UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

IV-K-1

(8)

November 6, 1984

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NOV - 9 1984

OFFICE OF RESEARCH AND DEVELOPMENT

CENTRAL DOCKET SECTION

SUBJECT: Evaluation of Analyses Contained in Schwartz Memo to Lead Phasedown Docket (#EN-84-05)

FROM: Lester D. Grant, Director
Environmental Criteria and Assessment Office-RTP (MD-52)

TO: Richard G. Kozlowski, Director
Field Operations and Support Division (EN-397F)

THRU: Elizabeth L. Anderson, Director
Office of Health and Environmental Assessment (RD-689)

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THRU: Bernard Goldstein, Assistant Administrator
Office of Research and Development (RD 672)

NOV 15 1984

This memo responds to your recent request (October 18, 1984) that ECAO/RTP evaluate the scientific soundness of public health aspects of analyses contained in a memo placed in the EPA Lead Phasedown Docket (#EN-84-05) by Joel Schwartz (OPA). The subject analyses included statistical evaluations of: (1) relationships between blood lead (PbB) levels and increases in blood pressure among adult males (aged 40-59), based on data collected as part of the Second National Health and Nutrition Examination Survey (NHANES II); (2) further health implications of PbB-blood pressure relationships found by analysis of the NHANES II data, using risk factors for increased risk of serious health events (stroke, myocardial infarction, mortality) as a function of elevated blood pressure derived from the Framingham and Pooling Project Studies; and (3) monetized benefits associated with avoidance of health care costs projected to be gained by reduction of incidence of the above types of health effects (elevated blood pressure, stroke, etc.) by more rapid phasedown of lead in gasoline.

This ECAO/RTP evaluation focussed only on review of the first two (health effects) issues listed above and did not address the monetization aspects of the subject analyses. It was not possible to accomplish a full-scale peer review (including public comment and CASAC review) of the health effects analyses within the limited time available (approximately 10 days) to complete the present evaluation. However, ECAO was able to accomplish a reasonably complete preliminary assessment of the Schwartz memo via the convening of both EPA and non-EPA experts in biostatistics, epidemiology, and cardiovascular disease to critique statistical and other aspects of the health effects analyses reported in the review. (See Appendix A for a list of reviewers and their affiliations.)

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For purpose of clarity, note that the Schwartz memo first summarizes results and conclusions from a paper by Drs. Pirkle, Schwartz, et al. (accepted for publication without revision in the American Journal of Epidemiology, based upon expert peer review standardly obtained by that journal), then proceeds to deal with monetization of the public health implications of the findings reported by Pirkle, Schwartz, et al. A complication in carrying out review of the subject analyses was encountered in view of the fact that the journal which will publish the Pirkle et al. paper will not allow preprints to be circulated prior to the publication date (expected to be February, 1985) and that the Schwartz memo was of necessity very sparse in detail in deference to the proprietary concerns of the journal. It was therefore felt that an adequate review of this subject could only be conducted if the authors of the paper presented a detailed briefing to the reviewers, including an opportunity for the reviewers to read the manuscript accepted for publication by Amer. J. Epidemiology. Accordingly, Drs. Schwartz and Pirkle met with each of the reviewers listed in Appendix A at ECAO offices in RTP on October 17 and 23, during which time they gave an in-depth description of steps taken in the analysis of the data and made available for inspection copies of the accepted manuscript and other materials documenting the statistical analyses performed. Each of the reviewers was encouraged to ask questions or give comments, and all were individually interviewed by me or my staff after the briefings. In addition, written comments have been obtained from each of the reviewers.

The written individual comments by the reviewers are available in ECAO/RTP public files, and are attached. We strongly recommend that you read these written comments and review them with Joel Schwartz. The following summary, however, highlights the most salient points raised by reviewers in their written or oral comments and generally represents a broad consensus among the reviewers:

(1) The NHANES II data base represents a well-validated data base, with adequate quality control for blood lead determinations and consistency in standardized measurement of health endpoints (e.g., blood pressure) by well-accepted methods.

