Near Roadway Indoor Air Pollution: Assessing Health Effects and Strategies

Appendix B1. Comprehensive Description of Overview Methods

This document contains a detailed description of the methods used by CalSPEC to conduct a rapid overview of reviews on the health effects of NRAP exposure.

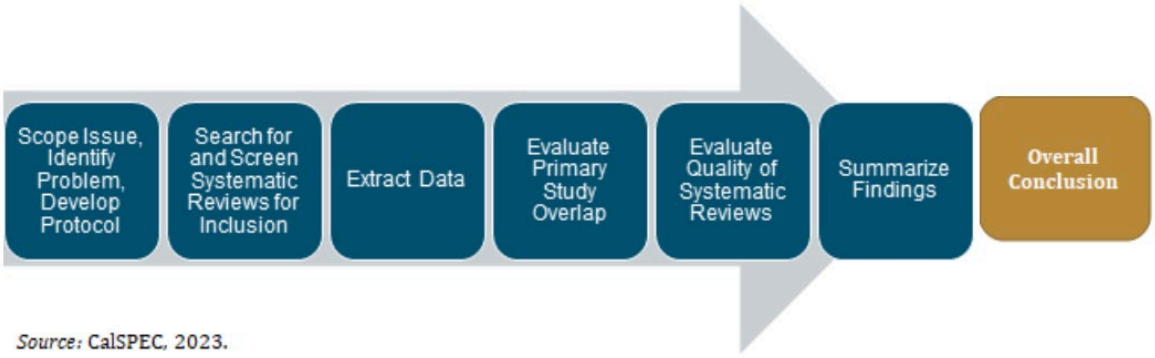
Methods

Robust systematic review methods have been developed and empirically validated in environmental health over the past decade to support evidence-based decision-making and to make science actionable by synthesizing what is known about environmental drivers of health, including near roadway air pollution (NRAP) (Sutton et al. 2021). As the number of primary studies on the same topics grows larger, researchers conduct systematic reviews to assess overall study quality and synthesize findings to draw broad evidence-based conclusions. Similarly, as the number of topical systematic reviews increase, researchers perform overviews of systematic reviews, which are at the apex of the hierarchy of the quality of evidence. Multiple systematic reviews have been published on NRAP, across a broad range of outcomes; thus, CalSPEC conducted an overview of systematic reviews (referred to as "overview" hereafter) using well-established methods to summarize the evidence on health effects of NRAP (Pollock et al. 2022; Lam et al. 2014).

Systematic review: a type of review that identifies and synthesizes all available evidence relevant to a specific research question using primary studies as the unit of analysis. Systematic reviews provide a summary of what is known and what is not known about a topic. Their main advantages over less formal literature or "narrative" reviews are comprehensiveness, transparency, consistency, reproducibility, and less susceptibility to bias (Cochrane Collaboration, 2023).
Overview of reviews: also referred to as "umbrella reviews," "reviews of reviews," and "meta-reviews," follow the steps of a full systematic review; however, instead of an evaluation of primary studies, overviews evaluate systematic reviews as the unit of analysis (Pollock et al., 2022).

CalSPEC used prespecified search terms and eligibility criteria to identify relevant systematic reviews and applied established scientific methods to evaluate the quality of the reviews included in this overview (Shea et al., 2017). A description of the methods used for conducting this overview can also be found in the pre-published protocol (**Appendix A**); a summary of the steps used is outlined in Figure 1.

Figure 1. Steps in the CalSPEC "Overview of Reviews" Process



Source: CalSPEC, 2023.

Study Screening and Selection

CalSPEC performed a comprehensive search with a medical librarian to identify systematic reviews that examined any human health effects of NRAP. CalSPEC did not restrict this search by publication date or language and included any relevant systematic review from the databases' inception published through May 15, 2023 (peer reviewed literature) or June 21, 2023 (grey literature), reflecting the dates on which the searches were run.

CalSPEC used a rigorous method of assessment to determine if a review used the required methodological principles to meet the definition of a systematic review, as narrative reviews are often incorrectly categorized as such in the environmental health literature (Page et al., 2021).

