Misuse of Pollution Reference Standards: No Safe Level of Air Pollution

The burden of ill health owing to exposure to air pollution is well established and widely accepted (1). Despite this, effective regulation of exposure to air pollution has lagged in many countries. The World Health Organization's updated guidelines (2) have recently been published, many years after the previous version. They are considerably strengthened and welcome. A key recommendation of these guidelines is that "the accumulated evidence is sufficient to justify actions to reduce population exposure to key air pollutants … " (2). This has important implications for policy and regulatory practice.

In this issue of the *Journal*, Wei and colleagues (pp. 1075–1083) highlight the limitations of the existing regulatory approach, at least in relation to protection from severe exacerbations of asthma requiring hospital admission (3). Increases in ambient concentrations of NO_2 and particulate matter ⩽2.5 μm in aerodynamic diameter (fine particulate matter) were associated with an increased risk of hospitalization for asthma over the succeeding 6-day period. For fine particulate matter, the effect was greatest on the day of the high pollutant exposure and the succeeding 3 days and then began to decay. For NO_2, the effect was greatest on the 4 days after the exposure event. In general, the effect was robust to differences in individual-level characteristics, except that it was stronger in people who have only had a single admission to hospital than those with multiple admissions. Some characteristics of communities made them more susceptible to the adverse effects of both pollutants: low population density, higher average body mass index, greater distance to the nearest hospital, and greater neighborhood degrees of disadvantage. An important finding was that effect sizes (that is, the magnitude of the increased risk of hospitalization for a unit increase in pollutant exposure) were greatest when the population being analyzed was limited to those with exposures well below the existing reference standard (National Ambient Air Quality Standards). The strengths of this study include its focus on vulnerable populations, those enrolled in Medicaid, the high spatial and temporal resolution of air pollutant exposure measurements, and the sophisticated adjustment for, and stratification by, both individual- and area-level covariates. These methodological strengths, together with the broad range of exposures, add value to the findings.

The finding that health effects were greatest at concentrations below the existing reference standard has two important implications: First, from a mechanistic standpoint, the slope of the exposure–response relationship is steeper at lower degrees of exposure; and second, from a policy standpoint, there are substantial benefits in reducing exposure to ambient pollutants, and in preventing increases in exposure, even at concentrations that are well below reference standards or proposed thresholds.

The present study (3) joins with several others that have failed to demonstrate a concentration below which adverse health effects of ambient pollutants do not occur. Indeed, steeper slopes at lower concentrations of fine particulates have also been demonstrated for daily mortality (4) and for cardiovascular hospitalizations (5). The all-cause mortality risk associated with long-term exposure to both fine particulates and NO_2 has been demonstrated in relatively low-range exposure settings, such as Australia (6), without evidence of a lower threshold and with evidence of steeper slope at lower concentrations. Finally, the effect of both lifetime cumulative exposure and current exposure to NO_2 on the risk of having current asthma among primary school children exists, in Australia, within a range of exposures well below usual reference standards (7). Hence, there is strong empirical evidence that there is no "safe" amount of air pollution below which adverse effects do not occur.

The finding that those living in disadvantaged neighborhoods were at greatest risk of experiencing more asthma hospitalizations when exposed to higher amounts of air pollution is important. It accords with evidence of a similar interaction in relation to adverse cardiovascular outcomes (8, 9) and represents an effect that is over and above the association between disadvantage and the risk of higher air pollutant exposures. The mechanism for this association remains unproven, but its existence is clear.

The policy implications of these findings are critical: there is no safe amount of air pollution (10). Treating reference standards as a license to pollute up to those concentrations and a free pass to allow continued emissions below those concentrations cannot be accepted based on the current evidence. Transport, industry, and planning decisions need to be based on the need to exert continuing downward pressure on emissions of fine particulates and NO_2 and the need to avoid any increases in these emissions, particularly where vulnerable populations may be exposed. Concern about vulnerable populations, particularly those who are disadvantaged but also the very young and the very old and those with preexisting health conditions, have important implications for decisions on the siting of sensitive facilities (e.g., childcare centers, schools, aged care facilities, and hospitals). Among other factors, planning should consider the need to minimize exposure to pollutants, not simply ensure they are below arbitrary threshold standards.

The challenge is immense, because anthropogenic sources of emissions contributing to ambient fine particulate and NO_2 are ubiquitous in most societies: transport, agriculture, energy, mining, and construction sectors all play a role. The good news is that there are cobenefits shared between the actions required for carbon pollution reduction, to combat global warming, and those required to ensure clean, safe air. As a global scientific and health-focused community, we need to ensure that we are in the vanguard of advocacy for achieving these benefits. ■

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Chronic Cough in Idiopathic Pulmonary Fibrosis: The Same Difference?

The world is divided into lumpers and splitters, if this is not a *non sequitur*. According to the American Lung Association, "Pulmonary fibrosis (PF) is a form of interstitial lung disease that causes scarring in the lungs. There are over 200 different types of PF and in most cases, there's no known cause." I have sat through many meetings where the "diagnosis" of interstitial lung disease (ILD) has been hotly debated. In an international study, Walsh and colleagues asked seven ILD multidisciplinary team meetings to comprehensively review 70 patients with ILD, and, although agreement on the diagnosis idiopathic pulmonary fibrosis (IPF) was fair (they say good) (weighted $\kappa = 0.71$), other categories fared less well (1). Kolb and Flaherty and others have suggested a simplification with the identification of a progressive fibrotic phenotype of ILD, irrespective of primary diagnosis (2). This view is supported by the INBUILD (Nintedanib in Progressive Fibrosing Interstitial Lung Disease) study demonstrating the beneficial effects of nintedanib in progressive fibrosing ILDs of various supposed etiologies (1). In the therapeutics of ILD, perhaps lumping is preferable to splitting.

In patients with chronic cough, a similar paradigm has unfolded. Chronic cough in the absence of other obvious pulmonary pathology was originally ascribed to three existing diseases: asthma, postnasal drip, and gastroesophageal reflux. However, many patients failed to respond to conventional treatments for these conditions, leading to prolonged morbidity over many years. The concept of cough hypersensitivity syndrome—aberrant vagal and central neuronal activation of the cough reflex—was suggested as the overarching etiology in such patients (3). International guidelines now recognize chronic cough as a disease with different phenotypes (4). Again, the proof of this lumping approach has been demonstrated by the results of COUGH-1 (A Study of Gefapixant [MK-7264] in Adult Participants with Chronic Cough [MK-7264-027]) and COUGH-2 (A Study of Gefapixant [MK-7264] in Adult Participants with Chronic Cough [MK-7264-030]) (5). Here, more than 2,000 patients with the typical demographics of patients with chronic cough (predominantly middle-aged women) were randomized to an entirely novel therapeutic approach: blockade of the ATP receptor. Gefapixant, a P2X3 antagonist, demonstrated significant reductions in objective and subjective cough versus placebo and a greater than 60% reduction in cough from baseline.

Where these two worlds collide is in the cough associated with IPF. Approximately 80% of patients with IPF report cough as a significant symptom, and it is a predictor of morbidity and mortality (6). So, is the coughing in IPF a manifestation of cough hypersensitivity, or is it an epiphenomenon of the disease? Cromolyn

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