Toxicology 335 (2015) 85–94

Contents lists available at ScienceDirect

Toxicology

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

Review

Conceptual model for assessing criteria air pollutants in a multipollutant context: A modified adverse outcome pathway approach

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ARTICLE INFO

Article history:
Received 12 May 2015
Received in revised form 25 June 2015
Accepted 10 July 2015
Available online 18 July 2015

Keywords:
Air pollution
Criteria pollutants
Multipollutant
Adverse outcome pathway

ABSTRACT

Air pollution consists of a complex mixture of particulate and gaseous components. Individual criteria and other hazardous air pollutants have been linked to adverse respiratory and cardiovascular health outcomes. However, assessing risk of air pollutant mixtures is difficult since components are present in different combinations and concentrations in ambient air. Recent mechanistic studies have limited utility because of the inability to link measured changes to adverse outcomes that are relevant to risk assessment. New approaches are needed to address this challenge. The purpose of this manuscript is to describe a conceptual model, based on the adverse outcome pathway approach, which connects initiating events at the cellular and molecular level to population-wide impacts. This may facilitate hazard assessment of air pollution mixtures. In the case reports presented here, airway hyperresponsiveness and endothelial dysfunction are measurable endpoints that serve to integrate the effects of individual criteria air pollutants found in inhaled mixtures. This approach incorporates information from experimental and observational studies into a sequential series of higher order effects.

The proposed model has the potential to facilitate multipollutant risk assessment by providing a framework that can be used to converge the effects of air pollutants in light of common underlying mechanisms. This approach may provide a ready-to-use tool to facilitate evaluation of health effects resulting from exposure to air pollution mixtures.

Published by Elsevier Ireland Ltd.

Contents

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http://dx.doi.org/10.1016/j.tox.2015.07.007
0300-483X/Published by Elsevier Ireland Ltd.

1. Introduction

Exposures to air pollutants, such as particulate matter (PM), ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2), have been linked to adverse respiratory and cardiovascular health outcomes (U.S. EPA, 2008a,b, 2009, 2013a,b). The U.S. Environmental Protection Agency has established National Ambient Air Quality Standards (NAAQS) to protect against health effects related to these pollutants, which are designated as criteria air pollutants or their indicator species under the Clean Air Act (Clean Air Act, 1990).

Criteria and other hazardous air pollutants are present in different combinations and concentrations across air sheds and within micro-environments. These complex mixtures of particulate and gaseous components are largely determined by local sources, long-range transport, atmospheric transformation, and local meteorological conditions. As a consequence, ambient air consists of an endless number of unique multipollutant mixtures, far exceeding the capacity of conventional epidemiologic or experimental approaches to characterize their health impact. The inability to adequately assess the impact of air pollution mixtures thus represents a significant gap in hazard assessment and will continue to foster uncertainty in risk characterization associated with exposure to ambient air. Strategies that minimize the need to assess a vast number of possible combinations are required to address this challenge.

New approaches are being developed for evaluating the health impacts of single pollutants in a multipollutant context and that of air pollution mixtures as a whole. The shift from a single to multipollutant approach has been encouraged by the National Research Council (NRC) and other scientists from academia, industry, and government (Johns et al., 2012). From an exposure science perspective, scientists have sought to achieve dimension reduction by identifying common physical or chemical properties shared by several components of the mixture and by generating models that address uncertainties related to the characterization of spatial and temporal variability of air pollutant mixture concentration profiles. In epidemiology, statistical techniques are being developed to evaluate mixtures of pollutants with similar biological properties. In toxicology, high throughput cellular and non-cellular assays are being used to increase the number of mixtures that can be studied in a narrow time-frame. Mechanistic evidence provided by these toxicological studies has implicated dozens of genes, biomarkers, proteins, and other factors. However, the utility of these findings is limited because of the inability to link changes to adverse outcomes that are relevant to risk assessment, such as measurable changes in organ responses, clinical consequences, and impacts to the population at-large.

Here we propose a conceptual model for assessing multiple criteria air pollutants based on the adverse outcome pathway (AOP) paradigm (Ankley et al., 2010). The AOP paradigm is a natural extension of other frameworks developed in the field of hazard and risk assessment for the purpose of characterizing the exposure to effects continuum. It synthesizes information relevant to the effects of a given chemical into a sequential series of steps which span multiple levels of biological organization. The AOP approach requires an understanding of mechanisms underlying the biological responses to pollutants of interest. Initiating events at the molecular level can include both specific receptor-ligand interactions and less specific events such as hydrophobic interactions between chemicals and cellular membranes. Results of experimental and epidemiologic studies can both be incorporated into this model. Thus, initiating events at the molecular level can be connected to adverse health effects at the individual or population level for which risk assessments are made.

Our approach extends the AOP model by requiring the identification of clinical endpoints that can be reliably measured in humans. It also requires that early events, even if caused by more than one mechanism, are upstream and predictive of clinical endpoints and health outcomes. Additionally, our approach groups pollutants by their ability to act through common mechanisms. Thus, we can use this model to integrate the effects of individual components of air pollutant mixtures at any converging intermediate endpoints along the pathway, irrespective of earlier events in the pathway.

In order to illustrate our approach, two case reports relevant to the effects of exposure to air pollution mixtures are presented below—one focusing on respiratory effects of irritant gases O_3, NO_2, and SO_2, and the other on cardiovascular effects of PM and O_3. Airway hyperresponsiveness (AHR) and endothelial dysfunction (ED), both measurable endpoints, are incorporated into AOPs that link early molecular and cellular changes to adverse population-based health outcomes.

2. Case report 1: irritant gases and respiratory outcomes

Respiratory health effects resulting from exposure to irritant gases SO_2, NO_2 and O_3 form the basis of NAAQS for sulfur oxides, nitrogen oxides, and O_3 and related photochemical oxidants, respectively (U.S. EPA, 2008a,b, 2013a,b). Experimental and epidemiologic studies demonstrate a wide range of effects from decrements in pulmonary function to increased visits to an emergency department or admission to a hospital. Some of these effects are related to asthma, which is a complex disease requiring a trigger such as an allergen or other stressor (O'Byrne et al., 2009). For an extensive review of evidence linking these criteria air pollutants to asthma, the readers are referred to recent Integrated Science Assessments (U.S. EPA, 2008a,b, 2013a,b). Key asthma-related findings and outcomes described in these documents are summarized below.

2.1. Definition of airway hyperresponsiveness

Enhanced airway responsiveness, here referred to as AHR, is a key feature of asthma, which is a chronic inflammatory disease of the airways (O'Byrne et al., 2009). Airway responsiveness reflects the sensitivity of airway smooth muscle to natural or pharmacological stimuli. It is measured in the clinic or laboratory by using a defined stimulus to challenge the airways in order to constrict the airway smooth muscle. This leads to airway narrowing and airflow limitation. Physiologic changes associated with variable airflow obstruction are usually measured in terms of forced expiratory flow in one second or specific airway resistance. Stimuli may be direct, i.e., act on specific receptors in the airway smooth muscle to cause constriction, or indirect, i.e., cause airway inflammatory cells to release mediators of bronchoconstriction. Methacholine and histamine are direct stimuli used in clinical and experimental