



Community and Environmental Medicine
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Irvine, CA 92697-1825

December 5, 2006

Dr. Richard Bode
Research Division
California Air Resources Board
1001 I Street
Sacramento, CA 95812

Sacramento, CA

Dear Dr. Bode:

The Air Quality Advisory Committee met on June 12 and 13, 2006 to evaluate the draft document "Scientific Basis of the California Ambient Air Quality Standard for Nitrogen Dioxide." 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 (OEHHA) made an analysis of the findings and recommended a list of standards that required re-review. The OEHHA analysis was deliberated by AQAC in a public meeting and the list of standards to be reviewed was prioritized. The standard for nitrogen dioxide was among those that were identified for review.

The committee went on record to complement the staffs of the ARB and OEHHA for performing a very comprehensive and careful compilation and analysis of the peer reviewed literature on sources, monitoring and health effects of ambient nitrogen dioxide. In most respects, the committee was pleased with the Technical Support Document "Scientific Basis of the California Ambient Air Quality Standard for Nitrogen Dioxide" and the Staff Report in which recommendations were made for modification of the existing standard.

Based on its review of the Staff Report and the Technical Support Document the Air Quality Advisory Committee endorses the Staff recommendations for a long term Standard

- Annual Average NO₂ at 0.030 ppm
- Not to be exceeded

The Committee also endorses the reduction of the 1-hr standard to a level below the current 0.25 ppm NO₂ and agrees with the Staff Report's recommendation of a 0.18 ppm 1-hr average standard (not to be exceeded). However, the committee requests expanded documentation to support the contention that this level of standard provides an adequate margin of safety for sensitive populations.

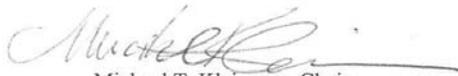
While the Committee endorses a 1-hr standard as the appropriate averaging time to capture acute events, the Committee suggests that the NO₂ monitoring network be realigned to provide better spatial resolution and include monitoring of "hotspots" and that ARB consider conversion of the form of the standard from ppm(v) to ppb(v) to avoid ambiguities due to rounding

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 nitrogen dioxide and its effects on human health, and in establishing a set of ambient air quality standards that will better 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 nitrogen dioxide on fetal and neonatal development, and that the nitrogen dioxide 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 on the Scientific Basis of the California Ambient Air Quality Standard for Nitrogen Dioxide

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 nitrogen dioxide (NO₂). The review provided a firm basis for establishing the needs for modification of the current NO₂ air quality standards and the committee was unanimous in its appreciation of the effort and diligence involved in producing the report.

The Air Quality Advisory Committee (AQAC) has 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.

In conducting its review the Committee specifically considered whether the documentation adequately addressed:

- The extent of evidence of effects at or below the existing ambient air quality standard.
- The nature and severity of those effects.
- The magnitude of risk when ambient levels are at or near the level of the existing standard.
- The available evidence that children may be more susceptible than adults.
- The degree of outdoor exposure relative to the level of the standard.

Children's protection, with an adequate margin of safety, is of paramount importance to public health. As the committee report indicates, this is an area in which more work is needed. 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 on health effects in these potentially susceptible groups. Since asthma affects nearly 10% of the child population, the effects of NO₂ on this group is of special importance. Having said this, the committee was particularly impressed with the efforts taken in the preparation of the reviewed documentation to thoroughly evaluate what is presently known about the effects of NO₂ on the health of children.

A previous evaluation of the health protection afforded by the current ambient air quality standards in California was mandated by SB25. The SB25 review which has been previously published identified clinical and epidemiological studies that suggested effects of NO₂ on pulmonary function, asthma exacerbation and acute morbidity in children and adults at or below the 1-hr CA standard of 0.25 ppm. Accordingly OEHHA and ARB staff have compiled and critically reviewed the scientific literature to determine whether:

- The current NO₂ standard provided an adequate margin of safety,
- A different averaging time was warranted.

In the Technical Support Document that was prepared, the published literature information was integrated and interpreted and the potential for exposures was assessed, the individuals at risk were identified, the potential health outcomes were determined and recommendations were made to establish new air quality standards that will better protect health for California citizens.

Based on its review of the Staff Report and the Technical Support Document the Air Quality Advisory Committee endorses the Staff recommendations for a long term Standard

- Annual Average NO₂ at 0.030 ppm
- Not to be exceeded

The Committee also endorses the reduction of the 1-hr standard to a level below the current 0.25 ppm NO₂ and agrees with the SR recommendation of a 0.18 ppm 1-hr average standard (not to be exceeded). However, the committee requests improved documentation of the support that this level of standard provides an adequate margin of safety for sensitive populations. While the Committee endorses a 1-hr standard as the appropriate averaging time to capture acute events, the Committee suggests that the NO₂ monitoring network be realigned to provide better spatial resolution and include monitoring of “hotspots” and that ARB consider conversion of the form of the standard from ppm(v) to ppb(v) to avoid ambiguities due to rounding

The Committee has identified some issues that should be addressed in a revised Technical Support Document. These issues are presented below.

Critique

Chapter 1.

Chapter 1 provides summary information of historical interest. Current Standards were summarized. The NAAQS provides an annual NO₂ standard but does not include a short term standard. CA currently has a short term but not a long term standard.

Standard	1 hr (ppb)	Basis	Annual (ppb)	Basis	Comment
NAAQS			53	Arithmetic mean of 1-hr measurements	
WHO	106		21		Guidelines
CA (Current)	250	1hr Arithmetic Mean			Not to be exceeded
CA (Proposed)	180	1hr Arithmetic Mean	30		Not to be exceeded

It would be appropriate to include in the summary the rationale for not having a Secondary standard. This might be an important consideration since in Chapter 2 the large contribution (50% during winter in SC basin) of NO₂ to fine secondary PM formation is discussed. In the Staff Summary of Welfare effects, visibility degradation which might be a basis for a secondary standard it was determined (1992 review) that meeting the 250 ppb NO₂ standard would adequately protect against visibility degradation because “the majority of the effect was due to fine particulate matter.” The reduction to 180 ppb will reduce visibility impacts further and this could be mentioned as an added potential benefit of the proposed standard.

Chapter 2.

Chapter 2 discusses issues of atmospheric chemistry. The complex interplay between NO₂ and other components of the atmosphere such as NO (the other portion of NO_x), ozone, particulate matter and VOCs is described in good detail. Future research will undoubtedly refine details, but NO₂ physics, chemistry, measurement, sources and sinks are all adequately well understood to regulate, and this review thoroughly covers the topics needed for updating and establishing new regulations. The section on visibility impairment (2-9) separates the direct light absorption of the gas from that of the secondary aerosol. It would be very useful to indicate NO₂-related PM contribution and what the effect would be of lowering the CA short term standard to 180 ppb.

Specific Comments

1. Definitions of NO_x and NO_y
 - o should be defined carefully and consistently (they are not--see pp. vii, 2-11, 3-1)
 - o should be defined when the term is first used in each chapter (e.g., p. 2-2 needs NO_x definition)
2. p. 2-2. last sentence in the 1st paragraph after equation 2; this sentence is awkward (although technically correct, "remainder" usually refers to the smaller portion, not 90%)
3. Make sure all equations are balanced (e.g., see p. 2-2, equations 2 and 3)
4. p. 2-4, section 2.3.2, 1st paragraph, last sentence--drop "Thus"
5. p. 2-4, next to last line:improve "in this chemistry" (perhaps with "similar reactions")
6. p. 2-15, 4th line: do the authors really mean NO_x?
7. p. 2-15, section 2.9, 8th line--get correct Section number

Chapter 3.

