measures of increased risk.

Our reanalysis of the authors' data was performed using a multiple-logistic model. Because it had been suggested that gender had an effect on the relationship with "gas cooker," interaction terms for gender were included in the original model. None of these proved to be significant, and they were subsequently dropped from the model. When separate terms for each gender were used for the effect of "gas cooker," an estimated odds ratio of 1.25 was obtained for boys and an odds ratio of 1.39 was obtained for girls, but the odds ratios were not significantly different. The combined odds ratio for both genders was 1.31 (95% confidence limits of 1.16 to 1.48) and was statistically significant from 1.00 ($p < .0001$). The other main effects of gender, socio-economic status, and age were all statistically significant.

Melia et al.[28] report further results of the national survey covering two groups: (1) a new cohort of 4,827 boys and girls, aged 5 to 10 years, from 27 randomly selected areas who were examined in 1977 and (2) 2,408 children first examined in 1973 who were followed-up for at least one year and whose parents reported the use of the same cooking fuel for each year the child was studied. The 1977 study collected information on the number of smokers in the homes. In the 1977 cross-sectional study, only the prevalence of day or night cough in boys ($p \approx 0.02$) and colds going to chest in girls ($p < 0.05$) were found to be significantly higher in children from homes where gas was used for cooking compared with children from homes where electricity was used. Grouping responses according to the six respiratory questions into one or more symptoms or diseases, or none, yielded a prevalence higher in children from homes where gas was used for cooking than in those from homes where electricity was used ($p \approx 0.01$ in boys, $p = 0.07$ in girls). The authors examined the effect of gender, social class, use of pilot lights, and number of smokers in the homes.

Our reanalysis of the authors' data was performed applying a multiple-logistic model. This model contained the same terms that were included in our analysis of Melia et al.[26] As in the previous analysis, none of the interaction terms proved to be significant, and they were subsequently dropped from the model. The maximum likelihood estimate of the odds ratio was 1.24 (95% confidence limits of 1.09 to 1.42. This effect was statistically significant ($p < .0001$). The other main effects of gender, socio-economic status, and age were all statistically significant.

This study was followed by a study in 1978 of 808 schoolchildren,[29] aged six to seven years, in Middlesborough, an urban area in northern England. Respiratory illness was defined in the same manner as in the previous study. Indoor NO_2 measurements were collected from 66% of the homes, with the remaining 34% refusing to participate. Nitrogen dioxide was measured by Palmes tubes[36] attached to walls in the kitchen areas and in children's bedrooms. In homes with gas stoves, levels of NO_2 in kitchens ranged from 10 to 596 $\mu g/m^3$ (0.005 to 0.317 ppm [1 $\mu g/m^3$ = 0.00053 ppm at 25 °C, 760 mmHg]), with a mean of 211 $\mu g/m^3$; and levels in bedrooms ranged from 8 to 318 $\mu g/m^3$, with a mean of 56 $\mu g/m^3$. In homes with electric stoves, levels of NO_2 in kitchens ranged from 11 to 353 $\mu g/m^3$, with a mean of 34 $\mu g/m^3$, and in bedrooms NO_2 levels ranged from 6 to 70 $\mu g/m^3$, with a mean of 26 $\mu g/m^3$. Outdoor levels of NO_2 were determined using diffusion tubes systematically located throughout the area, and the weekly average ranged from 26 to 45 $\mu g/m^3$.

One analysis by the authors[29] was restricted to those 103 children in homes where gas stoves were present and where bedroom NO_2 exposure was measured. A multiple logistic regression model was fitted to the presence or absence of respiratory illness. Measured NO_2 exposure was found to be associated with respiratory illness, independent of social class, age, gender, or the presence of a smoker in the house ($p = 0.06$). However, when social class was excluded from the regression, the association was weaker ($p = 0.11$). For the six- to seven-year-old children living in gas stove homes, there appeared to be an increase of respiratory illness with increasing levels of NO_2 in their bedrooms ($p = 0.10$), but no significant relationship was found between respiratory symptoms in those children or their siblings or parents and levels of NO_2 in kitchens.

