Comments of the American Lung Association on

EPA's Integrated Science Assessment for Oxides of Nitrogen -- Health Criteria

(First External Review Draft, November 2013)
EPA/600/R-13/202

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The American Lung Association offers these comments on EPA's first draft Integrated Science Assessment (ISA) for the review of the National Ambient Air Quality Standards (NAAQS) for oxides of nitrogen (NOx).

We view the draft as a rigorous effort to assess all the relevant evidence. The draft document represents advancement from earlier draft ISAs in several key respects. We appreciate the enhanced integration and clarity in the presentation of the information.

1) <u>The ISA is a Rigorous and Transparent Assessment</u>

The preamble of the draft ISA explicitly lays out the process of ISA development in a clear, transparent way. The document clearly indicates the how studies were selected for review and the criteria that were used to evaluate the scientific quality of the studies.

The document lays out the guidelines for individual study quality as well as specific considerations for specific disciplines such as exposure assessment, epidemiology, toxicology, and controlled human exposures. These guidelines safeguard the objectivity of the science assessment.

Importantly, the document considers studies looking at the health impacts of personal exposures and indoor exposures to nitrogen dioxide. We consider this important evidence that is critical to a comprehensive evaluation of the effects of outdoor NOx concentrations.

The explicit, thoughtful approach laid out in the preamble ensures that there is a consistent evaluation of the scientific evidence of health effects.

The weight of evidence approach for assessing causality is clearly articulated and is consistent with the recommendations of leading scientific bodies such as the Institute of Medicine and the Centers for Disease Control and Prevention.

The document similarly spells out its approach for classifying evidence of potential risk factors.

Additionally, the approach for evaluating public health impact is clearly articulated, and the factors considered in the assessment of the adversity of health effects are well documented.

Going forward, it will be important to set a cut-off date for inclusion of new studies. We have identified about 40 studies in-press or published since the completion of the first draft that provide critical additional evidence of adverse health

effects of nitrogen dioxide air pollution. These studies should be evaluated for inclusion in the second draft, but EPA must set a cut-off date, such as following the review of the second draft, so that the review process can move toward completion in a timely fashion.

2) The ISA Integrates Evidence Across Scientific Disciplines

The draft ISA represents an evolution in the structure of such documents by providing a true integrative assessment. Previous renditions have looked at health effects discipline by discipline. But this draft provides two integrative chapters, one on short-term health effects (Chapter 4), and another on long-term health effects (Chapter 5). Each of these chapters synthesizes evidence from the three major branches of science at play: controlled human exposure studies, epidemiology, and toxicology. Furthermore, the Integrated Summary presented in Chapter 1 pulls forward the most salient information from the subsequent chapters and unites them in a comprehensive approach. This cohesive assessment improves the communication of the evidence.

3) The Detailed Tables Summarize Critical Factors

The chapters on short- and long-term health effects each include detailed tables summarizing the key aspects of the studies that were evaluated. These tables, while encyclopedic in scope, allow for direct comparison of the critical elements of each scientific study. Importantly, the tables detail the exposure metrics analyzed in each study, which is valuable in considering the appropriate form and level of the ambient air quality standards.

The text of the document presents a balanced evaluation of the strengths and the weaknesses of the studies that have been evaluated.

4. The ISA Provides Clear Evidence for Stronger Causality Statements In This Review

The draft ISA explains explicitly how it derives its conclusions regarding causality for each health endpoint. Table ES-1 compares the causal determinations by exposure duration and health endpoint from the 2008 ISA and the current draft. Table 1-1 lays out the key evidence for the causal determinations in the current draft. Table 1-1 improves on the tables found in previous ISAs by adding key explanations with an improved format while still retaining the taut summary of the findings. The text of the document further elaborates on the specific factors considered, and explains the new science that informs the causal determination, and how and why the conclusions may differ from those reached in the last review.

The comparison to the conclusions reached in the last review of the NO_2 standards particularly reinforces the wisdom of the regular review of NAAQS required by the Clean Air Act. Science marches forward, and more recent research clarifies old questions and adds new information. The air quality standards must be periodically reevaluated to determine if they are adequate to protect public health with an adequate margin of safety, in light of the more recent evidence.

NO_2 Causes Adverse Respiratory Effects

Based on this transparent analytical approach, the draft ISA reaches important new conclusions about the toxicity of Nitrogen Dioxide (NO_2).

