

EPA Integrated Science Assessment of NO₂: Clean Air Scientific Advisory Committee Review and Recommendation

H. Christopher Frey
frey@ncsu.edu

NC STATE UNIVERSITY

**Department of Civil, Construction & Environmental Engineering
North Carolina State University
Raleigh, NC 27695**

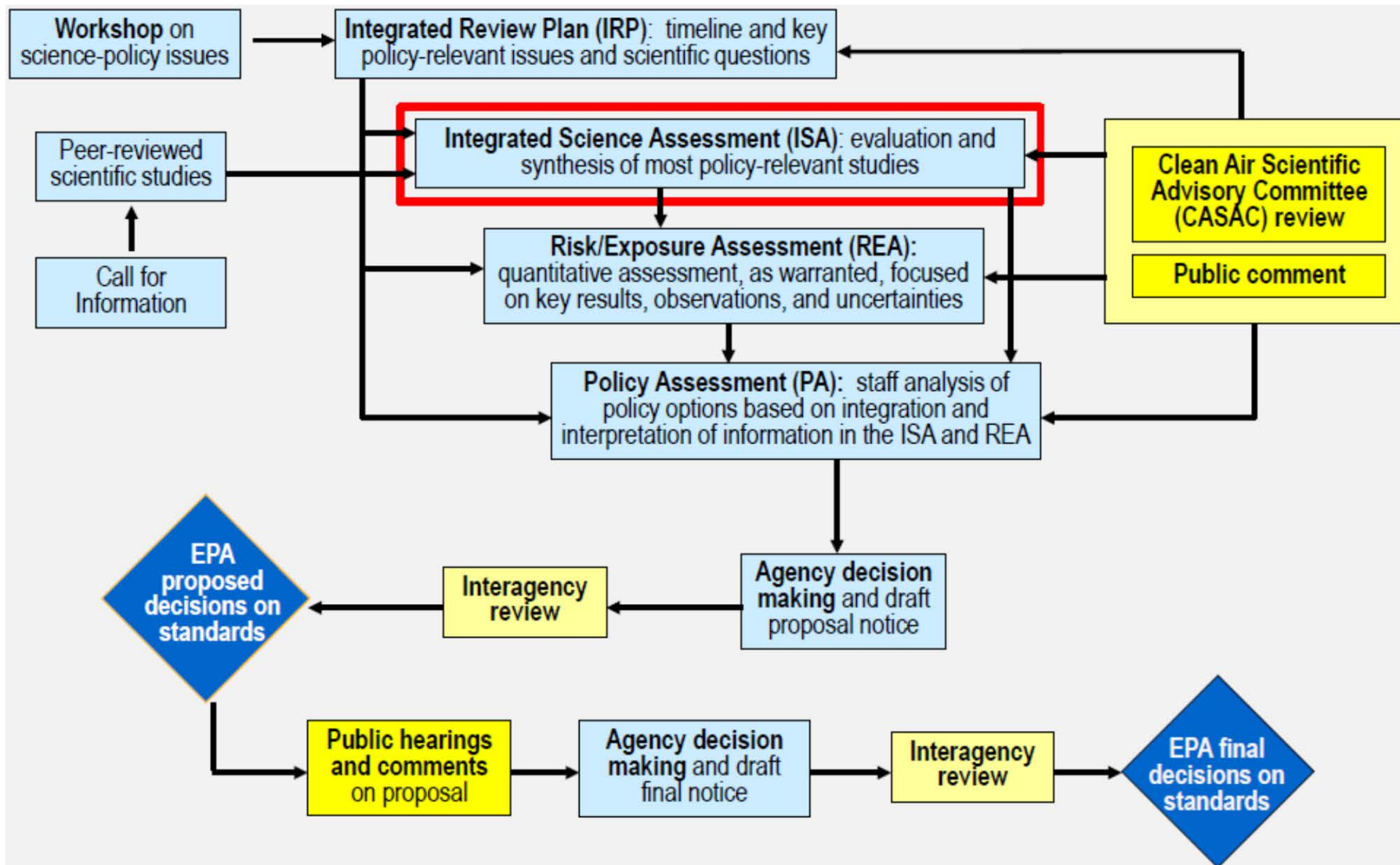
**2017 HEI Annual Conference
Alexandria, VA**

May 2, 2017

Outline

- National Ambient Air Quality Standard (NAAQS) Review Process
- Integrated Science Assessment (ISA)
- Causal Determination
- Findings:
 - Short-Term Exposure
 - Long-Term Exposure
- Policy Considerations
- Uncertainties and Research Needs

The National Ambient Air Quality Standard (NAAQS) Review Process



Statutory Mandate for Clean Air Scientific Advisory Committee (CASAC)

- Section 109(d)(2) requires that an independent scientific review committee
 - “shall **recommend to the Administrator** any **new . . . standards** and **revisions** of existing criteria and standards as may be appropriate”
- Clean Air Scientific Advisory Committee – charter filed with Congress every 2 years.

