RICHARD B. LEVINE/NEWSCOM

IMPOSED EXPOSURE Young women protest outside a clothing store that sprayed its retail space with perfume without shoppers' consent. They are worried that the fragrance contains hormone-disrupting chemicals and could trigger allergic reactions.

PERCEPTION PUZZLE

EMOTION AND TRUST play important roles in how the public views risks from chemicals

CHERYL HOGUE, C&EN WASHINGTON

IN YEARS TO COME, researchers are expected to tease out an increasingly detailed understanding of whether, how, and when exposure to specific chemicals can cause harm to humans or the environment. This expected onslaught of new scientific data could change the minds of people who view at least some products of the chemical industry as dangerous and to be avoided, say experts on how humans perceive risk.

Or it might not, they add. Human cognition "will take the facts and turn them into how we choose to feel about them, not some mythical objective, factual, everyone-agrees-on-it truth," says David Ropeik, a consultant on risk perception and author of two books on the topic.

Research demonstrates that information suggesting something can harm us carries more weight in the human mind than information suggesting a thing or activity is good for us, says Paul Slovic, a professor of psychology at the University of Oregon who studies risk analysis and is also president of Decision Research, a nonprofit research organization. A series of experiments by psychologist Daniel Kahneman, a Nobel Laureate in Economics, and Amos Tversky in the 1970s and '80s showed how people make judgments under conditions of uncertainty. They demonstrated that people strongly prefer to avoid losses over acquiring gains (*Amer. Psychol.* **1984,** *39,* 341).

Ropeik explains that this trait has been key to human survival through the millennia. This predilection means if people sense that using products containing a certain chemical could lead to harm, they will give it more weight than information suggesting the chemical is safe.

Unfamiliarity also heightens perceptions of risk, says Brian J. Zikmund-Fisher, assistant professor of health behavior and health education at the University of Michigan. For instance, people are generally unconcerned about familiar risks such as driving a car—an activity that is responsible for tens of thousands of deaths a year, he says. But people tend to have greater fear of risks associated with the myriad unfamiliar commercial chemicals used in products from smartphones to baby shampoo.

In addition, "we have strong ideological bents that color the way we react to information," Slovic says. People, by their very nature, associate with others who share their outlook on the world—such as distrust of government or of the chemical industry—and thus reinforce each other's standpoints, he says.

If people receive information that aligns with their views, they support it, Slovic explains. If the data go against their views, he continues, "they find ways to denigrate and reject it." For example, some who oppose greenhouse gas emission reductions frame the growing scientific evidence that links human activities to global warming as a ruse by climate researchers to get more money, Slovic says.

People also perceive risks that are under their control differently from risks that aren't, Zikmund-Fisher points out. "Imposed risks are so much worse in people's minds than things they choose to undertake voluntarily." Smokers are a prime example of this. They voluntarily accept risks of using cigarettes but likely would strenuously object if forced to work in a basement office containing radon—even if both posed the same risk of lung cancer, he says.

Then there's the issue of trust—or lack of it. "There's a lot of distrust of organizations and industries if you think these groups are trying to benefit at your expense or risk," Slovic says. For example, some people harbor negative feelings about the chemical industry, believing that it is focused on profits at the expense of the safety of its products.

WHAT'S WORSE, negative events—such as a catastrophic release of radiation from a nuclear reactor or evidence that a drug can cause birth defects—can destroy the public's faith in an institution or industry. "Trust is hard-earned, and it is quickly lost," Slovic says.

Yet improved communication about risk can help the public understand risk information better, says Baruch Fischhoff, professor of social and decision sciences and engineering and public policy at Carnegie Mellon University. Surveys show that the public views scientists as highly trusted sources of information, so scientists are prime candidates to communicate information about chemical risks, he says. That trust, however, can evaporate if scientists politicize their message by advocating on behalf of industry or activists or fail to acknowledge scientific uncertainties, Fischhoff warns.

"Imposed risks are so much worse in people's minds than things they choose to undertake voluntarily."

& VIDEO ONLINE **For short videos with Zikmund-Fisher explaining factors in human perception of risk, go to http://cenm.ag/riskper.**

Ropeik cautions that scientific data on risks are often complex and difficult to communicate. One result is that the growing body of information about chemical risks often seems to do more to worry people than to reassure them, Slovic says.

