Ozone Exposure and Cardiovascular Effects Epidemiology

Evaluation of the Science for the Review of the National Ambient Air Quality Standards

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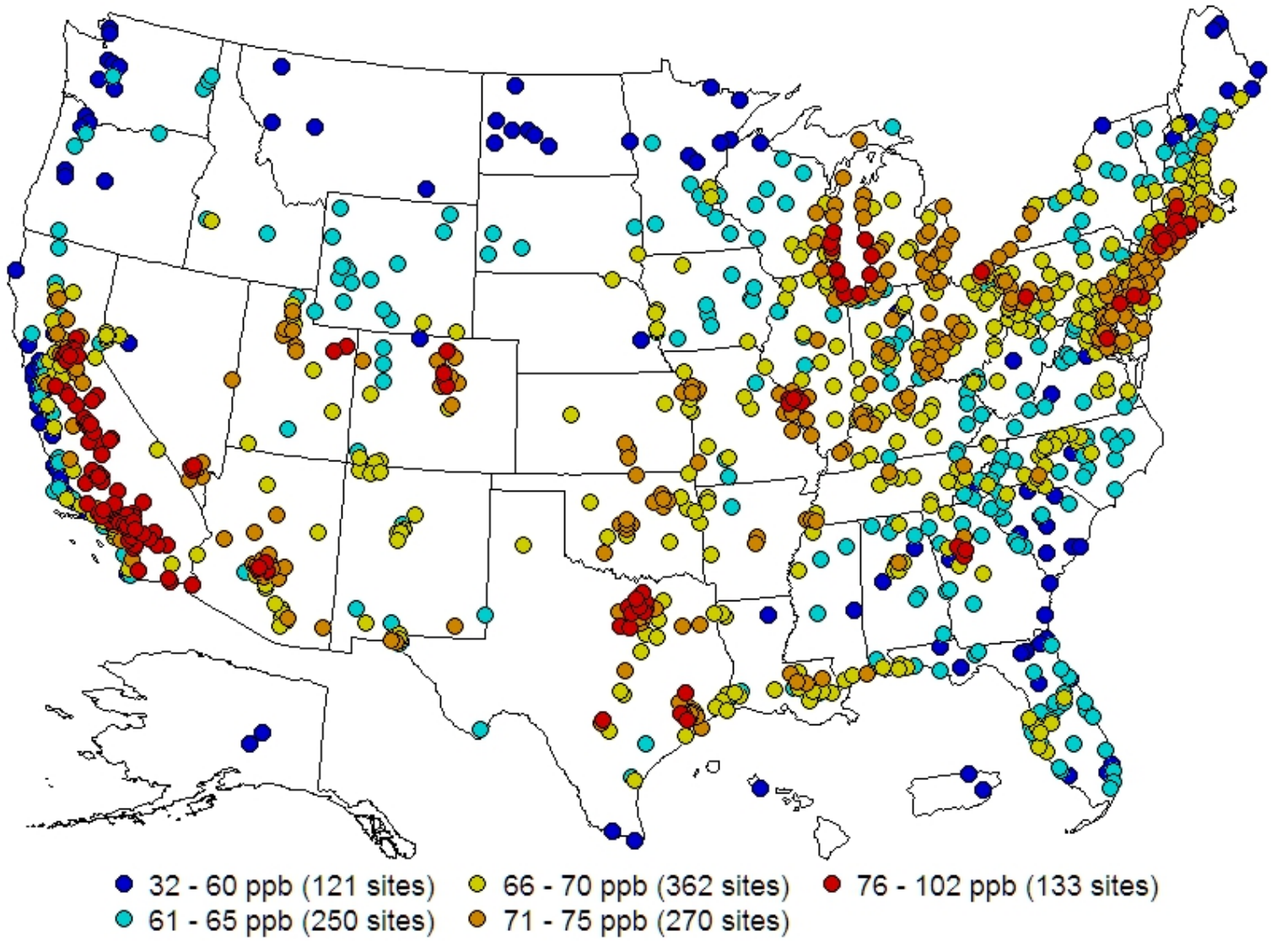
History of the primary (health-based) national ambient air quality standard for ozone

Final Rule	Indicator	Averaging Time	Level (ppb)	Form
October 2015	Ozone	8 hours	70	Annual 4th highest daily maximum 8-hour average, averaged over 3 years
March 2008	Ozone	8 hours	75	Annual 4th highest daily maximum 8-hour average, averaged over 3 years
July 1997	Ozone	8 hours	80	Annual 4th highest daily maximum 8-hour average, averaged over 3 years
March 1993	Standard retained, without revision.			
February 1997	Ozone	1 hour	120	Expected number of days per calendar year with maximum hourly average concentration greater than 120 ppb equal to or less than 1
April 1971	Total photochemical oxidants	1 hour	80	Not to be exceeded more than one hour per year

