Particles in the Air

The Deadliest Pollutant is One You Breathe Every Day

By Doug Brugge
Foreword by Kenneth Olden

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Former Director, US NIEHS

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Dustjacket Reviews

"Particulate matter still kills millions of people each year and urgent action is needed to reduce air pollution levels. This book describes in fairly simple fashion all you need to know about particulate matter and its effects on health. The book is informative and brings home the complexity and challenges related to the issues. It is a must read for anyone who wants to understand the basics of particulate matter and health, but it also provides advanced new knowledge. Air pollution concerns us all and this book raises further awareness of the importance of dealing with it."

– Mark J. Nieuwenhuijsen, Research Professor in Environmental Epidemiology, Director Air pollution and Urban Environment, Director Urban planning, Environment and Health Initiative, IS Global, Barcelona Institute for Global Health

"What a captivating journey through the rich topic of particles and PM pollution, where the sources of this killer pollutant – from ancient fire and cooking to cigarettes and cars – and the key public health research that brought us much of our current understanding are threaded into a compelling narrative. Doug Brugge artfully elucidates a complex and scientifically rigorous subject into a personable and easily digestible story, conveying an all-important punch line: the relevance of PM pollution for human health. Doug's book is about the forks in the road – the studies, the people, and the policy decisions – that righted our views on PM and saved lives. This is a great book for the casual reader as well as a good choice for the classroom."

– Alberto Ayala, Director, Sacramento Metropolitan Air Quality Management District, Adjunct Professor, Mechanical and Aerospace Engineering, West Virginia University, Former Deputy Director, California Air Resources Board

"As we better understand the inter-generational impact of air pollutants on our health, and we welcome the rise in citizen science focused on air quality, this book is an important resource for a lay audience of residents, advocates, and policy makers."

– Peggy Shepard, Executive Director, Co-founder, WE ACT For Environmental Justice, New York, NY

"Professor Doug Brugge's highly engaging and accessible prose will not only inform lay persons about the perils of translating science research into public health policies but also motivate and equip ordinary citizens to take social action that lends moral and political support to the brave scientists and public officials who put their careers and reputation on the line to engage in this high-stakes endeavor. In his own ground-breaking science research, Professor Brugge will enable policy makers to quantify the detrimental health costs of harmful externalities that would otherwise remain invisible to citizens and lawmakers alike. As an urban high school administrator, I have no doubt Professor Brugge's work will change our urban landscape--gone will be the busy highways and byways dotted with school buildings and playgrounds."

– Richard K. Chang, Esq., Headmaster Josiah Quincy Upper School, Boston, MA

“For Miho for her generosity, kindness, rigorous and critical thinking and companionship”

Foreword

As former director of the National Institute of Environmental Health Sciences (NIEHS) in the National Institutes of Health and the National Center for Environmental Assessment in the Environmental Protection Agency (EPA), I have been intimately involved in both identification of scientific needs to assess the human health effects associated with exposure to environmental toxicants and translation of the scientific discoveries into public policy. I am particularly pleased that the NIEHS was involved in funding most of the studies highlighted in this book. In fact, the NIEHS has developed many of the resources necessary to translate environmental health research into public policy and practice. This includes the journal *Environmental Health Perspectives*, promoting community-based participatory research, funding the children's environmental health centers, the "sister" breast cancer cohort, and the breast cancer and the environment centers. Therefore, I am intimately acquainted with the research and events described by the author.

The author tackles one of the most challenging problems in public health; that is, the translation of scientific knowledge into policy and practice. Unfortunately, the path from science to policy is not straightforward. This is especially true in the environmental health sciences, where the policy remedy often requires behavioral change (e.g., cessation of smoking) or investment in new technology (e.g., emission control on motor vehicles). Both the public and the affected industry have a right, in our democratic society, to comment on the science used in the risk assessment process and on the strategy proposed to manage the risk. These groups almost always have different perspectives on how much evidence is enough to warrant action; how much weight to assign to findings from different evidence streams (e.g., epidemiologic versus animal studies); how to deal with gaps and uncertainties in the science; and whether the risk should be framed in a precautionary framework. So while "sound science" is critical for informed public policy, it is not sufficient as risk assessment is inherently a subjective process supported by science.

This is a beautifully written account of how talented and committed scientists, whose works are summarized here, persevered under harsh attacks on the credibility of their science and efforts to besmirch their character by questioning their motives.

The author provides a factual account of important historical events associated with the development of the scientific foundation for assessment of the risk of human exposure to toxic substances and the challenges associated with translation of the science into public policy. The storytelling approach used by the author renders complex scientific information both interesting and comprehensible to the intended nonexpert audience. The narratives are presented in such a fashion that there is clarity with respect to (1) the problem that the investigators were interested in solving, (2) the exciting journey of scientific discovery, and (3) the human toll associated with the long and contentious process of translating their findings into policy. With the pending publication of this book, a larger segment of the public will have a greater appreciation of how the contentious nature of environmental health regulation can drive the best scientists out of the field. Personal attacks on their character and scientific credibility are unpleasant and time-consuming.

This book is replete with useful examples of research studies, personal insights, and role models that will inform nonexperts and inspire future scientists. The first narrative summarizes the immensely interesting and inspiring story of Kirk Smith and his research on the health effects of exposure to smoke and fumes derived from the use of solid fuel for cooking. His work demonstrated that smoke derived from fires fueled by wood contained a wide range of chemicals and particulates (PM) that are known to cause cancer and cardiovascular diseases. After many years of research, he was able to demonstrate a cause-effect relationship between indoor cooking on wood-burning stoves and adverse health outcomes. But after many years of unsuccessful efforts to improve cook stoves, Professor Smith finally decided that the solution was to substitute cleaner-burning liquid gas for wood as modified cook stoves and ventilation did not reduce exposure to desired levels. In fact, he led the effort to convince industry to make liquid gas widely available and affordable in India and other developing countries. It took more than 40 years to accumulate definitive evidence before the World Health Organization would list smoke from wood-burning stove as a leading public health problem and for liquid gas to be promoted as a more healthy alternative fuel.

The second narrative, focusing on the health effects of cigarette smoking, chronicles the history of scientific discovery and efforts to translate knowledge about the health effects into policy. There was suggestive evidence that cigarette smoking was a cause of lung cancer as early as the late 1920s; in fact, a comprehensive review of 8000 publications was published in 1939. These studies showed that heavy smokers were six times more likely to develop lung cancer than nonsmokers. Ultimately, it was the combined data from multiple evidence streams (e.g., epidemiology, animal studies, clinical studies, and cell culture) that convinced policy makers to publically acknowledge that cigarettes were linked to cancer, with the publication of the US Surgeon General's Report in 1964. However, by this time evidence was just as strong (if not stronger) that cigarette smoking was also a risk factor for cardiovascular disease, though not emphasized in the Surgeon General's Report.

Embedded in the narrative on the health effects of cigarette smoking is a discussion about the increase in lung cancer risk among nonsmoking wives of smokers.

Women married to smokers had a risk about twice that of women married to nonsmokers. This raised the issue of secondhand smoke. This should have been a predictable outcome given that cigarette smoke contains more than 70 chemicals known to be carcinogens. Also, the finding that environmental tobacco smoke could increase lung cancer risk in nonsmokers drove home the point that personal behavior (e.g., the decision not to smoke) is not protective against many environmental hazards including those in cigarette smoke.

In both the case of cigarette smoking and exposure to secondhand smoke, regulatory action was delayed for decades because of the well-funded and well-organized opposition of the tobacco industry. For example, epidemiologic studies linking secondhand smoke to lung cancer were first reported in 1981, yet it was not listed in the federal government's Report on Carcinogens until 2000.The pro-tobacco lobby has vigorously opposed every effort to require restrictions on advertising and warning labels. In the case of secondhand smoke, the tobacco industry joined forces with the restaurant industry and the chamber of commerce to oppose regulation to ban smoking in public places. Hired consultants (often former colleagues of mine from the National Cancer Institute and the EPA) would show up at public meetings to raise questions related to the fact that science can rarely conclude with 100% certainty that a given exposure is the cause of a given health outcome. They would also cast doubt on the science by exploiting the limitation on our ability to exclude other factors (called confounders) with 100% certainty. Given the press's appetite for controversy, they would sensationalize the debate which would raise doubt about the quality of the science used in the assessment and would confuse the nonexpert public. Such efforts have been highly successful in delaying policy even when the science is compelling.

I can remember when I made the recommendation to the Secretary of Health and Human Services to list secondhand smoke in the US Report on Carcinogens, as a known human carcinogen. My decision was challenged by the tobacco industry, as a consequence; I was cloistered in a conference room, accompanied by a very able lawyer provided by the Department of Health and Human Services, for several hours with a battery of tobacco industry lawyers to defend my decision. In this case, the science is compelling, so I had no problem in defending the decision. Therefore, secondhand smoke was listed as a known human carcinogen in the Report on Carcinogen in May 2000. However, such confrontations can be very intimidating to scientists and public servants.

The third narrative summarizes the Harvard Six-City Study. This was a large-scale complex epidemiologic study that monitored the air quality and health of over 8000 people living in six cities (three with highly polluted air and three with relatively pristine air) for 14–16 years. The study controlled for multiple possible confounders such as age, gender, smoking, education, body mass index, and occupation. It took approximately 20 years to complete the study and analyze the data. However, when published in 1993, it provided the first convincing evidence that fine particulate matter ($PM_{2.5}$) in the air was harmful to humans. A companion study supported by the American Cancer Society (ACS) published in 1995, confirmed the Harvard study.

The ACS study examined 1.2 million adults, representative of the US population, and found that exposure to $PM_{2.5}$ increased risk of dying by 15–17%. The Harvard and ACS studies provided the foundation for federal regulation of ambient PM air pollution announced by the EPA in 1997.

The investigators associated with the Harvard Six-City Study are my heroes! I "hold-up" this study up as the example of why the American people have been so generous in their support of biomedical research; they are investing in products to improve their health. In my opinion, this is the single most important study ever funded by the National Institutes of Health in terms of impact on public health. The number of lives saved annually worldwide is in the millions and the savings in healthcare costs are in the trillions of dollars, and both will continue to grow as countries like India and China implement more rigorous air pollution control standards. My optimism is justified by the follow-up studies conducted by Professor Francine Laden, a member of the Harvard group. Her studies have shown that air pollution levels have declined in all of the six cities since the new air quality standards were implemented in 1997, and that for every 10 μg per cubic meter reduction there was about a 25% reduction in risk of death. Also, more recent studies using "omic" technologies have suggested a plausible stress-related, neuroendocrine mechanism to explain $PM_{2.5}$ effects on mortality.

The fourth and final narrative focuses on ongoing research to investigate the health effects of ultrafine particles. These studies are being conducted in collaboration with local community groups, via community-based participatory research, which makes translation more efficient once possibilities for intervention are known. Ultrafine particulates are found along major roadways, so living near roadways is associated with a wide range of health problems (e.g., cancer, cardiovascular disease, and low-birth-weight babies). With funding from the NIEHS, Professor Brugge and his collaborators recruited people living close to and far from highways to participate in the study and controlled for SES and body mass index. The levels of ultrafine particles in the two neighborhoods were measured, and blood samples were collected to measure the amount of a biomarker (CRP) for heart attack or stroke. They found that people with higher exposure to ultrafine particles also had higher levels of CRP in their blood; whereas, the evidence suggested that exposure to ultrafine particles was causing inflammation, it was not strong enough to establish a cause-effect relationship.

Nevertheless, the community partners insisted that an intervention trial be developed. Therefore, filters were installed in homes of individuals living near roadways. The filters were effective in reducing the levels of ultrafine particulates by 50–80%; however, they observed no benefit with respect to the level of CRP in the blood. One can be optimistic that these studies, which are still in the early phase, will yield results with respect to whether ultrafine particulates are responsible for the increased morbidity and mortality associated with living near expressways.

In summary, as environmental health decision-making becomes more politicized and contentious, efforts to educate a larger sector of the public are a laudable goal. The author has done an outstanding job of describing the scientific and communication challenges involved in the development of environmental health

regulatory policy. He makes it clear that public policy is based on a mix of science and value-laden, subjective judgment, and that lack of knowledge of science is not the primary reason for conflict and controversy in environmental health decision-making. The fact that conflicts and controversies surrounding risk management policy play out in the media and in the adversarial legal system tends to create confusion and distrust among stakeholders, and these concerns are often unrelated to science.

Former Director, US NIEHS Kenneth Olden
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Acknowledgments

Thanks first to Eda Yiqi Lu and Yu "Fish" Li, who were my research assistants for this book. They made major contributions by assisting with citations, redrawing and obtaining approval to use figures, and so many other tasks. Ms. Li also conducted the interview in China. My deep and heartfelt appreciation for their tremendous skills and hard work. Thank you to Saraswathy Manivannan for conducting the interview in India and to old friends Karen Benally who interviewed her husband, Timothy. Also, a profound appreciation for everyone who consented to be interviewed and quoted in this book. Many of them took time out of busy schedules and were willing to share parts of their stories that were a bit personal or at least went beyond what would appear in academic publications. Thanks to Jim Repace, Wig Zamore, George Thurston, and Mohan Thanikachalam for reading parts of the manuscript and providing feedback. The reader will have to judge, but to the extent this book is more engaging than cold science writing, I feel I owe a lot to these people's stories. I worked on this book on the side, rather than as a core part of my day job, but the money I received with the Zucker Family Prize which is awarded annually to a member of the medical school faculty for research helped because I was able to use part of that money to cover costs associated with preparing the manuscript. My work was strengthened by my association with the Jonathan M. Tisch College of Civic Life, which values and supports my efforts to engage communities in research and translate research into policy and practice. The CAFEH study at the center of Chap. 5 is a decade-long collaboration with the Departments of Public Health and Community Medicine and Civil and Environmental Engineering at Tufts University through John Durant that has been funded primarily by NIEHS, NHLBI, NLM, HUD and the Kresge Foundation.

Introduction

Where there is fire there is smoke

What if I told you that you are exposed every day to one of the most toxic substances we know, and that this substance is, in fact, the leading environmental cause of death and illness? What if I also told you that this substance is so pervasive that every human being on the planet, not just you, is exposed every day also? How would you respond if I then added that in its various forms this pollutant constitutes three of the top ten causes of poor health and mortality worldwide? [1]. Additionally, I could add that, while you might reduce your exposure, you could never eliminate it completely. Finally, I would have to inform you that the evidence suggests that this toxic substance is hazardous at very low levels, below even the most stringent regulatory standards.

I suspect that you would be alarmed at what I told you. Perhaps you would even demand that action be taken to protect you, your family, and I hope, all human beings from this terrible risk. But the hazard I am writing about, airborne particulate matter, also called PM, is not nearly as well recognized or understood as many other environmental hazards. In fact, based on current estimates, all other environmental exposures *combined* take a smaller toll than PM. Maybe it is because the hazard of PM is so pervasive that it does not feel exotic or out of the ordinary compared to BPA (bisphenyl A) in baby bottles or mercury in fish. Or maybe it is because, at least in high-income countries, PM is often invisible and odorless, so out of sight and out of mind. Whatever the reason, it seems to me that PM does not get the attention or respect that it deserves.

The most toxic types of PM are usually the byproduct of combustion, that is of burning something – wood, coal, gasoline, jet fuel, heating oil, and so forth, with the greatest risk being from fossil fuel burning. Combustion produces tiny bits of solid or liquid that become suspended in the air. The PM that health researchers are most concerned about, because they can be inhaled deeply into the lungs, are so tiny that we cannot see the individual particles. The dust particles that you sometimes see floating in a ray of light are monstrous boulders in comparison.

PM is not new. Throughout human evolution, and indeed animal evolution more generally, there have been natural sources of PM. Natural sources include forest fires, volcanoes, and even trees release gasses that can become PM. But except for occasional bursts of release, such as from a forest fire, natural levels of PM are usually quite low compared to exposures we experience today.

While natural levels of PM are usually low, humans have been finding ways to expose themselves from early on. From the time that early humans harnessed fire to keep warm and to cook food, they began generating smoke that they breathed in. Based on what we know today about burning wood or other biomass fuels indoors, I am confident that these early humans were exposed to and inhaled substantial amounts of smoke.

It is interesting, given the health risk, that breathing wafts of smoke from and sitting next to fires is so compelling. I have many memories of sitting around campfires or in front of fire places. They are pleasant memories. Indeed, the smell of the smoke is integral to the pleasure and the memory. Clearly fire and smoke are associated with benefits in our minds as well as harms.

Knowing what I know now, after studying environmental health and focusing my research on air pollution from traffic for the last decade, what benefits might lead us to find the smell of one of the worst known environmental hazards so appealing? The obvious answer is that in ancient times fire meant cooked food, warmth, and protection. In those times we did not live long enough for many of the chronic diseases that haunt us today to develop. Or at least they developed well past our reproductive years and after our offspring were safely started on their own lives.

As human civilization advanced, though, we were exposed to increasing levels of PM, often with increasing levels of toxicity. With housing came more indoor burning, vented to varying degrees, but substantial build up indoors nonetheless and the vented smoke accumulating in the ambient air next to where we lived. Clear burning for agriculture probably generated some of the first large releases of ambient PM by humans. Evidence also suggests that people smoked plant materials, including tobacco, albeit on a much more limited basis than today, from very early times.

But it was industrialization that ratcheted up the scale of PM that was generated, resulting in qualitatively higher exposures. Even if the history of smog-cloaked cites in Western developed countries is almost forgotten, one has only to look at China and India today to see how industrialization can foul the air. From burning coal to unleashing massive fleets of automobiles and trucks that spew exhaust, industrial societies excel at polluting the air. Industrial production of cigarettes also ushered in addictive smoking for hundreds of millions of people. And smoking delivers a massive dose of PM directly to the lungs.

Until now I have framed PM as a singular entity, but as with many things, it is not that simple. In fact, PM comes in many forms. Because PM has most often been described based on size for both research and regulatory purposes, I will follow that convention in this book, as well. However, what the particles are made of, and what pollution source they came from, can make a big difference, too. Figure 1 shows a human hair as a point of reference for airborne particles of different sizes. If you hold up a single strand of human hair, you can see how tiny the distance is across it. But we will be concerned here with even much smaller sizes.

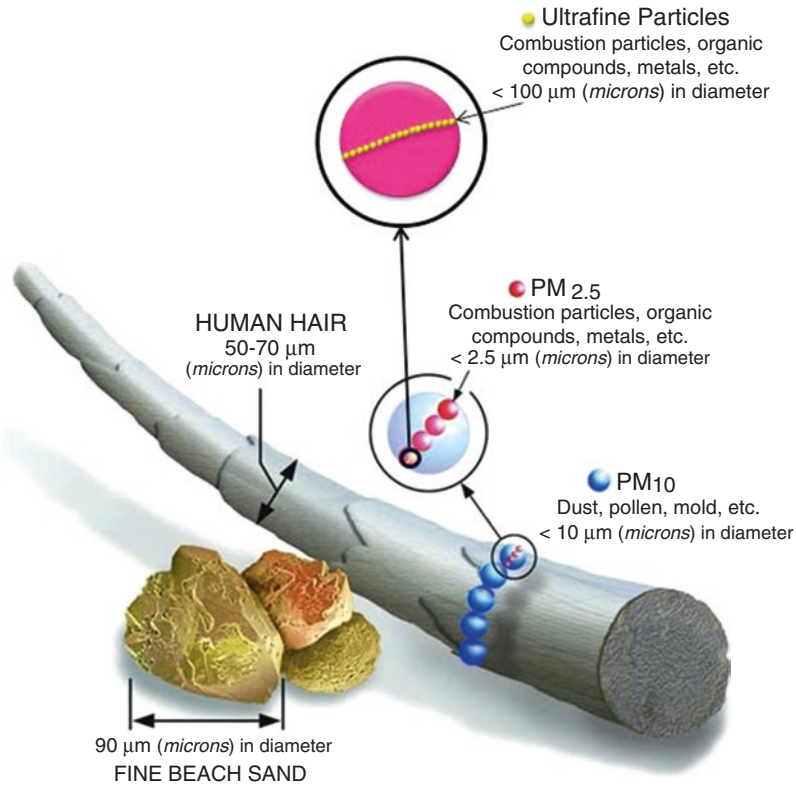

Fig. 1 Size classes of particulate matter (PM) compared against a human hair and grains of beach sand. The size classes are defined as particles of a certain diameter and all particles smaller than that diameter. The blue spheres are the largest PM_{10} particles, or PM with a diameter of 10 microns (a micron being one millionth of the length of a meter). The red spheres are the largest $PM_{2.5}$ particles, or PM with a diameter of 2.5 microns. The yellow spheres (compared to an enlarged 2.5 micron sphere) are the largest ultrafine particles, or spheres that are 0.1 microns in diameter. Illustration modified by Eda Lu, based on United States Environmental Protection Agency. *Particulate Matter (PM) Pollution*

Coarse PM is mostly composed of dust that is blown, kicked up, or generated by mechanical action. This PM is defined as having a diameter of less than 10 microns (the blue particles in Fig. 1). A micron (or micrometer) is one millionth of an inch, which is really small, but we will look at even smaller sizes. PM_{10}, as it is also referred to, is the largest size fraction that we usually consider relevant to environmental health today. Because PM_{10} particles are "large" in the context of PM overall, they tend to get stuck in the nose and throat and don't make it to the lungs. For reference, PM_{10} is generally smaller than the windborne pollen grains that aggravate your allergy.

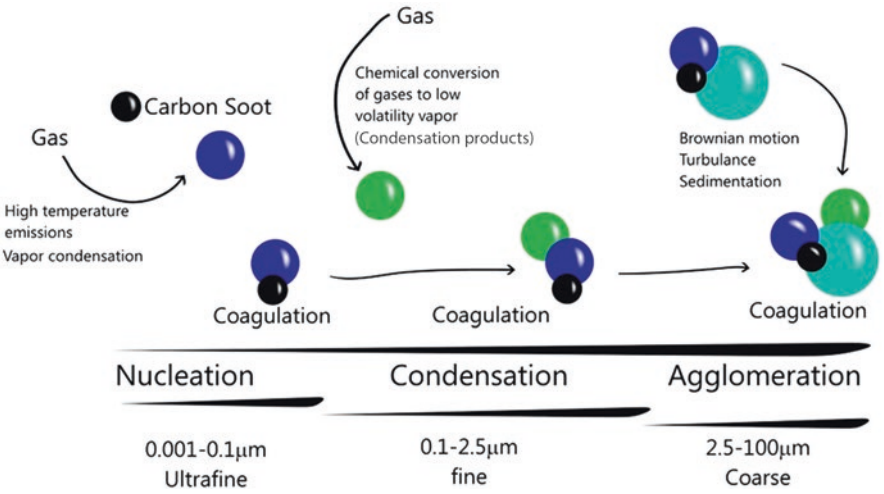

Fig. 2 The early stages of formation of particles first from gasses and then also by joining together to form larger particles. Open access: **Copyright:** © 2016 Falcon-Rodriguez, Osornio-Vargas, Sada-Ovalle and Segura-Medina

Particles formed by combustion are even smaller than PM_{10}. This is largely because they form from the incomplete combustion of solid, liquid, or gaseous fuels. Most combustion particles form through the condensation of very hot gasses in the air. PM can start out very tiny and grow by absorbing additional molecules from the air around it (Fig. 2). Particles, once they form in the air, may also combine, or coagulate, or even evaporate away. Under a strong microscope, airborne particles can also be seen to be quite variable in their shape.

Because combustion particles are so tiny, they can travel deep into your lungs when you breathe them in. Based on the size of particles that can reach the smallest passageways and air sacs (alveoli) in the human lung, fine PM is defined as PM that is smaller than 2.5 microns (one millionth of a meter) in diameter, or $PM_{2.5}$ (the red particles in Fig. 1).

The smallest particles of all are called ultrafine particles or UFP. UFP are defined as being less than 0.1 microns (or 100 nanometers, nm, one billionth of a meter) in diameter (the yellow particles in Fig. 1). Ultrafine particles are largely unregulated and have not been studied as much as fine PM. But they have some remarkable properties, including being able to cross into the blood from the lungs and even travel down a nerve at the back of the nose directly into the brain. There is growing evidence that we should also be concerned about ultrafine particles, which is the area of air pollution research that I conduct.

It is worth a brief cautionary note that particles of the same size class are not actually all the same. In fact, PM may be composed of quite different substances, depending on the fuel that is burning and the temperature and availability of oxygen. For example, PM from car exhaust, cooking fumes, and tobacco smoke will all have different chemical "fingerprints." It is likely that particles of different

composition also vary in their toxicity. While the science on PM composition is less developed than the science on particle size, it is advancing rapidly. And, as already mentioned, regulatory frameworks are mostly based on size classes of PM, though some constituents of PM, such as lead (Pb) in the air, have been regulated as well. In this book, for simplicity, I will dwell less on particle composition and more on size.

The rather startling impact of PM on health has been documented in recent years by the Global Burden of Disease studies that are published in one of the leading medical journals in the world, *The Lancet*. As these risk assessments show, the increased risk to any individual from ambient PM is small, but because every single person on the planet is exposed, the number of deaths and illnesses across the entire human population is quite large.

Also surprising to many people is the evidence that the greatest health impacts are cardiovascular diseases, such as stroke and heart attack. It is natural to assume that, if you breathe in particles, they would most affect the respiratory system, primarily the lungs. PM does cause and aggravate asthma, and leads to lung cancer and chronic obstructive pulmonary disease, but the biggest impact, because it results in many more deaths, is from cardiovascular illnesses.

The Global Burden of Disease studies have repeatedly shown that PM is the main contributor to three of the top ten causes of illness and death in the world. These are tobacco smoking (not a surprise I think), indoor solid fuel burning in developing countries, and ambient $PM_{2.5}$ (Fig. 3). In fact, these three environmental problems are on a par with or greater than diet and physical activity, two much better known public health problems that are discussed far more often in the public sphere [1].

I have long wondered why air pollution, and PM in particular, are not of greater concern than they are to the general public. As I noted at the start of this introduction, concern about BPA in baby and other bottles led to substantial changes in marketing of products. Why does it seem that concern about air pollution, at least in high-income countries, is more modest?

I suspect that several factors are at play. First, again in high-income countries, air pollution is mostly invisible, except when seen as summertime haze, or coming out an exhaust pipe. So perhaps it is largely out of sight and out of mind, unlike the water bottle that you carry in your hand and from which you drink. Second, to the extent people are aware that a pollution problem persists, they may not know the extent of the problem. They probably do not know that in the USA, with mostly clear skies, it is still estimated that over 100,000 deaths a year may be attributable to ambient $PM_{2.5}$ [2]. In comparison, secondhand smoke and radon in homes, both perhaps better known, each cause a fraction of that many deaths.

