Summary of Expert Opinions on the Existence of a Threshold in the Concentration-Response Function for $PM_{2.5}$-related Mortality

Technical Support Document (TSD)

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Compiled by:
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Office of Air Quality Planning and Standards
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Contents:

A. HES Comments on 812 Analysis (2010)

U.S. Environmental Protection Agency - Science Advisory Board (U.S. EPA-SAB). 2010. Review of EPA's DRAFT Health Benefits of the Second Section 812 Prospective Study of the Clean Air Act. EPA-COUNCIL-10-001. June. Available on the Internet at <http://yosemite.epa.gov/sab/sabproduct.nsf/0/72D4EFA39E48CDB28525774500738776/$File/EPA-COUNCIL-10-001-unsigned.pdf>.

Pg 2: "The HES generally agrees with other decisions made by the EPA project team with respect to PM, in particular, the PM mortality effect threshold model, the cessation lag model, the inclusion of infant mortality estimation, and differential toxicity of PM."

Pg 2: "Further, the HES fully supports EPA's use of a no-threshold model to estimate the mortality reductions associated with reduced PM exposure."

Pg 6: "The HES also supports the Agency's choice of a no-threshold model for PM-related effects."

Pg 13: "The HES fully supports EPA's decision to use a no-threshold model to estimate mortality reductions. This decision is supported by the data, which are quite consistent in showing effects down to the lowest measured levels. Analyses of cohorts using data from more recent years, during which time PM concentrations have fallen, continue to report strong associations with mortality. Therefore, there is no evidence to support a truncation of the CRF."

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B. Scientific Statement from American Heart Association (2010)

Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, Peters A, Siscovick D, Smith SC Jr, Whitsel L, Kaufman JD; on behalf of the American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism. (2010). "Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association." ***Circulation*****. 121: 2331-2378.**

Pg 2338: "Finally, there appeared to be no lower-limit threshold below which PM_{10} was not associated with excess mortality across all regions."

Pg 2350: "There also appears to be a monotonic (eg, linear or log-linear) concentration-response relationship between $PM_{2.5}$ and mortality risk observed in cohort studies that extends below present-day regulations of 15 $\mu g/m^3$ for mean annual levels, without a discernable "safe" threshold." (cites Pope 2004, Krewski 2009, and Schwartz 2008)

Pg 2364: "The $PM_{2.5}$ concentration– cardiovascular risk relationships for both short- and long-term exposures appear to be monotonic, extending below 15 $\mu g/m^3$ (the 2006 annual NAAQS level) without a discernable "safe" threshold."

Pg 2365: "This updated review by the AHA writing group corroborates and strengthens the conclusions of the initial scientific statement. In this context, we agree with the concept and continue to support measures based on scientific evidence, such as the US EPA NAAQS, that seek to control PM levels to protect the public health. Because the evidence reviewed supports that there is no safe threshold, it appears that public health benefits would accrue from lowering $PM_{2.5}$ concentrations even below present-day annual (15 $\mu g/m^3$) and 24-hour (35 $\mu g/m^3$) NAAQS, if feasible, to optimally protect the most susceptible populations."

Pg 2366: "Although numerous insights have greatly enhanced our understanding of the PM-cardiovascular relationship since the first AHA statement was published, the following list represents broad strategic avenues for future investigation: ... Determine whether any "safe" PM threshold concentration exists that eliminates both acute and chronic cardiovascular effects in healthy and susceptible individuals and at a population level."

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C. Integrated Science Assessment for Particulate Matter (2009)

U.S. Environmental Protection Agency (U.S. EPA). 2009. Integrated Science Assessment for Particulate Matter (Final Report). EPA-600-R-08-139F. National Center for Environmental Assessment – RTP Division. December. Available on the Internet at <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=216546>.

Pg 1-22: "An important consideration in characterizing the public health impacts associated with exposure to a pollutant is whether the concentration-response relationship is linear across the full concentration range encountered, or if nonlinear relationships exist along any part of this range. Of particular interest is the shape of the concentration-response curve at and below the level of the current standards. The shape of the concentration-response curve varies, depending on the type of health outcome, underlying biological mechanisms and dose. At the human population level, however, various sources of variability and uncertainty tend to smooth and "linearize" the concentration-response function (such as the low data density in the lower concentration range, possible influence of measurement error, and individual differences in susceptibility to air pollution health effects). In addition, many chemicals and agents may act by perturbing naturally occurring background processes that lead to disease, which also linearizes population concentration-response relationships (Clewell and Crump, 2005, 156359; Crump et al., 1976, 003192; Hoel, 1980, 156555). These attributes of population dose-response may explain why the available human data at ambient concentrations for some environmental pollutants (e.g., PM, O_3, lead [Pb], ETS, radiation) do not exhibit evident thresholds for health effects, even though likely mechanisms include nonlinear processes for some key events. These attributes of human population dose-response relationships have been extensively discussed in the broader epidemiologic literature (Rothman and Greenland, 1998, 086599)."

