UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

THE ADMINISTRATOR

EPA-COUNCIL-ADV-04-001

Dr. Trudy Cameron and Dr. Bart Ostro
Science Advisory Board
Mail Code 1400F
1200 Pennsylvania Ave, NW
Washington, DC 20460

Dear Drs. Cameron and Ostro:

The Agency greatly appreciates the thoughtful and thorough advisory reports submitted by the Council/HES in March and by the Council in June, pertaining to the analytic blueprint for the second section 812 prospective study. The purpose of this letter is to request clarification of the Council/HES and Council advice pertaining to a particular issue: the structure of cessation lags associated with reductions in PM2.5 exposure.

The Agency recognizes that the cessation lag issue is particularly difficult due to the lack of definitive scientific evidence supporting specification of any particular lag structure. In the absence of a definitive, consensus lag structure, the Agency has continued to employ a 5-year distributed lag for our base estimates, but we have also evaluated an alternative structure through sensitivity analysis. The Agency intends to address the issue of cessation lag in the upcoming full expert elicitation on PM mortality; however, this process will likely take at least one year. In the interim, given that the Council has opined on the appropriate structure of the cessation lag, the Agency needs to decide whether to continue using the current 5-year lag structure in our base estimates or to employ the alternative structure, which was modeled after the HES-proposed 3-segment lag approach. Therefore, the Agency requests that you consider providing clarification of your advice by indicating whether this particular alternative lag structure is more scientifically defensible than the 5-year lag structure that we have relied upon in the past and whether you have any recommended modifications to that alternative.

In the remainder of this letter, we summarize the background information and relevant review history of Council, SAB Arsenic Rule Benefits Review Panel (ARBRP), and NAS advice on cessation lags and describe the alternative cessation lag structure. Attachments to this letter provide the full text of 812 Council and Council HES, NAS, and ARBRP advice on cessation lags excerpted from the relevant reports.

The Agency acknowledges that actual analytical application of one or more cessation lag

structures will not be required for the section 812 study until late 2005. However, the Agency has several PM2.5-related rulemaking analyses, which will be initiated or completed during the coming months, and near-term clarification of the Council and Council/HES advice may significantly improve these rulemaking analyses.

Background

In the previous section 812 study, and in recent rulemaking analyses, EPA has employed a 5-year distributed lag structure to estimate the temporal path of incidence of premature mortality associated with reductions in PM2.5. The lag structure assumes 25 percent of the incidence reduction is manifest in each of the first two years, and the remaining 50 percent of the incidence reduction is spread evenly over the succeeding three years.

This 5-year distributed lag structure was adopted in 1999 after the Agency posed a charge question to the HEES regarding the use of a 15-year lag assumption based on a 1996 study by the World Health Organization (i.e., the Brunekreef study), which implied that EPA should adopt a 15-year lag assumption. Current Agency practice at the time was to assume no cessation lag given the lack of empirical data supporting any specific quantitative lag structure. During the subsequent HEES review, EPA presented three options for consideration: (1) zero lag, (2) 15-year lag, and (3) the 5-year distributed lag, which had been incorporated in the Tier II rulemaking analysis as a sensitivity test.

Initially, the HEES advised that the state of the relevant science was such that (a) adoption of any particular lag structure would be arbitrary, (b) inclusion of pollutant-related time lags in mortality at this time may therefore be premature, and (c) evaluation of the effects of long-term downward trends in pollutant concentrations presents an important research opportunity. [see Attachment A: HEES February 10, 1999 advisory report].

During their June 28-29, 1999 review meeting, the HEES panelists subsequently stated that they preferred the 5-year distributed lag to the zero and 15-year options, both of which they considered implausible. They further stated that the 5-year distributed lag was generally consistent with available data on smoking cessation.

The HEES then provided an in-depth response in their October 1999 report which, among other advice, stated that the HEES "...concurs with the [5-year distributed lag] approach proposed by the EPA ... as the best estimate for use in the 1999 Section 812 report. HEES also recommends that a sensitivity analysis of the time lag issue should also be presented in the report. The sensitivity analysis should include a higher end and a lower end mortality estimate (e.g., 0, 8, 15-year lags)." [see Attachment B: HEES October 29, 1999 advisory letter].

In August 2001, the SAB Arsenic Rule Benefits Review Panel (ARBRP) published their review of the EPA Office of Water (OW) arsenic rule benefits analysis. We include excerpts from their report as Attachment C, since their review included significant advice pertaining to lag structures. In addition, the panel clarified the distinction between latency periods and

"cessation lags", a term they coined, and pointed out that estimates for cessation lag and latency may be significantly different.

In 2002, the NRC evaluated EPA's use of the five-year lag model in the context of air pollution benefits analysis and stated that the NRC panel "found little justification for the 5-year time course of exposure and outcome assumed ... and recommends that EPA more fully account for the uncertainty regarding lags in health effects by incorporating a range of assumptions and probabilities on the temporal relationship." [see Attachment D: NRC 2002 report]

In response to the NRC report, the Agency identified three alternative options in the analytic blueprint for the second section 812 prospective study: (1) the currently employed 5-year distributed lag, (2) an alternative based on a range of lag structures from 0 to 20-30 years, and (3) construction of a 3-parameter Weibull distribution configured to match (undefined) expected low, most likely, and expected high values. EPA then submitted a charge question to the Council/HES requesting comment on these three approaches.