Finally, I find that when I talk to people outside of the field of air pollution, they often throw up their hands and say that there is nothing they can do. It is not as easy to change federal air pollution standards, to outfit cars with better controls on exhaust, or even to install an air filtration system in your home. Certainly, taking on national-level policy is an intimidating and, at best, long-term, high-intensity effort that may not succeed. But my colleagues and partners have found, as I will discuss

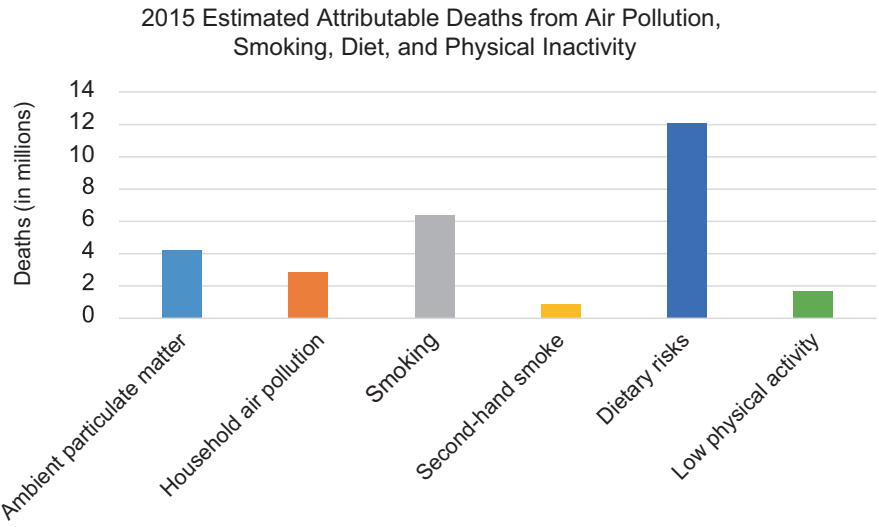

Fig. 3 Deaths from $PM_{2.5}$, indoor solid fuel combustion, smoking, and secondhand smoke according to estimates from the Global Burden of Disease analysis in 2015. These PM-related deaths are compared to more commonly recognized public health problems, diet, and low physical activity. Illustration by Eda Lu, based on Global Burden of Disease 2015 [1]

toward the end of this book, that there are also actions that can be undertaken on the local level, that are not as daunting, but that can make a difference.

The reality is that higher income countries have made substantial progress at the policy level in controlling ambient air pollution, restricting smoking indoors, and reducing smoking rates.

That, by itself suggests that we should not be fatalistic. What is more worrisome to me is that having developed the science to understand the health risks and the technology and public policy necessary to address a range of PM exposures, we are now witnessing staggering levels of pollution and smoking in China, India, Iran, and other countries that are following their own paths to industrialization.

To me, it is clear that the major factor that limits controlling air pollution and effective smoking cessation is that it costs money and eats into profits. But the alternative is something like one million deaths a year in both China and India! [2]. Imagine if those deaths were from war, terrorism, famine, or genocide. The outrage would be palpable and the media attention breathless and frenetic. But we tolerate tolls of this magnitude routinely when the outcomes are not from violence, and when the bloody instrument of death is not so easy to discern.

So, the death count from PM continues to rise with marginal awareness by most people.

Smoking rates increased in Asia as they decreased in North America and Europe. Indoor solid fuel burning in poorly ventilated homes is ongoing for vast numbers of

poor people across the globe. Power plants and motor vehicles continue to foul the air in too many countries despite our knowledge about how to prevent it.

For me, writing this book is an effort to raise awareness and generate interest. I have found that once the issue is laid out for people to see more fully, they become concerned. In fact, I have observed that populations that live close to centers of major air pollution research, in Los Angeles in the USA for example, tend to be more interested in the problem and in doing something about it.

I hope that you will read this in the spirit of learning and with an open mind. After all, science requires both respect for evidence and a healthy skepticism. The science of air pollution is ever advancing, and as it does, it teaches us new things. Sometimes it overturns ideas we thought were fact. That can be confusing and lead to uncertainty. But the hazards of PM, as we will see in the coming chapters, are well established.

Indeed, PM exposures are some of the best understood public health hazards. But around the edges, nuances of understanding continue to emerge, perhaps lowering the level of exposure known to present a health risk or adding a new type or source of particles to the list. I will present here evidence and understanding that is up to date as of the time of my writing.

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Chapter 1
An Ancient Frenemy

Humans, or possibly our ancestors, mastered fire eons ago. The exact timeframe is debatable, but Richard Wrangham in his book, Catching Fire: How Cooking Made Us Human [1], argues that cooking food, and hence controlling fire, was critical to human evolution. There is solid evidence that humans were using fire 300,000–400,000 years ago and suggestive evidence that fire was under control of one of our ancestors over a million years ago. To drive human evolution, fire use would probably need to have begun over a million years ago as Wrangham posits.

However long it has been, and whether or not it was a defining factor in what made us human, we have been sitting around fires of our own construction for generations untold. Throughout my life, I have found campfires or burning logs in a fireplace to be inviting, comforting, and appealing. It is a remarkably pleasant activity to sit and watch the flames, roast some food or tell stories around a fire. Even the smell of burning wood is enticing. I wonder if that comfort and familiarity could be deeply engrained in us because it is so incredibly ancient. Maybe there was selection for liking the smell of burning wood because using fire improved our chances of reproducing.

In any case, fire was and is a powerful tool that undoubtedly contributed to the survival and ultimate success of our species. As Wrangham documents, cooked food is healthier than raw food. It provides more energy for less consumption. It removes hazardous infectious agents. It frees up time so that we do not spend all day eating to meet our nutritional needs. Heat is also vital for us to be able to live in colder climates. The light from a fire pierces the night and can fend off predators. And fire is used to clear forest and brush for agriculture.

But fire has a nasty downside. During combustion hot gasses and tiny particles made of solids and liquids form and are released into the air. The complex chemistry of these gasses and particles includes transitions from gas to particle and visa versa. The chemical substances in the combustion products – called smoke when it is from fires burning solid fuels like wood – include a wide range of chemical compounds that are well known to be toxic, including polycyclic aromatic hydrocarbons or PAHs. PAHs are products of incomplete combustion that are carcinogens and affect cardiovascular health.

D. Brugge, *Particles in the Air*, https://doi.org/10.1007/978-3-319-89587-1_1

Standing over a fire or sitting next to it, especially in an enclosed space, assures that one will inhale high doses of particulate matter. Particulate matter consists of tiny bits of liquid or solid suspended in the air that are called PM by the people like me who study them. For our ancient ancestors breathing in smoke in exchange for warmth, cooked food and protection was probably a sensible trade-off. Their lives were not as long as ours are today. The immediate acute threats that they faced – starvation, infectious disease, hypothermia, fierce predators –were of more immediate concern than the risk of cancer or a heart attack that might happen decades later. Plus the fuels they used, wood primarily, might give off less toxic smoke than many of the fuels we use today which are fossil fuels like coal or gasoline.

Today the widespread use of solid fuel, most often indoors, is found predominantly in low-income countries where it is one of the leading causes of death and illness. This low tech, everyday hazard went unrecognized and unaddressed for far too long. The earliest record of recognition of the problem was a paper published in the medical journal *Circulation* in 1959 (Fig. 1.1) [2]. This paper reported a high prevalence of a serious heart disease called cor pulmonale in adult women living near Dehli, India. Cor pulmonale results from damage to the lungs that, in turn, causes resistance to blood flow and makes the heart work harder. Typically, the right ventricle of the heart becomes enlarged from overwork. Ultimately, heart failure and death may result.

Amazingly, the lead author of the 1959 study, Dr. Padmavati, was alive at the time of this writing, over 100 years old and still an active researcher! What was striking about her study was that non-smoking women without occupational hazards had developed cor pulmonale. Cor pulmonale is typically associated with occupations that predominantly employ men because they involve exposure to high levels of dust or combustion products, such as is encountered during mining or milling steel. Padmavati suggested in her paper several exposures that might explain her findings, including burning of cow dung for cooking, but also untreated infectious disease and dust storms. There appears to have been little reaction to her research so it lay dormant for decades while millions of women's lives were cut short.

Chronic Cor Pulmonale in Delhi

A Study of 127 Cases

By S. Padmavati, F.R.C.P., M.R.C.P., and S. N. Pathak, M.R.C.P., D.C.H.

The incidence of chronic cor pulmonale in Indian states, including Delhi, is the highest reported in nonindustrial populations. The patients presented as acute severe congestive heart failure and at younger ages than those reported. In many cases there was only a short history of respiratory symptoms. Following the first attack of failure, repeated attacks were the rule and death ensued within 2 years. A study is presented of 127 patients of this type in Delhi with clinical and laboratory data and autopsy data of 4 cases. The probable causes of these peculiar features are discussed.

Fig. 1.1 The title, authors and abstract of the 1959 paper by Padmavati and colleagues as it appeared in the journal *Circulation*

The issue would re-emerge in the late 1970s when Kirk Smith, then a graduate student at the University of California Berkeley, switched his interest from nuclear power to indoor solid fuel burning. Smith was trained as a physicist and he told me that he came to realize that the health consequences of nuclear power paled in comparison to smoke inhalation. From my perspective, Smith still feels like more of a hard sciences guy than the public health researchers in my academic department. He has a wry humor and straightforward delivery when he speaks. He also has a laser focused intensity and incredible persistence. He is a prototypical maven, in this case on the issue of solid fuel combustion, having devoted his whole career to this narrow issue.

Dr. Smith's first job out of graduate school was at the East-West Center in Honolulu, HI where he inherited a 6-country study about rural energy. Visiting the countries in that study changed his life. After observing people cooking over open fires when he returned home, he could find no literature about the risk that they posed. He did not find Dr. Padavati's paper until years later, probably because this was a pre-internet time and finding references was not so easy (recently it took me only 2 min to find her article on Google Scholar and download it and a little longer to read it!).

Smith's newfound interest led him to do the first study, which was unfunded, of exposure to smoke from cooking fires. He jokes that it was the most cost effective study he ever did, given that it cost nothing. That study led to a scientific paper published in the journal *Atmospheric Environment* and then a book, Biofuels, Air Pollution and Health, A Global Review [3], which is still in print from Springer.

Smith credits the book with his nomination to the National Academies of Science and he may well be correct. Reading his book 30 years after publication, I found that it holds up remarkably well. Where it is outdated, it is because the science advanced in the decades after he wrote it, for example with respect to the importance of cardiovascular disease as an outcome of PM exposure. The impact on cardiovascular disease was not emphasized until many years later and even today is often under-appreciated. He also does not discuss the emergence of interest in and concern about the tiniest particles, ultrafine particles, but that concern is also very recent (see Chap. 5).

His explanations of the products of combustion and the challenges of accurately assessing exposure to them are a pleasure to read for their clear thinking and careful adherence to the evidence of the time. In many ways the problems he identifies with exposure assessment remain only partially resolved today. Because exposures to PM from most sources are changing in time and space while people move in and out of microenvironments with differing concentrations, it remains daunting to accurately estimate exposure.

In Chap. 4 of his book, Smith conducts a necessarily preliminary estimate, based on significant assumptions, of the exposure that women cooking over solid fuel fires might be experiencing. One sentence stands out. He concludes, "[i]ndeed, only relatively few workers in rather obscure occupations [such as coke ovens] would receive….doses approaching the levels estimated for rural woman cooks [3, p. 132]." Even at this early stage and preliminary level of understanding, the rough magnitude of the problem was obvious to him.

Fig. 1.2 Image of women cooking with indoor solid fuel fires and their children nearby

For me, Smith's story is a wonderful example of the importance of careful observation and critical thinking. Most of us, most of the time are quite casual about what we see and experience. We might see woman cooking on a fire indoors (Fig. 1.2). Perhaps we have seen such a thing repeatedly in our lives, maybe since we were quite young. In fact, literally millions upon millions of people saw women cooking this way and failed to understand the seriousness of problem before Smith took it on. That is because seeing people cook over a fire is profoundly normal. It is what we expect. We might even find it appealing. We don't notice anything abnormal about it, let alone question or analyze the situation. We normalizing what we encounter on a regular basis.

The remarkable thing about Smith is that he actually saw what he was looking at and asked a key question, how can this be healthy? His assignment, to study, rather than casually observe, energy use in developing countries obviously positioned him to look more closely than would many people. Still, he could hardly have been the first person professionally trained in science to notice women cooking over open fires indoors and no one else pursued the issue seriously before he took it up. Indeed, as I already noted above, Smith's entrée into the field followed many decades of neglect. During those decades women were dying simply because they were cooking food for their families.

Unfortunately, as we shall see, it would take Smith additional decades to bring the issue to the attention of policy makers who would launch a large-scale response. After his initial measurements of exposure in homes in India in the early 1980s, he and others decided that the way forward would be to conduct a randomized controlled trial (or RCT) of improved stoves that would reduce exposure. This was not

surprising since the scientific world demands solid, scientific evidence and RCTs are the gold standard for proving that an intervention (often drugs in clinical medicine) is effective.

Smith accurately describes the dichotomy between what the public or community demands – immediate response to address the obvious problem – and what the scientific and regulatory communities expect – far more precise evidence of the exact nature of the problem and its risks. Of course, evidence is usually on a continuous scale, with increasing evidence accumulating to provide greater confidence. Thus, the question of how much evidence is enough to spur investment of resources in a response can be a thorny one.

Usually what appears obvious is upheld, in this case that smoke is bad for health, although often the research adds nuances that might not have been anticipated, such as most of the health effects being cardiovascular instead of respiratory. However, sometimes the evidence does not support a popular notion – it turned out, to use a clinical example, that hormone replacement therapy presented greater risks than was acceptable, for example. It is understandable that we do not want to invest scarce public health resources in problems of small scale when there are other problems that we know to be enormous, tobacco smoking being an example that I will take up in Chap. 2. So scientific investigation is justified. The question then becomes, how much evidence is enough?

There is no scientific answer to this question. Usually public health and environmental activists demand interventions based on early evidence of a problem while downplaying the costs. They often argue that it is unethical or immoral to put a cost on human life and suffering. The industries that are affected usually push back insisting on greater evidence, sometimes to ridiculous extremes, and bemoaning the impact on the economy, particularly jobs, but almost certainly also about their own profits. Non-partisan experts might employ cost-benefit or cost-effectiveness analysis to try to inform the resulting debate with dispassionate estimates of risk and benefit, but still no answer for the question of how much evidence is enough.

Thus, it is not surprising that in 1984 Smith and his colleagues chose to conduct a RCT. Unlike observational studies that simply look for associations, RCTs randomize participants to an intervention, in this case improved cook stoves, and standard practice, traditional open fires. The randomization of study participants, provided the study is large, should eliminate (but sometimes fails) other factors that might be responsible for associations. The problem with RCTs though is that they are expensive and time consuming to conduct. In addition, funding by NIH or another major funder is unlikely without sufficient preliminary data or pilot studies to convince reviewers of the potential of such an investment.

In the early 1990s, a committee of the World Health Organization conducted a review and determined that a site in Guatemala would be preferable for a trial of improved cook stoves. Smith sought funding for his RCT through the end of the 1990s without success. This is by no means a reflection on his abilities nor on the value of the research. The NIH funding process is highly competitive and often unpredictable. In my experience both as a reviewer for NIH and as an applicant, the quality of reviews can vary considerably. And even in the best cases, preparing an

application takes many months, the review takes many months more, the outcome usually results in a resubmission which takes additional months of work followed by another review and then, if you are extremely fortunate, you might get funded after another delay of months.

Only in 2001 did Smith receive the funding he needed to conduct an RCT of improved cook stoves in Guatemala. Typical of standard NIH research grants, his was a 5-year project. Also typical of much NIH funded research, publication of the main findings took additional years after the end of the grant. This is because the funding primarily covers conducting the research, in Smith's case fieldwork to test the improved cook stoves and collecting data on exposure and health outcomes of the participants. Analyzing the resulting data and getting the findings published can be a process that continues long after the funding expires.

By 2004 a World Health Organization report listed smoke from kitchen fires as responsible for 1.6 million deaths each year and a leading public health problem in the world [4]. Estimates of health impacts have changed in subsequent years, with the most recent estimate from the Global Burden of Disease studies putting the toll at a little less than three million deaths per year [5]. That makes household pollution from cook stoves the fourth leading cause of death in India with about 900,000 premature deaths per year, somewhat less than the toll from outdoor air pollution, which is ranked as the third leading killer (Fig. 1.3) [4].

In addition to mortality, estimates of the impact of health risk factors are also often reported as "disability adjusted life years," or DALYs. DALYs are the number of years lost because of poor health, disability or premature death. For household air pollution from solid fuels, DALYs were most recently estimated to be above 80 million per year worldwide, a substantial human toll by any measure.

Clearly, cooking with solid fuels, especially when unvented, was making tens of millions of people sick each year and killing millions of them. But the response to this massive public health concern was modest, resting primarily on one man and his long delayed research study.

Smith published the findings in 2011, 25 years after he decided to conduct an RCT of cook stoves to reduce smoke exposure in homes for low-income people using open fires. Published in *The Lancet*, a major and highly respected medical journal, the study showed 50% reductions in exposure and less physician diagnosed pneumonia in children [6]. While somewhat encouraging, the results were not as strong as hoped. Smith and his co-authors concluded that they would need even better stoves to achieve their desired results.

Today Smith notes that he has probably worked with more cook stoves than anyone and never found one that was "good enough." He says that, "there's been no biomass stove, approved or not, that comes close to being something you would want to have in your own kitchen." [7]. In fact, one would probably need a 90% reduction in exposure to obtain maximal health benefits. In addition, focusing on improving cook stoves does not address the pollution that is emitted out of the smoke stack that then pollutes the neighborhood. Furthermore, it may also be difficult to get users to adapt to the new equipment and failure to maintain the stoves could lead to reduced efficiency compared to the modest timeframe of an RCT.

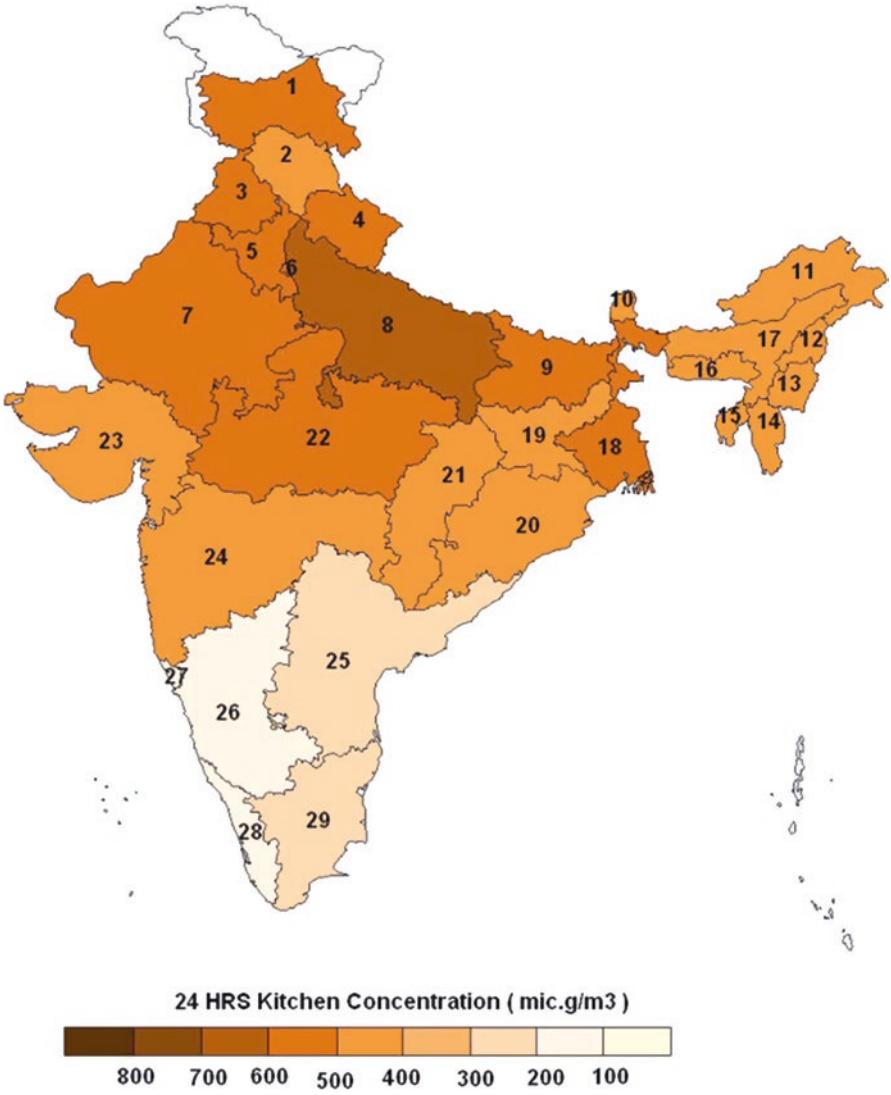

Fig. 1.3 Weighted estimates by state for the average 24-h kitchen area concentrations of $PM_{2.5}$ for solid- fuel-using households in India. Report of the Steering Committee on Air Pollution and Health Related Issues, August, 2015. http://ehsdiv.sph.berkeley.edu/krsmith/publications/2015/MoHFW%20AP%20Steering%20Com.pdf. (From GBD MAPS Working Group [8])

Overall, the long delays and disappointing results with improved cook stoves were discouraging. The lackluster response of governments and research funders contributed to the long slow, largely invisible, toll on health across much of the world. As a rough estimate, if you extrapolate back from the most recent estimates of deaths from indoor solid fuel combustion of three million per year it is difficult

not to conclude that over one hundred million people, mostly women and children, died from this exposure over the decades since Padmavati's 1959 paper. The public health community was largely a modern day Nero, fiddling while Rome burned.

Smith dispels the assumption that economic development will solve this problem as people become wealthier and move to cleaner forms of fuel for cooking. His argument, and it is one that I find convincing, is that the population in India is growing too fast. With population growth, even if the percentage of people who use solid fuel declines, the absolute number may stay about the same, around 700 million people. For this reason, Smith decided that it would take active efforts to push safer fuels into the lower-income sectors of the population.

Accordingly, today his focus is no longer on better cook stoves, but rather on cleaner fuel – liquid petroleum gas. LPG burns cleanly and efficiently, greatly reducing the amount of combustion products produced. Smith, now 70 years old and enjoying his first grandchild, claims he is at the end of his career, but he was involved in the effort to interest by the Government of India and petroleum producers in increasing use of LPG.

In 2013 Smith was invited to speak at the International Conference on Occupational and Environmental Health held by the oil industry in New Dehli. He had a thoughtful message for the petroleum industry. First he noted that they are blamed for all sorts of problems ranging from air pollution to climate change to oil spills and fracking. He then suggested they push back by claiming that they have the fuel that could save millions of lives. It was an ingenious framing of message by pointing out that the industry was doing nothing to promote LPG use in poor populations. Perhaps they could profit from the sale of one of their products while also addressing a pressing public health problem.

Sitting behind Smith during his talk was Viek Rae, the Secretary of Petroleum for India. After the presentation, Rae went back to his agency and confirmed what he had heard from Smith by consulting with Keshav Desiraju, secretary of the Ministry of Health. Smith had been pushing Desiraju on the issue so he was up to speed on the science and provided confirmation. Rea then suggested an increase in the number of distributors of LPG. With that single command, Rae replaced more smoky fires than all the attempted public health cook stoves could ever claim.

Rae subsequently called a meeting with the major oil companies and in January 2015 the first national project to expand LPG use, the PAHAL project, began. This project created direct transfers of the government LPG subsidy into recipient's bank accounts. Given the scale of India, this transfer set a global record for the largest bank transfer in history.

PAHAL was followed by another effort, the Give It Up campaign. This campaign asked middle class people to give up their LPG subsidy so that it could go, instead, to lower income folks. Smith was doubtful that large numbers of people would pass on their subsidy, but, thankfully, he underestimated. The slogan was, "A gift of good health to others and a cleaner environment for yourself." An excellent slogan that deserves some credit in the annals of public relations work.

As of February 2017, 12.5 million households had given up their subsidies of about $200 per year. That is about 1.5 billion dollars transferred from the well off

that could be used to reduce solid fuel combustion by lower income folks. To speed up the process, India added a third program, the Ujwalla program to their effort. Ujwalla aims to provide LPG connections to 50 million low-income families.

In India the effort to expand use of LPG has made rapid progress with 30 million new connections and plans to increase to 50 million by 2019.

While the story of cook stoves has an uplifting ending today, it is striking to me how long it took to begin to resolve what was, and still is, for too many people, a very serious public health problem. Moreover, reducing exposure from cook stoves is not technically very complex. The solution, cleaner fuel, was waiting in plain sight all along.

To me this raises a number of thorny questions. Why is research so slow at arriving at fairly simple and, after the fact anyway, apparently obvious answers. Also, why, even once the evidence is relatively strong, does the policy response lag so far behind? And, why is there not more interest in this problem by society, including my public health colleagues who rarely mention and probably are mostly unaware of this story?

Of course, research is, by its nature, quite slow. There are good reasons for this. Research seeks to be precise and exacting in its methods and profoundly careful in assessing evidence. From the standpoint of expanding knowledge, that makes sense. It is remarkably difficult to actually prove anything at the level of certainty that science demands. I certainly approve of scientific rigor and see value in the care and thoughtfulness of serious research.

One answer to the high standards of science has been to require lower standard for policy setting, sometimes framed as precautionary approaches because they aim to take action to prevent harm early in the discovery process. In some ways this makes sense and would have saved many lives if the research process had been short circuited for cook stoves. On the other hand, in less obvious cases where an apparent problem turned out not to be so serious after all and investing in addressing it was costly, there would be wasteful misappropriation of resources.

There may also be instances where lack of care in analytic thinking may have unintended adverse consequences. The digging of wells in Bangladesh to reduce waterborne infectious diseases is a prime example. The groundwater was contaminated by arsenic and led to widespread poisoning.

But, once scientifically derived evidence begins to emerge and the case for harm strengthens, one might expect that policy responses would follow promptly. This is rarely the case and I think the main reasons are the following. First, the response may require economic investment and there will always be hesitancy if not outright resistance to spending and fierce push back by private sector actors if they have to cover the cost. Second, the public and policy makers usually are stuck in well-worn patterns of thought and only slowly warm up to new ideas. The transition can literally take a decade or more in my experience.

That leaves us with the general lack of interest in the cook stove problem. From my vantage point it is remarkable that even within the public health circles in which I operate, there is little knowledge or awareness of the issue. Partly, I blame this on the increasing emphasis on behavior and personal responsibility for one's own

Fig. 1.4 Vasugi, a woman who lives in Thirumazhisai village, Tiruvallur district, Tamil Nadu being interviewed for this book. Photo provided by Saraswathy Manivannan and used with permission

health. It is on you to eat right, be physically active and to not smoke (more on that in the next chapter).

