UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

June 05, 2006

EPA-CASAC-06-007

Honorable Stephen L. Johnson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Clean Air Scientific Advisory Committee's (CASAC) Teleconference Meeting to Provide Additional Advice to the Agency Concerning Chapter 8 (Integrative Synthesis) of the Final Ozone Air Quality Criteria Document (AQCD)

Dear Administrator Johnson:

EPA's Clean Air Scientific Advisory Committee (CASAC or Committee), supplemented by subject-matter-expert Panelists — collectively referred to as the CASAC Ozone Review Panel (Ozone Panel) — met via a public teleconference on May 12, 2006, to provide additional advice to the Agency concerning Chapter 8 (Integrative Synthesis) of EPA's Final *Air Quality Criteria for Ozone and Related Photochemical Oxidants (Second External Review Draft), Volumes I, II, and III*, (EPA/600/R-05/004aF-cF, February 2006), also known as the Final Ozone Air Quality Criteria Document (AQCD). The current Clean Air Scientific Advisory Committee roster is found in Appendix A of this report, and the CASAC Ozone Review Panel roster is attached as Appendix B. Panel members' individual review comments are provided in Appendix C.

The members of the Ozone Panel are in general agreement that, in its development of the Integrative Synthesis chapter in the Final Ozone AQCD, the Agency has been reasonably successful in assembling the relevant information and incorporating findings from atmospheric sciences, toxicology, human clinical studies and epidemiology. Nevertheless, in view of the acknowledged role of the Ozone AQCD in informing the 2nd draft Ozone Staff Paper and, ultimately, potential revisions to the national ambient air quality standards (NAAQS) for ozone, the CASAC is of the opinion that there are some important issues that are not presented well, or at all, in this chapter. These include: the utility of time-series studies in assessing the risks from ozone exposure; the problem of exposure measurement error in ozone mortality time-series studies; use of ozone as a surrogate marker for other toxic photochemical pollutants; a general downplaying of animal-to-human extrapolation studies; and the need for inclusion of welfare issues (*i.e.*, leading to the establishment of secondary standards for criteria air pollutants) in an integrative synthesis chapter. Each of these issues is discussed in greater detail below.

1. Background

The CASAC, comprising seven members appointed by the EPA Administrator, was established under section 109(d)(2) of the Clean Air Act (CAA or "Act") (42 U.S.C. § 7409) as an independent scientific advisory committee, in part to provide advice, information and recommendations on the scientific and technical aspects of issues related to air quality criteria and NAAQS under sections 108 and 109 of the Act. Section 109(d)(1) of the CAA requires that EPA carry out a periodic review and revision, where appropriate, of the air quality criteria and the NAAQS for "criteria" air pollutants such as ozone. The CASAC, which is administratively located under EPA's Science Advisory Board (SAB) Staff Office, is a Federal advisory committee chartered under the Federal Advisory Committee Act (FACA), as amended, 5 U.S.C., App. The Ozone Panel consists of the seven members of the chartered (statutory) CASAC, supplemented by sixteen technical experts.

EPA is in the process of updating, and revising where appropriate, the AQCD for ozone and related photochemical oxidants published in 1996. This teleconference was a continuation of the Ozone Panel's peer review of the revised Ozone AQCD in this present NAAQS review cycle for ozone. In the CASAC's final letter/report to you from the Ozone Panel's December 6-7, 2005 meeting (EPA-CASAC-06-003, dated February 10, 2006, posted at the following URL: http://www.epa.gov/sab/pdf/casac_ozone_casac-06-003.pdf), we advised you that:

> "… given the critical importance of the exposure and human health effects integrative synthesis chapter in the development of the 2nd draft Ozone Staff Paper, after EPA issues the final Ozone AQCD on February 28, 2006, the CASAC will determine whether there is a need to convene a public meeting to conduct any additional review of Chapter 8."

On March 21, 2006, the Agency's National Center for Environmental Assessment (NCEA-RTP) published the Final Ozone AQCD. After canvassing the members of the Ozone Panel, we decided that, despite the fact that the AQCD has already been finalized, it would be beneficial to hold a public teleconference meeting to provide additional advice to the Agency concerning the integrative synthesis chapter of the Final Ozone AQCD in order to inform EPA's preparation of the 2nd draft Ozone Staff Paper and, ultimately, the proposed NAAQS for ozone.

2. CASAC's Additional Advice Concerning Chapter 8 of the Final Ozone AQCD

It is the assessment of the CASAC that, in its development of the Integrative Synthesis chapter in the Final Ozone AQCD, EPA has taken a fairly standard approach to putting together the relevant information, and incorporating findings from atmospheric sciences, toxicology, human clinical studies and epidemiology. In general, this is done reasonably successfully. Unfortunately, there are some issues that are important when considering revisions to the NAAQS that are not presented well, or at all, and that have substantial implications for the Ozone Staff Paper. A discussion of the major issues is presented below and, as previously noted, individual comments of Ozone Panel members are attached.

Utility of Time-Series Studies

The first area of concern is how time-series studies are used in assessing the risks from ozone exposure. While the epidemiological evidence on the health effects of ozone constitute

only a fraction of the totality of the scientific knowledge based on ozone health effects, this evidence plays a disproportionately large role in the policymaking process. The ozone time-series studies, particularly the mortality time-series studies, could potentially play an especially important role in this process, as they did for particulate matter (PM), and therefore deserve special attention. An issue that needs to be confronted relates to the utility of these time-series studies in the NAAQS-setting process. Motivation for this concern is partly based on the observation that time-series findings indicate associations of mortality with not only PM and ozone, but with all of the criteria pollutants (see Stieb *et al*., *J. Air Waste Manage. Assoc.* 2002, 2003; the complete references are below).

Since it is unlikely that each of these pollutants will have similar short-term effects on mortality, these findings suggest that while the time-series study design is a powerful tool, being able to detect very small effects that could not be detected using other designs, it is also a blunt tool. The Clean Air Act requires that NAAQS be set for individual criteria air pollutants using the best available science. Because results of time-series studies implicate all of the criteria pollutants, findings of mortality time-series studies do not seem to allow us to confidently attribute observed effects specifically to individual pollutants. This raises concern about the utility of these types of studies in the current NAAQS-setting process and could serve to motivate interest in taking a broader perspective on regulating air pollution that incorporates the entire mixture of community air pollutants.

Time-series studies typically make use of data from available air pollution monitoring network sites in which concentrations of various subsets of the criteria pollutants are measured. Study findings focus on identification of associations between day-to-day variation in these concentrations and daily mortality. Not only is the interpretation of these associations complicated by the fact that the day-to-day variation in concentrations of these pollutants is, to a varying degree, determined largely by meteorology, the pollutants are often part of a large and highly-correlated mix of pollutants, only a very few of which are measured. For the ozone and other photochemical oxidant NAAQS, this pollutant mix includes a large number of both gas- and particle-phase photochemical oxidant pollutants. Unfortunately, we have only limited information on the specific chemical composition, toxicity and, equally importantly, the population exposure of oxidant pollutants other than ozone.

Error in Estimating Exposure to Ozone

The Ozone Staff Paper should consider the problem of exposure measurement error in ozone mortality time-series studies. It is known that personal exposure to ozone is not reflected adequately, and sometimes not at all, by ozone concentrations measured at central outdoor monitoring sites. Typically, personal exposures are much lower than the ambient concentrations, and can be dramatically lower depending on time-activity patterns, housing characteristics and season. In addition, and of particular importance for the ozone time-series studies, there can be no correlation between personal concentrations of ozone measured over time and concentrations measured at central outdoor sites. The population that would be expected to be potentially susceptible to dying from exposure to ozone is likely to have ozone exposures that are at the lower end of the ozone population exposure distribution, in which case this population would be exposed to very low concentrations of ozone indeed, and especially so in winter. Therefore it

seems unlikely that the observed associations between short-term ozone concentrations and daily mortality are due solely to ozone itself.

Another implication of ozone measurement error that is relevant to the NAAQS-setting process is that this degree of measurement error would be expected to have a substantial impact on the ability to detect a threshold of the concentration-response relationship below which no ozone effects are discernible. Pollutant exposure measurement error obscures true thresholds in the concentration-response relationship, and this effect worsens with increasing degrees of measurement error. Since threshold assumptions are incorporated in the Agency's risk assessment and risk analyses, this issue will need to be addressed.

Ozone as a Surrogate for Other Toxic Agents

At least two questions arise from these observations that are relevant to the ozone NAAQS-setting process: (1) What chemical agent or agents are at least partly responsible for the observed associations between ozone and mortality in the time-series studies?; and (2) Do we require an immediate answer to this question of whether ambient ozone adequately serves as a surrogate marker that, when controlled, effectively mitigates health impacts of this entire mix of pollutants? One possible explanation for the observed associations of ozone with mortality is that ozone itself may be serving as a marker for other agents that are contributing to the short-term exposure effects on mortality. This would require that outdoor concentrations of these agents are correlated over time with outdoor ozone concentrations, which is to be expected if they are products of the same atmospheric processes that lead to ozone formation, and that these outdoor pollutant concentrations are better correlated with personal exposures than is the case for ozone itself.

We have very little information on these last two issues at this time to make a strong argument for this, although it is a plausible argument. It should be noted that the observed associations pertain to total mortality, which implies that ozone is causing acute effects on the cardiovascular system, and not merely on the respiratory system. As indicated in Chapter 8 of the air quality criteria document, our understanding of cardiovascular effects of ozone is currently very limited compared to our understanding of ozone's effects on the lung.

Animal-to-Human Extrapolation

The Integrative Synthesis chapter touches upon animal-to-human extrapolation issues in a number of places, with the general theme being one of concern that such extrapolations cannot be accomplished for ozone. The Ozone Panel did not agree with the extent to which these extrapolations are downplayed, and offers the following comments, primarily for the benefit of Agency staff who are involved in the development of the 2nd draft Ozone Staff Paper. The experiments by Hatch discussed on page 8-31 of the Final Ozone AQCD give the reader the impression that rats are more sensitive to ozone than are humans. However, if one adjusts for ventilation differences between exercising humans and resting rats and body mass differences, the relationships between inhaled dose and biological responses in these studies are in reasonably good agreement.

