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February 24, 2005

Dr. Richard Bode
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Sacramento, CA

Dear Dr. Bode:

The Air Quality Advisory Committee met on January 11 and 12, 2005 to evaluate the draft document "Review of the California Ambient Air Quality Standard For Ozone." The examination of the current air quality standards and the recommendations for modification of those standards derived from the Children's Environmental Health Protection Act (Senate Bill 25) and a resulting document "Adequacy of California Ambient Air Quality Standards: Children's Environmental Health Protection Act" which was published as a staff report in 2000. SB 25 prompted an analysis of the scientific basis of the California air quality standards for particulate matter, sulfates, ozone, carbon monoxide, nitrogen dioxide, lead, and sulfur dioxide.

In response to SB 25, an up to date examination of the scientific information relevant to each of these standards that was published in peer reviewed documents was commissioned to determine if the current California standards were adequately protective of children's health. The staff of the Office of Environmental Health Hazard Assessment (OEHHHA) made an analysis of the findings and recommended a list of standards that required re-review. The OEHHHA analysis was deliberated by AQAC in a public meeting and the list of standards to be reviewed was prioritized. The standard for ozone was among those of highest priority for review.

In most respects, the committee was pleased with the document "Review of the California Ambient Air Quality Standard for Ozone." The committee went on record to complement the staffs of the ARB and OEHHHA for performing a very comprehensive and careful compilation and analysis of the peer reviewed literature on sources, monitoring and health effects of ambient ozone.

The draft document made the following recommendations.

1. Retain ozone as the indicator for oxidant air pollution.

2. Retain the 1-hour-average standard for ozone at 0.09 ppm.
3. Establish an 8-hour-average standard for ozone at 0.070 ppm.
4. For both the 1-hour and 8-hour ozone standards, the concentrations for the standards noted above are to be established as "not to be exceeded".
5. Retain the current monitoring method for ozone which uses the ultraviolet (UV) absorption method for determining compliance with the state Ambient Air Quality Standard for ozone. Incorporate all federally approved UV methods (listed at <http://www.epa.gov/ttn/antic/criteria.html>) as California Approved Samplers for ozone.

The AQAC discussed whether the UV-absorption method adequately measured other oxidant gases. The AQAC submitted comments to the Chair and a list of findings and suggested modifications was prepared. The committee suggests the deletion of recommendation # 1 and unanimously endorses recommendations 2 through 5.

The specific comments of the AQAC on the draft document are appended to this letter.

The AQAC is extremely appreciative of the responsiveness and expertise of the the staffs of OEHHA and the ARB. We commend them on the excellent job they did in reviewing and summarizing the scientific literature in the complex area of ozone and its effects on human health, and in establishing a set of ambient air quality standards that will protect the health of California's citizens and especially their children.

Finally, the AQAC strongly recommends that additional research is needed on the possible effects of ozone on fetal and neonatal development, and that the ozone standard should be reviewed in 5 years or less if significant new research results become available.

Sincerely,



Michael T. Kleinman, Chair
Air Quality Advisory Committee

Cc: Bart Croes, Research Division

Summary Comments of the Air Quality Advisory Committee

The staffs of OEHHA and the ARB provided an excellent review of the current literature relevant to the sources, transport and health effects of ambient ozone (O₃). The review provided a firm basis for establishing the needs for health-based O₃ air quality standards and the committee was unanimous in its appreciation of the effort and diligence involved in producing the report.

The staffs' recommendations for retaining the 1-hour O₃ standard and adding a new 8-hour standard at 70 ppb are well supported by the scientific evidence summarized in the document. Given the charge to set standards protective of human health, the key factor is the lowest exposure at which health effects have been demonstrated. This is inevitably a matter of interpretation, but there are convincing clinical studies showing lung function impairment at exposures as low as 80 ppb (6.6-hour average) and in some cases lower. Epidemiology and toxicology studies, although not as useful for pinpointing a lowest effect level, provide ample evidence of serious health effects of O₃, including hospitalizations for respiratory illness and asthma exacerbation. Recent evidence also suggests that that long-term exposure may be associated with permanent lung injury and that higher daily O₃ concentrations are associated with higher mortality rates.

The Air Quality Advisory Committee (AQAC) provided comments on a chapter by chapter basis and also addressed specific overarching questions that were submitted to them during their review of the report.