Since no exposure-response estimates were given by the authors, a multiple-logistic model was fitted to the data with a linear slope for NO_2 and separate intercepts for boys and girls. Nitrogen dioxide levels for the groups were estimated by fitting a lognormal distribution to the NO_2 data, which was reported by intervals, and the average exposures within each interval were estimated.[37] The estimated logistic regression coefficient for NO_2 (in $\mu g/m^3$) was 0.015 with a standard error of 0.007. This result is not directly comparable with the previous two analyses since it gives the increase in the logarithm of the odds of respiratory illness per unit increase in NO_2 exposure. Since most studies of gas stove exposure (both in the United States and the United Kingdom) show an approximate increase of 30 $\mu g/m^3$ in the NO_2 levels, the slope was multiplied by 30 to get the increase due to gas stove exposure, and then converted to an odds ratio by exponentiation. All of this assumed that the logarithm of the odds ratio was linear in NO_2 exposure. The result was an odds ratio of 1.53, with 95% confidence limits of 1.04 to 2.24.

The study was repeated January through March of 1980 by Melia et al.[30] This time, five- and six-year-old children were sampled from the same neighborhood as the previous study, but only families with gas stoves were recruited. Environmental measurements were made and covariate data were collected in a manner similar to the previous study. Measurements of NO_2 were available from 54% of the homes. The unadjusted rates of one or more symptoms by gender and exposure level were analyzed by the authors, and they concluded that "... no relation was found between the prevalence of respiratory illness and levels of NO_2." A reanalysis of the data was made using a multiple-logistic model similar to the one used for the previous study. The model included a linear slope for NO_2 and separate intercepts for boys and girls. Nitrogen dioxide levels for the groups were estimated by fitting a lognormal distribution to the grouped bedroom NO_2 data. The estimated logistic regression coefficient for NO_2 (in $\mu g/m^3$) was 0.004 with a standard error of 0.005. As for Melia et al.,[29] the regression coefficient was converted to an odds ratio for an increase of 30 $\mu g/m^3$ in NO_2 assuming that the logarithm of the odds ratio was linear in NO_2 exposure. This gave an odds ratio of 1.11, with 95% confidence limits of .83 and 1.49.

Melia et al.[31] investigated the association between gas cooking in the home and respiratory illness in a study of 390 infants born between 1975 and 1978. When a child reached one year of age, the child's mother was interviewed by a trained field worker who completed a questionnaire. The mother was asked whether the child usually experienced morning cough, day or night cough, wheeze, or colds going to chest, and whether the child had experienced bronchitis, asthma, or pneumonia during the past 12 months. No relation was found between the type of fuel used for cooking in the home and the prevalence of respiratory symptoms and diseases recalled by the mother after allowing for the effects of gender, social class, and parental smoking. The authors gave prevalence rates of children having at least one symptom by gas stove use and gender. The combined odds ratio for presence of symptoms by gas stove use was 0.63, with 95% confidence limits of 0.36 to 1.10.

United States Six-Cities Studies

Several authors[24,35-46] have reported on a series of studies conducted in six U.S. cities. The six cities were selected to represent a range of air quality based on their historic levels of outdoor pollution and included Watertown, MA; Kingston and Harriman, TN; southeast St. Louis, MO; Steubenville, OH; Portage, WI; and Topeka, KS. Approximately 1,500 grade-school children were enrolled in each community and were followed for several years. Families reported the number of persons living in their homes and their smoking habits, parental occupations and educational backgrounds, and fuels used for cooking and heating. Outdoor pollution was measured at fixed sites in the communities and at selected households. Indoor pollution, including NO_2, was measured in several rooms of selected households. Results of monitoring in Portage, WI, verify that the presence of a gas stove contributes dramatically to indoor NO_2 levels. The results clearly show the effect of a gas stove on not only the indoor concentrations but also on the personal exposure of the individual. The study[42] was conducted very carefully with excellent quality control. It gave an average estimate of 29 $\mu g/m^3$ increase in exposure resulting from the use of gas stoves in cities studied in the United States.