In addition, the statement found on page 8-16 that "some" subjects are reproducible over time in their response to ozone is deceptive. The work of McDonnell and his EPA colleagues clearly shows that the vast majority of subjects are reproducible over time in their response to ozone exposure. Moreover, the 1996 publication by Overton *et al.* shows that anatomical dead space accounts for the major part of heterogeneity among subjects seen in acute pulmonary function responses in human clinical studies.

The chapter inconsistently presents the case for and against animal-to-human extrapolation by first contending that physiological differences lead to large uncertainties in such extrapolations, and subsequently stating the agreement between the species is sufficient to support a common mode of action for ozone in producing biological effects. The latter is, in fact, the more appropriate interpretation in view of the commonality of pulmonary function changes, protein in lavage fluid, and a number of other biological endpoints between animals and humans. In the preparation of the 2nd draft Ozone Staff Paper, EPA staff should pay particular attention to the book chapter published by Ozone Panel member Dr. Charles Plopper ("Time-response profiles: Implications for injury, repair and adaptation to ozone"; complete reference below) concerning the importance of the relationship between ozone exposure in different scenarios and the resulting biological responses (found in Appendix D). This gives rise to exposure/dosimetry issues in terms of the pattern of biological response, and most likely requires a translation of the animal exposures via a dosimetry model for full application to assessing human equivalent exposure scenarios.

Inclusion of Welfare Issues in Integrative Chapters

The members of CASAC understand that the exposures and adverse effects of criteria pollutants on public health have been the principal focus of the Agency's traditional sense of responsibility to the people of the United States. But the U.S. Congress, in passing the Clean Air Act Amendments of 1970, established that both public-health-based primary standards and public-welfare-based secondary standards for criteria air pollutants should be set as part of the NAAQS. Thus, the integrative chapters for criteria pollutants need to include discussion of issues related to the setting of the both the primary and secondary standards.

The issues addressed above have direct implications for the Ozone Staff Paper, and should be given thoughtful consideration in drafting the next version. They are particularly relevant to the ozone risk assessment and risk analyses in which mortality time-series studies have previously played a central role. The CASAC plans to have a general discussion of the utility of time-series epidemiology studies for risk assessment purposes in a meeting at a later date. We look forward to providing additional advice on this important issue in the future. As always, we wish the Agency staff well in this important endeavor.

Sincerely,

/Signed/

Dr. Rogene Henderson, Chair
Clean Air Scientific Advisory Committee

References:

Stieb, DM; Judek, S; Burnett, RT. Meta-analysis of time-series studies of air pollution and mortality: Effects of gases and particles and the influence of cause of death, age, and season *Journal of the Air & Waste Management Association*, 52 (4): 470-484, 2002

Stieb, DM; Judek, S; Burnett, RT. Meta-analysis of time-series studies of air pollution and mortality: Update in relation to the use of generalized additive models *Journal of the Air & Waste Management Association*, 53 (3): 258-261, 2003

Plopper, C.G., R. Paige, E. Schelegle, A. Buckpitt, V. Wong, B. Tarkington, L. Putney and D. Hyde. (2000) Time-response profiles: Implications for injury, repair and adaptation to ozone, pp. 23-37. In U. Heinrich and U. Mohr, (Eds.), *Relationships Between Acute and Chronic Effects of Air Pollution*. ILSI Press: Washington, DC.

Appendix A – Roster of the Clean Air Scientific Advisory Committee

Appendix B – Roster of the CASAC Ozone Review Panel

Appendix C – Review Comments from Individual CASAC Ozone Review Panel Members

Appendix D – "Time-response Profiles: Implications for Injury, Repair, and Adaptation to Ozone" (Hopper *et al.*)

Appendix A – Roster of the Clean Air Scientific Advisory Committee

U.S. Environmental Protection Agency
Science Advisory Board (SAB) Staff Office
Clean Air Scientific Advisory Committee (CASAC)

CHAIR

Dr. Rogene Henderson, Scientist Emeritus, Lovelace Respiratory Research Institute, Albuquerque, NM

MEMBERS

Dr. Ellis Cowling, University Distinguished Professor-at-Large, North Carolina State University, Colleges of Natural Resources and Agriculture and Life Sciences, North Carolina State University, Raleigh, NC

Dr. James D. Crapo, Professor, Department of Medicine, National Jewish Medical and Research Center, Denver, CO

Dr. Frederick J. Miller, Consultant, Cary, NC

Mr. Richard L. Poirot, Environmental Analyst, Air Pollution Control Division, Department of Environmental Conservation, Vermont Agency of Natural Resources, Waterbury, VT

Dr. Frank Speizer, Edward Kass Professor of Medicine, Channing Laboratory, Harvard Medical School, Boston, MA

Dr. Barbara Zielinska, Research Professor, Division of Atmospheric Science, Desert Research Institute, Reno, NV

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Appendix B – Roster of the CASAC Ozone Review Panel

U.S. Environmental Protection Agency
Science Advisory Board (SAB) Staff Office
Clean Air Scientific Advisory Committee (CASAC)
CASAC Ozone Review Panel

CHAIR

Dr. Rogene Henderson*, Scientist Emeritus, Lovelace Respiratory Research Institute, Albuquerque, NM

MEMBERS

Dr. John Balmes, Professor, Department of Medicine, University of California San Francisco, University of California – San Francisco, San Francisco, California

Dr. Ellis Cowling*, University Distinguished Professor-at-Large, North Carolina State University, Colleges of Natural Resources and Agriculture and Life Sciences, North Carolina State University, Raleigh, NC

Dr. James D. Crapo*, Professor, Department of Medicine, National Jewish Medical and Research Center, Denver, CO

Dr. William (Jim) Gauderman, Associate Professor, Preventive Medicine, Medicine, University of Southern California, Los Angeles, CA

Dr. Henry Gong, Professor of Medicine and Preventive Medicine, Medicine and Preventive Medicine, Keck School of Medicine, University of Southern California, Downey, CA

Dr. Paul J. Hanson, Senior Research and Development Scientist, Environmental Sciences Division, Oak Ridge National Laboratory (ORNL), Oak Ridge, TN

Dr. Jack Harkema, Professor, Department of Pathobiology, College of Veterinary Medicine, Michigan State University, East Lansing, MI

Dr. Philip Hopke, Bayard D. Clarkson Distinguished Professor, Department of Chemical Engineering, Clarkson University, Potsdam, NY

Dr. Michael T. Kleinman, Professor, Department of Community & Environmental Medicine, University of California – Irvine, Irvine, CA

Dr. Allan Legge, President, Biosphere Solutions, Calgary, Alberta, Canada

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

Dr. Frederick J. Miller*, Consultant, Cary, NC

Dr. Maria Morandi, Assistant Professor of Environmental Science & Occupational Health, Department of Environmental Sciences, School of Public Health, University of Texas – Houston Health Science Center, Houston, TX

Dr. Charles Plopper, Professor, Department of Anatomy, Physiology and Cell Biology, School of Veterinary Medicine, University of California – Davis, Davis, California

Mr. Richard L. Poirot*, Environmental Analyst, Air Pollution Control Division, Department of Environmental Conservation, Vermont Agency of Natural Resources, Waterbury, VT

Dr. Armistead (Ted) Russell, Georgia Power Distinguished Professor of Environmental Engineering, Environmental Engineering Group, School of Civil and Environmental Engineering, Georgia Institute of Technology, Atlanta, GA

Dr. Elizabeth A. (Lianne) Sheppard, Research Associate Professor, Biostatistics and Environmental & Occupational Health Sciences, Public Health and Community Medicine, University of Washington, Seattle, WA

Dr. Frank Speizer*, Edward Kass Professor of Medicine, Channing Laboratory, Harvard Medical School, Boston, MA

Dr. James Ultman, Professor, Chemical Engineering, Bioengineering Program, Pennsylvania State University, University Park, PA

Dr. Sverre Vedal, Professor of Medicine, Department of Environmental and Occupational Health Sciences, School of Public Health and Community Medicine, University of Washington, Seattle, WA

Dr. James (Jim) Zidek, Professor, Statistics, Science, University of British Columbia, Vancouver, BC, Canada

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* Members of the statutory Clean Air Scientific Advisory Committee (CASAC) appointed by the EPA Administrator

Appendix C – Review Comments from Individual CASAC Ozone Review Panel Members

This appendix contains the preliminary and/or final written review comments of the individual members of the Clean Air Scientific Advisory Committee (CASAC) Ozone Review Panel who submitted such comments electronically. The comments are included here to provide both a full perspective and a range of individual views expressed by Panel members during the review process. These comments do not represent the views of the CASAC Ozone Review Panel, the CASAC, the EPA Science Advisory Board, or the EPA itself. The views of the CASAC Ozone Review Panel and the CASAC as a whole are contained in the text of the report to which this appendix is attached. Panelists providing review comments are listed on the next page, and their individual comments follow.

Dr. Ellis Cowling

Dr. Ellis Cowling
North Carolina State University
May 1, 2006

Review of the Integrated Synthesis Chapter (Chapter 8) in the Final (2006) Criteria Document for Ozone and Related Photochemical Oxidants

My major concern about the Integrative Synthesis Chapter (Chpater 8) for the Final Air Quality Criteria Document for Ozone and Related Photochemical Oxidants (EPA/600/R-05/004aF) is its exclusive focus on "Ozone Exposure and [Public] Health Effects." Integrative Synthesis is at least as much needed with regard to "Ozone Exposure and Public Welfare Effects" as it is on "Ozone Exposure and Public Health Effects."

All of us on CASAC understand that the exposures and adverse effects of criteria pollutants on public health have been the principal focus of EPA's traditional sense of the Agency's sense of responsibility to the people of the United States. But many of us also believe that the intent of the US Congress in passing the Clean Air Act Amendments of 1970 was to establish both:

- public-health based Primary Standards, and also
- public-welfare based Secondary Standards

for Criteria Pollutants as part and parcel of the National Ambient Air Quality Standards.

The language of the Clean Air Act is quite explicit with regard to both the public-health effects and public welfare effects of criteria pollutants – the Congress directed that the Administrator of EPA shall: 1) identify air pollutants that "in his judgment, may reasonably be anticipated to endanger public health and welfare," and 2) define National Ambient Air Quality Standards that are "requisite to protect the public welfare from any known or anticipated adverse effects associated with the presence of [the] pollutant in the ambient air."

