

**Comments on the Use of the Cox Proportional Hazards
Model to Assess the Association Between Air Pollutant
Exposure and Health Effects in Semi-Ecological Studies**

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The American Petroleum Institute
1220 L Street, NW
Washington, DC 20005-4070

Prepared by
Julie E. Goodman, Ph.D., DABT
Juhi K. Chandalia, M.S.

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Table of Contents

	<u>Page</u>
Executive Summary.....	ES-1
1 Background.....	1
2 The Cox Proportional Hazard Model	2
3 Limitations of the Standard Cox Proportional Hazard Model	4
4 The Flexible Cox Model.....	6
References	9

Executive Summary

In the 2010 *Policy Assessment for the Review of the Particulate Matter National Ambient Air Quality Standards, Second External Review Draft*, US EPA relies on studies that use traditional and flexible Cox proportional hazard (PH) models to calculate the risks of health effects associated with exposure to particulate matter. There are several potential problems with these models, including:

- The assumptions of the traditional Cox PH model are often violated in these studies, which may result in biased risk estimates; and
- The flexible Cox PH models relax traditional assumptions to allow nonlinear and time-dependent effects at the price of model complexity and uncertainty, meaning one cannot always determine with certainty which flexible model is most appropriate.

The over-reliance on studies that do not verify model assumptions, or choose to relax those assumptions, may lead to biased concentration-response (C-R) functions, particularly at low exposure concentrations. Thus, US EPA should use caution when using these studies to inform rulemaking, such as the particulate matter (PM) National Ambient Air Quality Standards (NAAQS).

1 Background

In the 2010 *Policy Assessment for the Review of the Particulate Matter National Ambient Air Quality Standards, Second External Review Draft* (US EPA, 2010; hereinafter referred to as the PA), US EPA considers several semi-ecological studies of PM_{2.5} and health effects that rely on either traditional or flexible Cox proportional hazard (PH) models to estimate concentration-response (C-R) associations and calculate risks. As discussed below, the underlying assumptions of the traditional Cox PH model are not always met in these studies, which could possibly lead to biased risk estimates. While flexible Cox PH models used in other PM_{2.5} studies are not dependent on these assumptions, they are dependent upon parameter specification. Estimates of both nonlinearity and time-dependence vary depending upon the degrees of freedom and other parameters in flexible models, yet there is currently no standardized method for determining which parameters are most appropriate, and models that fit the data equally well can have different shapes and result in different risk estimates.

Because analyses based on traditional Cox PH models can be flawed when the basic model assumptions are violated, while flexible Cox PH models are not standardized or fully understood, US EPA should use caution when relying on PM health effects studies that use either the traditional or flexible Cox PH model to inform the PM National Ambient Air Quality Standards (NAAQS).

2 The Cox Proportional Hazard Model

The Cox PH model is a "survival" analysis model, meaning it assesses the hazard of an event occurring at time t given a person has not experienced that event up to time t . The Cox PH model is semi-parametric in that it has both a parametric and a nonparametric component. In semi-ecological studies of air pollutant exposure and health effects, individuals are followed through time and it is determined whether exposure increases risk over the baseline hazard rate. The time-dependent hazard rate is represented by $\lambda(t)$. The basic Cox PH model indicates that the hazard at time t for an individual i exposed to X at time t is

$$\lambda_i(t) = \lambda_0(t) e^{\beta X_i(t)} \quad (1)$$

with $\lambda_0(t)$ representing the unexposed or base-case hazard rate. In this model, neither $\lambda_0(t)$, nor $\lambda_i(t)$ need to be specified, as one is only concerned whether and how much the hazard increases at time t with X . This increase in risk over baseline is represented as the hazard ratio, $\lambda_i(t)/\lambda_0(t)$, and can be calculated by transforming equation (1) to:

$$\lambda_i(t) / \lambda_0(t) = e^{\beta X_i(t)} \quad (2)$$

Taking the natural log of both sides results in:

$$\ln[\lambda_i(t) / \lambda_0(t)] = \beta X_i(t) \quad (3)$$

To account for potential confounders (sex, age, and city in this example) and random error, the calculation of the log of the hazard ratio can be adjusted as follows:

$$\ln[\lambda_i(t) / \lambda_0(t)] = \beta X_i(t) + \theta_1 sex_i + \theta_2 age_i + \theta_3 city_i + \varepsilon_i(t) \quad (4)$$

The θ terms are the coefficients for each of the covariates, and are not functions of time or exposure. The coefficient, β , is the increase in the hazard of a health effect over baseline adjusted for the covariates and random error.