The so-called "social determinants of health", including air pollution, are frequently heralded as important. However, they rarely make it into the top tier of public health concerns and when it comes to the amount of resources devoted to addressing them, they may get short shrift. A major reason being that addressing issues that require political, social and economic changes are more daunting, or appear so anyway, than influencing the behavior of individuals.

Ironically, in reality, individual behavior change is also quite challenging, as anyone who has tried to diet or increase their physical activity can attest. Still, larger social change just seems to most people to be too big and overwhelming to attempt. For both behavior change and social-economic policy change, it often takes a critical incident, sometimes disastrous, or a long skillful campaign by a small group of dedicated individuals over long periods of time. Mothers Against Drunk Driving comes to mind in the US, where their clever and dogged efforts eventually helped shift both pubic opinion, policy and personal behavior about drinking and driving.

Another factor that can drive opinion and influence policy makers and the media are compelling stories of people who are affected. Vasugi (see Fig. 1.4) is a woman who lives in Thirumazhisai village, Tiruvallur district, Tamil Nadu. She was interviewed at my request in 2017 by associates of mine about her experience with using biomass as compared to liquid petroleum gas. She started cooking with biomass when she was 17 and continued doing so for 20 years as her exclusive source of fuel.

Vasugi reported that she hated using biomass. She had to walk several kilometers to collect biomass fuel. She said, "Cooking with solid fuel is a worst experience. I generally get eye irritation, cough and tiredness. We had may quarrels in the family due to the usage of the biomass. Cooking took a longer time, 2 h to cook for five persons per meal."

Seven years ago Vasugi was able to switch to LPG through one of the national programs. She heard about the opportunity through her village leader during the elections. She says, “It is much easier to cook in LPG comparatively. I need not take much effort to clean the vessels. My house is looking neater than earlier as the walls generally get shabby due to the smoke from the biomass.”

She acknowledges, “During the initial period, I was scared about the possibility of any leakage from the [LPG] cylinder. I will switch off the stove often and check for any smell around due to the leakage. Now I do not have any such fear.” She also uses biomass on a limited basis, “I still like to cook some specific dishes like non-vegetarian items using biomass to get the special taste. My family will prefer to use biomass while cooking in larger vessel for many people especially during special occasions. I also use biomass for boiling water for bathing.”

I tell a bit of Vasugi’s story and quote her directly for a reason. I think that it is important to get past the hard cold statistics and see and hear the people who are affected by an issue, in this case indoor solid fuel combustion in a developing country. What we see is that they are real people who might not neatly fit into our expectations or the statistical averages, but are human beings who have lives with which we can identify. Vasugi still uses some biomass. I have to admit that I was a little surprised at that, but once I heard why, the flavor, for example, I could see why someone might not let the biomass go entirely. In fact, once I stop to think about it, it is obvious that in the West, we also relish a barbeque or cooking over a camp fire now and then too.

I chose to begin this book with the story of indoor solid fuel burning because it is the oldest source of PM exposure. It predated industrialization and the use of fossil fuels and the mass manufacture of cigarettes, the topics of the chapters that follow. While it is ancient, it is also current, since millions of people, mostly women and children, are still exposed this way. Sadly, the long slow path to scientific understanding and adoption of interventions to reduce exposure will be echoed in the coming chapters as this is an underlying theme of this book as well.

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Chapter 2
Addicted to Poison

There are 95 species of tobacco plants in the taxonomic genus Nicotiana (Fig. 2.1). The genus is within the much broader Solanaceae family of plants that includes tomato, potato, jimson weed and petunia, among others. Solanaceae plants include valuable food crops such as chili and bell peppers as well as eggplant, but also plants that produce psychoactive compounds and deadly poisons. Nightshade is a member of the family [1]. Many plants, including many of the Solanaceae, have evolved complex and diverse sets of biochemical products that help them survive and reproduce. These compounds may discourage herbivores from eating them, encourage insects and birds to pollinate them, or fight off infections.

Tobacco plants apparently evolved the production of nicotine because it protects them from many insects. In essence, nicotine is a natural insecticide. Nicotine binds to nicotinic acetylcholine receptors that activate nerve cells. In the doses that are large relative to size for an insect, nicotine can be deadly. Humans take in much smaller doses when they smoke or ingest tobacco, but it might give one pause to consider that tobacco is essentially a neurotoxin and a poison [2].

Of the tobacco species, 20 can be found in Australia and Polynesia, one in Africa and the rest in the Americas. Thus, the main route by which humans first encountered tobacco was when they inhabited the Americas from Asia and, subsequently, when Europeans crossed the Atlantic and colonized the so-called "New World." It is not clear when Native Americans started using tobacco, but it is likely many thousands of years ago. One suggestion is that tobacco use dates back to 6000 B.C. soon after humans reached areas of South America in which tobacco grew. Tobacco use was likely facilitated because migrants from Asia to the Americas probably brought with them knowledge of the use of other psychoactive plants [3].

Regardless of how early tobacco use began in the Americas, there is no question that it is deeply ingrained in the culture and practices of many Native American tribes. To take one example, tobacco is part of the creation story for the Pima People:

> "Earth Doctor is the first primordial being. He unites the male sky and female earth, and Elder Brother is born as a result of the union. After Elder Brother kills an evil female monster, an old woman steals some of the monster's blood and then is killed. The original

D. Brugge, *Particles in the Air*, https://doi.org/10.1007/978-3-319-89587-1_2

tobacco plant grows from her grave. Elder Brother instructs the first people how to use it – rolled in corn-husk cigarettes and smoked" [3, p. 44].

Europeans encountered tobacco for the first time when Christopher Columbus landed in the present-day Bahamas and Cuba in 1492. The Taino Arawak Indians that inhabited the islands were reported to smoke cigars and present day research suggests that they cultivated tobacco plants and both smoked and chewed it.

Of course, that first contact between Native Americans and Europeans was disastrous for Native Americans. Columbus left a small settlement, which was destroyed and the inhabitants killed by the Native Americans. But it was a pyrrhic victory since within 30 years one million Taino in the Caribbean had perished and were virtually extinct, a prelude to the vast genocide that engulfed most of the Americas in the coming centuries [4].

The Navajo (Dine) People with whom I grew up consider tobacco one of the four sacred plants, along with corn, beans and squash [5]. I was a child on the Navajo Nation in the 1960s and early 1970s because my father worked with the Navajo People, first directly through the Tribal Government and then later via the US National Park Service. When I was young my father also smoked a pipe, inhaling unfiltered tobacco smoke. He eventually quit, but he had already set in motion

Fig. 2.1 Drawing of a tobacco plant (Source: Wikipedia)

progressive and irreversible damage to his lungs that would, many decades later, be the underlying cause of his death.

So, for me, tobacco and smoking is a deeply personal issue and one that I would eventually work on a bit during my career when I advocated to make restaurants smoke free in Massachusetts towns in the 1990s (see Chap. 3).

I had long thought that addictive smoking came with the advent of industrial production of cigarettes in the twentieth century. However, that seems to be at least partly inaccurate. There is evidence from the historic record that at least some Native Americans were addicted. For example, "a Jesuit" in 1634 describes the Montagnais People of present day Canada as smoking virtually all the time, including waking at night and stopping during travel to smoke [3]. Regardless of whether some Native Americans were addicted, their use was generally much less frequent and not anywhere near as widespread as became possible after industrialization of the manufacture of cigarettes.

Natural tobacco plants in many cases had nicotine concentrations well above the standard commercial levels used today of about 1.5%. In some cases samples have been found to have 2–4% or even 8%, 12% or 18% nicotine, making them particularly addictive. This does not mean that large numbers of Native Americans were addicted, indeed, most probably were not and there are stern warnings in Native American culture to be cautious about the power of tobacco. For example, Mohave men in the early twentieth century waited to smoke until they were in their 50s and 60s.

My friend and colleague, Timothy H. Benally Sr., who is Navajo, kindly provided me with his experience in modern times with traditional use of tobacco. He says, "In the beginning, corn, beans, pumpkin, and tobacco were given to the *Diné* as food. Navajo tobacco is a wild plant, usually found growing in a damp area near the foot of the mountain. The leaves of the plant have a kind of greasy, odd-smelling covering. The smell causes the plant-eating animals to avoid them during the summer."

"Traditional Diné [Navajo] collect the plants in late July and dry the leaves in the sun. When dried, the leaves are crushed and separated from the main stem. The crushed leaves are then stored in a deerskin pouch or tightly closed container. Traditional tobacco is usually used ceremonially. At the beginning of a ceremony, the medicine man (*hataałii*) may ask if there is a "family tobacco," or smoke. If so, he will use this local tobacco during the ceremony."

"The native tobacco is rolled in a fine, tissue-like corn husk to form a kind of cigarette. Hot charcoal from the fire is placed in front of the medicine man, along with a dried corncob. The medicine man uses the charcoal to light the tip of the corncob and then uses the corncob to light the cigarette."

"During the ceremony, the patient and other participants typically inhale only a single puff of the smoke before it is passed to the next person, so a single cigarette can easily last two rounds. In addition to inhaling, the person who is receiving the smoke also does a kind of personal prayer for protection, ceremonially moving the smoke from the cigarette over and around his or her body. Whatever substance the tobacco contains makes the smoker kind of "dizzy," so they may see or feel things

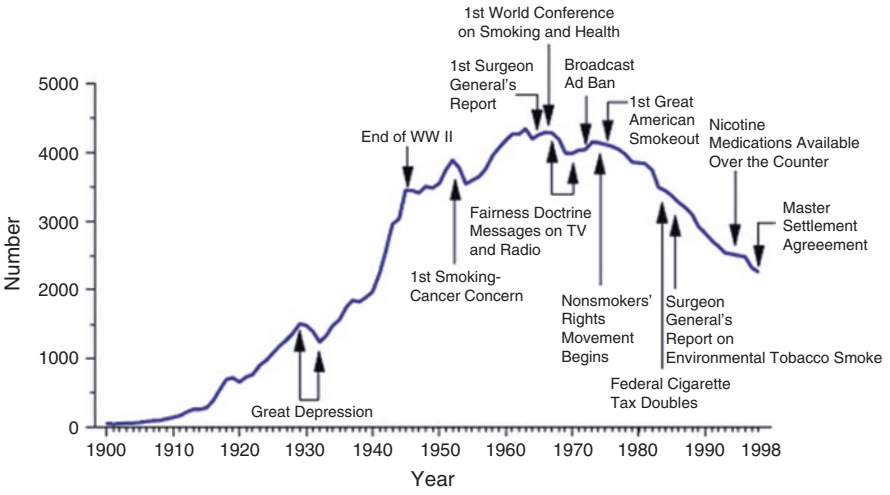

Fig. 2.2 Annual adult per capita cigarette consumption and major smoking and health events – United States, 1900–1998. (Source: CDC MMWR)

that they wouldn't otherwise experience. The medicine man will talk with the participants about what they experience, will interpret the meaning(s) of these, and will use this information to direct his singing and prayers. When the smoking is completed, any unsmoked tobacco in the cigarette is used as part of prayers for the patient and the tools are carefully put away."

"For non-ceremonial smoking," Benally says, "I usually do not inhale the smoke. Even then, I find that the smoke has the same kind of effect on me. The smoke from the native tobacco makes me dizzy or disoriented. When this occurs, I go outside and breathe in fresh air. Although I collect native tobacco and have dried tobacco available for my use, I don't use it very often. I use it only when I feel depressed, or when things in my life are out of balance. This is really rare for me, so maybe only once a year. For personal use, I used a clay pipe rather than a rolled cigarette."

It was under European colonialism, however, that tobacco became a consumer product with widespread health effects across the world and over the course of centuries (Fig. 2.2). In prerevolutionary America, tobacco became a cash crop deeply dependent on African slaves. The colony of Jamestown depended on growing tobacco and by 1628 the Chesapeake colonies were sending almost 400,000 pounds each year to England. While that number might seem impressive and, indeed it was given the manual labor that was involved, it is dwarfed by orders of magnitude by what was to follow [6].

By the American Revolution about 100 million pounds of tobacco leaf were being exported, still dependent on slaves and manual labor. Production quadrupled by the time just before the Civil War and grew again after the war, exceeding half a billion pounds by the turn of the century. In fact, the Civil War and World Wars I and II accelerated the uptake of smoking as soldiers were introduced to smoking and provided with cigarettes in their rations [7].

Prior to 1881, cigarettes were hand rolled, but in that year a patent was secured by James Bonsack for a machine that could automatically produce over 100,000 cigarettes each day, greatly increasing output. Within 3 years, James Duke obtained exclusive rights to the new machine and coupled mass production of cigarettes with advertising to "create a mass national market."[3, 7, p. 3]. The stage was set for mass addiction and death in the next century. Spanning the turn of the century, tobacco monopolies dominated the US and England, but a US Supreme Court ruling in 1911 broke up the American Tobacco Company into four entities that are still recognizable today: American Tobacco Company, Liggett and Meyers, RJ Reynolds and P. Lorillard [7].

Machines got better and better at making cigarettes so that by 1940, they were producing almost 200 million per year and by 1970 over half a trillion. Smoking rates increased along with cigarette production with 57% of American men and 28% of American women smoking in 1955 [7]. By then it was already apparent that smoking was driving an explosion of lung cancer cases, which had previously been a rare disease, into a major cause of death. As we will see, the industry fought tooth and nail against the emergence of evidence of health risks in order to protect its market and, in the process, developed what has become a classic industry strategy to cast doubt on science. First, let's review the early evidence of harm to health from smoking.

It appears that the earliest health research into the health effects of smoking tobacco that used modern scientific methods was conducted in Germany in the 1930s and 1940s. Robert N. Proctor wrote a masterful review of this history with support of the Holocaust Research Institute of the US Holocaust Museum. His review serves as the source of most of what follows [8].

Perhaps because the German research was partly under and responsive to the Nazi regime, it has been downplayed and even forgotten. To me though it deserves a hearing, not in any way to inject something positive into the abhorrent impact of the Nazis, but rather to render a more accurate record of history. In any case, the anti-tobacco impulse in Germany preceded the Nazis by centuries. Even in the late 1600s there were smoking bans in "Bavaria, Kursachsen and parts of Austria". Bans in other parts of Germany followed in later centuries [8].

By the early twentieth century there were a range of anti-tobacco societies and journals in Germany that often combined opposition to tobacco with opposition to alcohol. Well before the ascent of the Nazi regime there were calls for banning smoking in public places that eerily echo the debates I participated in 60 years later in Massachusetts [8]. All of this might have laid the basis for interest in researching the detrimental impacts of smoking

Similar also to doubts near the end of the twentieth century about the health consequences of secondhand smoke (breathing smoke left in the air by active smokers), there was initially confusion and uncertainty about the reasons for a rise in lung cancer. It was an open question as to whether the increase in lung cancer was due to better detection with the advent of x-rays or whether it might be a true increase. Speculation about the cause ranged from the rise in use of automobiles and of tar to pave roads [8], both plausible hypotheses since we will see in Chap. 4 that PM from transportation does indeed cause lung cancer.

Fritz Linkint was a physician from Dresden who published a case-series analysis in 1929 that in many ways marked a watershed in the development of statistical evidence of the health effects of smoking. Published in German, in a journal titled, Zeitschrift für Krebsforschung, his case-series found that lung cancer patients were likely to be heavy smokers [8]. By today's standards of causal evidence, Linkint's analysis would be considered suggestive, but not conclusive. Nevertheless, it served as a meaningful early warning, decades before federal action on smoking in the US.

Linkint went on to publish a 1200 page comprehensive review in 1939 of an amazing 8000 publications, titled "Tobacco and the Organism" in English translation, about the health hazards of smoking tobacco. While not based on the high standards of proof we usually demand today, Linkint nonetheless successfully identified many of the main concerns we now recognize. He noted that cancers formed along the track smoke travels through the body in the mouth, trachea and lungs. He also noted that there appeared to be cardiovascular effects as well as cancer. He correctly identified tobacco as addictive. And he even appears to have coined the term "passive smoking" in reference to what we now call secondhand smoke. For his efforts he became the doctor who was "most hated" by the tobacco companies [8].

Proctor points out in a footnote [8], that Linkint never joined the Nazi Party and that he was tried for being a member of the Veren sozialistischer Arzet. The initial court finding was that this made him a communist, but a later decision reversed the finding by reducing his affiliation to socialist. He was also defended on the basis of his important anti-tobacco work. Indeed, official Nazi policy was opposed to smoking, as was Hitler himself. Drenched in racism, and harkening back to the Native American origins of tobacco, Hilter is attributed to have said that tobacco is, "the wrath of the Red Man against the White Man, vengeance for having been given hard liquor" [8, p. 435–88].

Following on the work of Linkint, was a 1939 study by Franz H. Muller. Muller's research was a case-control study in which he compared the level of smoking between lung cancer patients and healthy controls. This study design allows one to ask whether people with lung cancer are more likely to be smokers and, if they are, suggests that smoking could be a factor. As with Linkint's case series, however, case-control studies are not the strongest epidemiological evidence, primarily because they usually depend on, as was the case for Muller's work, recall of participants, which can be inaccurate.

Muller found that lung cancer patients were more than six times as likely as his healthy controls to be heavy smokers. He further concluded that tobacco smoking was "the single most important cause of the rising incidence of lung cancer" [8, p. 435–88]. Another case-control study from Germany was published in 1943 that built on Muller's work. This study had better controls and similar findings.

Because subsequent higher quality studies proved Linkint and Muller, correct, it is tempting to conclude that the delay in regulating tobacco for another two decades in the US was unwarranted. In fact, the Nazi attempts to reduce smoking suggest that they were convinced it was a health hazard. Of course, Nazism, for all its evil aspects, was technologically and scientifically advanced, as is attested by their

powerful military weaponry. As in Chap. 1, the crux of the dilemma is how and when to enact policy responses to science that is highly suggestive, but not yet conclusive.

As a scientist who has seen what seemed to be obvious findings evaporate in the face of better studies, I have to grant some legitimacy to the skeptics and doubters who might not have been convinced by the evidence from Germany. The post war condemnation of unethical research conducted by the Nazis might have also tainted the more legitimate research on smoking. Moreover, as Proctor points out, the German researchers either died or were prosecuted after the war [8, p. 435–88]. He does not note, however, that this is in stark contrast to nuclear and military engineers from Germany who were often incorporated into the West despite their prior service to the Nazis.

In a second article, equally impressive as his earlier work, Proctor reviews the post-World War II evidence that emerged in the US and UK and the tobacco industry campaign to cast doubt upon that science. Studies conducted in the 1950s substantially increased confidence that smoking tobacco caused lung cancer. These studies were prospective cohort studies, that is, studies that followed people over time [9]. The field of epidemiology considers such studies to be higher quality evidence than the case control studies conducted in Germany. This is because prospective follow-up eliminates two important possible sources of error, recall bias and the possibility that smoking started after development of disease. In my opinion, neither of these concerns is of great concern in the case of smoking because smoking is easily remembered and addiction locks people into smoking for long periods of time. I would agree, however, that higher quality evidence would be more convincing to policy makers.

While epidemiology is a powerful tool, by itself it is rarely sufficient to make the case for a health risk. This is because the study of free ranging human beings will always have some doubt as to other factors that might not have been possible to control for in statistical models. In the case of smoking, it is at least plausible that smoking is associated strongly with some other behavior or exposure that is the true causal agent. Although farfetched in the case of smoking, one might imagine that smokers live in locations with higher air pollution or are much more likely to drink alcohol and that one of these other exposures could explain at least part of the apparent association between smoking and lung cancer.

Because of the limitations of epidemiology, animal and cell culture studies provide a critical compliment to the evidence base. Amazingly, as early as the 1930s, animal studies by a researcher from Argentina named Angel Ruffo showed that condensed smoke from burning tobacco could cause cancer when painted onto the shaved skin of rabbits. Ruffo also showed that tobacco smoke contained chemicals called polycyclic aromatic hydrocarbons, substances that had already been shown to be carcinogenic. Perhaps because his work was published in German and Spanish, it appears to have had little impact in the English-speaking world [9].

Additional research stretching from the 1930s to 1950s showed that tobacco smoke impeded the function of tiny hair like structures called cilia in the passageways of the lungs [9]. Cilia line the larger airways in order to remove particles that

are inhaled to keep the lungs healthy. Together with a layer of mucous they form the muco-ciliary pathway that traps and then exports tiny debris to the back of the throat where it can be swallowed. Without this pathway intact, inhaled particles, including those in tobacco smoke, will be retained in the lungs to a greater extent, causing more harm than if they were removed. It is this deadening of the cilia that we now know makes the combination of smoking and asbestos so much more deadly, as it allows carcinogenic asbestos fibers to lodge in the lungs to a greater extent.

The failure to recognize and respond to Ruffo's studies might have been understandable based on the language barrier and the limitations of communication of the time, but the record was set straight in English in 1953 when Life Magazine and Time Magazine both gave coverage to a similar study that showed that tumors were induced by cigarette tar when it was put onto the backs of mice. According to Proctor, "Public confidence in tobacco was shaken, and stock prices of American cigarette manufacturers plummeted." [9, p. 88].

Proctor sums up the situation in the 1950s nicely. He writes, and it is worth quoting at length because it is framed so well:

> "The confluence of these diverse forms of evidence – from epidemiology, animal experiments, clinical observation and chemical analysis, combined with diminishing evidence for alternative explanations, prompted health and medical authorities throughout the world to publicly acknowledge a cigarette-cancer link" [9, p. 88].

Thus, as Proctor notes, the US Surgeon General's report of 1964 (Fig. 2.3), a document that is often regarded as a turning point in the understanding of and response to tobacco in the US, came out a decade after the scientific evidence had reached a quality that was strong enough to support policy responses [9, p. 89]. Indeed, a more precautionary approach would have seen a basis for policy actions based on the German studies of the 1930s. In fact, in Germany, there was a degree of response under the Nazis, as we have seen. In any case, as with solid fuel combustion, which I reviewed in Chap. 1, the policy response lagged substantially behind the evidence of harm. However, in the case of tobacco, the issue was not neglect or disinterest as it was with indoor cook stoves, but rather there were active efforts to undermine the science by the tobacco industry.

Before exploring the role of the tobacco industry in casting doubt on the science, I found the historical narrative leading up to the 1960s and even long afterward to be interesting for its almost exclusive emphasis on the link between smoking and lung cancer. As it turns out, the evidence was almost as strong that smoking was associated with cardiovascular disease and the Surgeon General's report summarized that evidence as well as the evidence for increased cancer risk [10].

For cardiovascular disease there were (and continue to be) both issues with the epidemiology and issues of perception that make these outcomes less compelling to the public and policy makers. Lung cancer was a rare disease prior to addictive smoking. In contrast, cardiovascular illnesses, especially heart attacks and strokes, had long been common causes of death. Further, while smoking can be estimated to cause most lung cancers in populations that smoke, there are numerous other factors associated with cardiovascular outcomes, including diet, psychosocial stress and physical activity.

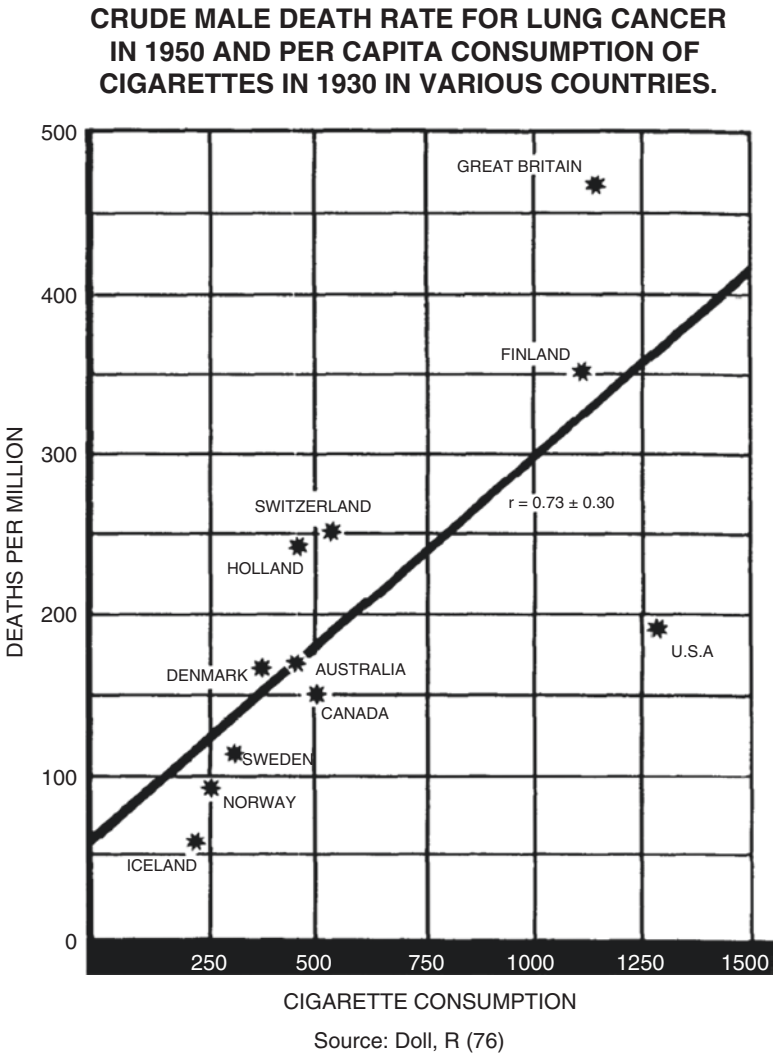

Fig. 2.3 A graph from the 1964 Surgeon General's report on smoking and health [10]

Separating out these influences on disease can be tricky and was especially so in the 1950s and 1960s because the statistical computing capacity was much more limited than it is today. The problem of teasing out the influence of multiple factors on a statistical association is called "confounding." In my opinion, confounding is one primary limitation of epidemiology. Because confounding can be caused by the myriad activities and behaviors of free ranging human beings, it is rarely possible to assign causality with absolute certainty, although, for smoking cigarettes, the degree of uncertainty became vanishingly small over time as the evidence grew.

While the report of the US Surgeon General avoided, possibly appropriately given the quality of the evidence, putting a number on the cardiovascular deaths from smoking, it was clear from the report that they were likely substantial and many more than the deaths from lung cancer [10]. Today we know that cardiovascular diseases exceed cancer and chronic respiratory diseases as adverse health outcomes from smoking.

