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Title: Using Different Models to Analyze the Effects of Measurement Precision of Ozone Exposure on Prediction of Acute Pulmonary Function

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Ozone is recognized as one of the most dangerous irritants to eyes, throat, lungs and etc.. Chamber studies consistently have demonstrated adverse effects of ozone on human lung function. The results of epidemiological studies, however, have been controversial, partly because there are many factors that affect human lung function. Thus it has been difficult to control confounding in epidemiological studies. Among these factors, retention and ventilation are two of the more important because of their strong influence on ozone's physiologically effective dose. This study used a computer simulation model, utilizing data from the "children's Camp Study", to analyze the effects of retention factors and ventilation on ozone's physiologically effective dose. The results of the simulations indicated appreciable improvement

in the estimated exposure to ozone when inhaled ozone exposure (effective dose) was included in the model. These results were consistent with the study's a priori hypothesis (that incorporating retention and ventilation factors into the model would improve the estimated exposure to ozone) primarily because of the greater precision and reduction in bias associated with the use of heart rate data that were child-and hour-specific. The study identified three simulation data sets for which the ozone dose model yielded a more significant coefficient than did the average ozone concentration model. Using the t-statistic, the three models were seen to follow the expected pattern, with statistically significant differences between the R^2 values (the coefficient of variation changed from 45.4 to 11.0 when the error term was 0.01). The results of the analyses support the hypothesis that ventilation and retention factors can be used to increase the precision of ozone exposure measurement and reduce exposure assessment errors significantly, thereby sharpening the power of studies evaluating ozone's acute health effects.

Using Different Models to Analyze the Effects of Measurement Precision of Ozone Exposure on Prediction of Acute Pulmonary Function

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INTRODUCTION

Ozone (O_3) is an unstable blue gas with an oxidizing power that is surpassed only by that of fluorine[1]. It owes its name to its characteristic odor, which is derived from the Greek "Ozein", to smell. In the past, ozone was considered beneficial in that it was believed to assist in oxygenation of blood. Now it is recognized as one of the most dangerous irritants to eyes, throat, lungs and etc.. It damages plants and even cracks rubber[2].

Ozone is by far the most ubiquitous oxidant. Within the past two and three decades, it rose to significance when it became recognized as a key component in oxidant smog created by the interaction of hydrocarbons, nitrogen oxides, and sunlight[3]. At times, ozone constitutes as much as 90% of the oxidants in smog. In urban areas, ozone concentrations have been found to be 0.001 to 0.9 ppm. In Los Angeles smog, the levels of ozone have been as high as 0.9 ppm[4]. 0.12 ppm is the national standard for the ambient environment and 0.05ppm is the maximum allowable concentration (MAC) in industry for an 8-hour exposure for healthy humans[6]. 0.5 ppm is the "first

alert" level in Los Angeles, California. Man-made sources of ozone are high voltage electrical equipment, such as X-ray apparatus, spectrographs, electrical insulators, brushes of motors, and ultra-violetray quartz lamps. Ozonizing equipment has been used for purification of water and sugar and for control of fungi and bacteria in cold-storage plants[5].

In a large number of controlled human studies (chamber studies) significant impairment of pulmonary function has been reported, usually accompanied by respiratory and other symptoms. The ozone exposure was generally to the concentrations ranging from 200 to 2000$\mu g/m^3$ and lasted 1-3 hours. In many studies, a pattern of 15 minutes of intermittent exercise alternating with rest was employed for the duration of the exposure. Minute ventilation has a profound influence on the onset and magnitude of response to ozone exposure. An increased level of exercise results in an increase in the volume of inhaled ozone and in deeper penetration of ozone into the periphery of the lung. Changes in pulmonary function associated with 1-3 hours of ozone exposure in normal subjects during exercise have been reported for the following parameters: 1) forced expiratory volume for 1 second decreased, 2) airway resistance increased, 3) forced vital capacity decreased, and 4) respiratory frequency increased. The severity of respiratory and other symptoms parallels the impairment of pulmonary function both in magnitude and time-scale. Symptoms that have been reported are

cough, throat dryness, thoracic pain, increased mucous production, chest tightness, substernal pain, lassitude, malaise and nausea. Chronic effects were reported in animal studies. Long-term exposure of rats for 6 weeks or more to ozone concentrations of 440-1600$\mu g/m^3$ resulted in increased lung distensibility, increased airway resistance and impaired stability. Incomplete recovery of monkeys exposed to 1280$\mu g/m^3$ for one year was found. During a 3-month recovery period, static lung compliance had decreased, suggesting ongoing injury and the development of central and peripheral airway constriction. Fibrosis has been observed by some researchers[6].

In chamber studies, effects of ozone on human lung function have been found frequently. The results in epidemiological studies, however, have always been controversial. There are lots of factors which affect human lung function. It is, if not impossible, very difficult to control these factors in epidemiological studies[7]. Of these complicated factors, retention factor (R) and ventilation (Ve) are two important factors because they determine the effective human exposure to ozone. These two factors are directly related to the dose of ozone. It is well known that relating of effective ozone dose to health effects is much more accurate than just ambient ozone concentration since concentrations of ozone indoor and outdoor are quite different, and the amount of ozone into human body depends on

ventilation and retention factors. Individual minute volume/ventilation rates can be monitored in chamber studies or under controlled experimental settings. However, in field studies involving both children and adults, continuous monitoring of Ve is impractical. Colucci[8] (1982) and, more recently Canadian researchers, Mark Raizenne and Douglas Haines[9] (cf. Raizenne and Spengler 1989) have developed techniques to continuously monitor heart rate (HR) and then relate that to ventilation rate. Additionally, Young[10] (1977) reported the penetration or retention factor of ozone in the nasal tract as a function of concentration and ventilation.

Better understanding of the relationship between exposure to ozone and observed health responses require prediction of personal exposures and delivered dose to the human respiratory tract[11]. Various models ranging from the simple calculation of average with effective dose to more complicated mathematical dose models for ozone have been developed[9] (cf. Kinney et al. 1986; Raizenne and Spengler 1989; Haines 1990; Overton and Miller 1987). Most models incorporate ventilation rate, duration of exposure, and average concentration during the period of exposure. Some of these models also include an estimate of the ozone retention or penetration in the pulmonary airways. However, there are few research studies which considered ventilation and retention factor at the same time.

The purpose of my study is to study the relationships

between ozone exposure and dose and acute effects on human lung function. In the study, I used different models to analyze the effects of retention factors and ventilation on the effective dose of ozone using the "Children Camps Study" data set. Some experiments have suggested that camps have provided valuable settings for studies assessing the acute health effects of ambient air pollution (M. Lippmann, 1983[12]; N. Bock, M. Lippmann, 1985[13]). Camp studies avoid some of the problems associated with traditional environmental epidemiology studies, particularly in the area of exposure assessment. Children attending summer camps spend a large fraction of time outdoors within a relatively small and well defined geographical area. They also tend to exercise heavily, enhancing the uptake of inhaled pollutants. While exercise levels, and thus minute ventilation, tend to be enhanced on average, one would expect a high degree of variability in Ve from child to child and from activity to activity. Minute ventilation can vary by a factor of 5 or more between rest and vigorous exercise. If pollution deposition in the respiratory tract (dose) is proportional to Ve, then variation in Ve could lead to significant variation in pollution doses across subjects and activities, even if the exposure concentration remained constant.

In my study, I used the simulation method, that is, I simulated FVC data based on an assumed linear relationship between FVC and ozone exposure. Inhaled exposure with actual

Camp Care (Canada 1986) ozone measurements was applied to simulate an effective ozone dose for each subject. Each child was randomly assigned a heart rate (and thus a ventilation rate) from an activity-specific normal distribution of heart rates. Then the total simulated data sets for ozone was generated. For the created data set, the three models were fitted for alternative exposure measures. The first regression of FVC (model 1) used ventilation-retention-weighted inhaled exposure (dose). The second regression (model 2) used ventilation-weighted inhaled exposure (doseve) in which the retention factor was removed. Finally, FVC was regressed on one hour ozone concentration previous to lung function measurement (model 3, OH1, typically used to represent exposure in an epidemiological study). The study results will show whether there is a consistent pattern of increase in the significance levels (R^2 value) in the models that use the more precise exposure measures and whether heart rate data support the notion that such data can be used to reduce exposure assessment errors significantly, thereby increasing the power of acute effects studies of ozone.