Prioritizing Exposures

CalSPEC included any systematic review in which authors indicated they were assessing the effects of NRAP on health outcomes inclusive of air pollutants that were measured near a roadway (NRAP) as well as traffic-related air pollution (TRAP—a term commonly used in the literature to describe NRAP.) To adhere to report timeline considerations, CalSPEC focused on reviews that looked specifically at measures of NRAP (i.e. distance to roadway, traffic density) and/or single pollutants nitrogen dioxide (NO_2) and elemental carbon (EC)[1] from near roadway air pollution. NO_2, EC, and PM are commonly used as indicators of NRAP in epidemiological studies. Studies on PM were excluded as PM has significant contributions from sources other than traffic (HEI 2022). Primary studies in the systematic reviews needed to indicate that they had measured the single pollutants specifically near roadways using dispersion models or land use regression models (LUR) to attribute measured health outcomes to NRAP exposure. Reviews also had to contain more than one relevant primary study to be included.

[1] HEI (2022) groups elemental carbon (EC), black carbon (BC), black smoke (BS), and PM absorption (PM_{abs}) together under the term elemental carbon. Levels of PM_{abs} have been shown to be well correlated with EC (Cyrys et al. 2003).

NRAP vs TRAP

Near roadway air pollution (NRAP): air pollution "within a few hundred meters - about 500-600 feet downwind from the vicinity of heavily traveled roadways or along corridors with significant trucking traffic or rail activities. This distance will vary by location and time of day or year, prevailing meteorology, topography, near land use, traffic patterns, as well as the individual pollutant" (EPA, 2014).
Traffic related air pollution (TRAP): "ambient air pollution resulting from the use of motorized vehicles such as heavy-duty and light-duty vehicles, buses, coaches, passenger cars, and motorcycles" (Khreis et al. 2020).

Prioritizing Outcomes

To rapidly evaluate and summarize the evidence on this topic, CalSPEC focused on clinical or apical outcomes including mortality and health effects related to respiratory, cardiovascular, reproductive, nervous, endocrine systems, and cancer. CalSPEC excluded outcomes related to childhood adiposity, sleep apnea, allergic rhinitis, atopic dermatitis, and rheumatoid arthritis, and made these decisions without looking at study results. CalSPEC extracted key information from each eligible review to construct an evidence table.

Clinical outcomes: a measurable change in symptoms, overall health, ability to function, quality of life, or survival outcome (FDA-NIH Biomarker Working Group, 2016)
Apical outcomes: observable outcomes in an organism (such as a clinical sign or pathological state) that indicates disease; outcomes observed at an organ level or higher (Krewski et al. 2010)
Mechanistic outcomes: mechanisms/biological pathways that are thought or known to be linked to apical endpoints

Assessing Primary Study Overlap Across Systematic Reviews

An important consideration when conducting an overview is the potential overlap of primary studies (Lunny et al., 2021; Pieper et al., 2014; Pollock et al., 2022). This means that systematic reviews on a similar topic may include the same primary studies, which may overstate impacts due to overcounting. To address this and reduce the potential of using the same exact study more than once to inform the overall conclusions, CalSPEC used the established GROOVE tool (Graphical Representation of Overlap for OVErviews) to calculate overlap across and between reviews (Perez-Bracchiglione et al., 2022). When overlap was identified, CalSPEC prioritized reviews of higher quality, those with more recent publication dates, and those with meta-analyses.

Evaluating the Quality of Systematic Reviews

CalSPEC assessed the quality of the systematic reviews using the validated AMSTAR (A MeaSurement Tool to Assess systematic Reviews) tool that was modified with expert input to better address the available evidence (Shea et al., 2017; Puljak et al., 2023). The tool was developed to enable more detailed assessment of systematic reviews that include randomized or non-randomized studies of healthcare interventions, and not specifically studies of exposure used in systematic reviews for environmental health. CalSPEC applied 16 criteria to evaluate the quality of the selected systematic reviews which were assessed as yes, partial yes, or no. Out of these 16 criteria, six were considered critical domains that are used in determining the overall rating of the systematic review, including: 1) protocol registration prior to commencement of the review, 2) adequacy of the literature search, 3) justification for inclusion of individual

studies, 4) risk of bias from individual studies, 5) appropriateness of analytical methods, and 6) consideration of risk of bias when interpreting results.

Based on this methodology, the rating scale for overall quality of systematic reviews includes high, moderate, low, or critically low:

> **High** – The systematic review has no or one non-critical weakness and provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.
>
> **Moderate** – The systematic review has more than one non-critical weakness and may provide an accurate summary of the results of the available studies that were included in the review.
>
> **Low** – The systematic review has one critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.
>
> **Critically low** – The systematic review has more than one critical flaw with or without non-critical weaknesses and should not be relied on to provide an accurate and comprehensive summary of the available studies (Shea et al., 2017).