Pg 2-16: "In addition, cardiovascular hospital admission and mortality studies that examined the PM_{10} concentration-response relationship found evidence of a log-linear no-threshold relationship between PM exposure and cardiovascular-related morbidity (Section 6.2) and mortality (Section 6.5)."

Pg 2-25: "2.4.3. PM Concentration-Response Relationship
An important consideration in characterizing the PM-morbidity and mortality association is whether the concentration-response relationship is linear across the full concentration range that is encountered or if there are concentration ranges where there are departures from linearity (i.e., nonlinearity). In this ISA studies have been identified that attempt to characterize the shape of the concentration-response curve along with possible PM "thresholds" (i.e., levels which PM concentrations must exceed in order to elicit a health response). The epidemiologic studies evaluated that examined the shape of the concentration-response curve and the potential presence of a threshold have focused on cardiovascular hospital admissions and ED visits and mortality associated with short-term exposure to PM_{10} and mortality associated with long-term exposure to $PM_{2.5}$.

"A limited number of studies have been identified that examined the shape of the PM cardiovascular hospital admission and ED visit concentration-response relationship. Of these studies, some conducted an exploratory analysis during model selection to determine if a linear curve most adequately represented the concentration-response relationship; whereas, only one study conducted an extensive analysis to examine the shape of the concentration-response curve at different concentrations (Section 6.2.10.10). Overall, the limited evidence from the studies evaluated supports the use of a no-threshold, log-linear model, which is consistent with the observations made in studies that examined the PM-mortality relationship.

"Although multiple studies have previously examined the PM-mortality concentration-response relationship and whether a threshold exists, more complex statistical analyses continue to be developed to analyze this association. Using a variety of methods and models, most of the studies evaluated support the

use of a no-threshold, log-linear model; however, one study did observe heterogeneity in the shape of the concentration-response curve across cities (Section 6.5). Overall, the studies evaluated further support the use of a no-threshold log-linear model, but additional issues such as the influence of heterogeneity in estimates between cities, and the effect of seasonal and regional differences in PM on the concentration-response relationship still require further investigation.

"In addition to examining the concentration-response relationship between short-term exposure to PM and mortality, Schwartz et al. (2008, 156963) conducted an analysis of the shape of the concentration-response relationship associated with long-term exposure to PM. Using a variety of statistical methods, the concentration-response curve was found to be indistinguishable from linear, and, therefore, little evidence was observed to suggest that a threshold exists in the association between long-term exposure to $PM_{2.5}$ and the risk of death (Section 7.6)."

Pg 6-75: "6.2.10.10. Concentration Response
The concentration-response relationship has been extensively analyzed primarily through studies that examined the relationship between PM and mortality. These studies, which have focused on short- and long-term exposures to PM have consistently found no evidence for deviations from linearity or a safe threshold (Daniels et al., 2004, 087343; Samoli et al., 2005, 087436; Schwartz, 2004, 078998; Schwartz et al., 2008, 156963) (Sections 6.5.2.7 and 7.1.4). Although on a more limited basis, studies that have examined PM effects on cardiovascular hospital admissions and ED visits have also analyzed the PM concentration-response relationship, and contributed to the overall body of evidence which suggests a log-linear, no-threshold PM concentration-response relationship.

"The results from the three multicity studies discussed above support no-threshold log-linear models, but issues such as the possible influence of exposure error and heterogeneity of shapes across cities remain to be resolved. Also, given the pattern of seasonal and regional differences in PM risk estimates depicted in recent multicity study results (e.g., Peng et al., 2005, 087463), the very concept of a concentration-response relationship estimated across cities and for all-year data may not be very informative."

