Environmental Research 160 (2018) 391–397

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Short-term ozone exposure and asthma severity: Weight-of-evidence analysis

Julie E. Goodman[a,*], Ke Zu[a], Christine T. Loftus[b,1], Heather N. Lynch[a], Robyn L. Prueitt[b], Isaac Mohar[b], Sara Pacheco Shubin[b], Sonja N. Sax[a,2]

[a] Gradient, 20 University Rd., Cambridge, MA, United States
[b] Gradient, 600 Stewart St., Seattle, WA, United States

ARTICLE INFO

Keywords:
Ozone
Asthma
Weight of evidence
NAAQS
Evidence integration

ABSTRACT

To determine whether evidence indicates that short-term exposure to ambient concentrations of ozone in the United States can affect asthma severity, we systematically reviewed published controlled human exposure, epidemiology, and animal toxicity studies. The strongest evidence for a potential causal relationship came from epidemiology studies reporting increased emergency department visits and hospital admissions for asthma following elevated ambient ozone concentrations. However, while controlled exposure studies reported lung function decrements and increased asthma symptoms following high ozone exposures 160–400 parts per billion [ppb]), epidemiology studies evaluating similar outcomes reported less consistent results. Animal studies showed changes in pulmonary function at high ozone concentrations (> 500 ppb), although there is substantial uncertainty regarding the relevance of these animal models to human asthma. Taken together, the weight of evidence indicates that there is at least an *equal* likelihood that either explanation is true, *i.e.*, the strength of the evidence for a causal relationship between short-term exposure to ambient ozone concentrations and asthma severity is "***equipoise and above***."

1. Introduction

Ozone, a colorless gas with a distinctively pungent smell, is naturally present in the upper atmosphere. In the presence of sunlight, ozone is also generated at ground level from photochemical reactions between precursor pollutants, including volatile organic compounds (VOCs), oxides of nitrogen (NO_x), and carbon monoxide (CO) (US EPA, 2013). Ozone is a powerful oxidizing agent and, at high concentrations, can harm living organisms and materials. People are exposed to ground-level ozone both indoors and outdoors as they participate in normal daily activities (US EPA, 2013). Ambient ozone concentrations are routinely monitored in the US, and the median daily average, 8-h maximum, and 1-h maximum ozone concentrations across all US sites between 2007 and 2009 were 29, 40, and 44 parts per billion (ppb), respectively (US EPA, 2013). The 99th percentiles of these ozone concentration metrics are 60, 80, and 94 ppb, respectively (US EPA, 2013). Ground-level ozone is one of the six criteria air pollutants regulated by the United States Environmental Protection Agency (US EPA). The current National Ambient Air Quality Standard (NAAQS) for ozone is 70 ppb for the annual fourth-highest daily maximum 8-h concentration, averaged over three years.

Asthma is a multifactorial, heterogeneous disease involving chronic airway inflammation, variable airflow obstruction, and airway hyperresponsiveness (AHR) to various triggers (Currie and Baker, 2012; Grainge and Davies, 2013; Myers and Tomasio, 2011). It is a relatively common disease, with an estimated prevalence in the US between 2008 and 2010 of 9.5% in children 0–17 years old and 7.7% in adults (Moorman et al., 2012). Asthma etiology is complex, and a specific cause has yet to be identified. Genetics and respiratory infections are the most well-established risk factors (Myers and Tomasio, 2011). A diagnosis of asthma is typically based on lung function tests showing reduced expiratory flow rate, reactivity to bronchoconstrictors such as methacholine, and response to bronchodilators such as albuterol (Mayo Clinic, 2014a). Common pathological features of the airways include epithelial hyperplasia, increased smooth muscle mass, fibrotic thickening of the subepithelial basement membrane, and decreased antioxidant capacity (Barnes, 2008; Currie and Baker, 2012; Grainge and Davies, 2013).

* Corresponding author.
E-mail address: jgoodman@gradientcorp.com (J.E. Goodman).
[1] Current address: Department of Environmental and Occupational Health Sciences, University of Washington, 4225 Roosevelt Way NE, Suite 301, Seattle, WA, United States.
[2] Current address: Ramboll Environ; 28 Amity St., Amherst, MA, United States.

http://dx.doi.org/10.1016/j.envres.2017.10.018
Received 12 May 2017; Received in revised form 15 September 2017; Accepted 11 October 2017

Asthma exacerbations (*i.e.*, asthma attacks), which involve reversible narrowing of the airways, and symptoms such as wheezing, shortness of breath, and chest tightness or pain, are hypothesized to occur when an acute inflammatory response is added to the underlying chronic airway inflammation (Barnes, 2008; Moorman et al., 2012). Although inflammation appears to play a role, how inflammatory cells interact and how this interaction translates into asthma symptoms that might constitute an asthma exacerbation requiring intervention is uncertain (Reddel et al., 2009; Barnes, 2008). While several cell types have been implicated in severe asthma (eosinophils, neutrophils, and granulocytes), the number of these cells in sputum varies widely across patients and even intraindividually on a monthly basis (Chung et al., 2014). Common triggers for asthma exacerbations include allergens, viral respiratory infections, exercise, tobacco smoke, cold air, gastroesophageal reflux disease, and stress (Barnes, 2008; Sears, 2008; Mayo Clinic, 2014b). In addition, several air pollutants, including ozone, nitrogen dioxide (NO_2), and particulate matter (PM) have been hypothesized to trigger asthma exacerbations (Barnes, 2008a, 2008b; Guarnieri and Balmes, 2014; Sears, 2008).