Chapter 3 deals with measurement methods and endorses the chemiluminescence method as the approved method in CA. Measurement of NO₂ is well-defined, sensitive, quantitative and selective. To avoid the need for correction due to elevation or weather changes in barometric pressure, it is appropriate to continue measuring, reporting and regulating in units of volume fraction – rather than mass concentration such as ug/m³. For clarity, it might be helpful to move toward uniformly using ppb(v) units (for

example: 180 for 1 hour, 30 for annual average) -- rather than ppm(v) which requires a trailing zero that can lead to confusion about rounding/truncating data and hence determining resulting exceedances. The literature uses both ppm(v) and ppb(v), as with ozone, so either is acceptable. The measurement precision is not discussed. What is the degree of uncertainty around a 1-hr average concentration? Given that the standard is listed as “not to be exceeded”, an analysis of precision vs. the expected number of exceedances at the level of the standard might provide useful guidance. Also in Chapter 5 the calculation of a “peak indicator value” which is used to exclude “extreme concentration events” is discussed. How does measurement error and instrument precision factor into the peak indicator value?

Chapter 4.

Chapter 4 discusses sources and emissions. The report adequately describes the combustion sources of NO₂. It would be appropriate to also discuss non-combustion sources of NO, which inter-converts with NO₂. There are entirely natural (sometimes called biogenic) emissions from soil, grasses and trees, as well as anthropogenic non-combustion sources, generally in the area of managed annual and perennial plants, as well as animal agriculture. These processes include fertilizing, composting, feed and waste management, etc...and including non-commercial activities such as gardening. As management of combustion sources steadily improves, non-combustion sources will rise in relative importance. Natural/biogenic sources must be included since they contribute to the background, even if they are relatively uncontrollable; managed/anthropogenic sources must be included since they are becoming a larger factor on a relative basis – and possibly even on an absolute basis in some regions and/or seasons. Improving the summer-time ozone problem in the San Joaquin Valley will probably only be achieved with reductions in NO_x. One could therefore mention that NO₂ regulation will have a secondary benefit i.e. reducing ozone and PM, and may actually be essential. It is clear from the data that the fractional contribution of mobile sources to ambient nitrogen emissions is decreasing. Stationary source emissions are expected to increase slowly over the next few decades due to population pressures. How the projections were made is not presented. Were changes in fuels considered given the increased costs and decreased availability of the fuels currently in use? The extent to which these changes are driven by NO₂ regulations per se or by reductions in combustion emissions related to reduction of PM could be made clearer.

Specific Comments

1. p. 4-1 and 4-2--same sentence repeated (1st sentence of 4.1.1 4th sentence of 4.2)
2. the graph on p. 4-2 and figure on p. 4-3 are difficult to read

Chapter 5.

Chapter 5 discusses ambient air quality with respect to NO₂ for CA. Data for each air basin in the state are presented. The discussion however centers on overall trends and ignores the increasing trends in the North Central Coast and Sacramento Valley basins.

General Comments

An explanation of the peak indicator needs to be moved from 5-43 to 5-3. It is not clear why the Statewide average of maximum 1-hr NO₂ is greater than in any of the individual air basins. Tables 5.3 and Figure 5.4 need some explanation of this.

Table 5.1 shows all air basins in CA average below the proposed annual average standard of .030 ppm, but presumably the standard has to be met at every monitor? If so, then data for individual monitors should also be shown. Table 2 in the staff report shows several monitors in the South Coast district exceeded 0.030 ppm in 2004.

Chapter 5 reports that no districts are out of compliance with the current 1-hour standard after adjustments for the Expected Peak Daily Concentration (EPDC), but it does look like Salton Sea and South Coast districts are at risk of exceeding the proposed new 1-hour standard. However, Table 5.7 shows that the EPDC based on 3 years of data is below the proposed new hourly standard in all districts.

Data reported in Chapter 3 show declining concentrations of NO₂ in most districts, and especially in those that have been reducing emissions to meet the federal standards for PM and ozone. Reducing NO_x emissions is one of the strategies being used to meet the PM and ozone standards, because NO_x is a precursor to both PM and ozone.

All of this means that the new standards are either currently met or not far out of reach and may be met soon as a result of efforts to meet the PM and ozone standards. The standards are supposed to be health and welfare based so this is not a limiting consideration, but as a practical matter the effect of these changes to the standards will be mostly to encourage districts to continue to reduce NO_x emissions as part of their strategies to meet PM and ozone standards.

Section 5.5 presents an Analysis of Peak Nitrogen Dioxide Exposure in California. This section used inverse-distance weighting (IDW) from monitor location to estimate population averaged exposures. However, actual population exposures are likely to be higher on average because of in-vehicle and other personal exposures, and more importantly because a subpopulation will have high exposures simply based on proximity to sources such as traffic that are not included in the IDW model. This results in over-smoothing of the true spatial pattern of exposure (see Jerrett 2005, JEAE 15:185-204). Some estimate based on this should be included given the indication from the epidemiologic studies that NO₂ effects are found at concentrations much lower than standards. NO₂ is serving at least in part as an indicator for traffic and other sources of unmeasured air pollutants. The spatial distribution of NO₂ secondary to traffic should receive some additional attention (see below).

Section 5.7.1.5 starting on page 5-74, presents important information on the spatial variability of ambient NO₂ concentrations. The information presented suggests that because NO₂ reacts quickly in the atmosphere, central monitors may not fully reflect concentrations relevant for the population living, working, or attending school near major traffic sources. An important topic for future research is whether the exposures measured at stationary monitors are sufficiently protective of public health. The report notes that 10% of public school children spend their school days within 150 meters of a busy road. Given the apparent effects of NO₂ exposure on lung function development, it will be important to determine whether this population is adequately protected by these standards. There probably are not sufficient data available at this time to answer this question, but it is important for ongoing research.

Specific Comments

1. Pg 5-3 Para 3 L 4- Peak indicator was not previously described. The information from 5-43 should be placed here.
2. Pg 5-12-Section 5.4.3, first sentence: it's NO₂ not ozone. It's 0.25 not 0.025 ppm.
3. Pg 5-14 Para 2 L1– Table 5.3 (not 5.4).
4. Pg 5-15 The note on Table 5.3 is not clear. Are these ppm concentrations or counts?
5. Pg 5-55 Section 5.6.2.1.1 *Concentrations in Homes*: What is meant by “Indoor/outdoor NO₂ ratios were positively associated with the community”?
6. Pg 5-74 Section 5.7.1.5 *Spatial Variability of NO₂ Concentrations*-This section was limited compared with the long section on indoor sources. Given that the ambient standard is the topic of concern, it would be appropriate to place a considerably larger emphasis on how spatial variability affects the inaccuracy of NO₂ measurement at stations in relation to population exposure. Additional information from the Singer 2004 study for instance would be helpful. They found a school located directly adjacent to a major freeway and a shopping center showed normalized NO₂ and NO_x were around 60% and 100% higher than regional background levels. At three schools within 130–230m downwind of a freeway, normalized NO₂ and NO_x were around 20–30% and 50–80% higher than regional levels. The levels at the regional site in the East Bay study would underestimate their exposure. Given that children are a susceptible subpopulation, this is an important issue. Wu et al found overall within-community variability of personal exposures was highest for NO₂ (+/- 20-40%), and that traffic was a major determinant:

Wu J, Lurmann F, Winer A, et al. Development of an individual exposure model for application to the Southern California children's health study. *ATMOSPHERIC ENVIRONMENT* 39 (2): 259-273 JAN 2005.