CASAC and FACA

- FACA: Federal Advisory Committee Act
- **Public notice of meetings**
- **Meetings held in public**
- **Opportunity for public comment**
- **Deliberations are in public**
- CASAC issues written letter reports with attachments to the Administrator

Science and Policy

- CASAC differs from some other FACA committees
 - Statutory mandate to advise the Administrator on a specific regulatory-related scope
 - Judgments regarding indicator, level, averaging time, and form of a NAAQS
 - “adequate margin of safety”
 - Court decisions acknowledge role for CASAC in providing scientific and policy advice.

CASAC NO_x Review Panel

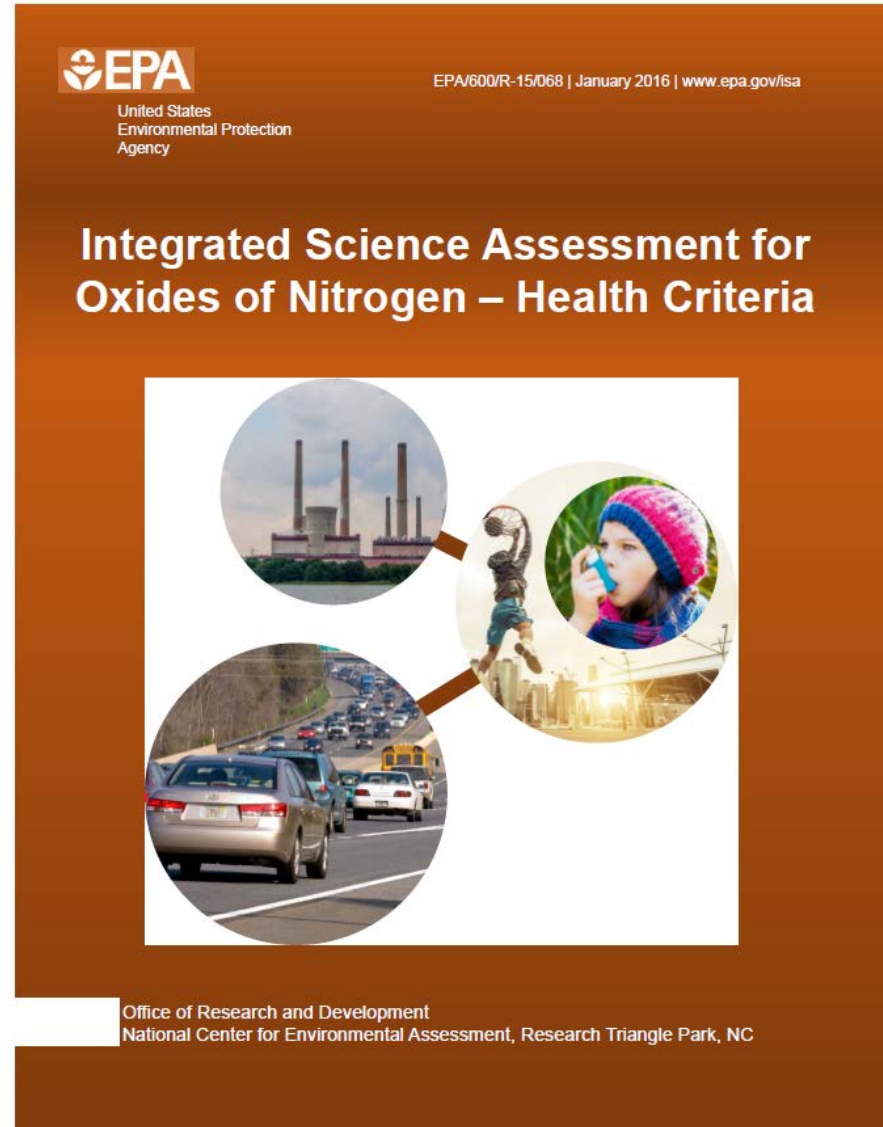
- **Mr. George A. Allen**, Northeast States for Coordinated Air Use Management, Boston, MA
 - **Dr. Matthew Campen**, University of New Mexico, Albuquerque, NM
 - **Dr. Ronald Cohen**, University of California, Berkeley,
 - **Dr. Douglas Dockery**, Harvard University, Boston, MA
 - **Dr. Philip Fine**, South Coast Air Quality Management District, Diamond Bar, CA
 - **Dr. H. Christopher Frey**, North Carolina State University, Raleigh, NC
 - **Dr. Panos Georgopoulos**, Rutgers University, Piscataway, NJ
 - **Dr. Jack Harkema**, Michigan State University, East Lansing, MI
 - **Dr. Michael Jerrett**, University of California, Los Angeles
 - **Dr. Joel Kaufman**, University of Washington, Seattle, WA
 - **Dr. Michael T. Kleinman**, University of California, Irvine
 - **Dr. Timothy V. Larson**, University of Washington, Seattle, WA
 - **Dr. Jeremy Sarnat**, Emory University, Atlanta, GA
 - **Dr. Richard Schlesinger**, Pace University, New York, NY
 - **Dr. Elizabeth A. (Lianne) Sheppard**, University of Washington, Seattle, WA
 - **Dr. Helen Suh**, Northeastern University, Boston, MA
 - **Dr. Junfeng (Jim) Zhang**, Duke University, Durham, NC
 - **Dr. Ronald Wyzga**, Electric Power Research Institute, Palo Alto, CA
- SCIENCE ADVISORY BOARD STAFF**
- **Mr. Aaron Yeow**, Designated Federal Officer, U.S. Environmental Protection Agency, Science