In the March 2004 advisory report, the Council/HES provided an in-depth assessment of the cessation lag issue and the three options. The report echoes the earlier HEES and NAS reports by noting, "Empirical evidence is lacking to inform the choice of the lag distribution directly and agrees with the NAS report that there is little empirical justification for the 5-year cessation lag structure used in the previous analyses." The Council / HES report then "urges the Agency to begin to move from the relatively arbitrary assumptions of the 5-year lag structure to an approach based on some plausible models of the disease processes involved", and states that "[l]acking direct information from the cohort studies themselves, new insights regarding the shape of the cessation lag can only come from improved understanding of the mechanism of the exposure-response relationship." The Council / HES report discusses several potentially relevant disease modeling approaches and suggests consideration of a 3-segmented lag structure reflecting acute effect (0-6 month), medium-term effect (2-5 year), and long-term effect (15-25 year) patterns of exposure-response, using either a Weibull distribution or a simpler distributional form with a smoother to mitigate discontinuities. Finally, the Council/HES report recommends that cessation lags "be considered for inclusion in future expert elicitation efforts and/or sensitivity analyses." [see Attachment E: March 2004 Council / HES advisory report]

In response to this cumulative advice, the Agency intends to address the cessation lag question in the full expert elicitation on estimation of PM mortality. In the interim, our joint collaboration with OMB on the nonroad diesel rule, led to the identification of an alternative lag structure, which assumes 20 percent of the incidence reduction occurs in the first year of a reduction in PM exposure, another 50 percent of the incidence reduction is evenly spread among years 2 through 5 (i.e., 12.5 percent each year), and the remaining 30 percent of the incidence reduction is evenly spread out among years 6 through 20 (i.e., 2 percent each year). This alternative lag structure was evaluated as part of the sensitivity analysis for this rule.

The central premise of the alternative lag structure is that estimates of the size of the cessation lag should be based on our current understanding of the mechanism associated with PM2.5 related-mortality and the empirical results of a variety of epidemiological and clinical studies. As noted by the Council/HEES (EPA-SAB-COUNCIL-ADV-00-001, 1999), "some of the mortality effects of cumulative exposures will occur over short periods of time in individuals with compromised health status, but other effects are likely to occur among individuals who, at baseline, have reasonably good health that will deteriorate because of continued exposure. No animal models have yet been developed to quantify these cumulative effects, nor are there epidemiologic studies bearing on this question." In its recently published fourth volume, the NRC's Committee on Research Priorities for Airborne Particulate Matter (NRC 2004) concludes that in addition to exacerbation of chronic respiratory disease, "results from epidemiological, clinical, and animal studies are converging to indicate that PM exposures, both to PM2.5 and ultrafine particles, have adverse cardiovascular effects." The Committee highlights clinical and animal studies that suggest changes in heart rate variability, cardiac arrhythmias, ischemic events, and congestive health failure should be considered among particle-related health outcomes. Pope et. al. (2004) presents epidemiological evidence regarding cardiovascular mortality and long-term exposure to air pollution to particles. Therefore, the distribution of deaths over the latency period is intended to reflect the contribution of short term exposures in the first year, cardiopulmonary deaths in the 2 to 5 year period, and longer term lung disease and lung cancer in the 6 to 20 year period. The relative magnitudes of these segments are proposed as interim estimates, to be used in benefits analyses until expert elicitation among those who specialize in the natural course of disease can be completed, and/or whether modifications to that alternative are recommended.

Request for Clarification of Council / HES Advice on Cessation Lag Structure

The Agency respectfully requests that the Council consider providing clarification of its existing advice pertaining to cessation lags; specifically, whether the alternative lag structure described above is more scientifically defensible than the five year lag structure the Agency has used previously for its base estimates, and whether there are any modifications to this alternative the Council would recommend.

Conclusion

EPA continues to place a very high value on the sound and thoughtful advice of the Council and its technical subcommittees, and we appreciate your willingness to consider providing additional elaboration and clarification of your advice so that we may continue to improve our analyses.

Sincerely,

/Signed/

Jeffrey Holmstead
Assistant Administrator for
Air and Radiation

/Signed/

Jessica Furey
Associate Administrator for Policy,
Economics, and Innovation

cc: Vanessa Vu, Director, SAB Staff
Holly Stallworth, SAB Staff, Council DFO

5 attachments

EPA-SAB-COUNCIL-ADV-99-005
Council / HEES February 1999 advisory report
February 10, 1999

[Cover letter from Cropper and Lioy, page 2:]

With regard to mortality time lags, the HEES agrees with the Agency that current studies on animal mortality do not have an implied time lag, and the inclusion of pollutant-related time lags in mortality at this time is premature.

[page 12:]

3.5.4 Modeling Time Lags for Cumulative Effects of Long-Term Exposure

HEES agrees that consideration of time lags on annual mortality outcomes might be premature. The current studies on animal mortality do not have an implied time lag, and selection of a value for such a time lag would be arbitrary. The long-term downward trend in pollutant concentrations, especially for PM, presents an important research opportunity for revisiting the issue of time lags using already assembled data bases, and would be a good candidate for sensitivity analysis. An effort of this nature, however, is most likely beyond the scope of the current prospective study.