Ross et al reference below was not discussed. This that might shed more light on spatial variability:

Ross Z, English PB, Scalf R, et al. Nitrogen dioxide prediction in Southern California using land use regression modeling: potential for environmental health analyses. JOURNAL OF EXPOSURE SCIENCE AND ENVIRONMENTAL EPIDEMIOLOGY 16 (2): 106-114 MAR 2006

Chapter 6.

Chapter 6 describes data from controlled human exposures. These data are used as the primary basis for reducing the short term standard from 250 ppb to 180 ppb. The chapter adequately discusses the recent toxicology information available.

General comments

It would be good to be a bit more consistent about the meaning of the variable findings in some subjects with asthma. The wording in section 6.1, paragraph 3 (e.g. "...suggest that some individuals experience increased airway responsiveness to NO₂ in the range of 0.2-0.3 ppm" seems more on target than the wording on page 6-18, para 3 "These recent studies involving allergen challenge appear consistent in demonstrating effects...." Otherwise, the chapter did an excellent job of capturing a challenging body of literature.

Specific Comments

P6-7, para 3 The description of effects of IL-5 and IL-13 is slightly inaccurate. These are cytokines produced by Th2 lymphocytes, but neither "can induce a Th2 response in T helper cells." Actually, T cells don't express receptors for these cytokines. IL-4 is the major cytokine that induces Th2 cell differentiation.

P6-16, para 4. Do you mean "decreased peak flow" rather than "increased"?

P6-24, para 2 – The statement that "The divergence of findings from various studies suggests that some individuals with asthma are particularly susceptible..." might be overstated. It might be preferable to simply say "...suggests that some individuals with asthma might be particularly susceptible...."

Chapter 7.

Chapter 7 presents an evaluation of the epidemiological data reviewed.

General comments:

Overall, this is a comprehensive review of the epidemiologic literature on NO₂. It points to well-known methodological weaknesses that are inherent to the study of ambient air pollution in free-living human populations, or weaknesses that have not been addressed yet by researchers. None of these weaknesses takes away from the coherence of the

epidemiologic evidence with the clinical and toxicological data. The choice of an NO₂ standard based on susceptible populations is well supported by the evidence presented. Susceptible subpopulations were clearly identified in several reviewed studies, including children with asthma, infants, patients with pre-existing cardiovascular or respiratory disease, and the elderly. The time series studies evaluating the relationship between hospital admission or ED visits and asthma in children were remarkably consistent and robust for NO₂. Often in the face of significant particle associations, the associations with NO₂ remained after inclusion of the particle measurements. The chapter's organization could be improved by adding some summary figures or tables that provide an overview of the available science.

An important issue discussed was that in many of the epidemiologic studies, NO₂ is likely acting as good indicator of the complex gas-particle mixture originating from vehicular traffic. Depending on the region, other important sources significantly contribute to this mixture (e.g., ports). What is important in this concept is that the regulatory standards currently used focus on a very limited set of pollutants, most of which are in part surrogates of other potentially more harmful pollutants. The ultimate focus of air pollutant regulation is rightly on sources, and the ability of the pollutant to function as an indicator of sources is important in this regard, apart from its independent effect on health.

The summary conclusion 7.3.1.1 after the text on cohort studies is inaccurate and misleading. It reads as follows:

“The studies in this review show little evidence for effects of long-term concentrations of NO₂ on prevalence and/or incidence of asthma, allergic rhinitis, and atopic eczema. For asthma diagnoses and symptoms, two cross-sectional studies show positive and three show negative associations.”

The summary conclusion does not reflect what is in Tables 7-10. The word negative is not correct. It might be better to refer to the findings as “null”, and the count does not reflect the tables. The Table shows no negative associations and in general, the ORs or RRs are positive but not always statistically significant. The words “little evidence” is misleading. For instance, in the case of allergic sensitization, the words should be “there are few studies.” Describing the literature as “little evidence” suggests that many studies find no association. The one cross-sectional study (Janssen 2003) with high power showed associations between NO₂ and total IgE and positive skin prick tests to allergens. This finding was consistent with the robust findings of the smaller study by Kramer et al. 2000 for atopic sensitization and allergic rhinitis in relation to outdoor home NO₂. The conclusion about the surrogate nature of NO₂ holds, but does not diminish its usefulness in the regulation of unmeasured and largely unregulated air pollutants that NO₂ probably represents. The CHS findings for OC and EC (solely measured for the CHS) along with NO₂ further support that view.

The authors have been very careful to acknowledge the limitations of the epi literature in terms of being able to specifically identify NO₂ as the causative pollutant. The co-occurrence of the set of traffic-related pollutants that includes NO₂ is the primary

difficulty. However, it is clear that this mix of pollutants is associated with adverse health effects. When the epi results are considered along with the clinical and toxicological evidence, there is reasonable support for the conclusion that NO₂ is at least one of the harmful constituents of this mix. This is a prudent interpretation of the evidence in terms of protecting public health.

The epidemiology results are strongest for an association between NO₂ and respiratory illness, especially asthma exacerbations. This is consistent with the evidence from the clinical studies. These associations are observed in the epi studies at ambient concentrations that exist in CA.

Gauderman et al. (2004) and related studies seem especially important because they suggest lung function development decrements in children over an 8-year study. This is a very serious effect that is a risk factor for chronic disease and premature mortality later in life. This elevated risk is observed at long-term concentrations of 25-30 ppb, which exist in some CA locations. Questions regarding co-pollutants are still important, but this association is consistent with toxicological study results showing adverse effects of NO₂ on lung function development in some animal studies. It is also important to note that this effect could lead to premature mortality, but it would not show up in time-series mortality studies because it is a function of childhood exposure, not short-term exposure fluctuations.

It should be pointed out that little is known about the impact of NO₂ inhalation on vulnerable pediatric populations which include the fetus, infants born prematurely, newborn infants, early infancy, infants and children with chronic lung conditions, such as chronic lung disease of infancy (BPD), cystic fibrosis, interstitial lung disease. The target population usually studied in assessing the response to inhaled environmental pollutants has been healthy children, usually older than 7 years old, who are often compared to children with asthma, a surrogate for children with airway or lung disease. These studies are difficult to interpret due to the grouping of the children and adolescents who cough and/or wheeze in the same study without controlling for sex, race, socio-economic status or age groups [0-1 year, 1-2 years, 2-5 years, and 5-13 years]. There are developmental and physiological reasons for the necessity to study children in these age groups. First, establishing the diagnosis of asthma in young children prior to the age of 4-5 years old is difficult, often impossible, even those with atopy or a family history of asthma. Wheezy bronchitis is common in infants and young children from birth to 4 years. In fact, of the infants and young children [less than 4 years old] with chronic or recurrent cough or wheeze, less than 25% will have persisting cough or wheeze by 5 years of age. Some reasons for this diagnostic dilemma are:

1. boys being born with smaller airways than girls (Taussig), making cough and wheeze more common in infant males than females during and following routine respiratory tract infections. In the first two years boys airways grow more rapidly than girls so that after 2 years of age airway caliber of males exceed that of females of the same age, so that after 2 years old females experience more cough and wheeze than females;

2. the lack of a specific serologic or lung function test to make the diagnosis asthma which makes the diagnosis of asthma problematic in the child less than 4-5 years of age in the absence of a strong family history.
3. Difficulty in performing reliable pulmonary function tests in very young children.