Pg 6-197: "6.5.2.7. Investigation of Concentration-Response Relationship
The results from large multicity studies reviewed in the 2004 PM AQCD (U.S. EPA, 2004, 056905) suggested that strong evidence did not exist for a clear threshold for PM mortality effects. However, as discussed in the 2004 PM AQCD (U.S. EPA, 2004, 056905), there are several challenges in determining and interpreting the shape of PM-mortality concentration-response functions and the presence of a threshold, including: (1) limited range of available concentration levels (i.e., sparse data at the low and high end); (2) heterogeneity of susceptible populations; and (3) investigate the PM-mortality concentration-response relationship.

"Daniels et al. (2004, 087343) evaluated three concentration-response models: (1) log-linear models (i.e., the most commonly used approach, from which the majority of risk estimates are derived); (2) spline models that allow data to fit possibly non-linear relationship; and (3) threshold models, using PM_{10} data in 20 cities from the 1987-1994 NMMAPS data. They reported that the spline model, combined across the cities, showed a linear relation without indicating a threshold for the relative risks of death for all-causes and for cardiovascular-respiratory causes in relation to PM_{10}, but "the other cause" deaths (i.e., all cause minus cardiovascular-respiratory) showed an apparent threshold at around 50 $\mu g/m^3$ PM^{10}, as shown in Figure 6-35. For all-cause and cardio-respiratory deaths, based on the Akaike's Information Criterion (AIC), a log-linear model without threshold was preferred to the threshold model and to the spline model.

"The HEI review committee commented that interpretation of these results required caution, because (1) the measurement error could obscure any threshold; (2) the city-specific concentration-response curves

exhibited a variety of shapes; and (3) the use of AIC to choose among the models might not be appropriate due to the fact it was not designed to assess scientific theories of etiology. Note, however, that there has been no etiologically credible reason suggested thus far to choose one model over others for aggregate outcomes. Thus, at least statistically, the result of Daniels et al. (2004, 087343) suggests that the log-linear model is appropriate in describing the relationship between PM10 and mortality.

"The Schwartz (2004, 078998) analysis of PM_{10} and mortality in 14 U.S. cities, described in Section 6.5.2.1, also examined the shape of the concentration-response relationship by including indicator variables for days when concentrations were between 15 and 25 $\mu g/m^3$, between 25 and 34 $\mu g/m^3$, between 35 and 44 $\mu g/m^3$, and 45 $\mu g/m^3$ and above. In the model, days with concentrations below 15 $\mu g/m^3$ served as the reference level. This model was fit using the single stage method, combining strata across all cities in the case-crossover design. Figure 6-36 shows the resulting relationship, which does not provide sufficient evidence to suggest that a threshold exists. The authors did not examine city-to-city variation in the concentration-response relationship in this study.

"PM_{10} and mortality in 22 European cities (and BS in 15 of the cities) participating in the APHEA project. In nine of the 22 cities, PM10 levels were estimated using a regression model relating co-located PM10 to BS or TSP. They used regression spline models with two knots (30 and 50 $\mu g/m^3$) and then combined the individual city estimates of the splines across cities. The investigators concluded that the association between PM and mortality in these cities could be adequately estimated using the log-linear model. However, in an ancillary analysis of the concentration-response curves for the largest cities in each of the three distinct geographic areas (western, southern, and eastern European cities): London, England; Athens, Greece; and Cracow, Poland, Samoli et al. (2005, 087436) observed a difference in the shape of the concentration-response curve across cities. Thus, while the combined curves (Figure 6-37) appear to support no-threshold relationships between PM_{10} and mortality, the heterogeneity of the shapes across cities makes it difficult to interpret the biological relevance of the shape of the combined curves.

"The results from the three multicity studies discussed above support no-threshold log-linear models, but issues such as the possible influence of exposure error and heterogeneity of shapes across cities remain to be resolved. Also, given the pattern of seasonal and regional differences in PM risk estimates depicted in recent multicity study results (e.g., Peng et al., 2005, 087463), the very concept of a concentration-response relationship estimated across cities and for all-year data may not be very informative."

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D. CASAC comments on PM ISA and REA (2009)

U.S. Environmental Protection Agency - Science Advisory Board (U.S. EPA-SAB). 2009. Review of EPA's Integrated Science Assessment for Particulate Matter (First External Review Draft, December 2008). EPA-COUNCIL-09-008. May. Available on the Internet at <http://yosemite.epa.gov/sab/SABPRODUCT.NSF/81e39f4c09954fcb85256ead006be86e/73ACCA834AB44A10852575BD0064346B/$File/EPA-CASAC-09-008-unsigned.pdf>.