The phrase "known or anticipated" provides both a significant degree of discretion, and a substantial responsibility for the Administrator to use prudent professional judgment in dealing with uncertainties and deficiencies in available scientific evidence regarding the exposure and effects of ozone and other photochemical oxidants on crops, forests, and natural ecosystems and their relationship to values held dear by the people of our country.

Thus, we hope that the Integrative Synthesis Chapters of all future Criteria Documents, (and Staff Papers based on these Criteria Documents), will include Integrative Synthesis Chapters that are indeed inclusive – chapters that describe the science that undergirds wise public policy decisions aimed at protecting both the public-health concerns and interests of our people -- as well as the public-welfare concerns and interests of our people.

Dr. William (Jim) Gauderman

Chapter 8, Integrative Synthesis
Jim Gauderman
5/12/05

Throughout the document, the term 'inconclusive' is used to denote non-significant. A large, well-conducted study that finds no significant association should not be characterized as inconclusive. Smaller studies that do not find a significant association should also be characterized as such, perhaps with a caveat about low power.

Consistent units (ppm or ppb) should be used throughout

8-9, line 13: replace 'an optimal' with 'the'

8-12, line -9: eliminate 'sham' and remove parentheses from 'clean air'. Two lines down, replace 'versus more closely mimicking' with 'rather than'

8-14: The last sentence that carries over onto 8-15 does not make sense.

8-15: I found the paragraph beginning with 'New uptake…' unsatisfying in that it did not provide a clear summary of the directions of differences. For example, rather than saying there were gender differences, the paragraph should indicate whether effects were higher for males or females. This would not take much space and would improve the value of this summary paragraph.

8-29, Table 8-1: 'Interindividual variability' is not a susceptibility factor. Eliminate 'being recognized'.

8-33, line 13: Why focus only on studies from U.S. and Canada? Despite this caveat, the document goes on to reference studies from Europe, for example on 8-38 and 8-58.

8-40, line -4: define 'per standardized O_3 increment'

8-41, line -10: replace 'quantitative results' with 'quantitatively equivalent results'

8-43, line -5: 'analyses' should be 'analysis'

8-44, line 5: This sentence seems like a copout. If this is the case, how can we move forward to consider a revised standard? If the difficulty of finding a threshold below 0.08 is what is meant, this should be stated more explicitly

8-47, line -9: replace 'pulmonary function' with 'response'

8-50, line 7: replace ‘cross-section’ with ‘longitudinal’. In the last paragraph, caveats should be included to point out the high exposure levels to which the monkeys were exposed and the limited relevance of these levels to current ambient O_3 levels.
8-53, lines 6, 7: replace ‘fine’ with ‘ultrafine’

8-54, line -3: replace ‘of’ with ‘to’

8-60, line 11: replace ‘smaller increases’ with ‘growth deficits’.

8-61, line 9: replace ‘diminished’ with ‘smaller’ here and 13 lines below.

8-79, line 10: insert ‘exposure to current ambient levels of’ between ‘long-term’ and ‘O_3’

Dr. Henry Gong

COMMENTS ON CHAPTER 8 (INTEGRATIVE SYNTHESIS)
Draft AQCD, February 2006.
Henry Gong, Jr., M.D., 4/30/06 (revised 5/1/06)

I have reviewed the revised chapter 8. I also concur with the comments by several CASAC colleagues (Drs. Vedal, Zidek, and Lippmann).

The Staff has generally produced an improved chapter (integration) with sharper focus and exposition on key issues such as those posed by the review in December 2005. The "integration" will always remain a challenging task but I am comfortable with the current version, in particular, in the area of the clinical studies.

Specific Comments:

1. I am pleased that Dr. Adams' recently published study was reviewed accordingly since we lack many clinical studies using such low ozone exposure concentrations. The inclusion of Fig 8-1B is an excellent example of the pitfalls of relying on group means and the concept of adjusting for filtered-air responses ("ozone-induced"). The total number of subjects in Adams' studies remains much smaller than in McDonnell's study. I wonder if one can calculate post hoc the expected real effect size versus the probability of finding a statistically significant effect for Dr. Adams' studies with ozone levels at 0.04 and 0.06 ppm, given the small number of subjects and inherent variability of FEV1 responses. This calculation might provide some measure of confidence about a "true negative."
2. Page 8-50/1st para: "There are no data available from controlled human chamber studies that evaluated chronic exposure regimens." This sentence is unnecessary and should probably be deleted. The statement is misleading since its interpretation relies on your perspective. One reaction is that it is obviously impractical and unethical to study subjects inside an environmental chamber for 5 or 10 years! Some investigators have reported intrasubject reproducibilty of ozone responsiveness over months (McDonnell and Bedi, I believe) but not over years. However, aging is an unavoidable factor since people apparently develop less ozone responsiveness with aging.

Dr. Rogene Henderson

Comments on Chapter 8
Rogene Henderson

My major comment is on the content of the chapter. If it is too late to consider my suggested changes, I would hope they might be taken into account for subsequent integrative chapters in CDs.

I think the purpose of this integrative chapter is to facilitate the development of the Staff Paper. The main concerns are whether ozone causes specific health effects and, if so, AT WHAT LEVEL OF EXPOSURE. Based on these findings, the Staff Paper will attempt to discern whether the current regulatory levels for ozone need to be altered.

I found Chapter 8 placed much emphasis on what health effects are induced, but did not focus enough on the level of exposure required to induce the effects. For example, the first 27 pages of the chapter are a summary (repeat) of what was said in earlier chapters. I did not think it needed, or at least not in such a lengthy form. There is a shortened version of this summary starting on page 8-73 (sort of a summary of a summary) and it might serve as a better starting point than the detailed repeated report in the initial part of the chapter. Another approach might be to develop a summary table with references to the place in earlier chapters where the study is described in detail.

The lack of focus on the level causing the effects can be seen in the tables. In Table 8-1, 8-2, and 8-3, we need a column(s) indicating the level of ozone exposure associated with the effects. The exposure level is key to setting the regulations.

Dr. Michael Kleinman

Dr. Michael Kleinman
Chapter 8 Comments

General Comments

This chapter is very comprehensive but loses focus. It could be significantly shortened. It might be useful to focus on the integrated findings that directly support the recommendations for revisions to the NAAQS that are presented in the Staff Paper. It is important to clearly establish that the data used to support the recommendations are coherent, consistent and rational.

Specific Comments

Pg 8-31 L9-11 The Hatch findings need to be placed in context with the dosimetry information, i.e. after adjustment for ventilation differences between exercising humans and resting rats and body mass differences, the relationships between inhaled dose (µg/kg bw) and biological response for humans and rats are in agreement. The way this is presented suggests that the rat is 5 times less sensitive than the humans, which is not true!

Pg 8-32 L 8-10 I assume that this information relates to ambient as opposed to laboratory exposures. If so one needs to acknowledge that there might be some efforts to self-medicate before seeing a physician. In addition, this discussion needs to be integrated with observations of duration of O3 episodes. O3 episodes are rarely a 1 day event. The controlled study data clearly show that effects of O3 are worse on the second day of an intermittent exposure. By the third day there may be some attenuation of responses. To further complicate things, there may be cumulative effects as well as progressive effects that relate to lags. The paragraph should be expanded to take these factors into account.

Pg 8-36 L5 It should be noted that observation of attenuation of O3-induced inflammatory response (Kopp et al. 1999) was consistent with earlier pulmonary function studies (Linn et al. 1988) which showed that individuals in Los Angeles were responsive to controlled O3 exposure in the spring but that the response was attenuated when measured in the fall after a summer of relatively high ambient O3 exposures. Sensitivity to O3 was recovered by the following spring indicating that response attenuation is transient.

Pg 8-36 L11 The basis for stating why "these findings must … be considered inconclusive" should be presented. For example, … due to possible confounding by PM2.5, elemental carbon and NO2 (Chan et al. 2005; Holguin et al. 2003; Liao et al. 2004; Park et al. 2005).

Pg 8-37 L5-6 Several studies showed an association between ambient ozone exposures and emergency room visits for respiratory disease (Bates et al. 1990; Castellsague et al. 1995; Cody et al. 1992; Ponce de Leon et al. 1996; Stieb et al. 1996). The statement could lead one to presume that the association is due to lack of control for confounding by

temperature. There should some more detailed explanation or interpretation offered. For example, could it be noted that reasons for finding relationships with warm weather ozone exposure but not for year-round exposure might be that during winter there is less photochemical production of O3 and that the O3 effects might be masked by other pollutants whereas this is less of a problem during the high O3 season?

Pg 8-38 L28-30 Should some statement be made that given the significant associations between mortality and exposures at or below 98th percentile 8-h max O3 levels of 80-85 ppb there is little or no margin of safety offered by the current NAAQS?

Pg 8-42 L 20-21 In terms of public health it is important to note that the percent of individuals showing decreased pulmonary function showed a dose-related response with respect to O3 at levels of 0.06 ppm. The group mean differences rely on only part of the entire data set. It might be more useful in the establishment of health protective standards to use all the data in a regression format to better estimate the region for which significant numbers of individuals might experience adverse effects.

Pg 8-43 L 9-10 Again, relating to margin of safety, these findings suggest that the current standard is less protective than it should be. Shouldn't this be one of the conclusions in the Staff Paper??

Pg 8-43 L 27 Change to "A more formal threshold analysis…"

Pg 8-44 L 5 Perhaps it would be more accurate to state that there is insufficient evidence to support a threshold for adverse effects of O3. Furthermore, if there is a threshold, the data seem to indicate that it would be lower than the current 8-h standard of 80 ppb.

Bates DV, Baker-Anderson M, Sizto R. 1990. Asthma attack periodicity: a study of hospital emergency visits in Vancouver. Environ Res 51(1):51-70.

Castellsague J, Sunyer J, Saez M, Anto JM. 1995. Short-term association between air pollution and emergency room visits for asthma in Barcelona. Thorax 50(10):1051-1056.

Chan CC, Chuang KJ, Su TC, Lin LY. 2005. Association between nitrogen dioxide and heart rate variability in a susceptible population. Eur J Cardiovasc Prev Rehabil 12(6):580-586.