Specific comments:

P 7-1: Clarify the comment about epidemiologic studies that:

“it is not possible to quantify exposure for individuals, as is commonly done in chamber studies.”

I assume you are excluding personal exposure monitors because hourly sampling is not yet available.

For 95% CI, I would suggest using commas to separate upper and lower limits instead of dashes. Some journals do this to avoid the misinterpretation of interval sign and to make reading easier.

P 7-6, bottom: The following sentences are unclear

“For asthma, a stronger effect was detected considering distributed lag models (lags 0 to 13 days), with PM₁₀, NO₂ (4.7% for 20 pbb, 95%CI=1.1-8.5%), and CO, showing a statistically significant effect.”

Suggest separating out the numbers for the NO₂ association.

“In multipollutant models, the NO₂ effects were attenuated when PM₁₀, NO₂, and CO were considered simultaneously. However, the effect of NO₂ on emergency visits for asthma was not attenuated in multi-pollutant models while the estimates for the other pollutants suggested weaker or no associations.”

Attenuated or not?

Throughout, for the time series results, there was a shift in the use RR and % change. For instance, in the text on page 7-7, results for Simpson et al. 2005 are in RR, but the table on p 7-52 is in % and not consistent if $100 \times \text{RR} = \% \text{ change in admissions}$.

Last line and word p 7-9: typo.

P 7-11 last paragraph: should be “...after adjusting for outdoor pollens and fungal spores.”

P 7-13: Just et al, 2002: Larger associations were seen between respiratory infections and NO₂ and BS. This is missing in text and table.

P 7-13: Moshammer et al 2006: This is a general population study of children as noted in Table 6. There is no information about clinical status, so this paper does not belong in a section on children with asthma. It is nevertheless important that they did find lung function deficits in relation to increased NO₂. There are several other studies that have studied otherwise healthy children or mixed populations, although the clinical relevance is lessened by this approach to sample selection.

Table 4 and related section: The two outcome and age groups are unrelated and is confusing to see asthma in children combined with arrhythmias in adults. Panel studies of medication use in asthmatic children is separated but would be more appropriately combined with the other panel studies of asthmatic children looking at a variety of other outcomes. The section could be “Panel Studies” and then subsections with the outcome groups as presented, including General Population and Other Pediatric Panels.

Table 6: Lung function in Asthmatic Children: Again, the title is inaccurate since many of the studies were not of asthmatics. In addition, nearly all studies have only looked at PEF, an inaccurate measurement of large airway function compared with FEV₁. Therefore, it is important to report in Table 6 and the text on panel studies using FEV₁, which are few in number. The review missed two recent papers in this regard:

- 1) 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.

Delfino et al (2004) followed a panel of 19 children with asthma for two weeks with personal PM nephelometers. They found central-site 5-day average 8-hr maximum NO₂ was inversely associated with percent predicted FEV₁ (per IQR increase in NO₂ of 10.5 ppb, -1.16%; 95% CI, -2.4 to 0.1), and associations were similar for the 3- and 4-day average and for 1-hr maximum NO₂. However, NO₂ was confounded by personal PM with parameter estimates falling near zero. Associations of FEV₁ with personal PM were largely independent of NO₂.

P 7-13, Cardiovascular Effects: An important paper was left out that is currently the only repeated measures study of ECG-measured ST segment depression. This is important because transient myocardial ischemia is clinically and/or biologically relevant to more severe outcomes such as MI:

- Pekkanen J, Peters A, Hoek G, Tiittanen P, Brunekreef B, de Hartog J, et al. 2002. Particulate air pollution and risk of ST-segment depression during repeated submaximal exercise tests among subjects with coronary heart disease: the Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study. *Circulation* 106:933-938.

This was a study of 45 adults with stable coronary artery disease that analyzed data from repeated biweekly in-clinic ECG measurements during submaximal exercise testing and outdoor ultrafine and fine particles measured at a central regional site of Helsinki, Finland. They found significant associations between risk of ST segment depression and ambient lag 2 day PM_{2.5} mass (OR 2.8, 95% CI: 1.42, 5.66). Similar magnitudes of association were found for ultrafine and accumulation mode particle number concentrations, but smaller but significant associations were also found for lag 2 day NO₂ (OR 2.02, 95% CI: 1.34, 3.04) and CO (OR 1.73, 95% CI: 1.26, 2.39), which were moderately correlated with the co-located particle measurements. Two pollutant models for PM and gases were not tested.

Table 7 and 8 titles would be clearer to contrast with 9 and 10 if it was “between-community”

Pp 7-66 to 7-67: ORs are for what increase in NO₂ in ppb?

P 7-17 statement: “In a West German study (Kramer et al. 2000), outdoor levels of NO₂, ...” To be clear, it’s outdoor home, a point that strengthens the following statement in the text on the importance of traffic given the null results for personal NO₂.

Table 9, Kramer: The report is somewhat inaccurate since I believe it includes the rural subjects, which biased estimates downwards. Here is what I found:

Associations were dominated by the urban subgroup as follows:

Outdoor home NO₂, but not personal NO₂, was significantly associated with reports of at least 1 week with symptoms of wheezing: OR for 10 µg/m³ increase, 14.9 (95% CI, 2.59, 86.4); and with symptoms of allergic rhinitis: OR 1.81 (95% CI 1.02, 3.21), which in pollen season increased to OR 3.09 (95% CI 1.38, 6.92).

An ever diagnosis of hay fever was associated with outdoor NO₂, OR 4.24 (95% CI: 1.01, 17.8), asthma was not, OR 1.82 (95% CI : 0.36, 9.36).

Atopic sensitization to pollen, house dust mite or cat, and milk or egg were each significantly associated with outdoor NO₂ (ORs ranged from 3.5 to 5.0), but not personal NO₂. (see text and Figure 2 in Kramer).

P 7-23, statement: “In addition, more localized panel studies could be used to attempt to separate the effects of NO₂ from other pollutants.” I hope to provide the committee with results from my panel study currently under review that makes notable advances in this area using eNO from asthmatic children in relation to personal and ambient NO₂, PM_{2.5}, EC and OC.

Chapter 8.

