

**Comments on the Draft Report on the
Clean Air Scientific Advisory Committee (CASAC)
Review of EPA's Integrated Science Assessment for
Oxides of Nitrogen – Health Criteria
(Second External Review Draft)**

Prepared for
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Abbreviations

| | |
|-----------------|---|
| AHR | Airway Hyper-responsiveness |
| CASAC | Clean Air Scientific Advisory Committee |
| ED | Emergency Department |
| EPA | United States Environmental Protection Agency |
| FVC | Forced Vital Capacity |
| HA | Hospital Admissions |
| ISA | Integrated Science Assessment |
| MoA | Mode of Action |
| NO ₂ | Nitrogen Dioxide |
| PD | Provocative Dose |
| TRP | Traffic-related Pollutants |

Executive Summary

While the Clean Air Scientific Advisory Committee (CASAC) discusses several important points in the "Draft Report on the Clean Air Scientific Advisory Committee (CASAC) Review of EPA's Integrated Science Assessment for Oxides of Nitrogen – Health Criteria (Second External Review Draft)" (US EPA, 2015a), there are a few key issues that were not sufficiently addressed:

- Epidemiology evidence does not support a likely causal relationship between long-term nitrogen dioxide (NO₂) exposure and respiratory effects;
- Evidence from controlled exposure studies does not support a causal relationship between short-term NO₂ exposure and respiratory effects;
- The evaluation of studies and selection of key evidence in the "Integrated Science Assessment for Oxides of Nitrogen – Health Criteria" is not consistent or transparent; and
- A thorough study quality evaluation needs to be conducted as part of evidence integration.

1 Epidemiology evidence does not support a likely causal relationship between long-term NO₂ exposure and respiratory effects.

The Clean Air Scientific Advisory Committee (CASAC) acknowledges several limitations with epidemiology evidence, such as bias, noise, exposure measurement error, and uncertainties distinguishing effects from nitrogen dioxide (NO₂) *vs.* other traffic-related pollutants (TRP). Despite these limitations, CASAC concurs with the United States Environmental Protection Agency's (EPA's) Integrated Science Assessment (ISA), which primarily relied on epidemiology evidence as a basis for concluding a likely causal relationship between long-term NO₂ exposure and respiratory effects (US EPA, 2015b).

As we discussed previously (Gradient, 2015), the ISA did not evaluate available epidemiology studies in a systematic, balanced, and rigorous manner; instead, it emphasized studies with positive findings over studies with null results. A critical review shows that results are inconsistent within and across studies. There is a large degree of heterogeneity in exposure windows evaluated in the studies with positive findings, including exposure in year of birth, in the year prior to diagnosis, and in the entire follow-up period, and in the observed effects associated with various exposure windows.

In addition, there are considerable uncertainties in the study findings with regard to confounding by TRP. With the exception of McConnell *et al.* (2010), none of the studies on which the ISA relied conducted multi-pollutant analyses. McConnell *et al.* (2010) acknowledged that in their study, "the attenuated association between asthma and NO₂ continuously measured at the community monitor in models with adjustment for TRP suggests that NO₂ was not causally related to asthma." Further, the evidence of new-onset asthma associated with long-term NO₂ exposure in animal studies is not robust, and the evidence regarding effects associated with the mode of action (MoA) for asthma development is not compelling.

Considering the significant limitations of and uncertainties in the epidemiology studies, the inconsistency and lack of coherence across the epidemiology studies, and the lack of robust, compelling evidence from animal toxicity and MoA studies, CASAC should acknowledge that the evidence is not sufficient to support a likely causal relationship.

2 Evidence from controlled exposure studies does not support a causal relationship between short-term NO₂ exposure and respiratory effects.

CASAC indicates that the meta-analysis of controlled exposure studies by Brown (2015), which is based on analyses in the ISA, provides primary evidence supporting the causal determination for short-term NO₂ exposure and respiratory effects.