ONE CONCERN IS that much of the risk-related data expected to come forth in the years ahead will be from traditional toxicology studies done on laboratory animals, computational toxicology, and epidemiology. The data will provide a great deal more information about hazards of chemicals, Ropeik points out, but not about exposure to them in particular circumstances. Without sufficient exposure data to combine with hazard data, the risk equation isn't fleshed out.

Nonetheless, given the preponderance of hazard data, environmental and health advocates are likely to conclude that many commercial chemicals pose a greater danger than previously thought, he says. Chemical producers, on the other hand, are likely to point to the new information and declare that their products are less problematic than activists have alleged.

The chemical industry, Ropeik says, "is stuck in this mind-set that more information will lead to objective choice" by consumers about commercial substances. But, as has been noted, research suggests this isn't the case.

Social science research has mapped out successful strategies for communicating scientific information about risks, Fischhoff says. For instance, scientists need to respect the audience to whom they are presenting the risk information. "Anybody who starts on the premise that people are idiots is doomed to failure," Fischhoff says. "First, the audience will immediately pick up the disrespect." Second, scientists who discount their audience are unlikely to expend the energy needed to make risk information as comprehensible as possible, he says. Ultimately, this attitude will turn the audience away from the scientist and the message and toward people they trust—those they identify with politically.

Despite this evidence, many of those working in natural science fields, including chemists and physicists, have to date spurned these scientific findings, he points out.

Nevertheless, effectively communicating information about chemicals' risks is important to society's well-being, stress Zikmund-Fisher and Ropeik. Accurate information is essential so consumers can make the best choices among products, according to Zikmund-Fisher. Otherwise, he says, they'll simply shun items containing a chemical pegged as "bad" without considering the risks of substitute products they select instead.

"The danger," Ropeik says, "is that we're less informed than we need to be to make the healthiest possible choices." ■

GETTING REAL ABOUT CHEMICAL RISKS

PREDICTIVE MODELS for hazards and exposure improve, but gaps remain

BRITT E. ERICKSON, C&EN WASHINGTON

MANY PEOPLE ASSUME that the chemicals in their detergents, floor cleaners, and other household products have undergone rigorous safety testing. But little is known about the potential risks associated with most of the estimated 80,000 chemicals in commerce today.

While industry tries to dispel links to illnesses that go beyond what science can prove, the public is skeptical because companies have a financial stake in showing their products are safe. This leads both sides to look to the federal government for help.

The agency charged with overseeing the safety of chemicals in the marketplace is the Environmental Protection Agency. EPA has the authority to require industry to provide extensive toxicity data for pesticides. But for most other chemicals, EPA must show that a substance is likely to be a risk to human health or the environment in order to require industry to provide safety data. Manufacturers don't often give toxicity data to EPA voluntarily, nor does the agency have the resources to assess tens of thousands of chemicals using traditional in vivo rodent-based studies.

Instead, EPA has turned to computational modeling. One ambitious effort, called ToxCast, aims to screen thousands of chemicals for biological activity using about 600 high-throughput biochemical and cell-based assays. The data are then integrated with existing in vivo animal toxicity data and structure-activity information to predict toxicity.

But ToxCast has had problems. Most of the assays were developed for drug discovery, not to assess the hazards of chemicals in the environment. For example, thyroid-disrupting compounds in the environment can work through multiple pathways, but commercial tests focus on just one—a chemical binding to the thyroid receptor. If a chemical acts on a different pathway it will test negative, even though it does disrupt the thyroid.

EPA HAS HAD SOME SUCCESS in developing an alternative thyroid assay that monitors inhibition of the enzyme thyroperoxidase. EPA has also developed a few novel tests for other chemical effects that are not detected by current ToxCast assays. But with only $7 million to $8 million per year to spend on ToxCast, it has been an uphill battle.

EPA is also struggling to get a handle on how much of each chemical people are exposed to. The agency has even less data about exposure than it does about the toxicity of chemicals. Exposure information is important because assessing chemical risk is a function of both a chemical's toxicity and how much exposure individuals have to that chemical.

Efforts are under way at EPA to estimate exposure through a program called ExpoCast. But that program is just getting off the ground.