Ware et al.[24] reported results from the six-cities studies based on 8,120 children, aged 6 to 10 years, who were followed from 1974 to 1979. An initial report on a subset of the data was given by Speizer et al.[39] Health endpoints were measured by a standard respiratory questionnaire that was completed by parents of the children. The authors used log-linear models to estimate the effect of gas stoves versus electric stoves on the rates of serious respiratory illness before age two. Directly standardized rates of reported illnesses and symptoms did not show any consistent pattern of increased risk for children from homes with gas stoves. Logistic-regression analyses controlling for age, gender, city, and maternal smoking level gave estimated odds ratios for the effect of gas stoves ranging from 0.93 to 1.07 for bronchitis, cough, wheeze, LRI index, and illness for the past year. The index for LRI was defined as the presence of either bronchitis, respiratory illness that kept the child home 3 days or more, or persistent cough for 3 months of the past year. None of these odds ratios were statistically different from 1. Only two odds ratios approached statistical significance: (1) history of bronchitis (odds ratio = 0.86, 95% confidence interval 0.74 to 1.00) and (2) respiratory illness before age two (odds ratio = 1.13, 95% confidence interval 0.99 to 1.28). When the odds ratio for respiratory illness before age two was adjusted for parental education, the odds ratio was 1.11, with 95% confidence limits of 0.97 to 1.27 ($p = 0.14$). Thus, the study suggests an increase in respiratory illness of about 11%, although the increase was not statistically significant at the 0.05 level. The endpoint in the Ware et al.[24] study most similar to that of the Melia studies was the LRI index. The authors gave the unadjusted rates, and from those an estimated odds ratio of 1.08, with 95%

confidence limits of 0.97 to 1.19, were calculated. Although this rate was not adjusted for other covariates, the effect of those adjustments on other endpoints was minimal.

Neas et al.[45,46] studied a cohort of 6,273 children from the same six cities. This cohort included children that were part of the Dockery et al.[44] analysis but was restricted to white children 7 to 11 years of age with complete covariate information and at least one valid indoor measurement of both NO_2 and respirable particles. This resulted in 1,286 children being included in the analysis. Methods for measuring indoor pollutants were described by Spengler et al.[38] Indoor pollutants were measured in each child's home for two weeks during the heating season and two weeks during the cooling season. Nitrogen dioxide was measured by Palmes tubes at three locations in each home.

The analysis of the Neas et al.[45,46] study was based on the third symptom questionnaire that was completed by parents following the indoor measurements. The questionnaire reported symptoms during the previous year, including shortness of breath, chronic wheeze, chronic cough, chronic phlegm, and bronchitis. The authors used a multiple-logistic model, which had separate-city intercepts, indicator variables for gender and age, parental history of chronic obstructive pulmonary disease and asthma, parental education, and single-parent family status. The sampling strategy minimized the association between NO_2 and passive-smoking exposure. The increases in symptoms were estimated for an additional 31 $\mu g/m^3$ NO_2 exposure. This corresponded to the average difference in NO_2 concentrations monitored in homes with a gas stove with a pilot light, based on exposure information from the study. Table I shows the odds ratios for the five separate symptoms associated with the increase in NO_2 exposure.

All of these odds ratios are consistent with the size of effect seen in the other analyses of the six-city data and the analyses of the British studies. The authors defined a combined

Table I. Odds ratios and 95% confidence intervals for the effect of an additional 31 $\mu g/m^3$ nitrogen dioxide on the symptom prevalence.