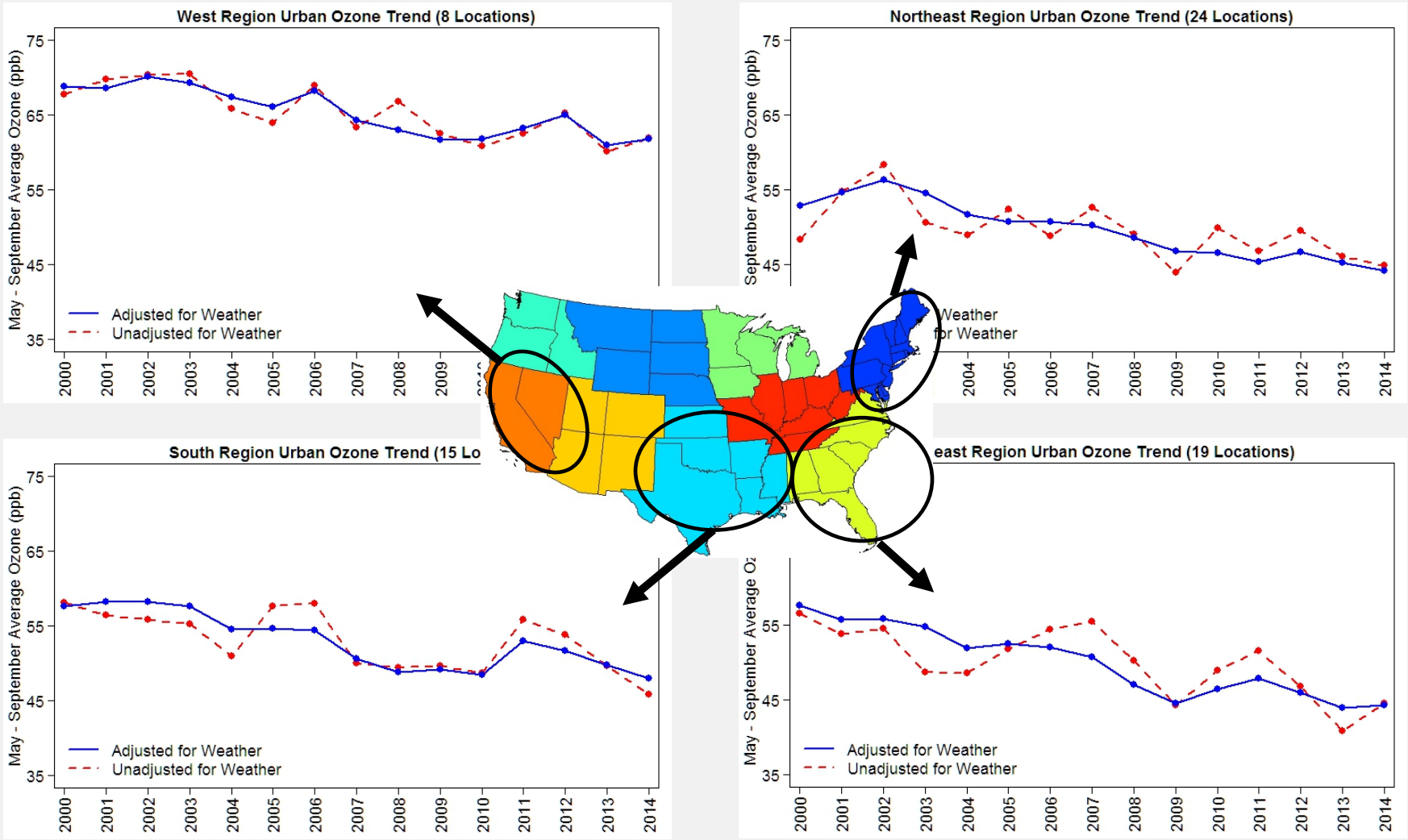
Modified from https://www.epa.gov/ozone-pollution/table-historical-ozone-national-ambient-air-quality-standards-naaqs

U.S. daily maximum 8-hour ozone concentrations annual 4th highest value, 2012-2014 average



Courtesy of the Office of Air Quality Planning and Standards

Annual trends in daily maximum 8-hour ozone concentrations in the urban U.S. - 2000-2014



https://www3.epa.gov/airtrends/weather.html

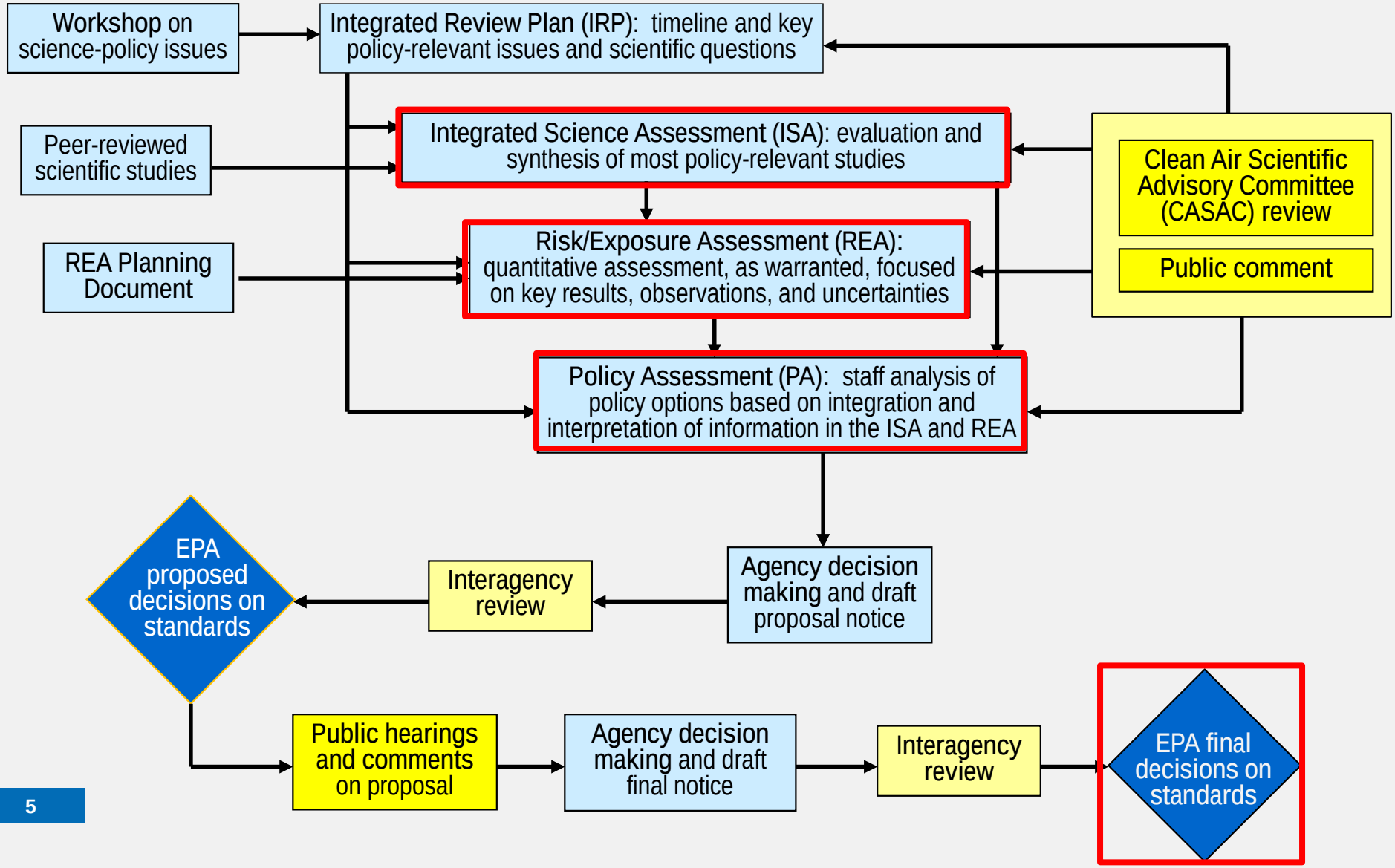
Key scientific considerations for revision to national ambient air quality standard for ozone