In contrast, the proof-of-concept phase for ToxCast was completed in 2009 when EPA scientists showed that ToxCast models could accurately predict the toxicity of about 320 data-rich pesticides. The agency is now completing the second phase of ToxCast, in which it screened another 700 or so chemicals using the same battery of high-throughput assays. This second set includes chemicals found in industrial and consumer products, food additives, and drugs that failed to pass clinical trials.

But as EPA considers using ToxCast data in regulatory decision making and risk assessments, it is getting a lot of pushback from industry and other stakeholders. C&EN recently visited scientists at EPA's Office of Research & Development (ORD) in Research Triangle Park, N.C., to find out why it is so difficult and taking so long to get the risk assessment community to accept high-throughput in vitro data as an alternative to animal-intensive in vivo studies.

One of the problems, EPA scientists point out, is the limited scope of effects covered by commercially available assays.

"When we first started this program, we didn't have the resources to do de novo assay development for relevant biologies, so we took off-the-shelf assays that seemed to have relevant biologies," says Tina Bahadori, head of EPA's Chemical Safety for Sustainability research program, which oversees the part of ORD responsible for ToxCast.

The ToxCast assays primarily screen chemicals for their potential to cause cancer and reproductive, developmental, and endocrine disruption effects. Some areas of toxicology are not addressed by commercially available assays, so EPA scientists have developed a handful of their own assays to help fill in the holes. In particular, they have developed high-throughput assays to evaluate thyroid inhibition, mitochondrial toxicity, neurotoxicity, and developmental effects of chemicals.

These EPA-developed "fit for purpose" assays are based on known adverse-outcome pathways. The assays rely on a mechanistic understanding of the way a chemical works, says Russell S. (Rusty) Thomas, director of ORD's National Center for Computational Toxicology, which oversees ToxCast.

For example, thyroid-disrupting chemicals are known to work through at least six pathways, and just one of those pathways involves the thyroid receptor. Some chemicals disrupt the thyroid by interfering with production of the enzyme thyroperoxidase (TPO) and do not bind to the thyroid receptor. Screening such chemicals with currently available assays that monitor receptor-specific binding would give a negative result.

To avoid such false negatives, EPA scientists are developing a high-throughput assay to screen chemicals for their ability to interfere with the TPO enzyme. They are also studying other enzymes involved in the other pathways of thyroid disruption as potential targets for future assays.

To build the TPO assay, the scientists used fractions of cells from rat thyroids. They also built a human version of the assay by cloning the human TPO gene and developing a cell line that expresses human TPO, says Stephen O. Simmons, a scientist at EPA's National Health & Environmental Effects Research Laboratory (NHEERL) in Research Triangle Park. "Once we analyze the rat data, we will repeat the studies using the human cell line," Simmons says.

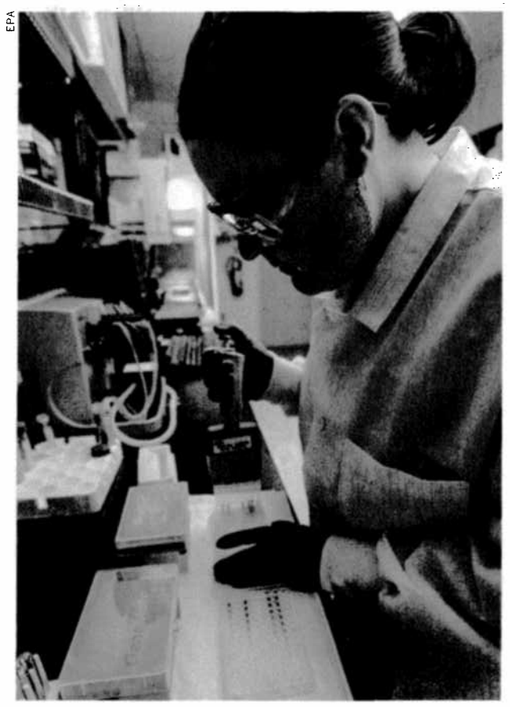
EPA IS ALSO INTERESTED in using the TPO assay in its Endocrine Disruptor Screening Program (EDSP). Thus far, the agency has tested the assay on 21 chemicals and gotten a few positive hits, Simmons says. The next step is to test 1,000 or so ToxCast chemicals and about 800 chemicals of interest to EDSP using the assay, he notes.