We concur that the evidence supports a causal relationship between short-term exposures and respiratory effects. We are concerned with studies showing that NO_2 exposure exacerbates asthma, and increases respiratory symptoms, triggering increased hospital and emergency department visits for asthma. While confounding by co-pollutants is always a consideration, we concur that recent studies point to the independent role of NO_2 as distinct from other air pollutants.

Of particular concern, are studies indicating positive associations with health endpoints such as hospital admissions, when the mean 1-hour maximum NO_2 concentration was between 22 to 66 ppb, and maximum concentrations ranged from 59 to 298 ppb.

Earlier evidence from chamber studies found increased airway responsiveness of adults with asthma after 1-hour exposures to 100 ppb, calling into question the adequacy of the current hourly standard of 100 ppb.

We are particularly concerned about the role of NO_2 in the development of asthma in children. We concur with the conclusion that long-term exposures are likely to cause adverse respiratory effects.

<u>Traffic Exposures Need Greater Consideration</u>

As we have argued in past reviews of other criteria pollutants, a large body of health studies now use distance from roadways as a surrogate for exposure to traffic pollution. These studies report positive associations between traffic pollution and serious health effects ranging from lung function to reproductive effects.

We are pleased that EPA also recognizes that traffic and transportation sources expose millions of Americans to oxides of nitrogen. EPA included the 2009 American Housing Survey finding that 17.5 percent of the U.S. population lives within 90 meters of 4-lane roads, airports and railroads, all major sources of NOx emissions. The Health Effects Institute report on traffic pollution concluded that the zone of harmful exposures was broader—roughly 300-500 feet from the roadway—and was where 45 percent of all North Americans in urban areas lived or worked.

In the past, EPA has recognized the need for enhanced monitoring because of the multi-pollutant character of the traffic pollution mix. We agree, given the evidence from multi-pollutant studies, that the effects of NO_2 stand independent of other pollutants. Given the scope of the exposures, the documented harm from NO_2, and the lifelong impact particularly on the children exposed, EPA should give greater weight to the traffic studies.

<u>Stronger "Likely Causal" Findings are Justified</u>

The draft ISA presents stronger findings of causality for a number of health endpoints than were reached in the previous review. Specifically, the ISA finds that NO_2 is likely causal for short-term cardiovascular effects, total mortality, and respiratory effects from long-term exposures. These important findings are well-substantiated by the current discussion in the ISA.

However, since the draft document was completed, a plethora of new studies have been published, many reporting positive, often statistically significant association between NO_2 and adverse health effects. For instance, a recently published meta-analysis reported that an independent effect of NO_2 emerged from multipollutant models. The meta-analysis concluded that evidence of a long-term effect of NO_2 on mortality was great as that of $PM_{2.5}$.[1]

EPA's causal findings need to be re-evaluated in light of substantial new evidence that short- and long-term exposures of NO_2 are associated with premature mortality, cardiovascular effects, respiratory disease, cancer, reproductive effects, immune system responses, neurological deficits, and other health problems.

Susceptible Populations

The draft ISA concludes that children and older adults are at increased risk for NO_2 health effects. Additional elevated risk factors are living near major roads, and pre-existing asthma, COPD, and other factors.

Another population that should be evaluated for potential susceptibility are people that are overweight or obese. This factor has been ignored in the recent review of the PM and the ozone NAAQS, and it should be considered here. A recent publication reports that overweight and obese people have elevated breathing rates, increasing their exposure to air

[1] Annunziata Faustini, Regula Rapp, and Francesco Forastiere. Nitrogen dioxide and mortality: review and meta-analysis of long-term studies. Eur. Respir. J. published 20 February 2014, 10.1183/09031936.00114713

pollutants.[2] A review of the literature finds that obesity impacts breathing mechanics and gas exchange in numerous ways, and that air pollution exposures my place an additional burden on the altered physiological, morphological and biochemical states typical of obese populations.[3]

ISA Documents Adverse Health Effects at Concentrations below the Current NAAQS

The Chapter 1 of the ISA needs to more specifically identify those studies that document adverse effects of NO_2 at concentrations below the current standards, as was done in the final ISA for ozone.

Assessment of the Adequacy of the Monitoring Network

Chapter 2 of the draft ISA includes a brief discussion at 2.4.5 of the ambient sampling network design. The chapter also includes some summary data from the monitoring network, and discusses spatial variability of NOx concentrations, particularly in the near road environment.