EPA-SAB-COUNCIL-ADV-00-001
Council / HEES October 1999 advisory letter
October 29, 1999

[pages 8 to 10:]

15-Year Lag for Particulate Matter Effects

Charge question: "It has been suggested to the Agency that the WHO (1996) study provides scientific evidence of the existence of a 15 year lag between changes in PM exposure and changes in associated adverse health effects. Heretofore, however, the Agency has interpreted the WHO authors' summing of incidences at the end of the 15 exposure period of the Dockery study as a matter of mathematical convenience, not evidence of the WHO authors' belief in the existence or magnitude of a lag between changes in exposure and changes in risk of adverse health effect. What is the SAB HEES view regarding the proper interpretation and use of the WHO (1996) study? Specifically, does the HEES believe it is reasonable to assume that, based on the WHO (1996) study or other evidence, there is no reduction in risk of adverse health consequences until 15 years following a reduction in PM exposure?

Response: Contrary to the June 17, 1999 letter from Arbuckle and Blank to Donald Barnes,[2] there are no statements in the 1996 World Health Organization (WHO) report to suggest that there is any scientific evidence for the existence of a 15-year lag between changes in PM exposure and mortality.[3] On page 35 of the WHO report (last paragraph, third line from bottom), the authors state that "for simplification [emphasis added], it was assumed that the effect of particulate matter only started to become manifest after 15 years in subjects who were 27.5 [years of age] initially . . . " No citations from the published literature are given to support the 15-year lag assumption, nor is the issue further discussed within the WHO report. Thus it is clear that the authors of the WHO report used a 15-year lag assumption strictly "for simplification," which can be interpreted as a convenient statistical device for estimating the mortality effects from chronic exposure of the population to particulate air pollution.

There is considerable evidence, cited in both the WHO report and EPA's 1995 Air Quality Criteria Document for Particulate Matter,[4] that daily variations in PM have an immediate effect on mortality risk within a one to five day interval between elevated PM concentrations and excess mortality. This effect was particularly apparent for cardiovascular and respiratory causes of death among the elderly. These observations are commonly interpreted as implying that the

[2] Donald R. Arbuckle and Rebecca M. Blank to Donald G. Barnes, June 18, 1999, Science Advisory Board, HEES Meeting, 6/28&29/1999.

[3] World Health Organization (WHO), "Final Consultation on Updating and Revision of the Air Quality Guidelines for Europe." Bilothoven, The Netherlands, 28-31 October, 1996 ICP EHH 018 VD 96 2.11.

[4] US Environmental Protection Agency, *Air Quality Criteria for Particulate Matter*, EPA/600/P-95/001aF-CF.

acute mortality effect of PM occurs among a particularly susceptible segment of the population whose health status is already compromised by pre-existing disease. Thus with a reduction in PM levels, it is reasonable to expect that there will be some immediate benefits from mortality reductions among susceptible individuals.

However, the magnitude of estimated mortality effects from the cohort studies of Dockery et al.[5] and Pope et al.[6] are different than the estimates from the time-series studies. The WHO report estimates a 10% mortality increase per 10µg/m3 annual difference in PM from the cohort studies, whereas the time-series studies show an overall 1-2% mortality increase per 10µg/m3 daily variation in PM. The different estimates from the cohort studies, even when they are adjusted for the differences in time duration, may be attributable to three consequences of PM exposures: (1) cumulative PM exposures of the entire population may result in a PM-induced increase in the number of individuals who become susceptible to the acute mortality effects observed in the time series studies; (2) cumulative PM exposure may cause chronic diseases which increase the mortality rate of the population, but the deaths of a portion of these chronically ill persons may occur independently of the daily variations in PM exposure, and these latter deaths are not captured by the time series studies; and (3) a 10µg/m3 change in annual average concentration may be associated with a much larger change in peak 24-hour exposure levels.

Given that the mortality effect of cumulative air pollution exposure exceeds that of daily variations in exposure, the question becomes, over what time period does the excess effect manifest itself in the population? As noted above, some of the mortality effects of cumulative exposures will occur over short periods of time in individuals with compromised health status, but other effects are likely to occur among individuals who, at baseline, have reasonably good health that will deteriorate because of continued exposure. No animal models have yet been developed to quantify these cumulative effects, nor are there epidemiologic studies bearing on this question. As the HEES previously stated, "consideration of time lags on annual mortality outcomes might be premature".[7] Neither the 1996 WHO report nor do any recently published studies provide reasons to revise this statement.

Although there is substantial evidence that a portion of the mortality effect of PM is manifest within a short period of time, i.e., less than one year, it can be argued that, if no a lag assumption is made, the entire mortality excess observed in the cohort studies will be analyzed as immediate effects, and this will result in an overestimate of the health benefits of improved air quality.

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[5] Dockery, D.W., C.A. Pope, X.P. Xu, J.D. Spengler, J.H. Ware, M.E. Fay, B.G. Ferris and F.E. Speizer, ""An association between air pollution and mortality in six U.S. cities," *N Engl J Med.*, 329(24): 1753-1759.

