Shanghai is one of 74 cities that has yet to meet the air-quality standards set by the Chinese government.

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PREVENTION

Air of danger

Carcinogens are all around us, so scientists are broadening their ideas of environmental risk.

BY REBECCA KESSLER

In November last year, an eight-year-old girl became China's youngest person to get lung cancer. The cause, according to her doctor, was fine particulate matter that accumulated in her lungs and led to malignant changes in her cells. Air pollution has been enveloping Chinese cities in smog, periodically closing schools and businesses, and drastically reducing visibility.

A month before the girl's diagnosis, outdoor air pollution and one of its main constituents, particulate matter, were declared carcinogenic to humans by the International Agency for Research on Cancer (IARC). The announcement capped a decade-long review that examined the cancer-causing potential of several airborne pollutants, including dusts, solvents and metals emitted by vehicles, industry, farms, homes and natural sources.

Scientists have suspected since the 1940s that air pollution causes lung cancer, but it has taken seven decades of research to establish the connection. During that time it became clear that smoking causes most lung-cancer deaths (70% globally) and that air pollution kills more people through cardiovascular disease than through cancer. Nevertheless, air pollution's cancer toll adds up. Researchers blamed it for 223,000 lung-cancer deaths in 2010, nearly 15% of all such deaths. The IARC also noted evidence linking air pollution to bladder cancer[1].

"Everybody is exposed to it," says Aaron Cohen, an epidemiologist at the Health Effects Institute in Boston, Massachusetts, a research organization funded by the US government and the motor-vehicle industry. "You can't avoid breathing the air no matter who you are."

Scientists are making progress in understanding the effects of air pollution and other environmental carcinogens. They are learning that certain chemicals may increase cancer risk at lower-than-expected doses, that people may be particularly vulnerable during certain periods of their lives and that the consequences of exposure may cause ripples for generations. Researchers are also looking into environmental triggers that can lead to the onset of particular cancers. Although it is the quest for a cancer cure that draws the most funding and talent, a small but vocal chorus is calling for more attention to environmental carcinogens, in the hope that reducing exposure to them will help to keep the disease from starting.

The IARC has evaluated a total of 970 natural and artificial agents and identified 464 as having some level of carcinogenicity to humans. With some overlap, a catalogue by the US National Toxicology Program lists 240 substances as 'known' or 'reasonably anticipated' human carcinogens. Some cancer-causing agents occur naturally, such as aflatoxins — poisonous compounds produced by moulds that grow in nuts, seeds and legumes. Others are man-made, such as ionizing radiation from medical imaging and various commercial chemicals. Yet of the 80,000 chemicals in commerce, only a tiny fraction has been tested for carcinogenicity.

The proportion of cancers attributable to environmental carcinogens is subject to debate. The most widely cited estimate, made in 1981, attributes 2% of US cancer deaths to pollution

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and 4% to occupational exposures[2]. Those figures are dwarfed by the numbers for smoking and diet, which claimed 30% and 35% of the burden, respectively. But a 2010 report by the US President's Cancer Panel assailed the 1981 estimate and stated that "the true burden of environmentally induced cancer has been grossly underestimated"[3]. And a global estimate by the World Health Organization (WHO) is much higher: 19% of the world's cancers — and 1.3 million deaths annually — are attributed to environmental and occupational factors.

Even so, many researchers, charitable foundations and government agencies continue to underestimate the importance of environmental carcinogens, says Richard Clapp, an epidemiologist at the University of Massachusetts Lowell. "There's more to it than is generally given credence that environmental exposures are causing a portion of our cancer burden and that we can do something about it," he says.

Designating a substance as a carcinogen and making recommendations about its use can be controversial. For example, in 2011, the US National Toxicology Program listed formaldehyde, a chemical common in building materials and household products, as a carcinogen, and styrene, which is used to make plastics and rubber, as reasonably anticipated to be a human carcinogen[4]. Despite similar designations by the IARC and other agencies, industry groups such as the American Chemistry Council successfully advocated for a review of the report by the National Academies in an effort to get the chemicals delisted and avoid further regulation. The outcome of the review is expected soon.

A QUESTION OF QUANTITY

Research is painting an increasingly complex picture of how the body reacts to environmental chemicals. In the past two years, debate has peaked about the behaviour of endocrine-disrupting chemicals. A 2012 review[5] of more than 800 studies concluded that it is "remarkably common" for these chemicals to induce biological responses at much lower doses than expected, and for the responses to be non-monotonic — that is, for higher doses not necessarily to produce greater effects than lower doses. The assertion has huge regulatory implications because safety testing for most chemicals is done not at the low doses at which agents occur in the environment, but at high doses. The results are extrapolated to lower doses, a methodology that would be unsound if non-monotonic behaviour were widespread.