Chapter 8 deals with toxicology of NO₂. The chapter is well written but most of the real information is contained in the Appendix. The information from the Appendix should be incorporated into the body of the TSD. The brief presentation made to the Committee provided a very good overview of the key factors and salient features of that presentation should be added to the TSD also. The chapter mentions dosimetry, but the use of dosimetry for bridging between data in animal models to application to humans needs to be discussed. For example the TSD mentions that estimation from Miller et al. suggests that, for the same exposure, the dose to the rat’s epithelium would be ¼ of that delivered to a human’s. The Miller modeling should be checked but, if correct, one could use such information to put the data from rat studies at concentrations from .5 to 5 ppm NO₂ into context of “equivalent” human exposures at ~0.1 to 1 ppm. This suggestion is obviously an oversimplification of a very complex issue – the Committee provides it as an example of one method to strengthen the link between the mechanistic studies available from toxicological studies to possible mechanisms in humans. It would be useful to mention that while there are some areas in which specific mechanisms in rodents might differ

from those in human and non-human primates, there are several biological pathways that are sufficiently similar that useful comparisons can be drawn.

Since the mandate for this review was specific for the health/welfare of infants and children, it would be helpful if this chapter emphasized the issues that are specific to infants and children such as: growth, proliferation, differentiation, respiratory rates/pulmonary functions, time/activity outdoors. This then leads into a discussion of choosing the proper model and the advantages and limitations of available models. Also, since allergic/asthmatic individuals are discussed, some discussion regarding proper choice of the immunologic models would be helpful.

Also, some mention of *in utero* exposures and issues would be helpful (if for no other reason than to highlight the lack of information available).

Specific Comments regarding the Appendix:

Page A-3-5: The dosimetry section is well-written, but under utilized. This information could be used to help extrapolate the doses used for the animal studies (especially since the animal tissue dose is 2-4 times less than humans). It could be useful to point out that after taking dosimetry into account a rat study at 0.25 ppm is approximately equivalent to a human study at 0.0625 to 0.125 ppm.

Page A-4, last ¶: Is there a reference for measuring reduction in lung lining fluid thickness in distal airways? Was this inferred or actually measured?

Page A-5-6: Clarify whether this refers to tissue or BAL effects. Also, it would be helpful to contrast the kind of information that can be obtained from BAL vs. tissue (i.e. site-specific data vs whole lung data).

Page A-6: 1st full ¶: line 6: define “continuous” exposure (also p9, 2nd ¶, line5). If “continuous” actually means 24 h/day, then these studies should be moved to a separate section and given little weight. A continuous exposure will result in an adaptive or tolerant pulmonary response completely different from the response to a more realistic intermittent or episodic exposure.

Page A-9, lines 6-7: It would be helpful to specify which studies in the 1992 review were used.

Page A-10: ferret work: Please discuss the appropriateness of the ferret as a model. For example, the lung development of the ferret may be similar to the human, but it would be appropriate to mention that their long trachea can scrub out pollutants before they reach the lungs, therefore underestimating the effective dose in extrapolation.

Page A-11: In vitro studies: need to clarify that the morphological lesions for NO₂ are *focal*, therefore caution should be used in interpreting negative data from BAL or whole

lung homogenates (the small percentage of tissue affected may be overwhelmed by the large percentage of tissue not affected in these non-specific methods).

Page A-11: In vitro studies, 1st ¶, last sentence: What studies specifically in the 1992 review are being referenced?

Morphological data should come first in the Tox studies. Knowing *where* the injury is will affect how the biochemical effects are interpreted.

Page 26: 4th ¶: same issues for morphological affects in ferret as described above.

Page 26-27: The study of newborn mice with the structural changes should be placed to have more emphasis.

Chapter 9.

Chapter 9 discusses effects on vegetation. Welfare effects are not being used as the basis for the proposed changes in the standards, but it is important to note that some welfare benefits are likely to occur as a result of reducing NO₂ emissions (or preventing increases), especially in the South Coast and Central Valley areas. The summary statements in the Staff Report (p. 13-14) are too weak on this and unnecessarily suggest minimal benefit.

Chapter 9 focuses a lot on foliar injury and it may be that most areas do not have ambient concentrations of NO₂ sufficiently high to cause visible foliar damage. However, a more significant ecosystem concern is total nitrogen deposition. This is discussed in Chapter 9, but not carried over to the summary in the Staff Report. The discussion on page 9-23 suggests that critical loads (deposition rates that can be tolerated without harmful effects on an ongoing basis) for California mountain ecosystems may be higher than in other locations, but the specific critical loads for these areas have not been established. Nitrogen deposition rates reported in Figure 9.5 are some of the highest in the country. NAPAP (2005) reports that the highest annual total nitrogen deposition rates in the Midwest and Northeast range 8-11 kg/ha/yr. Figure 9.5 shows rates at 9 kg/ha/yr or higher (up to 97.5!) at multiple sites in Sequoia, Angeles, and San Bernardino National Forests. The superintendent of Rocky Mountain National Park recently proposed a critical load standard of 1.5 kg/ha/yr for the park because it is now showing signs of nitrogen saturation (with annual N deposition rates in the range of 3-4). NAPAP (2005) notes evidence of elevated concentrations of nitrate in surface and ground water in the San Gabriel and San Bernardino Mountains, which suggests possible N saturation in those forests. Reducing NO₂ emissions, especially in the South Coast basin, will result in reduced nitrogen deposition and this can be expected to benefit the forest ecosystems and reduce nitrogen concentrations in surface and ground water.

National Acid Precipitation Assessment Program. NAPAP Report to Congress: An Integrated Assessment. Washington DC, August 2005
<http://www.al.noaa.gov/AQRS/reports/napapreport05.pdf>

Staff Report and Recommendations.

The SR is generally well written but some areas need to be improved. There is no discussion of whether or not there is a threshold for NO₂ effects. There are some articles that were not cited in the TSD that could be added. Samoli and Vedal, respectively, discuss epidemiological data from European and Canadian studies (Samoli *et al.*, 2003; Vedal *et al.*, 2003) that provide some discussion on the identification of thresholds and why measurement errors could obscure detection of a threshold. Another factor that could be mentioned is that if a contaminant was a surrogate for another contaminant a threshold might not be detectable. Vedal *et al.* report that “increases in air pollutant concentrations, even when concentrations are low, are associated with adverse effects on daily mortality. Although this observation may support the argument that there are no threshold concentrations of air pollution below which adverse effects cannot be detected, it also raises concern that the associations are not reflecting the effects of the measured pollutants, but rather some factor or combination of factors, such as, for example, unmeasured air pollutants or uncontrolled features of meteorology that are correlated with the measured pollutants.” The APHEA-2 data (Samoli *et al.*, 2003) was unable to detect a threshold (i.e. a linear non-threshold model could adequately describe the data), however they provide the caution “The NO₂–mortality association in the cities included in the present analysis could be adequately estimated using the linear model. However, it became evident that the linear model should not be applied without investigating the city specific dose-response curves first.”

The committee endorses the addition of the long term 30 ppb annual standard and also endorses the “not to be exceeded” form of the proposed standard. The short term standard is based primarily on human clinical studies rather than on epidemiological studies. The TSD and SR both make the point that effects are relatively robust at or above the current 250 ppb standard but that some studies also demonstrate significant changes at levels of about 200 ppb. Data used in Germany to set a short term standard (Kraft *et al.*, 2005) showed effects down to about 200 ppb but effects on patients with mild asthma were not observed after short-term exposure to concentrations below about 100 ppb. This is consistent with the data summarized in the TSD. The logic applied to arrive at the proposed lowered short term standard (180 ppb) needs to be better described. The criteria for assuring an adequate margin of safety should be transparent. There is a dilemma in that the epidemiological data could be interpreted as indicating that a lower short term standard is warranted. However the committee also recognizes that causality in the epidemiological studies is difficult to ascribe solely to NO₂, hence the use of the chamber studies to develop the standard is acceptable. The committee is also concerned that the location of the NO₂ ambient monitors is not adequate to provide protection to individuals living in “hot spots.” The relocation of monitors to provide better spatial representation of NO₂ exposures in each of the air basins, similar to the approach used for CO, would benefit protection of public health.

