

# **NTP Evaluation Concept: Pregnancy Outcomes Associated With Traffic-Related Air Pollution**

## **Project Leader**

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## **Background and Rationale**

The Office of Health Assessment and Translation (OHAT) received a nomination to evaluate emerging children's health issues associated with ambient air (<http://ntp.niehs.nih.gov/go/37853>). The nomination asked OHAT to consider a broad range of types of ambient air pollution, including traffic. The nomination also asked OHAT to consider a broad range of emerging children's health outcomes, including adverse birth outcomes. The nomination requested that OHAT focus on children's health outcomes that had not been as extensively reviewed compared to the traditional emphasis on prevalence or exacerbation of respiratory disease. To help refine the focus, OHAT undertook an exploratory search of the literature to identify areas that could be considered "emerging", yet developed enough to permit an evaluation. During the exploratory literature search, citations were broadly characterized (e.g. by evidence stream (human, animal or in vitro), type of health outcome, and type of exposure) but no results were summarized. The exploratory literature search revealed an abundant number of studies on pregnancy outcomes (including infant mortality), childhood cancer, childhood mortality, and a smaller number of studies evaluating neurological outcomes following exposure to ambient air pollution (See [Supplemental Materials](#)).

Considering the results from exploratory searching of the literature, the focus of other recent or ongoing evaluations, and subsequent discussions with scientists at other federal agencies, OHAT is proposing a systematic review of the literature to evaluate the association between pregnancy outcomes and traffic-related pollution. OHAT is also considering evaluations for other outcomes, but these would be approached as separate, subsequent projects. Traffic-related air pollution is broadly defined as direct traffic measures (e.g., density or proximity to traffic), environmental gases [e.g., carbon monoxide (CO), ozone (O<sub>3</sub>), nitrogen oxides (NO<sub>x</sub>), sulfur oxides (SO<sub>x</sub>)], particulate matter (e.g., PM<sub>2.5</sub>, PM<sub>10</sub>, black carbon, ultrafine and coarse PM, total suspended particulates), diesel exhaust, and two major traffic-related constituents (benzene and polycyclic aromatic hydrocarbons). The pregnancy outcomes under consideration are: congenital malformations, fetal growth, peri- and postnatal mortality, preterm birth, and pregnancy complications.

### ***Recent evaluations of pregnancy outcomes***

The most recent comprehensive review of the evidence for an association between traffic-related air pollution and health outcomes was conducted by Health Effects International (HEI), which reviewed the scientific literature through October 2008 (HEI 2010). The epidemiological studies were restricted to those studies that reported direct traffic measures (e.g., proximity or

volume of traffic). Studies using other exposure surrogates for traffic-related air pollution were only considered if they also reported (or modeled) proximity to traffic, i.e., a study reporting only environmental gas or PM as an exposure metric would have been excluded. Regarding infant and children's health outcomes, they reported suggestive evidence for associations of traffic-related air pollution and asthma incidence or prevalence, and supportive evidence of traffic-related air pollution associated with asthma exacerbation. The literature on pregnancy outcomes and childhood cancer studies were reviewed, but there were too few studies that met the inclusion criteria for traffic-related exposure.

The United States Environmental Protection Agency (EPA) prepares Integrated Science Assessments for six principal air pollutants (called criteria air pollutants) for which it sets National Ambient Air Quality Standards (<http://www.epa.gov/ncea/isa/>). These documents are updated in a cyclical fashion to ensure the most policy-relevant studies are considered when establishing the standards; the ISAs include reviews of both epidemiological and toxicological research. The publication dates for the ISAs of the criteria air pollutants included in the proposed OHAT evaluation are: CO (2010), NO<sub>x</sub> (2008; new assessment currently under external review), O<sub>3</sub> (2013), PM (2009) and SO<sub>x</sub> (2008; call for published health studies in 2013).

We are also aware of an evaluation nearing completion on adverse pregnancy outcomes associated with direct traffic exposure metrics (e.g., traffic density, proximity to traffic) by researchers at the Center for Disease Control and Prevention (CDC). The CDC recently completed a review of childhood cancer and traffic-related air pollution.