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Dr. Morton Lippmann

Comments of Dr. Morton Lippmann
NYU School of Medicine
April 17, 2006

Chapter 8 (Integrative Synthesis) of Final Ozone AQCD

I've read through Chapter 8 of the Feb. 2006 draft of the Ozone CD, and find it to be generally satisfactory. It could be condensed somewhat if time and resources permitted tighter editing. Also, it should be more consistent in its use of ozone concentrations. There are many places where they are in ppm, others where they are in ppb, and still others where they are in ppm, with ppb in parentheses. Also, "in vivo" and "in vitro" should be italicized.

My major criticism is that there is not nearly enough emphasis in the discussion of the epidemiological studies of the fact that O3 needs to be considered as a surrogate index for the photochemical mixture containing O3. I point this out first in my note for page 8-2 below. There needs to be a new introduction to the discussion of the epidemiology that explains why this distinction is needed in the integrative discussion of the laboratory-based studies and the field and larger population epidemiology. This was an issue discussed by the CASAC ozone Panel at our last meeting, and I sensed that we felt it was important for NCEA to implement it when revising Chapter 8.

The following are some specific corrections and suggested edits:

p. 8-1, para. 2, l. 3: change "nitrogen oxides (NOx)" to "nitrogen dioxide (NO2)."

p. 8-2, para. 1, l. 5-7: change "whereas less attention is accorded to the distinctly much more limited available information on other photochemical oxidants, e.g., PAN or H2O2." to "and on O3 as an index of the mixture of photochemical oxidants, including PAN, H2O2, and oxygen containing radicals, for which much more limited information is available."

p. 8-3, para. 2, l. 5: change "clean" to "cleaner."

p. 8-3, para. 3, l. 2: insert "finer scale" before "spatial."

p. 8-4, para. 2, l. 8: insert "due to springtime intrusions of stratospheric O3" after "Hemisphere."

p. 8-8, para. 2, l. 14: change "O3" to "photochemical oxidant."

p. 8-8, para. 3, l. 4: delete "somewhat."

p. 8-15, para. 2, l. 4: insert "generally" before "having."

p. 8-25, para. 2, l. 7-12: A reference should be provided to support this statement.

p. 8-63, para. 1, l. 8, 10, and 14: insert “onset” before “risk.”

p. 8-69, para. 2, l. 12: insert “Thurston et al. (1997) showed that asthmatic children did receive a physician-ordered increase in medication in proportion to the ambient O3 concentration.” before “Such.”

p. 8-74, para. 2, l. 12: add “below 0.08ppm, and even below 0.06ppm” after “levels” (Spektor et al. 1988).

p. 8-75, para. 2, l. 2: change “0.08” to “0.06” (based on Adams 2006)

p. 8-75, para. 2, l. 12: delete “likely.”

p. 8-75, para. 2, l. 13: insert (Thurston et al. 1997)” after “children.”

p. 8-80, para. 1, l. 3: change “increased risk of mortality” to “reduced longevity.” (This is to distinguish between the evidence from the time-series studies of daily mortality, and the lack of evidence for increased annual mortality.)

p. 8-80, para. 2, l. 8: insert “short-term” before “responsiveness.”

Dr. Frederick J. Miller

Dr. Fred J. Miller
May 18, 2005

Integrative Synthesis: Ozone Exposure and Health Effects
Chapter 8

General Comments

This second version of the integrative synthesis chapter is greatly improved over the first. The collective evidence for ozone health effects based upon dosimetry, animal toxicological, human clinical, and epidemiological data is well presented and laid out in a logical manner. The sections of the chapter are inconsistent in their use of references, a situation that a final edit could correct. Despite the improvements, there are a number of points made in the chapter that are either incorrect or that would benefit from expansion or rewording if it were not for the fact that the Ozone Criteria Document has already been finalized. Nonetheless, the following comments are offered so that EPA staff charged with development of the Ozone Staff Paper can benefit from them.

- The discussion of Policy Relevant Backgrounds does not bring out that these values are dependent on the time of the year. In addition, I would echo the comments of Dr. Zidek concerning the influence of measurement error on PRB values and their usefulness in assessing risk.
- The section on dosimetry still does not discuss one of the most important findings since the last CD, namely that anatomical dead space is a major driver of the delivered dose of ozone and probably accounts for a major part of the heterogeneity seen in responses in human clinical studies. I noted this in my comments on the first draft of this chapter.
- The statement is made on page 8-8 that ambient and personal exposures are well correlated. As Dr. Zidek noted in his comments, the available studies do not support a strong conclusion on this point.
- At the start of Section 8.3.1, the statement is made that "Children tend to be more active outside and, therefore, often manifest a higher breathing rate than most adults". The fact is that children have a higher basal rate period. So the sentence is somewhat misleading.
- On page 8-12, the statement is made that "Earlier animal toxicology studies were carried out using relatively high O_3 exposure concentrations/doses that do not reflect "real world" exposure scenarios". This was in reference to studies available for the 1996 AQCD. This statement is incorrect. The EPA chronic O3 study conducted in the 1980s mimicked real world patterns and started with a background exposure of only 0.06 ppm.
- There are discrepancies on pages 8-13 and 8-14 concerning animal to human extrapolations. First it is contended that molecular differences between animals and humans lead to large uncertainties in animal to human extrapolations. Yet on the next page, there is discussion purporting a common mode of action for O3 between animals and humans. In the opinion of this reviewer, extrapolation for various endpoints is quite possible, has been done successfully in the past, and is done a disservice by the statements of the author(s) of this section. Some of the examples and discussion in Chapter 4 support the practicality of animal to human extrapolation for ozone effects.

- In the last paragraph on page 8-14, the statement is made that newer studies show that uptake decreases as airflow rate increases. This observation has been known since the 1970s based upon the work of Aharonson and also by Frank and colleagues.
- On page 8-16, the statement is made that some subjects are reproducible over time in their response to ozone. I would submit that the work of McDonnell and colleagues shows that the vast majority of subjects are reproducible over time in their response to ozone exposures. Thus, the use of "some subjects" is misleading.
- Triangle exposures (p. 8-19) are said to reflect ambient patterns better than square wave exposures, which is correct. However, has the length of time to the peak of the triangle in the exposure studies been truly reflective of "real world" patterns? The reasonableness of triangle versus square wave exposure scenarios most likely varies depending upon geographic location, particularly across the United States.
- In Figure 8-3, the authors should have made clear in the legend that these resolution times relate to brief exposures to ozone.
- On page 8-31, some aspects of animal to human extrapolation are discussed. Here would have been a good place to make reference to studies on protein in lavage fluid and how dosimetry models have been used to integrate the experimental findings across species. This presumes that this material was reworded in Chapter 4 in response to my comments on the August 2005 version of Chapter 4.
- "Tolerance" is used incorrectly in multiple places in this integrative synthesis chapter. Tolerance has a very specific definition arising from animal toxicological studies wherein exposure to a lower level of a chemical imparted protection from effects when animals were subsequently exposed to higher concentrations of the chemical. The authors should have stuck with "attenuation" in describing the diminishing or lack of occurrence of changes with repeated ozone exposures.

Dr. Maria Morandi

Comments on Chapter 8 – Maria T. Morandi

Chapter 8 appears to give more weight to the cardiovascular and mortality effects (Sections 8-3 on page 8-27 to 8-32; pages 8-36 to 8-39 and section on cardiovascular effects, and section 8.6.3) studies than the Panel considered scientifically appropriate given the available evidence and uncertainties, the latter being especially important with regards to exposure estimate error. The other consideration, as discussed by the Panel, is the discrepancy between the levels of ozone at which exposure-effects are observed in chamber studies of acute lung function, and the significantly lower measurements (compared to the chamber exposures and outdoor concentrations) reported by studies that have conducted personal exposure measurements of ozone, and the results of epidemiology studies of acute effects that use the ambient measurements as the surrogate for exposures. These differences suggest that ozone may be acting at least in part as a surrogate for other oxidants that are formed via chemical reactions leading to ozone formation and accumulation.

Page 8-3

Quote: "Median values of daily 1-h max O_3 were typically much higher in large urban areas or in areas downwind of them. For example, in Houston, TX they approached 0.20 ppm during the same 2000-2004 period."

The text appears to imply that the median values of daily-1-h max of ozone for Houston in the 2000-2004 period approached 0.20 ppm, which cannot not be correct. 0.20 ppm is reasonable as the maximum 1-hr concentration over the period, not the median of the 1-hour max. On pages 8-4 and 8-5 the text says that 1-hour maximum values approach 0.20 ppm in the Eastern US and California, the latter been similar to maxima in Houston.

Page 8-8

Quote: "Thus, activity level is an important consideration in determining potential O_3 ~~exposure and~~ dose received"

Exposure is concentration X time only. Potential dose is concentration X time X inhalation rate (such as minute volume); inhalation rate varies with activity level.

Section 8.3

1st two paragraphs: This section needs to be tempered regarding the assumption that ambient measurements are a good estimate of personal exposures in a population. This is a reasonable assumption in many, but not all, cases. Thus, there could be significant exposure estimate errors when comparing exposure-response across different subgroups in a population, or across different populations, because correlations between outdoor and indoor concentrations may not be necessarily high everywhere. For example, in Houston, which has a very high utilization of

conventional air conditioning (and, consequently, very low indoor ozone concentrations in a large fraction of homes during the ozone season), the ambient concentrations may not be good indicators of personal exposures for a large proportion of the population because the indoor residential concentrations remain essentially unchanged - frequently at or below the detection limit of the ozone monitor- while the outdoor concentration varies significantly increasing, peaking, and declining during the day (see prior versions of the AQD for citations to the 1980 Houston Asthma Study). In other cities where natural ventilation or evaporative AC predominates, outdoor concentrations are indeed a better surrogate of personal exposures because they correlate with the indoor concentrations. Perhaps the text should be modified to indicate that the outdoor concentrations are the only available index (rather than "most useful") of exposure distributions at this time.

Section 8.3.2:

This section does not mention at all the impact of HVAC systems on indoor ozone concentrations, which is more than just due to low AER. In residences or commercial buildings with HVAC systems, a large fraction of the indoor air re-circulates in the ductwork which provides additional surfaces for ozone decay and reactions with materials deposited in the filter.

Some additional editorial suggestions:

Page 8-12:

"...to help identify potential mechanisms~~(s)~~ of action..."