Scope of the NO₂ review

- Health effects from exposure to nitrogen dioxide (NO₂)
- Not included:
 - NO₂ → PM: PM is a separate standard that is reviewed separately
 - NO₂ → O₃: O₃ is a separate standard that is reviewed separately
 - NO₂ → acid deposition:
addressed under the
“secondary” SO_x/NO_x review

Purpose and Scope of the ISA

- The Integrated Science Assessment (ISA) provides a concise (1,148 pages)
 - Review
 - Synthesis
 - Evaluationof policy-relevant science
- Scientific foundation for NAAQS review
- Scope:
 - air quality
 - exposure
 - dosimetry and mode of action
 - health effects
 - at risk populations and lifestages



Aspects to Aid in Judging Causality

- Consistency
- Coherence
- Biological Plausibility
- Biological Gradient
- Strength of the Observed Association
- Experimental Evidence
- Temporality
- Specificity
- Analogy

Weight of Evidence for Causal Determinations

- Causal relationship
- Likely to be a causal relationship
- Suggestive of, but not sufficient to infer, a causal relationship
- Inadequate to infer a causal relationship
- Not likely to be a causal relationship

Causal Determinations

Exposure Duration	Health Effects Category	Causal Determination
Short-Term (minutes up to 1 month)	Respiratory	Causal relationship
	Cardiovascular	Suggestive of, but not sufficient to infer, a causal relationship
	Total mortality	Suggestive of, but not sufficient to infer, a causal relationship
Long-Term (more than 1 month to years)	Respiratory	Likely to be a causal relationship
	Cardiovascular & Diabetes	Suggestive of, but not sufficient to infer, a causal relationship
	Reproductive and developmental effects	Fertility, reproduction, and pregnancy: Inadequate to infer a causal relationship Birth outcomes: Suggestive of, but not sufficient to infer, a causal relationship Postnatal development: Inadequate to infer a causal relationship
	Total mortality	Suggestive of, but not sufficient to infer, a causal relationship
	Cancer	Suggestive of, but not sufficient to infer, a causal relationship

Table 3-2. Resting exposures to nitrogen dioxide and airway responsiveness in individuals with asthma.^a

