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TOXIC COCKTAIL

By Bijal Trivedi

Today, and every day, you can expect to be exposed to some 75,000 artificial chemicals. All day long you will be breathing them in, absorbing them through your skin and swallowing them in your food. Throughout the night they will seep out of carpets, pillows and curtains, and drift into your lungs. Living in this chemical soup is an inescapable side effect of 21st-century living. The question is: is it doing us any harm?

There are good reasons to think that it might be. Not because of the action of any one chemical but because of the way the effects of different components combine once they are inside the body. As evidence stacks up that this "cocktail effect" is real, regulators around the world are rethinking the way we measure the effects of synthetic mixtures on health.

Environmentalists have long warned of this danger, but until recently there was no solid evidence to confirm their fears -- nor any to allay them. Most toxicity testing has been done on a chemical-by-chemical basis, often by exposing rats to a range of concentrations to find the maximum dose that causes no harm. It's a long way from gauging the effects of the complex mixtures we experience in everyday life, and that could be a dangerous omission.

"When you get a prescription the doctor will ask what else you are taking, because they are concerned about drug interactions, which everyone knows can be quite devastating," says Shanna Swan, director of the Center for Reproductive Epidemiology at the University of Rochester in New York. This also happens with chemicals like pesticides and endocrine disrupters, she adds. "You have to consider their interactions, and we are just starting to do that."

To assess the risk posed by such mixtures, a small number of scientists in Europe and the US are now testing chemical brews on yeast, fish and rats. The effects could be additive, or they might be synergistic -- that is, greater than the sum of the parts. They could even cancel each other out. Finding out is important, because we don't have enough data on many compounds to anticipate how they will interact when mixed. Other researchers are probing for associations between disease in humans and past exposure to groups of chemicals.

Andreas Kortenkamp, an environmental toxicologist at the School of Pharmacy, University of London, and his colleagues developed an interest in these mixture effects after they noticed a rise in endocrine disorders, suggesting that the body's hormonal systems may have been disrupted. In men there were increases in congenital malformations like hypospadias -- in which the urethra is on the wrong side of the penis -- and cryptorchidism, a

condition in which the testes fail to descend into the scrotum. There was also a rise in testicular cancer and lower sperm counts. In women there were more breast cancers and polycystic ovaries.

These increases posed a conundrum for the researchers. When they examined people who had these disorders, and their mothers, they found they had only very low levels of the chemicals that are known to cause the disorders; in the lab, only much higher concentrations of these individual compounds have been found to produce the same effects. This led Kortenkamp to suspect that mixtures were the missing link. He wondered if the effects of different chemicals, acting through the same biochemical pathway, could add up.

Kortenkamp's group focused on groups of chemicals called xenoestrogens, compounds that disrupt the activity of the hormone oestrogen and induce the development of female sexual characteristics. High levels of xenoestrogens in the environment have been shown to feminise male fish, and have even driven one species in an isolated experimental lake in Canada almost to extinction.

In 2002 Kortenkamp and his colleagues tested a mix of eight xenoestrogens on yeast. These included chemicals used as plasticisers, sunscreen ingredients and others found in cooling and insulating fluids. In the mixture, each was below the level that toxicologists call the "no-observed-effect concentration" -- the level that should be safe. Sure enough, the combination triggered unusual effects in the yeast. Kortenkamp and his colleagues dubbed the mixture effect "something from nothing" (see Diagram).

Kortenkamp and his colleagues found that if the doses of all eight chemicals were simply added together, after adjusting for the varying potencies, this new cumulative dose could be used to predict the effect -- a principle called "dose addition". "This result was to be expected, but it had never been shown with endocrine disrupters until our work," says Kortenkamp. Intuitively this makes sense, he says: "Every mixture component contributes to the effect, no matter how small."

Since then the effect has been shown with other species, too. Kortenkamp and his colleagues now report that mixtures of xenoestrogens feminised males to varying degrees even though the individual components should have been harmless. In July this year the team showed that a blend of anti-androgens -- chemicals that block the effect of male sex hormones -- can work in the same way. They exposed pregnant rats to two common fungicides, vinclozolin and procymidone, and the prostate cancer drug flutamide, and then screened the male offspring for reproductive deformities. At higher doses, each of these three chemicals wreaks havoc with sex hormones, and they all do it via the same mechanism: they disrupt male development by blocking androgen receptors and so prevent natural hormones from binding. The researchers found that even when the chemicals were used in doses that had no effect when given individually to pregnant rats, a mixture of them disrupted the sexual development of male fetuses.