Children's protection, with an adequate margin of safety, is of paramount importance to public health. While the measurable injury and morbidity may be small, there is a developing body of knowledge that suggests that O₃ exposures early in life may contribute to lung compromise later in life (i.e. effects may be cumulative). As the committee indicates this is an area that has not been adequately researched and more work is needed. In addition, children with chronic lung diseases such as bronchopulmonary dysplasia, asthma and cystic fibrosis could be at special risk but, with the possible exception of asthma, there has been little research effort in these areas. Since asthma affects nearly 10% of the child population, the effects of O₃ on this group is of special importance. Although commented on in the draft document, it is important to recognize that children have higher minute ventilation rates per unit lung volume than do adults, hence their lungs receive greater doses of inhaled pollutants than do adults for comparable exposures. It is important to recognize that children are not "miniature adults" and this should be stressed in discussions of dose-response relationships.

Although Chapters 11 and 12 and Appendix A summarize the literature regarding the effects that ozone has on subjects (epidemiological and experimental) with chronic respiratory diseases, most specifically asthma, this information is not mentioned in Chapter 11 (Staff Recommendations). Individuals with chronic respiratory diseases are more likely to have acute adverse effects than healthy individuals.

Since there is little experimental data regarding the long-term effects of ozone on infants and children, the evidence has been interpreted cautiously. This should be highlighted as an area for research.

The Committee's primary responsibility is to assess the adequacy of the scientific basis for the proposed standards to protect public health. For this reason, our specific comments are more detailed when dealing with health-related chapters than for other chapters of the Draft Report. Our comments on the other chapters are primarily focused on factors that might influence the interpretation of ambient air quality vis-à-vis public health implications.

The document is in general extremely comprehensive and the committee appreciates the extensive effort undertaken in its preparation. Below are suggestions and comments of a more specific nature on a chapter-to-chapter basis. The committee supports the suggested standards and the suggested form of the standards being expressed as not to be exceeded, but suggests that even though this document does not specifically deal with the efforts to meet the proposed standards, greater precision in the discussion of how O₃ is measured, what constitutes an exceedance and how limitations in the monitoring capabilities may affect the exact level that "will not be exceeded".

The committee does have some concerns. The previous standard was assessed with respect to whether it adequately protected the health of children with some margin of safety. The proposed 8 hr standard provides some margin of safety by limiting the incidences of peak exposures that could be important in children's exposures. The decreased FEV1 reported in Kunzeli et al [Environ Res 72:8-23, 1997] in college students and Gauderman et al [N Engl J Med 351:1057-67, 2004] suggest that O₃ exposure during lung development may permanently impact lung function. One can ask whether these effects start during fetal life similar to the impact of pre-natal ETS exposure on the fetus (Hanrahan et al Amer J Respir Crit Care Med 145:1129-35, 1992 - higher airways resistance and smaller lungs; Tepper et al Am J Respir Crit Care Med 171:78-82, 2005 - lower airway function [FEF50, FEF25-75%, and 30% reduction in FEF75%] but not increased airway reactivity [to methacholine] in infants with pre-natal ETS exposure). The parallel to ETS exposure is should provoke interest in other studies on newborns and early infancy to determine whether there are other similar untoward effects of O₃. Pre-natal ETS exposure is well documented to impair development of respiratory control and increase the incidence of infant apnea and SIDS. While there have been reports of a similar effect of O₃ to ETS on birth weight [Parker et al, Pediatrics 115:121-8, 2004] and body growth during adolescents [Jedrychowski et al Environ Res 90:12-20, 2002], potential impaired CNS development with pre-natal O₃ exposure has not been studied. The Committee feels that additional research efforts on maternal, in utero and exposures during lung development are needed. If this preliminary evidence is supported in future research results it may be necessary to reconsider the form of the standard and include a longer terms exposure limit.

The Committee also feels strongly that an ozone-related research agenda should be supported over the next 5 years and that it is of very high priority that the ozone air quality standards be revisited in at most 5 years from now.

Important research issues to be addressed prior to the next cycle of review for ozone?

Acute toxicity mechanisms in sensitive populations (i.e. individuals with chronic respiratory and heart diseases)

Long-term effects of early exposure to ozone on cardiorespiratory system, nervous system and the developing organism.

Effects of O₃ exposure below 0.08 ppm using current more sensitive methods related to mechanisms of O₃ effects on the cardiopulmonary system.