Symptom	Odds Ratio	95% Confidence Interval
Shortness of breath	1.27	0.92 to 1.73
Chronic wheeze	1.19	0.87 to 1.61
Chronic cough	1.21	0.86 to 1.71
Chronic phlegm	1.29	0.93 to 1.79
Bronchitis	1.05	0.71 to 1.56
Combined symptoms score	1.47	1.17 to 1.86

Source: Neas et al.[45]

symptom, which was the presence of one or more of the symptoms just reported, and an analysis of this combined indicator of respiratory symptoms gave an estimated odds ratio of 1.47, with 95% a confidence interval of 1.17 to 1.86. When split by gender, the odds ratio was higher in girls, and when split by smoking and nonsmoking homes, it was higher in smoking homes.

Tayside Study

Ogston et al.[47] studied infant mortality and morbidity in the Tayside region of northern Scotland. The subjects were 1,565 infants born to mothers who were living in Tayside in 1980. Episodes of respiratory illness were recorded during the first year of life. The information was supplemented by observations made by a health visitor and scrutinized by a pediatrician who checked diagnostic criteria and validity. One health endpoint assessed was defined as the presence of any respiratory illness during the year. This endpoint was analyzed by the authors using a multiple-logistic regression model that included terms for parental smoking, age of mother, and presence of a gas stove. The estimated odds ratio for the presence of a gas stove was 1.14, with 95% confidence limits of 0.86 to 1.50. Only the coefficient for parental smoking was statistically significant ($p < 0.01$).

Iowa Study

Ekwo et al.[48] surveyed 1,355 children 6 to 12 years of age for respiratory symptoms and lung function in the Iowa City School District. Parents of the school children completed a questionnaire that was a modification of the questionnaire developed by the American Thoracic Society.[49] Eight different measures of respiratory illness were reported by the authors, but only the endpoint of chest congestion and phlegm with colds was similar to the endpoints used in the British studies and the six-city studies. Information on parental smoking was obtained and used as a covariate in the analysis. The result of the analysis, which was based on 1,138 children, was an odds ratio of 1.10 for gas stove use. The 95% confidence limits of 0.79 and 1.53 were derived from the authors' data. No NO_2 concentrations, either inside or outside the homes, were reported.

Dutch Studies

In the Netherlands, Houthuijs et al.,[50] Brunekreef et al.,[51] and Dijkstra et al.[52] studied the effects of indoor factors on respiratory health in children. The population consisted of 6- to 9-year-old children from 10 primary schools in five nonindustrial communities in the southeast region of the Netherlands. Personal exposure to NO_2 and home concentrations were measured. An important NO_2 emission and exposure source in these homes are geysers, which are unvented gas-fired hot water sources at the water tap. Exposure to tobacco smoke was assessed with a questionnaire that also reported symptom information. Pulmonary function was measured at school. The study used Palmes tubes to measure a single weekly average personal NO_2 exposure. Potential high peak exposures from the geysers may not be well characterized by the weekly average personal exposure measurements. In January and February of 1985, the homes of 593 children who had not moved in the last four years were measured for one week for NO_2. Personal exposure was also estimated from time budgets and room monitoring.

Three measures of health (cough, wheeze, and asthma) were obtained from the questionnaire, which was a modified form of the World Health Organization questionnaire.[53] Asthma was defined as attacks of shortness of breath with wheezing in the last year. The presence of any of the three symptoms was used as a combination variable, and a logistic-regression model was used to fit the combination variable. Exposure was estimated by fitting a lognormal distribution to the exposure data, which was reported in intervals; and the mean exposure values for each group were estimated by a maximum likelihood technique.[37] The estimated logistic-regression coefficient was -0.002, corresponding to an odds ratio of .94 for an increase of 30 $\mu g/m^3$ in NO_2, with 95% confidence limits of 0.66 to 1.33. This assumed a linear relationship between the logarithm of the odds ratio and the NO_2 exposure. The rates were not adjusted for covariates such as parental smoking and age of the child.