Key conclusions of Brown's meta-analysis are that airway hyper-responsiveness (AHR) was observed in a significant fraction (*i.e.*, 70%) of individuals with asthma when exposed to NO₂ while at rest, and that clinically relevant reductions in the airway challenge provocative dose (PD) was experienced by approximately 25% of individuals. While these conclusions may seem compelling, their significance is tempered by the following observations:

- A smaller fraction of individuals (54%) experienced AHR when exposed to NO₂ while exercising;
- Clinically relevant reductions in the PD involved non-specific airway challenges (*e.g.*, pharmacological agents and relatively high concentrations of sulfur dioxide), which have

questionable relevance for assessing potential responsiveness to airway challenges that would be encountered outside of a laboratory setting (*e.g.*, allergens); and

- Clinically relevant PD reductions did not increase with increasing NO₂ concentrations.

Although Brown offered hypotheses to explain the paradoxical lack of an AHR effect for individuals exposed to NO₂ while exercising or when exposed to specific airway challenges, Brown's hypotheses are not supported either by the controlled exposure studies he reviewed or by other scientific evidence. Specifically, Brown posited that the paradoxical lack of an effect for studies in which individuals were exposed while exercising or when exposed to specific airway challenges is because a greater percentage of these studies assessed AHR using forced vital capacity (FVC) maneuvers, which might cause a partial reversal of bronchospasm. However, studies that used FVC maneuvers were actually *more* likely to observe increased bronchoconstriction following NO₂ exposure than following air. Brown also posited that the lack of an NO₂ effect for studies in which individuals were exposed while exercising can be explained by an exercise-induced refractory period. However, Brown's hypothesis is not well supported:

- It invokes circular reasoning by citing results from two of the NO₂ studies, one with and one without exercise, that were conducted at comparable exposure levels, without considering other plausible explanations for the results from these studies (*e.g.*, exposure *via* mouthpiece *vs.* an exposure chamber), and while overlooking results from other NO₂ studies that do not support his hypothesis.
- Brown cited evidence from studies in which exposure to the airway challenge occurred either during or prior to exercise, rather than following exercise (as was done in the NO₂ studies) while overlooking results from studies in which the airway challenge was administered following exercise, which do not provide evidence of a refractory period.
- It does not consider whether the intensity and frequency of exercise in the NO₂ studies was sufficient to induce a refractory period.
- It does not consider that the refractory effect would not necessarily abolish the AHR effect; rather, it would increase the threshold for an effect, and thus would apply to both NO₂ and clean air exposures.

3 The ISA's evaluation of studies and selection of key evidence is not consistent or transparent.

CASAC indicates that EPA should revisit the selection of key studies and evidence in Tables 5-7 and 6-5 in the ISA. Currently, the ISA does not provide explicit rationale for why certain studies are considered key evidence for causal determination while others of similar quality are not.

EPA developed specific criteria in the ISA to evaluate study quality based on features such as the adequacy of study population selection, the representativeness of the exposure assessment, the appropriateness of the statistical analyses, the sufficient control of potential confounders, the validity and reliability of health endpoints, and the overall biological coherence, internally and externally, of the study findings (see Table 5-1 in the ISA). While this is a step in the right direction, the ISA is not always explicit in describing how decisions should be made regarding these factors when evaluating individual studies.

Table 1, below, demonstrates that the ISA did not apply study quality criteria in a consistent and systematic manner, using short-term NO₂ exposure and hospital admissions (HA) and emergency

department (ED) visits for asthma as an example. The ISA indicated that 23 epidemiology studies supported a causal association between short-term NO₂ exposure and asthma exacerbation and indicated in Table 5-45 that several of these studies are of higher quality than others (also see section 5.2.2.4 of the ISA). In Table 1, we present each of the 23 studies according to various study quality characteristics listed in Table 5-1 in the ISA and highlighted, in green, the characteristics that the ISA indicated are indicative of a higher quality study. Table 1 provides a systematic perspective on overall and comparative study quality and shows that the studies designated as "high quality" in the ISA do not appear to be of higher quality than others.

Similarly, we evaluated the quality and relevance of the 12 epidemiology studies of long-term NO₂ exposure and asthma development in children cited in the ISA, and our findings are presented in Table 2. Again, the studies considered as "key evidence" in Table 6-5 in the ISA do not appear to be of higher quality than others.

This shows that EPA's analysis may be biased, because higher quality studies were not given more weight in its analysis. CASAC should recommend that EPA better document its study quality evaluation to minimize bias.

4 A thorough study quality evaluation needs to be conducted as part of evidence integration.

Several CASAC members expressed concern that study quality criteria will "encourage a deconstructive evaluation" of individual studies and will be used as a checklist. While it is true that using these criteria as a checklist is inappropriate, it is critical that all of these criteria are considered.