Interactions of ozone with organic vapors to form secondary organic aerosols (the toxicity of these compounds is nearly unknown).

Several other suggestions are interspersed in the specific comments.

SPECIFIC COMMENTS

Chapter 1

Executive Summary – some modifications will be needed to include suggested changes in specific chapters below. The standards are adequately supported. The document is very comprehensive and it might be useful to insert into the Summary of Staff recommendations, a list (not a paragraph) of known adverse effects for ozone exposure to make it easier to put the rationale for the standards into context.

Chapter 2

Introduction and Overview – This chapter was very well written and provides the context for the process of setting the O₃ standard in a well balanced manner.

Chapter 3

Physics and Chemistry of O₃ - To avoid any chance of confusion it should be specified that ozone concentration is measured by volume, usually indicated with '(v)' following the unit. It would be less confusing if a single way of expressing concentration were chosen and used throughout the document. Another issue is 'significant figures.' This could impact the interpretation of the standard. The attribution at 0.070 ppm suggests a precision with 3 significant figures. Some discussion of how this is taken into account in the establishment of guidelines for ozone monitoring and reporting should be inserted to Chapter 6.

Chapter 4

Background O₃ in California - For research issues in the next cycle: background vs. elevation, season and region might be further addressed – although 40 ppb(v) is a reasonable estimate of the background for the discussion of the standard. The issue of unusual incursions of O₃ are important in the context of defining what constitutes an

exceedance for regulatory purposes. This should be specified in this chapter as well as in the monitoring chapter.

Chapter 5

O₃ Precursor Emissions – This chapter does not mention natural emissions of precursors. The information in Chapter 4 could be reintroduced to put the anthropogenic precursors in perspective. This is especially important since unusual circumstances (e.g. wildfires) will be considered in the evaluation of whether an area exceeds the standard. If there are not enough data to include in the pie charts, perhaps a qualitative summary statement could be included.

Chapter 6

The precision of ozone measurements is an issue that should be discussed. If a monitoring method has a standard deviation of x , than any given reading would really have a true value (t) of $t \pm 2x$. (i.e. there is a limit on what would constitute an exceedance). It would be useful to spell out what we mean by exceedance in Chapter 8.

Chapter 7

Exposure to O₃ – The Committee did not request any additions.

Chapter 8

As mentioned for Chapter 6, there is some ambiguity with respect to precision of measurements as to what constitutes a measurable difference above the standard. If it is specified that the data will be in ppm with one significant figure rounding would allow 0.0749ppm to be truncated down to 0.07ppm—dropping to meet the standard as a result. Rounding specification have been used in the past by USEPA. (For example, EPA guidelines for data handling sometimes specify such round-off: see EPA-454/R-98-017, which allows 0.084ppm to be “less than, or equal to, 0.08ppm”.)

On the other hand using ppb(v), with 70ppb(v) as the standard (to be reported to the nearest 1ppb(v)), any concentration above 70.5ppb(v) is correctly seen as an exceedance, rather than allowing 74 to comply.

It might make sense to specify something like “...ozone will be measured by volume fraction, and recorded in ppb(v) to the nearest 1ppb(v).” The standards could be stipulated as 90ppb(v) and 70ppb(v), respectively.

Chapter 9

The Committee did not address the Welfare Benefits, since its priority was human health effects. It might be worthwhile, however, to mention that the benefits analysis does not include the value of reducing ozone damage to cash crops, degradation of property (i.e. premature wearing of painted surfaces).

Chapter 10 Health Benefits Analysis (now listed as Appendix B)

The health benefits assessment is not being used to set the health standards, and it is not being used in a cost-benefit analysis, so an explanation about its purpose would be helpful. Many comments from the public concerned the differences between the studies used as the basis of the standard selection versus the studies used in the health benefits assessment. It is appropriate that the two are different because the purposes of

the two analyses are different, as the staff have pointed out in the response to public comments. The introduction would help clarify and respond to some of these comments if it included: (1) an explanation about the purpose of the health benefit assessment in the context of the health standard review process, (2) an explanation of the reasons why clinical studies are useful for standard setting but are not as useful for health benefit assessment, and (3) an explanation of why monetary values for health effects are not included.