We would like to see an objective evaluation of the adequacy of the current monitoring requirements to accurately measure compliance with the NAAQS for NO_2.

In the last review, EPA established new requirements for the largest metropolitan areas to institute monitoring in the near road environment. The first of these monitors were deployed

[2] Pierre Brochu, Michèle Bouchard, Sami Haddad. Physiological Daily Inhalation Rates for Health Risk Assessment in Overweight/Obese Children, Adults, and Elderly. *Risk Analysis*, 22 October 2013. DOI: 10.1111/risa.12125.

[3] Koman PD. How Does the Obesity Epidemic Affect Pulmonary Risk from Air Pollution. University of Michigan Risk Science Center Occasional Papers, 12.1.2012.

in summer of 2013, ahead of the January 2014 deadline. Additional monitors will be phased in for the next several years, until a total of about 120 NO_2 monitors are deployed in areas of maximum expected highway emissions.

These 120 monitors are far too few and monitoring will be too limited in every urban area in the nation. It is impossible for a single monitor, or two monitors to adequately characterize NO_2 pollution from traffic sources in a large metropolitan area.

We recognize that the ISA may not be the best place for an evaluation of the monitoring network, and monitoring may be better considered in some other aspect of the review. However the monitoring regime is an important attribute of any NAAQS and should be thoroughly evaluated in the course of the review.

<u>2013-14 Research Bolsters Causal Findings</u>

An occupational hazard of authors of Integrated Science Assessments is the difficulty in keeping the documents current during the period from document preparation through the review phase. In the case of the NO_2 ISA, draft chapters were reviewed at a public workshop in June 2013, but the overall document was not published as a first draft for public review until November 2013.

We have identified a number of studies that we do not believe have been discussed in the first draft ISA, and that have bearing on the causal findings and the question of what levels cause adverse effects.

We include a list of some of the most important studies here, but this list is not comprehensive. The length of the list should not diminish the importance of any individual study.

Exposure

Levy I, Mihele C, Lu G, Narayan J, Brook JR. Evaluating Multipollutant Exposure and Urban Air Quality: Pollutant Interrelationships, Neighborhood Variability, and Nitrogen Dioxide as a Proxy Pollutant. Environ Health Perspect 2013.
PMID: 24225648
DOI: 10.1289/ehp.1306518

Zhang L, Guan Y, Leaderer BP, Holford TR. Estimating Daily Nitrogen Dioxide Level: Exploring Traffic Effects. Ann Appl Stat 2013; 7 (3): .
PMID: 24327824
DOI: 10.1214/13-AOAS642

Respiratory Effects

Lung Function

Rice MB, Ljungman PL, Wilker EH, Gold DR, Schwartz JD, Koutrakis P, Washko GR, O'Connor GT, Mittleman MA. Short-term exposure to air pollution and lung function in the Framingham Heart Study. Am J Respir Crit Care Med 2013; 188 (11): 1351-7.
PMID: 24200465
DOI: 10.1164/rccm.201308-1414OC

Urman R, McConnell R, Islam T, Avol EL, Lurmann FW, Vora H, Linn WS, Rappaport EB, Gilliland FD, Gauderman WJ. Associations of children's lung function with ambient air pollution: joint effects of regional and near-roadway pollutants. Thorax 2013.
PMID: 24253832
DOI: 10.1136/thoraxjnl-2012-203159

Asthma

Park M, Luo S, Kwon J, Stock TH, Delclos G, Kim H, Yun-Chul H. Effects of Air Pollution on Asthma Hospitalization Rates in Different Age Groups in Metropolitan Cities of Korea. Air Qual Atmos Health 2013; 6 (3): .
PMID: 24223075
DOI: 10.1007/s11869-013-0195-x

Fuertes E, Standl M, Cyrys J, Berdel D, von Berg A, Bauer CP, Krämer U, Sugiri

D, Lehmann I, Koletzko S, Carlsten C, Brauer M, Heinrich J. A longitudinal analysis of associations between traffic-related air pollution with asthma, allergies and sensitization in the GINIplus and LISAplus birth cohorts. PeerJ 2013; 1: e193.
PMID: 24255809
DOI: 10.7717/peerj.193

Dell SD, Jerrett M, Beckerman B, Brook JR, Foty RG, Gilbert NL, Marshall L, Miller JD, To T, Walter SD, Stieb DM. Presence of other allergic disease modifies the effect of early childhood traffic-related air pollution exposure on asthma prevalence. Environ Int 2014; 65C: 83-92.
PMID: 24472824
DOI: 10.1016/j.envint.2014.01.002