[6] Pope, C.A. III; Thun, M.J.Namboodiri, M.; Dockery, D.W.; Evans, J.S.; Speizer, F.E., and Heath, C.W., Jr. Particulate Air Pollution is a Predictor of Mortality in a Prospective Study of U.S. Adults. *Am. J. Respir. Care Med*., Vol. 151, March 1995, pp. 669-674.

[7] "Clean Air Act Amendments (1990) Section 812 Prospective Study Health & Ecological Effects Initial Studies," EPA-SAB-COUNCIL-ADV-99-005.

Thus some time lag is appropriate for distributing the cumulative mortality effect of PM in the population. The HEES concurs with the approach proposed by EPA at the June 29th meeting on this issue, and recommends that the Tier 2 SA Lag estimates as presented at the meeting (Table entitled "Sensitivity to Lag Assumption" Attached in Appendix A) be considered as the best estimate for use in the 1999 Section 812 report. HEES also recommends that a sensitivity analysis of the time lag issue should also be presented in the report. The sensitivity analysis should include a higher end and a lower end mortality estimate (e.g., 0, 8, 15-year lags), in which the higher end estimate would include a no-lag assumption, as given in the second column of the above table, and the lower end estimate would replicate the analysis used in the 1996 WHO report. The latter analysis has been published in the peer-reviewed literature.[8] The Brunekreef analysis clearly results in an underestimate of the immediate mortality effect of PM, since, as discussed above, there is ample evidence for a short term mortality effect of PM, but the 15-year lag analysis presented by Brunekreef provides a statistically simplified approach to estimating the potential delayed effect of PM exposures for a young and relatively healthy segment of the population.

[8] Brunekreef B., "Air pollution and life expectancy: is there a relation?" *Occupational Environmental Medicine*, 1997; 54:781-4.

EPA-SAB-EC-01-008
SAB Arsenic Rule Benefits Panel (ARBRP)
Arsenic Rule Benefits Analysis: An SAB Review
August 2001

[pages 3 to 7:]

2. RESPONSE TO THE CHARGE QUESTIONS

2.1 The Impact of the Timing of Exposure on Avoided Cancers

Charge Question 1: How should latency be addressed in the benefits estimates when existing literature does not provide specific quantitative estimates of latency periods associated with exposure to arsenic in drinking water?

2.1.1. Introduction

A central component in analyzing the benefits of reduced exposure to a carcinogen is the prediction of the annual reduction in cancer cases following reduction in exposure. If a population previously exposed to 50 g/L of arsenic in drinking water is exposed, beginning in 2006, to only 10 g/L, cancer risks in the population will eventually decline to a steady-state level associated with a lifetime of exposure to 10 g/L. How fast this reduction in risk occurs depends on the cessation-lag following reduction in exposure. We believe that this is more appropriately termed a “cessation-lag,” rather than “latency.” This distinction is clarified below.

In order to explain what should be done when the length of this cessation-lag is unknown, we must describe how the timing of the relationship between exposure and response (death due to cancer) should be treated in a benefits analysis. We emphasize that we believe that this is how such an analysis is conducted; it does not refer to the approach taken in the arsenic benefits analysis. As in the case of arsenic, we analyze a policy that would reduce exposure from a current level of d0 (e.g., 50 g/L) to dN (e.g., 10 g/L). We assume that this policy would continue into the indefinite future.

For a benefits analysis we would like to:

a) Calculate the expected number of cancer fatalities avoided each year, as a result of the policy, beginning with the year in which the policy is implemented and continuing into the future.

If benefits are to be monetized in accordance with conventional economic practice:

b) The expected number of cancer fatalities avoided each year should be multiplied by the value of a statistical life in that year. This will give the dollar value of benefits each

year, beginning with the year in which the policy in implemented.

The dollar value of benefits in each year should be discounted to the year in which the policy is implemented and summed. The present discounted value of benefits, so calculated, should be compared with the present discounted value of costs, calculated over the same period.

The timing of the relationship between exposure and cancer mortality is implicit in the calculations in (a). As described more fully below, if the lag between reduction in exposure and reduction in risk of death is long, there will be fewer cancer fatalities avoided in years immediately following the policy than if the lag were shorter. Uncertainties in the timing of the exposure-response relationship will be reflected in uncertainties in the number of cancer fatalities reduced each year after the policy is implemented. These uncertainties should be treated as described in the answer to Charge Question 5.

2.1.2 Calculation of Reduced Cancer Fatalities Associated with Reduced Exposure to a Carcinogen

The approach taken here is to relate the age-adjusted risk of death due to cancer to the history of exposure to the carcinogen. This relationship, together with information on the age distribution of the population affected by the policy, can be used to calculate the expected number of cancer fatalities avoided by the policy.