Ohio Study

Keller et al.[54] and Mitchell et al.[55] originally conducted a 12-month study of respiratory illness and pulmonary function in families in Columbus, OH, prior to 1978. The study measured NO_2 exposure by both the Jacobs-Hochheiser and continuous-chemiluminescence methods. The electric stove users averaged 38 $\mu g/m^3$ NO_2 exposure, whereas the gas stove users averaged 94 $\mu g/m^3$. Thus, the estimated average difference between gas and electric stove use was 58 $\mu g/m^3$. The paper did not report which rooms were measured in order to get these averages. In a second related study,[56] 580 persons drawn from households that participated in the earlier study were examined to confirm the reports and to determine the frequency distribution of reported symptoms among parents and children in gas or electric stove homes. A nurse-epidemiologist examined selected persons who were reported ill. Unfortunately, these rates were not adjusted for other covariates. The percentage of children having lower respiratory symptoms in homes with a gas stove was 53.2% (n = 267) and 50.7% (n = 286) in homes with electric stoves. Although the difference is not statistically significant, these rates give an estimated odds ratio of 1.10, with 95% confidence limits of 0.74 to 1.54.

Synthesis of the Evidence

In order to combine the studies just described, several assumptions were necessary. First, although each study used a slightly different health outcome as an endpoint, we assumed that the endpoints are similar enough to warrant their combination. Second, the exposure levels were different in each study. An increase of 30 $\mu g/m^3$ was used as a standard increase, and all studies were used to estimate the effect of an increase of 30 $\mu g/m^3$, even if they had a different exposure range. Third we assumed that each study controlled for key covariates, or that those covariates were properly adjusted for or are of minimal significance. The omission of covariates such as parental education almost certainly biases the results towards the null, and for this reason we retained some studies, which arguably could have been excluded.

The studies described used different indicators to study health endpoints. The symptoms describing LRI evaluated in the studies varied but are, in general, reasonable indicators of LRI. They include colds going to chest, chronic wheeze and cough, bronchitis, chest cough with phlegm, episodes of respiratory illness, and various respiratory indexes, which are combinations of more than one of these symptoms. These symptoms are comparable to indicators of LRI in children that were used in other studies. In order to compare these studies on respiratory effects of NO_2, a common endpoint was defined, and then each study was compared with this standard endpoint. The endpoint was the presence of reported LRI symptoms in children age 12 or younger.

An attempt was made to include as many studies as possible. The requirements for inclusion were (1) the health endpoint measured must be reasonably close to the standard endpoint; (2) exposure differences must exist, and some estimate of exposure (either direct or indirect) must be available; and (3) an odds ratio for a specified exposure must have been calculated, or data presented so that it can be calculated. These studies are summarized in Table II.

The approximate likelihoods for each study are shown in Figure 1. Each curve can be treated as a likelihood function or posterior-probability distribution. If treated as a likelihood function, then 95% confidence limits for the odds ratio can be calculated as those two points on the horizontal axis between which 95% of the area under the curve is contained. If treated as a posterior-probability distribution, then the area under the curve between any two points is the probability that the odds ratio lies between those two points. Note that all 11 likelihoods show some overlap. A chi-square goodness-of-fit test of the homogeneity of the 11 studies gives a chi-square of 18.75 with 10 degrees of freedom ($p = 0.0436$), suggesting some lack of homogeneity in the 11 studies.

The studies were combined using four methods: (1) the variance-weighted method, assuming a fixed-effects model; (2) the Confidence Profile Method, assuming a fixed-effects

Table II. Summary of the results of the effects of nitrogen dioxide exposure on respiratory disease in children.