The basic Cox PH model is based on two main assumptions:

1. The hazard rate of individual i at time t , $\lambda_i(t)$, is proportional (*via* the multiplicative term $e^{\beta X_i(t)}$) to the base-case hazard rate at time t , $\lambda_0(t)$. That is, the size of the effect of the exposure and other covariates on the hazard (*i.e.*, β and all θ terms) are constant over the study period and not functions of X or t .
2. Exposure and other covariates contribute linearly to the natural log of the hazard ratio.

3 Limitations of the Standard Cox Proportional Hazard Model

When all of the assumptions of the Cox PH model are not met, it is possible that subsequent analyses and risk estimates will be biased. Some of these assumptions are usually violated in semi-ecological studies of exposure to air pollutants and health effects (Moolgavkar, 2005), including several long-term PM_{2.5} exposure studies referenced in the *Integrated Science Assessment for Particulate Matter* (PM ISA, US EPA, 2009) and the PA (*e.g.*, Beelen *et al.*, 2008; Miller *et al.*, 2007; Jerrett *et al.*, 2005; Laden *et al.*, 2006). In these studies, the model assumptions are generally violated in two ways. First, the assumption of the time-independence of the hazard ratio may not be correct – the impacts of exposure and other potential confounders likely vary over time. For instance, Moolgavkar (2006) noted that cigarette smoking, a potential confounder of the PM_{2.5} mortality association, has a time-varying effect on cardiovascular mortality. Second, the assumption of linearity may fail; *e.g.*, body mass index (BMI), another potential confounder of the PM_{2.5} exposure and mortality association, contributes nonlinearly to mortality risk (Krewski *et al.*, 2000; Abrahamowicz *et al.*, 2003).

As stated by Abrahamowicz *et al.* (2003):

[T]he proportional hazards (PH) assumption... implies that the impact of each covariate on hazard remains constant during the entire follow-up time. While testing the PH assumption is interesting in its own right, simultaneous modeling of nonlinear and time dependent effects of the exposure of interest may be necessary to avoid biased estimates and incorrect conclusions.

Two papers cited by US EPA in the PM PA used the Cox PH model assuming linearity and time-independence without a systematic check of the validity of these assumptions (Miller *et al.*, 2007; Pope *et al.*, 2002). Miller *et al.* (2007) did not conduct any analyses to examine the validity of these assumptions and, while Pope *et al.* (2002) did to an extent, they did not do so systematically. Specifically, Pope *et al.* (2002) partially addressed the PH assumption by stratifying across such demographic variables as sex, race, and 1-year age category in order to allow for different baseline hazard functions across the categories. In the main analysis, they employed a two-stage model fitting. The first step used the standard Cox PH model and the second step used an explicitly linear model. As an additional analysis, they examined non-parametrically smoothed C-R relationships and concluded they are not significantly different from linear associations ($p > 0.20$). While Pope *et al.* (2002) relaxed the linear assumption by allowing linear and quadratic covariates, a more general spline model may have been more appropriate than explicit parametric functions (discussed below).

Because the validity of the assumptions of the Cox PH model were not systematically tested in the Miller *et al.* (2007) and Pope *et al.* (2002) studies, and the impacts of potential violations were not systematically assessed, US EPA should use caution when developing PM C-R functions based on these studies.

4 The Flexible Cox Model

To more accurately describe real-world data, several researchers relaxed the assumptions of time-independence and linearity required for the traditional Cox PH model and reanalyzed key data sets. Though the new Cox PH model offers added flexibility and the means to relax standard assumptions of the original Cox PH model, this comes at the cost of a more complicated model. For instance, though employing a smooth spline model is an improvement over explicitly specifying functions for the C-R relationship, it requires one to specify degrees of freedom (including such things as the number and placement of the knot points) and the order of the regression spline model (quadratic, cubic, quartic, some combination of different orders, *etc.*). Furthermore, polynomial spline models must be constrained by goodness-of-fit characteristics based on the actual data, resulting in penalty functions and other such criteria that cannot be universally applied to varying datasets (Schwartz *et al.*, 2008). The large parameter space for determining appropriate spline models can lead to very different C-R relationships and subsequent risk estimates, and there is no standard way of determining the most appropriate model.