The epidemiology underlying the arsenic benefits analysis (Morales et al. 2000) assumes that the conditional probability of dying from cancer at age t, h(t) is related to cumulative exposure to a carcinogen as of age t, xt, by a proportional hazard model:

(1) $h(t,x) = h_0(t)g(x_t)$

where $h_0(t)$ = baseline risk of dying from cancer at age t (assuming survival to age t) and $g(x_t)$ represents the impact of exposure incurred up to age t on risk of death.[2]

2.1.2.1 The Timing of the Exposure-Response Relationship

The key question is how cumulative exposure (xt) depends on the dose of arsenic received at ages 0 through t. Let d_i = dose received at age i. A general form that this relationship could take is:[3]

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2 A proportional hazard model (Pope et al. 1995) is also used to measure the association between particulate matter and all-cause mortality in *The Benefits and Costs of the Clean Air Act 1970-1990* (USEPA 1997) and *The Benefits and Costs of the Clean Air Act 1990-2010* (USEPA 1999). The issue of the length of the cessation-lag after a reduction in exposure also arises in these studies.

3 The function ft ( ) could also be conditioned on other factors such as smoking.

(2) $x_t = f_t (d_0,d_1,...,d_t)$

The exact form of this function reflects the answers to the following four questions (Tollerud et al. 1999):

(a) How long does it take after an exposure until an increase in risk is observed?
(b) How long does the effect of an exposure last after exposure has terminated?
(c) How does the effect of exposure vary by the age at which it was received?
(d) Does the exposure act at an early or late stage in the carcinogenic process?

The relevant questions for the implementation of changes in the drinking water standard for arsenic are questions (b)-(d). In contrast, most of the epidemiologic literature addressing the issue of latency has focused on question (a), which is the usual definition of latency. The committee wishes to underscore that data addressing question (a) do not necessarily provide information answering questions (b)-(d). Unfortunately, much less work has been done to evaluate questions (b)-(d) in the epidemiologic literature in general, and in the research on arsenic carcinogenicity in particular.

The NAS report Veterans and Agent Orange: Update 1998 (Tollerud et al. 1999) addresses the second question, regarding how long effects last after cessation of exposure. With respect to arsenic in drinking water, the charge of our committee is an expansion of this question: when does the excess risk (compared to a lifetime of exposure to dN (e.g., 10 g/L)) begin to attenuate and how long does it take until all of the excess is eliminated? Since the term latency has a traditional usage that is not the charge given to this committee, we have coined the phrase “cessation-lag” to clarify and emphasize the difference.

An important point is that the time to benefits from reducing arsenic in drinking water may <u>not</u> equal the estimated time since first exposure to an adverse effect. A good example is cigarette smoking: the latency between initiation of exposure and an increase in lung cancer risk is approximately 20 years. However, after cessation of exposure, risk for lung cancer begins to decline rather quickly. A benefits analysis of smoking cessation programs based on the observed latency would greatly underestimate the actual benefits. We return to the issue of how to estimate the length of the cessation-lag below.

2.1.2.2 Calculating the Time Path of Cancer Cases Avoided

If the relationships in (1) and (2) are known, it is, in principle, a simple matter to compute the expected number of cancer fatalities avoided at age t (and, by analogy, for all other ages) in each year following the policy. In the first year of the policy it is only the most recent dose of the carcinogen (dt for persons who are age t in the year the policy is implemented) that is affected by the policy. The expected reduction in risk of death due to cancer at age t in the first year of the policy is:

(3) $h_0 (t)[g(f_t (d_0^0,d_1^0,...,d_t^0)) - g(f_t (d_0^0,d_1^0,...,d_t'))]$

where the superscripts 0 and N refer to doses with and without the policy, respectively. In the second year of the policy, for persons of age t, both dt-1 and dt are affected by the policy, and the formula in (3) would be adjusted accordingly. Eventually, a steady-state will be reached in which persons of age t face the same mortality risk from cancer as people who have been exposed to the lower level of the carcinogen (dN) throughout their lifetime.

In each year, the number of fatalities avoided by the policy among persons of age t would be the expression similar to (3) multiplied by the number of persons of age t. Similar computations would be performed for persons of all ages. In this manner, it should be possible to compute the expected number of fatalities avoided, by age (or age-group), in each year following the implementation of the policy. Because the age distribution of avoided cancer fatalities is calculated, it should be reported in a benefits analysis even if information on the age distribution of avoided fatalities is not used in valuing avoided mortality.

2.1.3 Quantifying the Relationship Between Exposure and Mortality Risk

Most epidemiologic studies ignore the time pattern of exposure in estimating the proportional hazard model in equation (1). For example, Morales et al. (2000) effectively assume that

$$(4) \quad x_t = \sum_{i=0}^{t} di \, .$$

Given sufficient data, the time pattern of exposure and effect can be estimated in the context of equations (1) and (2).[4] In order to properly study effects of protracted exposures, detailed exposure histories for each study subject, including the dates and ages when the individual was exposed and the level of exposure at all points in time, are needed. Appropriate statistical methods have been developed for an investigation of the effect of exposure accrued as a function of time since that exposure (Thomas 1983; Breslow and Day 1987; Thomas 1988). In general, the ability to investigate the issues of timing of exposure in a given data set will depend on the quality of the exposure measure, the quality of the timing of exposure information, the number of people developing the disease of interest, and variation of exposure over time within the study group. These aspects of study quality are, of course, important in evaluating any epidemiologic investigation. But there are special problems that arise in the evaluation of time related factors (Enterline and Henderson 1973; Thomas 1987).