Authors	Where/When	NO_2 Exposure Measure Used in Analysis	Age (years)	Sample Size	Odds Ratio for Respiratory Disease	95% Confidence Limits
Melia et al.[26]	28 areas of England and Scotland (1973)	Gas stove vs. electric stove.	6-11	5,658	1.31	1.16 to 1.48
Melia et al.[28]	27 areas of England and Scotland (1977)	Gas stove vs. electric stove.	5-10	4,827	1.24	1.09 to 1.42
Melia et al.[29] Florey et al.[34] Goldstein et al.[32]	Middlesborough, England (1978)	NO_2 measured with Palmes tubes.	6-7	103	1.53	1.04 to 2.24
Melia et al.[30]	Middlesborough, England (1980)	NO_2 measured with Palmes tubes.	5-6	188	1.11	0.83 to 1.49
Melia et al.[31]	London (1975 to 1978)	Gas stove vs. electric stove.	<1	390	0.63	0.36 to 1.10
Ware et al.[24]	Six U.S. cities (1974-1979)	Gas stove vs. electric stove.	6-10	8,240	1.08	0.96 to 1.37
Neas et al.[45]	Six U.S. cities (1983-1986)	NO_2 measured with Palmes tubes.	7-11	1,286	1.47	1.17 to 1.86
Ogston et al.[47]	Tayside region, Scotland (1980)	Gas stove vs. electric stove.	<1	1,565	1.14	0.86 to 1.50
Ekwo et al.[48]	Iowa City, Iowa	Gas stove vs. electric stove.	6-12	1,138	1.10	0.79 to 1.53
Dijkstra et al.[52] Brunekreef et al.[51]	Netherlands (1986)	NO_2 measured with Palmes tubes.	6-12	775	0.94	0.66 to 1.33
Keller et al.[54,56]	Columbus, Ohio (1978)	Gas stove vs. electric stove.	<12	553	1.10	0.74 to 1.54