In contrast to thyroid toxicity, where much is known about adverse-outcome pathways, less is known about the pathways involved in developmental neurotoxicity. To better understand such effects, EPA is using high-content imaging. The approach allows researchers to obtain data on the size, shape, and location of hundreds of cells from a single image.

"We don't know all of the molecular initiating events involved in developmental neurotoxicity," emphasizes William Mundy, a neurotoxicologist at EPA's NHEERL. "So there may not be a target that you can measure a chemical binding to, and there may not be a gene expression assay you can use," he says. Instead, EPA researchers are using what is essentially an automated epifluorescence microscope to examine whether ex-

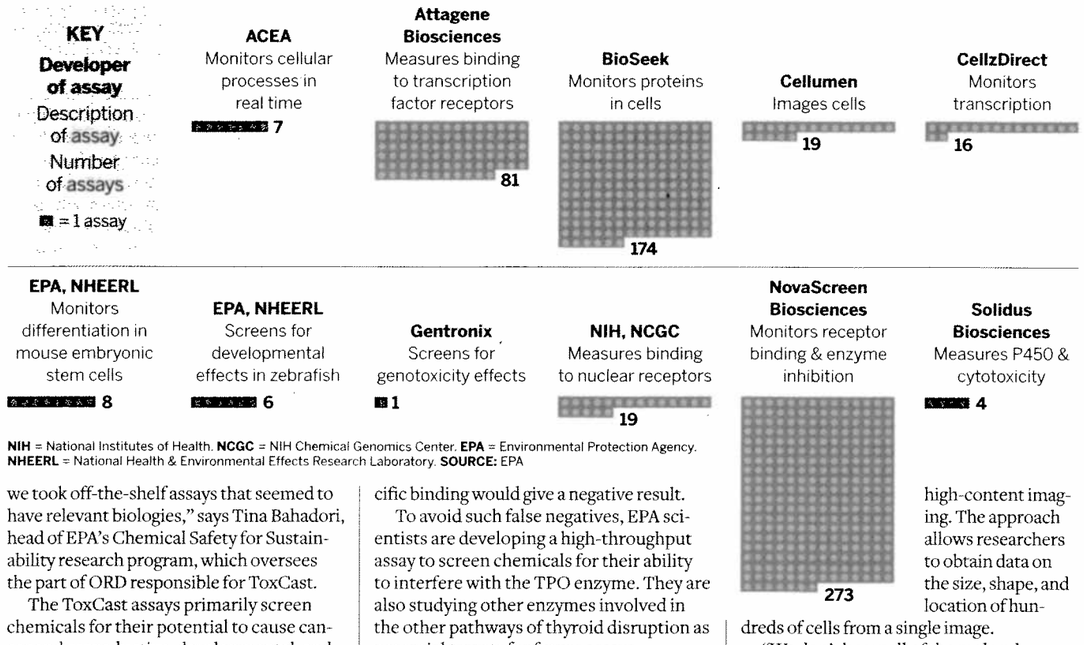
TESTING FOR DANGER

Scientists and the public have had trouble getting a firm handle on risk, creating scares and frustrations for everyone. In this three-part report, C&EN examines successes and failures in the latest attempts to assess chemical safety, different methods to ascertain public hazards, and why people perceive the results of risk studies so differently.


EPA

THYROID TEST EPA researchers are developing a high-throughput assay for evaluating whether chemicals inhibit the enzyme thyroperoxidase.

OFF THE SHELF Most of the assays used in ToxCast were created by pharma for drug discovery, not by EPA.



NIH = National Institutes of Health. **NCGC** = NIH Chemical Genomics Center. **EPA** = Environmental Protection Agency. **NHEERL** = National Health & Environmental Effects Research Laboratory. **SOURCE:** EPA

& VIDEO ONLINE Go behind the story in a video at http://cenm.ag/tox to learn more about EPA's lab in Research Triangle Park.

posure to chemicals changes how rat brain cells grow axons and form synapses.

Researchers at EPA are also taking advantage of microfluidics to create a network of individual cells that act as a functional neuronal network. The neurons are grown on chips, each of which has 64 electrodes. The cells are then exposed to various chemicals and their spontaneous firing rate and patterns are monitored.