Given the significance of the threshold assumptions for the results of the assessment, and the limited information from the literature, it is appropriate to calculate benefits under two alternative assumptions: (1) no threshold for any health effect category and (2) the same threshold (based on asthma emergency room visits studies if that is the best source) for all health effect categories, with adjustments to the estimated slope of the concentration response above the threshold.

It is appropriate to change to a census tract level extrapolation from ambient monitor concentrations for the health benefits assessment, rather than a county level aggregation. A more detailed exposure assessment than this is not needed for the health benefits assessment based on epidemiology studies because these are also based on ambient concentrations.

Bell et al. (2004) recently published an analysis of the NMMAPS data focused on ozone and their mean results are slightly higher than the previous NMMAPS results reported: 0.52% per 10 ppb 24-hour average ozone, which translates to about 0.21% per 10 ppb daily 1-hour high. This is still lower than the WHO central estimate, and the analysis still includes the use of multiple temperature and season variables. However, it covers 95 US cities, including 12 in California. The authors suggest that publication bias could be one reason why their results are lower than Anderson et al., Levy et al., and Stieb et al. report because the latter are based mostly on published studies for individual cities. It also may be appropriate to include a sensitivity analysis based on the “nearly significant” results for summer ozone based on recent ACS publication to show what the implications are of these results relative to the daily mortality estimates. There were also public comments given regarding forthcoming publications in *Epidemiology* reporting new analyses of the potential relationship between ozone and mortality. Given the significance of this health effect, the staff should consider incorporating this new evidence if possible.

There are inevitably important uncertainties in a quantitative benefits analysis, not so much about the nature of the health benefits but about their specific quantitative level. The uncertainties have been described in Section 10.6, but it is a difficult section to read. We suggest that the discussion of uncertainties in section 10.6 be edited to clarify the main points and incorporate the results of the revised threshold sensitivity analysis.

Chapter 11

1. Controlled Exposures:

The committee find that the review of human exposure studies was complete, current and accurate, with a few small exceptions. Some areas could be strengthened. For example, with respect to effective dose, the paragraph on p 11-212 could be improved by repeating some of the details given on p 11-4, citing Adams' (2003) comparison of FEV1 responses to 6.6 hr exposure to 0.08 ppm vs. 2 hr exposure to 0.30 ppm O₃.

In several places, reference is made to O₃ inhalation effects on respiratory symptoms or respiratory irritation when symptoms of breathing discomfort would be more accurate.

The examination of gender differences appears to be based on the corresponding section of the USEPA Criteria O₃ Document. It is the Committee's understanding that this section of the USEPA Criteria Document has been revised and there might be some updated material that could be incorporated into the revised report.

The section on heat and humidity effects on O₃-induced pulmonary function and symptoms responses does not mention that Gibbons and Adams (1984) noted that the ability to complete a given O₃ exposure was shortened when subjects were exercised under higher temperature conditions than when studies were performed under normal room temperature conditions. This could have some implications for summer exposures in California when O₃ exposures might be highest.

The summary statement on Adaptation (p 11-174) ["First, research suggests that ventilatory responses and reduced exercise performance do not show response attenuation with repeated exposures to O₃ concentrations that lead to diminution of pulmonary function responses"] is not accurate. Foxcraft and Adams (1986) performed a repeated O₃ exposure study. They did find reduced symptoms and improved exercise performance after 4 consecutive days of 0.35 ppm O₃ exposure, while they also reported diminution of the Day 1 pulmonary function reduction by Day 4 of exposure.

The summary statement on p 11-17 ["exercise performance can be reduced under conditions where O₃ inhalation has induced pulmonary function decrements and/or symptoms of respiratory discomfort. Significant reductions in exercise performance have been reported at O₃ concentrations as low as 0.06 ppm."] should be qualified. The Linder (1988) observations have not been observed by others using similar protocols at 0.06 ppm and higher (0.12 ppm) concentrations (Gong et al. 1986; Schlegle and Adams, 1986). Also exercise tolerance and PF changes are not always seen in concert (Gong et al., 1986; Foxcraft and Adams, 1986; Schlegle et al., 1987).

Toxicological Studies

Although there is to be discussion regarding ozone toxicity in infants and children, some of the literature is missing in this document (Chapters 11 and Appendix A). Also, the information regarding pre/postnatal exposure to ozone could be highlighted in separate sections in Chapter 11 and Appendix A. Doing so could make it easier to tease out the important information regarding age susceptibility/toxicity.