Pg 9: "There is an appropriate discussion of the time-series studies, but this section needs to have an explicit finding that the evidence supports a relationship between PM and mortality that is seen in these studies. This conclusion should be followed by the discussion of statistical methodology and the identification of any threshold that may exist."

U.S. Environmental Protection Agency Science Advisory Board (U.S. EPA-SAB). 2009. Consultation on EPA's Particulate Matter National Ambient Air Quality Standards: Scope and Methods Plan for Health Risk and Exposure Assessment. EPA-COUNCIL-09-009. May. Available on the Internet at <http://yosemite.epa.gov/sab/SABPRODUCT.NSF/81e39f4c09954fcb85256ead006be86e/723FE644C5D758DF852575BD00763A32/$File/EPA-CASAC-09-009-unsigned.pdf>.

Pg 6: "On the issue of cut-points raised on 3-18, the authors should be prepared to offer a scientifically cogent reason for selection of a specific cut-point, and not simply try different cut-points to see what effect this has on the analysis. The draft ISA was clear that there is little evidence for a population threshold in the C-R function."

U.S. Environmental Protection Agency - Science Advisory Board (U.S. EPA-SAB). 2009. Review of *Integrated Science Assessment for Particulate Matter (Second External Review Draft, July 2009)*. EPA-CASAC-10-001. November. Available on the Internet at <http://yosemite.epa.gov/sab/SABPRODUCT.NSF/81e39f4c09954fcb85256ead006be86e/151B1F83B023145585257678006836B9/$File/EPA-CASAC-10-001-unsigned.pdf>.

Pg 2: "The paragraph on lines 22-30 of page 2-37 is not clearly written. Twice in succession it states that the use of a no-threshold log-linear model is supported, but then cites other studies that suggest otherwise. It would be good to revise this paragraph to more clearly state – well, I'm not sure what. Probably that more research is needed."

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E. Krewski et al. (2009)

Krewski, Daniel, Michael Jerrett, Richard T. Burnett, Renjun Ma, Edward Hughes, Yuanli Shi, Michelle C. Turner, C. Arden Pope III, George Thurston, Eugenia E. Calle, and Michael J. Thun with Bernie Beckerman, Pat DeLuca, Norm Finkelstein, Kaz Ito, D.K. Moore, K. Bruce Newbold, Tim Ramsay, Zev Ross, Hwashin Shin, and Barbara Tempalski. (2009). Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. *HEI Research Repor*t, 140, Health Effects Institute, Boston, MA.

Pg 119: [About Pope et al. (2002)] "Each 10-μg/m^3 increase in longterm average ambient $PM_{2.5}$ concentrations was associated with approximately a 4%, 6%, or 8% increase in risk of death from all causes, cardiopulmonary disease, and lung cancer, respectively. There was no evidence of a threshold exposure level within the range of observed $PM_{2.5}$ concentrations. "

Krewski (2009). Letter from Dr. Daniel Krewski to HEI's Dr. Kate Adams (dated July July 7, 2009) regarding "EPA queries regarding HEI Report 140". Dr. Adams then forwarded the letter on July 10, 2009 to EPA's Beth Hassett-Sipple. (letter placed in docket #EPA-HQ-OAR-2007-0492).

Pg 4: "6. The Health Review Committee commented that the Updated Analysis completed by Pope et al. 2002 reported "no evidence of a threshold exposure level within the range of observed $PM_{2.5}$ concentrations" (p. 119). In the Extended Follow-Up study, did the analyses provide continued support for a no-threshold response or was there evidence of a threshold?

"Response: As noted above, the HEI Health Review Committee commented on the lack of evidence for a threshold exposure level in Pope et al. (2002) with follow-up through the year 1998. The present report, which included follow-up through the year 2000, also does not appear to demonstrate the existence of a threshold in the exposure-response function within the range of observed $PM_{2.5}$ concentrations."

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F. Schwartz et al. (2008)

Schwartz J, Coull B, Laden F. (2008). The Effect of Dose and Timing of Dose on the Association between Airborne Particles and Survival. *Environmental Health Perspectives*. 116: 64-69.

Pg 67: "A key finding of this study is that there is little evidence for a threshold in the association between exposure to fine particles and the risk of death on follow-up, which continues well below the U.S. EPA standard of 15 $\mu g/m^3$."

Pg 68: "In conclusion, penalized spline smoothing and model averaging represent reasonable, feasible approaches to addressing questions of the shape of the exposure–response curve, and can provide valuable information to decisionmakers. In this example, both approaches are consistent, and suggest that the association of particles with mortality has no threshold down to close to background levels."