That brings us to perception. I have long observed that the public, including policy makers, gravitate easily to a narrative that says that smoke, or other forms of particulate matter, affect the lungs. I think that is natural. We breathe particles in the air into our lungs. It makes sense that they would affect the lungs and, in fact, as we have seen, they do. But they also affect the circulatory system (blood and blood vessels), which, in turn, can cause heart attacks, strokes and other problems. That link is less intuitively obvious and, in my opinion, is all too often lost in public discussion and education.

Let's turn to the industry response to the emerging science. It is clear now, based on internal documents released decades later, that people within the tobacco industry knew that smoking was damaging to health by the 1950s. A prime example, but not the only one, was a report by Claude Teague for RJ Reynolds that cited both clinical and animal studies showing associations between smoking and cancer. The tobacco industry response, however, was not to disavow their product or warn the public of its hazards. Rather, it was to deny the problem and spend large sums of money on efforts to confuse and distract the public from the evidence [9].

From a practical standpoint, most scientists and reasonable people would conclude based on the evidence available at the time that smoking tobacco was bad for one's health. But science is rarely able to provide 100% certainty or absolute proof. It was the element of doubt that the tobacco industry, starting in 1953, sought to exploit. In December of that year the CEOs of the major tobacco companies meet in New York City to plan their response to the growing body of science and the increasing awareness of the public and policy makers.

We know a lot about the internal process within the tobacco companies because of provisions in the settlement of lawsuits between 46 US states and the major tobacco companies in 1998. That settlement, among other things, required the companies to release for public access all documents that they assembled for the litigation. These documents provide extensive insight into how the companies developed and implemented their strategy.

Allan Brandt, of Harvard University has summarized nicely the approach that the industry took and how well it succeeded [12]. The tobacco industry hired the public relations firm Hill & Knowlton, led by John W. Hill, to head up their effort to stave off what seemed to have the potential of a devastating blow to their profitability. Hill came up with what was, for the time, an original and brilliant approach. Instead of denying the science, he proposed that the industry essentially coopt the science and position itself as supporters of better science.

Hill saw an opportunity in the inherent nature of research because research is imbued with skepticism and uncertainty. Indeed, while a bit of a running joke, there is a kernel of truth to the idea that every research study ends with a call for

more research. Hill proposed emphasizing doubt in the research and allying the industry with researchers who were skeptical about the evidence linking smoking to disease [13].

He proposed, and the industry established, the Tobacco Industry Research Group, which engaged numerous prominent scientists and doled out research funding, albeit not to investigate the relationship of smoking to health, but rather to study the basic science of cancer. The Scientific Advisory Board for this group had a sometimes strained relationship to the research group, but ultimately, many scientific researchers gave the industry increased credibility and contributed to a growing conflict of interest in the research world [13].

In addition to enrolling scientific researchers in their effort to gain credibility, Hill & Knowlton also worked the media as well with a public relations approach that, as they did with science, exploited weaknesses in journalism. In particular, they knew that the media was more excited by controversy than substance and that they liked to present "both sides" of issues. Thus, the idea that there was another side to the tobacco and health story was appealing and made compelling news coverage that generated a degree of doubt in the public [13].

The final arms in the tobacco industry campaign arsenal were a strong lobbying effort and vigorous defense against lawsuits. As early as 1964 there were lawsuits accusing the industry of negligence. Defense in court relied on the same argument that was meant to delay legislation and cast doubt in the mind of the public, that there was not conclusive proof that smoking caused illness, and particularly that it caused lung cancer [13].

Brant summarizes the result of the tobacco industry campaign neatly and succinctly:

> "The industry insistence, at the direction of Hill & Knowlton, on the notion of no proof and the need for more research was an inspired if cynical manipulation of the natural tendencies within science to encourage skepticism and seek more complete answers to important questions" [12, p. 70].

What is remarkable to me about this history is that not only did the tobacco industry delay public awareness of the hazards of smoking, but that the industry continued to thrive and that to this day, even after the 1998 settlement agreement, remains vastly profitable. Equally important, they established a model for how corporations under attack from scientific evidence could defend themselves, a model that continues to be employed by companies that would prefer to deny climate change or avoid culpability for hazardous consumer products.

While the industry effort to protect itself from the science that showed that smoking causes harm to smokers was critical, there is another aspect of smoking that bolstered its marketability and preserved a loyal customer base. As mentioned above, nicotine is the key ingredient in tobacco that leads to stimulation of pleasure centers in the brain as well as addition. Nicotine causes a rapid, short-term pleasure response and leaves a craving for more after the stimulation has passed. A cigarette is, in that way, almost a perfect product since the customer is trapped wanting more and has a hard time quitting due to withdrawal symptoms that can be severe.

The toxic particulate matter that is inhaled with the nicotine is purely incidental to the main purpose of a cigarette which is merely a nicotine delivery device that has been optimized to deliver a dose of the substance. However, while nicotine replacement strategies have been developed and may help some people stop smoking, they are not always effective, despite retaining the nicotine hit while removing the toxic smoke. Some of the reasons for this might be that people are also addicted behaviorally to the process of buying, touching the cigarette, lighting up, and other aspects of the smoking ritual.

I think that there is increasing awareness that addictive products are too often the result of deliberate development intended to hold on to a captive market. Certainly cigarettes are the prime example of this. They were modified early on to make it easier to inhale the smoke deeply and regularly. Nicotine levels were carefully calibrated. There is a need for research on the role of addiction more broadly in marketing – do you just like a tasty treat you eat more and more regularly or has it been manufactured to elicit that response in you? I like a recent article in Science that stated, "Addiction will do massive and increasing damage to humanity if drugs with addictive liability are treated as ordinary commodities, with a lightly regulated free market left to sort out supply and demand [13]."

Despite its addictive properties, smoking rates have declined in developed countries since the 1960s, with adult smoking rates in the US now around 15%. Hidden within the overall rate though, is a disturbing difference in smoking by socioeconomic status, with less educated populations smoking at rates as high as 40% [14]. Even more disturbing though, is the successful turn that tobacco manufacturers have made to lower-income countries, especially China (Figs. 2.4 and 2.5). By 2011, China was manufacturing 2.4 trillion cigarettes per year! One factory in China alone, the Yuxi Cigarette Factory in Hongta, churns out 90 billion cigarettes each year. The speed with which machines can produce a cigarette has become phenomenal and would be a marvel of technological progress if it were not for the serious damage [9].

Proctor estimates that "only", his word choice, 100 million people died from smoking in the twentieth century. He anticipates that number to increase substantially in our current century due to the high prevalence of smoking in populous countries such as China [9]. In one of his articles, he even speculates that tobacco could kill one billion people this century [14]! Whatever the number turns out to be, it is clear that the toll from smoking is increasing rather than declining. I suspect though, that many middle class professionals in developed countries might feel inclined to think the beast has already been beaten.

I asked Vinayak M Prasad, Program Manager for Tobacco Control at the World Health Organization in Geneva, Switzerland about the global tobacco situation. He was somewhat more optimistic than Proctor. While he agreed with me that researchers had lost some interest in tobacco as a focus, he said that adoption of policies to discourage smoking had picked up in the last decade (since 2005). He noted that prevalence of smoking was coming down very slowly which surprised me since I assumed it was probably climbing because of countries like China.

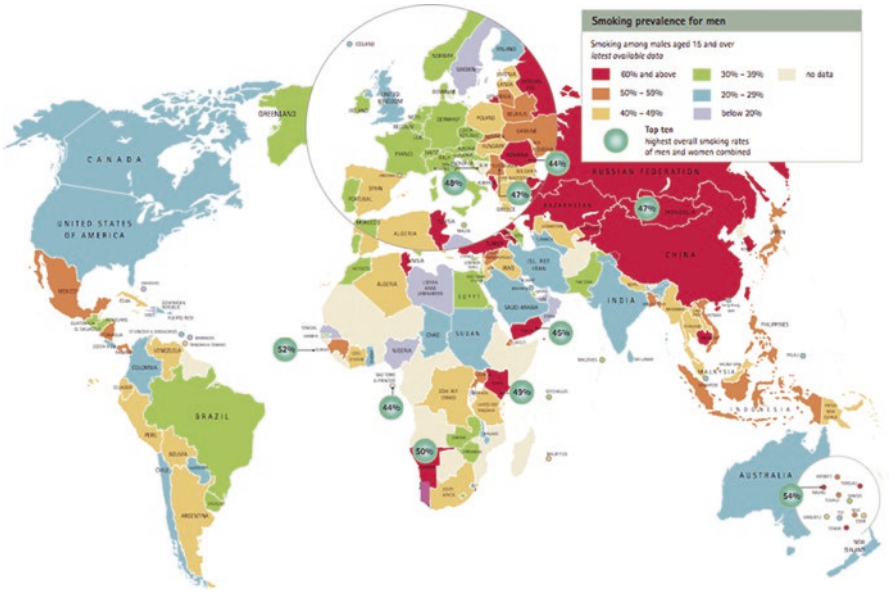

Fig. 2.4 Smoking prevalence for men. (Source: reproduced from The Tobacco Atlas, WHO https://tobaccoatlas.org/topic/prevalence/)

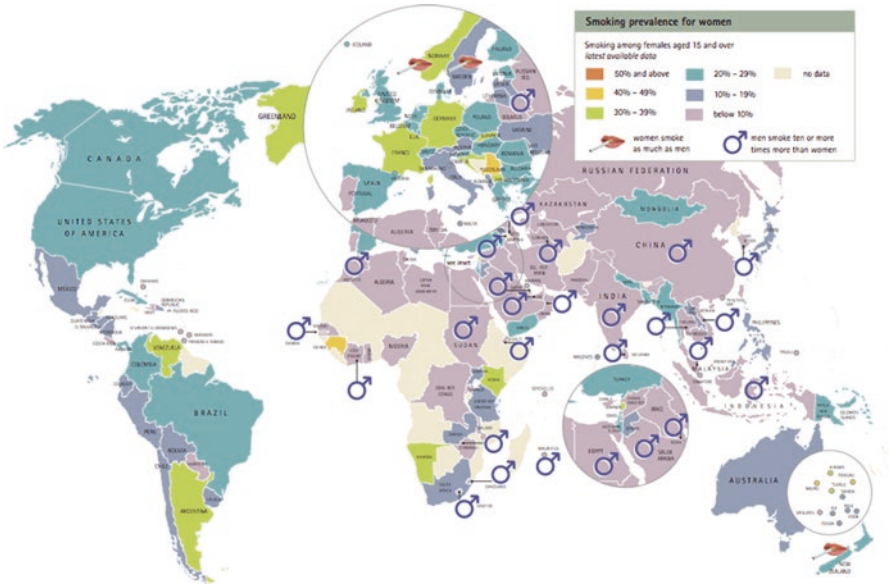

Fig. 2.5 Smoking prevalence for women. (Source: reproduced from The Tobacco Atlas, WHO [https://tobaccoatlas.org/topic/prevalence])

In fact, he said that while smoking had increased in China in the 1980s and 1990s, it had declined more recently. A similar trend could be found in India. He reported that smoking was, however, on the rise was in the Middle East and Africa. This appears to be due to tobacco companies targeting Africa and promoting use of water pipes in the Middle East. But even in Africa Prasad could point to some progress, for example in Kenya where implementation of a tax had led to declines in smoking.

Still, Prasad confirmed to me that the tobacco industry was still up to their old tricks. That they were diversifying their products with electronic cigarettes and water pipes to "keep the addiction going" and using bribery. There are legions of public health professionals like Prasad who fight the good fight, but in the end, I am still left marveling at the tobacco industry. Even if they are suffering some setbacks from the work of good people like Prasad, the industry has still managed to make this century more profitable than the last. In some ways they have succeeded despite the science and policy emerging from more developed countries.

When I was a child, my father was a good playmate after work and on the weekends. He would lead my younger brother, sister and me on walks, notably up the hill and past the horse corrals and back down to the tiny duplex in which we lived in Window Rock, Arizona. We could climb around his body and he would make elaborate birthday cakes for us, including one for an early birthday of mine that had a lake, palm trees and dinosaurs. He gave all of us an abiding love of and interest in nature that led me to pursue biology all the way through a PhD.

But during my childhood and into early adulthood, my father smoked a pipe. He would carry a can of lose tobacco and damp it down into his pipe and light up regularly. I do not know whether the Navajo culture in which he was so deeply engaged influenced his decision to take up smoking. More likely it was the culture of anthropology, his field. In any case, at that time, the Navajo people did not smoke appreciably except for periodic ceremonies and cultural practices. I do not recall seeing the Navajo People who we lived among smoking. Rather, it was always the smattering of white folks on The Rez that I saw smoking.

There is an idea that pipe smokers do not inhale or do not inhale deeply, but at least in the case of my father that was not the case. It took him years to quit smoking long after the risks became apparent and I heard my mother say to him that she thought he inhaled. He was a quiet man in many ways and did not respond, at least in my hearing. It was evident that he inhaled from the fact that early in my youth he developed a smoker's hacking cough.

I hated his cough that would start up at unpredictable times and places and got worse and lasted longer as he aged. He would be racked by his cough and left tired and breathless after an episode. His early coughing was the beginning of the development of chronic obstructive pulmonary disease. COPD is a constellation of symptoms and health problems caused by underlying scarring of lung tissue. Although my father eventually quit smoking and did not smoke for the latter half of his adult life, the disease was in him and, as it usually is, progressive and irreversible even after he ceased smoking.

I was embarrassed by his illness in my teen years and early adulthood. I also assumed it would result in his early death. That was not, however, the outcome for him. Instead, he outlived our mother by more than two decades into his mid-80s. From his experience living with COPD for so many years, I learned that it is not just about how long one lives, but also about one's quality of life. The COPD eventually did kill him by causing opportunistic infections in his weakened lungs and, at the end, throughout his body. Still, the harm from smoking could be best measured in him from the ways in which the illness undermined his quality of life.

My father never lost his zest for life and pursued his intellectual passions up until the end, including writing his last academic paper essentially on his deathbed. I never heard him complain or blame the tobacco industry. Perhaps he blamed himself. He overcame his disability as well as anyone possibly could, but it remains almost certain that in the absence of smoking he would have lived longer, enjoyed life more and had greater accomplishments.

I raise my experience with my father's smoking induced illness to personalize what could be otherwise lost in the bland and overwhelming statistics of the toll of tobacco. I do not intend his story to be representative. There are millions upon millions of stories of smokers, some with worse and some with better outcomes. Simply, he is the smoker that I knew best. I expect the reader knows at least one smoker as well. It is rare not to know even many smokers. While their stories might be partially obscured by a desire for privacy, by shame or because they are almost banal, they are so common, I would argue that we need their stories along with the statistics to fully understand the damage done by tobacco. Damage that appears to continue with no end in sight as far as we can see.

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Chapter 3
Secondhand Toxins

It is not a huge leap to consider that if direct smoking causes serious health problems then breathing in the tobacco smoke left in the air by smokers might also present a risk (Fig. 3.1). Yet it was not until 1981 that the first epidemiology studies were published showing that lung cancer risk was higher in non-smoking wives of smokers than in wives of non-smokers. The author of the most prominent of those studies (there were three, including his, that came out at about the same time) was Takeshi Hirayama, a physician at the National Cancer Centre Research Institute in Tokyo, Japan. His research and the controversy that followed, stoked by the tobacco industry, in many ways replicated the arguments about smoking and lung cancer a few decades earlier.

Hirayama was born in Kyoto, Japan in 1923, went to high school there and then attended Manchurian Medical College in Harbin, China, where his father was a professor of surgery. After his undergraduate studies, Hirayama studied medicine back in his birthplace at Kyoto University. He subsequently came to the US and obtained a master's degree in public health from Johns Hopkins University. While in the US, he studied smoking and lung cancer at the Sloan Kettering Memorial Cancer before returning to Japan. In 1965 he became Chief of the Epidemiology Division of the National Cancer Institute in Tokyo. He married, had two children and passed away in 1995 [1, 2].

In the 1970s Hirayama focused on smoking and lung cancer in a large cohort in Japan recruited from 29 health centers across six prefectures. After analyzing health effects of direct smoking, he turned to the issue of secondhand smoke exposure in non-smoking wives of smokers. The study design, prospective follow-up over time, combined with the large study population of over 250,000 older adults, were the primary strengths of the study. The large population was particularly important because lung cancer cases in non-smokers are so rare that one needs to follow many people to see an appreciable number. Japan was a good setting for the study because smoking rates among women were extremely low at that time.

During 14 years of follow up, there were 174 lung cancer cases among married women who claimed to be non-smoking. Self-report of smoking habits would

D. Brugge, *Particles in the Air*, https://doi.org/10.1007/978-3-319-89587-1_3

Fig. 3.1 Combustion products from smoking tobacco are released into the air around smokers as well as inhaled by the smoker

become the line of attack by the tobacco industry when they later tried to cast doubt on or discredit the study. Indeed, reading Hirayama's paper today, I am bothered by a line in the methods, which reads, "No subjective bias was therefore conceivable." I don't know how that line made it into print in as fine a journal as the *British Medical Journal*, but I wish it were not there since there is always the possibility of bias in self-reported data [2].

When adjusting for age and occupation, Hirayama found that women married to non-smokers or occasional smokers had a risk of 8.7 per 100,000, based on 32 lung cancer cases. For women married to ex-smokers or current smokers the rate was 14.0 per 100,000, based on 86 lung cancer cases. For women married to men who smoked 20 cigarettes or more daily, the value was even higher, 18.1 per 100,000 (56 lung cancers). Hirayama found even higher ratios for "agricultural families," but the number of lung cancer cases was much smaller in that subset, reducing, for me anyway, confidence in the values [2].

Hirayama compared the effect of being married to a smoker to direct smoking and found the effect of passive smoking to be one third to one half of that from smoking, clearly what one might expect. He also reported that non-smoking wives married to smokers did not have elevated risk of other cancers or heart disease. He acknowledged that he was not able to control for factors that might explain the association instead of second hand smoke. This problem is called confounding and, at the time, with limited computer power, it was not so easy to put multiple variables into statistical models and see how they affected an outcome. The advent of powerful personal computers changed what was possible in terms of statistical analysis subsequent to his paper [2].

The Hirayama study was important not only for being one of the first studies of secondhand smoke exposure, but also because it had a disproportionate impact on regulatory processes, risk assessments and was featured in the media. Being a focal point of public debate meant it also came into the cross hairs of the tobacco industry, as documented by Mi-Kyung Hong and Lisa A. Bero [3]. Interestingly, the tobacco industry published their counter study to Hirayama in 1995, the year that he died.

The tobacco industry sought to challenge Hirayama's 1981 study on a well-chosen weakness, that some of the wives who claimed to be non-smokers actually smoked. If this were the case, then at least some of the lung cancer that Hirayama attributed to secondhand smoke, would actually be due to direct smoking by the wives themselves, thus reducing the apparent risk from passive smoke exposure. Documents released by the tobacco industry as part of their settlement in the US, reveal some aspects of the process behind the research that was initially submitted as a proposal to their Center for Indoor Air Research by two Japanese researchers [3].

What became known as the "Japanese Spousal Study" was funded directly by multiple tobacco companies. The result was deep and extensive involvement of the industry in the design, analysis and writing of the resulting paper. The involvement of the tobacco industry is troubling because it represents not just an appearance of conflict of interest, but a genuine conflict of interest given what we know from industry documents obtained after publication. In fact, these documents show that industry insiders actively sought to hide their roles. While the resulting publication acknowledged tobacco industry funding, that acknowledgement failed to disclose the deep level of involvement of the industry [3].

The tobacco industry documents provide some clues as to what happened leading up to publication. Early drafts had the Japanese investigators as the authors. However, they were subsequently joined by a tobacco industry consultant, Peter Lee, who ultimately replaced them entirely and became the sole author of the paper. It would be very interesting to learn why the Japanese investigators dropped off. Did they disagree with the direction the manuscript was taken? Or did the industry simply want greater control than they could exercise with authors who were not fully aligned with their goals? [3].

In any case, the paper was submitted to several major journals at which it was rejected. That alone does not mean that it was a bad paper since very few articles make it into the top journals. Most articles that fall short at the top journals are eventually published in respectable, but lesser journals. The industry paper finally made it into print in the *International Archives of Occupational and Environmental Health*, a legitimate journal, but far from the level of the *British Medical Journal* in which Hirayama had published his paper [3].

I was curious to read the industry article. I knew in advance, of course, that it was the product of considerable conflict of interest, but I also thought that the concern about exposure misclassification, Hirayama's empty assurance notwithstanding, was legitimate. The Peter Lee paper is based on recruitment of 400 married Japanese women. Besides asking them whether they or their husbands smoked, urine samples were also analyzed for cotinine.

Cotinine is a metabolite of nicotine that is made in the body [4]. It is excreted in the urine and can be measured by an accurate laboratory method. I was part of a study around the turn of the century that collected urine and analyzed it for cotinine so I am familiar with the approach and also know that it sometimes revealed that self-report of smoking was incorrect. In the paper that Lee is listed as authoring, he reports a very high rate of misclassification of wives who reported that they did not smoke. Of 106 women in the study with high levels of cotinine in their urine, 22 reported never

smoking. There is a subtlety about what the cut off should be for high levels of cotinine, but it makes little difference to the findings so I will ignore it here [4].

There are a couple of odd findings in the Lee paper. Most obvious is that among confirmed non-smoking wives, the wives who had husbands who were smokers somehow had lower cotinine levels than those who had husbands who did not smoke. Whatever you think about the ability of secondhand tobacco smoke to cause lung cancer, it is hard to explain why women living with smoking husbands would inhale less than women living with non-smoking husbands. Given that the paper provides very little information about who was recruited and how, one has to wonder whether there are some peculiar characteristics of the study population [4].

In addition to concerns about the underlying data, I found that the Lee article had numerous overstatements and exaggerations. For example, Lee writes that, "…it is clear the EPA corrections [for smoking bias] are invalid" [4, p. 293] and that, "the high misclassification rates in Japan…undermine conclusions from epidemiological studies conducted there." [4, p. 287]. I would be unwilling to put such strong statements in an article with evidence of the sort he had. Were I to review such an article, while I might recommend publication, I would insist on removing the over interpretation (regardless of its orientation).

Finally, Lee bases part of his conclusion on the assumption (he seems to consider it fact) that smoking by women is socially unacceptable in Japan which would lead them to lie about their smoking status. My close female friend who grew up in Japan in the relevant timeframe does not buy that argument. She says many women avoid smoking because of the harm it can do during pregnancy, but she doubts many women would lie about their smoking status. I suspect Lee just made the assumption based on stereotypes as his statement is not supported by a citation or any evidence.

Ultimately, I am unconvinced by the Lee article. When I read scientific papers, I approach them with about an equal dose of open mindedness and skepticism. In this case my doubts begin with the tobacco industry influence which appears to have been considerable, perhaps even overwhelming. I am further bothered by some inconsistencies in the data (no elevated cotinine in non-smoking wives of smokers) and lack of detail about recruitment. The over interpretation also grates against my professional standards. I have seen exaggeration of this sort before in industry sponsored research (about uranium mining) and remain critical of the editors and reviewers who allow it into print.

The noted Harvard social epidemiologist, Ichiro Kawachi, writing in 1996 [5] with a co-author, acknowledges the problems with measuring exposure to secondhand tobacco smoke (passive smoking, in his term, as was commonly the phrase then). In my opinion, he correctly identifies the main issues. Critically, self-report correlates rather poorly with measured cotinine, explaining only 30% of cotinine levels. One problem is that cotinine has a brief half-life in the body (less than 1 day) and its transit time through the body varies from one individual to another. Thus, depending on when a sample of urine is taken relative to the last exposure to secondhand smoke, one would get varying levels of cotinine.

In the final decade or two of the twentieth century, people were also less conscious about tobacco smoke exposure than they are today in the US. Cigarette smoking was ubiquitous and not of enough concern to be noticed by most people. Because of this, self-report tended to underestimate exposure. Further, smoking of a spouse at home was not the only, or necessarily, the major source of exposure. Most workplaces had not yet banned smoking and the density of smokers at work was usually higher than at home. Thus, studies that focused on risk to non-smoking wives of smoking husbands might miss a substantial occupational exposure that would be difficult to quantify.

Worse yet, what we really want to know is lifetime exposure to tobacco smoke. A single measure of cotinine in urine at one point in time is unlikely to be fully representative of long-term exposure. Kawachi wrote that he hoped for development of a biomarker that would indicate long-term exposure. However, a marker of this sort has not materialized in the decades since, probably because it is not easy to separate biological damage from different combustion-related exposures given the similarity of their effects. Cotinine is an ideal marker for tobacco because tobacco contains nicotine and it is found in only a small number of other plants and at much lower levels. As we have seen, nicotime turns into cotinine and is short lived in the body. It is also not the toxin responsible for the main health risks of smoking, that would be PM.

While the tobacco industry might have had a legitimate concern about exposure misclassification, the validity of their research is questionable. It is, however, an irony that exposure misclassification might have led to under-estimations of risk of exposure to second hand tobacco smoke. Usually, but not always, exposure misclassification reduces apparent associations between the exposure and a health outcome. For this reason, it seems possible to me that even to this day, we might be underestimating the health consequences of second hand smoke.

In a very similar time frame to the first epidemiology studies conducted by Hirayama and others, a physicist named Jim Repace and a chemist named Alfred Lowrey published a series of papers that took a completely different approach to assessing the risk that second hand tobacco smoke might pose. Repace was then at the US EPA, while Lowrey was the Naval Research Laboratory. Without conducting epidemiology, they set out to characterize the level of exposure people might have to second hand smoke and to estimate the risk it posed through statistical calculations.