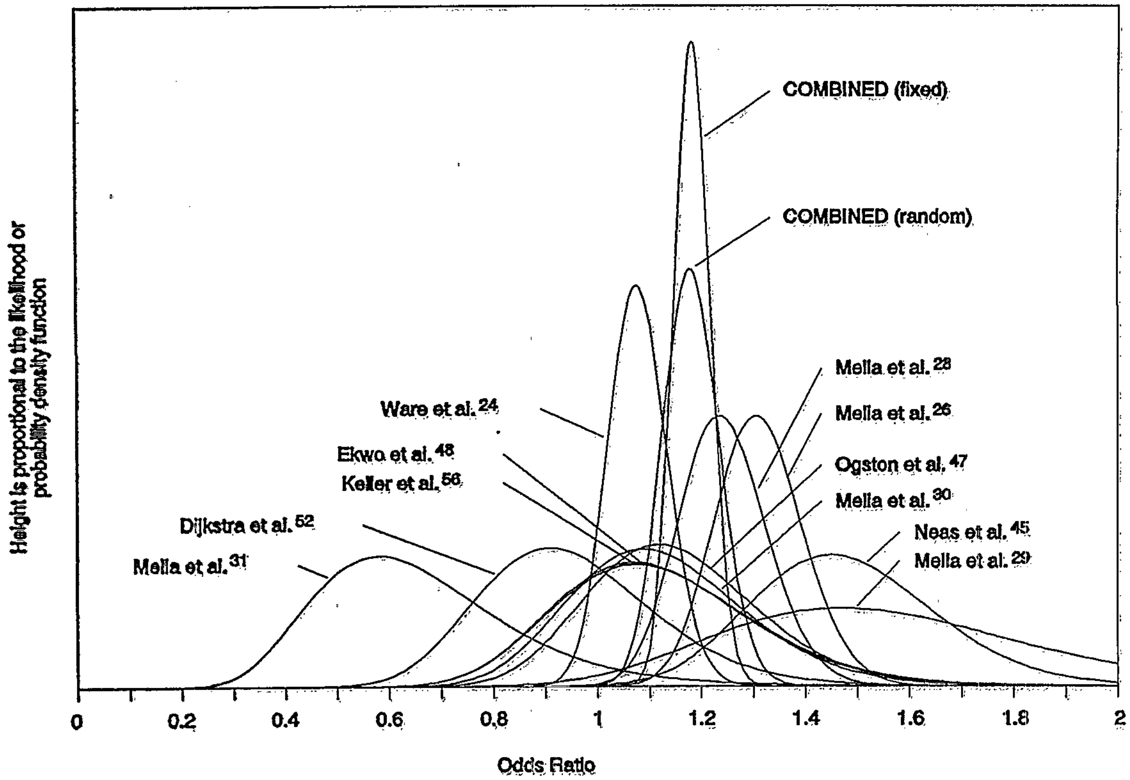

Figure 1. Meta-analysis of epidemiologic studies of 30 $\mu g/m^3$ nitrogen dioxide exposure increase on respiratory illness in children ≤12 years old.

model; (3) the DerSimonian and Laird method, assuming a random-effects model; and (4) the Confidence Profile Method, assuming a random-effects model. Results of the use of these models in synthesizing the NO_2 evidence are presented in Table III for four subsets of the studies. The first includes all 11 studies; the second excludes the two studies on children less than one year of age; the third excludes the younger children and those studies that did not measure NO_2 directly; and the fourth excludes the younger children and those studies that measured NO_2 directly.

Table III. Summary of synthesis of studies on respiratory illness effects of nitrogen dioxide.

	Model-Method			
	Fixed		Random	
Studies	Variance-Weighted Method[6]	Confidence Profile Method[5]	DerSimonian and Laird[2]	Confidence Profile Method[5]
All 11 studies	1.18 (1.11, 1.25)[a]	1.18 (1.11, 1.25)	1.18 (1.08, 1.30)	1.18 (1.08, 1.29)
Children aged 5-12 years, 9 studies	1.19 (1.12, 1.27)	1.19 (1.12, 1.27)	1.19 (1.09, 1.30)	1.20 (1.10, 1.31)
Measured NO_2, children aged 5-12 years, 4 studies	1.27 (1.09, 1.47)	1.27 (1.09, 1.47)	1.27 (1.02, 1.58)	1.25 (0.99, 1.58)
Surrogate NO_2 estimate based on presence of gas stove, children aged 5-12 years, 5 studies	1.18 (1.10, 1.26)	1.18 (1.10, 1.26)	1.18 (1.07, 1.29)	1.18 (1.09, 1.28)

[a]95% confidence limits given in parentheses.

The results from all analyses are reasonably similar. The variance-weighted method and the Confidence Profile Method have identical answers because the log normal approximation for the likelihood function was used in the calculation of the solution by the Confidence Profile Method. In general, the results should be nearly identical for reasonable sample sizes. The DerSimonian and Laird[2] method and Confidence Profile Method[5] for the analysis of a random-effects model gave similar but not identical results.

The analysis of the nine studies with children 5 to 12 years old was done separately because the other two studies were of infants. The exclusion of these two studies made little difference in the results.

All studies that used the presence of a gas stove as a surrogate for NO_2 exposure obviously suffer from measurement error. In general, measurement error will decrease the estimated effect. When the four studies of children over age 5 years with measured NO_2 levels were combined, the estimated odds ratio did increase from about 1.18 to about 1.27. Thus there is some reason to believe that the use of a surrogate for exposure did bias the estimated effect, but the confidence limits of all estimates overlap significantly.

The evidence for effects on respiratory illness in children under age 12 years is clearly very strong. All but one of the studies used in the synthesis showed increased respiratory illness rates associated with increased exposure. A few of the individual studies were statistically significant. When combined, the studies indicated that an increase of 30 $\mu g/m^3$ in NO_2 exposure would result in an increase of about 20% in respiratory illness, subject to the assumptions made for the synthesis. This result is not dependent on the results of any single study. Furthermore, the estimated effect is likely to be an underestimate, given the problems of misclassification of exposures and outcomes.