Reference	NO ₂ ppb	Exp. (min)	Challenge Type	N	Change in AR ^b		Average PD ± SE ^c		p-value ^d
					+	-	Air	NO ₂	
Ahmed et al., 1983a	100	60	Non-specific, CARB	20	13	7	6.0 ± 2.4	2.7 ± 0.8	NA
Orehek et al., 1976	100	60	Non-specific, CARB	20	14	3	0.56 ± 0.08	0.36 ± 0.05	<0.01 ^e
Hazucha et al., 1983	100	60	Non-specific, METH	15	6	7	1.9 ± 0.4	2.0 ± 1.0	n.s.
Ahmed et al., 1983b	100	60	Specific, RAG	20	10	8	9.0 ± 5.7	11.7 ± 7.6	n.s.
Tunnicliffe et al., 1994	100	60	Specific, HDM	8	3	5	-14.62 ΔFEV ₁	-14.41 ΔFEV ₁	n.s.
Bylin et al., 1988	140	30	Non-specific, HIST	20	14	6	0.39 ± 0.07	0.28 ± 0.05	0.052 ^f
Orehek et al., 1976	200	60	Non-specific, CARB	4	3	0	0.60 ± 0.10	0.32 ± 0.02	n.s.
Jörres et al., 1990	250	30	Non-specific, SO ₂	14	11	2	46.5 ± 5.1	37.7 ± 3.5	<0.01
Barck et al., 2002	260	30	Specific, BIR, TIM	13	5	7	-5 ± 2 ΔFEV ₁	-4 ± 2 ΔFEV ₁	n.s.
Strand et al., 1997	260	30	Specific, BIR, TIM	18	9	9	860 ± 450	970 ± 450	n.s.
Strand et al., 1998	260	30	Specific, BIR	16	11	4	-0.1 ± 0.8 ΔFEV ₁	-2.5 ± 1.0 ΔFEV ₁	0.03
Bylin et al., 1988	270	30	Non-specific, HIST	20	14	6	0.39 ± 0.07	0.24 ± 0.04	<0.01
Tunnicliffe et al., 1994	400	60	Specific, HDM	8	8	0	-14.62 ΔFEV ₁	-18.64 ΔFEV ₁	0.009
Bylin et al., 1985	480	20	Non-specific, HIST	8	5	0	>30	>20	0.04
Mohsenin et al., 1987	500	60	Non-specific, METH	10	7	2	9.2 ± 4.7	4.6 ± 2.6	0.042
Bylin et al., 1988	530	30	Non-specific, HIST	20	12	7	0.39 ± 0.07	0.34 ± 0.08	n.s.

Meta-Analysis (Brown, 2015)

- A statistically significant fraction (i.e. 70% of individuals with asthma exposed to NO₂ at rest) experience increases in airway responsiveness following
 - 30-min exposures to NO₂ in the range of 200 to 300 ppb
 - 60-min exposures to 100 ppb
- The fraction experiencing an increase in responsiveness was statistically significant and robust to exclusion of individual studies.
- Following resting exposure to 100 ppb NO₂, 66% of study participants experienced increased non-specific airway responsiveness

Meta-Analysis (Brown, 2015)

- In general, the subjects ranged from 18 to 50 years old
- One study was for children aged 8–16 years
- Mild asthma in most studies, with range from inactive to severe asthma in a few cases
- Airway responsiveness
 - Log-normally distributed
 - Individuals with asthma generally more responsive than healthy age-matched controls