"Since then ~~a few newer~~, more recent human clinical and... air pollutant mixtures~~; and~~ . ~~t~~The results..."

Page 8-21

Quote: "..most important biological markers of O_3-induced injury response ~~mechanisms~~ in both humans..."

Dr. Charles Plopper

CASAC-Chapter 8
Integrative Synthesis: Ozone Exposure and Health Effects
Comments by C.G. Plopper

One of the fundamental issues missing in the overview of the section (8.4.1) dealing with Integration of Experimental and Epidemiologic Evidence is a discussion of the patterns of biologically relevant exposure conditions. The issues which are involved include establishing the biological impact when:

1) The peak exposure concentration exceeds the threshold necessary to produce a response an acute biological response;
2) the duration of the exposure period where the peak exceeds the threshold for acute biological response;
3) The number peak days that reach biologically relevant concentrations with less than 24 hour intervals of non-biologically responsive concentrations;
4) The extent of this interpeak interval.

When peaks are separated by 24 hours or less (usually approximately 18 hours) the biological response is less as exposure progresses than if the interexposure interval extends beyond seven days. Short interexposure periods (less than 24 hours) during multiple repeated exposure results in the production of a phenomenon called tolerance. In other words, a repeated history of exposures above the threshold on successive days results in a depression of the acute response and decreased sensitivity. An additional aspect of this response is that once a series of these exposure regimens have occurred in which repeated peak days last over a significant period of time, generally 4-7 days, the biological response will be altered when additional exposures occur in the future.

It is difficult to address the cross cutting issues relevant to assessment/interpret of ozone health effects without including the relationship between exposure scenarios and the biological response. The chapter as written does not clearly separate acute responses, versus chronic responses, versus the development of tolerance and how exposure history influences both acute and chronic responses. While this section summarizes earlier animal studies, it does not really address the exposure/dosimetry issue in terms of the pattern of biological response.

There are discussions throughout section 8.4.1 and .2 which refer to doses and assessments, but do not clearly differentiate how the pattern of exposure can influence the measurements. This is especially critical for the section on lung inflammation. The paragraph ending at the top of page 8-36 is a good example of how the exposure scenario impacts the biological response and how this alters the endpoints that are measured physiologically.

It would be helpful for the discussion to break out the differences between long term exposure and chronic effects, because the effects depend on the population exposed, the history, and the pattern of exposure during the acute phases of response. In section 8.6.2 no mention is made of the fact that exposure history for subjects in the human studies were not addressed. The same situation was true when the bottom of page 8-50 which discusses long term infant studies, but

does not include the studies of young adult rhesus monkeys which found essentially the same time of response.

In the beginning of section 8.7 there is a discussion of the susceptible and vulnerable populations and issues which may alter susceptibility. The issue of exposure history is ignored in this section. Some discussion somewhere needs to be included, because this is a critical factor in judging the level of sensitivity of populations and dictates whether individuals will appear more or less susceptible to chronic injury.

The same is true for the discussion on page 8-58 and on pages 8-60 and 8-61, especially the last paragraph in section 8.7.2.

Dr. Frank Speizer

Comments on Chapter 8, Feb. 2006 Final Ozone AQCD

Submitted by Frank E. Speizer, MD

General Comment:

The organization of the chapter works well. I particularly like the way the added new data are presented as an extension of the 1996 document. Notably, no negative or inconsistent findings are mentioned until the epidemiology section. Does this mean that there are no tox or human exposure studies that are null, or is the publication bias stronger than in the epi field? Some discussion of this is warranted.

The integrated discussion of the possible mechanisms from tox and human studies as related to the epidemiological finding is a useful addition in pulling the data together. The summary of the finding is complete. What are missing are staff recommendations for a standard. I would have thought that the concluding section of this chapter should contain this discussion. Is it still to come? When will we have a chance to see it?

Specific Comments:

Page 8.2, first full para, line 8: Take out word "various"

Page 8.2, last paragraph. Whole paragraph is totally redundant with last sentence of previous paragraph and can be left out.

Page 8.3, section 8.2.1, lines 8-9. I think this should be qualified with something like "except for Los Angeles and Houston as well as other sites in California".

Page 8.12, first full paragraph. It doesn't make sense to leave out Chapter 7 in this intro paragraph, particularly since the title of the section includes Epidemiology and 2 paragraphs later on page 8.13, the Epidemiology studies are introduced.

Page 8.17,text lines 5-6: suggest take out "and seem physiologically insignificant". This is simply catering to the lack of understanding of group mean differences and the rest of the sentence adequately addresses the issue.

Page 8.18, last para, line 1: "triangular exposure profile" is jargon. Needs to be defined up front rather than at end of paragraph on page 8.19.

Page 8.20, last para, line 8: Change "common" to "Spirometric"

Page 8.21, last para, line 1: Take out word "most"

Page 8.34, second full para, lines 8-9: Take out sentence, already said above.

Page 8.34, last para, line 2: Change 40.3ppb (SD 15.2) to .04ppm (SD .015)

Page 8.38, para 1, line 6: This is a bit of overstatement. Most of the studies presented were not really "designed specifically to examine the effects of O3"… I think the word "specifically" might be removed without changing the meaning of the sentence and would be more accurate.

Page 8.39, para 1, lines 14-18: These two sentences may lead to confusion. I think I know what the author is trying to say, but there is a whole science about omission and commission in using underlying and contributory cause of death. None of it has to do with causality as expressed here. The fact that a contributory cause of death may be the underlying cause and is misclassified has little to due with causality as related to air pollution. (It is for this reason that many authors use cardiopulmonary when doing analysis of air pollution health effects, and can use cardiovascular since it represents more than 60% of the total.) The last sentence presumes the coding rules are being ignored. Suggest simply leave off the last two sentences.
Page 8.55, second full para, last line: Agree with statement but I did not see many O3 epi studies quoting exposures below .08ppm.

Page 8.67, 8.68, Tables 8.2 and 8.3: Not clear that the definitions of small, moderate and large are correct for change in bronchoresponsiveness. Footnote says a 100% change equivalent to a 50% decrease in PD20. (I recognize that this table is reproduced from 1996, but that doesn't mean it should be accepted without comment). I would have thought a 20% decrease in PD20 was significant, and adjusting up from there would change cut off points. Similarly for changes with airways resistance, the cuts offs are too high.

Dr. James Ultman

Comments on Revised Chapter 8
James Ultman
May 20, 2006

It is apparent that considerable effort has gone into the development and refinement of this chapter, and it does provide a useful (but unnecessarily lengthy) summary of the previous chapters and their annexes.

The authors of the chapter successfully demonstrate that there is a strong homology of ozone-induced responses between animals and people, implying that the underlying biological mechanisms are similar among the different species. On the other hand, the authors point out that there are differences in gene transcription between animals and man, implying that ozone-induced responses may not occur by the same mechanisms. In addition, the chapter says very little concerning the application of dosimetry to bridge the gap between exposure, dose and response. Overall, this chapter should have sent a much clearer message that we have the tools to perform quantitative interspecies or intraspecies extrapolations using quantitative dosimetric analyses.

I would hope that the staff document would, in fact, not hesitate to use such analyses, where appropriate. A particular situation that comes to mind is the extrapolation of health effects observed in adults to the comparable effects in children by taking into account differences in lung sizes and ventilation rates.

Also, I strongly agree with Rogene Henderson's comment that there are no definitive statements in the chapter regarding specific exposure levels at which ozone-induced health effects of various types are likely occur. Thus, very little explicit guidance is provided to those developing the Staff Document.

Dr. Sverre Vedal

Comments on Feb 2006 draft Ozone Criteria Document, chapter 8 (Integrative Synthesis)

This version of chapter 8 has improved its focus on observational study effects at or below the current NAAQS, and it continues to do a good job in integrating findings from different disciplines. But, in my opinion, some major issues that would seem to be critical for moving ahead with the Staff Paper are not handled well.

1. The issue of exposure (or the lack of it) in the new mortality time series studies, studies that will likely play a central role in discussions on revising the standard, is not really touched on, as it was to some extent in Ch.7. I previously made extensive comments in this regard on Ch.7 and Ch.8 of the last draft, and will not repeat them now. The points remain relevant. I agree with Jim Zidek's points on measurement error as well, and refer you to his comments. I would not relish the prospect of a risk analysis carried out by OAQPS on the basis of the time series mortality studies until the issue of exposure has been thoroughly aired.

2. Exposure measurement error in the case of ozone will have a much more substantial effect on obscuring a concentration-response threshold than in the case of PM. This would seem to be an important issue when planning an ozone risk analysis, but is not mentioned.

3. If we think, on the other hand, that ambient ozone concentration in observational studies is important more as a measure of photochemical pollutants in general, rather than as a measure of ozone exposure specifically, then this should be stated. Then an issue will become one of evaluating what evidence we have for exposure to, and effects of, these pollutants, about which I suspect we know relatively little.

4. The bottom line on chronic effects puts more emphasis on the studies of seasonal lung function effects in children than those of longer-term effects - I think this is a misplaced emphasis.

5. There are also some factual errors (e.g., the Gong study did in fact show increased heart rate due to ozone).

Dr. James (Jim) Zidek

COMMENTS ON CHAPTER 8 OF THE AQCD FOR OZONE
Prepared by Jim Zidek, April 17, 2006

The synthesis chapter seems quite well written. I have just a few comments limited to topics connected with comments I submitted during the Draft AQCD reviews.

Page 8-7: In the revised AQCD, I was pleased to see some discussion of CTM estimation errors on page 2-21 and 2-22 and the need to evaluate them "by comparison with field data". Moreover, interesting discussion of such errors for GEOS-CHEM has been included in Chapter 3 (eg page 3.52) and even in the Executive Summary. Yet Chap 8 ignores them. This omission highlights the need to address them in the Staff paper and how they are to be accommodated in calculating the ozone standard. In particular, should the standard be raised, lowered of left unadjusted in view of that error in estimating the PRB? Would a big error lead to the adoption of a different PRB level than a small one?