Discussion

The use of meta-analysis is becoming more common in the medical literature,[57] but is not common in environmental assessments. The ability to estimate a small but meaningful change in the risk of a health outcome measure from a single study may be difficult. Individual studies may not provide an accurate estimate of a potential risk. But the accuracy may be greatly improved by analyzing the total evidence from all studies simultaneously, that is, by conducting a meta-analysis. A potential limitation of a meta-analysis is that the studies available for use may represent a spectrum of quality. Well executed studies may be mixed with studies containing flaws—studies with missing data or confused definitions and outcome measures. On the other hand, such problems may be slight compared to problems with alternative traditional reviews. Meta-analysis fills a need by assisting in the reconciliation of conflicting research results. While some physical sciences may allow the identical replication of experiments, many fields such as environmental science allow only the repetition of studies that introduce variation and produce uncertainty. Meta-analysis is one way of dealing with uncertainty.

All meta-analysis methods previously discussed assume that each piece of evidence (study) is independent of the others. Under the fixed-effects model, the evidence is assumed to pertain to a common parameter. Under the random-effects model, this assumption is relaxed to allow for a distribution for the parameter of interest. The computations for both models are relatively straightforward and can be made on a personal computer. The method of calculation has less impact on the conclusion than does the choice of model.

In *Air Quality Criteria for Oxides of Nitrogen*, prepared 10 years ago by U.S. EPA,[58] a group of studies examining the relationship between respiratory illness and exposure in the home to gas combustion products from cooking fuel were evaluated. At that time, those studies inferred the presence of NO_2 by the presence of gas combustion emission sources. The evidence from individual studies of the effect of NO_2 on respiratory illness was somewhat mixed. Since then, new studies have been conducted, and earlier ones updated, that provide data on NO_2 concentrations and estimates of exposure.

The studies of respiratory illness in children exposed to increased levels of NO_2 provides an excellent example of the application of meta-analysis. Taken by themselves, most of the 11 studies were reported as not being statistically significant at the 0.05 level based on analyses performed by the original authors. The studies differed in design and sample size, and this likely contributed to the lack of significance of some of the studies. However, use of the meta-analysis methods described above indicates that, taken as a whole, the collective evidence from the evaluated studies strongly suggests an increase of at least 20% in the odds of respiratory illness in children exposed to an increase of 30 $\mu g/m^3$ NO_2 for extended periods of time.

The choices of model (fixed or random) and computational method make little difference in the estimates in this particular example. In particular, the estimates do not depend strongly on the assumption that each study is estimating the same parameter. Thus, any lack of homogeneity is not a major concern. The choice of the computational method (e.g., DerSimonian and Laird[2] versus the Confidence Profile Method[5]) also makes little difference in the estimates when restricted to the particular problem described in this paper. The Confidence Profile Method can be applied to a much broader class of problems, however.

There is always the concern that the studies described are not the complete list of studies, but contain primarily the positive studies, since these are the studies most likely to be published. This is referred to as "publication bias". There are two reasons not to be concerned with publication bias in this particular situation. First, prospective epidemiological studies are very expensive and require the work of many individuals. The studies are usually described to the scientific community before the results are even known. Second, most of the studies cited were reported as negative studies by the authors themselves, indicating that there was no difficulty in publishing negative results. In spite of this, it is of interest to contemplate an undiscovered study with results so negative that, when combined with the other studies, produces a confidence interval for the odds ratio that includes the value 1. If we assume that the hypothetical study is the size of the Ware et al.[24] study, then its odds ratio for increased respiratory symptoms as the result of a 30 $\mu g/m^3$ exposure would have to be 0.766.

Although there may be reasons to weight certain studies or groups of studies more heavily than others, the final conclusion has to be that there is an increase in the odds of respiratory illness of children, especially those of elementary-school age. The estimates are generally centered about an odds ratio of 1.2, with 95% confidence limits of 1.1 to 1.3, although the studies using measured NO_2 give a slightly higher estimate of the odds ratio. This kind of synthesis may be possible for other areas of environmental assessment where multiple studies of a given health endpoint are available.

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