Study quality evaluation is a critical part of the systematic review process because methodological limitations in air pollution epidemiology studies (such as exposure measurement error, model specification bias, confounding, and multiple testing) undermine the validity of the results. Because lower-quality studies are more likely to contribute to biased findings in the published literature than studies with more methodological rigor, they should receive less weight during evidence integration.

The study quality criteria in the ISA are tailored towards air pollution epidemiology studies and reflect the best practices and most recent methodological advances in this field. Applying these criteria in the evaluation of individual studies provides a rigorous and comprehensive assessment for the validity of the study findings, and rather than being "deconstructive," will ensure a more balanced, rigorous analysis.

CASAC should recommend that EPA better document its study quality evaluation process and be more explicit regarding how it makes decisions on comparative study quality (*i.e.*, how it considers some studies as "key evidence" for causal determinations, but not others). CASAC should acknowledge that it is critical to integrate the study quality evaluation in the systematic review process to assess the impact of biases on the overall weight of evidence, particularly when the body of literature includes a large number of heterogeneous studies.

5 Conclusion

CASAC should recommend that EPA consider the limitations of epidemiology and controlled exposure studies and acknowledge that these studies do not support causal and likely causal relationships between respiratory effects and short-term and long-term NO₂ exposures, respectively. CASAC should also

recommend that EPA continue to use the criteria it developed to evaluate study quality (but not as a checklist), but to do so in a well-documented, consistent, and transparent manner.

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Table 1 Study Quality Characteristics – Epidemiology Studies of Short-term NO₂ Exposure and Asthma HA/ED Visit