G. Expert Elicitation on PM-Mortality (2006, 2008)

Industrial Economics, Inc., 2006. ***Expanded Expert Judgment Assessment of the Concentration-Response Relationship Between $PM_{2.5}$ Exposure and Mortality*****. Prepared for the U.S.EPA, Office of Air Quality Planning and Standards, September. Available on the Internet at <http://www.epa.gov/ttn/ecas/regdata/Uncertainty/pm_ee_report.pdf>.**

Pg v: "Each expert was given the option to integrate their judgments about the likelihood of a causal relationship and/or threshold in the C-R function into his distribution or to provide a distribution "conditional on" one or both of these factors."

Pg vii: "Only one of 12 experts explicitly incorporated a threshold into his C-R function.[3] The rest believed there was a lack of empirical and/or theoretical support for a population threshold. However, three other experts gave differing effect estimate distributions above and below some cut-off concentration. The adjustments these experts made to median estimates and/or uncertainty at lower $PM^{2.5}$ concentrations were modest."

> "[3] Expert K indicated that he was 50 percent sure that a threshold existed. If there were a threshold, he thought that there was an 80 percent chance that it would be less than or equal to 5 $\mu g/m^3$, and a 20 percent chance that it would fall between 5 and 10 $\mu g/m^3$."

Pg ix: "Compared to the pilot study, experts in this study were in general more confident in a causal relationship, less likely to incorporate thresholds, and reported higher mortality effect estimates. The differences in results compared with the pilot appear to reflect the influence of new research on the interpretation of the key epidemiological studies that were the focus of both elicitation studies, more than the influence of changes to the structure of the protocol."

Pg 3-25: "3.1.8 THRESHOLDS
The protocol asked experts for their judgments regarding whether a threshold exists in the $PM_{2.5}$ mortality C-R function. The protocol focused on assessing expert judgments regarding theory and evidential support for a population threshold (i.e., the concentration below which no member of the study population would experience an increased risk of death).[32] If an expert wished to incorporate a threshold in his characterization of the concentration-response relationship, the team then asked the expert to specify the threshold $PM_{2.5}$ concentration probabilistically, incorporating his uncertainty about the true threshold level.

"From a theoretical and conceptual standpoint, all experts generally believed that individuals exhibit thresholds for PM-related mortality. However, 11 of them discounted the idea of a population threshold in the C-R function on a theoretical and/or empirical basis. Seven of these experts noted that theoretically one would be unlikely to observe a population threshold due to the variation in susceptibility at any given time in the study population resulting from combinations of genetic, environmental, and socioeconomic factors.[33] All 11 thought that there was insufficient empirical support for a population threshold in the C-R function. In addition, two experts (E and L) cited analyses of the ACS cohort data in Pope et al. (2002) and another (J) cited Krewski et al. (2000a & b) as supportive of a linear relationship in the study range.

"Seven of the experts favored epidemiological studies as ideally the best means of addressing the population threshold issue, because they are best able to evaluate the full range of susceptible individuals at environmentally relevant exposure levels. However, those who favored epidemiologic studies generally acknowledged that definitive studies addressing thresholds would be difficult or impossible to conduct, because they would need to include a very large and diverse population with wide variation in exposure and a long follow-up period. Furthermore, two experts (B and I) cited studies documenting difficulties in detecting a threshold using epidemiological studies (Cakmak et al. 1999, and Brauer et al., 2002,

respectively). The experts generally thought that clinical and toxicological studies are best suited for researching mechanisms and for addressing thresholds in very narrowly defined groups. One expert, B, thought that a better understanding of the detailed biological mechanism is critical to addressing the question of a threshold.

"One expert, K, believed it was possible to make a conceptual argument for a population threshold. He drew an analogy with smoking, indicating that among heavy smokers, only a proportion of them gets lung cancer or demonstrates an accelerated decline in lung function. He thought that the idea that there is no level that is biologically safe is fundamentally at odds with toxicological theory. He did not think that a population threshold was detectable in the currently available epidemiologic studies. He indicated that some of the cohort studies showed greater uncertainty in the shape of the C-R function at lower levels, which could be indicative of a threshold.

"Expert K chose to incorporate a threshold into his C-R function. He indicated that he was 50 percent sure that a threshold existed. If there were a threshold, he thought that there was an 80 percent chance that it would be less than or equal to 5 $\mu g/m^3$, and a 20 percent chance that it would fall between 5 and 10 $\mu g/m^3$."