These phenomena have been highly contentious. The US Environmental Protection Agency (EPA) has concluded that non-monotonic responses do occur but are uncommon. Its draft report is currently under review by a National Academies committee. Even so, the WHO, the United Nations Environment Programme and the US Endocrine Society all underscore the importance of low-dose and non-monotonic responses.

Another idea gathering steam is that people are particularly vulnerable at certain times, such as during gestation, puberty and pregnancy, and after giving birth. For example, a study[6] on human prostate stem cells implanted into mice indicated that early-life exposure to low doses of the endocrine-disrupting chemical bisphenol A, which is used in the manufacture of food containers and drink bottles, may increase the risk of a man developing prostate cancer.

Human studies, too, support 'windows of susceptibility'. The Child Health and Development Studies (CHDS) have found that women who have high levels of polychlorinated biphenyls (PCBs) in their blood immediately after giving birth have a tripled risk of developing breast cancer nearly two decades later[7]. The pesticide DDT has an even greater effect[8].

Another CHDS study[9] found that mothers of sons who developed testicular cancer in their thirties tended to have had a suite of DDT-related compounds in their blood when they gave birth. It is now becoming clear "that those really early exposures and events in life could influence the health trajectory of a lifetime", says epidemiologist and CHDS director Barbara Cohn.

"We've got to stop pouring this carcinogenic stuff out into the economy."

Dozens of environmental chemicals are regularly detected in people. Figuring out how these mixtures influence the risk of cancer and other problems may be the most puzzling question for researchers. Most studies investigate the effect of just one chemical at a time, and even that is tricky. "It is very unlikely for us to unravel what we need to know about chemicals until we can understand the implications of mixtures," says Cohn. "We're just learning how to do this."

Looking ahead, Cohn says that she plans to study whether chemical exposures reverberate into the third and fourth generations; the first great-grandchildren of the women who originally participated in the study will soon be born. Rodent studies have shown that exposure to toxic agents can increase the risk of cancer and other illnesses not only in the exposed animal and its offspring, but also in its offspring's offspring — often as a result of epigenetic alterations to gene expression[10].

IARC director Christopher Wild has coined the term 'exposome' to describe every exposure a person experiences during his or her lifetime — including chemicals, infectious agents, diet, social milieu and more. To better understand what might trigger cancer, Wild suggests that researchers hunt for the hallmarks of exposures, for instance in metabolic products or the pool of RNA molecules transcribed in certain cells.

A promising advance is that the genomes of some tumours have been found to contain distinct mutations when the person has been exposed to particular environmental risks such as tobacco or ultraviolet light. "The tumour starts to reveal its own secrets of its origins," Wild says. Wild has spent three decades researching cancer. During that time, he says, "I don't think anybody's ever asked me: 'Have we found out how to prevent it?' It's always, 'Have we found a cure?'"

Moreover, Wild and others say, prevention efforts usually focus on lifestyle changes for which the individual is responsible, such as stopping smoking and eating well, rather than regulatory changes that would place the responsibility on companies or governments to protect people from exposure to carcinogens.

A CALL TO PREVENT

The IARC's *World Cancer Report 2014* notes that cancer rates are rising fastest in developing countries (see page S64) and that some of the latest treatments will be too expensive for most people to access. It calls for a renewed commitment to prevention, including legislation limiting exposure to environmental carcinogens. "It just seemed an obvious conclusion that you couldn't treat your way out of cancer," Wild says.

Clapp agrees. He points to the promise of green chemistry, the development of safe molecules and techniques to replace harmful ones. An example is replacing dry-cleaning that uses perchloroethylene (classified by the IARC as probably carcinogenic) with soap-based 'wet-cleaning'. Clapp also applauds the European Union's chemical regulation, known as REACH, which puts the onus on companies to demonstrate a chemical's safety before it hits the market. "We've got to stop pouring this carcinogenic stuff out into the economy so that people don't get cancer in the first place," he says

China has started to do just that with air pollution. But curbs on exhaust and industrial emissions and fines for polluters have not yet had much effect: just 3 of the 74 cities the government monitors have met air-quality standards. For now, some citizens resort to wearing face masks outdoors and running air filters in their homes — but that only goes so far. "To clean up the air — that's the solution," Cohen says. "It's not to make people sit in their houses or walk around with masks on." ■

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