IT IS LIKE AN "IN VITRO EEG," says Timothy J. Shafer, a toxicologist in EPA's Integrated Systems Toxicology Division at ORD. EEG, or electroencephalography, measures the change in voltage resulting from current flows within the neurons of the brain. But whereas an EEG records the average signal from many cells in a pathway, EPA's microelectrode array device monitors the electrical signal flowing through individual cells in a network. "The advantage is that you get an integrated response, not to one channel but to many different neuronal target proteins and ion channels," Shafer explains.

EPA is working with Atlanta-based Axion Biosystems to increase the throughput of the device. Rather than analyzing one chip at a time, the researchers have created a device in a 48-well-plate format. In each well is a separate network of neurons. And unlike typical cell culture plates, the wells are all connected by microelectrodes. The trade-off, however, is that as you increase the number of wells, you have to decrease the number of electrodes, Shafer notes.

Another major effort by EPA involves using zebrafish as model organisms to screen for developmental effects of chemicals. Zebrafish are a "wonderful model organism for what I'd call moderate-throughput assays," says Ronald N. Hines, associate director for health at EPA's NHEERL.

EPA researchers have already tested about 1,000 chemicals for developmental effects using zebrafish. The throughput is much greater than with traditional rodent-based assays, because zebrafish grow rapidly, from a fertilized egg to a fish in five to six days. And although the throughput is lower than that of cell-based assays, zebrafish have full metabolic capability. Such capability is lacking in many of the high-throughput ToxCast assays, Hines points out.

Zebrafish can be used to learn more about the effects of chemicals during development on a host of important biological systems. EPA researchers are using them to examine chemical effects on blood vessel formation, eye formation, heartbeat, and

"When it comes to chemical exposure, the action is within the home."

body shape. These systems are highly integrated, making them difficult to understand with cell-based assays, says Stephanie Padilla, a toxicologist at EPA's NHEERL.

Mouse embryonic stem cells, and in some cases human induced pluripotent stem cells, are also being used to evaluate the developmental effects of chemicals. In particular, EPA researchers have developed an assay to look at the effect of chemical exposure on differentiation of stem cells into different cell types.

"The amount of effort and time that goes into developing these different assays is huge," Thomas emphasizes. And even with the handful of assays that EPA has developed in-house, there are still areas that ToxCast does not currently address. One area, for example, is pharmacokinetics. "You may have a very potent chemical, but it may be cleared by your body in such a rapid fashion it may not matter," Thomas says.

Another area not addressed by ToxCast is variability in how humans respond to chemicals. "Some individuals or life stages are going to be more sensitive than others," says John Vandenberg, national program director of EPA's Human Health Risk Assessment research program within ORD.

In addition to ToxCast, which is focused on predicting the hazards of chemicals, EPA also has an effort to estimate chemical exposures called ExpoCast. "We haven't made as much progress on the exposure side as the hazard side," Thomas says. "Tools and data for estimating chemical exposures have been lacking, but I think that is starting to change," he tells C&EN.

The goal of ExpoCast is to develop computational models for estimating chemical exposures using data from epidemiology studies, retail information, and household consumption patterns.

"When it comes to chemical exposure, the action is within the home," says Timothy J. Buckley, director of EPA's Human Exposure & Atmospheric Sciences Division. "We spend a lot of time paying attention to the ambient environment. But we need to be focused on the chemicals that we bring into our homes, which tend to be chemicals in consumer products," he stresses.

Part of the problem is that EPA doesn't know all of the products that a particular chemical is in, or at what concentrations. To help fill in some of those data gaps, ExpoCast is using material safety data sheets posted by retail giant Walmart to extract information about what chemicals are in consumer products. Walmart has curated the data to include chemicals and concentrations across all products it sells.

EPA IS ALSO MINING other household product databases, such as the Nielsen Homescan program. In the Nielsen program, about 15,000 households across the U.S. voluntarily scan the bar codes of every product they bring into their homes. Nielsen has rich demographic data to accompany the consumption data, including household income, number of occupants, and ages. By monitoring purchase patterns within a home over time, EPA can determine use, Buckley says.

Google Trends is also being explored to map product use and intensity. For example, search terms such as personal care products, automotive, landscape and yard, and home maintenance have turned up data that could indicate trends in the use of consumer products across the U.S., Buckley notes.