DATA SET AND METHODS

1. Data Set:

The Ozone data are from the Camp Care study examining lung function associations with ozone concentration among a group of 112 children, 7 to 14 years of age, over the course of a twelve-day camp in the summer of 1986. The residential summer camp was located on the north shore of Lake Erie, Ontario, Canada. Measurements of forced vital capacity (FVC) were collected twice each day using a spirometer. Ambient ozone pollution measurements were collected on-site for 2 weeks. The data of heart rate come from a Watertown study in Massachusetts in 1985. The Watertown study was conducted as part of the Harvard Air Pollution Health Study, a prospective epidemiological air pollution study carried out in six United State cities. The heart rates of the children from this study are close to normal distribution with a mean of 120 and standard deviation of 25 beats/minute. Heart rates for the models are simulated based on the distribution assigning 20% of each value as standard deviation correspondingly. In order to smooth the distribution, each child's average of three heart rates is used for each day. Inhaled exposure simulated for ozone pollutant is used to simulate FVC data for each child based on an assumed linear relationship. Then the total simulated data sets for ozone dose and acute lung function was created.

2. Methods:

Simulation Analysis

Realization of random processes are the raw materials of classical statistical inferences. Most applications of statistical methods in substantive research require a "random sample" or a "random assignment". Another, quite different way in which observations on random processes may be used is in the development of statistical methods and theory. The sampling experiment leading W. S. Gosset to discover the distribution of the correlation coefficient is an early instance of this latter use of random processes[14].

Computer simulation is to use random number generator via equation and algorithm to mimic a real situation and testify how it changes as a function of other variables. In the actual world, lots of problems can been resolved by simulation if the parameters and its relationship can be specified. For example, a problem that needed to be solved involved which one of the two equations was better to calculate the mean of a sample. The equations evaluated are ordinary mean equation and trimmed mean equation. The conclusion from simulation is that the first is better if the sample comes from a normal distribution population and the second will be better if the sample dose not come from normal distribution.

Simulation is used in the study to generate heart rate, ventilation and retention factors with a random number

according to their distribution and create lung function data (FVC) according to its relationship with ozone exposure and distribution of error term for the model. The major procedure included 1) simulation is used to create heart rate, ventilation and retention factors, thus ozone dose for each child, 2) the ozone dose is used to generate FVC according to the linear relationship, and 3) simulated FVC is used to fit three regression models. The heart rate data is converted to minute ventilation using the formula[15]:

$$Ve=\exp(0.7884+0.016\times HR) \quad (1)$$

Where Ve: minute ventilation in liters Per minute

HR: heart rate in beats per minute

The penetration (retention factor) depends on ventilation and ozone concentration, and this relationship is nonlinear. Young (1977) reported the penetration of ozone in the nasal tract as a function of concentration and ventilation for seven male subjects ranging in age from 22 to 48 years. Data from the Young study was used to simulate retention factor for each child assuming a uniform distribution with a range between 70% and 130% for each level of ventilation. The value of the retention factor comes from the formula[10]:

$$R=Ve70\%+uniform(o)\times(Ve30\%-Ve70\%) \quad (2)$$

One hour average ozone concentration before measurement (OH1) of child's lung function from Camp Care data is used to estimate ozone dose. The exposure for each child is computed as[9]:

$$Dose = Ve \times OH1 \times R \times T \quad (3)$$

Where: OH1: One hour average ozone concentration before lung function measurement

R: retention factor

T: length of exposure period

The FVC data sets is simulated using equations of the form[9]:

$$FVC = \beta \times dose + \varepsilon \quad (4)$$

Where β : choose -0.0002 as a reference point for simulating FVC. This β value was selected based on the FVC regression on a hour-average inhaled ozone exposure presented by P. L. Kenney[16]. The ambient ozone data used in my study was one hour average ozone concentration before lung function measurement.

ϵ: the error term, is assumed to be normally distributed with a mean of zero and std of 0.01, 0,02, 0.03, and 0.04 liters, which are for the sensitive analysis of error term. The valuer of error term estimated from previous studies was

ranged from 0.01 to 0.1.

The size of the error term is crucial. The error term can be estimated from Camp Care data. Since there are not enough data to estimate the error term for dose of ozone from Camp Care data (only ambient ozone pollution measurement OH1 was collected on size), the error term is estimated only for model 3, However through the relationship between model 1 and model 3, the error term can be estimated as the following for models 1 and 2[17]:

$$SS_t = SS_e + SS_m \tag{5}$$

$$R^2 = \frac{SS_m}{SS_t} = \frac{(SS_t - SS_E)}{SS_T} = 1 - \frac{SS_E}{SS_t} \tag{6}$$

$$\frac{SS_e}{SS_t} = 1 - R^2 \tag{7}$$

$$SS_e = (1 - R^2) \times SS_t \tag{8}$$

$$std(r) = \varepsilon(r) = \sqrt{\frac{SS_E}{n-2}} = \sqrt{\frac{(1-R^2) \times SS_t}{n-2}} \tag{9}$$

$$\frac{std\ (r1)}{std\ (r3)} = \frac{\sqrt{\frac{(1-R_1^2)\times SS_{t_1}}{n_1-2}}}{\sqrt{\frac{(1-R_3^2)\times SS_{t_3}}{n_3-2}}} \tag{10}$$

$$SS_{t_1} = SS_{t_3},\ n_1 = n_3 \tag{11}$$

$$\frac{std\ (r1)}{std\ (r3)} = \frac{\sqrt{1-R_1^2}}{\sqrt{1-R_3^2}} \tag{12}$$

Where SS_t: total variation

SS_e: variation of residual

SS_m: variation of model

Then the regression models are as follows:

$$Model\ 1 : FVC = \beta 1 \times dose + \varepsilon 1$$

(considering the retention factor and ventilation)

$$Model\ 2 : FVC = \beta 2 \times doseve + \varepsilon 2$$

(ignoring the retention factor)

$$Model\ 3 : FVC = \beta 3 \times OH1 + \varepsilon 3$$

RESULTS

A total of 20 simulated data sets (dose, doseve, and FVC), are created for one error term. The simulated FVC is used to fit three regression models. The first regression is on ventilation-retention-weighted inhaled exposure (dose). The second regression is on ventilation-weighted inhaled exposure (doseve), where the retention factor is ignored. Finally, FVC is regressed on ozone concentration (OH1), which is typically used to represent ozone exposure in epidemiological studies.

The results from the regressions of each simulation FVC on alternative ozone exposure models are shown in Table 1. Model 1 for each simulation has the best R^2 value. The β value is close to -0.0002 for model 1 but not for model 2 and model 3. The standard deviation of heart rate represents its variation. The larger standard deviation leads to the bigger R^2 value and the difference of R^2 between model 1 and model 3 becomes wider. That is to say, Model 1 can explain more variation than the other models when ventilation of a child changes to a great extent. For the t value, model 1 also has biggest t value, then model 2, and model 3. The figures listed in the last three rows of the table show that different models have a different mean R^2 value, standard deviation, and C.V.. C.V. is the coefficient of variation (standard deviation divided by mean). The C.V. of β for different models are 6.96,

17.93 and 41.64 respectively. The C.V. of model 1 is obviously much smaller than other models. This C.V. shows good precision of β estimation for model 1. The R^2 from the first regression is much larger than those from other regressions. This also indicates that the model 1 can explain the more of total variation than other models so that the model 1 is more accurate. From R^2 and C.V. of table 1, it can be seen that model 2 is better than model 3. As the error terms increased, the same patterns are shown in table 1 except that the difference in the C.V. between models becomes smaller.