The welfare benefits of controlling NO₂ could be expanded. On page 14 the Staff Report suggests that there may be little improvement in visibility as a result of the reduction in the NO₂ standard. It was mentioned that the 0.25 hourly standard was expected to be protective of the discoloring effect that NO₂ causes (the brown color to the air). Has it really been established that there is no brown color at concentrations below 0.25 ppm? Also, the statement that most of the haze is caused by particulate fails to acknowledge that NO₂ emissions contribute to the formation of secondary particulate. Thus, some visibility improvements can be expected as a result of further reduction in NO₂ emissions even if the discoloration is no longer an issue.

APPENDIX

Some members of the committee provided extensive comments which were integrated into the above summary. This necessitated extraction of material for insertion into comments on specific chapters. To ensure that the sense of these comments was not lost, they are included below in their entirety.

Individual Member Comments

Russell P. Sherwin, M.D.

A first consideration for standard setting is a definition of adverse health effect. I believe the definition should encompass the following major areas of concern: Mortality, Morbidity, and Morbidity, the latter including clinically covert disease (subclinical disease), pathobiological alterations, and the depletion of health reserves (hypopenia). With respect to the body of data presently available that address a large part of those concerns, I wish to commend the Staff for their excellent work in reviewing the vast amount of literature regarding the adverse health effects of ambient levels of nitrogen dioxide. In my opinion, the data presented in the Staff Report fully support the Staff's recommendations for a 0.18 NO₂ one-hour and a 0.03ppm yearly average standards. A reservation in the latter respect is an understatement of Morbidity concerns. Some degree of Morbidity in the form of serious subclinical disease is ubiquitous in the adult population and is reflected in the large proportion of especially susceptible individuals found in the general population, from infants to the elderly. Relatively little data are available on ambient NO₂ exposure and effects on Morbidity and a critical question has received little attention, namely whether or not NO₂ exposure in community air is playing a significant role in the causation, promotion, facilitation, and/or exacerbation of subclinical disease. An important case in point is pulmonary emphysema, now the fourth leading cause of death nationally but expected to rise to become the third leading cause of death. While cigarette smoking is clearly a major etiological factor, emphysema is ubiquitous in all adults. Of interest, emphysema in Antelope Valley is said to be the second leading cause of death, presumably related in part to the severe dust storms but the principle of multicausative factors is undoubtedly operative. Of special pertinence to Antelope Valley in particular is the lack of adequate technology to measure lung reserve depletion (the pathological hallmark of emphysema) with respect to rate and magnitude. The inadequacy of presently available technologies in general is a major concern for setting reasonable air pollution quality standards. For appropriate insight in the absence of hard data, I would recommend greater emphasis on pathobiological findings that suggest an adverse health effect with the potential of serious harm to the body. Mention should be made that a few personal research studies and related reports by others may warrant consideration for inclusion in the Staff Report, in particular protein leakage in the respiratory tract. Leaky lungs predispose the individual to infection, impair

gaseous exchange, alter metabolic functions, facilitate thrombotic events and metastases, and place an added burden on the cardiovascular system. In the latter respect, Wellenius GA, et al have recently reported a salient finding with respect to leaky lungs, bearing in mind that pulmonary edema is the major complication of congestive failure (cf., below). They pointed out that triggering by particulate exposure of acute decompensation in patients with congestive heart failure has not been evaluated in a systematic manner, but when carried out the “results support the hypothesis that elevated levels of particulate air pollution, below the current limits set by the United States Environmental Protection Agency, are associated with an increase in the rate of hospital admission for exacerbation of CHF” -- Wellenius GA, Schwartz J, Mittleman MA. Particulate air pollution and hospital admissions for congestive heart failure in seven United States cities. *Am J Cardiol.* 2006;97:404-8; cf. also, #10 and following citations, below). With the foregoing in mind as examples of the Morbidity problem, it is apparent that adoption of the recommended standard will provide some margin of safety but will nevertheless leave in question the proportion of the general population that will be adequately protected.

I. A review of pertinent literature cannot establish a no-harm level for NO₂ and advances in technologies can be expected to uncover presently unrecognized injuries from exposure to ambient NO₂. To reach a level of Best Judgmental Value (BJV), a very broad spectrum of health effects reports should be evaluated. Note judgmental differences in reviews by German and French sources, below). From a brief review of key issues involved in NO₂ standard setting, I believe that some studies, not cited in the *draft* Staff Report (in part recent publications), may warrant consideration for inclusion in the *final* Staff Report:

1: McConnell R, Berhane K, Yao L, Jerrett M, Lurmann F, Gilliland F, Kunzli N, Gauderman J, Avol E, Thomas D, Peters J. Traffic, susceptibility, and childhood asthma. *Environ Health Perspect.* 2006;114:766-72.

2: Millstein J, Gilliland F, Berhane K, Gauderman WJ, McConnell R, Avol E, Rappaport EB, Peters JM. Effects of ambient air pollutants on asthma medication use and wheezing among fourth-grade school children from 12 Southern California communities enrolled in The Children's Health Study. *Arch Environ Health.* 2004;59:505-14.

3. Hwang BF, Lee YL, Lin YC, Jaakkola JJ, Guo YL. Traffic related air pollution as a determinant of asthma among Taiwanese school children. *Thorax.* 2005;60:467-73.

“The results are consistent with the hypothesis that long term exposure to traffic related outdoor air pollutants such as NO_x, CO, and O₃ increases the risk of asthma in children”.

4. Hwang JS, Chen YJ, Wang JD, Lai YM, Yang CY, Chan CC. Subject-domain approach to the study of air pollution effects on schoolchildren's illness absence. *Am J Epidemiol.* 2000 1;152:67-74.

“School children’s risk of illness absence were significantly related to acute exposures to nitrogen dioxide and nitrogen oxides with a 1-day lag ($p < 0.01$) at levels below the World Health Organization's guidelines. By contrast, the authors could not detect significant associations between air pollution and schoolchildren's absenteeism using time-domain approaches. Such findings imply that the models built on subject domain may be a general solution to the problem of the ecologic fallacy, which is commonly encountered in environmental and social epidemiologic studies”.

5. Richters A, Damji KS. Changes in T-lymphocyte subpopulations and natural killer cells following exposure to ambient levels of nitrogen dioxide. *J Toxicol Environ Health*. 1988;25:247-56. [Intermittent exposure to NO₂ at 0.25 ppm for 27 days or 0.35 ppm for 60 days]

“This is the first report providing evidence linking alterations in T-lymphocyte subpopulations and natural killer cells to NO₂ exposure at ambient levels. Changes in T-lymphocyte subpopulations detected by FACS and correlated to impaired immune function may provide an extremely sensitive means of demonstrating NO₂-induced changes in the immune system.