The proposed OHAT evaluation would expand on the HEI, EPA, and CDC reviews in several important ways. First, the range of exposure surrogates is much broader and will allow evaluation of the consistency of associations both within and across a wider range of exposure metrics. While broad, we think this approach is feasible based on the number of studies identified during our exploratory searching of the literature (~200 references). Second, the literature on pregnancy outcomes associated with ambient air pollution and direct traffic measures has expanded considerably since the 2008 publication year cutoff in the HEI evaluation. During the preliminary literature screening, OHAT identified approximately 200 primary research articles reporting pregnancy outcomes (including peri- and postnatal mortality) (Supplemental Figure 1). Of these 200 studies on pregnancy outcomes, the majority of the studies focused on exposure surrogates of traffic-related pollution beyond direct traffic measures, and, thus, would not be included in the HEI or CDC reviews. Third, the proposed OHAT evaluation will be using systematic review methodology with steps to evaluate individual study quality and establish confidence in the body of evidence (<http://ntp.niehs.nih.gov/go/38673>). Data management will be conducted in a manner that permits public sharing of the exploratory literature search results as well as the sharing of data extracted from included studies in a database format when the monograph is finalized following peer-review. The sharing of extracted data in a database format should facilitate future updates to this evaluation conducted by NTP or other organizations.

## **Key Issues**

The major challenge to this evaluation will be determining the extent to which conclusions can be integrated across the variety of exposure metrics used in relevant studies. Direct traffic measures (i.e., density or proximity to traffic) provide some of the more accurate exposure metrics for estimating exposure to traffic pollution (HEI 2010). Several air pollutants have been used as surrogates of traffic-related air pollution, including carbon monoxide (CO) and nitrogen oxides (NO<sub>x</sub>); for example, 33% of ambient levels of NO<sub>x</sub> were emitted from on-road vehicles (USEPA 2008). Particulate matter (PM) exposures are, in part, traffic-related and their composition varies depending on the fuel type (e.g., diesel exhaust contain predominantly elemental or black carbon) as well as the PM source (e.g., coarse PM is related to road dust containing tire and engine wear). Other markers of traffic-related exposure may be mixtures (e.g., diesel exhaust) or individual constituents (e.g., benzene and polycyclic aromatic hydrocarbons (PAHs) of traffic air pollution).

Other factors to consider in this evaluation include: (1) the composition of traffic-related air pollution in the United States has changed over time since 1975, based on new technologies and regulation of vehicle emissions. (2) Many of the exposure surrogates used to identify traffic-related pollution are also generated by other sources (e.g., industrial pollution). (3) The synthesis of the international literature on traffic-related air pollution with studies in the United States is complicated by differences in the composition of the vehicle fleet; for example, diesel-fueled vehicles make up a larger portion of the vehicle fleet in Europe than in the United States.

An additional challenge in elucidating the causal effects of traffic-related air pollution on pregnancy outcomes is the lack of developmental toxicology studies in laboratory animals using the same exposure measures (e.g., NO<sub>2</sub> or PM<sub>2.5</sub>) as were used in the human studies, preferably inhalation route of administration. The preliminary literature search identified only 11 studies in laboratory animals that evaluated pregnancy outcomes with the majority (7) of the studies evaluating the effects of exposure to CO.