Figure 1 demonstrates R^2 distribution in different models with different error terms, which make the results in table 1 more apparent. R^2 value explains the proportion of the total variation that is explained by the models. The R^2 value of model 1 is the biggest, then model 2 and model 3 when the error term is fixed. The bigger the value of error term is, the smaller the value of R^2 it has, the wider the variation is when the model is fixed. Therefore model 1 is much more precise than other 2 models, and model 2 is better than model 3.

Figure 2 shows coefficients in the different models with different errors. It is apparent that the value of the error term has little influence on the average coefficient for each model. However, the coefficients of variation of the different models increase as the error terms become larger. For each error term, model 1 demonstrates the best results.

The regression results for the three models are summarized in Table 2. The P-value is used to estimate the fitness of the different models. Note that in most cases the coefficients are statistically significant. The relative significance of the alternative exposure measurements are of greater interest. Using different ozone exposure models and different values for the error term results in different P-values. When the value of the error term is 0.01, all coefficients of the 20 regressions are statistically significant for model 1; 19 coefficients of the 20 regressions are statistically significant for model 2; and just 15 coefficients of the 20 regressions are positive for model 3. When the value of the error term increases, the number of regressions which are statistically significant decreases for the same exposure model. For example, in model 2, when the error term is 0.01, the number of significant regressions is 19; when error term is 0.04 the number of significant regressions is 13. Model 1 and model 3 show the same trends. This means the size of the error term is crucial. The bigger the value of the error term chosen, the more variation in the model and fewer number of significant models it produces. Not surprisingly, the number of significant regressions does show a consistent pattern of increase in going to more precise exposure measures.

Table 3 shows the results from regressions of simulated FVC on alternative ozone exposure models, and the influence of

individual variation and the value of the error term. Columns 2-4 and columns 5-7 list the results of regressions for controlling and non-controlling individual variation separately. It can be seen that the results of controlling individual variation are better than that from not-controlling variation. For example, the R^2 value in controlling individual variation for model 1 is 0.9778, for model 2 is 0.8640, and for model 3 is 0.5722. But when individual variation is not controlled, the R^2 value for model 1 is 0.9764, for model 2 is 0.8553, for model 3 is 0.3116. Meanwhile, for either controlling individual variation or not, for either bigger or smaller values of the error term, the model 1 (dose) has the best R^2 value, model 2 (doseve) has the better R^2 value, and model 3 (OH1) has the smallest R^2 value. For example, when the error term is 0.01, the R^2 value of model 1 for not controlling individual variation is 0.9764, of model 2 is 0.8553, and of model 3 is 0.3116. When the error term is 0.03, the R^2 value of model 1 is 0.8196, of model 2 is 0.7134, and of model 3 is 0.2852. It also can be seen that the error term influences the results of the regression. When the value of the error term increases, the value of R^2 for different models decreases. For example, for model 1, when the value of the error term is 0.01, the value of R^2 is 0.9764; when value of error term is 0.02, the value of R^2 is 0.8938; when error term is 0.03, the value of R^2 is 0.8196; and when the error term is 0.04, the R^2 is 0.6738. The same situation occurs for model 2

and model 3, for controlling and not-controlling individual variation. In fact, there are three models for which the ventilation-retention-weighted exposure model yields a more significant coefficient than do the ventilation-weighted and average OH1 models. Overall, patterns are most easily seen in the summary statistics printed in columns four and seven of the table. From the t value, the three models are seen to follow the expected pattern, and, when the value of the error term is fixed on 0.01 the differences between R^2 values are significant with C.V. changing from 11.03 (model 1) to 23.44 (model 2), a 2.13 times change; from 23.44 (model 2) to 45.41 (model 3), a 1.93 times change; and from 11.03 (model 1) to 45.41 (model 3), a 4.12 times change.

DISCUSSION

In this study, I examined the general application of quantitative ozone exposure-dose models and assessed the importance of collecting data on minute ventilation or heart rate and retention factor in studies of the acute pulmonary effects of ozone exposure.

It is possible to define an "ozone exposure" equal to the concentration and exposure duration, which can account for a large proportion of the observed variation in responses. However, this concept does not account for the importance of other factors in determining response[18]. At a given "ozone exposure," the response is greater when the concentration is high and Ve low than when concentration is low and Ve high. It is also important to note that predictions based on ozone exposure are, at best, useful for the mean population response. The considerable inter-individual variability in response means that accurate predictions of health responses for individuals often are not possible with the existing ozone data collected by the past health effects studies. The non-linear relationship between ambient ozone concentration and the penetration rate of ozone to the lower airways during various levels of exercise should be considered in interpreting results from different chamber and field studies on ozone[19]. The definition of ozone exposure in terms of an

"ozone dose" should be the product of concentration, ventilation rate, retention factor, and the duration of exposure, which is straightforward in terms of modeling in my study.

To examine the influence of Ve variation on the analytical results of the study, the heart rates of children in Watertown engaged in various types of camp activities were used. The data provided an estimate of the mean heart rates associated with each of the several activities, as well as an indication of the variation in heart rates within activities. The approach of simulation is taken in my study, that is, the simulated acute study data sets of known structure are modeled after the Camp Care data set. Here, FVC data were simulated based on an assumed linear relationship with inhaled exposure. The actual Camp Care ozone measurements was used to simulate an effective ozone dose for each subject. Each child is randomly assigned a heart rate (thus a ventilation rate) from an activity-specific normal distribution of heart rates. The "true" relationship between ozone dose and lung function response is known, and the ability of various imperfect exposure measures to extract the "true" relationship in the context of regression analysis is tested in my study.

The results of my study (β=-0.0002) indicate appreciable change going from the traditional average ozone concentration to the inhaled exposures (effective dose). Because the heart rate data is child-and hour-specific, the findings of

difference and improvement in the precision of the estimates are expected. My study also found a consistent pattern of increase in the significance levels in going to more precise exposure measures. In fact, there were three simulation data sets for which the ozone dose model yielded a more significant coefficient than did the average ozone concentration model. Using the t-statistic, the three models were seen to follow the expected pattern, and the differences were very significant with C.V. changing from 11.03 to 45.41, a 4.12 times change (when the error term is 0.01). The results of the analyses support the notion that ventilation and retention factor can be used to reduce exposure assessment errors significantly, thereby sharpening the power of acute health effects studies. I also chose several other values of β and got similar results.

The analysis of my study assessed the value of "inhaled" pollution exposure as compared to the more traditional average concentration model in assessing acute lung function effects of air pollution. My analysis considered "true" effective dose, which required information on penetration and deposition of air pollution in the lower respiratory tract. The results suggest that a larger improvement in the precision of the slope estimate was obtained because the concentration-specific retention factors in the effective dose calculations had been used.

Level of activity has been determined to be an important

factor influencing the change in the ventilation rate and, consequently, the ozone dose delivered to the respiratory tract[20]. Use of heart rate measurements, along with subject-specific adjustments of calibrations have been found to be useful in predicting ventilation rate. However, the magnitude and functional form of the retention or penetration factor of ozone is not yet reliably known. Penetration of ozone beyond the oropharyngeal region is a complex function of both the ventilation rate and the ozone concentration. Data on ozone retention factors for children do not seem to exist. The mode of breathing (deep or shallow, or nasal or oral) is expected to influence the amount of delivered dose of ozone to the lower lungs[21]. Subject-specific data on the mode of inhalation and pattern of dose delivery rate were found to be among the largest uncertainties of the dose-response characterization of the acute affects of ozone[22]. This is consistent with my results, in which there is some improvement in R^2 from model 2 to model 1. There is no improvement with the coefficient precision going from model 2 to model 1, however. Therefore more studies are needed to explore the retention rate and its effect on effective ozone dose.