Roman, Henry A., Katherine D. Walker, Tyra L. Walsh, Lisa Conner, Harvey M. Richmond, Bryan J. Hubbell, and Patrick L. Kinney. (2008). "Expert Judgment Assessment of the Mortality Impact of Changes in Ambient Fine Particulate Matter in the U.S." *Environ. Sci. Technol.*, 42(7):2268-2274.

Pg 2271: "Eight experts thought the true C-R function relating mortality to changes in annual average $PM_{2.5}$ was log-linear across the entire study range (ln(mortality)) $\beta \times PM$). Four experts (B, F, K, and L) specified a "piecewise" log-linear function, with different β coefficients for PM concentrations above and below an expert-specified break point. This approach allowed them to express increased uncertainty in mortality effects seen at lower concentrations in major epidemiological studies. Expert K thought the relationship would be log-linear above a threshold."

Pg 2271: "Expert K also applied a threshold, T, to his function, which he described probabilistically. He specified $P(T > 0) = 0.5$. Given $T > 0$, he indicated $P(T \leq 5\ \mu g/m^3) = 0.8$ and $P(5\ \mu g/m^3 < T \leq 10\ \mu g/m^3) = 0.2$. Figure 3 does not include the impact of applying expert K's threshold, as the size of the reduction in benefits will depend on the distribution of baseline PM levels in a benefits analysis."

Experts:

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Dr. Dan Krewski, University of Ottawa

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Dr. Morton Lippmann, Professor, Nelson Institute of Environmental Medicine, New York University School of Medicine, Tuxedo, NY

Dr. Joe Mauderly, Lovelace Respiratory Research Institute

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Dr. Arden Pope, Professor, Department of Economics, Brigham Young University, Provo, UT

Dr. Richard Schlesinger, Pace University

Dr. Joel Schwartz, Harvard School of Public Health

Dr. George Thurston—Department of Environmental Medicine, NYU, Tuxedo, NY

Dr. Mark Utell, University of Rochester School of Medicine and Dentistry

H. CASAC comments on PM Staff Paper (2005)

U.S. Environmental Protection Agency - Science Advisory Board (U.S. EPA-SAB). 2005. EPA's Review of the National Ambient Air Quality Standards for Particulate Matter (Second Draft PM Staff Paper, January 2005). EPA-SAB-CASAC-05-007. June. Available on the Internet at <http://yosemite.epa.gov/sab/sabproduct.nsf/E523DD36175EB5AD8525701B007332AE/$File/SAB-CASAC-05-007_unsigned.pdf>.

Pg 6: "A second concern is with methodological issues. The issue of the selection of concentration-response (C-R) relationships based on locally-derived coefficients needs more discussion. The Panel did not agree with EPA staff in calculating the burden of associated incidence in their risk assessment using either the predicted background or the lowest measured level (LML) in the utilized epidemiological analysis. The available epidemiological database on daily mortality and morbidity does not establish either the presence or absence of threshold concentrations for adverse health effects. Thus, in order to avoid emphasizing an approach that assumes effects that extend to either predicted background concentrations or LML, and to standardize the approach across cities, for the purpose of estimating public health impacts, the Panel favored the primary use of an assumed threshold of 10 $\mu g/m^3$. The original approach of using background or LML, as well as the other postulated thresholds, could still be used in a sensitivity analysis of threshold assumptions.

"The analyses in this chapter highlight the impact of assumptions regarding thresholds, or lack of threshold, on the estimates of risk. The uncertainty associated with threshold or nonlinear models needs more thorough discussion. A major research need is for more work to determine the existence and level of any thresholds that may exist or the shape of nonlinear concentration-response curves at low levels of exposure that may exist, and to reduce uncertainty in estimated risks at the lowest PM concentrations."

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I. HES Comments on 812 Analysis (2004)

U.S. Environmental Protection Agency - Science Advisory Board (U.S. EPA-SAB). 2004. Advisory on Plans for Health Effects Analysis in the Analytical Plan for EPA's Second Prospective Analysis – Benefits and Costs of the Clean Air Act, 1990-2020. Advisory by the Health Effects Subcommittee of the Advisory Council on Clean Air Compliance Analysis. EPA-SAB-COUNCIL-ADV-04-002. March. Available on the Internet at <http://yosemite.epa.gov/sab%5CSABPRODUCT.NSF/08E1155AD24F871C85256E5400433D5D/$File/council_adv_04002.pdf>.