Page 8-8: Here we find the following statement: "Nevertheless, although substantial variability may exist among personal measurements, human exposure studies have observed that daily average personal O_3 exposures for the general population tend to be reasonably well correlated with monitored ambient O_3 concentrations." This seems to be an example of the ecologic effect, making its relevance for the Staff paper doubtful. Moreover, it seems at odds with the preceding, "However" sentence. Finally, I would note that pages 3-72 & 3-73 give a mixed picture of this association. One study produced an insignificant or barely significant association, the other a significant association. Moreover the second found that "ambient O_3 levels overestimated personal exposures 3- to 4-fold in the summer and 25-fold in the winter" hardly giving one confidence that the population average exposure is reasonably "well correlated" with ambient levels.

Page 8-8: The next sentence to that above concludes: "Therefore, ambient O_3 monitoring data appear to provide the most useful index of human O_3 exposure currently available to help characterize health outcomes associated with O_3 exposures of large population groups." This sentence suggests indices other than ambient levels were considered and rejected but I cannot find such alternatives in the AQCD. Instead many indices (i.e., "metrics") based on ambient monitoring measurements are discussed.

The real aim of these two sentences seems to be support for ambient monitoring based criteria. Even more support appears in the "Thus" sentence in the middle of **Page 8-10.** However, based on the evidence offered in the AQCD, that support seems more tenuous than Chap 8 lets on. If additional evidence can be found, the Staff paper should cite it, as this is a contentious issue. It is one reason why APEX and other such methods have to be used in contexts like this to try to forecast the actual effect a change in the AQS might have on human exposure.

Dr. Barbara Zielinska

Comments on Chapter 8 (Integrative Synthesis) of the Ozone AQCD

By Barbara Zielinska, April 30, 2006

In general, I found Chapter 8 well written and informative. However, there are still some issues that are not represented adequately in this integrative synthesis. I agree with Jim Zidek that the uncertainties of the GEOS-CHEM global model estimates of Policy Relevant Background (PRB) should be mentioned in the integrative synthesis – this is important for the future ozone standard determination. I also think that the Section 8.3 on human exposures to ambient ozone has some problems. Although the Section mentions briefly the problems with estimating human exposure on the basis of central monitoring data, it still maintains that the ambient O_3 concentrations measured outdoors at community monitoring sites provide the most useful index of human O_3 exposure (page 8-8 and 8-10). I don't think that the AQCD provides strong evidences for such a statement. I'm also not sure if ambient O3 concentrations and/or (?) personal O_3 exposure monitor measurements may serve as "surrogate indices of exposures to broader O_3 –containing ambient mixtures of photochemical oxidants and/or other pollutants" (page 8-10). Which "other pollutants"? I don't think that there are sufficient evidences provided in the Ozone AQCD supporting such a statement.

Appendix D – "Time-response Profiles: Implications for Injury, Repair, and Adaptation to Ozone" (Hopper *et al.*)

Time-response Profiles: Implications for Injury, Repair, and Adaptation to Ozone

C. PLOPPER, R. PAIGE, E. SCHELEGLE, A. BUCK-PITT, V WONG, B. TARKINGTON, L. PUTNEY, AND D. HYDE
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Introduction

The biological response of the respiratory system to exposure to oxidant air pollutants such as ozone follows a well-characterized pattern of cellular injury, inflammatory and repair events which is highly dependent upon the inhaled concentration and the length of the exposure. There is clear dose-response curve of acute injury for the initial exposure of naive animals and humans under experimental conditions. The initial cellular injury sets in motion a series of inflammatory and repair processes which follow a relatively uniform time course regardless of the extent of the acute injury, unless it is so massive as to be fatal. Under experimental conditions, these repair processes lead to the reestablishment of the pre-exposure steady-state within a finite period of time. Imposition of additional periods of exposure to injurious concentrations during the repair process alters the cellular events and leads to the establishment of a new steady-state where inflammation is markedly reduced and the cells which repopulate the injury site are resistant to further acute injury by oxidant gases. This is true regardless of how long the exposures are continued. Despite the very large number of long-term exposure studies, the utility of experimental animal studies for estimating the long-term risk to human populations of ambient exposure conditions appears limited. One of the limitations is that concentration multiplied by time does not equal effect (Gelzleichter et al., 1992). Depending on the measures used to assess effects, the response may actually appear to diminish over time. A second limitation is that ambient conditions are such that the periods when oxidant gas concentrations are elevated to levels which can produce injury are highly variable. The period below threshold concentrations can vary from as little as 18 hours to as long as many months.

Additionally, these periods generally cycle annually. The intent of this review *is* to examine the issue of time in terms of the temporal characteristics of exposure conditions and the pattern of biological responses on which exposures are imposed.

Exposure Pattern

For the purposes of this discussion, exposure patterns will be characterized by three key parameters: *concentration, duration* of exposure (or exposure period), and the length of time between exposures when the concentration is below the biological response threshold (the *interexposure interval* (Figure 1 a). Ambient exposures are variable in nature, with daily and seasonal variations in concentration (Figure 1 b-d) (USEPA, 1996). As the examples in Figure 1 illustrate, under ambient conditions the duration of exposure to elevated ozone concentrations on a daily basis is approximately 6 hours. The peak concentrations during this 6-hour period are highly variable by season. And there are many days, even during seasons associated with high average ambient levels, when the ambient concentration is very low or near background.

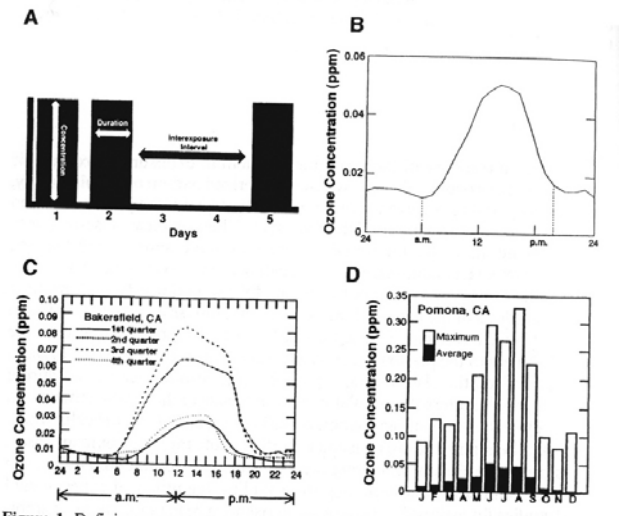


Figure 1. Defining ozone exposure parameters. a) Illustrates the parameters characterizing an exposure; peak concentration, duration and length of time between exposures (interexposure interval). b) Is a graphic representation of daily variation in ambient ozone concentration (USEPA, 1996). c) Shows the daily variation of ozone concentration during the four quarters (or seasons) of the year as measured in Bakersfield, CA (USEPA, 1996). d) Emphasizes the extremes in peak ozone concentration experienced by month. This bar plot shows minimum and maximum concentrations measured at one California monitoring station over the course of 12 months (January (J) through December (D)) (USEPA, 1996).

Biologic Response

The response of the respiratory system to ozone exposure can be characterized in terms of the initial injury and inflammatory responses, followed by proliferation and repair of the epithelium at the site of injury. While there are a variety of biologic responses following ozone exposure, for the sake of comparison we will consider only the epithelial and inflammatory responses summarized in Figure 2.

Initial responses include injury and death of ciliated cells in conducting airways and squamous epithelial cells in the centriacinar region of the parenchyma. This phase, which appears to occur within the first 8-12 hours of exposure, is associated with marked increases in intraluminal exudate that initially contains primarily epithelial cells and serum proteins, with minimal or no changes in the interstitium. This phase also includes degranulation of secretory cells. Subsequently, injured epithelium exfoliates and there is an increase in exudate containing inflammatory cells, primarily neutrophils and eosinophils. (See Paige and Plopper, 1999, for detailed review.)

Proliferation of the epithelium, concurrent with downregulation of intraluminal exudates, marks the next stage of response. Significant numbers of inflammatory cells may still be found migrating through the epithelium at this stage, but within 7 days the acute inflammatory response is almost completely resolved. At this time, epithelial proliferation has greatly diminished, the epithelium is often hyperplastic, and proliferation of matrix components is in progress. After completion of this series of events, subsequent responses are dependent upon whether or not exposure to injurious concentrations

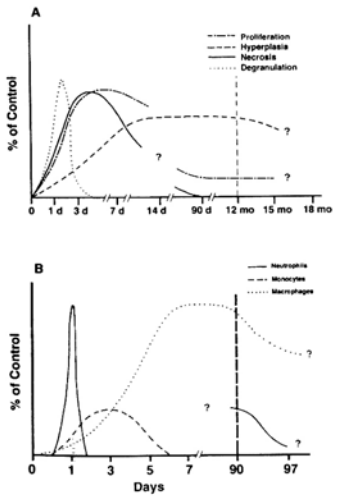


Figure 2. Graphic representation of the biologic response to oxidant gas (ozone) exposure. a) epithelial response b) response of inflammatory components.

continues. If exposure ceases, the affected compartments will revert to pre-exposure steady-state within 7-10 days.

Effects of continued long-term exposure include persistent hyperplasia, low-grade chronic inflammation with few exudative cells (primarily macrophages), and increased synthesis of collagen.

Short-term Exposures

Very short exposures (as little as 2 hours) initiate the acute response to ozone (Figure 3) (Plopper et al., 1998). After 2 hours exposure to 1 ppm ozone there was a significant increase in abundance of necrotic cells corresponding with a significant decrease in abundance of intact epithelial cells. While polymorphonuclear leukocytes and eosinophils were significantly increased in number following a 2 hour exposure to 1 ppm ozone, macrophages exhibited a significant decrease.

When the exposure duration is increased (50-hour exposure of Rhesus monkeys to 0.8 ppm ozone) necrosis occurs immediately after the onset of exposure, peaks after about 12 hours of exposure and is completely resolved by 24 hours (Figure 4) (Castleman et al., 1980). Proliferation increases to maximum over the 2 days of exposure. After 50 hours of exposure, the acute necrotic phase is complete and repair has begun.

As the length of time for the exposure episode is increased, the pattern of response changes. Schwartz et al., 1976 contrasted the biologic response in a continuous versus intermittent exposure. Rats were exposed to ozone for 7 days for either 8 hours per day (interexposure interval of 16 hours) or continuously (no interexposure interval). As the biologic response graphs illustrate (Figure 5), the early neutrophil infiltration is indistinguishable between the two exposure regimes. Epithelial hyperplasia is also equivalent in both exposure regimes, reaching maximum after 4 days of exposure and remaining elevated for the remainder of the 7 days. The key difference observed in this study was in the response of macrophages. An 8-hour per day exposure resulted in an increase in the number of alveolar macrophages, reaching maximum after about 3 days of exposure. In animals exposed for 24 hours per day, the same temporal relationship is observed with the maximum increase observed after about 3 days, but the number of macrophages is considerably greater than that observed in the 8 hour per day rats. Histopathology in the two different exposure groups is indistinguishable after the first 2 days.