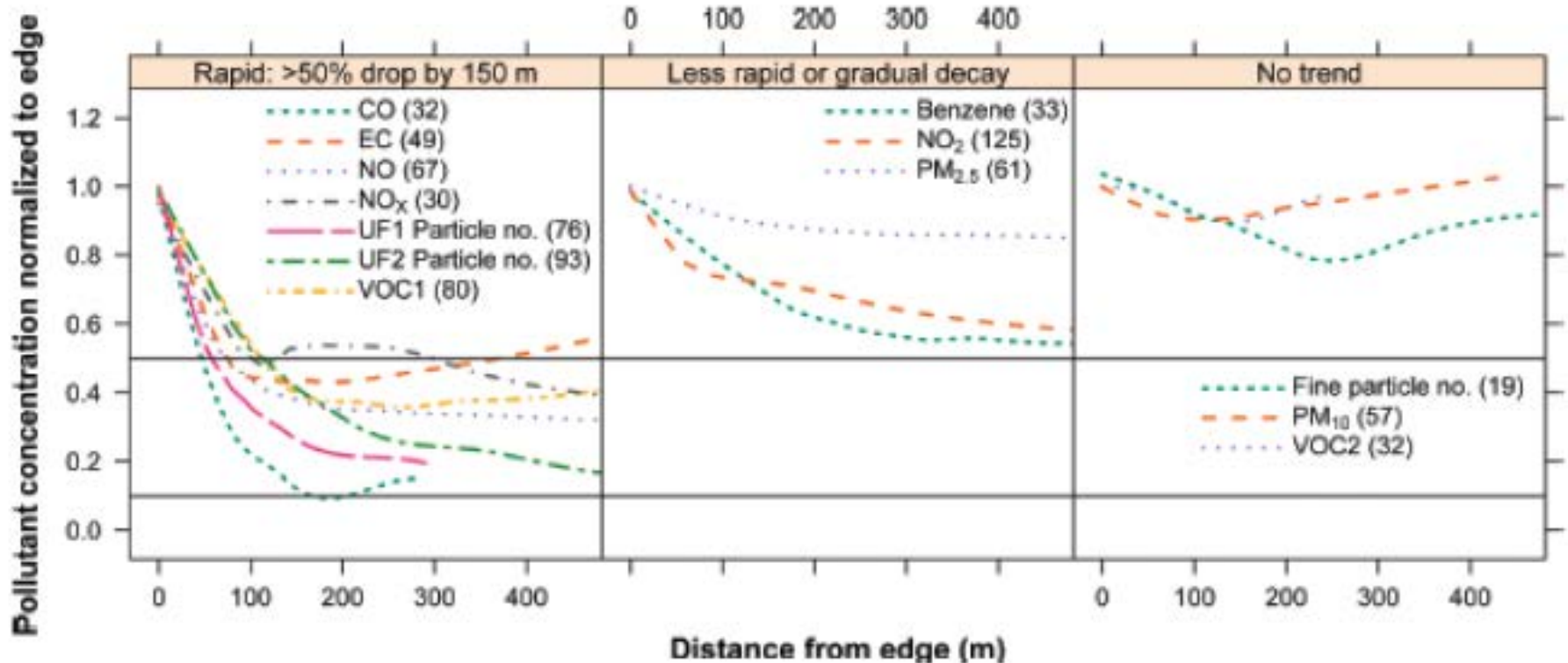
Causal Findings for Short-Term Exposure and Respiratory Effects

- Short-term exposures to NO₂ are causal for respiratory effects
 - Evidence for asthma exacerbation
 - Increase in airway responsiveness based on controlled human exposure studies
 - Supporting evidence from epidemiologic studies
 - Coherence and biological plausibility based on integration of:
 - Controlled human exposure studies
 - Various asthma-related outcomes examined in epidemiologic studies
 - Experimental animal studies

NO₂ Air Quality

- Ambient NO₂ concentrations are highly correlated with concentrations of other pollutants from
 - Combustion sources in general
 - Motor vehicles in particular
 - Strong correlations between ambient NO₂ and
 - Carbon monoxide
 - Black carbon
 - Organic species
 - Some transition metals
 - Ultrafine particulates
- Ozone often has a strong negative correlation with NO₂

Spatial Variation in Concentration of Near-Road Pollutants



Karner et al. (2010).

Note: Concentrations are normalized by measurements at the edge of the road. NO₂, NO, and NO_x concentration gradients are presented in the center panel. NO₂ = nitrogen dioxide, NO = nitric oxide, NO_x = sum of NO₂ and NO; CO = carbon monoxide; m = meter; PM_{2.5} = particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm; PM₁₀ = particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 μm; EC = elemental carbon; VOC1 = volatile organic compounds whose concentrations varied with distance from the road; VOC2 = volatile organic compounds whose concentrations did not vary with distance from the road; UF1 = ultrafine particles larger than 3 nm; UF2 = ultrafine particles larger than 15 nm.

Data presented from Karner et al. (2010) were synthesized from 41 peer-reviewed references, 11 of which reported data for NO₂, 5 of which reported data for NO, and 6 of which reported data for NO_x. The number in parentheses refers to regression sample size. UF1 and UF2 are measures of ultrafine particle number.