Pg 20: "The Subcommittee agrees that the whole range of uncertainties, such as the questions of causality, shape of C-R functions and thresholds, relative toxicity, years of life lost, cessation lag structure, cause of death, biologic pathways, or susceptibilities may be viewed differently for acute effects versus long-term effects.

"For the studies of long-term exposure, the HES notes that Krewski et al. (2000) have conducted the most careful work on this issue. They report that the associations between $PM_{2.5}$ and both all-cause and cardiopulmonary mortality were near linear within the relevant ranges, with no apparent threshold. Graphical analyses of these studies (Dockery et al., 1993, Figure 3 and Krewski et al., 2000, page 162) also suggest a continuum of effects down to lower levels. Therefore, it is reasonable for EPA to assume a no threshold model down to, at least, the low end of the concentrations reported in the studies."

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J. NRC – Committee on Estimating the Health Risk Reduction Benefits of Proposed Air Pollution Regulations (2002)

National Research Council (NRC). 2002. Estimating the Public Health Benefits of Proposed Air Pollution Regulations. Washington, DC: The National Academies Press.

Pg 109: "**Linearity and Thresholds**

"The shape of the concentration-response functions may influence the overall estimate of benefits. The shape is particularly important for lower ambient air pollution concentrations to which a large portion of the population is exposed. For this reason, the impact of the existence of a threshold may be considerable.

"In epidemiological studies, air pollution concentrations are usually measured and modeled as continuous variables. Thus, it may be feasible to test linearity and the existence of thresholds, depending on the study design. In time-series studies with the large number of repeated measurements, linearity and thresholds have been formally addressed with reasonable statistical power. For pollutants such as PM_{10} and $PM_{2.5}$, there is no evidence for any departure of linearity in the observed range of exposure, nor any indication of a threshold. For example, examination of the mortality effects of short-term exposure to PM_{10} in 88 cities indicates that the concentration-response functions are not due to the high concentrations and that the slopes of these functions do not appear to increase at higher concentrations (Samet et al. 2000). Many other mortality studies have examined the shape of the concentration-response function and indicated that a linear (nonthreshold) model fit the data well (Pope 2000). Furthermore, studies conducted in cities with very low ambient pollution concentrations have similar effects per unit change in concentration as those studies conducted in cities with higher concentrations. Again, this finding suggests a fairly linear concentration-response function over the observed range of exposures.

"Regarding the studies of long-term exposure, Krewski et al. (2000) found that the assumption of a linear concentration-response function for mortality outcomes was not unreasonable. However, the statistical power to assess the shape of these functions is weakest at the upper and lower end of the observed exposure ranges. Most of the studies examining the effects of long-term exposure on morbidity compare subjects living in a small number of communities (Dockery et al. 1996; Ackermmann-Liebrich 1997; Braun-Fahrländer et al. 1997). Because the number of long-term effects studies are few and the number of communities studied is relatively small (8 to 24), the ability to test formally the absence or existence of a no-effect threshold is not feasible. However, even if thresholds exist, they may not be at the same concentration for all health outcomes.

"A review of the time-series and cohort studies may lead to the conclusion that although a threshold is not apparent at commonly observed concentrations, one may exist at lower levels. An important point to acknowledge regarding thresholds is that for health benefits analysis a key threshold is the population threshold (the lowest of the individual thresholds). However, the population threshold would be very difficult to observe empirically through epidemiology, because epidemiology integrates information from very large groups of people (thousands). Air pollution regulations affect even larger groups of people (millions). It is reasonable to assume that among such large groups susceptibility to air pollution health effects varies considerably across individuals and depends on a large set of underlying factors, including genetic makeup, age, exposure measurement error, preexisting disease, and simultaneous exposures from smoking and occupational hazards. This variation in individual susceptibilities and the resulting distribution of individual thresholds underlies the concentration-response function observed in epidemiology. Thus, until biologically based models of the distribution of individual thresholds are developed, it may be productive to assume that the population concentration-response function is

continuous and to focus on finding evidence of changes in its slope as one approaches lower concentrations.