6: Richters A, Richters V. Nitrogen dioxide (NO₂) inhalation, formation of microthrombi in lungs and cancer metastasis. *J Environ Pathol Toxicol Oncol*. 1989;9:45-51.

“The main lesions observed were microthrombi and injury to capillary endothelial cells, following 6 weeks of 0.35 +/- 0.05 ppm NO₂ exposure. --- A correlation was observed between increased incidence of microthrombi, endothelial cell injury and lung metastasis in exposed animals --- *more metastases developed in the exposed group (p<.04)*”.

7: Kuraitis KV, Richters A. Spleen cellularity shifts from the inhalation of 0.25-0.35 PPM nitrogen dioxide. *J Environ Pathol Toxicol Oncol*. 1989;9:1-11.

“The effects of ambient level (0.25-0.35 ppm)NO₂ on percent spleen cell counts, relative percentages of spleen lymphocyte subpopulations, spleen lymphoid nodule size, and differential peripheral blood cell counts were investigated in 170 young adult male mice following various NO₂ exposure periods. The total spleen cell counts, surface IgM-positive lymphocytes and spleen mean lymphoid nodule area were all significantly decreased in the groups exposed to NO₂ following extended time periods”.

(cf. 6-8: “NO₂ levels as low as 4 ppm”; compare with above citations)

8. Protein leakage in the lungs of mice exposed to 0.5 ppm nitrogen dioxide. Sherwin RP, Layfield LJ. *Arch Environ Health*. 1976;31:116-8.

(Forty-four mice continuously exposed to 0.47 ppm nitrogen dioxide for ten, 12, and 14 days. --- homogenized lung tissue assayed fluorometrically intravenous fluorescamine -- exposed animals had increased levels (p<.025).

See also:

Sherwin RP, Carlson DA. Protein content of lung lavage fluid of guinea pigs exposed to 0.4 ppm nitrogen dioxide. *Arch Environ Health*. 1973 Aug;27(2):90-3.

Tohyama Y, Kanazawa H, Fujiwara H, Hirata K, Fujimoto S, Yoshikawa J. Role of nitric oxide on airway microvascular permeability in patients with asthma. *Osaka City Med J*. 2005;5:1-9.

(significant correlation between exhaled NO level and airway vascular permeability index -- Interaction between airway microcirculation and NO may be a key element in disordered airway function in asthma).

9. Gehring U, Heinrich J, Kr Amer U, Grote V, Hochadel M, Sugiri D, Kraft M, Rauchfuss K, Eberwein HG, Wichmann HE. Long-Term Exposure to Ambient Air Pollution and Cardiopulmonary Mortality in Women. *Epidemiology*. 2006 May 30; [Epub ahead of print]

("Living close to major roads and chronic exposure to NO₂ and PM₁₀ may be associated with an increased mortality due to cardiopulmonary causes).

10. Samoli E, Aga E, Touloumi G, Nisiotis K, Forsberg B, Lefranc A, Pekkanen J, Wojtyniak B, Schindler C, Niciu E, Brunstein R, Dodic Fikfak M, Schwartz J, Katsouyanni K. Short-term effects of nitrogen dioxide on mortality: an analysis within the APHEA project. *Eur Respir J*. 2006 Mar 15; [Epub ahead of print]

("We found a significant association of NO₂ with total, cardiovascular and respiratory mortality, with stronger effects on cause-specific mortality. -- The results of this large study are consistent with an independent effect of NO₂ on mortality, but the role of NO₂ as a surrogate of other unmeasured pollutants cannot be completely ruled out".

11. Liu S, Krewski D, Shi Y, Chen Y, Burnett RT. Association between maternal exposure to ambient air pollutants during pregnancy and fetal growth restriction. *J Expo Sci Environ Epidemiol*. 2006 May 31; [Epub ahead of print]

("Previous research demonstrated consistent associations between ambient air pollution and emergency room visits, hospitalizations, and mortality. -- A 20 ppb increase in NO₂ -- in the first, second, and third trimesters) and a 10 µg/m³ increase in PM_{2.5} -- were also associated with an increased risk of IUGR (intrauterine growth restriction). Consistent results were found when ORs were calculated by month rather than trimester of pregnancy. Our findings add to the emerging body of evidence that exposure to relatively low levels of ambient air pollutants in urban areas during pregnancy is associated with adverse effects on fetal growth"

12. Kraft M, Eikmann T, Kappos A, Kunzli N, Rapp R, Schneider K, Seitz H, Voss JU, Wichmann HE. The German view: effects of nitrogen dioxide on human health--derivation of health-related short-term and long-term values. *Int J Hyg Environ Health*. 2005;208(4):305-18.

("Ministry of the Environment and Conservation, Agriculture and Consumer Protection of the state of North Rhine-Westphalia, Dusseldorf, Germany. -- The presented overview concerning health relevant effects caused by nitrogen dioxide (NO₂) resumes the current state of results from animal experiments and human studies (epidemiology and short-term chambers studies). NO₂ concentrations applied in animal experiments were mostly considerably higher than in ambient air. Therefore, short- and long-term limit values were derived from human data. Experimental studies conducted with humans demonstrate effects after short-term exposure to concentrations at or above 400 µg NO₂/m³. Effects on patients with light asthma could not be observed after short-term exposure to concentrations below 200 µg/m³. On basis of epidemiological long-term studies a threshold below which no effect on human health is expected could not be specified. Two short-term limit values have been proposed to protect public health: a 1-h value of 100 µg/m³ and a 24-h mean value of 50 µg/m³. Due to the limitations of epidemiological studies to disentangle effects of single pollutants, a long-term limit value cannot be easily derived. However, applying the precautionary principle, it is desirable to adopt an annual mean of 20 µg NO₂/m³ as a long-term mean standard to protect public health".

13. Eilstein D, Declercq C, Prouvost H, Pascal L, Nunes C, Filleul L, Cassadou S, Le Tertre A, Zeghnoun A, Medina S, Lefranc A, Saviuc P, Quenel P, Campagna D. The impact of air pollution on health. The "Programme de Surveillance Air et Sante 9 villes" (Air and Health surveillance program in 9 cities *Presse Med*. 2004 Nov 6;33(19 Pt 1):1323-7.

("If the levels of air pollution were reduced to 10 microg/m³ in the nine cities, 2800 premature deaths and 750 hospitalisations for respiratory disorders in children would be avoided, every Year").

II. On susceptible populations:

1. An update on estimated proportions of susceptible populations would be desirable (? Available from the American Lung Association --- early one by Gladys Meade)

2. Examples of key issues may have merit for judgment purposes, particularly with respect to arguments that only clinically manifested responses constitute an adverse health effect. Emphysema may especially warrant singling out for evaluation, particularly since it has not been clearly defined and pathological as well as clinical diagnosis is often inaccurate or entirely unreliable. From a clinical standpoint, a lung function evaluation for a person being tested for the first time may not indicate an abnormality until 25% of lung tissue has been irreversibly lost. Data are presently insufficient to establish whether the 25% estimate regarding a Pulmonary Function Test (PFT) should be lower or higher. In view of the relative insensitivity of PFTs, the lack of an altered PFT following an NO₂ challenge is by no means assurance that injury has not occurred. Moreover, tests carried out on healthy young volunteers will necessarily have variable results in view of individual variation that, from our studies of youths who died suddenly from violence had shown, will most likely if not invariably include some individuals with serious lung disease at clinical and/or subclinical levels. From a pathological standpoint, a scientifically valid diagnosis of emphysema is obviated by a virtually total failure nationally if not universally to process the lung properly at autopsy. Yet, there is no question from the results of appropriate studies that some degree of emphysema is ubiquitous in the general population and is contributing to the rise of emphysema to become the fourth leading cause of death.