Abrahamowicz *et al.* (2003) tested the validity of the time-independence and linearity assumptions in the basic Cox PH model and proposed a new flexible model for a subset of the American Cancer Society (ACS) Cancer Prevention Study II, which had PM_{2.5} data for 50 cities and sulfate data for 151 cities. In this test, Abrahamowicz *et al.* (2003) allowed the effects of the covariates to both vary with time and contribute to the hazard function in a nonlinear fashion. Specifically, Abrahamowicz *et al.* (2003) used quadratic spline models to examine the effects of both nonlinearity and time-dependence. They examined the effects of PM_{2.5} and sulfate on all-cause mortality in two different datasets: (1) a sub-cohort of 1,200 individuals and an additional 1,300 cases (*i.e.*, deaths) and (2) 10 pooled disjoint random subsets of the entire dataset, each with ~2,200 participants. They found that for both PM_{2.5} and sulfate, there was a statistically significant deviation from the traditional linearity assumption. This was also true of body mass index (BMI), a confounder in the model. Based on a flexible regression spline generalization of the Cox PH model, which was not restricted to the same assumptions of the traditional Cox PH model, they found that risk estimates for both PM_{2.5} and sulfate differed from those based on models using the traditional assumptions. While risks for PM_{2.5} were inflated at low doses, sulfate was shown to have a threshold, demonstrating that traditional Cox PH models do not necessarily give accurate risk estimates, particularly at low exposure concentrations.

Schwartz *et al.* (2008) examined the validity of the traditional Cox PH model assumptions in the Harvard Six Cities Study by employing a linear spline model to investigate the possible nonlinear

relationship between PM_{2.5} and mortality. In contrast to the Abrahamowicz *et al.* (2003) study, this study supported a linear C-R relationship. Though this study addresses the problems of specifying the degrees of freedom of the spline model as well as the goodness-of-fit criteria (employing the Akaike Information Criterion and Bayesian Model Averaging, respectively), the linear C-R association could be an artifact of the linear spline models used. The authors' claim that because "any differentiable function can be locally approximated as a straight line, a reasonable approximation to fitting any such curve is to specify a relationship that is piecewise linear" may not be true. Linear spline models as employed by Schwartz *et al.* (2008) result in sharp changes in slope at specified points, and a higher order polynomial may be more appropriate because it ensures no abrupt changes in slope and is arguably more biologically plausible. A quadratic or higher order regression spline model allows for more gradual changes in C-R functions. Also, although a linear spline function could potentially capture some amount of nonlinearity or a threshold, if one exists, a higher order spline function might be more likely to capture small nonlinearities. In addition, even as many as five knot points might be too coarse a grain to capture possible effects at the low end of the exposure spectrum for a linear spline model.

The previously published Health Effects Institute (HEI) follow-up analysis of both the ACS and Harvard Six Cities cohorts by Krewski *et al.* (2000) is supported by the findings by Abrahamowicz *et al.* (2003) of nonlinearity of effects of fine and sulfate PM on mortality as well as the sensitivity of results to model specification discussed by Schwartz *et al.* (2008). Krewski *et al.* (2000) relaxed the assumptions of time-independence and linearity of risk factors, using a quadratic spline model with five degrees of freedom for the time-dependent effects and four degrees of freedom for the nonlinear effects for fine and sulfate PM and other covariates, for both datasets. They also conducted a thorough sensitivity analysis in which the degrees of freedom were reduced and the statistical significance for the nonlinear and/or time-dependent effects were re-examined.

In the ACS study, though departures from the time-independent PH assumption were evident, the pattern of temporal dependence was not consistent across different sub-samples. Krewski *et al.* (2000) also detected evidence of a nonlinear C-R relationship between fine particulates and mortality after adjustment for various confounders. For sulfate, the C-R relationship was quite flat below exposures of 14 µg/m³ and then rose sharply at higher concentrations.