If possible, it would be desirable to use information about the mechanism by which cancer occurs in estimating the length of the cessation-lag.[5] For example, if arsenic primarily

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4 Latencies and cessation-lags would be expected to vary by cancer site, would probably be shorter for cardiovascular disease than for cancer, and may be shortest for reproductive effects. We emphasize that the same model should be used to estimate the time pattern of exposure and response as is used to estimate the potency of the carcinogen.

5 We emphasize that the same model should be used to estimate the time pattern of exposure and response as is used to estimate the potency of the carcinogen.

exerts a late-stage effect in the cancer formation process, the cessation-lag will be shorter than if arsenic primarily exerts an early-stage effect. Appendix 2.1 to this report discusses how the time pattern of exposure and response could be estimated in the context of the multi-stage model of cancer formation.

In addition, two published studies have attempted to address either latency or cessation lag, or the stage at which arsenic acts in the carcinogenic pathway. Brown and Chu (1983, 1987) attempted an analysis based on one of the arsenic-exposed occupational cohorts and demonstrated that two models provided good fit to the data: one with only a late-stage effect and the other with both an early- and late-stage effect. There was a slightly better fit for the model with only a late-stage effect but the difference in fit was not sufficient to exclude an early-stage effect. A more recent analysis (Hazelton et al. 2000) examined an occupational cohort with exposures to arsenic, radon and tobacco using biologically based models. They evaluated the time between generation of the first malignant cell and death from lung cancer. This would appear to assume an early-stage effect only; nevertheless, it is notable that the best fit was given for a gamma distribution of lags that had a mean of 4.1 years and a variance of 2.9 years. Under this distribution, which is consistent with a minimal first stage effect of arsenic, the bulk of the benefit following cessation would be expected to occur within the first five years after exposure is reduced.

It thus appears that some information about the length of the cessation-lag is available in the case of arsenic. Additional information on the length of the cessation-lag could be evaluated from data on arsenic-exposed populations in Taiwan and Chile, and we urge that such research be undertaken. In Taiwan, the water supply was changed in the early 1970's, thereby eliminating the arsenic exposure. In Antofagasta, Chile, water treatment beginning in 1970 reduced the arsenic concentration from 800 to 110 g/L within a short time, and over a few more years to 40-50 g/L.

If, however, such information were not available (as the charge question assumes), what could be done? One extreme assumption that would yield an upper bound to the benefits of the program is to assume that the program immediately attains the steady-state result, i.e., that the reduction in the age-t mortality rate is given by:

(5) $h_0(t)[g(f_t(d_0^0, d_1^0, ..., d_t^0)) - g(f_t(d_0', d_1', ..., d_t'))]$

This is the assumption made in the Agency's primary analysis.

If it should prove infeasible to estimate the cessation-lag and account for it as described above, it would still be desirable to examine the influence of this lag by performing sensitivity analyses similar to those carried out for the PM-mortality relationship in the Agency's analysis of The Benefits and Costs of the Clean Air Act: 1990-2010 (USEPA 1999). In the context of the multi-stage model described in Appendix 2.1, we would suggest that the testing of extreme cases of potential mechanisms (i.e., arsenic's effects being exerted entirely at an early stage v. all at a late stage) be done as part of the uncertainty analysis.

NRC Report: Estimating The Public Health Benefits Of Proposed Air Pollution Regulations
Committee on Estimating the Health-Risk-Reduction Benefits of Proposed Air Pollution Regulations
National Research Council of the National Academies
2002

[page 64:]

Finally, the health benefits of reducing emissions in a single year might not occur solely in that year but might occur in subsequent years because of physiological and other lags. The analyses should carefully state and document the lag relationships between pollution reductions and health improvements that have been used (see Chapter 4).

[pages 114 to 115:]

Effect Lags and EPA's Assumptions

Understanding long-term disease processes is important for benefits analysis. For example, certain health benefits resulting from a change in air quality may occur only after several years. Although it appears that mortality following short-term exposure to PM occurs within a relatively short time, little is known about the temporal relationship between longer-term exposure and mortality as demonstrated in the prospective cohort studies. For example, the ACS study (Pope et al. 1995) provided little information as to whether the observed geographic differences in mortality risks are due to a 1-year average or some multiyear history of PM exposures preceding mortality. Thus, it is not known which period of exposure is the most important and how quickly benefits from air pollution reductions will appear in the case of long-term disease processes. In the Swedish lung cancer study (Nyberg et al. 2000), effects were strongest for the exposure 20-30 years ago. For other outcomes, other time periods may be relevant.

The time course relating exposure to outcome is an important assumption in benefits analysis, especially when long-term mortality effects dominate the analysis, as occurs in PM analyses. It is important because health benefits that occur far into the future may count less based on the way the benefits are monetized. In EPA's benefits analyses for the Tier 2 rule and the HD engine and diesel-fuel rule, EPA assumed a weighted 5-year time course of benefits in which 25% of the PM-related mortality benefits were assumed to occur in the first and second year, and 16.7% were assumed to occur in each of the remaining 3 years. Although recommended by EPA's Science Advisory Board, the committee found little justification for a 5-year time course and recommends that future benefits analyses more fully account for the uncertainty regarding lags in health effects by incorporating a range of assumptions and probabilities on the temporal relationship.