Numerous observational and experimental (*i.e.*, controlled exposure and animal toxicity) studies have investigated whether short-term ozone exposures may affect asthma severity (US EPA, 2013). Epidemiology studies have assessed this relationship by evaluating respiratory symptoms, medication use, and changes in lung function among people with asthma. Severe asthma exacerbations manifest as visits to primary care doctors or emergency departments (ED), or as hospital admissions (HA), which have also been evaluated extensively in observational studies. In experimental settings, people with asthma have been exposed to specific ozone concentrations in a controlled environment, and their responses (usually changes in lung function parameters) have been measured. Laboratory studies have also been conducted in different animal models for asthma, although their relevance to humans is unclear (*e.g.*, Hatch et al., 2013).

In its most recent review of the ozone NAAQS, US EPA concluded that short-term ozone exposure causes respiratory morbidity, and that individuals with asthma constitute a group susceptible to ozone. US EPA based these conclusions largely on observed associations between short-term ozone exposure and various outcomes related to asthma severity, including ED visits and HA for asthma, as well as changes in lung function and reported respiratory symptoms in individuals with asthma (US EPA, 2013).

We conducted detailed systematic reviews of the epidemiology and controlled human exposure studies that focused on ozone exposure and asthma severity on this issue (See Supplemental materials). We also systematically reviewed animal toxicity studies that evaluated the effects of ozone exposures in laboratory animal asthma models (See Supplemental materials). Herein, we integrate evidence across disciplines to determine whether the weight of evidence (WoE) indicates that short-term exposure to ambient ozone concentrations can impact asthma severity, as reflected by measures of lung function, symptoms, and frequency of exacerbation events.

2. Methods

We addressed the question: Does short-term exposure to ozone at ambient concentrations affect asthma severity? We defined short-term as fewer than 30 days, based on criteria established by US EPA (2013). Although our research question is focused on ambient exposure concentrations, we evaluated studies of any concentration of ozone, to enable an evaluation of overall hazard as well as a biological gradient. We relied on asthma severity endpoints as defined by recent American Thoracic Society (ATS) guidance, including symptoms, hospitalization, medication use, and lung function (Reddel et al., 2009). As discussed in the Supplemental materials, because inflammatory endpoints are variable and their relevance is unclear, we did not review studies of inflammatory cells or markers.

In WoE analyses, evaluating study quality is critical because results from studies with more robust designs and methodology should carry more weight in evidence integration. We developed distinct study quality criteria for each realm of evidence (*i.e.*, controlled human exposure, epidemiology, and laboratory animal studies). The study quality criteria were based on those used in previous study quality evaluations (*e.g.*, Goodman et al., 2014; Prueitt et al., 2014), and the criteria were informed by several existing guidelines and quality evaluation systems, including the National Toxicology Program (NTP) Office of Health Translation (OHAT) risk-of-bias (RoB) tool, the Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) guidelines (Kilkenny et al., 2010), and other international research guidelines, such as those of the Organization for Economic Co-operation and Development (OECD) and World Health Organization (WHO) (OECD, 1998). The specific criteria for each realm of evidence are described in more detail in the Supplemental materials.

We relied on these criteria to evaluate the quality of individual studies and to categorize them as being of higher or lower quality. We used a scoring system in which we assigned each study a score of − 1 or + 1 for each criterion. These scores are intended to be only a crude measure of quality and are not intended to be summed for a ranking of studies, since we did not assign any weight to each criterion. Instead, based on the quality scores, we simply grouped the studies into two tiers: Tier I indicates a study with a greater number of strengths than limitations (the number of positive attributes outweighed the number of negative attributes), and Tier II indicates a study with a greater number of limitations than strengths (the positives did not outweigh the negatives). Because even one particular strength or limitation could "outweigh" all the others in terms of its impact on the interpretation of results, we only used this system to divide the studies into two groups. We also evaluated all of the study quality criteria for each individual study and addressed additional factors not included in our scoring system that may affect the interpretation of individual study results (discussed below). We evaluated all individual studies in both tiers but gave Tier I studies more weight in the analysis, because Tier II studies are of lower quality.

We integrated the evidence from controlled human exposure studies, epidemiology studies, and animal toxicity studies (Described in Supplemental materials). We integrated the evidence across these realms in the context of several of the Bradford Hill aspects, including strength of association, consistency of associations, coherence, biological gradient, biological plausibility, and temporality, as well as confounding, bias, and the clinical relevance of effects. We did this to determine whether the collective evidence indicates that short-term exposure to ambient ozone concentrations can affect asthma disease severity. Our causal determination is based on the categorization of the strength of the overall evidence across all realms for or against a causal relationship proposed by the Institute of Medicine (IOM, 2008). The four categories are:

1. *Sufficient*: The evidence is sufficient to conclude that a causal relationship exists.
2. *Equipoise and above*: The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists.
3. *Below equipoise*: The evidence is not sufficient to conclude that a causal relationship is at least as likely as not, or is not sufficient to make a scientifically formed judgment.
4. *Against*: The evidence suggests the lack of a causal relationship.

3. Overview of evidence

3.1. Controlled human exposure studies

We included 34 controlled human exposure studies of individuals with asthma in our systematic review (Described in detail in the