A man guides a car through the Great Smog of 1952 in London. The acidity of the particles in air pollution affects how harmful they are to humans.

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Particle toxicity's role in air pollution

In their Report "Abating ammonia is more cost-effective than nitrogen oxides for mitigating $PM_{2.5}$ air pollution" (5 November 2021, p. 758), B. Gu and colleagues propose that reducing ammonia (NH_3) emissions could decrease air pollution caused by particles of less than 2.5 μm in diameter ($PM_{2.5}$), a change that they predict would benefit human health. However, not all particles affect health equally (*1*–*4*). Because ammoniated $PM_{2.5}$ is less acidic than sulfuric particulate matter formed by, for example, burning coal (*5*), decreasing particles formed with NH_3 may make the remaining air pollution more lethal. Air pollution mitigation strategies should consider the risk to health posed by various components, not just the total particulate mass.

The role of acidity in enhancing particle toxicity has been recognized since the Great Smog of London in 1952. During the 5 days of extreme air pollution in the city, animals with higher NH_3 exposures were less adversely affected, and physicians placed vials of NH_3 in hospital wards to protect patients (*6*, *7*). Subsequent research has confirmed that NH_3 in the air reduces the acidity of ambient particles (*8*) and that acidity mobilizes toxic transition metals, inducing oxidative stress (*9*–*11*). Moreover, a recent epidemiological study has determined that the oxidative potential of outdoor $PM_{2.5}$ is associated with acute cardiovascular events, and combined exposure to transition metals and acidic sulfate enhances those cardiovascular effects (*12*).

Because $PM_{2.5}$ components' toxicities vary, estimates of the health impacts of each component should take into account its individual properties. Gu *et al.*'s suggested reduction in NH_3 emissions might well reduce $PM_{2.5}$ mass but would also increase the acidity of the aerosol mixture. Rather than achieve the predicted health benefits, the change could regionally increase adverse health effects where acid-neutralizing NH_3 emissions are diminished. The health benefits that Gu *et al.* expect must be confirmed experimentally before the implementation of such a policy.

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Response

Thurston *et al.* argue that ammonia (NH_3) abatement may not reduce the adverse health effects of particles with a diameter of less than 2.5 μm ($PM_{2.5}$) due to the dependence of toxicity on the acidity of $PM_{2.5}$. Although they have usefully highlighted the effect of acidity of $PM_{2.5}$ on human health, there is no definitive evidence that quantification of the effects of $PM_{2.5}$ components separately should be recommended in policy-making (*1*) or that emission controls of ammonia like those we suggest would substantially change the aerosol acidity. We are not arguing for NH_3 controls in isolation; rather, we contend that NH_3 abatement can play an important role in reducing exposure to $PM_{2.5}$ and associated health impacts in the context of

continued mitigation of other pollutants, such as sulfur dioxide (SO_2) and nitrogen oxides (NO_x).

$PM_{2.5}$ can vary across regions from highly acidic (pH of ~0.5) to mildly acidic (pH of ~6) (*2*). In the United States and Canada, large reductions in SO_2 and NO_x emissions over the past decade have not resulted in clear changes to acidity (*3*, *4*). Global reduction of agricultural NH_3 emission alone by 50% (similar to the proposed mitigation in our study) would reduce $PM_{2.5}$ pH (i.e., increase acidity) by about 0.6 units (*5*), and we would expect even weaker changes with joint controls of SO_2 and NO_x. Whether such changes in aerosol acidity are sufficient to affect the mobilization of harmful transition metals is still unknown.

Emissions of air pollutants have changed substantially since the 1952 Great Smog of London (*6*). At that time, SO_2 emissions from coal burning were indeed a dominant reason for adverse health effects (*7*), likely due in part to acute acidity. The use of NH_3 alleviated the acute acidity, but its effect could also be ascribed to a reduction in exposure to toxic concentrations of SO_2 (*8*).

Emission controls of SO_2 and NO_x have a long history, whereas NH_3 has too often been ignored (*6*, *9*). It would thus be unrealistic to imagine effective control of NH_3 and unregulated emissions of SO_2 and NO_x. We argue for the need to start to control NH_3 emission given its large contribution to $PM_{2.5}$ formation and its high cost-efficiency of abatement, thereby catching up to the progress already made in reducing SO_2 and NO_x emissions.

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The protein-folding problem: Not yet solved

We agree with H. H. Thorp ("Proteins, proteins everywhere," Editorial, 17 December 2021, p. 1415) and numerous others (*1*) that the advance in protein structure prediction achieved by the computer programs AlphaFold (*2*) and RoseTTAfold (*3*) is worthy of special notice. The accuracies of the predictions afforded by these new approaches, which use machine-learning methods that exploit the information about the relationship between sequence and structure contained in the databases of experimental protein structures and sequences, are much superior to previous approaches. However, we do not agree with Thorp that the protein-folding problem has been solved.

AlphaFold achieves a mean C-alpha root mean square deviation (RMSD) accuracy of ~1 Å for the Critical Assessment of Structure Prediction 14 (CASP14) dataset (*2*). This accuracy corresponds to that of structures determined by x-ray crystallography or single-particle cryo–electron microscopy at very low resolution. The accuracy of these methods is several times better than machine learning methods; for example, at 3 Å resolution, the coordinate C-alpha RMSD accuracy for empirically determined structures is far better than 1 Å. At present, for the best cases, the C-alpha coordinate RMSD accuracy of AlphaFold-predicted structures roughly corresponds to the accuracy expected for structures determined at resolutions no better than ~4 Å. Thus, although structural predictions by AlphaFold and RoseTTAfold may be accurate enough to assist with experimental structure determination (*3*), they alone cannot provide the kind of detailed understanding of molecular and chemical interactions that is required for studies of molecular mechanisms and for structure-based drug design.

A further complication for structure prediction is the dynamic structural variation in a given sequence. Allosteric states, which can differ dramatically, may be in an intrinsic equilibrium or depend on a binding partner, which may be a ligand or cofactor (e.g., ATP or cobalamin), another macromolecule (e.g., DNA or a protein partner), or aberrant self-association (e.g., pathogenic amyloids). Work is in progress to address protein complexes (*4*, *5*), but structure prediction remains to be achieved for those in complicated molecular machines and for those with ligands that affect conformation, which may be as yet unidentified.

Recent advances should be taken as a call for further development. Moreover, lessons should be learned from history. In 1990, Alwyn Jones and Carl-Ivar Brändén published a commentary on errors in x-ray crystal structures (*6*) that stimulated the development of cross-validation and validation tools for structural biology (*7*–*9*) and that ultimately made the databases of experimental structures much more reliable. Thus, tools should be developed to assess coordinate accuracy of predictions and alleviate bias toward structural patterns observed in repositories.

Finally, it is necessary to reflect on what the word "solved" might mean in the context of the protein-folding problem. Some may feel that this problem will have been solved once any method has been found that enables one to obtain accurate predictions of the structures of proteins from their sequences. AlphaFold and RoseTTAfold represent a major step forward in that direction, but they are not the final answer. Others, including us, feel that solving the protein-folding problem means making accurate predictions of structures from amino acid sequences starting from first principles based on the underlying physics and chemistry. Despite these major advances in protein structure prediction, experimental structure determination remains essential.

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