[page 118:]

- The committee found little justification for the 5-year time course of exposure and outcome assumed in the more recent EPA analyses and recommends that EPA more fully account for the uncertainty regarding lags in health effects by incorporating a range of assumptions and probabilities on the temporal relationship.

[pages 136-137:]

EPA expressed much less certainty about alternative lag structures than it did about thresholds in the Tier 2 analysis. The lag structure used in the primary analysis was recommended by the Science Advisory Board (EPA 1999a, pp. 4-6, 4-7), but the agency considered a range of alternative lag structures plausible. Here a probabilistic weighting of alternative lag structures based on expert judgment might have led to a more appreciable widening of the health benefit probability distribution.

Although EPA considered alternative lag structures to vary in plausibility, these variations were not, but could have been, approximately captured by subjective probability distributions. The incorporation of these distributions into the final probability distribution for the primary analysis would have resulted in a more realistic presentation of acknowledged sources of uncertainty.

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[Executive Summary, page 2:]

The HES also provides advice on how to address the question of cessation lag, which is the time lag between reductions in concentrations of air pollutants and manifestation of health benefits in the population. The HES notes that for long-term PM effects, empirical evidence is lacking to estimate the lags. Given this problem, the HES recommends that the Agency consider developing models for each cause of death category expected to make up PM mortality, since the lag structure most likely differs for different PM-associated disease processes. Although specific causes of death would not be specifically calculated in the base case, the literature provides enough information to guide estimates of the likely proportion of PM mortality by disease type (Pope et al., 2002, 2004).

[pages 22 to 24:]

3.6. Agency Charge Question 16: Cessation Lag.

Charge Question 16. In recent EPA rulemakings, EPA's "base estimate" of benefit from PM control has been based on cohort epidemiological studies that characterize the chronic effects of pollution exposure on premature death as well as capturing a fraction of acute premature mortality effects. If these chronic effects occur only after repeated, long-term exposures, there could be a substantial latency period and associated cessation lag. As such, a proper benefits analysis must consider any time delay between reductions in exposure and reductions in mortality rates. For the acute effects, such as those considered in EPA's alternative benefit analyses, the delays between elevated exposure and death are short (less than two months), and thus time-preference adjustments are not necessary.

(1) In the previous 812 analysis and in recent rulemakings, EPA assumed a weighted 5-year time course of benefits in which 25% of the PM-related mortality benefits were assumed to occur in the first and second year, and 16.7% were assumed to occur in each of the remaining 3 years. Although this procedure was endorsed by SAB, the recent NAS report (2002) found "little justification" for a 5-year time course and recommended that a range of assumptions be made with associated probabilities for their plausibility. Do you agree with the NAS report that EPA should no longer use the deterministic, 5-year time course?

(2) One alternative EPA is considering is to use a range of lag structures from 0 to 20-30 years, with the latter mentioned by NAS in reference to the Nyberg et al. PM lung cancer study, with 10 or 15 years selected as the mid-point value until more definitive information becomes available. If this simple approach is used, should it be applied to the entire mortality association characterized in the cohort

studies, or only to the difference between the larger mortality effect characterized in the cohort studies and the somewhat smaller effect found in the time series studies of acute exposure? Should judgmental probabilities be applied to different lags, as suggested by NAS?

(3) Another option under consideration is to construct a 3-parameter Weibull probability distribution for the population mean duration of the PM mortality cessation lag. The Weibull distribution is commonly used to represent probabilities based on expert judgment, with the 3-parameter version allowing the shaping of the probability density function to match expected low, most likely, and expected high values. EPA is still considering appropriate values for the low, most likely, and expected high values –and therefore for the Weibull shape and location parameters– and EPA is interested in any advice the Council wishes to provide pertaining to the merits of this approach and/or reasonable values for the probability distribution.

HES Response: Given the purpose of the 812 Studies (to estimate a future situation), the cessation lag is a very important issue. As noted by EPA, for short-term effects (including time-series based observations of mortality) this is not a problem, and there is even published evidence that these short-term effects closely follow changes in the pollution, thus, benefits are 'immediate' (on the annual aggregate level). For long-term effects, the HES notes that empirical evidence is lacking to inform the choice of the lag distribution directly and agrees with the NAS report that there is little empirical justification for the 5-year cessation lag structure used in the previous analyses. This is because the cohort mortality studies reported to-date have lacked data on the long-term time-course of exposures for each cohort member; such data, if available, might enable testing hypotheses regarding alternative exposure lag structures, if sufficient statistical power was available. However, the HES notes the importance of developing some estimates of the cessation lag rather than assuming there is no lag and urges the Agency begin to move from the relatively arbitrary assumptions of the 5-year lag structure to an approach based on some plausible models of the disease processes involved. Lacking direct information from the cohort studies themselves, new insights regarding the shape of the cessation lag can only come from improved understanding of the mechanism of the exposure-response relationship. Information that may prove valuable in this regard could include results from clinical, experimental animal, and in-vitro studies, and analogies with the health effects of other long-term inhalation exposures, such as cigarette smoking. The clinical intervention literature (e.g., cardiovascular trials) or smoking cessation data may be useful.