- Respiratory effects - causal relationship with short-term exposure
  - Controlled human exposure: pulmonary inflammation, lung function decrements with 60 ppb ozone, broader array of respiratory effects at 70-80 ppb
  - Epidemiology: respiratory emergency department visits and hospital admissions associated with ozone concentrations below 75 ppb
- Level of 70 ppb will provide increased public health protection[1]
  - Reduce ozone exposures of concern – based on 8-hour concentrations at/above health benchmarks
  - Reduce risk of lung function decrements
  - Less weight on epidemiologic risk estimates of mortality and respiratory effects, uncertainty about heterogeneity, presence of association at low concentrations
- Policy Assessment evaluates epidemiologic study of cardiovascular mortality (and other effects) in consideration of alternative standard levels below 75 ppb[2]
  - Assessing ozone concentrations associated with health effects

[1]National Ambient Air Quality Standards for Ozone. Final rule. Federal Register. Volume 80, page 65292. October 26, 2015. https://www.gpo.gov/fdsys/pkg/FR-2015-10-26/pdf/2015-26594.pdf

[2]Policy Assessment for the Review of the Ozone National Ambient Air Quality Standards, August 2014. https://www3.epa.gov/ttn/naaqs/standards/ozone/data/20140829pa.pdf

Process for reviewing the national ambient air quality standards



Integrated Science Assessment for Ozone February 2013

The Integrated Science Assessment accurately reflects "the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health which may be expected from the presence of [a] pollutant in ambient air."
(Clean Air Act, Section 108, 2003)

Review of studies published through July 2011

"There is likely to be a causal relationship between short-term exposure to O_3 [ozone] and cardiovascular effects."

https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=247492

Framework for causal determination

Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures (e.g., doses or exposures generally within one to two orders of magnitude of current levels). That is, the pollutant has been shown to result in health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. For example: (1) controlled human exposure studies that demonstrate consistent effects; or (2) observational studies that cannot be explained by plausible alternatives or that are supported by other lines of evidence (e.g., animal studies or mode of action information). Generally, the determination is based on multiple high-quality studies conducted by multiple research groups.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures. That is, the pollutant has been shown to result in health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. For example: (1) observational studies show an association, but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or (2) animal toxicological evidence from multiple studies from different laboratories demonstrate effects, but limited or no human data are available. Generally, the determination is based on multiple high-quality studies.
relationship	absence of an effect.
Not likely to be a causal relationship	Evidence indicates there is no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering at-risk populations and lifestages, are mutually consistent in not showing an effect at any level of exposure.

-Rule out chance, confounding, and other biases
-Consistency, coherence, biological plausibility, high-quality studies