SUMMARY AND CONCLUSIONS

In summary, it is important to note that the results of my study are consistent with the hypothesis that an effective dose measure will represent an improvement over conventional concentration-based measures of ozone in the investigations of acute health effects of ozone. As Raizenne and Spengler (1989) stated[9], the application of a child-specific dose calculation is an advantage over the alternative methods for exposure estimates, judging by the substantial variation in the calculated dose among the children during a single six-hour pollution episode. However, during a particular episode, calculated dose varied from 150μg to 750μg. Sample size limitations and lack of detailed knowledge on Ve and R for each child, at each hour, have most likely contributed to the inconclusive findings (Kenney 1986 and Haines 1989), when more refined exposure and dose measures for ozone are tested in health effects investigations. Use of simple effective dose formulations or more complicated ozone dosimetric models have provided new insights into the exposure-response relationships of ozone. The parameter certainties (eg., ventilation) in the dosimetric models can provide a successful demonstration of why these more refined measures of exposure or dose are better in the evaluation of an epidemiologic health data set than the conventional concentration measures of average exposure. Both

clinical and field experiments are recommended to develop new or better information on the specification of the ventilation and retention rates as a function of a subject's age, sex, activity level and type, and ozone concentration. Dosimetric models need to be improved to account for varying patterns and modes of exposure to ozone. The potential effects of changing the dose rate can be studied through numerical simulation studies and animal experiments. It is also worthwhile to re-analyze the data from past camp studies on the acute effects of ozone using alternative dosimetric models, which incorporate parameter uncertainty and temporal tending in the reported spirometry data.

REFERENCES

1. Glossary On Air Pollution, WHO Regional Publications, European Series, No. 9, 73, 1980.

2. S. D. Lee, J. Brian Mudd. Assessing Toxic Effects of Environmental Pollutants, Ann Arbor Science Publishers inc, 151-172, 1979.

3. Frank E. Guthrie and Jerome J. Perry, Introduction to Environmental Toxicology. Elsevier New York, Oxford, 137, 1980.

4. George C. Waldbett, Health Effects of Environmental Pollutants, The C. V. Mosy Company, Saint Louis, 88-91, 1973.

5. Georgel. Waldbott, Health Effects of Environmental Pollutants, Second Edition, 93, 1978.

6. Air Quality Guidelines for Europe, WHO Regional Office for Europe Copenhagen, WHO Regional Publications, European Series, No. 23, 315-325, 1987.

7. Frederick C. Kopfler, Gunther F. Craun. Environmental Epidemiology, Lewis Publishers, INC. 109-122, 1986.

8. A. V. Colucci, Comparison of the Dose / effects Relationship between NO_2 and Other Pollutants, in Air Pollution by Nitrogen Oxides, T. Schneider and L. Grant, eds., Elsevier Scientific Publishing Company, Amsterdea 1982.

9. Relationship between Exposure and Dose and Application of Ozone Dose Models, Department of Environmental Health, Harvard University, Not Published, Internal Material, 1989.

10. J. Young, The Nasal Uptake of Ozone in Human, Master's Essay, Johnes Hopkins University School of Hygiene and Public Health, Baltimore 1977.

11.H. Ozkaynak, B Burbank, A. Garsed, and J. D. Spengler, Statistical Analysis of the Lake Conchiching Health and Aerometric Data, Phase II Draft Report, Report produced for Health Protection Branch, Department of National Health and Welfare, Canada, 1985.

12.M. Lippmann, P. J. Lioy, et al., Effects of Ozone on the Pulmonary Function of Children, Advances in Environ. Toxic. 5: 423-446, 1983.

13. N. Bock, M. Lippmann, et al., The Effects of Ozone on the Pulmonary Function of Children, In Evaluation of the Scientific Basis for Ozone/oxidant Standards, S. D. Lee, ed., Air Pollution Control Association, Pittsburgh 1985.

14. William J. Kennedy Jr., James E. Gentle, Statistical Computing, Marcel Dekker Inc., New York and Basel, P133, 1980.

15. M.E. Reizenne and J.D. Spengler, Dosimetric Model of Acute Health Effects of Ozone and Acid Aerosols in Children. T.Schneider et al., (editors), Atmospheric Ozone Research and Its Policy Implications, Elsevies Science Publisher, B.V., Amsterdam, P319, 1989.

16. Patrick L. Kinney, Haluk Ozkaynak. Choosing an Exposure Metric for Investigating Acute Pulmonary Function Effects of Air Pollution. 79th Annual Meeting of the Air Pollution Control Association, Minneapolis, MN June 22-26,

1986.

17. David g. Kleinbaum, Lawrence L. Kuppre, and Keith E. Muller, Applied Regression Analysis and Other Multivariable Methods, PWS-KENT Publishing Company, Boston, 80-91, 1987.

18. E. P. Radford, Jr., B. G. Ferris, et al., Clinical Use of a Nomogram to Estimate Proper Ventilation During Artificial Respiration, N. E. J. Med., 251: pp877-883, November 25, 1984.

19. Folinsbee, L.J., Drinkwater, B.L., and Horvath, S.M. The Influence of Exercise on the Pulmonary Changes Due to Low Concentrations of Ozone, in Environmental Stress: Individual Human Adaptations, L.J. Folinsbee, et al. Academic Press, New York, pp. 125-145, 1978.

20. Adams, W.C., Savin, W.M. Detection of Ozone Toxicity During Continuous Exercise Via the Effective Dose Content, J.Appl. Physiol., Resp. Environ. Exercise Physiol. 51:415_422, 1981.

21. J.D. Spengler, Exposures to Ozone and Respirable Particles in an Acute Health Study at Camp Couchiching : Indoor Air Pollution Monitoring, Final Report- Harvard School of Public Health, Boston 1984.

22. D. T. Mage, Statistical Relationships between Exposure and Dose, In Quality Assurance in Air Pollution Measurements. T. R. Johneson and S. R. Penkala, eds., TR-3, pp279-286, Air Pollution Control Association, Pittsburgh 1985.

APPENDICES

1. TABLES

Table 1 The Results from the Regressions of Simulated FVC on Alternative Ozone Esposure Models

error=0.01

			DOSE			DOSEVE			OH1		
	mean	std	R2	β	t	R2	β	t	R2	β	t
1	91	18	0.9328	-0.00023	-12.40	0.8211	-0.00010	-7.18	0.5925	-0.00078	-4.12
2	120	24	0.9659	-0.00021	-17.69	0.4305	-0.00007	-3.05	0.0520	-0.00046	-1.27
3	140	28	0.9920	-0.00020	-36.98	0.6714	-0.00007	-4.85	0.6644	-0.00173	-4.77
4	137	27	0.9808	-0.00021	-23.76	0.8945	-0.00010	-9.71	0.2297	-0.00168	-2.07
5	125	25	0.9850	-0.00020	-26.87	0.8897	-0.00010	-9.47	0.8470	-0.00189	-7.87
6	89	18	0.7700	-0.00021	-6.15	0.7454	-0.00010	-5.76	0.6692	-0.00079	-4.82
7	137	27	0.9910	-0.00019	-34.75	0.7752	-0.00010	-6.24	0.0876	-0.00105	-0.98
8	104	21	0.9874	-0.00019	-29.34	0.9462	-0.00010	-13.95	0.4400	-0.00132	-3.11
9	107	21	0.8748	-0.00021	-8.82	0.6497	-0.00008	-4.63	0.3575	-0.00080	-2.67
10	141	28	0.9721	-0.00019	-19.59	0.9173	-0.00010	-11.09	0.6398	-0.00181	-4.53
11	86	17	0.5523	-0.00018	-3.82	0.2098	-0.00005	-1.98	0.2315	-0.00033	-2.08
12	137	27	0.9739	-0.00019	-20.28	0.8568	-0.00010	-8.17	0.4629	-0.00215	-3.24
13	124	25	0.9864	-0.00024	-28.22	0.8336	-0.00009	-7.49	0.6142	-0.00189	-4.30
14	104	21	0.8801	-0.00021	-9.04	0.6084	-0.00006	-4.25	0.4922	-0.00075	-3.42
15	128	26	0.9685	-0.00021	-18.41	0.9055	-0.00010	-10.32	0.6240	-0.00152	-4.39
16	121	24	0.9814	-0.00021	-24.10	0.8819	-0.00010	-9.12	0.6997	-0.00179	-5.16
17	121	24	0.8908	-0.00022	-9.53	0.6461	-0.00007	-4.59	0.4242	-0.00086	-3.02
18	121	24	0.9736	-0.00022	-20.17	0.7460	-0.00011	-5.77	0.7310	-0.00194	-5.56
19	112	22	0.9821	-0.00019	-24.61	0.8247	-0.00009	-7.26	0.7503	-0.00169	-5.84
20	141	28	0.9764	-0.00019	-21.36	0.7567	-0.00010	-5.93	0.2423	-0.00109	-2.13
MEAN			0.9308	-0.00020	-19.7945	0.7505	-0.00008	-7.0405	0.4926	-0.00132	-3.7675
STD			0.1026	0.000014	9.042504	0.1759	0.000016	2.871014	0.2236	0.000541	1.654995
C.V.			11.03	-6.96	-45.68	23.44	-17.93	-40.78	45.41	-41.04	-43.93