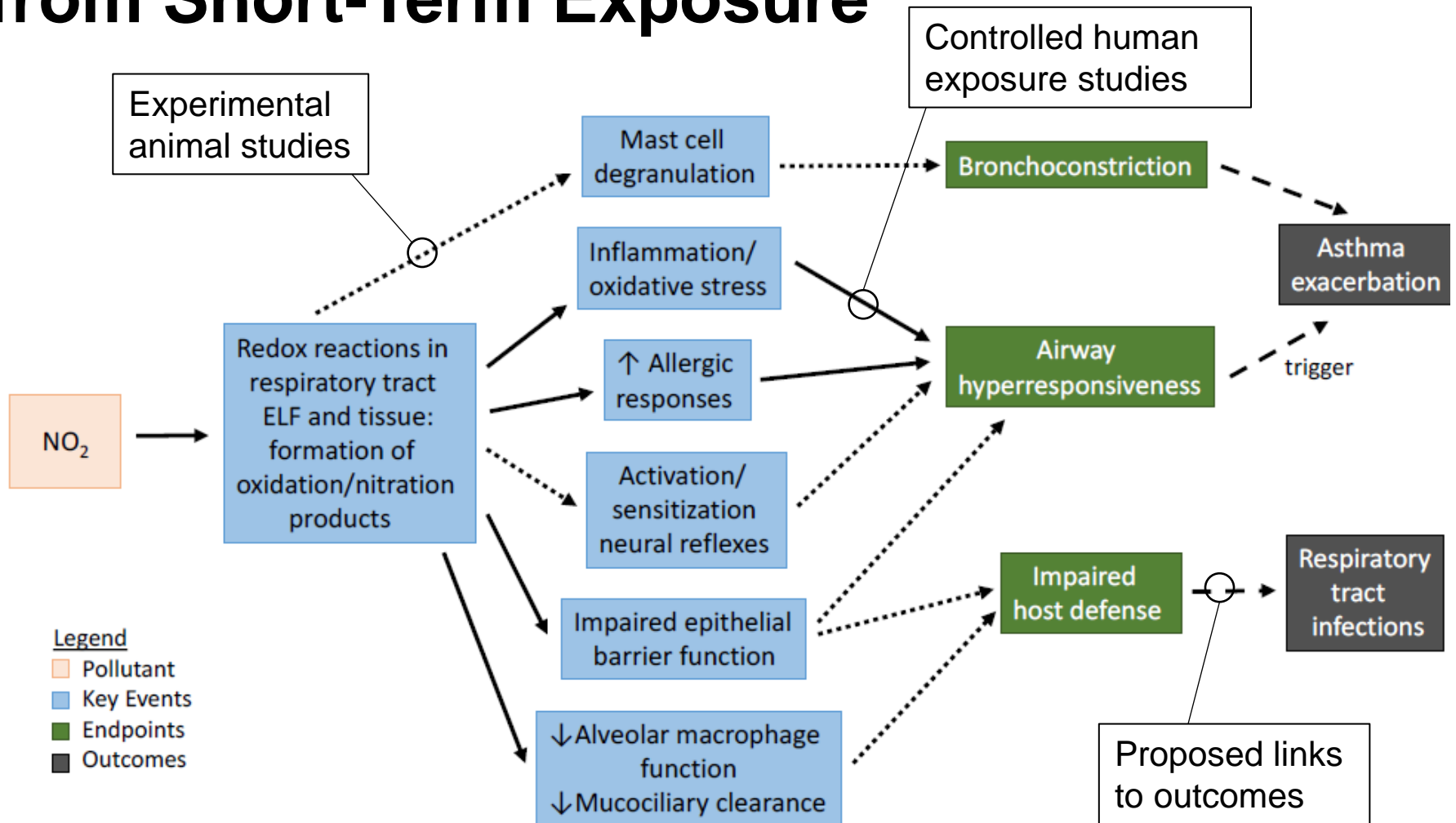
Causal Findings for Short-Term Exposure and Respiratory Effects

- Short-term exposures to NO₂ are causal for respiratory effects
 - NO₂ associations with asthma-related effects persist with adjustment for temperature; humidity; season; and PM₁₀, SO₂, or O₃
 - NO₂ associations generally persist with adjustment for key copollutants, including PM_{2.5} and traffic-related copollutants such as elemental carbon (EC) or black carbon (BC), ultra-fine particles (UFPs), or carbon monoxide (CO)
 - Copollutant models have inherent limitations and cannot conclusively rule out confounding
 - Personal exposures or pollutants measured at people's locations provide support for NO₂ associations that are independent of PM_{2.5}, EC/BC, OC, or UFPs

Dose-Response Considerations

- No indication of a dose-response relationship for exposures between 100 and 500 ppb NO₂ and increased airway responsiveness (AR) in individuals with asthma
- Methodological differences across studies
 - Subject activity level (rest vs. exercise) during NO₂ exposure
 - Asthma medication usage
 - Choice of airway challenge agent (e.g., direct and indirect non-specific stimuli)
 - Method of administering the agents
 - Physiological endpoint used to assess AR
- Lack of an apparent dose-response relationship adds uncertainty to interpretation of controlled human exposure studies of AR, but does not necessarily indicate the lack of an NO₂ effect