I met Repace in the mid-late 1990s, long after the work I will describe here was completed and after he had left US EPA. At that time, the effort to restrict or ban smoking in restaurants in the State of Massachusetts was unfolding and I played a tiny role by testifying a couple of times at board of health hearings. My testimony drew significantly on the work of Repace and Lowrey. The board of health meeting in the town of Barnstable on Cape Cod stands out starkly in my mind. The restaurant association brought several filtration companies with elaborate displays intended to show that the solution to smoking in restaurants was better filtration. One had an enclosed clear case into which smoke could be injected and then the filter would

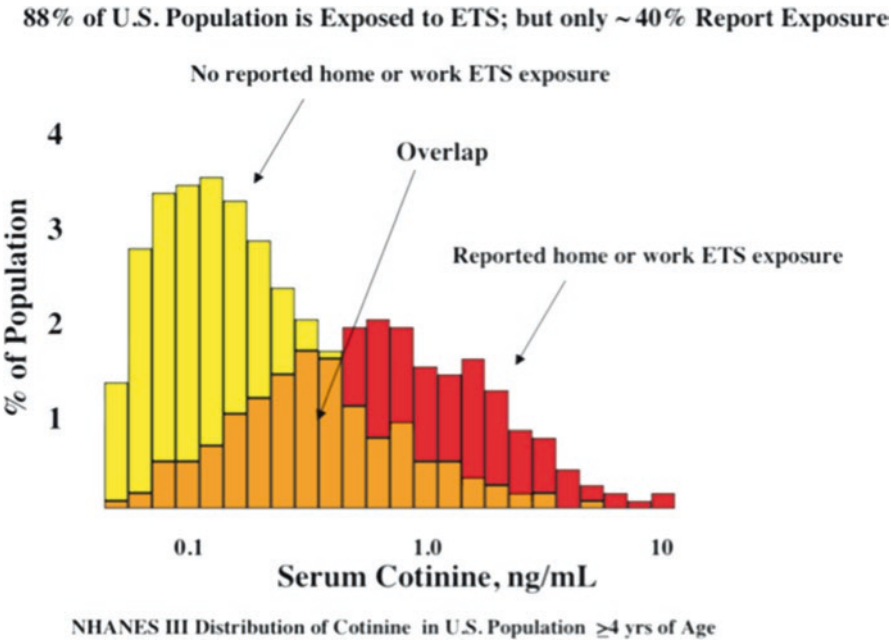

Fig. 3.2 Shows that many people do not report second hand smoke exposure, but nonetheless have cotinine, a metabolite of nicotine, which comes from tobacco, in their blood. (Illustration by Jim Repace, based on Pirkle et al. [6] and Repace [7])

clean it all out. Of course the flaw was that it was a tiny space requiring little mixing of air through a large room.

I sought Repace out to discuss the exposure misclassification issue while writing this chapter. He agreed with me that misclassification of exposure is a real problem and added to my understanding. In particular, he pointed to a 1996 article in the *Journal of the American Medical Association* that reported cotinine levels for a representative sample of Americans [6]. He developed a figure based on a graph in that paper, that shows that there are (or were at that time anyway) a large number of people who self-reported no exposure to second hand smoke, but had appreciable cotinine levels (Fig. 3.2). The effect of this sort of misclassification would be to reduce apparent associations with health outcomes. For me, this reinforced my suspicion that, counter to the tobacco industry effort to distort the science, self-report of second hand smoke exposure leads to underestimates of risk in epidemiology studies such as Hirayama's work.

Back in 1980, Repace and Lowrey published a paper in the leading journal *Science* [8] in which they measured respirable particulate matter (they used $PM_{3.5}$ instead of $PM_{2.5}$, an artifact of the time) in indoor locations that had and did not have smokers. Not surprisingly, they found much higher levels of PM in the smoking

venues. Whereas the non-smoking values were less than 57 ug/m^3 (micrograms of PM per cubic meter of air), most of the smoking location had levels near or above 100 ug/m^3 with five of them weighing in above 400 ug/m^3. The highest levels of PM were in a lodge hall, which had 697 ug/m^3, a level comparable to an extremely bad day in Beijing or Delhi today.

Importantly, their paper began to explore the role that ventilation combined with frequency of cigarettes smoked determines the levels of indoor pollution from smoking. They also suggest that indoor levels of PM from smoking exceeded the federally permitted levels of PM outdoors, although the comparison is imperfect since the ambient PM standard had not yet been set for respirable particles and averaging of exposure would have to be over longer periods than they measured.

In a thought exercise they compare four hypothetical non-smoking people, one a "mailman" with no tobacco smoke exposure, the second an office worker, the third a musician at a nightclub and the last a flight attendant. They estimated that exposures would be three times higher for the office worker compared to the mailman, 15 times higher for the musician and twice as high for the flight attendant.

In a subsequent paper, this pair of scientists, from outside the mainstream of public health or medicine, again contributed to the emerging understanding that second hand smoke was bad for people. In this paper [9], they undertook to estimate the lung cancer risk from "passive smoking." They reviewed 13 epidemiologic studies that had been recently published on second hand smoke and lung cancer, including the study by Hirayama. The studies that they reviewed included others released about the time that Hirayama's study was published as well as additional studies published in the 4 years leading up to their review.

Their review paper compared the evidence base to the criteria of the International Agency for Research on Cancer (IARC). Evidence, according to IARC should include the following characteristics: (1) separate studies should agree; (2) associations between exposure and health should be large; (3) dose response relationships should be observed (higher dose, greater risk) and, (4) reduction in exposure should lead to reduced risk. Within the 13 studies that they reviewed, Repace and Lowrey found 20 sub-studies divided into men and women. Of these, 18 had indications of increased risk and 12 of those reached statistical significance. The review depended on the literature for direct smoking to address the concern about strength of association. But they did observe that five of the 14 studies that assessed dose response found such a relationship. Finally, they could cite one study, by Hirayama again, that reduction in exposure reduced risk.

Using findings from one of the studies they reviewed, of Seventh Day Adventists, a population who are prescribed to not smoke by their beliefs, Repace and Lowrey estimated the quantitative lung cancer risk from second hand smoke exposure. Skipping over the details of the math, they estimated 7.4 lung cancer deaths per 100,000 person-years of exposure (One hundred thousand (100,000) person-years is equivalent to 100,000 people exposed for 1 year or to 10,000 people exposed for 10 years each or similar combinations of time and people). Looked at differently, they predicted 4700 lung cancer deaths per year in the US, or 30% of all lung cancer deaths in non-smokers.

There are reasons to doubt the accuracy of this risk estimate, but it was state of the art for the time in which it was calculated and Repace, looking back, told me that he was still, "pretty pleased" with their estimate and pointed to numerous risk assessments since then that came to similar conclusions.

One estimate that differs from Repace's early work is the 2011 Global Burden of Disease mortality estimates for second hand smoke (see chart in the Introduction). It is interesting that these estimates were still drawn from studies using self-report of smoking and spousal smoking. The GBD study states that, "Biomonitoring data were not directly used in exposure estimation in this analysis because exposure measures in relevant epidemiological studies were almost invariably self-report survey questions." [10]. As we have seen, there is reason to think that self-report introduces substantial error into second hand tobacco smoke exposure estimates. It is also my opinion (and the opinion of Repace as well) that misclassification based on self-report probably reduces risk estimates.

The GBD 2011 estimates of risk are not presented for individual countries. The closest approximation to the US includes not only the US, but also Canada and Cuba. For that category it was estimated that there were 596 lung cancer deaths in 2004. This is substantially less than the 1980s estimate from Repace and Lowrey. Heart disease is a much larger impact, with over 12,000 deaths in the three countries combined. The global total mortality is substantial, at a little over 600,000 deaths. Still, second hand smoke comes in with many fewer deaths per year than indoor solid fuel combustion or ambient fine PM ($PM_{2.5}$).

An analysis led by Arden Pope, a leading researcher on PM was published in 2011. That analysis estimated $PM_{2.5}$ exposure from second hand smoke using some assumptions about how much PM self-reported exposure might represent [11]. The result was risk estimates for direct smoking, ambient $PM_{2.5}$ and second hand smoke that fell along reasonably good-looking dose response curves for both lung cancer and cardiovascular disease (Fig. 3.3). Interestingly, the exposure response curve for lung cancer was relatively linear, that is, for every increase in exposure, there was a concomitant increase in risk. But for cardiovascular disease, the curve flattened out at higher exposures, so that high exposures from direct smoking resulted in smaller relative increases in risk compared to smaller exposures to ambient PM or second hand smoke [12].

In fact, in drawing conclusions from epidemiology, replication across large numbers of studies with different designs and limitations as well as studying different populations are all important. There have been many studies of second hand smoke exposure and lung cancer as well as other disease outcomes. Sticking with lung cancer, a paper published in 2000 in the journal *Lung Cancer* [13], found 40 studies and pooled the findings to calculate a combined risk in what is known in the field as a meta-analysis [14].

Because there were two study designs that had been used, the meta-analysis calculated two combined risk estimates. One indicated an increased risk for lung cancer of about 20% and the other about 30%. The fact that a majority of the studies showed associations and that the combined estimate of effect from all the studies

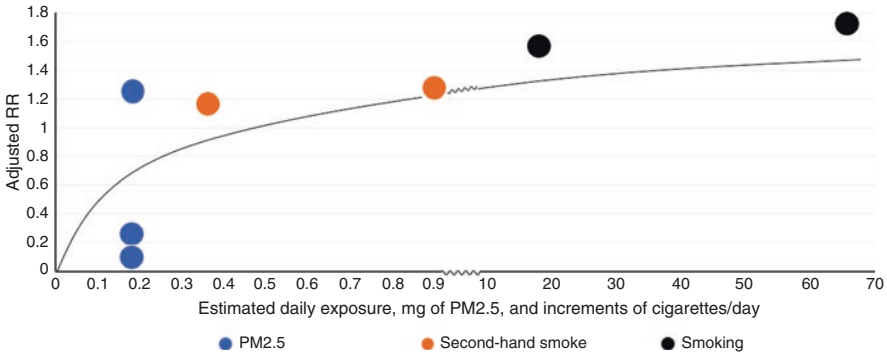

Fig. 3.3 Dose of $PM_{2.5}$ from air pollution, second hand smoking and direct smoking in relation to risk of death. The association is linear when the exposure axis is plotted as the log of exposure. (Illustration by Eda Lu, based on [https://ehp.niehs.nih.gov/1103639/])

was positive and statistically significant supports the conclusion that the risk is real. I would add that this is also eminently plausible since tobacco smoke had already been shown to cause lung cancer in smokers and the chemicals in tobacco smoke are well established to be carcinogenic in animals. More recently a meta analysis of studies with low cigarette use found about a 50% increased risk from smoking just one cigarette per day, similar to what one might inhale from second hand smoke.

In the 1990s when I was testifying at local boards of health about the hazards of second hand smoke, I used calculations from a third Repace and Lowrey article as prime evidence of the futility of using ventilation and filtration to reduce second hand smoke levels in buildings [15]. In this article, they undertook calculations to assess how much ventilation would be needed to reduce cancer risk from cigarette smoking in a "typical" office. This was critical to me because the argument of the restaurant industry representatives was that smoking hazards could be controlled by better ventilation, which obviated the need to ban smoking.

In their paper the chemistry and physics duo used the risk that they calculated from the Seventh Day Adventist study (above) to calculate a level of PM that would result in an "acceptable" risk which, according to the US EPA, would be a risk of 1 lung cancer death in 100,000 people. They then ask how much ventilation would be needed to reduce the second hand PM in an office if one third of the workers in the office smoked. Obviously, there are a lot of assumptions that go into a calculation of this sort, but it is valuable for giving one a sense of order of magnitude.

Their answer was that you would need 226 air changes per hour to reduce the risk below the EPA guideline. In other words, the air in the office would have to be completely changed over 200 times every hour. That level of ventilation, or even anything close to it, is unimaginable from a design standpoint. It is completely impractable because of the need to heat or cool so much air and even just in terms of the sheer amount of airflow the office would experience.

In this chapter, I have explored doubt and uncertainty in the second hand smoke case. Maybe it is a bit more math than some readers would prefer. I apologize if that

is the case, However, there is another risk that concerns me more. That is that the reader might throw up their hands and declare that there is no hope of figuring out what is true and what is not. Such a reaction might lead to paralysis and inability to act to prevent exposure and adverse health outcomes. Such was not my intent.

I hope the reader will, instead, reach the same conclusion that I came to decades ago. I decided that one must assess the evidence and act accordingly, but remain open to changing one's mind if new and better evidence comes along that suggests a different interpretation. I hope that leading you, the patient and forgiving reader, through some of the messiness that is science, especially public health science, is a bit of an antidote for the unrealistically simplistic reporting that one sometimes sees in the popular media.

Now, I would like to turn to a living example of someone I know who is severly affected by second hand smoke. I met Sarah (not her real name) when she was an undergraduate. I knew early on that she was advocating for banning smoking outdoors on her campus and felt a little conflicted about her passion for the issue. To me it had long seemed that outdoor smoking was probably too small a risk to be worth pursuing aggressively. But I was to learn that she had good reason to avoid even outdoor smoking.

The first time I experienced her reaction, we were walking in a small group outdoors at a scientific conference. She exclaimed that we had just passed a smoker whom did I not notice and started coughing. I am ashamed to say that my first reaction was to be a bit skeptical. I wondered whether she was overreacting. Apparently I was not the first to have such a reaction. She tells me that, "people don't believe me until they have consistently seen me have attacks with smokers." I can attest to that, being convinced only after seeing repeated attacks, some far worse than the first one that I witnessed.

Now that I have seen secondhand smoke repeatedly trigger her asthma attacks and force her to use her inhaler sometimes leaving her gasping for breath and coughing up blood, I have a new appreciation for the fact that there are people for whom a whiff of tobacco smoke precipitates a serious and acute health crisis. I mentioned Sarah to Repace, when I spoke to him for this chapter and he told me that severe hypersensitivity like hers is not that uncommon since he knows other cases.

Like others who know her, I have become protective of Sarah when I am with her in a public area where there might be smokers. She says others also do what I do, scanning for smokers and alerting her when I see one so she can cross the street or otherwise avoid them. She calls it' "hyper-protective," but to me the extra caution feels justified based on the risk.

Interestingly, Sarah did not realize that she was sensitive to tobacco smoke until she started college because she was not exposed enough to make the connection when she was younger. Like other people I have sometimes met and gotten to know who have a physical disability, Sarah is emphatic that she will not let hers interfere with living her life. She has traveled to Asia and Latin America despite the obvious risks. She reports a terrifying incident in which a smoker on a ski lift she was riding triggered her asthma, forcing her to call ahead for an emergency response when she got off. She says, "I'm not going to not live my life".

In light of the reactions she experiences from second hand smoke, it is not surprising that Sarah launched a campaign to ban smoking on her campus. Her effort was not particularly successful though since administrators and other students and even other public health people were not very supportive. Signs banning smoking were put up in a couple of places, but only in response to her collapsing from an asthma attack or having to go to health services after inhaling second hand smoke in those locations.

Ultimately, though, Sarah puts it all in perspective. She is aware that most people do not have her level of reaction to tobacco smoke. Rather than seeking broad-based bans to protect herself, she prefers to use her case as an example to raise awareness that second hand smoke is hazardous for everyone. She was also influenced by her reaction to second hand smoke to pursue graduate research in environmental epidemiology.

While Sarah met with little success seeking an outdoor smoking ban, Repace contributed mightily to the spread of indoor bans on smoking. In 2004 he published a study in the *Journal of Occupational and Environmental Medicine* in which he measured PM in a casino, a pool hall and some taverns before and after a smoking ban. His research was picked up by the Associated Press [16] due to his active effort to get coverage. As he pointed out to me when we spoke, being picked up by a news service spreads a story broadly through the media.

His simple pre-post study design, which was easily understood by the lay public and policy makers, combined with an interest in press coverage, in my opinion, positioned him to have a disproportionate influence on the adoption of indoor smoking bans internationally. While there are still places one can go that allow indoor smoking, they are fewer and father between, at least in high income countries. And today even outdoor smoking, for example, close to building entrances, is being restricted in some locations. I worry that smokers, who are addicted, have become tarnished as villains, rather than the industry that hooked them. But I am glad to see that exposure to second hand smoke is declining.

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Chapter 4
Everyone Is Exposed Every Day

The Harvard Six City Study may be one of the most underappreciated environmental research efforts by the public. Not only did the study provide one of the first two truly convincing pieces of evidence that fine particulate matter in the atmosphere was very unhealthy (the other being the American Cancer Society Study, more later), but it helped drive a change in federal policy in the US that has been shown to have saved innumerable lives.

Published in 1993 with lead author Doug Dockery in the *New England Journal of Medicine* [1], the simplicity of the main findings of the Six Cities Study belies the complexity of the effort to collect the data on which the analysis rests. I am extremely fortunate to have been able to interview and communicate with multiple leaders of this study, including Dockery, Frank Speizer, Jack Spengler as well as the Harvard archive that is preserving records from the study. My conversations with them inform what follows, although my interpretation and opinions are, as always, my own.

I discussed the study with Spengler over a lunch of lamb kabobs (his treat). I first met Spengler in 1988 during a year I spent at the Harvard School of Public Health studying industrial hygiene. He led the air pollution monitoring work on the Harvard Six Cities Study. In the interest of full disclosure, I should note that in the last couple of decades he and I have collaborated, first with me in a junior role, then in a senior role, on two research studies. I interviewed Speizer over the phone after meeting him for the first time at the Harvard archive. Dockery and I communicated only by email.

The Harvard Six City study was launched in the early 1970s, about two decades prior to publication of its most influential findings. Again, as in Chaps. 1 and 2, this shows the long timeframe from inception of major research studies to their publication. However, the Harvard Six City study research findings would translate quickly into federal policy in 1996. The main funder of the study was the National Institute of Environmental Health Sciences (NIEHS) with additional support from the EPA and the Electric Power Research Institute.

D. Brugge, *Particles in the Air*, https://doi.org/10.1007/978-3-319-89587-1_4

NIEHS and EPA had been newly established in the early 70s when Speizer (along with Ben Ferris, another Harvard professor) testified before an expert committee set up by NIEHS about the consequences of burning high sulfur coal. He told me that he thought that his testimony would be the end of it. But then he was asked to write up a proposed approach to studying the problem. He suggested that research should use a spectrum of locations around the country with varying levels of pollution.

The proposal that Speizer drafted ended up appearing "almost verbatim" in the federal register. He and his colleagues subsequently submitted a proposal to NIH which went through the review process and was approved for funding. Clearly they had an advantage, but they were not exempt from review and funding decisions. The resulting grant was a standard NIH grant called an R01, which was for 5 years of research. They had anticipated a national air monitoring network, but that was not approved by the Nixon administration, so they had to develop their own monitoring plan, including the use of new technology.

At the time the study was begun, air pollution was measured as total suspended particulates. TSP has largely been left behind because it is not a good measure of the fraction of particulate matter suspended in air that affects health. This is because most of the mass of TSP is from very large particles that do not make it into the lungs because they are, instead, caught in the upper respiratory tract, including the nose and throat. The innovation of the Harvard Six City study was that they measured *respirable* particles that could make it deep into the lungs.

It might surprise the naïve reader interested in air pollution or the environment, to learn that particulate matter is found in discrete size classes in the environment rather than a continuous distribution from tiny to large. The smallest particles, which will be discussed in Chap. 5, are ultrafine particles that include the nucleation and Aitken modes. Fine PM, the focus of this chapter, are mostly from the accumulation mode. Coarse PM, or PM_{10} (less than 10 micron in diameter) are formed mainly from abrasion or suspension of dust in the air.

These classes or modes of particle sizes form distinct peaks on a graph plotted by particle size (Fig. 4.1). I asked Spengler why the cut point of 2.5 microns was choosen for respirable PM because it has long puzzled me. Why 0.5? The fraction seems rather precise and another respirable value from around that time was rounded off to 3.0 (see Chap. 3). He thought, and it sounds plausible to me, that the 2.5 cut point was an attempt to maximize inclusion of accumulation mode particles while excluding coarse particles as much as possible.

In any case, it was a wise decision to include respirable PM, $PM_{2.5}$, in the Harvard Study since fine PM has subsequently come to be understood as one of the leading public health problems in the world, with a massive scientific literature that followed on the initial studies. The Global Burden of Disease studies, as was noted in the Introduction, attributed $PM_{2.5}$ with causing over four million deaths worldwide each year, with the largest numbers in populous countries in Asia that have very high levels of $PM_{2.5}$.

The design of the Harvard Six City study is deceptively simple, Spengler and his team placed a monitoring station in the center of six cities (hence the name) that

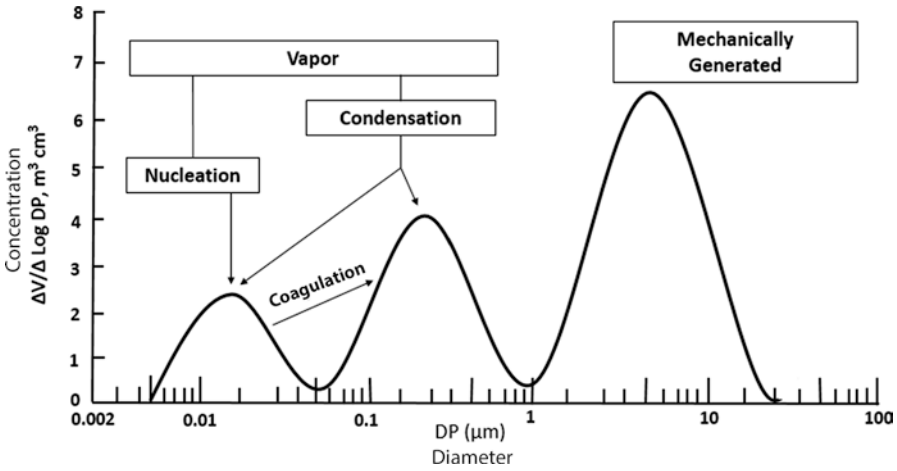

Fig. 4.1 The distinct size classes of PM that are found in the air. (Source: EPA)

differed in their levels of pollution. They choose cities with industries that were targeted for reductions in the pollution that they generate. From the beginning, the study was intended to document improvements in health as pollution levels were ameliorated, something that was only realized by a study published in 2006 which I will describe later.

Thus, Kingston, TN, for example, had a 1700 megawatt coal fired power plant with low stacks (that would later be elevated) and was in a valley in which the pollution was trapped so that it accumulated to high levels. The study started in Watertown, MA, where I live, which was close to Harvard and had relatively clean air. Speizer knew of Steubenville, another of the cities, through his wife. People there would repaint their house every year because the paint would turn black, probably, he thought, from acid sulphates in the air reacting with lead in the paint.

The reason that a single monitor could be placed at a central site in each of the six cities is that $PM_{2.5}$ is mostly a regional pollutant. That is, $PM_{2.5}$ levels are spread across large geographic areas changing little with distances of kilometers or miles within those areas. The reason for this, in turn, is that $PM_{2.5}$ is mostly formed as a secondary pollutant. Gasses released by combustion undergo reactions in the atmosphere that lead to particle formation rather than the particles being release directly. This means that regional $PM_{2.5}$ formation starts with a few molecules of gas joining to form extremely tiny nanoparticles (a few billionths of a meter in diameter) that then grow into micron size PM (a few millionths of a meter).

The details of how nano-scale PM forms has been studied using sophisticated technology to try to understand the phenomenon. A paper in the scientific journal *Science* in 2013 by investigators from Finland presented evidence that the formation of the smallest nanoparticles from atmospheric gasses is a two stage process [2]

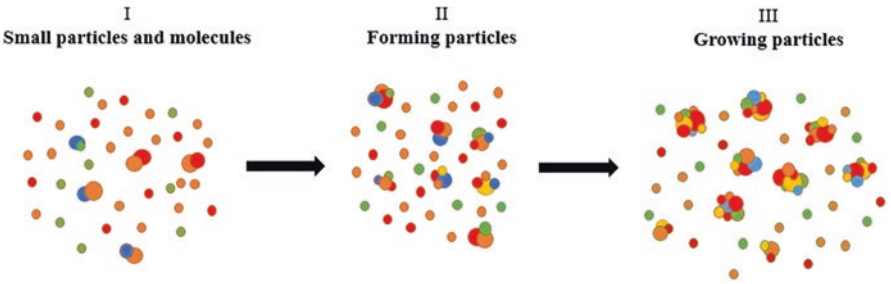

Fig. 4.2 Formation of particulate matter in two steps from gasses in the atmosphere. (Illustration by Eda Lu, based on Kulmala et al. [2])

(Fig. 4.2). In the first step, molecular clusters form. These clusters of molecules, less than 1.5 nm in size, consist of sulfuric acid formed when sulfur dioxide gas combines with water to form liquid particles. These particles are then stabilized by nitrogen containing molecules, primarily compounds called amines.

In the second step, the miniscule clusters formed in the first step grow in size. Sulfuric acid and amines are apparently not enough to drive this growth. Organic vapors seem to fuel growth at this stage. The authors describe this as analogous to the processes during condensation of water to form clouds in the sky. Thus, the presence of organic vapors in the air, which can come from human activity, especially combustion, is critical.

Secondary aerosol formation typically is substantial on some days and not evident on others. Event days or days with "blooms" of secondary PM across a region depend on the conditions in the atmosphere being right for particle formation. The reader is probably aware of days when pollution levels are higher, often during the summer. On high pollution days one might see a brownish haze over the city or on the horizon.

The Harvard Six City study was monitoring this type of regional pollution and followed over 8000 people, a "cohort", living in the six cities for 14–16 years. They managed to record most of the deaths (1401 out of 1430 deaths were documented) over the course of that time. They had an independent physician who was blinded to study design and pollution levels classify cause of death. Individuals enrolled in the study were assigned average pollution exposures for six pollutants that had been measured and mortality rate ratios were calculated for each city relative to Portage, WI, the least polluted city.

Associations were adjusted for a range of factors that might be responsible for associations other than the air pollutants. Basically, if a factor, perhaps body mass index, for example, were higher in the more polluted cities and also led to elevated risk of death, then it could look like the cause was air pollution when in fact it was overweight and obesity. Controlling for these factors, called confounders, is never perfect, and represents a common limitation of epidemiology studies. But the study is stronger if associations hold up even after controlling for the variables that are possible to include.

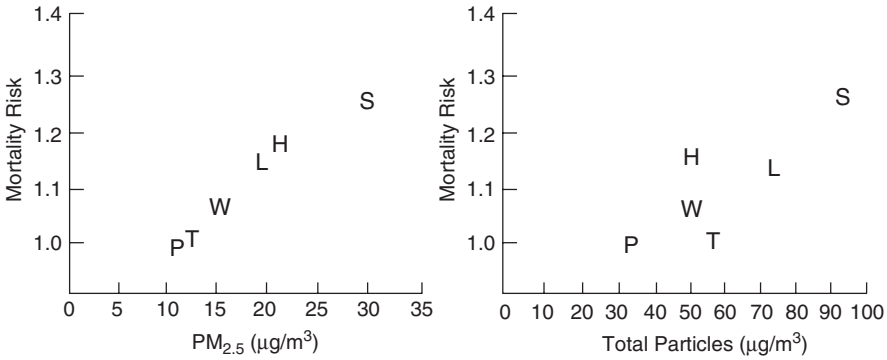

Fig. 4.3 Examples of the findings from the Harvard Six City Study. On the left are associations of $PM_{2.5}$ exposure by city with mortality. Each letter is one of the cities. On the right are associations with total particles (TSP). The total particles do not show as clear an association, suggesting that $PM_{2.5}$ is a better indicator of air pollution health risk. (Illustration by Eda Lu, based on Dockery et al. [1])

The Harvard Six City study found a 26% increase in mortality between the least and most polluted cities after controlling for age, sex, smoking, education, body mass index, and occupational exposure. Rereading their study, I am impressed not so much by what they controlled for as some factors I might be concerned about were not included (diet, stress), but more by the fact that controlling for possible confounders changed the associations with air pollution very little. To me, that suggests the associations were stable and not easily explained away.