The modified AMSTAR tool applied by CalSPEC and further details on the evaluation process can be found in the protocol (**Appendix A**). CalSPEC considered systematic reviews of 'Low', 'Moderate' or 'High' quality sufficient to draw conclusions from on the health effects of NRAP.

Summarizing Outcomes

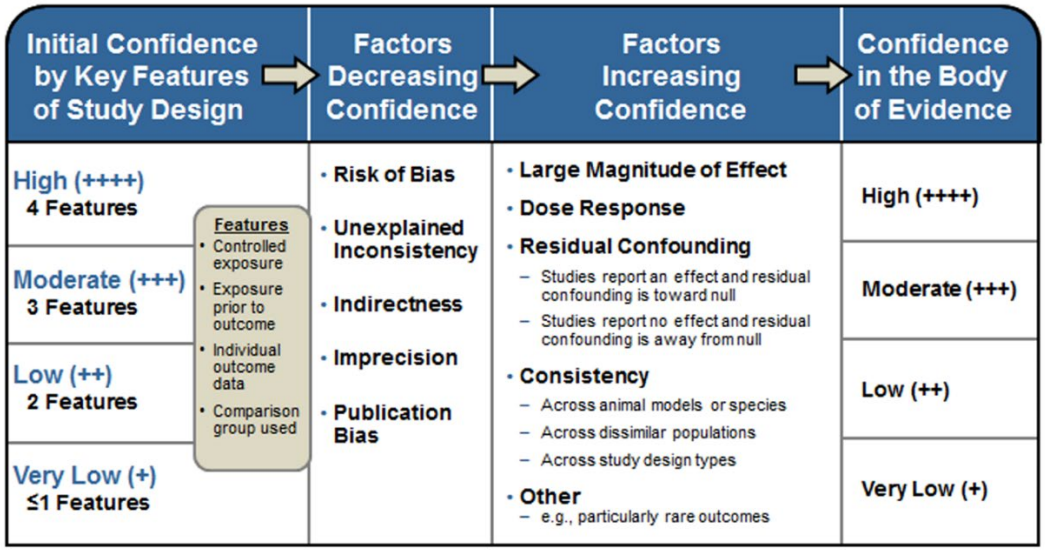
CalSPEC summarized outcome data using quantitative and qualitative information as reported in the systematic reviews and did not re-analyze any of the outcome data from the systematic reviews. When available, we reported the results of the most fully adjusted model of meta-analyses (the statistical model making the most complete statistical adjustments for potential confounders of the relationship between NRAP and health outcomes). We reported the bottom-line summary of the association if that was included in the review verbatim in **Appendix C8.**

For systematic reviews without a meta-analysis, a certainty in the body of evidence assessment or a bottom-line summary, CalSPEC narratively summarized the review findings and reported 1) the number of studies showing an association; 2) the number of studies that were statistically significant; and 3) the range of effect estimates (Risk Ratios (RR), Odds Ratios (OR) or Hazard Ratios (HRs) (see section below 'Evaluating the Certainty of the Evidence'). We report the individual study results included in each systematic review for each exposure/outcome pair (effect estimates and Confidence Intervals (CI)), in **Appendix C8.**

Systematic Review Evaluation of Certainty of the Evidence

To assess the certainty of the body of evidence within each systematic review, CalSPEC relied on the systematic review authors' evaluations. National Toxicology Program (2019) utilized GRADE (Grading of Recommendations Assessment, Development and Evaluation), displayed below in **Figure 2**. GRADE methods have been adopted by Cochrane and many other organizations. Similarly, Boogaard et al. (2022) utilized a modified version of the National Toxicology Program Office of Health Assessment Translation (OHAT) approach (**Table 1**). OHAT methods are based on GRADE, but are extended to include observational human studies, an additional upgrading factor (consistency), and can be applied separately for animal and human data (Boogaard et al. 2022).