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uncertainty
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unding, other biases
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nce is sizeable and
ally but not entirely
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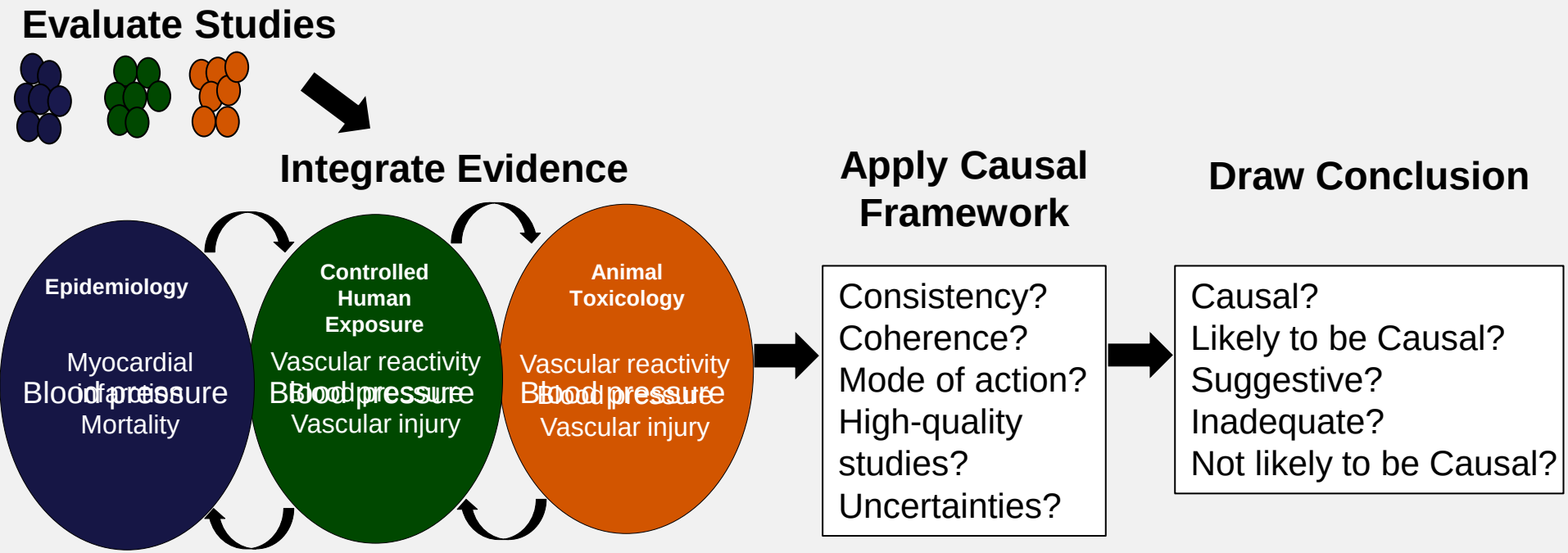
nce insufficient in
quantity, quality,
consistency

Multiple studies consistently show no effect

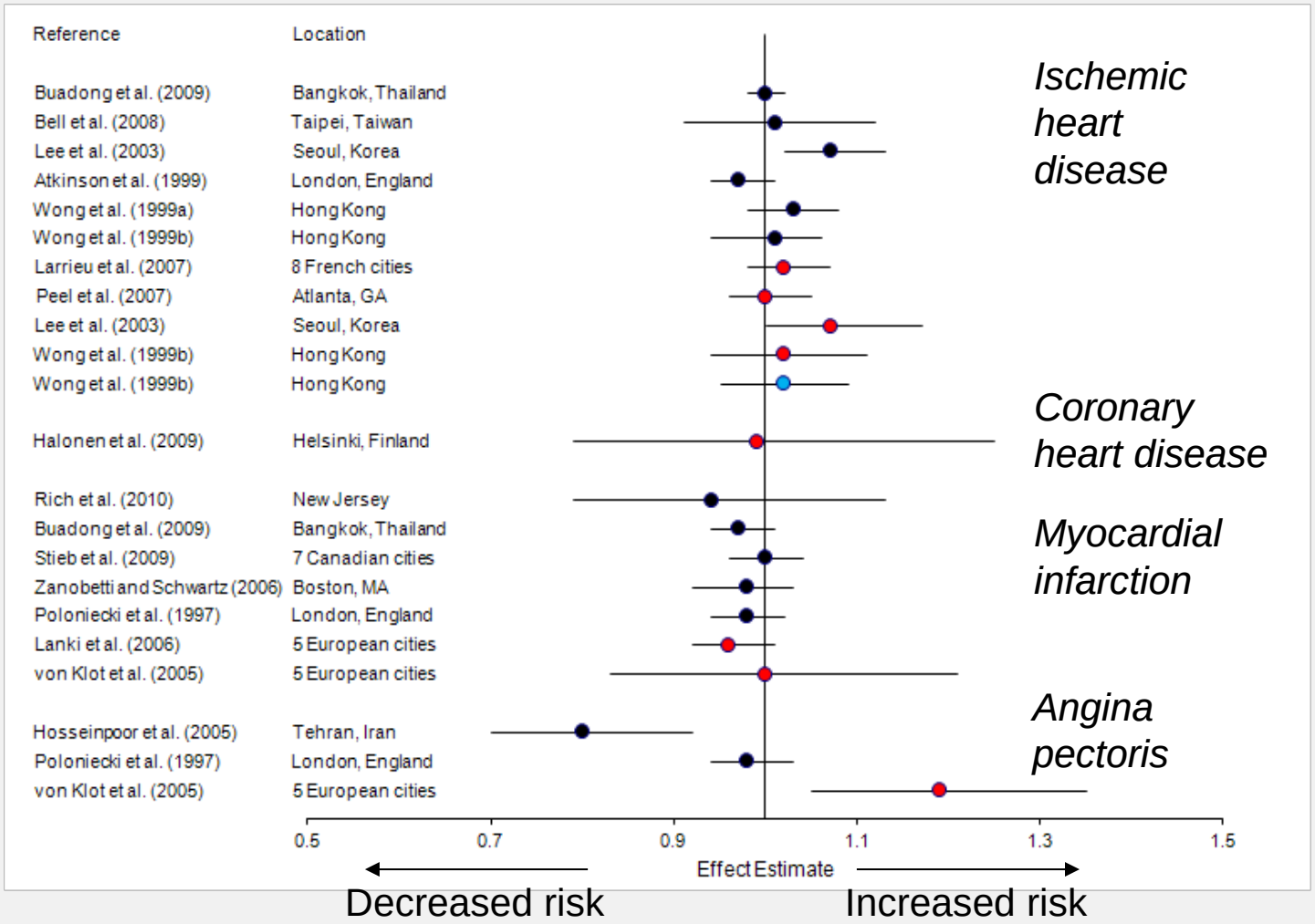
Modified from Table II of Preamble to the Integrated Science Assessment
https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310244

