

CALOZONE.doc

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REVIEW OF: THE REVIEW OF THE CALIFORNIA AMBIENT AIR QUALITY
STANDARD FOR OZONE: Public Review Draft June 21st, 2004

VOLUME II:

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GENERAL COMMENT:

This is a very complete review of the toxicology of ozone, starting with data derived from animal exposures and describing the morphological and biochemical changes that follow exposure, and continuing with human controlled exposure studies, and ending with the epidemiological observations based on existing ambient concentrations. The Review is characterized by excellent descriptions of a very large volume of experimental work, with sufficient detail given of individual experiments for the reader to assess their significance. The controlled human exposure studies which now cover a period of more than thirty years, are admirably summarized. The epidemiological evidence in general confirms the type of effect which the preceding information would lead one to expect, and the difficulties in interpretation are, in general, well described. In the document as a whole, difficulties and limitations in interpretation are clearly stated and not obscured, and it therefore comprises a very strong document and a unique guide to the difficult problem of establishing some standard for ozone that will provide a measure of protection of public health.

In the comments that follow, I have emphasized points in which my interpretation and assessment of the evidence differs, in some respect, from that of the document. Not all of these differences would affect the level chosen as a standard; but their consideration might be useful in the overall evaluation of the Review.

SPECIFIC COMMENTS:

Page 11-12:

The point might be made that there is concordance between the dosimetric calculations of the target area for the highest concentration of ozone (the terminal bronchiole), and the observed morphological effects which is the centriacinar region. The dosimetric calculations also indicate the higher delivered dose of ozone as the tidal volume increases, and this is consistent with the increased effects on exercise.

Page 11-15:

The complex problem of the variation of effect with different time courses of ozone delivery is well described. The genetic basis for differences in sensitivity to ozone demonstrated in breeding experiments deserves more analysis.

Page 11-45:

If the length of time between exposures is important, how can this be related to the time course of exposure that would usually occur to an exposed child?

This is mentioned on Page 11-46: “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 “. There is no follow-up as to how this might be done.

Page 11-48:

First paragraph: the FEV1 has the smallest coefficient of variation, but the FEF25-75 is much more sensitive than the FEV1 to changes in terminal bronchioles. More emphasis on the work of Weinman on the small airway effects of ozone is needed. This is important to offset the early FVC change which is due to stimulation by ozone of the C-fiber system – the changes in small airways are slower to resolve and very likely more important in terms of long term effects.

Page 11-51:

Is it fair to assume that human variability in response to ozone is genetic in origin? What is the role of anti-oxidants such as superoxide dismutase? What about the protective effect of Vitamin C?

Page 11-52:

The reader should be told that although a single subject may have a meaningful threshold value for the effects of ozone, no such threshold is derivable for a group if a statistically significant shift in the mean is taken as the criterion of some effect.

Page 11-87

Insufficient attention is given to the work of Frank, R. et al (Repetitive ozone exposure of young adults: evidence of persistent small airway dysfunction: Am J Respir Crit Care Med 164: 1253-1260; 2001). The reference is quoted on page 11-226. In evaluating acute exposure data, it is important to separate the early FVC effect due to stimulation of the C-fiber system, and the later and more persistent small airway effects as shown by these authors. Their work also

suggests that the reduced effect of ozone on subsequent days after an initial effect is to be explained by the protective mucus layer induced by the inflammatory response to the exposure on the first day, which has the effect of diminishing the response on subsequent days. These observations are relevant to standard-setting.

Page 11-92:

The complex data on asthmatics is well described here.

Page 11-110:

The emphasis on the joint ozone/Allergen exposures is important, even though, as noted on the top of page 11-111, “they do not directly contribute to the evaluation of the level of the standard”. It should be noted here that sequential exposures to ozone and allergens must be very common in real life situations.

Page 11-112:

Summary: the Southern California Children’s study found that lung development, as judged by lung function tests, was being adversely affected by exposures to vehicle exhausts, but higher exposures to ozone were without effect.

Page 11-114; second paragraph: the point might be made that exacerbations of asthma are now thought to be primarily inflammatory in nature and hence aggravation by ozone which causes inflammation at very low doses, is to be expected.

Page 11-127:

Penultimate paragraph: might be better expressed as follows: “Chronic obstructive pulmonary disease, as well as chronic asthma, lead to nonuniform distribution of inhaled air in the lungs. This will have the effect of increasing the delivered dose of an inhaled pollutant to the regions of the lung which are relatively over-ventilated”.