Table 1 continued

error=0.02

	mean	std	DOSE R2	DOSE β	DOSE t	DOSEVE R2	DOSEVE β	DOSEVE t	OH1 R2	OH1 β	OH1 t
1	91	18	0.7715	-0.00040	-6.18	0.3736	-0.00010	-2.75	0.1427	-0.00051	-1.68
2	120	24	0.8345	-0.00019	-7.51	0.7469	-0.00010	-5.78	0.2112	-0.00088	-1.99
3	140	28	0.9650	-0.00021	-17.44	0.6320	-0.00008	-4.46	0.1101	-0.00150	-1.54
4	137	27	0.7914	-0.00016	-6.54	0.7810	-0.00008	-6.34	0.6434	-0.00164	-4.57
5	125	25	0.7305	-0.00017	-5.55	0.6916	-0.00009	-5.07	0.1230	-0.00063	-1.60
6	89	18	0.2397	-0.00017	-2.11	0.1780	-0.00006	-1.84	0.1451	-0.00046	-1.69
7	137	27	0.9648	-0.00021	-17.39	0.9047	-0.00014	-10.27	0.3974	-0.00275	-2.87
8	104	21	0.5826	-0.00015	-4.04	0.7185	-0.00006	-5.39	0.6889	-0.00072	-5.04
9	107	21	0.7842	-0.00020	-6.40	0.6363	-0.00007	-4.50	0.3639	-0.00082	-2.70
10	141	28	0.9252	-0.00023	-11.71	0.7789	-0.00012	-6.31	0.4044	-0.00165	-2.91
11	86	17	0.1778	-0.00013	-1.84	0.1487	-0.00004	-1.71	0.1015	-0.00033	-1.50
12	137	27	0.8885	-0.00018	-9.41	0.6608	-0.00007	-4.74	0.4530	-0.00163	-3.18
13	124	25	0.5056	-0.00013	-3.50	0.2605	-0.00006	-2.21	0.1134	-0.00061	-1.55
14	104	21	0.7089	-0.00020	-5.27	0.7005	-0.00009	-5.17	0.6140	-0.00111	-4.30
15	128	26	0.8056	-0.00021	-6.83	0.7440	-0.00010	-5.74	0.4586	-0.00119	-3.21
16	121	24	0.8543	-0.00017	-8.09	0.6822	-0.00008	-4.96	0.3223	-0.00080	-2.50
17	121	24	0.7236	-0.00015	-5.46	0.7272	-0.00007	-5.51	0.3657	-0.00085	-2.71
18	121	24	0.9093	-0.00022	-10.55	0.8595	-0.00011	-8.26	0.6448	-0.00185	-4.58
19	112	22	0.5449	-0.00015	-3.76	0.4794	-0.00006	-3.34	0.3053	-0.00057	-2.42
20	141	28	0.8996	-0.00023	-9.98	0.8230	-0.00011	-7.22	0.3057	-0.00187	-2.42
MEAN			0.7303	-0.00019	-7.48	0.6263	-0.00008	-5.08	0.3457	-0.00112	-2.75
STD			0.2153	0.000056	4.21	0.2153	0.000024	2.07	0.1898	0.000609	1.09
C.V.			29.48	-28.33	-56.27	34.38	-29.42	-40.68	54.92	-54.29	-39.58

Table 1 continued

error=0.03

			DOSE			DOSEVE			OH1		
	mean	std	R2	β	t	R2	β	t	R2	β	t
1	91	18	0.1043	-0.00012	-1.08	0.0512	-0.00003	-0.74	0.0539	-0.0003	-0.75
2	120	24	0.4583	-0.00014	-3.21	0.4122	-0.00006	-2.95	0.3446	-0.0011	-2.61
3	140	28	0.8785	-0.00020	-8.98	0.8219	-0.00009	-7.19	0.8334	-0.0026	-7.49
4	137	27	0.7593	-0.00018	-5.98	0.5955	-0.00006	-4.15	0.5817	-0.0017	-4.04
5	125	25	0.9148	-0.00020	-10.92	0.7094	-0.00010	-5.28	0.3550	-0.0023	-2.66
6	89	18	0.2959	-0.00017	-2.37	0.2280	-0.00007	-2.06	0.3649	-0.0006	-2.71
7	137	27	0.6988	-0.00016	-5.15	0.6799	-0.00008	-4.94	0.4099	-0.0015	-2.94
8	104	21	0.4337	-0.00022	-3.07	0.1967	-0.00007	-1.92	0.2150	-0.0010	-2.00
9	107	21	0.7685	-0.00025	-6.12	0.8070	-0.00014	-6.86	0.5793	-0.0022	-4.02
10	141	28	0.8195	-0.00016	-7.14	0.9095	-0.00005	-4.26	0.4767	-0.0011	-3.32
11	86	17	0.0159	-0.00006	-0.40	0.0293	-0.00003	-0.55	0.0453	-0.0003	-0.69
12	137	27	0.8264	-0.00020	-7.31	0.7941	-0.00011	-6.59	0.6319	-0.0027	-4.46
13	124	25	0.8613	-0.00024	-8.32	0.6636	-0.00010	-4.76	0.2544	-0.0014	-2.18
14	104	21	0.6283	-0.00035	-4.43	0.7107	-0.00015	-5.29	0.4823	-0.0014	-3.35
15	128	26	0.4595	-0.00015	-3.22	0.4091	-0.00007	-2.94	0.1882	-0.0008	-1.88
16	121	24	0.9069	-0.00023	-10.40	0.9030	-0.00014	-10.17	0.7881	-0.0030	-6.47
17	121	24	0.5976	-0.00016	-4.16	0.6357	-0.00007	-4.49	0.3796	-0.0015	-2.78
18	121	24	0.6234	-0.00023	-4.38	0.4615	-0.00009	-3.23	0.2455	-0.0010	-2.14
19	112	22	0.5644	-0.00020	-3.91	0.3721	-0.00010	-2.74	0.1528	-0.0009	-1.73
20	141	28	0.9639	-0.00020	-17.17	0.8915	-0.00014	-9.56	0.3111	-0.0031	-2.44
MEAN			0.6289	-0.00019	-5.88	0.5640	-0.00009	-4.5335	0.3846	-0.00153	-3.03285
STD			0.2614	0.00006	3.82	0.2723	0.00003	2.534916	0.2134	0.00084	1.628176
C.V.			41.57	-29.93	-64.89	48.28	-39.57	-55.92	55.48	-54.86	-53.68