The study also found that there were greater risks, elevated 37%, for lung cancer and heart and lung- related causes of death, while there was no elevation in death for "all other causes." This specificity, helps exclude some potential risk factors, injuries comes to mind, that one would expect to not be elevated in relations to air pollution exposure.

Figure 4.3 reproduces two graphs in the original Harvard Six Cities study paper in the *New England Journal of Medicine*. Each graph plots air pollution level against mortality. One graph is for fine PM, the other is for total suspended particulates. TSP, as I noted above, does not reach the lungs as well as $PM_{2.5}$. What is obvious is that there is a nice linear relationship between fine PM and mortality, but that the relationship is not as strong for TSP. To me, this suggests a degree of specificity in that the exposure response relationship is much more linear for $PM_{2.5}$ than for TSP. We would expect a true association to be smooth rather than jump around the way the association does for TSP.

Taken together, the evidence from the Harvard Six Cities study is overall convincing, but not conclusive by itself. For one thing, a single epidemiology study is rarely enough to definitively show causation, even a very good study such as this one. For another, one might prefer that each individual in the study be assigned their own exposure, rather than everyone in each city getting the same exposure. But this is the nature of epidemiology, as we have seen in previous chapters. Its limitations

do not render it useless, but rather its strengths contribute to a broader literature that could, if the hypothesis is correct, align to point to a convincing body of evidence.

However, the Harvard Six City study was not the only evidence. Prior to and in the period immediately adjacent to publication of the Harvard results, there were a slew of other studies that provided additional indications that air pollution, and particulate air pollution specifically, were affecting health. Most of these studies had inferior study designs to the Harvard study. They were, for example, time series that compared air pollution levels to mortality day by day rather than assessing the long-term effect of chronic exposure. Or they were cross sectional, at one point in time, instead of longitudinal follow-up. But overall, these secondary studies provided additional confidence in the Harvard findings.

The American Cancer Society study of $PM_{2.5}$, which was published in 1995 with Arden Pope of Brigham Young University as the lead author, became the companion study to the Harvard work that supported federal regulations [3]. The ACS study took a different approach. Rather than recruiting their own study participants, they grafted air pollution data onto a cohort that was recruited and followed originally for reasons unrelated to air pollution. This is, in fact, a time honored approach in air pollution research, since the resources necessary to develop a study population solely to study air pollution are rarely available.

The full ACS study cohort consisted of about 1.2 million adults in the US who were recruited by volunteers in the early 1980s. The volunteers mostly recruited people they knew, which probably means that the cohort is not representative of the overall US population. But it is quite large and spread across the country, making it ideal for a study of $PM_{2.5}$. The $PM_{2.5}$ study, however, limited its analysis to about half a million people who had complete data and for whom air pollution levels could be assigned using values from EPA monitoring stations that had been installed since the inception of the Harvard Six Cities Study.

The two air pollution measures used in the ACS study were sulfates and $PM_{2.5}$. $PM_{2.5}$ levels varied from a minimum of 9.0 micrograms per cubic meter of air to 33.5 ug/m^3.

The main finding from the ACS study was that both sulfur and fine PM were associated with overall mortality after controlling for a wide range of possible confounders including body mass index and smoking. The effect was smaller than smoking in the cohort as smoking doubled risk of dying, while PM increased the risk by only 15–17%. But remember that only some people smoke while everyone is breathing PM air pollution, so the overall health impact of air pollution is larger than this comparison suggests.

The ACS paper, published in a prominent journal called the *American Journal of Respiratory and Critical Care Medicine*, awkward name, but a great journal, does a nice job of discussing the limitations of their analysis [3]. They acknowledge that their assignment of exposure likely has some error due to historical exposure possibly being different, but also suggests that air pollution levels had not changed much over the decade before the study took place. They argue, and I would agree, that $PM_{2.5}$ levels are relatively constant across metropolitan areas. Perhaps they are

a little too confident that indoor and outdoor levels are sufficiently correlated. But they also recognize that death certificate records can contain errors as well.

This is the essence of epidemiology as science. We use the data that is available. Then we address its limitations as best we can in the analysis. And, in the end, we forthrightly point out the limitations of the work eschewing the desire to skew it into the best possible interpretation for our preferred hypothesis.

As I indicated above, the Harvard Six City study and the ACS study were the basis for new federal regulations on ambient $PM_{2.5}$ air pollution that were promulgated by the US EPA in 1997. But the story of how the new legislation came to be and remained permanent is one of conflict and controversy because the regulation was fought fiercely by industries that would be affected financially.

It is helpful to review the history of EPA regulation of ambient PM before delving into the controversy around the $PM_{2.5}$ standard. In 1971 the EPA set the first standard for particulates in the atmosphere. That standard was for total suspended particulates, TSP, and was measured using high volume samplers. Of course, using this method, the measurement was, as I noted above, dominated by very large particles that would not make it into the lungs.

In 1987, the EPA changed its standard from total suspended particulates to PM less than 10 microns in diameter, or PM_{10}, which continues to be one of the standards enforced by EPA today. Unfortunately, PM_{10} is also not composed primarily of respirable particles. In fact, most commonly, PM_{10} is made up of material found in soil or rock, rather than the more toxic and concerning compounds found in combustion products that are smaller in size.

The starting point for revising the PM standard a third time was a lawsuit by the American Lung Association filed in 1993 that was based on the EPA failing to review its PM standard every 5 years as is required under the Clean Air Act. The court ordered EPA to review and finalize its PM standard by 1997, leading the EPA to announce its new proposed National Ambient Air Quality Standard for $PM_{2.5}$ (as well as a new standard for ozone) in 1996.

A coalition of industries that produced electrical power and manufactured motor vehicles, steel and other products fought the new regulation fiercely in the media, halls of congress and the courts. The US EPA estimated the cost of the regulation between $6 and 8 billion, enough to stoke the controversy and fuel push back from the industries that would have to pay. The projected benefits on the health side were also anticipated to be substantial – 15,000 deaths and hundreds of thousands of asthma attacks averted.

But costs and benefits are fraught domains in many ways. While society as a whole would benefit, the sectors of society that pay the costs are not the same as the ones that see savings. Industry pays the bulk of costs while the savings are primarily in health care. Even if the attribution of costs and benefits were not an issue, the EPA is restricted from considering costs in its standard setting anyway. On one level that is good, the standards don't have to trade off lives for profits. From another angle, I have long thought that there should be some proportionality – cost-effectiveness instead of cost-benefit – in terms of how we invest resources in health

with more resources allocated to health problems that the evidence suggests are larger.

There is another problem as well with estimating economic impact and health consequences of policies such as regulating air pollution. Both the health outcomes and the expenses are estimates with varying degrees of accuracy and even in the best cases likely contain considerable error.

The industry public relations campaign against the $PM_{2.5}$ standard was described in the Washington Post as, "an extraordinary, multimillion-dollar campaign". Their campaign had farmers worried that EPA would limit which days they could plow their fields. An ad said, "I suppose EPA is going to tell us we can't plow on windy days", an obvious falsehood since plowing kicks up larger particles, PM_{10}, not combustion-related $PM_{2.5}$. Behind the campaign was a coalition called the Air Quality Standards Coalition which was made up of 500 business and trade groups drawn from petroleum, automobile and utility companies according the Post [4].

But the core of the attack by industry against the $PM_{2.5}$ standard was to question the science in ways that were reminiscent of the approach pioneered by the tobacco companies decades earlier. They questioned the quality and certainty of the science and demanded that the original data from the Harvard Six Cities Study be released so that it could be reanalyzed by independent parties. The Harvard team refused to release their data based on ethical concerns. The participants in the study had been promised that their personal information and participation in the study would remain confidential. In addition to ethics concerns though, there was also a fear that industry might conduct a biased analysis that distorted the findings [5].

Ultimately, under pressure and accused of having something to hide in their "secret" data, Harvard and EPA agreed to a compromise which was to release the data to the Health Effects Institute for reanalysis. HEI is a private organization with a mission to study and address the problem of air pollution. Because they are funded by both the EPA and the automobile industry, they are a bit of a neutral third party that could be trusted by both sides.

While the HEI reanalysis ultimately vindicated the original Harvard outcomes, it would take until 2000 to be reported, long after the new standard had been put in place. Speizer says that he was opposed to releasing the data. "We had done as credible a job as we could," he told me over the phone. I agree with him that if someone with ill intent goes fishing in a data set without a prior hypothesis they could, "find all sort of things" including spurious associations there by chance that should not be given any credence.

However, the controversy around releasing or not releasing the data did not cut neatly along industry-academic research lines. For example, Harvard School of Public Health Professor John Graham has been quoted saying that the findings, "sit as the foundation for multibillion dollar decisions in China, Brazil and elsewhere. I would still like to see the data made publicly available. It's the basic principle of transparency in science [5]."

Republican Senator Richard Shelby inserted language in a budget bill that requires researchers funded by the federal government to share their data via the Freedom of Information Act [5]. While I think the industry and Shelby were using

their request to release data for political purposes and probably saw a public relations advantage in Harvard's refusal to do so, overall, I do think data should be available for reanalysis and secondary analyses. After all, that is how science is checked for its accuracy. Can results be replicated, either from the same data or other, similar, studies?

The ethical concern can sometimes be addressed by releasing only "deidentified" data that removes personal identifying information about participants. But concerns about biased or low quality analyses by parties, mostly industry, that have a vested interest in distorting or undermining findings, is another issue.

Dockery, the lead author on the main outcomes of the Harvard Six City study, has been quoted as saying, "It was a painful time. You'd get up in the morning and look at the paper and there you'd be again" [5]. Having never been in their situation, I can only imagine what it must be like to not only face accusations that your work is fraudulent, but also to see the controversy splashed across the national media.

Both Dockery and Spengler had what I think are critical insights into the relationship between science and policy. That "good science" perseveres in the long run, which places a premium on the quality of research. Also among their lessons was that how one translates scientific evidence for the public and policy makers matters. I have seen repeatedly that it causes problems when academics present science in ways that are lost on an audience without highly technical training or knowledge. Spengler adds that scientists need a "steel backbone" [5].

Speizer pointed out to me something I had not considered previously that was a positive outcome of the Harvard Six City study. A "huge number," of people, he did not know exactly how many, but 30 theses at least, had been trained in environmental science and health research because of the study. Many of them went on to make considerable contributions to the field. Speizer says, correctly in my opinion, that it is, "hard to put a value on that."

A key criterion for assessing causality in epidemiology is that reducing the exposure should also reduce the health effects. Interestingly, even prior to publication of the Harvard Six City study, there was evidence that this was the case. For me the most "famous" example is from Utah and was published by Pope, who was also (later) lead author of the American Cancer Society Study as well. The Utah Valley offered an almost ideal natural experiment in 1987 when the steel mill there was shut down for a year by a labor strike. Conveniently, PM_{10} had been measured at a central monitor in the valley since 1985 and the mill was the largest source of air pollution in the valley [6].

One of his papers analyzing the effect of shutting down the mill on air pollution levels and respiratory health outcomes was published in the *American Journal of Public Health* in 1989. In it, Pope reported using hospital data for in-patient admissions from the main nearby hospitals to assess monthly cases of serious respiratory problems such as asthma, bronchitis and pneumonia. As I have mentioned previously, in the earlier years the focus was almost exclusively on respiratory outcomes as it was only later that cardiovascular outcomes were understood to be the major source of morbidity and mortality.

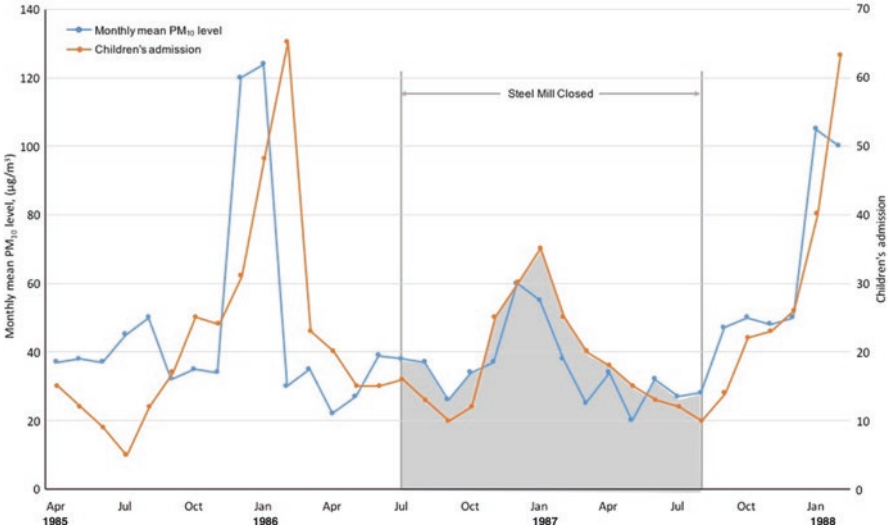

Fig. 4.4 PM_{10} levels declined in the year that a steel mill in Utah was on strike and not generating its usual pollution. Along with the reduction in air pollution, children's admissions to hospitals for respiratory problems also declined. Based on Pope, 1989

Pope sliced and diced the data multiple ways that were the standard of the time, but a little short of what we could do statistically today. That is understandable as the power of personal computers was just emerging in the 1980s. He reported that when PM_{10} levels exceeded the EPA 24-h standard of 150 ug/m^3 that the number of admissions for children nearly tripled while adult admissions went up over 40%. Admissions also increased, although not as much, when PM_{10} levels exceeded the EPA annual standard of 50 ug/m^3.

Perhaps, though, the most compelling way to see the effect is graphically. Figure 4.4, reproduces part of the graphical data in Pope's paper. By plotting both PM_{10} and hospital admissions on the same graph, which Pope did not do, the tight association is visually apparent and quite compelling in my opinion.

As all researchers associated with epidemiology know, correlation does not equal causation. Pope fully understood this, so he also tested the possible role of other variables. Perhaps the winter had been unusually warm the year of the strike or there had not been outbreaks of the flu that year. He used statistical models called regression equations, which are calculations used to test the relationship between a variable and an outcome, often controlling for additional variables. In his regression models, he found that same month and prior month PM_{10} was strongly associated with hospitalization. He also found that low temperatures were as well.

While the associations with temperature remained for hospital admissions outside of the valley, there was no association with PM_{10} for hospital admissions away from the mill. If infectious illnesses had been to blame, one would expect to see

similar effects in nearby communities. The one thing I see missing from Pope's analysis is $PM_{2.5}$ which had not yet emerged as an important focus of air pollution research. I suspect, much as Pope argued in this paper that if he had had $PM_{2.5}$ data, it would have been an even stronger predictor.

If the Utah Valley example is the bookend prior to the Harvard study, the bookend after it would have to be a paper by Francine Laden that was published in 2006 [7]. In her paper, Laden, also of the Harvard School of Public Health, and recently the first tenured woman in environmental health there, extended the analysis of the six cites for another 8 years during which pollution levels declined. Spengler, when I had lunch with him to discuss this research, reminded me that it was always the intention of the study to assess the impact of reductions in pollution levels. But, obviously, that took decades and a new generation of environmental epidemiologists, to come to fruition.

Unfortunately, the air monitoring campaign in the six cities had lapsed, so Laden had to estimate the $PM_{2.5}$ levels in each city for the 8 years of follow-up. I suspect that the estimates were relatively good, but nonetheless, it is a limitation in my opinion that exposure was not assigned the same way in the follow-up period as it had been in the original study. An additional issue is that health of Americans was improving overall during the time period, a secular trend which could be mistaken for a result of reduced pollution exposure.

Laden found that air pollution levels declined in all six cities, but that they declined fastest in the cities that were dirtiest to begin with, which were Steubenville, St. Louis and Harriman. She also found that the association between $PM_{2.5}$ and mortality were quite similar to the original six cities analysis. The main finding though, was that for every 10 ug/m^3 reduction in $PM_{2.5}$ during the follow-up period, there was about a 25% reduction in risk of death. The analysis included a statistical method to adjust for broader secular trends in mortality and she notes in her discussion that the reductions in risk were greatest in the cities with the largest reductions in $PM_{2.5}$, which argues for the effect being attributable to air pollution improvements.

In the latest analysis of the ACS cohort, the effects of $PM_{2.5}$ air pollution have been parsed into the constituents and the pollution sources from which the $PM_{2.5}$ originated [8]. Coal combustion was found to be a far greater cardiac risk than particles from other major particular matter sources in the U.S. This result is consistent with earlier ACS work identifying sulfur and fossil fuel combustion particles as the greatest contributors to the mortality from $PM_{2.5}$.

While air pollution levels have declined in much of North America, Europe and the more developed countries in Asia, air pollution has dramatically worsened across much of the rest of the world as industrialization takes off in formerly undeveloped countries. Media attention has focused specifically on China in the last decade, but the problem is wide spread in Asia, including India and Pakistan, and the Middle East, Iran for example, as well as in Africa and elsewhere. Delhi, India has been observed to have even higher levels of air pollution than China. Iran was recently reported to have the worst air pollution of any country.

The impact of this pollution showed up in the Global Burden of Disease reports with estimates of as many as one million deaths per year from $PM_{2.5}$ in China alone. Perhaps the media attention and the scientific evidence have spurred the growth of research conducted in China on air pollution. In recent years a steady stream of high quality studies has come from China about air pollution and health. I would like to describe one very recent and striking example of this research.

Published in the major medical journal *Circulation* in 2017, the study by Huichu Li and colleagues was designed to investigate the effects of $PM_{2.5}$ on biological pathways inside the human body [10]. The research team recruited 55 healthy college students into their study. The students had real or sham air filters placed in their dorm rooms for 9 days each. This design is called a double blind, randomized cross over study because each study participant receives both real and sham filtration in random order.

The study was blinded so that behavior changes and psychological reactions of the participants were minimized in terms of their potential to influence the outcomes. In the case of this study, the authors also included 12 days between the first and second exposure for each participant as a "wash-out" period, so that if there were effects from the previous period, they would not influence the second exposure period. An important aspect of this study design is that the study participants were compared to themselves in the two periods so differences between participants, body weight, diet, etc., are not a concern.

The study collected blood samples from the participants at the end of each exposure period. The samples were analyzed for some well-known biomarkers, which is not uncommon in air pollution research. What was much more original was that they also analyzed the blood samples for a wide range of metabolytic molecules, a method known as metabolomics analysis. In metabolomics analysis it is possible to measure thousands of different types of small molecules in the blood. In the case of this study, they detected over 2000 metabolites.

Finding the needles in the haystack of such a massive amount of data is complicated and may limit the value of the resulting data. But in this case, I found the findings to be highly interesting and suggestive of the biochemical and cellular pathways by which PM might be affecting health. In fact, the pathways that seemed to show changes might surprise you.

As I have stated previously, the public has been conditioned to think that pollution affects primarily respiratory health. But, the largest health impacts are to the cardiovascular system. Given that effects of PM are so considerable to the heart and blood, leading to, among other things, heart attacks and strokes, attention has focused heavily on blood pressure and inflammation in the blood. Indeed, this study in China did find effects on blood pressure, which was higher without active air filtration. There were similar effects on inflammation.

What the metabolomics analysis allowed, however, was to look at a wide range of other biological molecules that would not normally be studied. Their analysis of the metabolomics data suggests that $PM_{2.5}$ exposure acts on the nervous system to activate two important hormone pathways. The first is called the hypothalamus-pituitary-

adrenal axis, which, I realize, is a mouthful and off putting immediately. Regardless of the technical language, this pathway is very important as it regulates many body systems, including the immune system, which, in turn, influences inflammation.

The second pathway activated by higher pollution levels during sham filtration was the sympathetic-adrenal-medullary axis, another mouthful and another vital regulatory pathway that leads from the nervous system to hormones. One way of thinking about this pathway is that it triggers the fight or flight response to stress, which affects heart rate (you've noticed your heart beat fast when you are scared, I am sure), blood pressure and other aspects of your body function. Taken together, these pathways make a lot of sense to me since they are connected to major outcomes we see over and over again in air pollution research, inflammation and blood pressure primarily. These outcomes that are well established to cause adverse cardiovascular events such as heart attacks and strokes.

Why do I get excited about this study? First, it suggests that reducing $PM_{2.5}$ pollution by use of air filters could be protective of health. Given the slow process of cleaning up the air in most developing countries, I see in this a way to protect people from PM pollution in the meantime. I don't think this study, by itself, is definitive about the health benefits of air filters because it is small, does not include actual health outcomes, includes healthy young people who are probably the least at risk and was a highly controlled situation rather than real life. But I find it encouraging and expect that other studies will follow that might be more convincing.

The second reason for my enthusiasm about this study is that it adds considerably to the evidence for a causal relationship between $PM_{2.5}$ and adverse cardiovascular health outcomes. If we know the biological pathways by which $PM_{2.5}$, or any PM for that matter, acts within the body, our confidence, which was already quite high, grows even stronger as any remaining doubts we might have can probably be put to rest. Given the stakes, huge health impacts and considerably economic costs associated with reducing air pollution, we need to have a strong scientific case.

While federal regulations reduced ambient particulate pollution in the US and other developed countries, some developing countries, notably China and India, underwent industrialization. Regrettably, they did so in ways that privileged economic development over environmental quality. Economically, this has been quite successful, but air quality declined substantially in the process (Fig. 4.5).

Jingjing Wu lives with her two children, one in kindergarten and the other in in elementary school in Nanjing province (Jiangsu). She and her husband are chemical engineers who spend the majority of time at the office. They are in their 30s and report that the air pollution where they live is okay some of the time, but worse in the winter. They did not originally buy their air filtration system because of ambient particulate pollution, but rather to be able to close their windows and keep out traffic noise and also to address formaldehyde released from a renovation they did. Their air filtration units are stand-alone, commercially available high efficiency particulate arrestance, or HEPA, machines.

HEPA filtration is a standard approach to reducing PM in indoor air. The principle is a pleated paper filter with a fan that pulls air through the filter, leaving behind on the filter most of the PM that was in the air. In fact, these filters are very good at

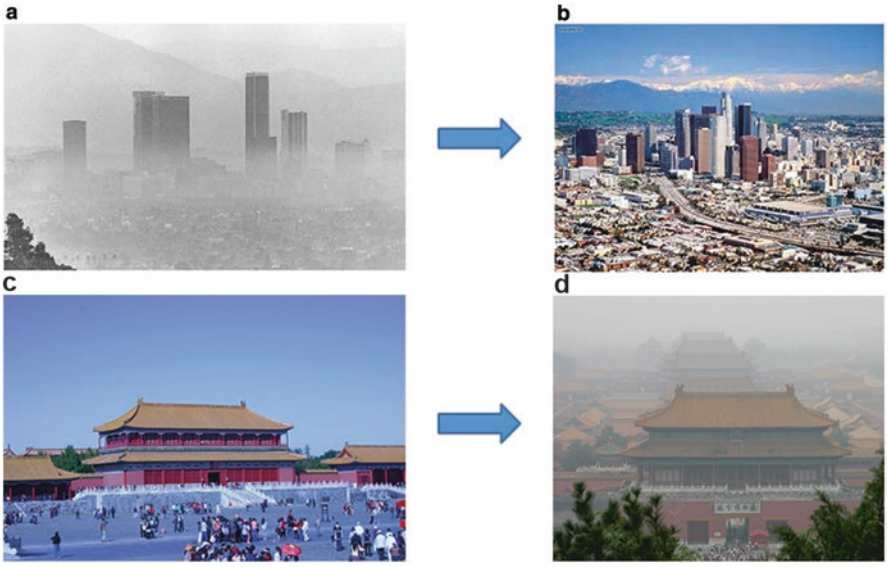

Fig. 4.5 Air pollution levels were once as bad in Western cities as they are today in Eastern cities. Los Angeles went from having a dense smog in the 1970's (**a**) to skies that are mostly blue (**b**). While Beijing went the other direction, from blue skies (1980) (**c**) to a thick soupy grey (2005) (**d**). (Credits: (**a**) From the Los Angeles Times Photographic Archive, UCLA Library. (Licensed under CC-BY); (**b**) Retrieved from http://wallpaperweb.org/wallpaper/buildings/los-angelescalifornia_20597.htm; (**c**) Cangul, Forbidden City-Beijing-China. Retrieved from https://www.flickr.com/photos/farsongul/4002672335 (Licensed under CC BY 4.0); (**d**): Brian Jeffery Beggerly/Flickr. Retrieved from https://www.flickr.com/photos/94509941@N00/48951277 (Licensed under CC BY 4.0))

removing PM, but they have some limitations. While the air that exits the unit is very clean, the air in the room is less so. This is because the units can only recirculate a limited amount of air and they have to pass a lot of air through to clean a large room. Also both outdoor and indoor sources of PM can be replenishing the PM in the room unless the building is very tightly sealed and no indoor source exist.

Buildings that have a mechanical air handling system, a series of ducts, fans, air intakes, exhausts and filters, are better at reducing indoor PM than are stand-alone units like those that Wu and her family and many others in China and elsewhere use. This is because buildings of this sort tend to be tightly sealed and the air inside is recirculated so that less outside air gets in. It is also possible to put high quality HEPA filters in the path of the air flow and further reduce PM. But most single family housing and especially lower income housing, does not have air handling systems of this sort.

Wu reports that, "every couple of days, we can see that there is a layer of filtered particles accumulated on the filter, and we wash them very frequently. The inner layer of the filter can be used without cleaning for a little longer. However, after a period of time, we can also see dust accumulating on it." Her report is typical of

what I hear from people living near a source of combustion pollution, such as a major roadway. I have, over the years, spoken to many people who complain about having to wash the accumulated soot off their windows or porch railings. I will address the issue of local traffic-related PM in the next chapter.

Wu notes that her children seem to have less allergy after installing their filter units. That is unlikely to be due to reduced ambient $PM_{2.5}$, but rather from also reducing indoor allergens, such as dust mite and mold particles. These particles are much larger than $PM_{2.5}$, but the utility of air filtration to address multiple hazards is one of its strengths. The main health effects of ambient PM, increased blood pressure or systemic inflammation leading to elevated risk of cardiovascular events, are not so easily noticed. That, in turn, is a limitation of reducing ambient PM exposure. The health benefits may be subtle or only apparent after years or even decades.

When asked about her perspective on the Chinese government's response to air pollution, Wu was optimistic. She said, "China is in the middle of development and we have large-scale construction in the urban areas. It is very hard to prevent dust from forming. However, I feel that this is only temporary. The government is working hard to control dust emission levels of the factories. In recent years, the requirements regarding environmental protection have been strengthened and refined a lot. In my working experience, I have observed the level of outlet dust changing from 50 to 30 mg/m^3."