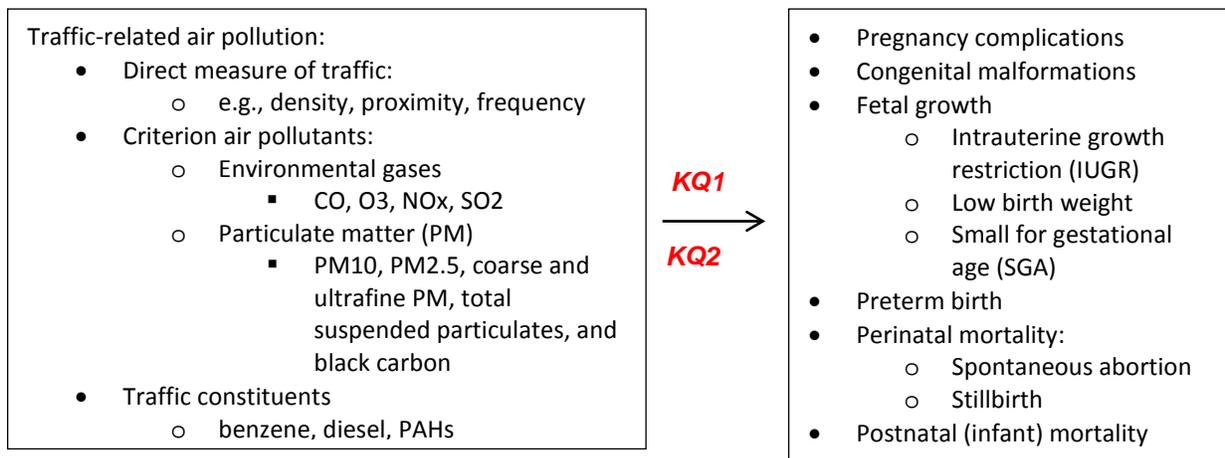
## **Specific Aims**

The overall objective of this evaluation is to determine a hazard conclusion(s) (“known”, “presumed”, “suspected”, or “not classifiable”) for the association between exposure to traffic-related air pollution and pregnancy outcomes, by integrating the evidence from human observational studies. The key questions (KQ) for the proposed evaluation are:

- **Key question 1** (KQ 1): What is our confidence in the body of evidence for an association in humans between traffic-related air pollution based on considering individual types of exposure surrogate and pregnancy outcomes (Figure 1)? (For example, what is the association between NO<sub>2</sub> and pregnancy outcomes?)
- **Key question 2** (KQ 2): How do the associations between pregnancy outcomes and environmental gases, PMs, diesel exhaust, benzene, or PAHs compare to each other and to the associations based on direct traffic measures (e.g., density, proximity, frequency)?

Figure 1 conveys the relationship between the key questions and the type of evidence included in the evaluation.

**Figure 1. Analytical framework**



## **Proposed Approach**

The HEI review of traffic-related air pollution, EPA air quality criteria assessments, CDC documents, and other reviews identified during literature screening will be utilized as background materials and scanned to ensure we have not missed relevant studies. OHAT will work with non-federal technical advisors as well as researchers at the EPA and CDC to further refine the scope of the proposed evaluation (e.g., possibly reduce the number of exposure surrogates of traffic-related air pollutants) and consider statistical approaches to deal with the complexity of exposure metrics included in the evaluation. As noted above, the project is being approached using the OHAT approach to systematic review and evidence integration (<http://ntp.niehs.nih.gov/go/38673>). After additional steps to refine the project and develop a protocol, the protocol will be posted and other key milestones in the evaluation will be announced on the NTP listserv (e.g., posting list of included studies).

## **Significance**

The proposed OHAT evaluation will build upon and extend the HEI, EPA and CDC efforts to understand the effects of traffic-related air pollution on children's health. Based on a sufficient literature base, the proposed evaluation will reach hazard conclusions for the relationship of pregnancy outcomes with traffic-related air pollution. The evaluation should help elucidate how well the effects of exposure surrogates of traffic-related pollution (some of which have contributions from industry pollution), compare to the effects of more direct measures of traffic-related air pollution regarding their association with adverse pregnancy outcomes. Data management will be conducted in a manner that permits public sharing of the exploratory literature search results as well as the sharing of data extracted from included studies in a database format when the monograph is finalized following peer-review.