Table 1 continued

error=0.04

			DOSE			DOSEVE			OH1		
	mean	std	R2	β	t	R2	β	t	R2	β	t
1	91	18	0.1563	-0.00016	-1.74	0.1675	-0.00006	-1.79	0.0919	-0.0009	-1.45
2	120	24	0.4373	-0.00020	-3.09	0.3323	-0.00007	-2.55	0.0585	-0.0007	-1.30
3	140	28	0.9126	-0.00024	-10.76	0.9020	-0.00013	-10.11	0.6756	-0.0038	-4.89
4	137	27	0.6592	-0.00019	-4.72	0.6339	-0.00006	-4.48	0.3469	-0.0012	-2.62
5	125	25	0.6231	-0.00014	-4.38	0.5310	-0.00006	-3.67	0.5522	-0.0013	-3.82
6	89	18	0.0304	-0.00050	-0.56	0.0949	-0.00004	-1.02	0.0749	-0.0037	-0.90
7	137	27	0.7857	-0.00018	-6.43	0.4138	-0.00007	-2.96	0.0729	-0.0012	-1.37
8	104	21	0.1869	-0.00019	-1.88	0.0747	-0.00007	-1.37	0.0486	-0.0004	-0.79
9	107	21	0.5876	-0.00017	-4.08	0.6552	-0.00010	-4.68	0.4691	-0.0020	-3.27
10	141	28	0.3697	-0.00022	-2.73	0.0387	-0.00004	-1.20	0.1289	-0.0009	-1.62
11	86	17	0.0565	0.00010	0.77	0.0234	0.00002	0.49	0.0580	0.0004	0.79
12	137	27	0.7749	-0.00026	-6.23	0.6888	-0.00011	-5.03	0.2124	-0.0018	-1.99
13	124	25	0.7253	-0.00021	-5.48	0.6969	-0.00014	-5.13	0.5982	-0.0024	-4.17
14	104	21	0.0750	-0.00006	-1.38	0.1651	-0.00004	-1.78	0.2222	-0.0006	-2.04
15	128	26	0.7632	-0.00021	-6.04	0.7121	-0.00011	-5.31	0.3760	-0.0021	-2.76
16	121	24	0.6966	-0.00019	-5.12	0.6930	-0.00009	-5.08	0.3589	-0.0010	-2.68
17	121	24	0.6029	-0.00021	-4.21	0.4507	-0.00009	-3.17	0.5380	-0.0017	-3.72
18	121	24	0.4614	-0.00018	-3.23	0.6406	-0.00011	-4.54	0.5354	-0.0015	-3.70
19	112	22	0.0737	-0.00010	-1.37	0.0577	-0.00003	-1.29	0.1450	-0.0007	-1.69
20	141	28	0.7594	-0.00023	-5.98	0.7465	-0.00001	-5.78	0.3556	-0.0025	-2.66
MEAN			0.4868	-0.00019	-3.93	0.4359	-0.00007	-3.52305	0.2959	-0.00150	-2.3318
STD			0.2852	0.00010	2.55	0.2829	0.00004	2.313929	0.2050	0.00102	1.328893
C.V.			58.58	-56.11	-64.80	64.90	-55.96	-65.68	69.29	-67.62	-56.99

Table 2 The Number of Statistically Significant Coefficients by Alternative Ozone Exposure Models

		ERROR			
		0.01	0.02	0.03	0.04
DOSE	NO	20	20	20	20
	N+	20	18	18	14
DOSEVE	NO	20	20	20	20
	N+	19	17	16	13
OH1	NO	20	20	20	20
	N+	15	13	13	10

NO: sample size

N+: number of regressions being statistically significant

Table 3 The Summarized Results from the Regression of Simulated FVC on Alternative Ozone Exposure Models

		Not controlling individual variation			Controlling individual variation		
		R2	β	t	R2	β	t
ERROR=0.01	dose	0.9764	-0.00020	-99.34	0.9778	-0.00021	-84.19
	doseve	0.8553	-0.00010	-37.61	0.8640	-0.00009	-31.24
	OH1	0.3116	-0.00132	-10.45	0.5722	-0.00132	-12.69
ERROR=0.02	dose	0.8938	-0.00021	-44.86	0.9224	-0.00020	-37.00
	doseve	0.7794	-0.00010	-29.08	0.8352	-0.00009	-22.99
	OH1	0.1698	-0.00110	-7.06	0.6106	-0.00110	-9.87
ERROR=0.03	dose	0.8196	-0.00020	-32.96	0.8309	-0.00020	-27.81
	doseve	0.7134	-0.00010	-24.41	0.7392	-0.00010	-20.60
	OH1	0.2852	-0.00150	-9.82	0.5220	0.00151	-11.49
ERROR=0.04	dose	0.6738	-0.00019	-22.24	0.7023	-0.00020	-19.59
	doseve	0.5942	-0.00009	-18.74	0.6344	-0.00089	-16.49
	OH1	0.2366	-0.00134	-8.66	0.4202	-0.00134	-9.52

one simulation for each kid for 12 days
20 kid simulations
β=-0.0002
fvc=β*dose+N(0,error)
dose=r*Ve*OH1; doseve=Ve*OH1
Ve=exp(0.7884+0.016*hr)
r:retation rate; hr: heart rate
OH1: ozone conc. one hour before measurement of fvc

2. FIGURES

Figure 1 The R^2 Variation in Alternative Ozone Exposure Models with Different Error Terms