Figure 2. Assessing Confidence in the Body of Evidence



Source: National Toxicology Program, 2019

Table 1. Characteristics of the Modified OHAT Assessment

	Modified OHAT Assessment
Main Purpose	To assess confidence in the quality of the body of evidence
Inclusion of studies	All studies, though heavily geared toward the studies entering a meta-analysis
Number, location and size of the evidence base	Partial
Study design	Yes
Study population (generalizability)	No
Direction and magnitude of the association	No[a]
Risk of bias	Yes
Confounding	Yes
Selection bias	Yes
Exposure assessment	Yes
Outcome assessment	Yes
Missing data	Yes
Selective reporting	Yes
Consistency of the findings (e.g., across locations, time periods, study designs, and different pollutants and indirect traffic measures)	Partial
Unexplained inconsistency	Yes
Imprecision (chance)	Yes
Publication bias	Yes
Exposure-response	Yes
Residual confounding	Yes

Source: Boogaard et al. (2022)

[a]The OHAT has an upgrading factor for *large magnitude of effect* that applies only if the effect size is large or very large (i.e., large relative risk > 2 or very large relative risk > 5) because residual confounding is then less likely. However, the Panel consider a *large* effect to be both ambiguous to define and unlikely to occur. Thus, the Panel has decided not to consider this specific upgrading factor.

CalSPEC extracted certainty/confidence ratings regarding the overall body of evidence (high, moderate, low, or very low) which are based on the: risk of bias, indirectness, inconsistency, imprecision, publication bias, magnitude of effects, dose response, and the extent to which controlling for potential confounders reduced any observed associations.

Due to time restrictions, CalSPEC did not conduct certainty assessments for reviews not reporting them. Instead, CalSPEC prioritized systematic reviews with exposure/outcome pairs with a certainty assessment as there is greater confidence in the reported results than in those without a certainty assessment. We therefore stratified the results into two tiers, Tier 1 and Tier 2.

Tier 1: the systematic review conducted a certainty assessment of the body of evidence which we can rely on to draw conclusions on whether there is an association between exposure and outcome.
Tier 2: the systematic review did not conduct a certainty assessment of the body of evidence; therefore, CalSPEC cannot rely on it confidently to draw conclusions on whether there is an association between the exposure and outcome.

Drawing Conclusions

Because the systematic reviews summarized the results between NRAP exposures and outcomes using various nomenclature, CalSPEC translated the summary of findings from the systematic reviews to a consistent nomenclature about the strength of evidence of an association. Our approach is based on the certainty/confidence ratings of the overall body of evidence from the systematic reviews (high, moderate, low, or very low) and the size and precision of the effect. CalSPEC used the following descriptors in drawing conclusions:

- *Established Evidence of an Association:* Overall body of evidence high or moderate with a positive association (risk ratio (RR) or Odds Ratio (OR)) ≥ 1.01, and lower bound confidence interval (CI) ≥ 1.01 (For example: RR 1.03; 95% CI: 1.01 to 1.09, Moderate certainty evidence.)

- *Likely Evidence of an Association:* Overall body of evidence low with a positive association (risk ratio (RR) or Odds Ratio (OR)) ≥ 1.01, and lower bound confidence interval (CI) ≥ 1.01 (For example: RR 1.03; 95% CI: 1.01 to 1.09, Low certainty evidence.) or Overall body of evidence high or moderate with a positive association (risk ratio (RR) or Odds Ratio (OR)) ≥ 1.01, and lower bound confidence interval (CI) ≥ 0.95. (For example, RR 1.03; 95% CI: 0.97 to 1.09, Moderate certainty evidence.)

- *Suggestive Evidence of an Association:* Overall body of evidence low with a positive association (risk ratio (RR) or Odds Ratio (OR)) ≥ 1.01, and lower bound confidence interval (CI) ≥ 0.95. (For example, RR 1.03; 95% CI: 0.97 to 1.09, Low certainty evidence.)

- *Uncertainty of an Association:* Overall body of evidence high, moderate, low or very low and with a negative association (risk ratio (RR) or Odds Ratio (OR)) ≤ 1.00, and/or a lower bound confidence interval (CI) ≤ 0.95. (E.g. RR 0.99; 95% CI: 0.97 to 1.09,

Moderate certainty evidence) or overall body of evidence very low when there is a positive association (RR/OR ≥ 1.01), and precise estimate (CI) ≥ 1.01.

CalSPEC recommends taking immediate action to mitigate and/or prevent exposures from NRAP based on findings with:

- Established Evidence of an Association
- Likely Evidence of an Association, and
- Suggestive Evidence of an Association

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