(2) The reviewers unanimously felt that the rigor and thoroughness of the statistical approach to determining the relationship between PbB and blood pressure were outstanding (words such as "meticulous," "exemplary," and "impressive" were used freely by the reviewers with regard to the statistical analyses). Furthermore, the reported association between PbB and blood pressure elevations (at PbB levels ranging from 30 ug/dl to below 10 ug/dl) appears to be quite robust in view of it remaining highly statistically significant even after controlling for a myriad of potentially confounding factors and with use of varying model specifications (a model using the log of PbB provided the best fit for the PbB-blood pressure data). This model implies an initial steep rise in risk (i.e., in the 10-30 ug/dl range), followed by a plateauing at higher blood lead levels. This means that, normally, small increments in risk may occur at PbB levels over 30 ug/dl, making such increases difficult to detect at higher levels unless compared to markedly lower blood lead levels (i.e., < 10 ug/dl).

(3) Most of the reviewers concluded that the reported relationship between PbB and hypertension is biologically plausible. It is, in fact, supported by toxicologic studies demonstrating experimental induction of hypertension in rats as a consequence of lead exposure.

One reviewer, however, was concerned by the fact that the relationship did not hold for females and questioned the existence of any biological reason for this.

The PbB-hypertension relationship is also corroborated by the work of other, independent investigators (i.e., Weiss and collaborators), who evaluated a different sample of adult male Americans. However, these corroborative analyses are not expected to be published for another 6 to 12 months. These latter findings, as well as the Pirkle, Schwartz et al. analyses, are in contrast to (but not necessarily negated by) other recently reported study results (e.g., Pocock et al., 1984) found weaker or non-significant associations (depending upon specific analyses used) between PbB and hypertension at PbB levels below approximately 35-40 ug/dl.

(4) The causal significance of the strong PbB-hypertension associations reported by Pirkle, Schwartz, et al. remains to be more definitively established, although cogent arguments are advanced by the authors for the likely causitive role of lead in producing the blood pressure elevations (versus the converse); and the plausibility of such a causitive role of lead is supported by experimental animal data, as noted above. The reviewers offered specific suggestions for further follow-up work by which the causal nature of the relationship could be evaluated and underlying mechanisms elucidated. The reviewers generally concurred that lead should be viewed, in the meantime, as probably playing a causitive role in producing hypertension.

(5) The one area which might be regarded as a weakness in the paper by Pirkle et al. concerns the use of the multiple logistic risk factors from the Framingham and Pooling Project Studies to predict the incidence of increased myocardial infarction (MI), strokes, and death from all causes as a function of PbB-hypertension relationships derived from the NHANES II data base. While most of the reviewers felt that it was likely appropriate to use these risk factors in this way, most seemed to feel that sufficient caveats were not expressed about the assumptions underlying these risk factors. It was also pointed out that it is not possible at present to experimentally validate the application of these risk factors to the NHANES II population and that the coefficients may change over time. Caution should, therefore, be applied in viewing or using the resulting estimates of numbers of serious events (MI, stroke, mortality) projected by the analyses in the Schwartz memo to be likely associated with lead-induced hypertension in adult American males (or to be avoided by alternative lead phasedown options). Statements regarding this subject, then, should probably be couched, for example, in terms of "the reported PbB-hypertension relationships are provisionally projected to cause up to X cases of MI, of stokes, etc." On the other hand, one reviewer expressed reservations about using only the Framingham and Pooling Project risk factors because they did not

include renal disease; as such, he felt that the projections in the Pirkle et al. paper were probably an underestimate of the public health implications of elevated blood lead levels because they did not also project estimates of likely later renal disease related to the observed blood pressure elevations.

In summary, overall, ECAO's preliminary review concludes that the Pirkle, Schwartz, et al. study of PbB-blood pressure relationships represents a solid, statistically-sound analysis of pertinent NHANES II data, and their finding of significant associations between PbB and hypertension are likely to be corroborated soon by publication of work by other, independent investigators. The observed association, while likely causal (i.e., lead probably induced the hypertension in the NHANES II subjects), remains to be more definitively understood and the underlying mechanisms elucidated. The observed PbB-hypertension relationship, further, might possibly be viewed as implying likely increased risk of MI, strokes, mortality (and, probably, higher risk of progressively developing renal disease). The quantitative estimation of such increased risk for cardiovascular-related serious events, however, must be viewed cautiously and should be appropriately caveated when discussed or used for decision-making purposes. It would also be desirable to have a full-scale peer review (including CASAC evaluation and opportunity for public comment on the subject analyses and their use in regulatory decision making) once the published paper by Pirkle, Schwartz, et al. appears in the Amer. J. Epidem. early next year, in order for EPA to be in the strongest position procedurally in basing any regulatory decisions on the subject analyses.

Attachments

APPENDIX A

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