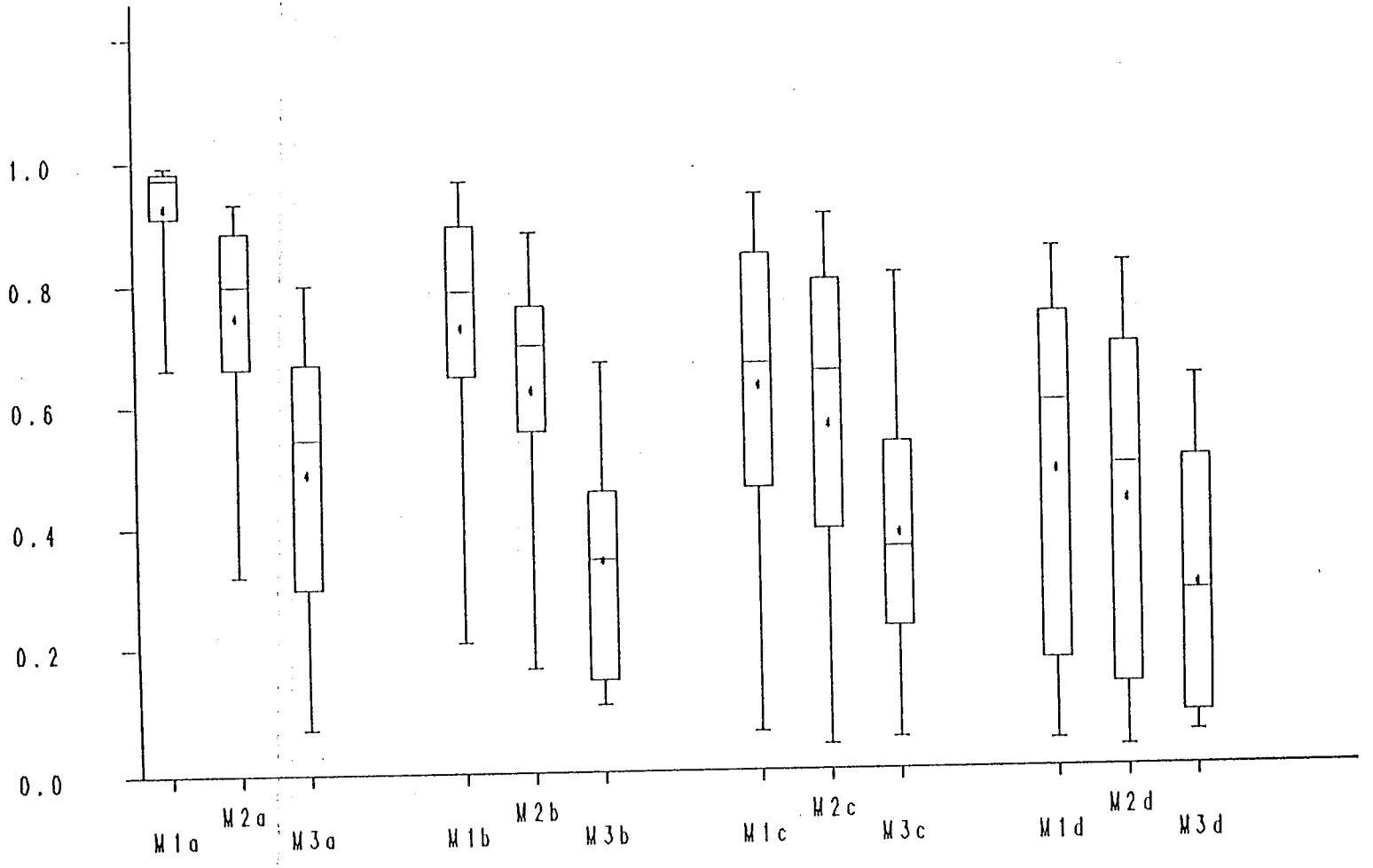
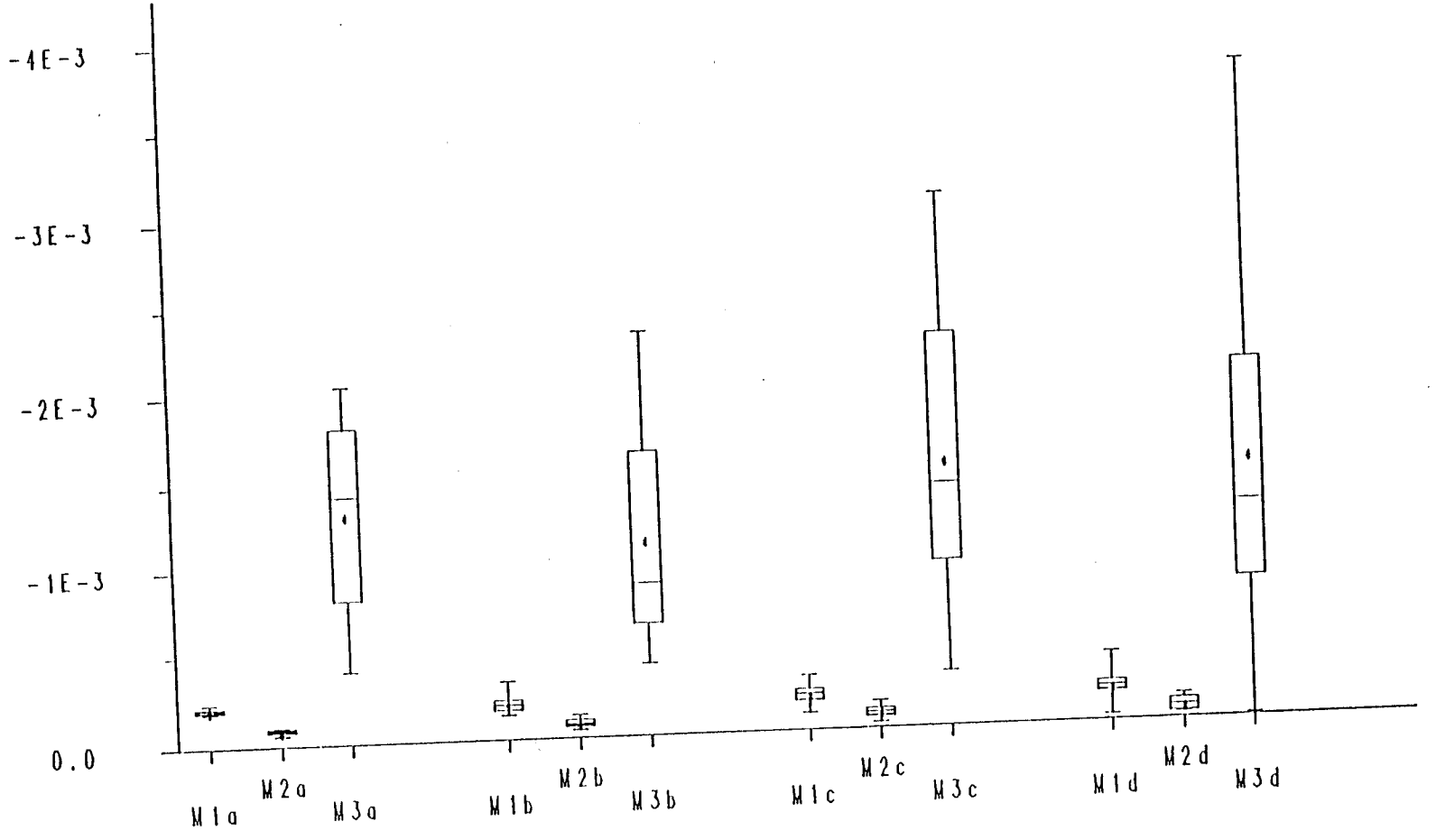


Figure 2 The Coefficient Variation in Alternative Ozone Exposure Models with Different Error Terms



3. LIST OF DEFINITIONS

1. Ventilation Rate: Volume of the air taken in by the respiratory tract per unit time, eg., minute ventilation.

2. Retention Factor: The proportion of inhaled pollutant which penetrates to the trachea and get into the circulative system.

3. Error term: In simple linear regression model, an observation deviates from the line by a random amount ϵ, The random deviation is assumed to have a normal distribution with mean zero and standard deviation , and random deviations for different observation are assumed independent of one another.

4. Simulation: One of statistical methods which uses an random number generator via an equation and algorithm to mimic a real situation and testify how it changes as a function of other variables.