| Citation | Inclusion in ISA | | Study Design | | | Exposure Assessment | | | | Outcome Assessment | | Confounding by Co-pollutants | | | Other Confounders | | | | Statistical Methods | | |
|---------------------------------|----------------------|----------------|---------------------------------|-----------------------|------------------------------|-----------------------------------|----------------------------|-------------------------|------------------------------|---|------------------|-------------------------------------|-------------------------------------|-----------------------|---|-------------|-------------|--------|---------------------|---|---|
| | "High-quality" Study | Main Text Only | Design | Single vs. Multi-city | Size/Duration ¹ | NO _x | Comparisons Between Oxides | Central Site Monitoring | Spatial Variability Assessed | Comparison of Exposure Assessment Methods | Type of Outcome | Exclusion of Children < 2 Years Old | Traffic-related Pollutants Assessed | Correlations Reported | Relative Measurement Error in Co-pollutants Discussed | Meteorology | Day of Week | Season | Allergens | Cautious Interpretation of Multi-pollutant Models | Sensitivity Analysis: Alternate Model Specification |
| Strickland <i>et al.</i> (2010) | √ | | Case cross-over | Single | 91,386 ED visits/12 years | NO ₂ | No | Yes | No | No | ED visits | Yes | No ² | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Villeneuve <i>et al.</i> (2007) | √ | | Case cross-over | Single | 57,912 ED visits/10 years | NO ₂ | No | Yes | No | No | ED visits | Yes | CO | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No |
| Jalaludin <i>et al.</i> (2008) | √ | | Case cross-over | Single | 1,826 ED visits/5 years | NO ₂ | No | Yes | No | No | ED visits | No ³ | CO, PM _{2.5} | Yes | No | Yes | Yes | Yes | No | Yes | No |
| Ito <i>et al.</i> (2007) | √ | | Time series | Single | 4 years | NO ₂ | No | Yes | Yes | No | ED visits | No | CO, PM _{2.5} | Yes | Yes | Yes | Yes | No | Yes | Yes | |
| Iskandar <i>et al.</i> (2012) | √ | | Case cross-over | Single | 8,226 HAs/8 years | NO ₂ , NO _x | Yes | Yes | Yes | No | HA | No ⁴ | UFP, PM _{2.5} | Yes | No ⁵ | Yes | Yes | Yes | No | Yes | Yes |
| ATSDR and NYSDOH (2006) | √ | | Time-series | Single | 2 years | NO ₂ | No | Yes | Yes | No | ED visits | No ⁶ | PM _{2.5} | Yes | No | Yes | Yes | Yes | No ⁷ | Yes | Yes |
| Stieb <i>et al.</i> (2009) | √ | | Time series | Multi-city | 4-10 years ⁸ | NO ₂ | No | Yes | No | No | ED visits | No | No ⁹ | Yes | No | Yes | Yes | Yes | No | NA | Yes |
| Samoli <i>et al.</i> (2011) | | √ | Time series | Single | 4 years | NO ₂ | No | Yes | Yes | No | HA | No | No | Yes | No | Yes | Yes | Yes | Yes ¹⁰ | Yes | Yes |
| Peel <i>et al.</i> (2005) | | √ | Time series | Single | 8 years | NO ₂ | No | Yes | Yes | Yes ¹¹ | ED visits | No ⁴ | CO | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes |
| Son <i>et al.</i> (2013) | | √ | Time-series | Multi-city | 6 years | NO ₂ | No | Yes | No | No | HA | No | No ¹² | Yes | No | Yes | Yes | Yes | No | NA | Yes |
| Ko <i>et al.</i> (2007) | | √ | Time-series | Single | 6 years | NO ₂ | No | Yes | No | No | HA | No | PM _{2.5} | Yes | No | Yes | Yes | Yes | No | Yes | Yes |
| Sarnat <i>et al.</i> (2013) | | √ | Time series | Single | 4 years | NO _x | No | Yes ¹³ | Yes | Yes | ED visits | No | No ⁹ | Yes | Yes | Yes | Yes | Yes | No | NA | Yes |
| Orazio <i>et al.</i> (2009) | | √ | Case cross-over | Multi-city | 53,272 ED visits/7 years | NO ₂ | No | Yes | Yes | No | ED visits | No | No ¹² | No | No | Yes | Yes | Yes | No ⁷ | NA | Yes |
| Strickland <i>et al.</i> (2011) | | √ | Time series | Single | 41,741 ED visits/12 years | NO ₂ | No | Yes | Yes | Yes | ED visits | Yes | No ² | No | Yes | Yes | Yes | Yes | No | NA | Yes |
| Li <i>et al.</i> (2011) | | √ | Time series and case cross-over | Single | 12,933 asthma events/3 years | NO ₂ | No | Yes | No | No | ED visits and HA | Yes | No ⁹ | Yes | No | Yes | Yes | Yes | No | NA | Yes |
| Gass <i>et al.</i> (2014) | | √ | Case cross-over | Single | 11 years | NO ₂ | No | Yes | No | No | ED visits | Yes | CO, PM _{2.5} | No | No | Yes | Yes | Yes | No | Yes | No |
| Winquist <i>et al.</i> (2014) | | √ | Time series | Single | 6 years | NO ₂ | No ¹⁴ | Yes | No | No | ED visits | Yes | CO, PM _{2.5} , EC | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes |
| Burnett <i>et al.</i> (1999) | | √ | Time series | Single | 15 years | NO ₂ | No | Yes | No | No | HA | No | CO, PM _{2.5} | Yes | No | Yes | Yes | Yes | No | Yes | Yes |

| Citation | Inclusion in ISA | | Study Design | | | Exposure Assessment | | | | Outcome Assessment | | Confounding by Co-pollutants | | | Other Confounders | | | | Statistical Methods | | |
|-------------------------------|----------------------|----------------|----------------------|-----------------------|--------------------------------------|---------------------|----------------------------|-------------------------|------------------------------|---|--------------------------|-------------------------------------|-------------------------------------|-----------------------|---|-------------|-------------|--------|---------------------|---|---|
| | "High-quality" Study | Main Text Only | Design | Single vs. Multi-city | Size/Duration ¹ | NO _x | Comparisons Between Oxides | Central Site Monitoring | Spatial Variability Assessed | Comparison of Exposure Assessment Methods | Type of Outcome | Exclusion of Children < 2 Years Old | Traffic-related Pollutants Assessed | Correlations Reported | Relative Measurement Error in Co-pollutants Discussed | Meteorology | Day of Week | Season | Allergens | Cautious Interpretation of Multi-pollutant Models | Sensitivity Analysis: Alternate Model Specification |
| Linn <i>et al.</i> (2000) | | √ | Time series | Single | 4 years | NO ₂ | No | Yes | Yes | No | HA | Yes | CO | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes |
| Burra <i>et al.</i> (2009) | | √ | Time series | Single | 10 years | NO ₂ | No | Yes | No | No | Physician visits | No ³ | No ¹⁵ | No | No | Yes | Yes | Yes | No | NA | Yes |
| Sinclair <i>et al.</i> (2010) | | √ | Time series | Single | 4 years | NO ₂ | No | Yes | No | No | Acute out-patient visits | No | No ¹⁶ | Yes | No | Yes | Yes | Yes | No | NA | Yes |
| Tolbert <i>et al.</i> (2000) | | √ | Retrospective cohort | Single | 5,934 ED visits for asthma/3 summers | NO _x | No | Yes | No ¹⁷ | No | ED visits | No | No | Yes | No | Yes | Yes | Yes | No ⁷ | Yes | Yes |
| Jaffe <i>et al.</i> (2003) | | √ | Time series | Multi-city | 6 summers | NO ₂ | No | Yes | No ¹⁷ | No | ED visits | Yes | No | Yes | No | Yes | Yes | Yes | No | NA | No |