The HES recommends that the Agency consider developing models for each cause of death category expected to make up PM mortality, since the lag structure most likely differs for different PM-associated disease processes. Although specific causes of death would not be specifically calculated in the base case, the literature provides enough information to guide estimates of the likely proportion of PM mortality by disease type (Pope et al., 2002, 2004). As a general rule, one may assume that the longer the air-pollution-sustained disease process is, the longer the delay. This may be true whether pollution is an initiator or a promoter. For example, if inhalation of carcinogens from ambient air contributes to the incidence of lung

cancer, the pathophysiologic process between exposure and death may take many years (for the average case) and the benefit of a reduction in carcinogenic constituents in PM between the year 2000 and the year 2010 may lead to a reduction in lung cancer rates only after many years. For effects of long-term PM exposures on pulmonary disease (e.g., COPD), a useful model may be the change in the natural history of lung function with exposure to air pollution. Several studies show effects of long-term PM exposures on decreased lung function (e.g., Gauderman et al., 2002)). By analogy with cigarette smoking, this may put people on steeper trajectories of lung function decline, which is a known risk factor for premature mortality. This might imply distributed lags extending over a substantial fraction of a lifetime. On the other extreme, some cardiovascular deaths captured in the cohort studies may be due to air pollution during the last months to years prior to death whereas the underlying susceptibility to a cardiovascular death may be due to non-air pollution causes (e.g., diabetes). Lifetime lost, captured in the cohort, may still be rather long (see comments in response to Charge Question 17). Clean air policies would bring a rather immediate benefit for such kind of cases. For example, Lightwood and Glantz (1997) conducted a meta-analysis of studies to determine how excess risks of myocardial infarction and stroke in smokers decline after quitting. They reported that risks would be reduced after roughly 1.5 years. Finally, to the extent that cohort results capture a portion of the acute time-series mortality effects of PM, there may be an even shorter lag.

EPA staff has presented several alternative lag structures, including the use of a flexible Weibull distribution spanning up to 25 years. It would be useful to utilize a distribution that could incorporate time lag to benefits based on different patterns of exposure-response consistent with models developed of the various response mechanisms. For example, acute effects may be reduced within the first 6 months of an exposure change, medium-term effects may be reduced within 2 to 5 years, and long-term effects may be reduced after 15 to 25 years. Thus, the HES supports either the use of a Weibull distribution or a simpler distributional form made up of several segments to cover the response mechanisms outlined above, given our lack of knowledge on the specific form of the distributions. An important question to be resolved is what the relative magnitudes of these segments should be, and how many of the acute effects are assumed to be included in the cohort effect estimate. The Subcommittee suggests that a smoother might be applied to the lag function to smooth the discontinuities. Given the current lack of direct data upon which to specify the lag function, the HES recommends that this question be considered for inclusion in future expert elicitation efforts and/or sensitivity analyses. As noted, time lag to benefits may depend on the cause of death and the underlying morbidity processes that ultimately lead to premature death.

[pages 28 to 29 :]

If the Agency adopts the approach discussed in response to Charge Question 16 of modeling the exposure-response processes to estimate the range of cessation lags, a similar approach could be used to estimate life-years saved. Just as likely ranges of cessation lags may be estimated by looking at what is known about different causes of death and how PM may be contributing to the disease processes and attempting to build some models/ranges of that

process, ranges of life-years lost could be similarly estimated. Whether the Agency uses a static or dynamic life table, the assumption made in the life tables approach is that the average remaining disease-specific life expectancy for the people whose deaths are predicated on air pollution exposure is the same as the average remaining life expectancy for all individuals (i.e., where deaths are both related and non-related to air pollution) of the same age and gender. This may result in an overestimate of life-years saved due to PM reductions if the disease profile of the subgroup impacted by air pollution is different from the profile of the full group (i.e., if the air pollution-impacted people with previous cardiovascular disease are more frail than people who die from cardiovascular disease, in general). It would be reasonable to assume, consistent with the cessation lag estimates, that some share of the deaths are among people with lower than average life expectancy. The Agency could use available information on causes of death and likely disease processes to propose a set of reasonable assumptions for both cessation lags and life-years saved that are consistent with one another. For example, some share of the COPD deaths associated with PM exposure consists of individuals who developed COPD because of long-term PM exposure. In this instance the cessation lag may be many years and the life-years lost are consistent with standard life tables. In another category, there may be heart attack deaths associated with PM exposure that include individuals who had already existing coronary heart disease. In this case the cessation lag may be quite short and the life-years saved, although substantial, may be less than the standard life table's calculation because of the pre-existing disease. In yet another category, there may be PM-related deaths due to pneumonia in individuals with rates of pre-existing disease comparable to the general population. If in the absence of PM exposure a full recovery would have been made, then the cessation lag is quite short and the life-years saved is consistent with the standard life tables.

The HES acknowledges, however, that uncertainties remain, given that no study has formally analyzed the years of life lost and the dependence of years of life lost on causes of death, pre-existing diseases, and the underlying distributions of other susceptibilities. Even though a considerable amount of judgment would be involved, an approach that uses available information to estimate the shares of PM-associated deaths in each of several categories may provide a more defensible set of assumptions for estimating both cessation lags and life-years saved than more arbitrary assumptions.

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