A few additional articles could be considered:

Carl, J., Bruce, H., and Jacob, F. (2004). Differential proinflammatory cytokine responses of the lung to ozone and lipopolysaccharide exposure during postnatal development. *Exp Lung Res* 30, 599-614.

Elsayed, N. M., Mustafa, M. G., and Postlethwait, E. M. (1982) Age-dependent pulmonary response of rats to ozone exposure. *J Toxicol Environ Health* 9:835-48.

Finkelstein, J. N., and Johnston, C. J. (2004). Enhanced sensitivity of the postnatal lung to environmental insults and oxidant stress. *Pediatrics* 113, 1092-1096.

Mariassy, A. T., Sielczak, M. W., McCray, M. N., Abraham, W. M., and Wanner, A. (1989) Effects of ozone on lamb tracheal mucosa. Quantitative glycoconjugate histochemistry. *Am J Pathol* 135:871-9.

Myers, B. A., Dubick, M. A., Gerriets, J. E., Reiser, K. M., Last, J. A., and Rucker, R. B. (1986). Lung collagen and elastin after ozone exposure in vitamin B-6-deficient rats. *Toxicol Lett* 30, 55-61.

Phalen, R. F., Crocker, T. T., McClure, T. R., and Tyler, N. K. (1986). Effect of ozone on mean linear intercept in the lung of young beagles. *J Toxicol Environ Health* 17, 285-296.

Rivas-Manzano, P., and Paz, C. (1999). Cerebellar morphological alterations in rats induced by prenatal ozone exposure. *Neurosci Lett* 276, 37-40.

Romero-Velazquez, R. M., Alfaro-Rodriguez, A., Gonzalez-Pina, R., and Gonzalez-Maciel, A. (2002). Effect of ozone prenatal exposure on postnatal development of cerebellum. *Proc West Pharmacol Soc* 45, 65-67.

Sarangapani, R., Gentry, P. R., Covington, T. R., Teeguarden, J. G., and Clewell, H. J., 3rd (2003). Evaluation of the potential impact of age- and gender-specific lung morphology and ventilation rate on the dosimetry of vapors. *Inhal Toxicol* 15, 987-1016.

Sorace, A., de Acetis, L., Alleva, E., and Santucci, D. (2001). Prolonged exposure to low doses of ozone: short- and long-term changes in behavioral performance in mice. *Environ Res* 85, 122-134.

Stephens, R. J., Sloan, M. F., Groth, D. G., Negi, D. S., and Lunan, K. D. (1978) Cytologic responses of postnatal rat lungs to O₃ or NO₂ exposure. *Am J Pathol* 93:183-200.

Tyson, C. A., Lunan, K. D., and Stephens, R. J. (1982) Age-related differences in GSH-shuttle enzymes in NO₂- or O₃-exposed rat lungs. *Arch Environ Health* 37:167-76.

3. Have potential differential exposure and dose patterns among infants and children been examined sufficiently in the document?

Sections 8.4 (Consideration of Infants and Children) and 8.7.4 (Consideration of Infants and Children in Recommending the Ozone Standards) present general statements to the effect that children receive a larger exposure of ozone. There is some literature on this topic that could be cited. A table similar to that in Kleinman (1991) could be used.

Kleinman, M.T. Effects of ozone on pulmonary function: The relationship of response to effective dose. *J. Exposure Analysis and Environmental Epidemiology*, 1:309-325, 1991.

Chapter 12. Epidemiologic Studies.

General comments:

Overall, this chapter provides a very thoughtful and comprehensive review of the epidemiologic literature that fairly points to methodological weaknesses that in general, have likely underestimated the impact of ozone on human health. This critique adds some additional interpretation of these weaknesses. The choice of an ozone standard based on susceptible populations is well supported by the evidence presented. Below are some additional data to support the protection of populations at risk.