Notes:

CO = Carbon Monoxide; EC = Elemental Carbon; ED = Emergency Department; HA = Hospital Admissions; ISA = Integrated Science Assessment Oxides of Nitrogen; NO = Nitrogen Monoxide; NO₂ = Nitrogen Dioxide; NO_x = Oxides of Nitrogen; O₃ = Ozone; OC = Organic Carbon; PM = Particulate Matter; UFP = Ultrafine Particles; VOC = Volatile Organic Compound.

(1) In Table 5-1, EPA did not indicate what sample size and duration are required for a study to be considered "large" and, therefore, more reliable. For the purposes of this table, we highlight time series studies of at least 10 years in duration and case cross-over studies of at least 10,000 events as higher quality.

(2) Several traffic-related co-pollutants were measured and examined in single-pollutants models, but authors did not attempt to determine whether NO₂ associations were confounded by traffic-related co-pollutants.

(3) < 1-year-old subjects excluded.

(4) 0- to 1-year-old subjects analyzed separately.

(5) Limited discussion of exposure measurement error in co-pollutants: only in the context of UFP and the potential that other pollutants were measured more accurately and served as proxies.

(6) Included additional diagnostic criteria for children < 1 year old to mitigate outcome misclassification.

(7) Aeroallergens measured but not included in statistical models as a confounder.

(8) Duration varied by city.

(9) CO and PM_{2.5} measured and analyzed in separate models, but no multi-pollutant models were conducted.

(10) Desert dust, which includes bio-allergens.

(11) Compared monitoring systems.

(12) CO measured and analyzed in separate models, but no multi-pollutant models were conducted. Authors did not assess potential co-pollutant confounding in any other manner.

(13) Dispersion modeling used in addition to measurements from central site monitors.

(14) Nitrate also examined.

(15) PM_{2.5} measured and analyzed in separate models, but no multi-pollutant models were conducted. Authors did not assess potential co-pollutant confounding in any other manner.

(16) PM_{2.5}, CO, oxygenated VOCs, EC, OC, and metals were measured and analyzed in separate models, but no multi-pollutant models were conducted. Authors did not assess potential co-pollutant confounding in any other manner.

(17) Spatial variability of other pollutants (*i.e.*, O₃ and PM) only was assessed, but not variability of NO₂.

The cell is shaded green if a study characteristic meets a quality criterion; otherwise, the cell is shaded red.

Table 2 Study Quality Characteristics – Longitudinal Cohort Studies of Long-term NO₂ Exposure and Asthma Development in Children