Mode of Action for Respiratory Effect from Short-Term Exposure



Pathways indicated by a dotted line are those for which evidence is limited to findings from experimental animal studies, while evidence from controlled human exposure studies is available for pathways indicated by a solid line. Dashed lines indicate proposed links to the outcomes of asthma exacerbation and respiratory tract infections. Key events are subclinical effects, endpoints are effects that are generally measured in the clinic, and outcomes are health effects at the organism level. NO₂ = nitrogen dioxide; ELF = epithelial lining fluid.

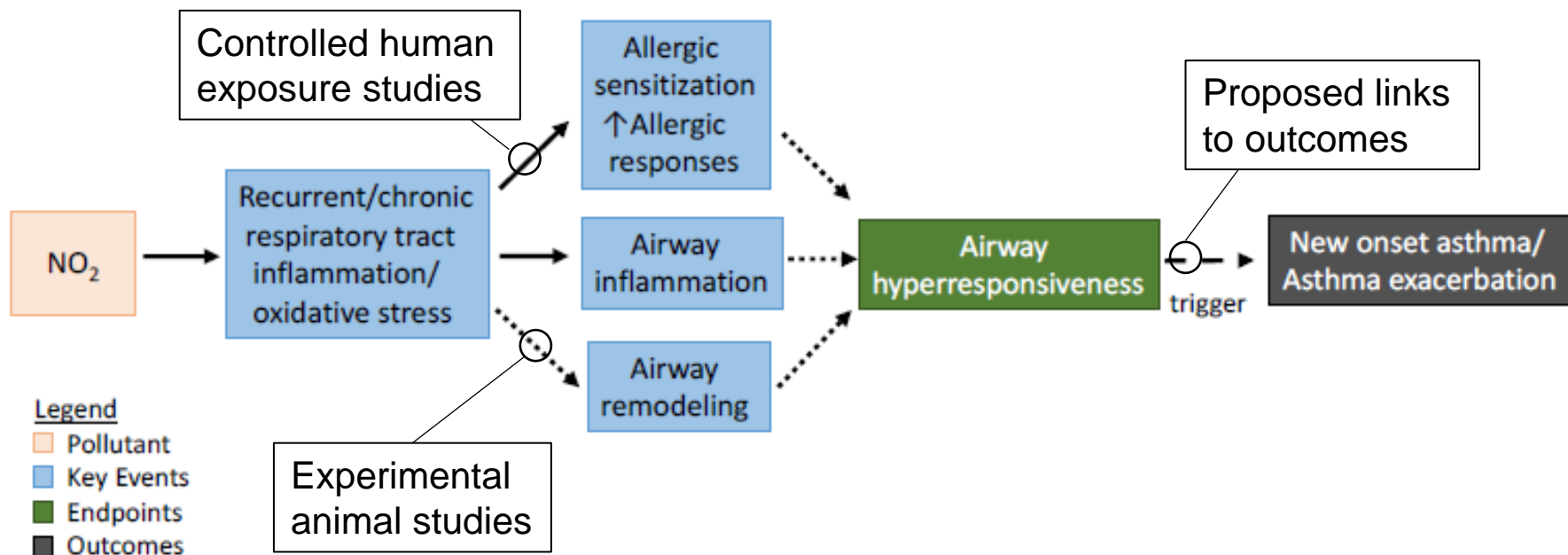
Causal Findings for Long-Term Exposure and Respiratory Effects

- Long-term exposures to NO₂ are likely to be causal for respiratory effects
 - Based on asthma development
 - Strongest evidence is for asthma incidence in children in epidemiologic studies
 - Several recent longitudinal studies indicate positive associations between asthma incidence in children and long-term NO₂ exposures
 - Improved exposure assessment in some studies
 - Based on NO₂ modeled estimates for children's homes or NO₂ measured near children's homes or schools

Causal Findings for Long-Term Exposure and Respiratory Effects

- Long-term exposures to NO₂ are likely to be causal for respiratory effects
 - Inability to determine if NO₂ exposure has an independent effect from that of other pollutants
 - Uncertainty is partly reduced by coherence of findings from experimental animal studies and epidemiologic studies
 - Experimental studies
 - Demonstrate effects on key events in mode of action proposed for development of asthma
 - Provide biological plausibility for the epidemiologic evidence