Page 11-149:

The interaction between heat stress and the effects of ozone is important, and as noted below, there have been recent attempts to separate the higher mortality in heat waves into the deaths attributable to heat and the deaths attributable to the concomitant elevated ozone levels. Increased temperature leads to increased ventilation, which in turn will increase the delivered dose of ozone to the lungs.

Page 11-172:

Second paragraph: note the work of Frank et al which suggests that the mucus secretion initiated by the first ozone exposure plays a part in lessening the effect (on FVC) of subsequent exposures. It should be noted that it is not clear whether successive exposures result in a reduced effect at the level of the small airways, although the work of Christian et al noted on Page 11-173 suggests that the effects on distal airways may also be attenuated. As noted on Page 11-174, whether this applies to lung tissue is unclear. These distinctions should be made

clear in the Summary on page 11-174. My opinion is that the reduced FVC response on successive exposures cannot be assumed to indicate a reduction of effect in other parameters within the lung.

Page 11-177:

In the Summary, a reference should be given to the reduction in exercise performance noted at ozone levels of 0.06 ppm.

Page 11-198:

Tokyo-Yokohama asthma was almost certainly due to high particulate and SO₂ levels and had nothing to do with ozone. It is not really relevant to this review.

Page 11-200:

Peden's observation about an increased eosinophilic response should be put earlier when the interaction of ozone and allergens was being reviewed.

Page 11-207:

First paragraph: more emphasis should be given to this work in the interaction between combined O₃ and allergen exposures.

Page 11-211: Pollutant mixtures: More discussion is needed on the factors affecting simultaneous exposure to ozone on the one hand, and to vehicle exhaust on the other. Perhaps a few paragraphs specifically on patterns of exposure would be helpful. This is because PM_{2.5} in the urban environment is associated with a variety of adverse health effects.

CHAPTER 12:

An important point should be mentioned at the outset, which is that it is now known that a peak in asthma attendances and admissions occurs in the third week of September. This was first documented in Vancouver (see Environ Research 51: 51-70; 1990 quoted in another context in the reference list here) but has since been shown by the group at McMaster (see ATS Abstracts) to occur across Canada. It is independent of air pollution, but may interfere with ongoing panel studies by obscuring an association with air pollution during other periods of the year. See Gent et al 2003 quoted here for a September asthma peak not detected by the authors which might have affected their ongoing panel study. See annotation of the Gent study also in the second paragraph on Page 12-5.

Page 12-3:

In relation to data on PM_{2.5} and ozone in Mexico City, see comment above under Page 11-211:

Page 12-4:

A comment should be added to the note on Brauer's study that the ozone exposures were measured by personal badges as well as by an ozone monitor very close to the workers.

Page 12-7:

The recent study by Hall et al of the economic costs of school absences, based on the Gilliland study, might be noted here.

Page 12-23:

I was surprised that no mention was made of the Atlanta study:

FRIEDMAN, M.S., POWELL, K.E., HUTWAGNER, L., GRAHAM, L.M., & TEAGUE, W.G.

Impact of changes in transportation and Commuting behaviors during the 1996 Summer Olympic Games in Atlanta on Air Quality and Childhood Asthma
JAMA 2001; 285; 897-905

For many people, the documentation of a reduced adverse health effect synchronous with a reduced ambient ozone level constitutes very convincing evidence that the data being derived from epidemiological associations is real. My own opinion is that this study deserves special emphasis, not least when the effect of a possible "standard" is being discussed.

Page 12-25:

This comment on the Petroeschovsky study in Brisbane fails to make two important points, first that it involved over 13,000 hospital admissions for asthma, and second that aerosol sulfates were not present so the effect was due to ambient ozone alone.

Page 12-39:

Last paragraph: "On this issue, the evidence is fairly supportive of independent effects for ozone". This is too weak a statement in my opinion. It should read: "On this issue, the evidence is conclusive that ozone is responsible for exerting direct effects" – see data from Mexico City and from Brisbane and Atlanta already discussed.

FINAL COMMENT:

This is a well written and remarkably comprehensive Review and I congratulate the authors on it. The suggestions I have made above are generally minor in a document of this size. I would hope to see the authors discuss the implications of different levels of a standard, such as pointing out that adverse effects of maximal exercise in 0.06 ppm of ozone would be expected, but that if this level were not exceeded, it is probable that direct associations between school absences or hospital admissions would not be demonstrable.

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