EPA is using the consumer-use data to develop models for predicting exposure to chemicals in consumer products. It then calibrates the models with biomonitoring data from the Centers for Disease Control & Prevention's National Health & Nutrition Examination Survey.

In the end, the goal is to use the hazard and exposure information predicted by the ToxCast and ExpoCast computational models to help inform different types of risk assessments and decision making at EPA.

As a first step toward that goal, EPA plans to use ToxCast data to help prioritize which chemicals will be screened in its endocrine disruptor program. ToxCast data may also be used in the near future to help managers at Superfund sites decide which chemicals to look for and to set cleanup goals, Vandenberg says.

But it is likely to be a long time before EPA stops using in vivo animal studies, particularly to support risk assessments, such as its Integrated Risk Information System assessments, Vandenberg says. "The goal is to position ourselves to use fewer animals and have more information," he notes. "But we are not there yet." ■

CENTER FOR ENVIRONMENTAL RESEARCH & CHILDREN'S HEALTH

SPOT-CHECK A researcher conducts a neurological assessment of a girl as part of a study to gauge the impact of environmental exposure to flame retardants.

RISK BY ASSOCIATION

Scientists often start with an **OBSERVED LINK** between chemical exposure and a health risk, then design studies to confirm it

STEPHEN K. RITTER, C&EN WASHINGTON

YOU ARE WHAT YOU EAT, so the saying goes. But now that expression isn't so simple. Synthetic chemicals are increasingly entering our bodies through our food and drink and our material surroundings. On top of that, scientific studies are showing that exercise, sleep, stress, and social support affect our biochemistry. Yet the human machine is so complex that any specific beneficial or harmful effect stemming from diet or lifestyle can usually only be guessed at.

So why do we care? Most people already know that eating and living well have a bearing on one's state of mind and overall health. But that doesn't switch off our appetite for wanting to know more precisely whether something we consume or might be exposed to is healthy for us or whether it is going to give us heart disease or cancer, or make our kids hyperactive.

Newspapers, magazines, and Internet reports bombard us with stories on association studies that link a cause, such as exposure to a ubiquitous chemical, with an effect, such as obesity or Alzheimer's. Advocacy groups often are quoted invoking the precautionary principle and suggesting that for public benefit the food or consumer product containing the suspect chemical should be avoided. And the chemical industry typically points out that the proven usefulness of the chemical outweighs unproven health or environmental risks. With those divergent points of view, it's difficult to make sense of the findings.

Behind the scenes, scientists are looking more carefully at the associations and using them to guide the design of more definitive studies to solidify the cause-effect link. How researchers start with a simple association and work beyond it is a lesson in the scientific method—forming a hypothesis and then testing predictions to find proof. Meanwhile, regulatory agencies weigh the scientific evidence at hand and new scientific evidence as it becomes available to determine safe levels of exposure and whether a problematic substance should be banned or not when the answer isn't obvious.

The process isn't perfect. A guiding principle underlying risk assessment is that causality can't be proven early—usually it can only be inferred with different degrees of certainty. That constraint doesn't, however, prevent informed decisions from being made in the absence of absolute certainty.

The associations prompting the headlines typically come from epidemiology studies in which scientists sift through piles of collected data—they are often called data-mining studies. These studies have long been a cornerstone of public health research by suggesting targets for preventive medicine and clinical studies. They usually have limited value in that they gather cross-sectional data, which is to say a snapshot of data at one moment in time. Analyzing the data presents a chicken-egg problem, as one doesn't know if the outcome being considered came before or after the associated exposure.

One of the most popular data sets for such studies is the National Health & Nutrition Examination Survey (NHANES), a program of the Centers for Disease Control & Prevention. NHANES was established in the 1960s to assess risk factors that may increase the chances of developing a certain disease or reproductive/developmental problem. It is now bulging with information from blood and urine tests, personal interviews, and survey forms. Researchers typically look broadly at the data set or select individuals on the basis of demographic information and look for an association of interest.

FOR EXAMPLE, one recent study of 766 12- to 19-year-olds found a strong association between the urinary concentration of the phthalate DEHP, which is used as a plasticizer in food packaging and medical equipment, and insulin resistance, a condition that frequently leads to diabetes (*Pediatrics* 2013, DOI: 10.1542/peds.2012-4022). Globally, diabetes is increasing in young people, and the research suggests environmental exposures to potentially causative substances such as DEHP should be minimized.