Integration of evidence for causal determination



- Epidemiology, controlled human exposure, animal toxicology and related endpoints
- New study findings and evidence from previous assessments
- Causality determined for broad health category (cardiovascular effects) or group of related outcomes (cognitive function)
- Causality determined for range of concentrations considered relevant - generally within 1-2 orders of magnitude of current levels

Evidence on hospital admissions, emergency department visits for coronary heart diseases



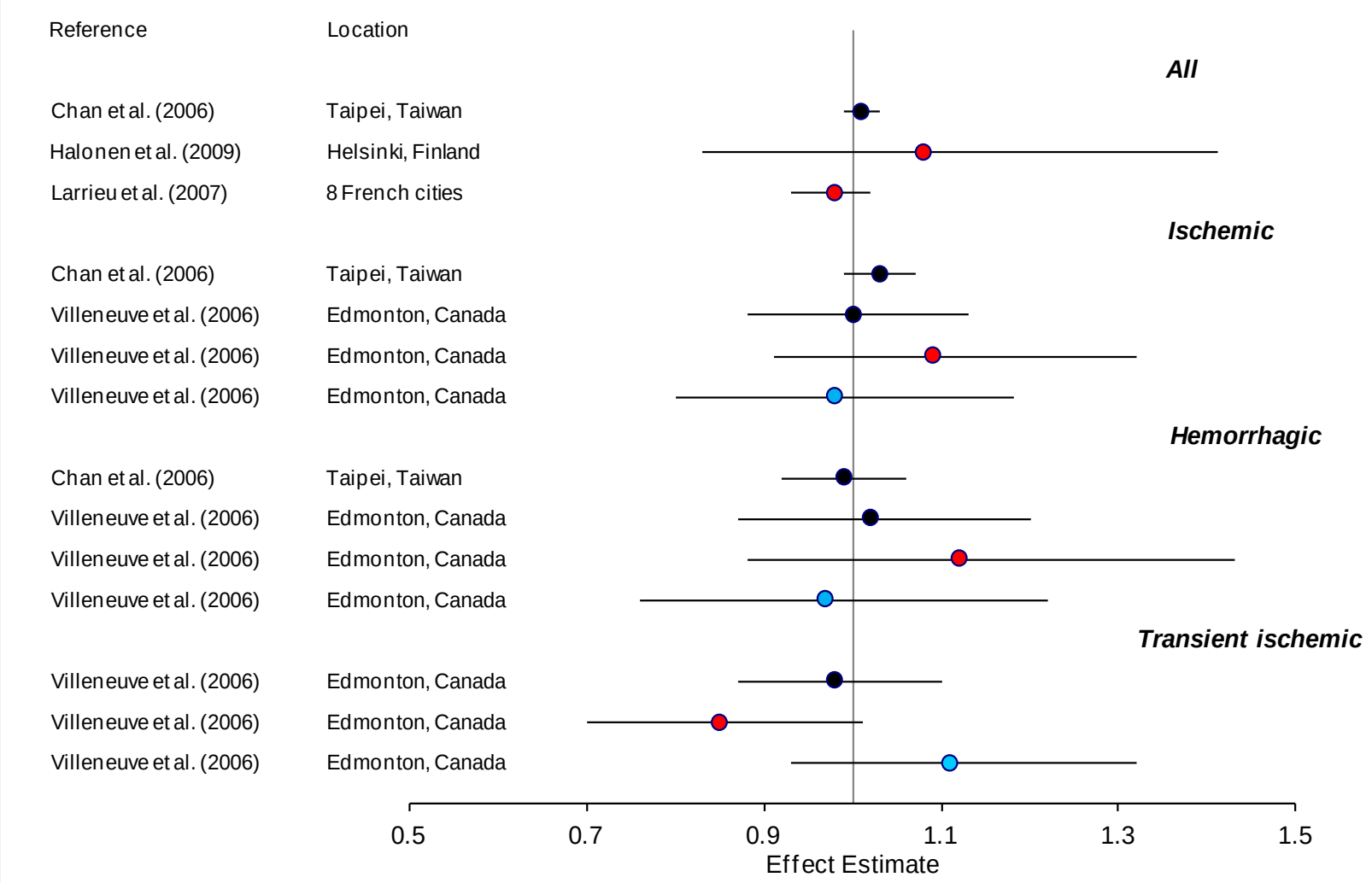
No clear evidence for association by

- Season
  - Warm season
  - All year
- Averaging time
  - Maximum 8-hour
  - Maximum 1-hour
  - 24-hour average
- Exposure lag
  - Same day
  - Previous day
  - 2- to 3-day average
- Age group
  - All ages adults
  - Older adults

Black = all-year, Red = warm season, Blue = cool season

Figure 6-24. 2013 Integrated Science Assessment for Ozone and Related Photochemical Oxidants.