5. Exposure: Amount of pollutant which is measured or measurable in the environment.

6. Dose: Amount of pollutant which is delivered to the organs or tissues where the effect is manifested.

7. FVC: Forced vital capacity.

8. Short-term Effects: Acute biologic response caused by exposure to a toxic agent in a short period of time.

9. Long-term Effects: Chronic biologic response caused by exposure to a toxic agent in a long period of time.

4. SAS PROGRAMS

```
OPTIONS PS=55;
  libname gin 'c:\canada\';
%let hmean=104;
%let hstd=21;
%let kid=8;

DATA A;
SET GIN.CARE1;
WHERE ID=4001;
KEEP ID OH1;
*****************************
DATA GIN.n&kid;
SET A;
k=&kid;
H1=&hmean + &hstd*NORMAL(0);
H2=&hmean + &hstd*NORMAL(0);
H3=&hmean + &hstd*NORMAL(0);
*****************************


H=MEAN(OF H1-H3);
VE=EXP(0.7884+0.016*H);

R5=0.084+UNIFORM(0)*(0.156-0.084);
R15=0.2478+UNIFORM(0)*(0.4602-0.2478);
R30=0.3178+UNIFORM(0)*(0.5902-0.3178);
R50=0.3752+UNIFORM(0)*(0.6968-0.3752);
IF VE LE 5 THEN R=R5;
  ELSE IF VE LE 15 THEN R=R15;
  ELSE IF VE LE 30 THEN R=R30;
  ELSE R=R50;
DOSE=R*VE*OH1;
DOSEVE=VE*OH1;
err=0.020*normal(0);
fvc=(-0.0002)*dOSE+err;
fvc=fvc*1000;
DROP H1-H3 R5 R15 R30 R50;

proc reg;
model fvc=dOSE;
run;

proc reg;
model fvc=dOSEVE;
run;

proc reg;
model fvc=OH1;
run;
```

```
goptions device=HPLJ5P2 rotate;
OPTIONS PS=55;
libname gin 'c:\CANADA\YU\';


data Y missover;
input  FUNCTION $  X  Y TEXT $ 28-31;
XSYS='5'; YSYS='5';
cards;
move        20        83
draw        20        20  /*  Y axis from 20% to 83%  */
draw        90        20  /*  X axis from 20% to 90%  */
move        20        20
draw        19        20
move        20        30
draw        19        30
move        20        40
draw        19        40
move        20        50
draw        19        50
move        20        60
draw        19        60
move        20        70
draw        19        70
move        20        80
draw        19        80
label       14        20      0.0
label       14        30      0.2
label       14        40      0.4
label       14        50      0.6
label       14        60      0.8
label       14        70      1.0
label       14        80
;

DATA DATAD;
SET GIN.R2B;
IF PARA='B' THEN DELETE;
ARRAY UU A1-A3 B1-B3 C1-C3 D1-D3;
DO OVER UU;
IF PARA NE 'M1' AND PARA NE 'M2' THEN UU=UU*50+20;
END;



data PP missover;
input xx $  YY  text $  20-30  size  35-37;
cards;
TOP     70
HIGH    62
MEDIAN  50
```

```
MEAN     53          *              0.8
LOW      39
BOT      29
M1       19.2                       0.8
M2       20
LABEL    14
;

DATA A1;
MERGE DATAD(KEEP=A1) PP;
Y=A1;
IF XX='LABEL' THEN DO; TEXT='M1a';Y=15;END;
DROP A1 YY;

DATA A2;
MERGE DATAD(KEEP=A2) PP;
Y=A2;
IF XX='LABEL' THEN DO; TEXT='M2a';Y=17;END;
DROP A2 YY;

DATA A3;
MERGE DATAD(KEEP=A3) PP;
Y=A3;
IF XX='LABEL' THEN DO; TEXT='M3a';Y=15;END;
DROP A3 YY;

DATA b1;
MERGE DATAD(KEEP=b1) PP;
Y=b1;
IF XX='LABEL' THEN DO; TEXT='M1b';Y=15;END;
DROP b1 YY;

DATA b2;
MERGE DATAD(KEEP=b2) PP;
Y=b2;
IF XX='LABEL' THEN DO; TEXT='M2b';Y=17;END;
DROP b2 YY;

DATA b3;
MERGE DATAD(KEEP=b3) PP;
Y=b3;
IF XX='LABEL' THEN DO; TEXT='M3b';Y=15;END;
DROP b3 YY;

DATA c1;
MERGE DATAD(KEEP=c1) PP;
Y=c1;
IF XX='LABEL' THEN DO; TEXT='M1c';Y=15;END;
DROP c1 YY;

DATA c2;
MERGE DATAD(KEEP=c2) PP;
```

```
Y=c2;
IF XX='LABEL' THEN DO; TEXT='M2c';Y=17;END;
DROP c2 YY;

DATA c3;
MERGE DATAD(KEEP=c3) PP;
Y=c3;
IF XX='LABEL' THEN DO; TEXT='M3c';Y=15;END;
DROP c3 YY;

DATA d1;
MERGE DATAD(KEEP=d1) PP;
Y=d1;
IF XX='LABEL' THEN DO; TEXT='M1d';Y=15;END;
DROP d1 YY;

DATA d2;
MERGE DATAD(KEEP=d2) PP;
Y=d2;
IF XX='LABEL' THEN DO; TEXT='M2d';Y=17;END;
DROP d2 YY;

DATA d3;
MERGE DATAD(KEEP=d3) PP;
Y=d3;
IF XX='LABEL' THEN DO; TEXT='M3d';Y=15;END;
DROP d3 YY;

DATA BA1 MISSOVER;
input function $ x XX $;
xsys='5'; ysys='5';
X=X/2.5+21;
N=_N_;
cards;
move        1        TOP
draw        3        TOP
move        2        TOP
draw        2        HIGH
move        0        HIGH
draw        4        HIGH
draw        4        LOW
draw        0        LOW
draw        0        HIGH
move        2        LOW
draw        2        BOT
move        1        BOT
draw        3        BOT
move        0        MEDIAN
draw        4        MEDIAN
move        2        M1
draw        2        M2
LABEL       2        LABEL
```

```
LABEL       2         MEAN
;

DATA BA2 MISSOVER;
input function $ x XX $;
xsys='5'; ysys='5';
X=X/2.5+4+21;
N=_N_;
cards;
move        1         TOP
draw        3         TOP
move        2         TOP
draw        2         HIGH
move        0         HIGH
draw        4         HIGH
draw        4         LOW
draw        0         LOW
draw        0         HIGH
move        2         LOW
draw        2         BOT
move        1         BOT
draw        3         BOT
move        0         MEDIAN
draw        4         MEDIAN
move        2         M1
draw        2         M2
LABEL       2         LABEL
LABEL       2         MEAN
;

DATA BA3 MISSOVER;
input function $ x XX $;
xsys='5'; ysys='5';
X=X/2.5+4+4+21;
N=_N_;
cards;
move        1         TOP
draw        3         TOP
move        2         TOP
draw        2         HIGH
move        0         HIGH
draw        4         HIGH
draw        4         LOW
draw        0         LOW
draw        0         HIGH
move        2         LOW
draw        2         BOT
move        1         BOT
draw        3         BOT
move        0         MEDIAN
draw        4         MEDIAN
move        2         M1
```

```
draw        2        M2
LABEL       2        LABEL
LABEL       2        MEAN
;


PROC SORT DATA=BA1 OUT=BA1;
BY XX;
RUN;

PROC SORT DATA=BA2 OUT=BA2;
BY XX;
RUN;

PROC SORT DATA=BA3 OUT=BA3;
BY XX;
RUN;

PROC SORT DATA=a1 OUT=a1;
BY XX;
RUN;

PROC SORT DATA=a2 OUT=a2;
BY XX;
RUN;

PROC SORT DATA=a3 OUT=a3;
BY XX;
RUN;

PROC SORT DATA=b1 OUT=b1;
BY XX;
RUN;

PROC SORT DATA=b2 OUT=b2;
BY XX;
RUN;

PROC SORT DATA=b3 OUT=b3;
BY XX;
RUN;

PROC SORT DATA=c1 OUT=c1;
BY XX;
RUN;

PROC SORT DATA=c2 OUT=c2;
BY XX;
RUN;

PROC SORT DATA=c3 OUT=c3;
BY XX;
```

```
RUN;

PROC SORT DATA=d1 OUT=d1;
BY XX;
RUN;

PROC SORT DATA=d2 OUT=d2;
BY XX;
RUN;

PROC SORT DATA=d3 OUT=d3;
BY XX;
RUN;

DATA a1;
MERGE a1 BA1;
BY XX;

DATA a2;
MERGE a2 BA2;
BY XX;

DATA a3;
MERGE a3 BA3;
BY XX;

DATA b1;
MERGE b1 BA1;
BY XX;

DATA b2;
MERGE b2 BA2;
BY XX;

DATA b3;
MERGE b3 BA3;
BY XX;

DATA c1;
MERGE c1 BA1;
BY XX;

DATA c2;
MERGE c2 BA2;
BY XX;

DATA c3;
MERGE c3 BA3;
BY XX;

DATA d1;
MERGE d1 BA1;
```

```
BY XX;

DATA d2;
MERGE d2 BA2;
BY XX;

DATA d3;
MERGE d3 BA3;
BY XX;

PROC SORT DATA=a1 OUT=a1;
BY N;
RUN;

PROC SORT DATA=a2 OUT=a2;
BY N;
RUN;

PROC SORT DATA=a3 OUT=a3;
BY N;
RUN;

PROC SORT DATA=b1 OUT=b1;
BY N;
RUN;

PROC SORT DATA=b2 OUT=b2;
BY N;
RUN;

PROC SORT DATA=b3 OUT=b3;
BY N;
RUN;

PROC SORT DATA=c1 OUT=c1;
BY N;
RUN;

PROC SORT DATA=c2 OUT=c2;
BY N;
RUN;

PROC SORT DATA=c3 OUT=c3;
BY N;
RUN;

PROC SORT DATA=d1 OUT=d1;
BY N;
RUN;

PROC SORT DATA=d2 OUT=d2;
BY N;
```

```
RUN;

PROC SORT DATA=d3 OUT=d3;
BY N;
RUN;


DATA AA;
SET A1 A2 A3;


DATA BB;
SET B1 B2 B3;
X=X+17;

DATA CC;
SET C1 C2 C3;
X=X+17*2;

DATA DD;
SET D1 D2 D3;
X=X+17*3;


DATA TOT;
SET Y AA BB CC DD;

proc gslide annotate=TOT;
TITLE2 h=2 F=CENTX 'Figure 1 The R2 Variations in
Alternative Ozone';
TITLE3 h=2 F=CENTX 'Exposure Models with different Error
Terms';
run;
```