Researchers can't make any claims about whether DEHP actually leads to diabetes later in life, but the data point to a concern nonetheless. To complicate matters, reverse causality is a possibility. That is, higher levels of DEHP in the teenagers might only be a biomarker for a bad diet—the packaged foods they eat might be the sole culprit. Or it could be something else entirely.

The next step in the research progression might be an observational study in which the investigators observe the subjects over time and measure their outcomes. These types of so-called longitudinal studies are more powerful than data-mining because researchers can confirm that the exposure preceded the outcome. In the DEHP case, scientists would monitor diet and health and see how many of the study participants actually develop diabetes.

To confirm the cause-effect relation-

ship, researchers might then conduct a more rigorous interventional study, a type of clinical trial in which they treat the research subjects with a particular intervention, such as a specialized diet to follow. The treated subjects are then compared with members of a control group, who make no changes.

Medical researcher Dean Ornish of the University of California, San Francisco, who directs the nonprofit Preventive Medicine Research Institute, is known for such clinical intervention studies. For more than 30 years Ornish has carried out research showing that comprehensive lifestyle changes involving diet, exercise, stress reduction, and social interaction can delay or even reverse the progression of heart disease, early-stage prostate cancer, and other health conditions (*Proc. Natl. Acad. Sci. USA* 2008, DOI: 10.1073/pnas.0803080105). Ornish says his body of work is showing that lifestyle changes can moderate gene expression—turning on disease-preventing genes and turning off genes that promote diseases.

Ornish recently led a team that found that lifestyle changes can promote production of telomerase, an enzyme that lengthens and repairs telomeres. Telomeres are DNA-protein complexes that cap the ends of chromosomes to protect them, similar to the plastic tips on shoelaces. As telomeres wear out, they can start to affect cell division and how quickly cells age and die. Shorter telomere length is associated with an increased risk of age-related diseases, including prostate and other cancers, heart disease, obesity, osteoporosis, and diabetes.

IN WORK WITH UC San Francisco colleague Elizabeth H. Blackburn, who received the Nobel Prize for her telomere research, Ornish's team compared two groups of men—with and without lifestyle intervention—who had been diagnosed with low-risk prostate cancer and who had not undergone conventional treatment with surgery or radiation (*The Lancet* 2013, DOI: 10.1016/s1470-2045(13)70366-8). The researchers measured the length of the men's telomeres at the start of the study and again after five years. In the group that made the lifestyle changes, Ornish says, telomere length increased by an average of 10%, but in the control group, telomere length decreased by an average of 3%.

Although the study shows a cause-effect relationship and provides a plausible mechanism, there are still too many variables and potential biases to determine a precise cause-mechanism-effect chain with a strong degree of certainty. For that reason, the results are still being viewed cautiously by the medical research community.

A guiding principle underlying risk assessment is that causality can't be proven early—usually it can only be inferred with different degrees of certainty.

To make the case for such cause-effect observations and pin down a mechanism, scientists turn to toxicology research studies, using lab animals or human cells to determine whether the suspected causative agent actually leads to the purported beneficial effect or disease when introduced to a healthy organism. Toxicology also has a broader role in testing new drugs and chemicals to determine possible toxicity without any known association. But harmful effects revealed in lab tests often don't correlate to harmful effects in people, because the biochemistry is not the same or the dosing is not proportional to what people experience.

For example, toxicology studies in the late 1960s suggested that the artificial sweetener cyclamate caused bladder cancer in rats. The Food & Drug Administration banned cyclamate in the U.S., but it remained available elsewhere. The artificial sweetener saccharin, which was around before cyclamate was discovered, had also been under scrutiny for possible toxicity. In the early 1970s, saccharin was also associated with bladder cancer in lab rats. Saccharin was not banned in the U.S., but products containing it were required to carry a warning label. Over time, there's been no strong evidence to support the idea that cyclamate or saccharin causes cancer in people. Cyclamate is still banned in the U.S., but saccharin was delisted as a possible carcinogen in 2000.

The case of artificial sweeteners points to a difficulty when it comes to evaluating risk: Risk assessment and risk management are two different but linked activities.