Nishimura KK, Galanter JM, Roth LA, Oh SS, Thakur N, Nguyen EA, Thyne S, Farber HJ, Serebrisky D, Kumar R, Brigino-Buenaventura E, Davis A, LeNoir MA, Meade K, Rodriguez-Cintron W, Avila PC, Borrell LN, Bibbins-Domingo K, Rodriguez-Santana JR, Sen Ś, Lurmann F, Balmes JR, Burchard EG. Early-life air pollution and asthma risk in minority children. The GALA II and SAGE II studies. Am J Respir Crit Care Med 2013; 188 (3): 309-18.
PMID: 23750510
DOI: 10.1164/rccm.201302-0264OC

Lin W, Brunekreef B, Gehring U. Meta-analysis of the effects of indoor nitrogen dioxide and gas cooking on asthma and wheeze in children. Int J Epidemiol 2013; 42 (6): 1724-37.
PMID: 23962958
DOI: 10.1093/ije/dyt150

Pneumonia

Negrisoli J, Nascimento LF. Atmospheric pollutants and hospital admissions due to pneumonia in children. Rev Paul Pediatr 2013; 31(4): 501-6.
PMID: 24473956
DOI: 10.1590/S0103-05822013000400013

Cystic Fibrosis

Goeminne PC, Kiciński M, Vermeulen F, Fierens F, De Boeck K, Nemery B, Nawrot TS, Dupont LJ. Impact of air pollution on cystic fibrosis pulmonary exacerbations: a case-crossover analysis. Chest. 2013 Apr;143(4):946-54.

Johannson KA, Vittinghoff E, Lee K, Balmes JR, Ji W, Kaplan GG, Kim DS, Collard HR. Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure. Eur Respir J 2013;
PMID: 24176998

DOI: 10.1183/09031936.00122213

Johannson K, Collard HR. Acute Exacerbation of Idiopathic Pulmonary Fibrosis: A Proposal. Curr Respir Care Rep 2013; 2 (4): .
PMID: 24416637
DOI: 10.1007/s13665-013-0065-x

General

Amster ED, Haim M, Dubnov J, Broday DM. Contribution of nitrogen oxide and sulfur dioxide exposure from power plant emissions on respiratory symptom and disease prevalence. Environ Pollut 2013; 186C (): 20-28.
PMID: 24361356
DOI: 10.1016/j.envpol.2013.10.032

Faustini A, Stafoggia M, Colais P, Berti G, Bisanti L, Cadum E, Cernigliaro A, Mallone S, Scarnato C, Forastiere F. Air pollution and multiple acute respiratory outcomes. Eur Respir J 2013; 42 (2): 304-13.
PMID: 23314899
DOI: 10.1183/09031936.00128712ville

Hansel NN, McCormack MC, Belli AJ, Matsui EC, Peng RD, Aloe C, Paulin L, Williams DL, Diette GB, Breysse PN. In-home air pollution is linked to respiratory morbidity in former smokers with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013; 187 (10): 1085-90.
PMID: 23525930
DOI: 10.1164/rccm.201211-1987OC

Payam Dadvand, Mark J. Nieuwenhuijsen, Àlvar Agustí, Jordi de Batlle, Marta Benet, Rob Beelen, Marta Cirach, David Martinez, Gerard Hoek, Xavier Basagaña, Antoni Ferrer, Jaume Ferrer, Robert Rodriguez-Roisin, Jaume Sauleda, Stefano Guerra, Josep M. Antó and Judith Garcia-Aymerich. Air pollution and biomarkers of systemic inflammation and tissue repair in COPD patients. ERJ February 20, 2014 erj01688-2013.
Published online before print February 20, 2014,
DOI: 10.1183/09031936.00168813

Cardiovascular Effects

Yu IT, Qiu H, Wang X, Tian L, Tse LA. Synergy between particles and nitrogen dioxide on emergency hospital admissions for cardiac diseases in Hong Kong. Int J Cardiol 2013; 168 (3): 2831-6.
PMID: 23608392
DOI: 10.1016/j.ijcard.2013.03.082

Chen L, Villeneuve PJ, Rowe BH, Liu L, Stieb DM. The Air Quality Health Index as a predictor of emergency department visits for ischemic stroke in Edmonton, Canada. J Expo Sci Environ Epidemiol 2013.
PMID: 24301354
DOI: 10.1038/jes.2013.82