Although studies conducted in other parts of the country and internationally are clearly relevant, studies in California are particularly relevant to this review. It is important for this review to further interpret results of studies in California with respect to the misclassification of O₃ exposure based on region. The details of this were covered in the exposure section but results of epidemiologic studies need to be interpreted with this in mind. The use of air conditioning, air exchange rates and time indoors will all dramatically influence personal O₃ exposure. This was described in 12.2 under time series studies in the last paragraph on page 12-22, but it also applies to the other study designs. Studies conducted in inland areas of California where outdoor O₃ is highest may have subjects who are less exposed to O₃ than areas closer to the coast. The California studies most influenced by this phenomenon are the studies by Delfino et al. cited in section 12.1 and above, the 7th Day Adventist Cohort, and the Children's Health Study (CHS) (Gilliland et al., 2001, and 12.3.5 CHS references). The CHS included schoolchildren living in hotter inland areas of southern California. This phenomenon may have partly explained the isolated results in the CHS for the increased risk of asthma onset only among children playing three or more sports in the six out of 12 communities with higher O₃ (McConnell et al., 2002). More outdoor exposure and

increased O₃ dose may have been a function of the physical activities. The text reviewing McConnell et al, 2002 on p 12-54 only refers to "effect modification by physical activity."

The impact of weather on behavior, air conditioning use, and therefore indoor exposure to O₃, may have also led to null results for lung function growth and O₃ in the prospective analysis of 4th graders in the CHS (12.3.5, p. 12-52, Gauderman et al, 2000). This contrasts significant results for particles, which have considerably greater penetration and persistence in indoor environments. Note that the Gauderman et al. (2000) study was notably updated recently with an 8-year follow-up of fourth graders (Gauderman et al, 2004) in contrast to the 4-year follow-up in the 2000 publication. The new study also found acid vapor and elemental carbon were associated with lung function declines along with PM_{2.5} and NO₂.

Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, McConnell R, Kuenzli N, Lurmann F, Rappaport E, Margolis H, Bates D, Peters J. The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med. 2004;351(11):1057-67.

Also of great importance in interpreting epidemiologic results is the issue of excessive control for presumed confounding by outdoor temperature on effects of outdoor (ambient) O₃, particularly where there is lack of evidence for a direct health effect of local temperature ranges. Often results are not presented for O₃ models without temperature. This issue was described in section 12.2 under time series studies in the second paragraph on page 12-22 and later in reference to the studies reviewed, but it also needs to be referenced to the other study designs. An example of why ambient temperature can have little direct relevance to health is shown in a personal PM exposure assessment study of 19 asthmatic children living in inland San Diego County. The magnitude of correlation between personal temperature and ambient O₃ was far less than for central site temperature over a 14-day monitoring period ($r = 0.50$ for 8-hr O₃ and 1-hr maximum outdoor temperature, vs. $r = 0.10$ for 8-hr O₃ and 1-hr maximum personal temperature) (Delfino et al., 2003). There was no association between personal temperature and lung function in that study, but there were strong inverse associations between personal PM and lung function. Ambient O₃ was not associated with lung function but the study was designed to assess personal PM effects and had limited power to assess effects of central site exposures.

Delfino RJ, Quintana PJE, Floro J, Gastañaga VM, Samimi BS, Kleinman MT, Liu L-JS, Bufalino C, Wu C-F, McLaren CE. Association of FEV₁ in asthmatic children with personal and microenvironmental exposure to airborne particulate matter. Environ Health Perspect 2004; 112:932-41.

Specific comments:

12.1. Some relevant acute field studies were not discussed in this section, including studies conducted in California. These include:

Delfino RJ, Zeiger RS, Seltzer JM, Street DH. Symptoms in pediatric asthmatics and air pollution: Differences in effects by symptom severity, anti-inflammatory medication use, and particulate averaging time. Environ Health Perspect, 1998; 106: 751-61.

This study of schoolchildren with asthma in inland San Diego County showed significant associations between asthma symptoms (bothersome or interfered with daily activities) and O₃, with similar associations for minimum to 90th percentile 1-hr (58 ppb) and 8-hr O₃ maximums (46 ppb). Associations for O₃ and PM₁₀ were largely independent in models incorporating both pollutants, and O₃ associations were not confounded by outdoor fungal spores. The study also showed significantly stronger associations between asthma symptoms and O₃ in a subset of asthmatics not taking anti-inflammatory medications. Threshold analyses suggested effects below 80 ppb 1-hr O₃ maximum in this subset, but not among other subjects. 80 ppb 8-hr maximum O₃ was exceeded 25 times during the three-month study.

Mortimer KM, Tager IB, Dockery DW, Neas LM, Redline S. The Effect of Ozone on Inner-City Children with Asthma. Identification of Susceptible Subgroups. Am J Respir Crit Care Med 162:1838-1845 (2000).