She continues, "In some areas where the requirement is more strict, I have seen 10 mg/m^3 in my projects. In addition, the level of traffic emissions has been more and more strictly controlled. According to the environmental protection agency's data, the air pollution level in Nanjing is alleviated from year to year, and the number of days when air pollution is mild increases continuously. I have the confidence that the air quality will be better in the future!"

Having experienced the air pollution in Beijing and Shenyang myself a number of years ago, I find her report encouraging. I will never forget the thick soup of air pollution I encountered in those cities. Frankly, it was a bit scary coming from the generally clear skies of New England. Robert Brook, a leading air pollution researcher from the University of Michigan, along with Sanjay Rajagopalan, wrote an editorial to go with the Chinese metabolomics study. In it he notes that indoor air filters and N95 face masks outdoors might offer an intervention that could save lives and improve health in heavily polluted environments. But, amazingly perhaps, he observed that, "there have been no large-scale randomized controlled outcome studies with hard cardiovascular end points [e.g., heart attack and stroke] to conclusively support the basis for any such formal recommendations" [9].

I would like to end this chapter with a plea that there be robust and fruitful efforts to both regulate air pollution and reduce it on a societal level while also assessing the efficacy of individual level interventions – home air filters and personal masks – and community-level interventions, which I will discuss more in the next chapter.

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Chapter 5
The Tiniest Particles: An Invisible Hazard

Lilian Calderon-Garciduenas began her work on tiny particles in the brains of dogs and children in Mexico City and has continued it more recently as a professor at the University of Montana. She was raised in a small town on the Gulf of Mexico by parents who were both physicians. Seeing her parents practice medicine and talking with them over dinner sparked her interest in becoming a physician. Amazingly, she was able to start medical school at the young age of 15. The following year, on her first day as a teaching assistant for the Chair of Embryology at the National University Medical School in Mexico City she was told she was in the wrong place. Having been mistaken as too young to be a medical student, she was told that the middle school was down the street. She did not let that stop her and after medical school went on to study at many universities across the US and Canada [1].

When I began working on ultrafine air pollution from traffic over a decade ago, I encountered the work of Calderon-Garciduenas and found one aspect of it particularly intriguing [2]. In her early work she had obtained and conducted detailed microscopic studies of brain tissues from dogs and children who had died accidental deaths in Mexico City. Of course the city was highly polluted and she compared the urban brains to brains from outside of the city where pollution levels were much lower. The observational nature of these studies and the small sample sizes always rendered them less than conclusive for me.

However, I could not help noticing one aspect of her data that was hard to explain away as being caused by something other than particulate air pollution and, specifically, the tiniest particles, ultrafine PM. In many of her photomicrographs from Mexico City children and dogs she observed tiny, dense black spots that she identified as air pollution particles embedded not only in the brain, but within cells within the brain. How did they get there, if indeed that is what they were?

It turns out that the presence of tiny particles from air pollution in the brain is not as farfetched as one might initially imagine. Running from the back of the nose into the brain is the olfactory nerve. This nerve provides a pathway by which particles can travel directly into the brain without having to traverse the lungs and blood

D. Brugge, *Particles in the Air*, https://doi.org/10.1007/978-3-319-89587-1_5

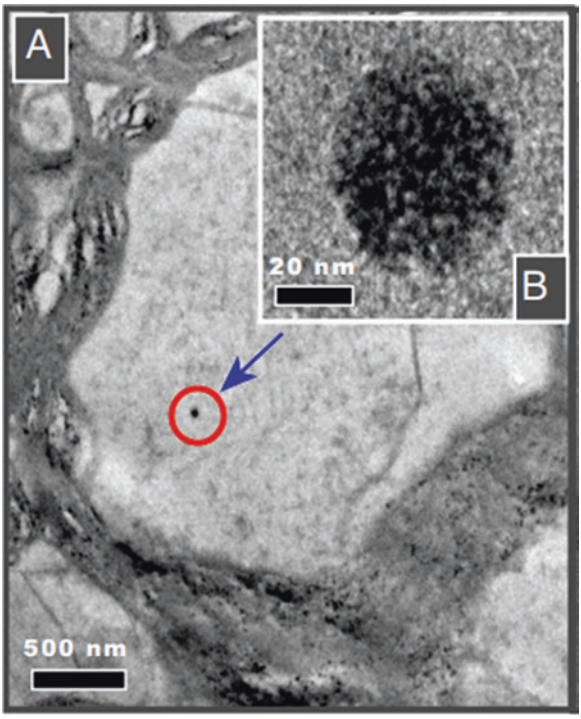


Fig. 5.1 A nano particle believed to be formed by combustion inside a cell in human brain tissue. (Source: PNAS)

stream or cross the blood-brain-barrier. I think most of the public and policy makers do not yet realize that particles could be going directly into the brain by this route of entry. They may also not realize that there is growing evidence that PM exposure affects brain and nerve function, including studies on elevated risk of developing autism for children and increased rate of cognitive decline in the elderly.

What I recently found convincing about her work was a high profile paper on which she was senior author that examined the tiny particles she was seeing in brain tissue in more detail. Published in a top line journal, the *Proceedings of the National Academy of Sciences* in 2017 [3], the aim of the study was to better understand the nature of these particles and where they might have come from (Fig. 5.1). It is worth quoting at length from the abstract of this truly impressive paper:

> [the particles] display rounded crystal morphologies and fused surface textures, reflecting crystallization upon cooling from an initially heated, iron-bearing source material. Such high-temperature magnetite nanospheres are ubiquitous and abundant in airborne particulate matter pollution. They arise as combustion-derived, iron-rich particles, often associated with other transition metal particles, which condense and/or oxidize upon airborne release. Those magnetite pollutant particles which are <200 nm in diameter can enter the brain directly via the olfactory [nerve]. Their presence proves that externally sourced iron-bearing nanoparticles, rather than their soluble compounds, can be transported directly into the brain, where they may pose hazard to human health [3].

When the US EPA first started regulating particulate matter the tiniest particles were not on the agenda. EPA, as I noted in chap. 4, initially focused on total sus-

pended particulates, or almost all of the particles in the air. By the 1980s, they had refocused on PM less than 10 microns (millionths of a meter) in diameter. And, again, as was presented in Chap. 4, in the 1990s emerging science, hotly contested by industry, led the US EPA to also regulate fine PM, or $PM_{2.5}$. The justification for concern about $PM_{2.5}$ included the fact that fine particles could make it deep into the lungs, while larger particles were mostly stopped in the upper respiratory tract. The obvious trend was toward greater concern as the evidence accumulated for the health risks of smaller and smaller particles.

To me it is not surprising then that in the last 10–15 years an additional concern has begun to emerge, a concern about particles even smaller than $PM_{2.5}$. These tiniest of the tiniest of particles are called ultrafine particles, or, hereafter, ultrafines. Ultrafines are particles less than 0.1 microns in diameter, or less than 100 nm in diameter. They are the combustion product cousins of manufactured nanoparticles that you hear are being put into all sorts of products these days. Nano means billionth, so the smallest of these particles approach being a billionth of a meter in diameter (see Fig. 1, Introduction).

Because ultrafines are so incredibly tiny, and invisible to the naked eye, we have to measure their presence in air differently from larger particles. The "large" particles can be collected on filters which are weighed before and after to obtain the amount of PM that was deposited on the filter. They can also be measured by electronic instruments that assess their weight in a volume of air. But ultrafines have so little mass, or weight, that measuring them this way is usually not possible. Instead, we use sophisticated (and expensive) instruments, typically condensation particle counters, to count the number per volume of air.

Counting ultrafines requires first growing them to larger size by making them absorb water or butanol, then counting the swollen particles with a laser. We usually report ultrafine concentrations as particles per cubic centimeter of air (a volume that is about the size of a sugar cube). A very clean environment, perhaps inside a well-sealed building with recirculation of air and a good filter in the ventilation system, might have a few thousand particles per cubic centimeter. A highly polluted area, next to a highway or in a highway tunnel, for example, might have 50,000–100,000 or even a million or more particles per cubic centimeter of air. These concentrations tend to vary rapidly and "spike" when, for example, a diesel truck passes by.

It might be surprising to learn that ultrafines, despite being a subfraction of $PM_{2.5}$, are usually distributed quite differently in the environment from $PM_{2.5}$. $PM_{2.5}$ tends to be a regional pollutant, which is why the Harvard study, described in Chap. 4, could use a single monitor in each city. The $PM_{2.5}$ levels spread out across each city and people living there receive similar exposures. But ultrafines vary much more on a small geographic scale as well as rapidly in time. As we will see, this makes assigning exposure to them quite challenging.

When Yifang Zhu reported in the journal *Atmospheric Environment* in 2005 [4] on the nature of ultrafine levels near the 405 freeway in Los Angeles, awareness of ultrafine particles was still low, even in environmental health circles. What she found, which would soon become a classic in the field, was that with a steady sea

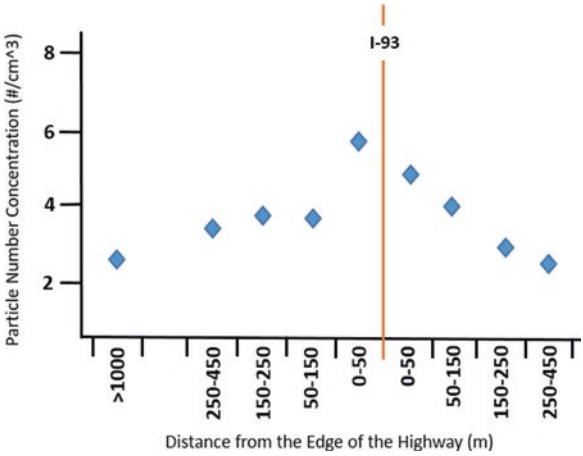


Fig. 5.2 Ultrafine particles are higher near a highway than farther away. Average levels of ultrafine particles are higher than the medians (50th percentile) because there are frequent very high levels of ultrafine in "spikes" of concentration. (From Brugge et al. [5])

breeze from the ocean toward the north-south running freeway, a clear gradient of ultrafines could be measured, with higher levels close to the freeway that dropped off substantially by about 200 m (an example of this effect from our research is shown in Fig. 5.2). The clear implication was that if you spent a lot of time near a source such as the freeway, by living there or driving on the roadway, you would be exposed to much higher concentrations of ultrafines than if you did not.

In fact, since Zhu's early work, there have been dozens of studies of ultrafine concentration next to highways and major roadways in many countries, including work my colleagues have done as part of our research collaborations in the Boston area. The picture that all this research paints is consistent with her work, although slightly more complicated, at least in part because not all locations have such a well-defined perpendicular wind direction relative to roadways as the location she studied. But, overall, it is clear that living next to or driving on major roads or highways results in higher levels of exposure to ultrafines than most other locations in modern cities in high income countries.

Studies of long term exposure to ultrafines were slow to be conducted because the concentration of ultrafines changes in space and time so rapidly, making it challenging to assign exposures. However, a robust literature on the risks of living near roadways has grown to maturity in the last two decades. What these studies show, conclusively in my opinion, is that living close to highways and major roadways is associated with a wide range of adverse health outcomes.

An infographic from the collaboration of air pollution researchers at the University of Southern California (Fig. 5.3) nicely and succinctly summarizes the health concerns across the life course for living next to high traffic areas. The health concerns begin during pregnancy and continue into infancy. Studies have seen associations with high blood pressure in mothers and low birth weight and premature birth in their babies.

For children and adolescents, the near highway focus has been on asthma and lung development, primarily because of the excellent work of the Children's

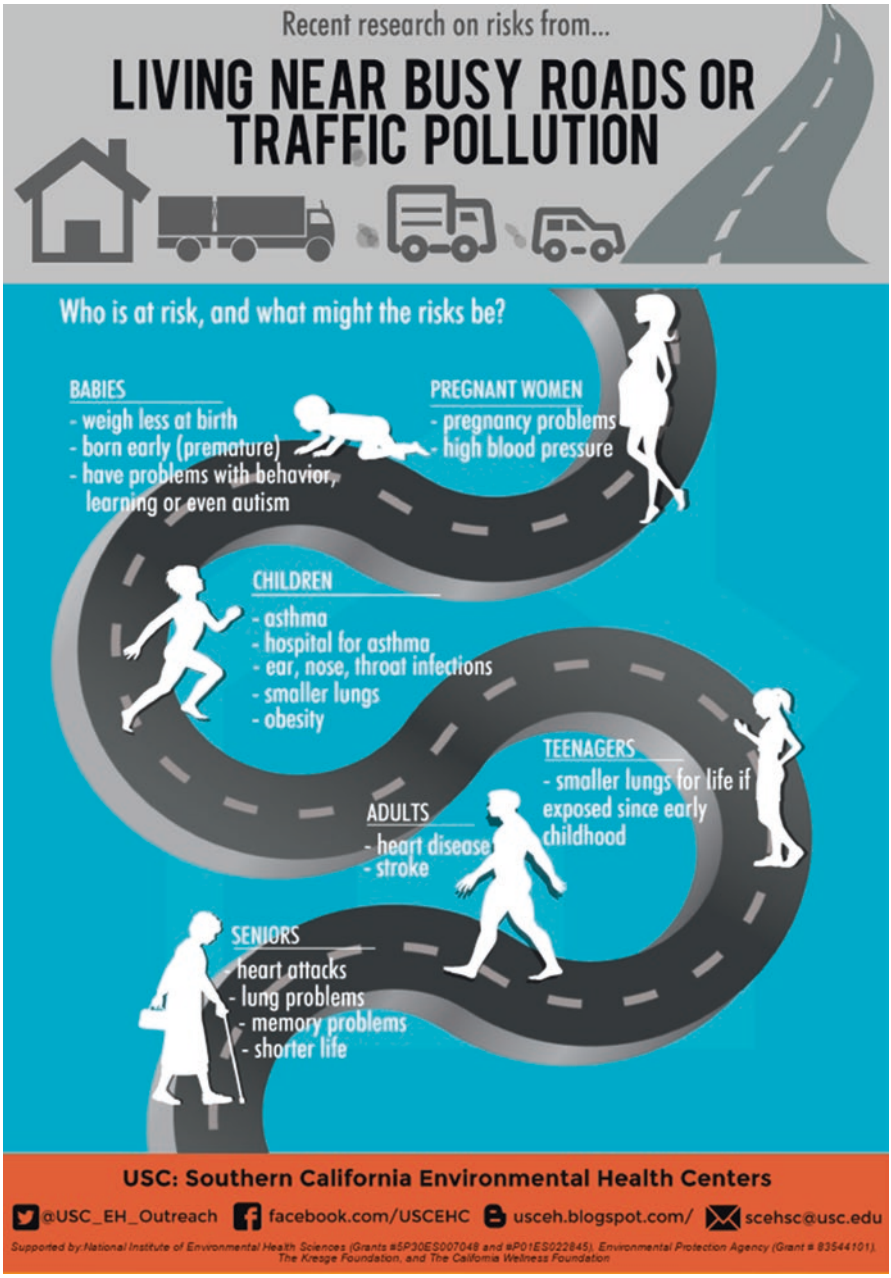


Fig. 5.3 This infographic from the University of Southern California shows the reported health effects of living near major roadways and highways across the course of life and aging

Health Center at USC. Children, especially girls, are more likely to develop asthma if they spend their early years next to a highway. And the lungs of children up through adolescence tend to be smaller if they live next to a highway. In adults, living near highways seems to advance heart disease leading to increased risk of stroke and heart attack as they advance into their older years. The elderly also have greater cognitive decline and shorter life if they have these traffic exposures.

But probably you have sensed that these associations are not sufficient by themselves. It is tempting to say that ultrafine levels next to highways might be responsible for the health outcomes reported to be elevated next to highways and major roadways. But that would be unscientific and potentially wrong. The easiest way to see the problem, in my opinion, is to consider what else might be elevated next to highways and roads besides ultrafines.

In addition to ultrafines, there are a slew of other pollutants, both gasses and particles, which are usually higher near traffic than farther away. Among the other pollutants found in high levels near traffic are black carbon which are larger PM particles, often called soot, that accumulate on surfaces as a black grime. Near-highway residents often complain about this accumulation on their windows and other surfaces. Gasses that are high near traffic include oxides of nitrogen and carbon monoxide. Separating out which of these pollutants are more or less responsible will take quite a bit of work. Although based on the existing science about PM, and the lack of biological plausibility, the gasses are unlikely to be contributors to cardiovascular risk.

In addition to the chemical and particle pollutants found in motor vehicle exhaust, the traffic generates substantial noise. The engines, braking and the movement of tires on asphalt all produce sound, plus at times there are sirens and other noises emanating from the traffic. In addition, there is meaningful evidence that sound exposures are associated with some of the same health concerns that USC listed on their infographic, including heart disease and impaired learning.

The really big hulking 400 pound gorilla in the room, metaphorically, is socio-economic status (SES), a somewhat imperfectly defined concept usually measured by education and income, but actually much more complicated. The situation with traffic proximity and SES is somewhat complex. There are, for example, high SES locations adjacent to heavy traffic, Manhattan comes to mind. Still, in many locations land near major highways and roadways is relatively inexpensive leading to preferential siting of low income housing closer to traffic and high income housing farther away.

Because SES is often lower next to highways and SES is also well established to be associated with adverse health outcomes, one has to be concerned that apparent associations between near roadway pollution and health might actually be due to underlying effects of SES, which is called “confounding” in epidemiology, as I noted in earlier chapters. Traditionally, confounding is addressed by controlling for variables of concern in statistical analyses. One often reads that a statistical association remained after controlling for sex, age, SES and other factors.

Given the highly coincident mix of exposures near highways and major roadways – air pollution, including ultrafines, sound and SES – one has to be thoughtful

interpreting near roadway association studies. Most of these studies control for multiple potential confounders, but the variables used to control for such factors are themselves imperfect, so there might be residual effects.

One way to gain confidence about the causal nature of an association is to conduct controlled exposure studies in humans or laboratory animals. These studies suffer from some limitations also, but they are different limitations from epidemiology. In controlled exposure studies, pollution levels are tightly regulated and extraneous factors such as noise, can be excluded. But human exposure studies are usually for only brief periods and usually with healthy volunteers for ethical and safety reasons. Animal studies can be lifelong, but the small animals used have relatively short lives and differ in their physiology in significant ways from human beings, leaving some doubt about extrapolation from the animals to us.

My favorite animal study of near highway ultrafine health effects was led by Jesus A. Araujo of the University of Southern California in Los Angeles. He and his colleagues placed mice in a vehicle 300 meters from the 110 Freeway for 5 h per day, 3 days a week for a total of 75 h of exposure. The mice were divided into three groups. One was exposed to air containing $PM_{2.5}$ concentrated from the outside air, another got ultrafines while a third got fully filtered air. The main limitation of the study is that the $PM_{2.5}$ mice were exposed to ultrafines as well as larger particles [6].

After exposure, the mice were sacrificed and the aorta, a major artery leading from the heart, was examined. What Araujo and colleagues found was that the mice exposed to highly filtered air had far less damage to their aorta. The type of injury that were looking at was what is commonly referred to as hardening of the arteries and technically known as atherosclerosis. It is basically development of fatty deposits on the artery wall that can lead to heart attacks and strokes.

To me, this study is strong evidence that the PM found next to highways is capable of causing harms associated with cardiovascular disease. We often talk about the plausibility of an association found in epidemiology studies. In this case, the evidence from animal studies greatly strengthens confidence that PM near highways and major roadways is capable of affecting cardiovascular health. Although it is also worth noting that the mice used were a special breed that is prone to developing fatty plaques in their arteries. For me, that does not lesson the relevance much since normal mice do not develop these problems while humans do.

A few years before the Araujo study, the *New England Journal of Medicine* published an epidemiology study by Annette Peters and colleagues from Ludwig-Maximilians-Universität in Munich, Germany [7]. Peters and her colleagues recruited people who had already had heart attacks. Nurses interviewed them about what they had done hourly for the 4 days prior to their heart attack. Thus, the point of the study was to look for things that the patients were doing in the time period right before they became ill that might have triggered their heart attack.

The key finding of this study was that people with heart attacks were about three times more likely to be exposed to traffic in the hour immediately preceding their heart attack than at other recent times. This suggests that something about traffic exposure might be triggering some of their heart attacks. The risks were similar whether they were in cars, on bicycles or on public transportation. The study design

that was used can be criticized because patients might have bias in their recall of what happened, although the statistical analysis tried to assess this and found little evidence for concern. It is also possible that being in traffic was stressful and caused the heart attacks or that physical activity associated with biking was the cause. Although not entirely ruled out in my opinion, the authors did what they could to exclude such possibilities and I think their results strengthen the case for hazardous health effects of near roadway pollution.

The third, and last, study that I want to briefly describe here was conducted by Nicholas L. Mills and his co-authors from Edinburgh University in England and also published in the *New England Journal of Medicine* in a similar time period [8] to the Peters study. It has long surprised me that the Mills study was even conducted. They exposed 20 men who had previous heart attacks to diesel exhaust and, alternately, clean air for brief periods in an exposure chamber while measuring how their hearts responded. My surprise comes from my own experience with research ethics review that is often hyper vigilant about risks to study participants that are far less than those in this study. But they did recruit only men with stable heart disease who had shown ability to do physical activity, which perhaps lessened concern.

Using an electrocardiogram, the test in which electrodes are attached to the chest that many of us have experienced, they found that when exercising, blood flow to the men's hearts was reduced, as expected. The interesting finding was that when the men were breathing air containing diesel exhaust blood flow was impaired more than when they were breathing clean air. Personally, I doubt this was truly double blinded since the men could almost certainly smell the exhaust, but I also suspect that this did not affect their findings.

What I hope that these three studies show is the need for evidence from different types of studies and different researchers to gain confidence about an association. Too often in the media associations are conflated with causation, which is jumping the gun. An association may, in fact, be causal, but it could also be that confounding or exposure error or other issues have created an association that is not as simple as it seems and that could even be wrong. What the evidence, which is far larger than just these three studies, suggests to me about ultrafines is that it is highly likely, but perhaps not yet proven, that they cause illness and death in human populations.

The case for ultrafines was less clear in 2005 than it is now when I was first approached by activists from the City of Somerville, which is just north of Boston, Massachusetts where I have my office. Their initial concern was one of several lawsuit that they had filed to try to influence development of the Assembly Square area next to Interstate-93, which runs through their city. They wondered whether I might be an expert witness and testify about the hazards of air pollution.

A key initial meeting between representatives of the Mystic View Task Force, as they called themselves, and me was held in the Tisch Library on the main Campus of Tufts University, just across the Somerville city line. Attending were Wig Zamore, about whom I will say more as this story unfolds, Don Meglio, who became the project manager on our first grant, and Bill Shelton. Zamore took the lead arguing their case. For me the critical point was that as they talked, as well as afterward when I looked into the literature more deeply for myself, I found their

perspective grounded in science and credible, even if I did not agree with everything that they said.

Having had a long history of working with affected communities, both earlier as an organizer and activist and more recently as the university partner to community-based participatory research collaborations, I was open to helping them out. Ultimately, while providing some technical assistance on their case, the lawsuit never went to trial as it was settled in their favor before going to court. The legal settlement was impressive, as it created a prescribed development and shared vision for Assembly Square. It also included the first new Massachusetts subway stop in 30 years, increased public open space and river access, bike and pedestrian connections to several adjoining neighborhoods, a cap on vehicle traffic as well as on large scale retail. It had a requirement for smaller local retail on-site and greatly increased non-retail jobs creation.

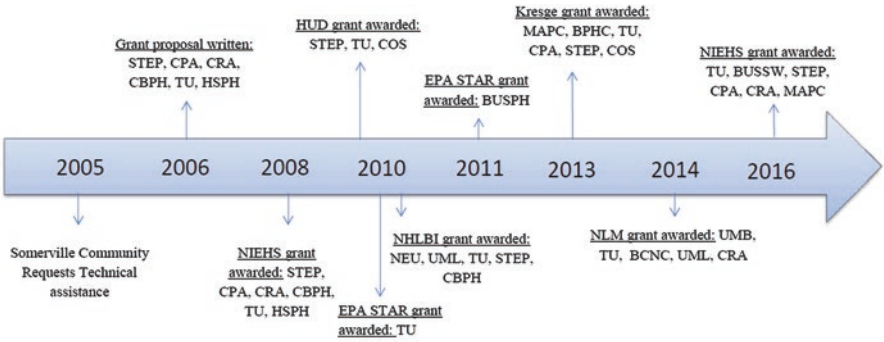
Subsequently, Zamore had a conversation with Ellin Reisner, President of the Somerville Transportation Equity Partnership, which was focused on transportation issues in their community. Reisner, who would go on to be another key partner in our research on ultrafines, suggested that perhaps Tufts, and me, would be good partners to conduct research. She felt that their homegrown, less rigorous, and unpublished data analyses were not enough to drive policy and that they should seek to do higher quality studies.

Over the coming months, we pulled together a collaboration and wrote a proposal to NIH for a study of near highway ultrafine particles and health. I brought in additional Boston-based community partners, the Chinese Progressive Association from Chinatown and the Committee for Boston Public Housing from Dorchester that represented neighborhoods also situated next to major highways. Zamore introduced me to a Tufts colleague I had not previously known, but with whom he had previously worked, John Durant, who was from the engineering school. Durant would lead our air pollution monitoring and modeling work.

Funding from what was then a startup, the Tisch College Community Research Center at Tufts (TCRC), gave us a critical boost in preparing the proposal. I had founded and continue to direct TCRC as a project within the Jonathan M. Tisch College of Civic Life at Tufts. Our primary mission is to promote research partnerships between faculty and students at Tufts and community-based organizations, primarily in the neighborhoods immediately adjacent to the university's campuses.

Together our newly minted research team identified a key missing link in the science at the time. We observed that there was copious evidence that living near busy roadways and highways was associated with adverse health outcomes. We also noted that ultrafines were elevated near high traffic lanes (along with other pollutants), but that there was no direct evidence that ultrafines were responsible for the near highway health effects. We submitted our proposal to a call from the National Institute for Environmental Health Research, the same agency that had funded the Harvard Six City Study in Chap. 4, for projects that employed community-based participatory research.

We were assisted immeasurably by Zamore's self-taught knowledge of the literature and his amazing recall of its content. He recently reminded me that in the



BCNC = Boston Chinatown Neighborhood Center; BCPH = Boston Public Health Commission;

BUSPH = Boston University School of Public Health; BUSSW = Boston University School of Social Work;

CBPH = Committee for Boston Public Housing;

COS = City of Somerville, CPA = Chinese Progressive Association; CRA = Chinatown Resident Association;

EPA STAR = Environmental Protection Agency Science to Achieve Results;

HSPH = Harvard School of Public Health; MAPC = Metropolitan Area Planning Council; NEU = Northeastern University;

STEP = Somerville Transportation Equity Partnership; TU = Tufts University: Medicine, Engineering & Tisch;

UML = University of Massachusetts in Lowell; UMB = University of Massachusetts in Boston

Fig. 5.4 Timeline and partnerships for the CAFEH study. (Modified based on [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5334703/])

course of our efforts to develop the grant proposal, he attended a key conference, the Ultrafine Particles: The Science, Technology, & Policy Issues Conference, in Los Angeles. There he heard from many leading ultrafine researchers and brought back what he learned. In fact, he was the one to suggest we focus on the blood biomarker C-reactive protein as our key outcome, which turned out to be a good choice.