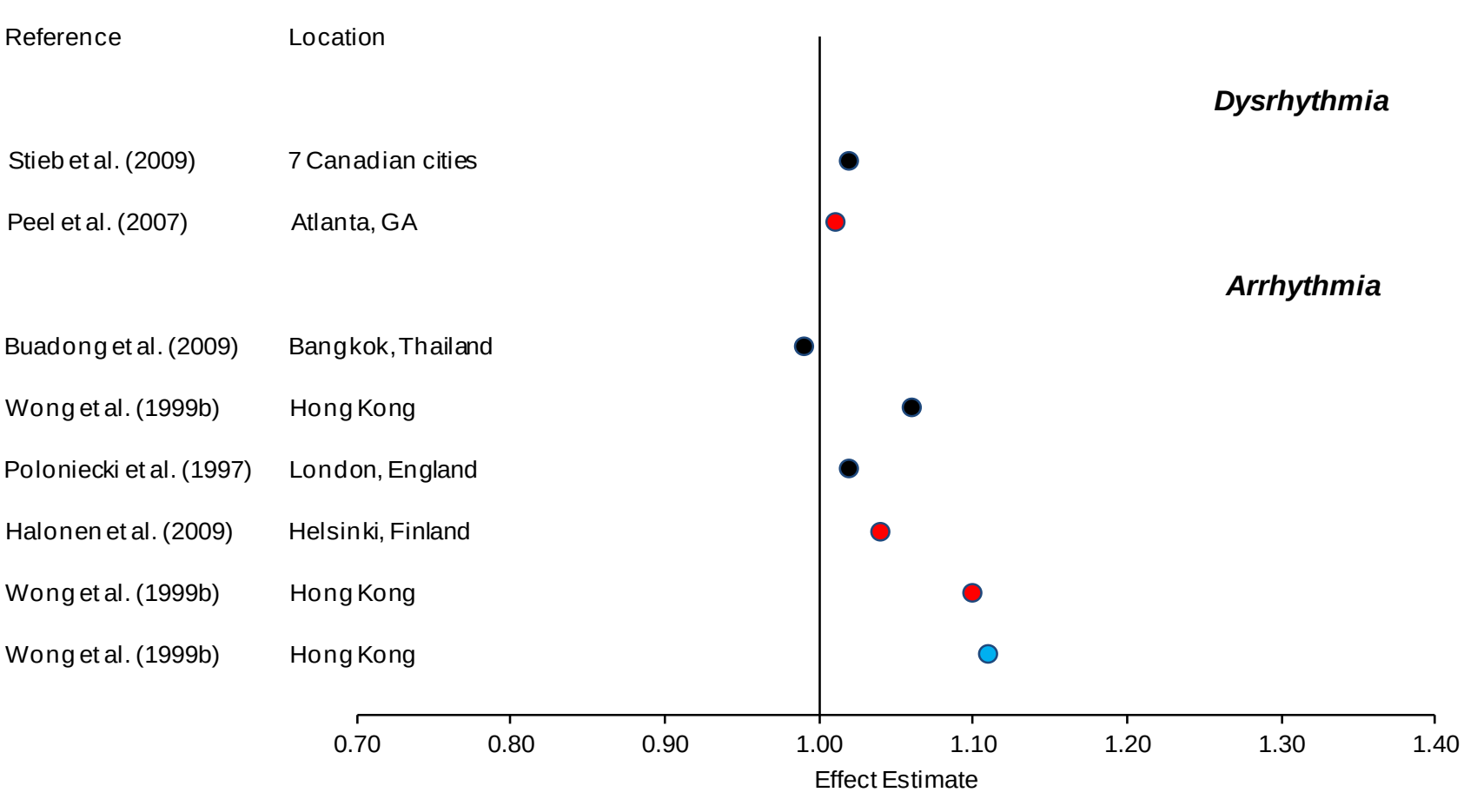
Evidence on hospital admissions, emergency department visits for stroke



Black = all-year, Red = warm season, Blue = cool season

Figure 6-25. 2013 Integrated Science Assessment for Ozone and Related Photochemical Oxidants.

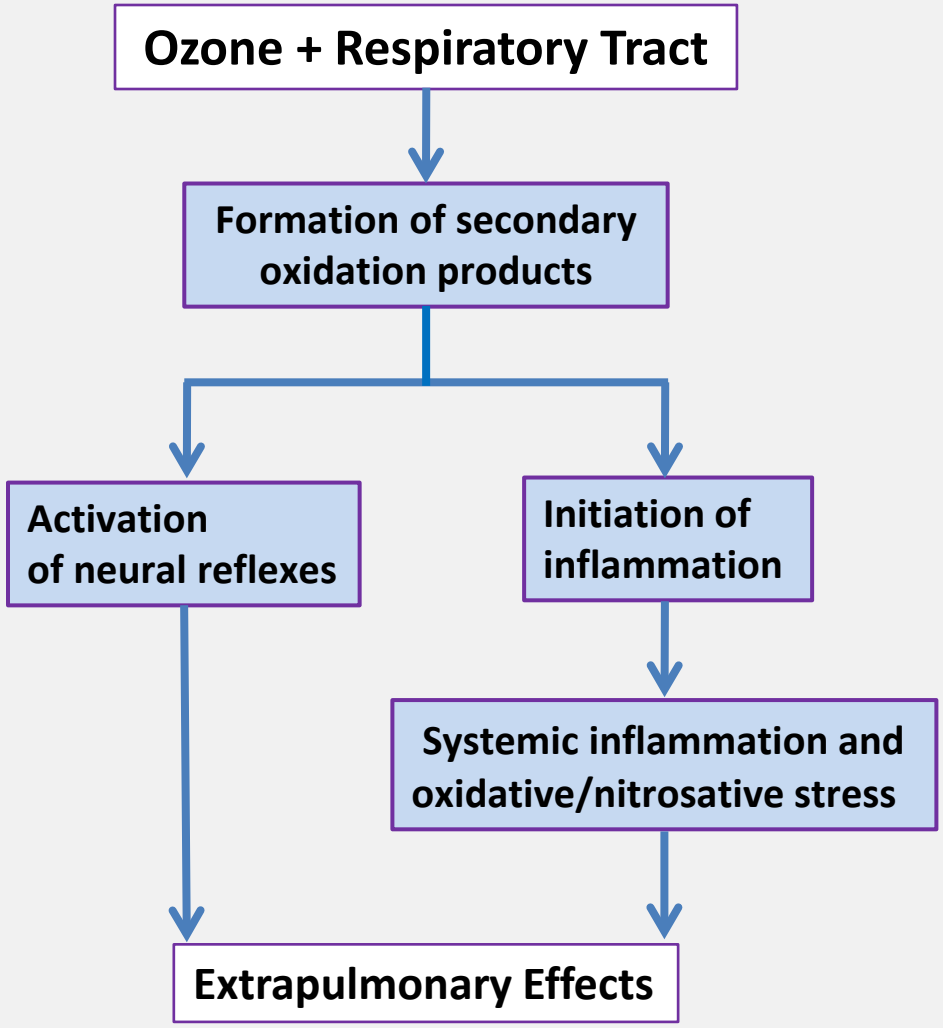
Evidence on hospital admissions, emergency department visits for arrhythmia