"Risk assessment is concerned with the nature and quality of the evidence describing a toxic effect, and it should describe the uncertainties surrounding the evidence," explains toxicologist Paul Illing, a former U.K. government scientist and now a risk assessment consultant based in England. "Risk management is the decision-taking process associated with evaluating the evidence concerning the risk, the public attitude to the risk, possible control processes, and the costs and benefits of the decisions."

With risk management, Illing adds, there may be a need to proceed in the presence of limited evidence of causation if the effect is likely to be serious—that is, to apply a form of the precautionary principle as a way to overprotect everyone until more definitive data are available. "But this requires that the right cause is being managed," he says. "When the effect is mediated by some other cause, the precautionary principle's application will be, at best, ineffectual."

BISPHENOL A, phthalates, and flame retardants are now in a similar pickle as artificial sweeteners. Among these examples, flame retardants, which are used in clothing, electronics, furniture, and building insulation, provide a good case study.

Epidemiologist Brenda Eskenazi and environmental health scientist Asa Bradman, cofounders of the Center for Environmental Research & Children's Health at UC Berkeley, have been leading studies designed to determine how exposure to pesticides, flame retardants, and other chemicals can impact human health.

Eskenazi and Bradman's study participants are part of the Center for the Health Assessment of Mothers & Children of Salinas (CHAMACOS, which in Spanish means young children), a long-term study group of nearly 600 primarily Hispanic women and their children living in California's agricultural Salinas Valley. When starting out, the research team looked at existing toxicological studies to help determine which research questions they wanted to ask. Some of their early work has revealed links between polybrominated diphenyl ether flame-retardant concentrations in the blood of the women and decreased fertility, changes in thyroid hormone levels when pregnant, and low birth weight.

The scientists are currently tracking the link between exposure to flame retardants and early childhood neurobehavioral development, childhood obesity, and other outcomes. Their most recent published results, on neurobehavioral development, have found that children with greater exposure to flame retardants have lower IQ, shorter attention span, and diminished fine motor skills compared with national averages (*Environ. Health Perspect.* 2012, DOI: 10.1289/ehp.1205597).

The researchers measured flame-retardant levels in the blood of some pregnant women and later in their children. The children were then evaluated at ages five and seven with a battery of standardized tests to determine their motor and cognitive skills. The physical tests were supplemented with surveys completed by the mothers and teachers on behavior, learning ability, and attention span.

IT IS AT THIS POINT, when it comes to pinning down the exact cause of the observed effects, that risk assessment research loses traction. "Epidemiological studies are observational," Bradman says. "What we are doing is assessing the exposures and pathways to exposure. In our data analysis, we use statistical methods to control for other possible chemical exposures, so we are able to more confidently home in on the independent health effect of flame retardants."

The team is now looking for a possible mechanism to cement the cause-effect relationship by conducting DNA methylation epigenetic studies on flame-retardant exposures in cells. But the biggest challenge in epidemiological studies, Bradman continues, is that people are exposed to a mix of synthetic chemicals, and individuals are susceptible to the exposures to different degrees. Scientists need more direct proof to verify that a chemical or set of chemicals causes the observed effect. "But we can't go out and intentionally expose children to a chemical and see what happens," he says.

To begin to take a hard look at causality and determine an acceptable level of use of a substance, Eskenazi says, the neurobehavioral study must be checked for consistency with multiple other studies, including other study cohorts. It also needs to be consistent with animal toxicology data and evaluated on the basis of the strength of the dose-response relationship. The work has to be considered as part of the overall weight of evidence to determine what any policy steps would be, she says, such as determining a threshold level of exposure to ensure safety.

To that end, the UC Berkeley team discusses its results in meetings with federal research and regulatory agencies, fire-safety officials, insurance industry groups, and chemical manufacturers—mostly outside the public eye. "We talk about the exposure data and the potential risks and fire safety," Bradman explains. "This is where the information from our studies really gets vetted and used."

"For me as a consumer, not as a scientist," Eskenazi adds when summing up her thoughts about risk, "I always consider what the downside is. What would happen if I didn't have flame retardants in my couch? Would I go up in a puff of smoke? If yes, then we need flame retardants. And if I wouldn't, then why am I being exposed to something I am suspicious of, even if the science on the risk is not definitive?" ■