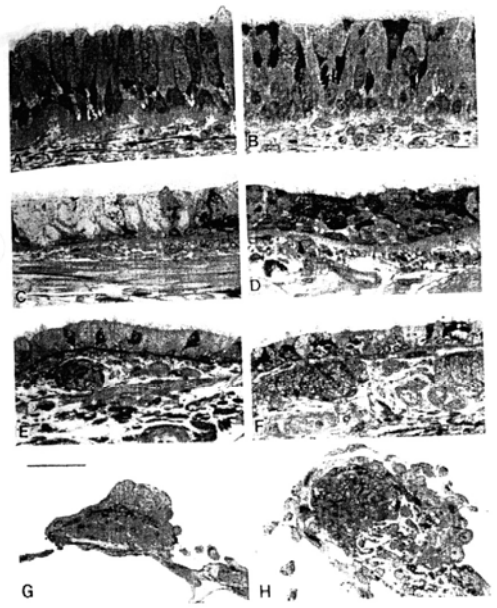
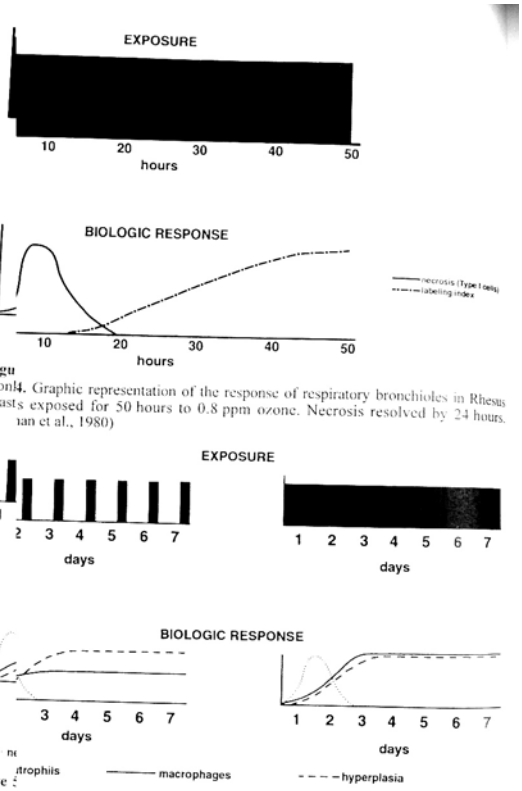


Figure 3. Light micrographs of acute histologic changes in Rhesus monkey tracheobronchial airways following a 2-hour exposure to 1 ppm ozone. Trachea (a,b), proximal intrapulmonary airways (c,d), distal intrapulmonary airways (e,f), and respiratory bronchioles (g,h) compared between filtered air-exposed (a,c,e,g) and ozone-exposed (b,d,f,h) animals. Bar equals 50μm. (Plopper et al., 1998.) Reprinted, with permission, from Plopper et al., 1998, Relationship of inhaled ozone concentration to acute tracheobronchial epithelial injury, site-specific ozone dose, and glutathione depletion in Rhesus monkeys. *American Journal of Respiratory Cell and Molecular Biology*, vol 19, pp 387-399. Official journal of the American Thoracic Society. © American Lung Association.



Figu monk**4.** Graphic representation of the response of respiratory bronchioles in Rhesus (Casts exposed for 50 hours to 0.8 ppm ozone. Necrosis resolved by 24 hours. nan et al., 1980)

Figure 5 for 8 or Graphic representation of the response of the central acinus of rats exposed dant in r-4 hours per day for 7 days to 0.8 ppm ozone. Macrophages were more abun- ts exposed 24 hours per day. (Schwartz et al., 1976)

Long-term Exposure

If the exposure period is extended beyond one week, and the interexposure interval is kept short enough (less than 3 days) to prevent later phases of the repair cycle to occur, chronic lesions develop. Bronchiolar hyperplasia in response to a relatively standard long-term exposure protocol is illustrated by Harkema et a1.,1993 (Figure 6). Macaque monkeys were exposed to 0.30 ppm ozone for 8 hours per day for 90 days, resulting in bronchiolar hyperplasia and interstitial fibrosis.

When the total exposure period is increased further hyperplastic lesions develop which are very similar to those observed in primates exposed everyday. Figure 7 illustrates the response of the rat terminal bronchiolar epithelium to a 20-month exposure 1 ppm ozone (6 hours per day, five days per week)(Plopper et al., 1994), including bronchiolarization of the alveolar duct (Figure 7).

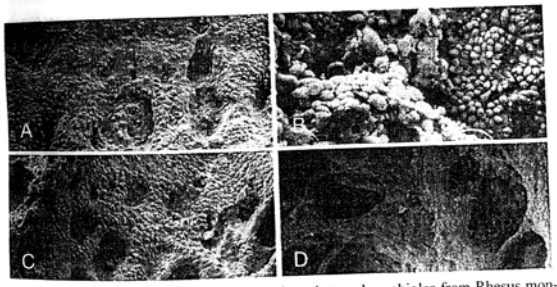


Figure 6. Scanning electron micrographs of respiratory bronchioles from Rhesus monkeys following exposure to filtered air (a), or ozone (b-d). In filtered air exposed animals, there is a continuous, uniform layer of epithelial cells lining respiratory bronchiole (250x). Four hours following an 8 hour per day, 90-day exposure to 0.8 ppm ozone, the epithelium is hyperplastic (b) and there is an accumulation of alveolar macrophages in alveolar outpockets (500x). Seven days following cessation of exposure, the epithelium is still somewhat hyperplastic (c) (250x). Six months following cessation of exposure, the epithelium has returned to normal (d) (300x). (Harkema et al., 1993)

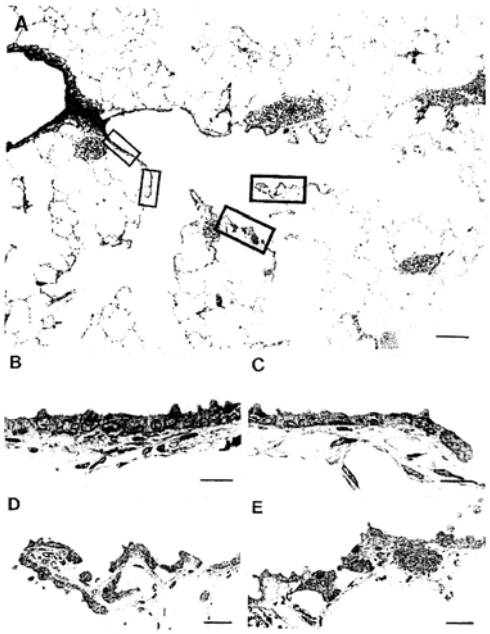


Figure 7. Distal bronchioles of rats exposed to 1 ppm ozone for 6 hours per day, 5 days per week for 20 months (A) (bar equals 150μm). Boxes B-D identify regions shown in higher magnification images below. Distal and terminal bronchiolar epithelium (B,C) appears somewhat flattened (epithelial thickness significantly decreased in terminal bronchioles (bar equals 15μm). Bronchiolarization of the alveolar duct (D,E) involved hyperplastic and metaplastic epithelium. Bar equals 30μm. (Plopper et al., 1994). Reprinted, with permission, from Plopper et al., 1994, Dose dependent tolerance to ozone: I. Tracheobronchial epithelial reorganization in rats after 20 months' exposure. American Journal of Pathology, vol 144, no 2, pp 404-421. © American Society for Investigative Pathology.

In a modification of the above exposure regimen, rats were exposed for 78 weeks to a peak concentration of 0.25 ppm ozone over the course of 8 hours for 5 days per week, with a continuous baseline subthreshold concentration of 0.06 ppm ozone for 15 hours per day 7 days per week (Chang et al., 1992). Inflammation peaked early and resolved within the first few days of exposure (Figure 8). Fibroblast proliferation initiated shortly after the resolution of inflammation, peaked after about 1 week of exposure, and continued at a lower level for the remainder of exposure. Type I cell hyperplasia peaked after 1 week of exposure, resolved by 3 weeks, and started a gradual increase at about 6 weeks of exposure, reaching maximum severity over the course of 78 weeks. The latter underscores that with continued exposure, events that appear to resolve early recur.

Extension of Interexposure Interval

The next issue is what happens when the interval between exposures is increased to a sufficient length of time for repair to be complete (over 7 days). Plopper et al., 1978 (Figure 9) compared the response of rats exposed either 6 or 27 days after an initial 3 day exposure to ozone. Early responses to ozone included an influx of neutrophils followed by necrosis. The neutrophils resolved by the end of the 3 day exposure. Necrosis reached maximum after day 3 and resolved by day 6 (3 days after cessation of exposure). Re-exposure on day 30 (27 days after cessation of exposure) results in the same pattern of neutrophil influx and necrosis. This is not necessarily surprising since the normal course of repair should result in an epithelium that is completely repaired more than three weeks after cessation of exposure. Re-exposure on day 9 (6 days after cessation of exposure) yields a response similar to that observed in naive animals and in rats re-exposed 27 days after the initial exposure. For two exposure cycles, the acute inflammatory response and subsequent necrosis are the same as the initial exposure.