EPA's Use of Thresholds

"In EPA's benefits analyses, threshold issues were discussed and interpreted. For the PM and ozone National Ambient Air Quality Standards (NAAQS), EPA investigated the effects of a potential threshold or reference value below which health consequences were assumed to be zero (EPA 1997). Specifically, the high-end benefits estimate assumed a 12-microgram per cubic meter ($\mu g/m^3$) mean threshold for mortality associated with long-term exposure to $PM_{2.5}$. The low-end benefits estimate assumed a 15-$\mu g/m^3$ threshold for all PM-related health effects. The studies, however, included concentrations as low as 7.5 $\mu g/m^3$. For the Tier 2 rule and the HD engine and diesel-fuel rule, no threshold was assumed (EPA 1999, 2000). EPA in these analyses acknowledged that there was no evidence for a threshold for PM.

"Several points should be noted regarding the threshold assumptions. If a threshold is assumed where one was not apparent in the original study, then the data should be refit and a new curve generated with the assumption of a zero slope over a segment of the concentration-response function that was originally found to be positively sloped. The assumption of a zero slope over a portion of the curve will force the slope in the remaining segment of the positively sloped concentration-response function to be greater than was indicated in the original study. A new concentration-response function was not generated for EPA's benefits analysis for the PM and ozone NAAQS for which threshold assumptions were made. The generation of the steeper slope in the remaining portion of the concentration-response function may fully offset the effect of assuming a threshold. These aspects of assuming a threshold in a benefits analysis where one was not indicated in the original study should be conveyed to the reader. The committee notes that the treatment of thresholds should be evaluated in a consistent and transparent framework by using different explicit assumptions in the formal uncertainty analyses (see Chapter 5)."

Pg 117: "Although the assumption of no thresholds in the most recent EPA benefits analyses was appropriate, EPA should evaluate threshold assumptions in a consistent and transparent framework using several alternative assumptions in the formal uncertainty analysis."

Pg 136: "Two additional illustrative examples are thresholds for adverse effects and lag structures.[2] EPA considers implausible any threshold for mortality in the particulate matter (PM) exposure ranges under consideration (EPA 1999a, p. 3-8). Although the agency conducts sensitivity analyses incorporating thresholds, it provides no judgment as to their relative plausibility. In a probabilistic uncertainty analysis, EPA could assign appropriate weights to various threshold models. For PM-related mortality in the Tier 2 analysis, the committee expects that this approach would have resulted in only a slight widening of the probability distribution for avoided mortality and a slight reduction in the mean of that distribution, thus reflecting EPA's views about the implausibility of thresholds. The committee finds that such formal incorporation of EPA's expert judgments about the plausibility of thresholds into its primary analysis would have been an improvement.

"Uncertainty about thresholds is a special aspect of uncertainty about the shape of concentration-response functions. Typically, EPA and authors of epidemiological studies assume that these functions are linear on some scale. Often, the scale is a logarithmic transformation of the risk or rate of the health outcome, but when a rate or risk is low, a linear function on the logarithmic scale is approximately linear on the scale of the rate or risk itself. Increasingly, epidemiological investigators are employing analytic methods that permit the estimation of nonlinear shapes for concentration-response functions (Greenland et al. 1999). As a consequence, EPA will need to be prepared to incorporate nonlinear concentration-response functions from epidemiological studies into the agency's health benefits analyses. Any source of error or

bias that can distort an epidemiological association can also distort the shape of an estimated concentration -response function, as can variation in individual susceptibility (Hattis and Burmaster 1994; Hattis et al. 2001)."

Pg 137: "In principle, many components of the health benefits model need realistic probabilistic models (see Table 5-1 for a listing of such components), in addition to concentration-response thresholds and time lags between exposure and response. For example, additional features of the concentration-response function—such as projection of the results from the study population to the target populations (which may have etiologically relevant characteristics outside the range seen in the study population) and the projection of baseline frequencies of morbidity and mortality into the future—must be characterized probabilistically. Other uncertainties that might affect the probability distributions are the estimations of population exposure (or even concentration) from emissions, estimates of emissions themselves, and the relative toxicity of various classes of particles. Similarly, many aspects of the analysis of the impact of regulation on ambient concentrations and on population exposure involve considerable uncertainty and, therefore, may be beneficially modeled in this way. Depending on the analytic approach used, joint probability distributions will have to be specified to incorporate correlations between model components that are structurally dependent upon each other, or the analysis will have to be conducted in a sequential fashion that follows the model for the data-generating process.

"EPA should explore alternative options for incorporating expert judgment into its probabilistic uncertainty analyses. The agency possesses considerable internal expertise, which should be employed as fully as possible. Outside experts should also be consulted as needed, individually or in panels. In all cases, when expert judgment is used in the construction of a model component, the experts should be identified and the rationales and empirical bases for their judgments should be made available."

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