Johnson JY, Rowe BH, Allen RW, Peters PA, Villeneuve PJ. A case-control study of medium-term exposure to ambient nitrogen dioxide pollution and hospitalization for stroke. BMC Public Health 2013; 13: 368.
PMID: 23597019
DOI: 10.1186/1471-2458-13-368

Shah AS, Langrish JP, Nair H, McAllister DA, Hunter AL, Donaldson K, Newby DE, Mills NL. Global association of air pollution and heart failure: a systematic review and meta-analysis. Lancet 2013; 382 (9897): 1039-48.
PMID: 23849322
DOI: 10.1016/S0140-6736(13)60898-3

Mortality

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DOI: 10.1183/09031936.00114713

Jerrett M, Burnett RT, Beckerman BS, Turner MC, Krewski D, Thurston G, Martin RV, van Donkelaar A, Hughes E, Shi Y, Gapstur SM, Thun MJ, Pope CA. Spatial analysis of air pollution and mortality in California. Am J Respir Crit Care Med 2013; 188 (5): 593-9.
PMID: 23805824
DOI: 10.1164/rccm.201303-0609OC

Alessandrini ER, Faustini A, Chiusolo M, Stafoggia M, Gandini M, Demaria M, Antonelli A, Arena P, Biggeri A, Canova C, Casale G, Cernigliaro A, Garrone E, Gherardi B, Gianicolo EA, Giannini S, Iuzzolino C, Lauriola P, Mariottini M, Pasetto P, Randi G, Ranzi A, Santoro M, Selle V, Serinelli M, Stivanello E, Tominz R, Vigotti MA, Zauli-Sajani S, Forastiere F, Cadum E. Air pollution and mortality in twenty-five Italian cities: results of the EpiAir2 Project. Epidemiol Prev 2013 Jul-Oct; 37 (4-5): 220-9.
PMID: 24293487

Goldberg MS, Burnett RT, Stieb DM, Brophy JM, Daskalopoulou SS, Valois MF, Brook JR. Associations between ambient air pollution and daily mortality among

elderly persons in Montreal, Quebec. Sci Total Environ 2013; 463-464 (): 931-42.
PMID: 23872247
DOI: 10.1016/j.scitotenv.2013.06.095

Vanos JK, Cakmak S, Bristow C, Brion V, Tremblay N, Martin SL, Sheridan SS. Synoptic weather typing applied to air pollution mortality among the elderly in 10 Canadian cities. Environ Res 2013; 126: 66-75.
PMID: 24012249
DOI: 10.1016/j.envres.2013.08.003

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PMID: 23714370
DOI: 10.1186/1476-069X-12-43

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Qian Y, Zhu M, Cai B, Yang Q, Kan H, Song G, Jin W, Han M, Wang C. Epidemiological evidence on association between ambient air pollution and stroke mortality. J Epidemiol Community Health 2013; 67 (8): 635-40.
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DOI: 10.1136/jech-2012-201096

Yang Y, Li R, Li W, Wang M, Cao Y, Wu Z, Xu Q. The Association between Ambient Air Pollution and Daily Mortality in Beijing after the 2008 Olympics: A Time Series Study. PLoS One 2013; 8 (10): e76759.
PMID: 24204670
DOI: 10.1371/journal.pone.0076759

Reproductive Effects

Dadvand P, Basagaña X, Figueras F, Martinez D, Beelen R, Cirach M, de Nazelle A, Hoek G, Ostro B, Nieuwenhuijsen MJ. Air pollution and preterm premature rupture of membranes: a spatiotemporal analysis. Am J Epidemiol 2014; 179 (2): 200-7.
PMID: 24125920
DOI: 10.1093/aje/kwt240

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DOI: 10.1093/aje/kws367

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Carcinogenicity

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DOI: 10.1016/j.chemosphere.2012.11.057

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PMID: 24236202
DOI: 10.1371/journal.pone.0080795

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PMID: 24148924
DOI: 10.1016/j.neuro.2013.09.004

Susceptible populations

Pierre Brochu, Michèle Bouchard, Sami Haddad. Physiological Daily Inhalation Rates for Health Risk Assessment in Overweight/Obese Children, Adults, and Elderly. *Risk Analysis*, 22 October 2013. DOI: 10.1111/risa.12125.