Black = all-year, Red = warm season, Blue = cool season

Figure 6-26. 2013 Integrated Science Assessment for Ozone and Related Photochemical Oxidants.

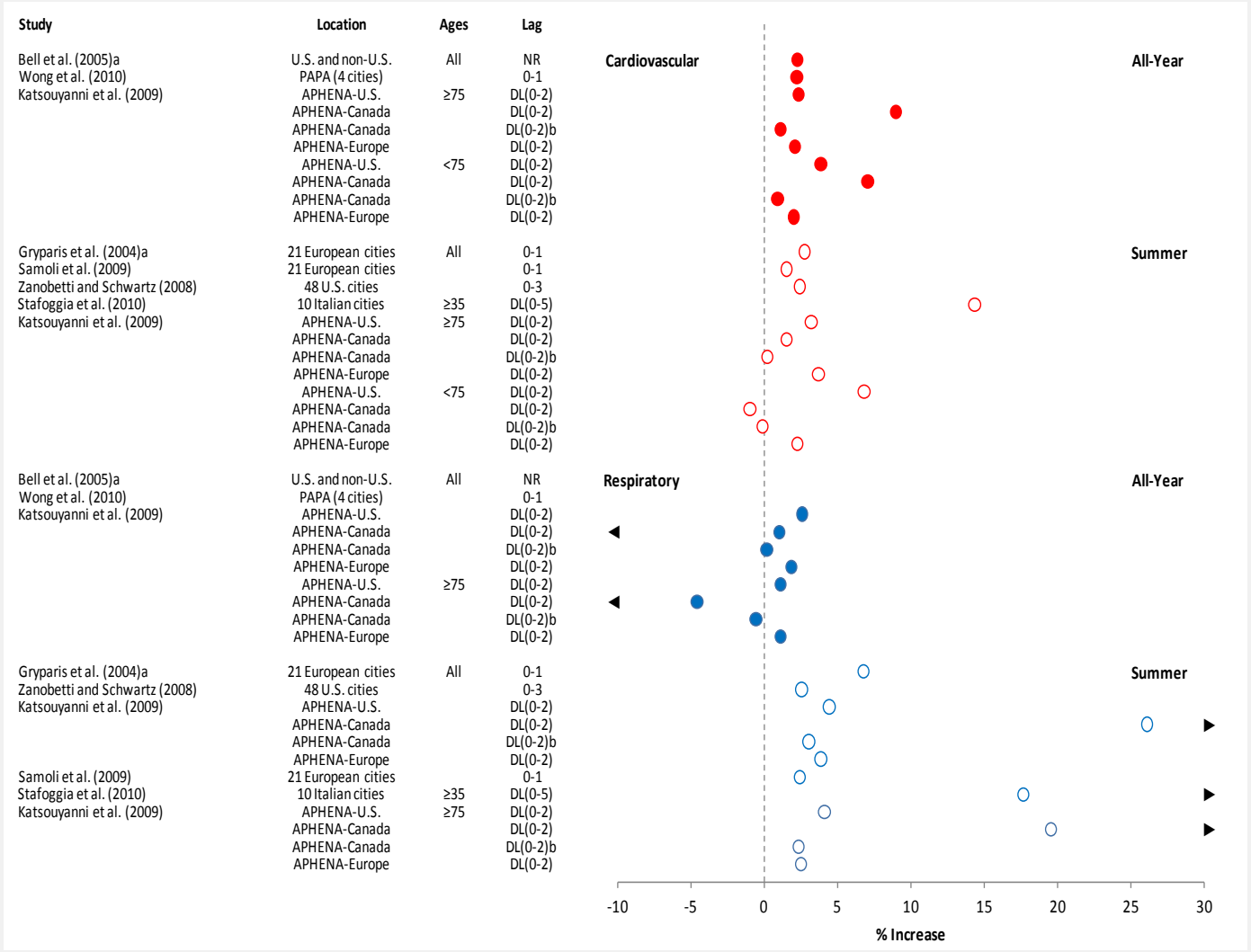
Evidence on cardiovascular biomarkers - events to propose a mode of action



- No clear evidence for
  - Healthy populations or populations with cardiovascular disease
  - Activation of neural reflexes
    - Decreased heart rate variability
    - Altered ventricular repolarization (ST segment changes)
  - Increases in inflammation
    - C reactive protein, interleukin-6
  - Increases in markers of heart failure, vascular disease
    - B-type natriuretic peptide, oxygen saturation, homocysteine, arterial stiffness

Modified from Figure 5-8. 2013 Integrated Science Assessment for Ozone and Related Photochemical Oxidants.