For the Six Cities Study, using the quadratic spline model with five degrees of freedom, Krewski *et al.* (2000) found statistically significant time-dependent effects for both fine and sulfate PM, but the time dependent effects were highly dependent on the degrees of freedom used to model the effects.

Whereas 4 and 5 degrees of freedom provided evidence for departure from the traditional Cox PH model assumption of time-independence, such departures were not observed for 3 degrees of freedom or fewer, and the latter (3 degrees of freedom or fewer) fit the model considerably *less* well. The hazard ratio for this analysis was non-monotonic, essentially decreasing to zero risk at about 5 years of follow-up, then increasing again up to 12 years, and falling off again. For both studies, BMI was associated with risks nonlinearly, as risks were higher at both low and high BMI.

Overall, flexible Cox PH models and risk estimates based on them are dependent upon parameter and model specification. Estimates of both nonlinearity and time-dependence vary depending upon the degrees of freedom and other parameters, and models that fit the data equally well can have different shapes and result in different risk estimates. Because there is currently no standardized method for determining which parameters are most appropriate, relying heavily on risk estimates based on these models may be inappropriate for determining PM NAAQS.

References

- Abrahamowicz, M; Schopflocher, T; Leffondré, K; du Berger, R; Krewski, D. 2003. "Flexible modeling of exposure-response relationship between long-term average levels of particulate air pollution and mortality in the American Cancer Society study." *J. Toxicol. Environ. Health* 66(16-19):1625-1654.
- Beelen, R; Hoek, G; van den Brandt, PA; Goldbohm, RA; Fischer, P; Schouten, LJ; Jerrett, M; Hughes, E; Armstrong, B; Brunekreef, B. 2008. "Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR Study)." *Environ. Health Perspect.* 116 :196-202.
- Jerrett, M; Burnett, RT; Ma, R; Pope, CA; Krewski, D; Newbold, KB; Thurston, G; Shi, Y; Finkelstein, N; Calle, EE; Thun, MJ. 2005. "Spatial analysis of air pollution and mortality in Los Angeles." *Epidemiology* 16(6):727-736.
- Krewski, D; Burnett, RT; Goldberg, MS; Hoover, K; Siemiatycki, J; Jerrett, M; Abrahamowicz, M; White, WH. 2000. "Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate air pollution and mortality, Part II: Sensitivity analyses." Particle Epidemiology Reanalysis Project, Health Effects Institute, Cambridge MA.
- Laden, F; Schwartz, J; Speizer, FE; Dockery, DW. 2006. "Reduction in fine particulate air pollution and mortality: Extended follow-up to the Harvard Six Cities Study." *Am. J. Respir. Crit. Care Med.* 173(6):667-672.
- Miller, KA; Siscovick, DS; Sheppard, L; Shepherd, K; Sullivan, JH; Anderson, GL; Kaufman, JD. 2007. "Long-term exposure to air pollution and incidence of cardiovascular events in women." *N. Engl. J. Med.* 356:447-458.
- Moolgavkar, SH. 2005. "A review and critique of the EPA's rationale for a fine particle standard." *Regul. Toxicol. Pharmacol.* 42:123-144.
- Moolgavkar, SH. 2006. "Fine particles and mortality." *Inhal. Toxicol.* 18(1):93-94.
- Pope, CA III; Burnett, RT; Thun, MJ; Calle, EE; Krewski, D; Ito, K; Thurston, GD. 2002. "Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution." *JAMA* 287(9):1132-1141.
- Schwartz, J; Coull, B; Laden, F; Ryan, L. 2008. "The effect of dose and timing of dose on the association between airborne particles and survival." *Environ. Health Perspect.* 116(1):64-69.
- US EPA. 2009. "Integrated Science Assessment for Particulate Matter (Final)." Office of Research and Development, National Center for Environmental Assessment (NCEA) - RTP Division, EPA/600/R-08/139F. December.
- US EPA. 2010. "Policy Assessment for the Review of the Particulate Matter National Ambient Air Quality Standards (Second external review draft)." Office of Air Quality Planning and Standards, Ambient Standards Group, EPA-452/P-10-007. 357p., June.