| Study | Inclusion in ISA | | Study Population | | Follow-up Period | Exposure assessment | | Outcome Ascertainment | Confounders Evaluated | | | | | | Linear CRF | Non-linear CRF | |
|---------------------------------|----------------------|----------------|---------------------|--------------------------|--|---------------------|-------------------------|---|--|-----|-----|------|-----|-----|------------|--------------------------|--------------------------|
| | "High-quality" Study | Main Text Only | Representativeness | Sample Size ¹ | | Method | NO _x | | Exposure Metric and Exposure Window Evaluated | TRP | SES | Race | Age | Sex | | | Smoking |
| Carlsten <i>et al.</i> (2011) | √ | | High risk | 184 | Birth to 7 years old | LUR | NO ₂ and NO | Annual mean in birth year | Diagnosis by allergist | No | Yes | Yes | Yes | Yes | No | Yes | Quartiles of exposure |
| Clark <i>et al.</i> (2010) | | √ | Birth cohort | 37,401 | Pregnancy through 3-4 years old | IDW & LUR | NO ₂ and NO | Long-term average from the year of pregnancy to first year of life | Physician diagnosis (billing record) | No | Yes | Yes | Yes | Yes | Yes | Yes | Quartiles of exposure |
| Gehring <i>et al.</i> (2010) | √ | | Population-based | 3,863 | Birth to 8 years old | LUR | NO ₂ | Long-term average since birth through 8 years old; annual mean in age 1 to 8 years | Parental report of physician diagnosis | No | Yes | Yes | Yes | Yes | Yes | Yes | None |
| Gruzieva <i>et al.</i> (2013) | | √ | Birth cohort | 4,089 | Birth to 12 years old | Dispersion | Traffic NO _x | Annual mean in first year of life; long-term average since the previous follow-up | Asthma defined by parental report of symptoms and medication use | No | Yes | No | Yes | No | No | Yes | None |
| Oftedal <i>et al.</i> (2009) | | √ | Population-based | 2,329 | Birth through 9-10 years old | Dispersion | NO ₂ | Long-term average since birth to asthma onset; annual mean in first year of life | Parental report of physician diagnosis | No | Yes | Yes | Yes | Yes | Yes | Yes | Cubic spline of exposure |
| Ranzi <i>et al.</i> (2014) | √ | | Birth cohort | 672 | Birth up to 7 years old | LUR | NO ₂ | Annual mean in birth year; annual mean prior to outcome assessment; long-term average since birth | Parental report of physician diagnosis | No | Yes | No | Yes | Yes | Yes | Yes | None |
| Shima <i>et al.</i> (2002) | √ | | Population-based | 1,910 | Age 6 through 6th grade | Central monitors | NO ₂ | Long-term average over the follow-up period (10 years) | Parental report of physician diagnosis | No | No | Yes | Yes | Yes | Yes | Yes | None |
| Clougherty <i>et al.</i> (2007) | √ | | Single community | 413 | Birth through age 6-7 years old | LUR | NO ₂ | Annual mean in birth year; annual mean in the year of diagnosis; long-term average since birth; <i>etc.</i> | Parental report of physician diagnosis | No | Yes | No | Yes | Yes | Yes | Overall D-R not reported | None |
| Jerrett <i>et al.</i> (2008) | √ | | Population-based | 217 | Age 10 years through HS graduation | Home-based monitors | NO ₂ | Summer, winter, and annual mean in 2000 (end of follow-up) | Child report of physician diagnosis | No | Yes | Yes | Yes | Yes | Yes | Yes | Tertiles of exposure |
| Lee <i>et al.</i> (2012) | | √ | Population-based | 2,818 | 2 years, starting at 7th grade | Central monitors | NO ₂ | Long-term average from 2007 to 2009 | Child report of physician diagnosis | No | No | Yes | Yes | Yes | Yes | Overall D-R not reported | None |
| McConnell <i>et al.</i> (2010) | | √ | Population-based | 2,497 | 3 years, starting at kindergarten or first grade | Central monitors | NO ₂ | Long-term average over the follow-up period (3 years) | Parental report of physician diagnosis | TRP | Yes | Yes | Yes | Yes | Yes | Yes | Cubic spline of exposure |
| Nishimura <i>et al.</i> (2013) | | √ | High risk, minority | 4,320 | 8 to 21 years old | IDW | NO ₂ | Long-term average since birth to age 3 years; annual mean in first year of life | Parental report of physician diagnosis | No | Yes | Yes | Yes | No | No | Yes | None |

Notes:

LUR = Land-use Regression; NO₂ = Nitrogen Dioxide; IDW = Inverse Distance-weighted; NO = Nitric Oxide; NO_x = Nitrogen Oxide; TRP = Traffic-related Pollutants; SES = Socioeconomic status; CRF = Concentration-response Function; D-R = Dose-response.

(1) In Table 5-1, EPA did not indicate what sample size is required for a study to be considered "large" and, therefore, more reliable. For the purposes of this table, we consider studies with sample size above the median (~2,400) as higher quality.

The cell is shaded green if a study characteristic meets a quality criterion; otherwise, the cell is shaded red.