Mortimer, et al. (2000) reported results of a series of 2-week asthma panels in 846 inner city children with asthma living in low income neighborhoods. They found that O₃ was inversely associated with PEF and positively associated with symptoms with the strongest associations among children born of low birth weight or premature.

Delfino RJ, Gong H Jr, Linn WS, Hu Y, Pellizzari ED. Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants. Environ Health Perspect 2003; 111:647-656.

This study of Hispanic schoolchildren with asthma in LA showed significant associations between asthma symptoms (bothersome or interfered with daily activities) and ambient VOCs, PM₁₀ elemental and organic carbon, but not O₃. However, O₃, along with formaldehyde and acetone were similarly associated with more severe symptoms interfering with daily activities among a subset of children, particularly those on maintenance medication. Odds ratios (OR) for interquartile increases in 1-hr O₃ (14 ppb) were identical to 8-hr O₃ (11 ppb) (both ORs around 2.0), even though 1-hr O₃ never exceeded 52 ppb. See Table 4 in that paper for details.

12.1.3. Page 12-5:

The study by Gent and colleagues (2003) is large panel study with key findings. The review should put the findings of effect modification from maintenance medication into proper perspective. First, the biological mechanism of O₃ is in large part related to airway inflammation as discussed in the Toxicology section. Therefore, medication that controls airway inflammation such as inhaled corticosteroids would be expected to dampen the effects of O₃. However, finding the opposite in a panel study such as Gent

et al. (2003) is not unexpected if use of such medication is largely restricted to more severe asthmatics, who are expected to be more susceptible to O₃. The results contrast findings of Delfino et al. (1998) showing significantly stronger association between asthma symptom severity and O₃ in asthmatic children not taking anti-inflammatory medications, largely inhaled corticosteroids (ICS). Mortimer, et al. (2000, discussed above) compared effects on asthma outcomes by outdoor O₃ levels across medication groups based on baseline data for prescribed medication. Associations between incidence of symptoms and an increase of 15 ppb in O₃ was largest among those prescribed cromolyn but not ICS (OR 1.46, 95% CI 1.06, 2.01) followed by nonsignificant ORs for those prescribed β-agonists or xanthines only (1.18), ICS (1.08), and no medication (1.04). The percentage change in PEF was also greatest among those prescribed cromolyn but not ICS (-1.27, 95% CI -2.47, -0.06) followed by nonsignificant PEF changes of around -0.5 for the other groups.

Section 12.2.

The review made the important point of describing residual confounding of ozone effects by the co-adjustment approach in time series models, and the lack of stratified analyses by season. This issue has not received adequate attention in the literature and may explain many null findings. These potential analytic weaknesses and control for temperature (see above) is particularly troubling for the null results in Los Angeles (Linn et al, 2000; Mann et al., 2002 and Nauenberg and Basu, 1999) suggesting that new studies and reanalysis of these studies are needed.

The committee concurs with Dr. Bates that the Atlanta study by Friedman et al. (2001) is particularly important in suggesting that lowering ozone will have major benefits in reducing hospital admissions and ED visits. It is also important to point out that the effects detected in Atlanta were related to a reduction in traffic, which includes a wide range of toxic air pollutants including particle-bound in addition to ozone. Strong correlation between ozone and PM in Atlanta has made it impossible to separate effects of the two on asthma ED visits as reported by Tolbert (2000) reviewed in section 12-35.

typo in title of Table 12-2 Hospital was misspelled.

The statement on p 12-36, third paragraph, lines 11-12 is unclear. What is meant by "self-selected" and "not quantitatively useful." All of these studies are subject to exposure misclassification and air pollutant components (most unmeasured) could differ by season, year and geographic location. These factors will lead to inconsistencies. For instance, for the Delfino 1997a study, concentrations of PM₁₀, PM_{2.5}, SO₄, and H⁺ were significantly higher during 1992 than 1993 due to sulfate transport episodes, and O₃ lower. Therefore, finding significant results in 1993 alone are not unexpected.

12.4.2: Similar to section 12.2.1, the presentation of important issues to understand in time series analysis is excellent and provides thoughtful direction to further research. The criticisms of smoothing functions that include midrange temperatures of questionable clinical relevance are particularly informative and suggest that studies using this method may have underestimated the effects of air pollutants including ozone.