Our first submission received a good score, but was not funded. One critique was that I had not previously had any major NIH funding, although I had had major grants from other federal agencies. To address this, we asked Jack Spengler, of the Harvard study in Chap. 4, to join us so we would have a senior NIH-style investigator. He graciously agreed and with him on board and many other revisions to our proposal, we were funded in 2008 for 5 years. That grant was the first of many for what became known as the Community Assessment of Freeway Exposure and Health studies (CAFEH; Fig. 5.4; https://sites.tufts.edu/cafeh/), a name I came up with while driving on the highway past affected neighborhoods in Somerville.

Findings from the CAFEH studies continue to emerge, but the main outcome of the original study has been published and can be briefly described. However, before I do that, let me say that the success of this study was anything but certain even after it was funded. Early on we found we had less funding than we needed when we ran into a serious financial shortfall during our work in Boston Chinatown, our final neighborhood. Willingness to share difficult rebudgeting decisions, together with fellowships from the US EPA obtained by two of our graduate students almost cer-

tainly saved us. That and hard work, dedication, perseverance and a few rolls of the dice going our way might have made the difference between success and failure.

One reason that I found Smith's story so compelling in Chap. 1 was that we lived, and in many ways continue to live, a miniature version of his experience with everything being harder than expected, taking longer and being at almost constant risk of failure. No one had tried to assign exposure to near highway ultrafines before. We had to figure it out on our own. This proved quite challenging because, as noted above, ultrafine concentrations change rapidly in space and time while the people we enrolled in our study were also moving around from place to place.

Research conducted by three PhD students – Allison Patton, Christina Fuller and Kevin Lane – who published in over a dozen academic papers over half a dozen years was necessary to accomplish our goal. Essentially, we had to recruit people living close and far from the highways, survey them and obtain samples of their blood. At the same time we had to drive a mobile monitoring lab around the study areas repeatedly, analyze the resulting data and build statistical models that predicted ultrafine levels at 20 m resolution for every hour of a year.

After we adjusted participant exposures based on when and where study participants spent their time, we were able to test associations of their assigned exposure with blood biomarkers, such as CRP, which predict or indicate risk of cardiovascular diseases like heart attacks and strokes. When we did that, in a paper published in the well respected journal *Environment International* in 2015 [9], we found that people with higher exposures to ultrafines also had higher levels of the biomarkers in their blood. We controlled for key potential confounders such as SES and body mass index, so our results suggested that ultrafine exposure was causing inflammation.

In the year before our paper, three other studies came out that also found some evidence of associations of long term exposure to ultrafines and various health measures. To me, the combined weight of these findings increase our confidence that ultrafines might be causing health problems. However, these studies do not entirely close the case since all of the studies, including ours, found marginal associations in terms of statistical significance and the problem of correlation with other pollutants also remains. Nevertheless, I suspect the main limitation of these studies is that even with exacting attention to exposure assessment, a lot of exposure error remains which reduces associations.

One interesting issue that arises when working with community partners is that the community tends to jump ahead of the science a bit. Despite the limitations of the evidence that I have acknowledged, our community partners wanted to start doing something to reduce their exposure and the apparent risk. This has led us to develop and begin to test the efficacy of individual and community-level interventions. We have focused on the local level because ultrafines are not regulated federally in almost any countries (Switzerland being a rare exception), a situation that seems unlikely to change anytime soon.

It is an interesting problem to decide what level of evidence merits action to address an environmental problem. Obviously, the stronger the evidence, the greater the impulse to respond. But also, the greater the cost and the less clear the remedies, the lower should be our enthusiasm. Parties that stand to incur substantial costs, as

we saw with fine PM and tobacco smoke, are often willing to fight back and resist regulation quite vigorously, even when the evidence is quite strong.

As I noted, our focus has been local and to a lesser extent state responses. We have pursued three levels at which to intervene. The first is local and state policies that are aimed at reducing exposure for people living near highways or major roadways. The second is with architects, urban planners, designers and developers. We usually seek out these professionals to influence individual projects – a housing development, school or park – one at a time. The final level is the individual. Our focus on individual homes has been to install air filters and assess whether they reduce ultrafine exposure and also improve biomarkers of health.

In our efforts to develop policy, we have followed in the footsteps of the State of California and the City of Los Angeles. Long before we started down a path to inform municipal and state policy, the west coast had meaningful regulations on the books designed to reduce exposure to traffic-related air pollution. The State of California first restricted siting of schools within 500 feet of freeways. More recently, the City of Los Angeles required through its building code that housing within 1000 feet of freeways must have high end air filtering systems. The development of these regulations undoubtedly derives in part from the concentration of air pollution research at universities in Los Angeles and Berkeley.

With funding from the Kresge Foundation, we developed and worked with the City of Somerville, whose mayor, Joseph Curtatone, has been very supportive, to develop a zoning ordinance that would require protective measures in homes near the highway and major roadways in the city. Unlike California, Massachusetts has a state building code that prohibited us from amending the municipal building code. Since zoning cannot be prescriptive, our ordinance, still under consideration and not yet implemented, would require developers of housing next to highways and major roadways to show that they reduced ultrafine levels by 80% using whatever means they choose.

For the state legislation, we advised State Representative Denise Provost who wrote bills that would require a study of the issue by the Massachusetts Department of Public Health as well as require enhanced air filtration in housing and schools built next to major highways, somewhat analogous to the Los Angeles regulation. Her legislation has been released from committee and had a hearing, but still faces an uphill struggle for passage.

Our efforts to influence individual developments have had successes and failures and we continue to learn and apply the lessons to new developments, most often by promoting use of better filters in housing that has air handling systems. It is usually easier to add effective filtration to buildings with forced air heating and cooling than to buildings with only natural ventilation. However, rather than describe particular cases we worked on, I would like to briefly write about our experience with design charrettes (Fig. 5.5). Charrettes are interactive exercises developed by architects to generate and explore design ideas. They are freed of constraints of financial and other practical limitations in order to surface creative concepts.

We have conducted two charrettes and plan to do more. I'll give a quick sense of our first charrette and its impact. Over a day and a half we brought together archi-

Fig. 5.5 A design charrette conducted as part of the CAFEH study that was funded by the Kresge Foundation. (Photo: Doug Brugge, used with permission)

tects, urban planners, environmental researchers, community members and staff from municipal agencies. We presented an overview of the problem of near highway pollution and then gave them two proposed near highway developments to redesign. The result was an energetic and engaged process that was lively and productive.

The proposals which came out of our first charrette were rendered into professional illustrations by Jim Newman's group at Linnean Solutions, one of our partners. They included an innovative "living lung" design for an atrium at a proposed high school in the midst of highways next to Boston Chinatown and a hatch shell stage as a shield to protect a near highway park in Somerville (Fig. 5.6).

The school next to Chinatown was subsequently scrapped for reasons unrelated to air pollution, but not before the ventilation system was designed to maximize removal of PM from traffic. The park remains as it was today. But that does not mean that our process was a failure, quite the contrary. The people who attended the charrette were strongly influenced by the experience. The architect and the headmaster of the school remain engaged with us years afterward. A site in Somerville had our input as it was being designed and the city seeks our opinion about developments. A site in Chinatown chose better filtration based on our advice. I came away convinced that design charrettes are a powerful tool to engage the design and planning world around environmental health.

The third level of intervention that we have sought to develop is the use of stand-alone air filters in homes. These filters come in many types and already have a substantial market in the US and elsewhere (see the story from China in Chap. 4), although perhaps not so much for traffic generated ultrafines yet. Before our involve-

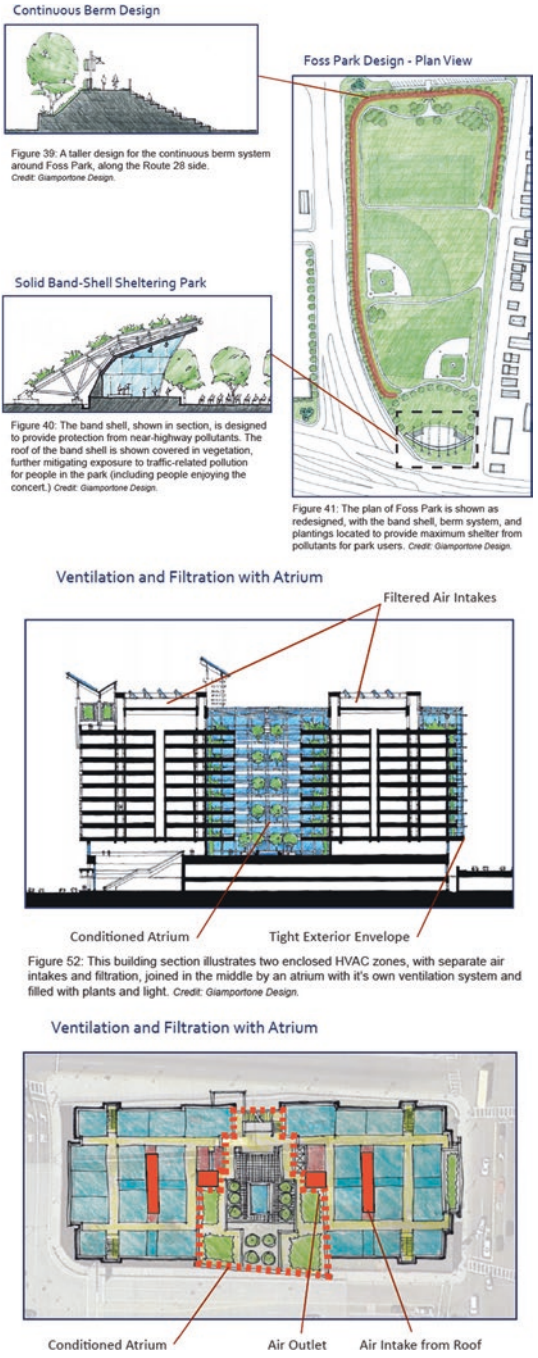


Fig. 5.6 Design ideas from a CAFEH study charrette. (Drawings by Linnean Solutions, Jim Newman Principle. Used with permission)

ment there had been numerous studies of home air filtration, often as an approach to improve asthma in children and frequently with low-income children living in less than ideal housing. In fact, many of these studies seemed to show benefits, which encouraged us to hypothesize that they would also be helpful for adults exposed to highway pollutants.

Accordingly, we ran two small intervention trials of air filtration in low-income homes, one in public housing next to the highway in Somerville, the other in homes of participants in the Boston Puerto Rican Health Study who were spread out across Boston and the City of Chelsea, which is just north of Boston and east of Somerville. But research does not always turn out the way you expect or hope, in fact that is sort of the point. If we could predict the outcome, we would not need to actually go to all the trouble and expense that is entailed.

We ran into two significant problems. First, we could not reduce the ultrafine levels as much as we hoped. This was due to the real world lives of our study participants interfering with our idealized expectation. They would open windows, short circuiting the benefits of their filters, and they would cook and burn candles (we excluded smoking households) generating indoor ultrafines in the process. Our second pilot was better than our first, but still we were reducing ultrafine levels by only 50–80% when we hoped for 80–90%.

Second, we saw no benefit on the blood biomarkers that we measured in our participants. As we looked into this farther, we began to realize that a significant problem was that participants might not be in the room with the filter enough of the time to benefit. The need for multiple filters in multiple rooms or for tracking more closely where participants spent their time arose as key lessons from our work. We still hope to run a larger randomized intervention trial that addresses the lessons we have learned. I hope it shows that filters are beneficial, but if it does not, that will be useful too, as it will suggest that these types of filters are not up to the task we have been giving them. I find myself thinking back to the long years Kirk Smith spent trying better cook stoves (Chap. 1) and wonder whether we are on a similar path and whether the solution might be something other than installing filters.

Working with filters to reduce ultrafine levels in homes teaches one a lot about how odd these tiniest of particles are. The thing to remember is that ultrafines are, in many ways, more similar to gaseous molecules in air than they are to larger particles. When large particles are traveling along with a stream of air and the air turns in a new direction, the larger particles might not be able to make the turn. This is because their mass carries momentum that cannot adjust to the change so that they slide out of line with the air stream. Ultrafines weigh so little that they are not subject to this effect and instead just turn along with the air stream.

When larger particles travel through a filter the fibers in the filter cause air to twist and turn repeatedly. As the air shifts directions, larger particles are deposited on the fibers as they fail to make the turns and instead hit the filter surfaces. This is called impaction. You might think that ultrafines are so small that they would just pass through filters, but it is not that simple. Because they are so small, ultrafines are affected by diffusion, the random movement of molecules in the air, which turns out to be another way to remove particles from air.

Diffusion is an effective mechanism for removing particles during filtration, although perhaps this is not obvious to the lay person. The reason diffusion works is that as air passes by fibers in the filter, the smallest particles move randomly within the air stream, sometimes moving to the side and making contact with a fiber. Ultrafines that touch a fiber in this way tend to stick and be left on the filter and thus removed from the air.

A problem arises for particles that are not small enough for diffusion to drive removal and not big enough to be removed by impaction. The result is that there is a sweet spot at an in between size for which filters are less effective. When I was studying industrial hygiene, the conventional wisdom was that it was 300 nm particles that were removed less well because they are too small for impaction and too large for diffusion. Today the evidence suggests that the minimum removal is around 100 nm, including the largest ultrafine PM.

The consequences of this problem for the best filters, called high efficiency particulate arrestance, or HEPA, filters is not entirely clear. These filters do remove the vast majority of PM. And there are many studies showing some health benefits of in-room air filtration. But there must be residual particles left in a narrow size range, albeit, probably at low concentrations. I think it would be worth researching the health effects of exposure to the particles that make it through filters. Perhaps they are just a minor problem since there are not that many of them, but it would be better to know than to assume.

In any case, for me at least, the argument for stand-alone filters to address PM that infiltrates from outside into homes without mechanical air handling systems, as is the case with most low income housing, is not strong yet. I hope such filters can be shown to be effective. A recent trial of filters on air conditioning units in Taiwan suggest they could be [10], but more research is needed.

I first met Barbara Cassesso and Dolores LaPiana when we were launching the CAFEH study. They attended a community breakfast that we hosted and said a few words at the restaurant in the shadow of the highway. Both of them were born, raised and lived their entire lives in the neighborhood of Somerville that came, during the course of their lifetimes, to be dominated by Interstate-93. They were there before there was a highway, they opposed it when it was about to be built and argued for mitigation once it was constructed.

When I interviewed her, LaPiana said that theirs was a, “very wonderful, neighborly neighborhood” from the start. It was, according to her, a great place to raise children and was family oriented. The area, which we now refer to as “States Ave.” was originally called the “Nunnery Grounds” based on a nunnery that existed there in the 1800s. She says it was known as “the most stable neighborhood in Somerville.”

In 1970 when they learned that the highway was being planned, LaPiana says they were, “not pleased, we were outraged that we learned so late about the plans.” She goes on to say that, “the neighbors were the last to find out.” And that an official who knew in advance had been buying up property to resell at a profit when it would be bought to make way for the highway.

Construction of the highway started in 1971 after they had lost their campaign to stop it, a campaign that included having a pro bono engineer propose an alternative design. They would have liked to see the highway depressed instead of elevated, a

shrewd choice in my opinion since a depressed highway would have dispersed pollution upward and reduced nearby exposure.

Cassesso describes a tragic accident that occurred in neighborhood during construction. The construction crews left a huge, unfenced hole that filled with water to which kids were attracted. While it might have looked shallow, it turned out that it was deep and, "two young neighborhood kids drowned." Casesso told me, "It had a terrible impact, as I say there was nothing to prevent all the children from playing in it." An East Somerville playground that is named Chuckie Harris Park was dedicated to one of the boys who died. Interestingly, a few years ago my community partner, Reisner, successfully advocated for moving the park away from the highway to reduce pollution exposure for children playing there today.

I wondered why Cassesso and LaPiana did not move after the highway was built. They were emphatic that while finances were an issue, that they also loved the people and the place too much to move. Cassesso says that she, "knew all along the dangers that were coming from the highway" and that she "thought the state would do something to mitigate, control some of the air pollution, put up some trees." LaPiana finishes her thought saying, "they [the state] just made promises and never did one thing."

They can recount over 20 people they know who have had cancer, including Cassesso, and wonder whether the highway pollution might be to blame. Today, the CAFEH project has begun working with local stakeholders and residents to consider the possibility of putting up a sound wall to reduce exposure in the near highway neighborhoods. How that will play out will not be known for years I think, but even if it succeeds, it will be another example of mitigation of PM exposure far too long in coming.

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Afterword

Not the whole story, yet

I hope this book, which is intentionally brief in order to try to make it accessible, has convinced you, the good reader, that PM is frequently denied the respect it deserves. My goal in writing this book was to raise awareness and expand the circles of people who know about the seriousness of PM impacts on health. I also sought to do so in a way that I hope, and only you can judge whether I succeeded, dug under the sometimes superficial and misleading way that science is too often reported in the media. I want critically minded people to have a better sense of how science works and the questions that it can and cannot answer. There is evidence and interpretation of evidence, but rarely unequivical hard "facts" that are too often casually tossed about. Yet, we have to make policy that is evidence based as best we can.

I would be remiss, however, if I left you, my faithful reader who made it this far into this book, thinking that what I presented was comprehensive. It is not. I choose the high points, the main and strongest themes that I could identify and I developed them into what I hope were reasonably accessible narratives. This book has only five short chapters. There is much more about each of the types of PM that could be told. But I did not want to write the kind of book, lengthy and technical, that only my colleagues would read. I had in mind someone who was perhaps college educated, but not trained in science.

If you, the reader, seeks more depth, and I would encourage you to start with the sources that I cited. One of the great things about our time is that finding material has never been easier. Even if you do not have access to a university library system, much of the literature I cited can be found open source and to the extent that I could, I have added links to open source versions of the primary sources I used. Also try Google. I find it amazing how often Google pulls up as the first choice exactly what I am looking for based on a few words or a short phrase.

I chose to highlight in this book the impacts of burning solid fuel indoors, smoking tobacco directly or as exposure to secondhand smoke, and breathing in ambient PM from fossil fuel combustion. I chose these types of PM because the evidence for their adverse effects is strong and together they comprise the largest environmental

D. Brugge, *Particles in the Air*, https://doi.org/10.1007/978-3-319-89587-1

health problem in the world as well as one of the largest public health problems overall. But these are not the only sources of exposure to PM.

Other types of PM that I have taken note of in my own observation and research include marijuana, candles, incense, fireplaces and cooking. In our work, which I briefly described in Chap. 5, on ultrafine particles, indoor sources of PM have complicated accurate assignment of exposure. Our interest is traffic-related ultrafines, but most of the homes in which we have worked also have notable, and sometimes dramatic, indoor generated combustion products as well. From my experience, cooking seems to be the most common indoor source. It is likely that the PM we see from cooking comes somewhat from gas flames on gas stoves, but mostly from the frying and burning of food itself on any type of stove.

An interesting anecdote was that one of our graduate students who had frequent sinus infections began to think about whether it was such a good idea that he and his wife burned candles frequently. His concern arose after experiments we conducted to measure ultrafines from a candle burned in his spare room. After he and his wife stopped burning candles he reported that his nasal symptoms cleared up. Clearly one anecdotal story does not constitute a scientific study, but given what I know about PM, I would not be surprised if the candle fumes were causing or aggravating his problem.

Which leads to one of the key points I would like to conclude with. PM is produced by combustion. We know that the composition of PM from different sources also differs in its composition, and hence probably also in its toxicity. But, I am doubtful that any PM produced by combustion is non-toxic. Why would burning tobacco as compared to marijuana be dramatically different in terms of the toxicity of the resulting PM in the smoke? I see no reason for any substantial distinction. Both are plant materials that are burned. True, they have different neurologically active agents in them – nicotine and cannabinoids – but that is independent of the nature of the chemicals that make up the bulk of the PM. Of course, as we have seen, PM carries with it potentially serious health risks independent of the psychoactive chemicals, as I hope was well demonstrated in this book.

Marijuana is an excellent case example because it is increasingly legalized and at the center of public debates about its benefits and harms. As a public health professional, I am a bit torn by the legalization controversies. On the one hand, I don't think drug use should be a leading cause of imprisonment and criminal records. On the other, I have deep doubts that smoking pot is harmless let alone unambiguously beneficial. While there is some evidence of value of marijuana as a treatment for some conditions, there is also, as I will briefly discuss next, evidence of some serious downsides. Why would anyone find that surprising? Most medications have adverse side effects. In too many cases once we learned more about a treatment, we even found that the side effects were worse than the benefits.

In 2017 the National Academies of Science released a report entitled, The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research [1]. In it they comprehensively review the evidence for benefits and harms of marijuana. They did report some therapeutic benefits of consumption of cannabis or cannabinoids, including pain relief, improved symptoms

for multiple sclerosis-related muscle spasms (with manufactured cannabinoids) and treating chemotherapy-induced nausea and vomiting.

But the National Academies report also pointed to both confirmed and developing evidence of serious adverse effects as well. Surprisingly to me, so much so that I am skeptical, they did not find evidence of increased lung or other cancers. Perhaps limited use limits cancer risk, but I doubt it eliminates the risk any more than secondhand smoke is risk free. While the academy reported evidence of triggering heart attacks, consistent with everything we know about PM generally, it is worrisome that so little research has been done on cardiovascular effects of smoking pot.

It is not surprising to me that the report found evidence of respiratory impacts of smoking marijuana, but they also report a need for more research into some outcomes. What is particularly disturbing though are the neurologically based outcomes that have been documented. These include increases in schizophrenia and psychoses, as well as anxiety disorders and depression. There is also evidence of cognitive impacts, most strongly shortly after use, but also possibly long term. Finally, more in line with the societal effects of alcohol consumption, there is evidence that intoxication while driving leads to increased risk of crashes and injuries and that having pot in the home contributes to inadvertent childhood poisonings.

Before concluding, I would like to touch on two of the themes that came up multiple times in telling the stories of the development of the science documenting harms and the backlash when that science led to regulatory restrictions aimed at reducing those harms. I noted with interest two articles, one an academic publication, the other in the *New York Times*, as I was finishing writing this book in the fall of 2017.

The first was a paper that listed Stan Glantz as senior author [2]. I know of Glantz from his prior work on the role of the tobacco industry's efforts to interfere with science and promote their deadly product. I was not surprised to see that he had moved on to look at the sugar industry and, again no surprise, that he found evidence that the Sugar Research Foundation had, in the 1960s and 1970s, surreptitiously funded a review article that somehow made its way into the *New England Journal of Medicine*. The role of the review was to deflect concerns about the role of sugar in promoting cardiovascular disease and encourage us to focus on fats instead.

My point is not to get into the discussion or debate about how bad for you consumption of sugar might be. Rather, it is to impress upon you how robust the pattern of industry interference in science is. We saw that in Chaps. 2, 3 and 4 of this book. These are not isolated or unusual instances. As recently as 2014, Volkswagen was caught having installed software on 11 million of its vehicles that helped them pass emissions tests, but let them emit high concentrations of contaminants otherwise [3]. This was blatant corruption aimed at getting around air pollution regulations.

I see no end to the conflict between the efforts to protect health based on scientific evidence of harm and the various ways that corporations will push back to protect their profits. To the extent that they do this as part of an honest public debate, I might not often be on their side, but I see such debate as healthy. However, if they sponsor tainted science or undermine, smear or block legitimate science, I think they are helping create serious societal problems and must be resisted.

Other well documented industry attacks on scientists included the work of Herbert Needleman whose work was on lead poisoning, the National Center for Injury Prevention and Control for trying to study guns as a public health concern, and the Agency for Health Care Policy and Research for questioning the value of surgery for back pain [4]. As was described in the *New York Times* at the end of 2017, lawsuits are another way that researchers are intimidated so that legitimate investigation that threatens powerful interests might be suppressed.

The *Times* article tells the story of a Harvard professor, Pieter Cohen, who confirmed a Food and Drug Administration analysis that some dietary supplements contained a stimulant that had the potential to cause cardiovascular harm. Cohen was sued for libel by one of the supplement manufacturers for $200 million. While a jury eventually found in his favor, Cohen was dragged through an excruciating legal case, a strategic lawsuit against public participation or SLAPP, that included examination of his research and drafts of his manuscript and diverted large amounts of his time and energy into defending himself. The lawsuit against Cohen was one of ten that went to court since 2000, with many others settled out of court.

My fear is that these lawsuits have as their primary purpose intimidating researchers from pursuing research that might affect powerful interests. A young scientist, or even a veteran one like me, has to honestly ask themselves, do I really want to put myself in harm's way? Am I sufficiently committed to following where the science leads and to put the public's health ahead of personal sacrifice? And every time a researcher shies away from studying a potentially important public health problem to instead work on safer, less impactful areas, the public and its health loses an ally and information that it needs.

Of course, the politics of science and public health are made all the more complicated because science is not infallible. As I noted above, we deal in evidence and interpretation, not cold hard, irrefutable facts most of the time. Often, as with indoor solid fuel combustion, $PM_{2.5}$ and tobacco smoking, the accumulation of evidence has reached a point that it is almost impossible to imagine the case ever being reversed. There will be adjustments to those stories, newly found health effects or changes to the dose response curves, but the main story will hold up.

For cases that are based on less robust evidence, secondhand smoke perhaps, or ultrafine where the science is just emerging, there is greater potential for surprises. Which raises the question of how much evidence is enough to prompt action to reduce or prevent exposures, as I touched on in Chap. 5. This is a fraught issue about which another entire book could be written. Environmental activists and advocates often call for action based on early evidence, a "precautionary" approach. Industries that would be affected by regulations, frequently want absolute proof and cling to any aspect of doubt to forestall action.

I often say that there is no scientific solution to this problem. The choices we make have to be based on the best understanding of the evidence that we can manage, but also need to be filtered through our values. How much risk and uncertainty can we tolerate? How much anger or sense of injustice is associated with the risk? What resources does it require to reduce the apparent risk? And so forth.

For me PM should be a high priority for policies and practices that reduce exposure for reasons that I hope are obvious at the end of this book. The science is robust, even overwhelming in many cases. The risks revealed by the science are among the largest we know in public health, up there with diet and physical activity. While some protective measures are costly for some industries – power plants, tobacco, auto – in my opinion the costs are well worth it given the consequences.

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