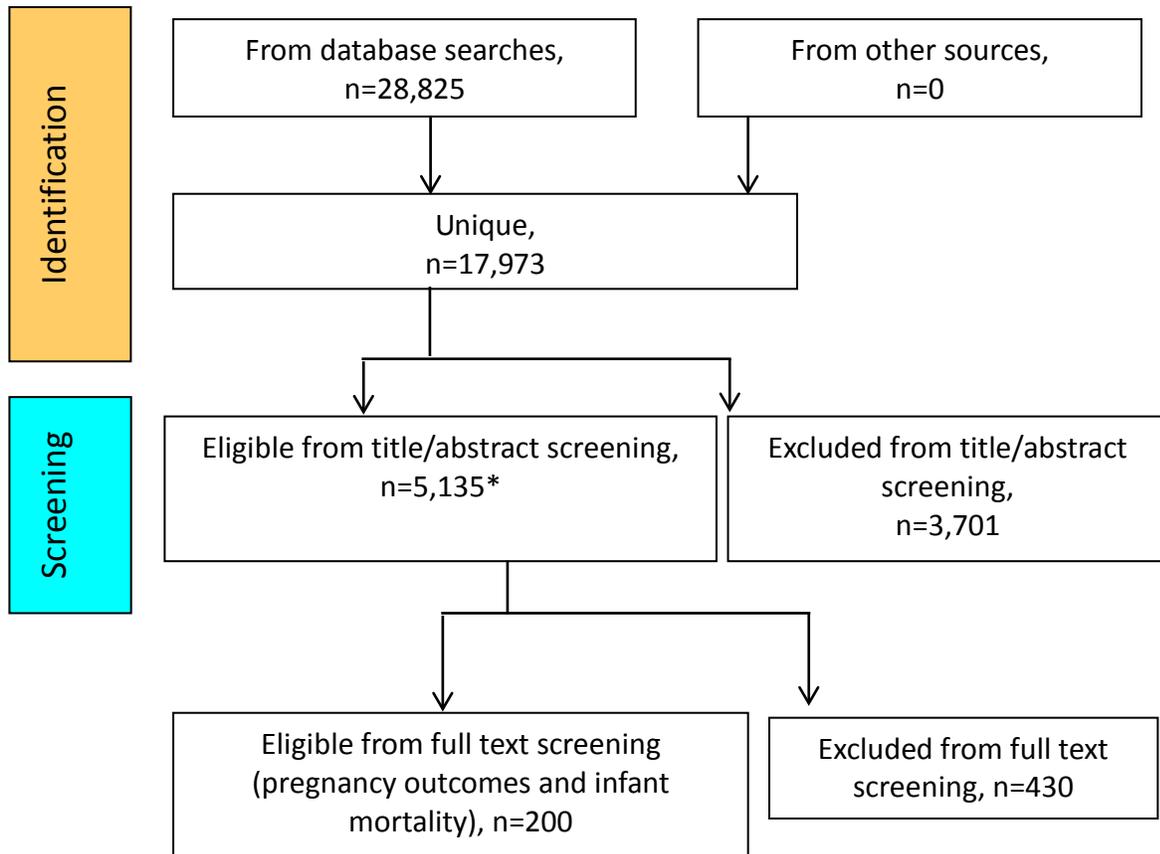
## **References**

HEI (Health Effects Institute) Panel on the Health Effects of Traffic-Related Air Pollution. 2010. Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects. HEI Special Report 17.

USEPA (United States Environmental Protection Agency). 2008. Integrated Science Assessment for Oxides of Nitrogen - Health Criteria. Federal Register. Available at <http://cfpub.epa.gov/ncea/> [accessed on 24 February 2014].

## Supplemental Materials

Supplemental Figure 1: Study selection flow diagram from preliminary literature screening



\*Estimated number of references (including reviews) per health outcome associated with traffic (i.e., proximity, density, frequency), environmental gases (i.e., CO, NO<sub>x</sub>, O<sub>3</sub>, SO<sub>x</sub>) and particulate matter (all types) in infants or children. The number of references published from 2009-2012 is in parentheses.

- Metabolic, ~2
- Neurological, ~40 (18)
- Mortality (childhood), ~103 (18)
- Cancer, ~104 (19)
- Reproduction, including pregnancy outcomes, ~200 (40)
- Respiratory, ~1365 (300)