Summary of evidence for the mode of action linking long-term exposure to nitrogen dioxide and respiratory effects



Pathways indicated by a dotted line are those for which evidence is limited to findings from experimental animal studies, while evidence from controlled human exposure studies is available for pathways indicated by a solid line. The dashed line indicates a proposed link to the outcome of new onset asthma/asthma exacerbation. Key events are subclinical effects, endpoints are effects that are generally measured in the clinic, and outcomes are health effects at the organism level. NO₂ = nitrogen dioxide.

Examples of epidemiologic studies of long-term exposures

- Consistent evidence for increases in asthma incidence in diverse cohorts of children in U.S., Europe, Canada, and Asia: Carlsten *et al.* (2011c), Clougherty *et al.* (2007), Gehring *et al.* (2010), Jerrett *et al.* (2008)
- NO₂ estimated for children's homes with well-validated LUR models or by monitoring at or near children's homes/schools: Carlsten *et al.* (2011c), Gehring *et al.* (2010), Jerrett *et al.* (2008), Shima *et al.* (2002)
- Severity of asthma: McConnell *et al.* (2003), Gehring *et al.* (2010), Hwang and Lee (2010)
- and others...

Policy-Relevant Findings Based on Long-Term Epidemiology

- The available evidence from epidemiologic studies does not provide support for NO₂-associated asthma development in locations that would have clearly met the existing annual (53 ppb) and 1-hour NO₂ (100 ppb) standards
- Potential for confounding by co-occurring pollutants

Populations and Lifestages at Increased Risk

- People with asthma, children, and older adults are at increased risk for NO₂-related health effects
- People living or spending time near or on roads, low socioeconomic status populations, and nonwhite populations may have increased NO₂ exposure
- There is suggestive evidence that people with low antioxidant diets, people of low SES, and females are at increased risk

National Ambient Air Quality Standards: “Primary Standard”

- “the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an **adequate margin of safety**, are **requisite to protect the public health**”
 - Intended to address uncertainties
 - Reasonable degree of protection
 - Does not require zero risk
 - Interpretation has been reviewed in numerous court cases

Policy Considerations

- Available scientific evidence, based on controlled human studies, indicates adverse effects from short-term (1-hour average) exposures at concentrations as low as 100 ppb NO₂
- There is insufficient evidence to support a level lower than 100 ppb NO₂
- The **suite of the current 1-hour standard and the current annual standard, taken together**, imply that attainment of the 1-hour standard corresponds with annual design value averages of 30 ppb NO₂
- There is insufficient evidence to make a scientific judgment that adverse effects occur at annual design values less than 30 ppb NO₂
- Therefore, the CASAC recommends retaining, and not changing, the existing suite of standards

Uncertainties

- Epidemiology-based risk estimates: key uncertainties include those related to
 - Co-pollutant confounding
 - Exposure characterization
 - Baseline incidence
 - Shape of the concentration-response function
- Role of single or repeated short-term NO₂ exposures versus persistent long-term exposures in the development of asthma

EPA, 2016. Integrated Science Assessment for Oxides of Nitrogen –Health Criteria (No. EPA/600/R-15/068). U.S. Environmental Protection Agency, Research Triangle Park, NC.

EPA, 2017. Policy Assessment for the Review of the Primary National Ambient Air Quality Standards for Oxides of Nitrogen (No. EPA-452/R-17-003). U.S. Environmental Protection Agency, Research Triangle Park, NC.

Diez Roux, A., Sheppard, E.A., 2017. CASAC Review of the EPA's Policy Assessment for the Review of the Primary National Ambient Air Quality Standards for Nitrogen Dioxide (External Review Draft – September 2016) (No. EPA-CASAC-17-001). Prepared by Clean Air Scientific Advisory Committee for U.S. Environmental Protection Agency, Washington, D.C.

Research Needs

- Multipollutant exposure and epidemiology
- Additional health effect endpoints (e.g., multiple asthma phenotypes, cardiovascular disease, premature mortality)
- Implications of effects for adversity and clinically significant outcomes
- Improved mechanistic understanding of modes of action
- Meta-analysis of existing and new studies
- Equity and environmental justice
- Temporal and spatial variability in NO₂ concentration
- Better characterization of at-risk populations