Evidence on cardiovascular mortality



- Consistently positive associations
  - North America, Europe, Asia
  - Warm season and all year
- Associations with
  - maximum 8-hour, 1-hour ozone
  - 2- to 6-day average
- Key evidence from multicontinent study
  - APHENA
  - Maximum1-hour ozone
  - City means: 7-42 ppb

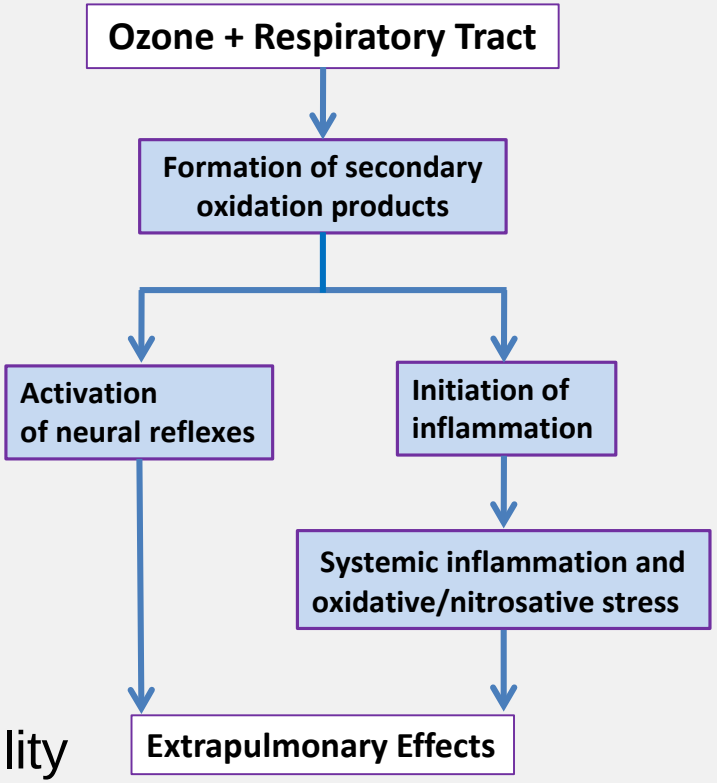
Figure 6-37. 2013 Integrated Science Assessment for Ozone and Related Photochemical Oxidants.

Evaluation of exposure assessment and copollutant confounding

- Ozone exposure estimated from central site monitors associated with cardiovascular mortality
  - Good correlation between ambient concentration and personal exposure – no specific information for cardiovascular studies
  - High within- and between-city correlations in Italy
  - High within-city correlations in Atlanta – no association with cardiovascular emergency department visits
- Ozone measured in subjects' locations not clearly associated with cardiovascular morbidity
  - Arterial stiffness associated with personal exposure in mail carriers
  - Blood pressure and ST-segment changes not associated with ozone measured outside residence of adults with coronary artery disease
- Ozone associations mostly robust to adjustment for $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, sulfate
  - Outcomes: biomarkers of oxidative stress, hospital admissions, mortality
  - Cardiovascular mortality associations robust to PM_{10} adjustment in European cities, more uncertainty in U.S. and Canadian cities

Integration of epidemiology with other disciplines

- Controlled human exposure studies show some coherence
  - Increased pro-inflammatory cytokines, decreased heart rate variability 300 ppb ozone (2 hours with exercise)
  - Inconsistent effects overall on formation of secondary oxidation products, heart rate variability, blood pressure 110-500 ppb ozone (2-3 hours resting or with exercise)



- Animal toxicology supports biological plausibility
  - Increased oxidative stress and inflammation in rodents and monkeys – 500-800 ppb ozone
  - Increased endothelin-1, blood pressure, atherosclerotic plaque, ischemia-reperfusion injury – 500-800 ppb ozone
  - Increased heart rate variability in some rodent strains – 600 ppb ozone

Weight of evidence evaluation and determination of likely to be a causal relationship

- Consistent epidemiologic evidence for cardiovascular mortality, not morbidity
- Biological plausibility from experimental studies
  - Inflammation and autonomic nervous system alterations in humans
  - Increased vascular damage and dysfunction in animal models
- Experimental evidence characterizes biological mechanisms by which ozone could cause cardiovascular mortality
- Key uncertainty is limited coherence in epidemiologic evidence for morbidity – link between early events and mortality
- Clean Air Scientific Advisory Committee: '…the designation should be "likely to be causal" based on consideration of the totality of the evidence…'

Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures. That is, the pollutant has been shown to result in health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. For example: (1) observational studies show an association, but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or (2) animal toxicological evidence from multiple studies from different laboratories demonstrate effects, but limited or no human data are available. Generally, the determination is based on multiple high-quality studies.

Excerpted from Table II of Preamble to the Integrated Science Assessments

https://yosemite.epa.gov/sab/sabproduct.nsf/264cb1227d55e02c85257402007446a4/60C2732674A5EEF385257AB6007274B9/$File/EPA-CASAC-13-001+unsigned.pdf

Gaps to address in epidemiology of ozone and cardiovascular effects

- Consistency in ozone exposure metrics examined
  - Daily maximum 8-hour
  - Analysis and presentation of associations for array of exposure lags (0, 1, 0-1 day, etc)
- Analysis of the shape of the concentration-response relationship and threshold
  - Days or cities with lower versus higher ozone concentrations
- Comparison of exposure assessment methods
  - Average concentrations across central site monitors in a city or county, nearest monitor, residential outdoor, personal
- Evaluation of confounding by PM with daily measurements
- Analysis of specific cardiovascular morbidity outcomes and coherence with mortality associations
- Potential at-risk populations – pre-existing cardiovascular disease

Acknowledgements

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