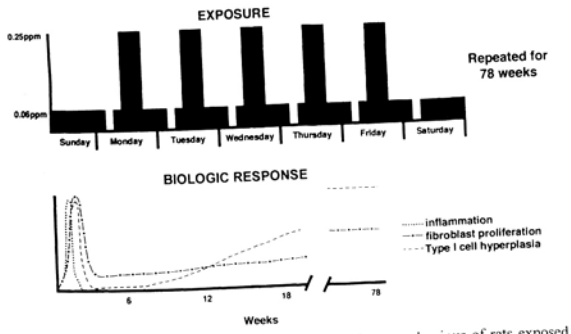


Figure 8. Graphic representation of the response of the central acinus of rats exposed in the weekly exposure scenario summarized at the top repeated for a total of 78 weeks. (Chang et al., 1992)

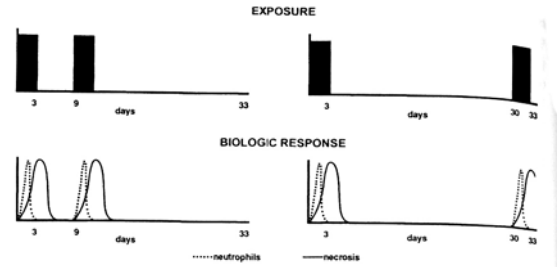


Figure 9. Graphic representation of the response of the central acinus of rats re-exposed 6 or 27 days following an initial 3-day exposure to 0.8 ppm ozone. Increasing the interexposure interval does not appear to change the acute injury phase. (Plopper et al., 1978)

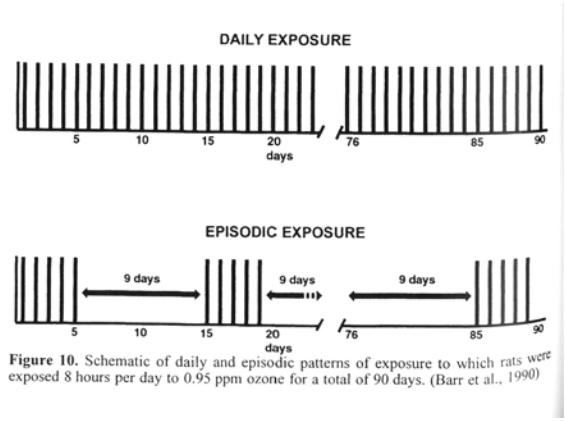


Figure 10. Schematic of daily and episodic patterns of exposure to which rats were exposed 8 hours per day to 0.95 ppm ozone for a total of 90 days. (Barr et al., 1990)

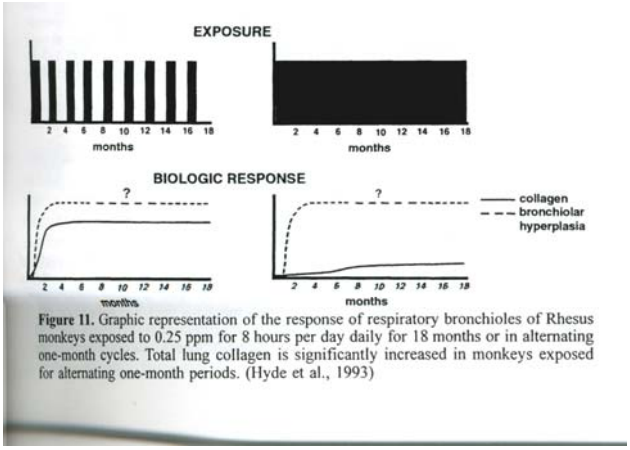


Figure 11. Graphic representation of the response of respiratory bronchioles of Rhesus monkeys exposed to 0.25 ppm for 8 hours per day daily for 18 months or in alternating one-month cycles. Total lung collagen is significantly increased in monkeys exposed for alternating one-month periods. (Hyde et al., 1993)

In an exposure regimen with a longer interexposure interval, Barr et al., 1990 (Figure 10) used an episodic exposure pattern of five 8-hour days of exposure to 0.95 ppm ozone followed by a 9-day recovery period. This pattern was repeated for a total of 90 days. Alternately, rats were exposed daily. While epithelial hypertrophy was not significantly different between daily and episodically exposed rats, the interstitial components were markedly different with a significant increase in interstitial thickness in episodically-exposed compared to daily-exposed rats.

Additional increases in the length of time between exposures appears to further alter the biologic response. Hyde et al., 1989 (Figure 11) assessed total lung collagen and bronchiolar hyperplasia in Rhesus monkeys exposed to 0.25 ppm ozone. Monkeys were exposed 8 hours per day for either 18 continuous months or for alternating one-month periods. There was no discernable difference in the degree of bronchiolar hyperplasia in either exposure group, yet monkeys exposed on alternate months had considerably greater total lung collagen compared to monkeys exposed for 18 continuous months. This suggests that while the acute response (e.g., necrosis, inflammation) appears to be equivalent for subsequent exposures, the late responses involving repair may be altered.

Given the previous data, it was apparent that an episodic exposure with an extended interexposure interval and multiple sampling points would provide a better understanding of the impact of variable exposure conditions on pathogenesis. Recently, we employed an exposure scenario similar to that of Barr et al., 1990, but with more frequent sampling. Rats were sampled at the beginning and end of each 5-day exposure period and at the end of each 9-day recovery period through day 29 (Figure 12). On the 5th day of the first exposure period, the epithelium appears hyperplastic (Figure 13c), yet the epithelium appears similar to control by 9 days after the first exposure period (Figure 14a). At the onset of the second set of 5-day exposures, inflammation, necrosis and hyperplasia were attenuated compared to that observed in the first exposure (Figure 14b). Nine days after the second 5-day exposure period, bronchiolarization of the central acinus persists (Figure 15).

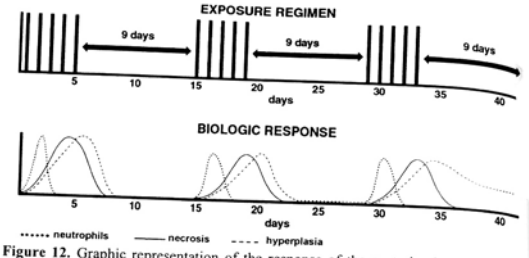


Figure 12. Graphic representation of the response of the central acinus of rats exposed to an exposure scenario modified from Barr et al. (1990). Rats were exposed to 1 ppm 8 hours per day for 5-day cycles followed by a 9 day recovery period. The biologic response curve summarizes the histologic findings presented in Figures 13, 14, and 15.

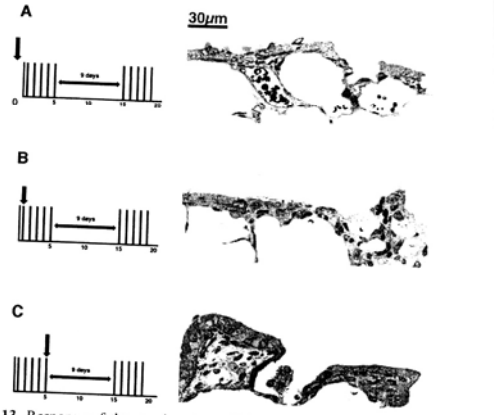


Figure 13. Response of the terminal bronchiolar epithelium after the first cycle of ozone exposures. Prior to exposure, the terminal bronchiolar epithelium is cuboidal in nature and comprised of ciliated and nonciliated cells (a). After a single 8-hour exposure to 1 ppm ozone, the epithelium is squamated following epithelial exfoliation (b). After five 8-hour exposures, the bronchiolar epithelium is hyperplastic and bronchiolarization of the alveolar duct is evident (c). Arrows on diagram indicate sampling point illustrated by histopathology.

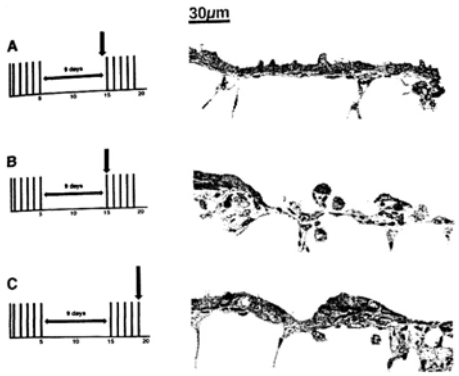


Figure 14. Response of the terminal bronchiolar epithelium to a second cycle of ozone exposures. After 9 days of recovery from the first cycle of ozone exposure, the epithelium appears normal (a). After the first re-exposure day, the epithelium exfoliates and squamates as seen previously (b). After the second cycle of five exposures, the epithelium is once again hyperplastic, but to a lesser extent than observed after the first cycle of five exposures (c). Arrows on diagram indicate sampling point illustrated by histopathology.

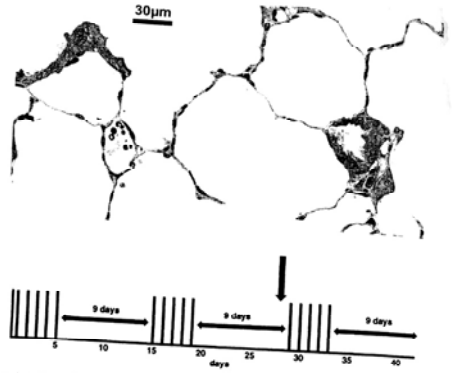


Figure 15. Nine days after the second cycle of five exposures, repair is not complete. The epithelium remains somewhat hyperplastic, and there is more extensive bronchiolarization of the alveolar duct. Arrows on diagram indicate sampling point illustrated by histopathology.

Summary and Conclusions

The response of the respiratory system to oxidant air pollutants such as ozone is highly dependent on inhaled concentration and time. In ambient conditions, the synthesis of tropospheric ozone is cyclic in nature, with ozone concentrations rising highest in mid-afternoon and dropping lowest in the pre-dawn hours. Additionally, tropospheric ozone concentrations exhibit daily and even seasonal variations. However, most experimental studies employ exposure proto**cols** with near-continuous exposures. The episodic nature of ambient exposure conditions in humans suggests that reliable assessments of risk must include a clear understanding of the impact of cyclic exposure conditions on biological time response profiles. The biological response of the respiratory system in naive animals to the initial ozone exposure follows a stereotypic cellular injury and inflammatory cycle. The imposition of additional oxidant stress by repeated exposure impacts the response variably, depending on the time during injury or repair when re-exposure occurs. The length of the interval between exposures appears to be more critical in determining the long-term impact of repeated exposures than the total duration of the exposure episode. Near-continuous exposure for a significant period of time (measured in months) fundamentally alters both the pattern of toxic cellular injury and the nature of the inflammatory response. Not only is the periodicity of the exposure important, but the duration of interexposure intervals also appears to effect biological response. The episodic nature of ambient exposure conditions appears to represent a greater health risk than would be expected based on extrapolation from experimental conditions relying on near-continuous exposure scenarios.

Acknowledgements

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