Lastly, as is the case with emphysema, subclinical disease involving the body in general and the lung in particular, is ubiquitous in the general population. Standard setting for NO₂ should be directed at reducing the frequency and severity of subclinical disease (more properly, Morbidity) by asking what role does an ambient level of NO₂ play in the causation, promotion, facilitation, and/or exacerbation of disease in general. Compensation by the body in response to injury may lead to false reassurance that a noxious effect is no longer harmful. However, the remodeling of tissues and reactive proliferative processes generally have a cost in structural and functional integrity, and also in long term potential for chronic and/or neoplastic disease. The public should be made aware of critical questions that investigators face in their assessment of adverse health effects in addition to well known cardiovascular and lung effects. Examples are the role of ambient NO₂ levels in: bronchiolitis in infants and children, endothelin and platelet alterations related to thrombotic phenomena (stroke, pulmonary embolism, deep vein thrombosis), cancer metastasis (seeding of cancer cells), and diverse immunodeficiencies. Our ongoing work with asthmatic bronchitis has shown an unexpectedly high frequency of severe Eosinophil Airway Disease of uncertain cause.

Additional References

Kraft, M., Eikmann, T., Kappos, A., Kunzli, N., Rapp, R., Schneider, K., Seitz, H., Voss, J. U., and Wichmann, H. E. (2005). The German view: effects of nitrogen dioxide on human health--derivation of health-related short-term and long-term values. *Int J Hyg Environ Health* **208**, 305-318.

- Samoli, E., Touloumi, G., Zanobetti, A., Le Tertre, A., Schindler, C., Atkinson, R., Vonk, J., Rossi, G., Saez, M., Rabczenko, D., Schwartz, J., and Katsouyanni, K. (2003). Investigating the dose-response relation between air pollution and total mortality in the APHEA-2 multicity project. *Occup Environ Med* **60**, 977-982.
- Vedal, S., Brauer, M., White, R., and Petkau, J. (2003). Air pollution and daily mortality in a city with low levels of pollution. *Environ Health Perspect* **111**, 45-52.

Arnold C.G. Platzker, MD

GOALS

1. Protection of the health of infants, children and adolescents
2. Protection of the most vulnerable pediatric populations
3. Allow normal outdoor activities for all children

BACKGROUND

Little is known about the impact of NO₂ inhalation on the most vulnerable pediatric populations which include the fetus, infants born prematurely, newborn infants, early infancy, infants and children with chronic lung conditions, such as chronic lung disease of infancy (BPD), cystic fibrosis, interstitial lung disease. The target population studied in assessing the response to inhaled environmental pollutants has been healthy children, usually older than 7 years old, who are often compared to children with asthma, a surrogate for children with airway or lung disease. These studies are difficult to interpret due to the grouping of the children and adolescents who cough and/or wheeze in the same study without controlling for sex, race, socio-economic status or age groups [0-1 year, 1-2 years, 2-5 years, and 5-13 years]. There are developmental and physiological reasons for the necessity to study children in these age groups. First, establishing the diagnosis of asthma in young children prior to the age of 4-5 years old is difficult, often impossible, even those with atopy or a family history of asthma. Wheezy bronchitis is common in infants and young children from birth to 4 years. In fact, of the infants and young children [less than 4 years old] with chronic or recurrent cough or wheeze, less than 25% will have persisting cough or wheeze by 5 years of age. The reasons for this diagnostic dilemma stems from:

1. boys being born with smaller airways than girls (Taussig), making cough and wheeze more common in infant males than females during and following routine respiratory tract infections. In the first two years boys airways grow more rapidly than girls so that after 2

- years of age airway caliber of males exceed that of females of the same age, so that after 2 years old females experience more cough and wheeze than males;
2. the lack of a specific serologic or lung function test to make the diagnosis asthma which makes the diagnosis of asthma problematic in the child less than 4-5 years of age in the absence of a strong family history.

Another intriguing unresolved issue in early childhood the impact of prenatal exposure to inhalant pollution on the fetus, that is, mother to fetus transmission of an inhaled environmental pollutants on lung development and lung function at birth and in infancy. For evidence of this potential impact on fetal development, one need only review the fetal impact of maternal cigarette smoking during pregnancy and lung function at birth and during infancy (Hanrahan, et al). Hanrahan studied pregnant women from an East Boston Health Clinic. He compared the neonatal and infancy lung function of infants whose mother's did and did not smoke during pregnancy through questionnaire and measurement of cotinine, a metabolite of nicotine, in the urine of mother and infant. Hanrahan found that the impact of in utero tobacco smoke exposure on the lung development and function in infancy was greater than that of post-natal environmental tobacco smoke exposure [ETS] during infancy and early childhood. Other studies published subsequently have confirmed the findings of Hanrahan, et al. Other major findings of in utero ETS which have been reported include reduced DNA, leading to lower birth weights smaller lungs (reduced TLC), higher total respiratory resistance [Rrs] indicative of smaller caliber of the airways, and lower maximal expiratory flow rates at functional residual capacity [V'maxFRC] and disordered breathing during sleep leading to increased risk of infant apnea or sudden death.

While studies of ETS on the fetus has revealed a major impact of ETS on birth weight and on fetal lung growth and function at birth, there are no comparable studies of NO₂ and related (fellow traveler) pollutant exposure on the fetus and newborn infant. NO₂ has been postulate to have a small effect on the odds ratio for low birth weight and for an increase in sudden infant death, but there have been no corresponding studies of lung function at birth or in early infancy focusing on the impact of NO₂ exposure of the fetus and in infancy. These studies been primarily on the impact in school-age children and longitudinal studies have been conducted to record the impact of NO₂ or NO₂ + PM₁₀ over time on school children. In summary, there have been no studies in which the impact of NO₂ have focused on the fetus, newly born, infant or in the early childhood pre-school years when the airway caliber is small and very reactive with airway obstruction is common with respiratory illnesses such as metapneumovirus or RSV infection.

CONCLUSIONS:

The studies of nitrogen oxide air pollutants are compromised by a lack of ability to discriminate between the effects of nitrogen dioxide and its companion air pollutants. There are inadequate or no pediatric studies which:

1. Define the relationship between maternal exposure and the impact on the fetus;
2. Post-natal exposures and respiratory function in
 - a. Prematurely born
 - b. Full term infants
 - c. Infants born with neonatal and early respiratory illnesses, RDS, chronic lung disease of infancy (BPD), cystic fibrosis, wheezy bronchitis;
 - d. Following sentinel lung infection (metapneumovirus, RSV infection, mycoplasma pneumonia, etc)
3. Studies of at risk populations
 - a. Proximity to freeways (traffic)
 - b. Socio-economically disadvantaged
 - i. Indoor pollutants + outdoor
4. Include impact of exposure on inflammatory markers, allergic inflammation