Earl Gray, an ecotoxicologist at the reproductive toxicology division of the US Environmental Protection Agency's Health and Environmental Effects Research Laboratory (HEERL) in Research Triangle, North Carolina, and his team also tried exposing pregnant rats to vinclozolin and procymidone. When they exposed the animals to the compounds individually, they too saw no effect. But when they combined the two, half of the males were born with hypospadias. Gray calls this phenomenon "the new math -- zero plus zero equals something".

Gray then tried the same experiment with phthalates -- the ubiquitous compounds that are used to soften plastics and thicken lotions, and are found in everything from shampoo to vinyl flooring and flexible medical tubing. They also disrupt male development, in this case by stopping the fetus from making testosterone. The mix of two phthalates that Gray used caused many of the same effects on male rat fetuses as a mixture of vinclozolin and procymidone.

It makes sense that chemicals targeting the same pathway would have an additive effect. But what about mixtures of chemicals that work via different mechanisms? Surely the individual doses of such chemicals would not be additive in the same way.

"The mixture of different chemicals shouldn't have had any effect. But it did" In 2004, Gray and his team put this to the test by mixing procymidone with a phthalate at levels that, on their own, would produce no effect. Because the chemicals work via different routes, he expected that the combination wouldn't have any effect either. But they did. Then the team mixed seven compounds - - with four independent routes of action -- each at a level that did not produce an effect. "We expected nothing to happen, but when we give all [the compounds] together, all the animals are malformed," Gray says. "We disrupted the androgen receptor signalling pathway by several different mechanisms. It seems the tissue can't tell the difference and is responding in an additive fashion."

All of this is throwing up problems for regulatory agencies around the world. Governments generally don't take into account the additive effects of different chemicals, with the exception of dioxins -- which accumulate to dangerous levels and disrupt hormones in the body -- and some pesticides. For the most part, risk assessments are done one chemical at a time.

Even then, regulation is no simple issue. First you need to know a chemical's potency, identify which tissues it harms and determine whether a certain population might be exposed to other chemicals that might damage the same tissue. Add in the cocktail effect and it gets harder still. "It is a pretty difficult regulatory scenario," admits Gray. "At this point the science is easier than implementing the regulatory framework."

Mixed up inside

For one thing, with many mixtures it's almost impossible to work out how

much we're getting. The endocrine disrupter diethyl phthalate, for example, easily escapes from plastics and is in so many different products -- from toothbrushes to toys, and packaging to cosmetics and drugs -- that it would be difficult to work out the aggregate exposure from all sources, says Gray. This also makes it tricky to investigate possible links between chemical mixtures and disease. "Everyone has exposure to chemicals, even people living in the Arctic," says John Sumpter, an ecotoxicologist at Brunel University in London. "We can't go to a group with a mixture of nasty chemicals and then go to another who have had no exposure and compare their rate of breast cancer risk or sperm count. We are doing a scientific experiment by letting these chemicals accumulate in our bodies, blood and wildlife."

That's why some researchers are suggesting new ways to gauge the effects of chemical mixtures on the body. For example, rather than trying to identify levels of individual xenoestrogens in a patient's blood, it may be more efficient to take a serum sample and determine the "oestrogenic burden" being imposed on their body from a variety of different sources by testing the sample on oestrogen-sensitive cells in the lab. "It might work well as a screening tool to identify people with potential problems," says Linda Birnbaum, director of the experimental toxicology division at HEERL. Then, for example, you could make cocktails of foods, water and other products from the person's life to try to identify the source of the chemicals.

Nicolas Olea, a doctor and oncologist at the University of Granada, Spain, is already trying this kind of approach. He is exploring whether exposure to chemicals with oestrogenic activity leads to genital malformations like cryptorchidism and hypospadias in men, and breast cancer in women. He and his colleagues took samples from various tissues and measured the ability of the environmental contaminants in them to trigger the proliferation of lab-cultured oestrogen-sensitive cells. Because it is difficult to predict from a compound's structure whether it might have oestrogenic effects, a cell-based assay like this is a cheap way to screen potentially harmful chemicals. They found that the higher this "total effective xenoestrogen burden" the greater the chance the contaminants could disrupt oestrogen-dependent processes.

Others are cautiously optimistic about Olea's approach. "The concept is correct, I cannot comment on how well the cell effect tracks a cancer effect," says James Pirkle, deputy director of the US Centers for Disease Control's Environmental Health Laboratory in Atlanta, Georgia.

Shanna Swan is doing something similar. In a study published in 2005 she showed that boys whose mothers had had higher levels of five phthalates while their babies were in the womb had a shorter distance between the anus and genitals -- a marker of feminising activity. They also had higher rates of cryptorchidism compared to sons of mothers with lower phthalate levels. Swan devised a cumulative score to reflect exposure levels to all five phthalates and found that score was "very predictive of ano-genital distance".

The method is still expensive, and a regular "phthalate scan" isn't on the cards just yet. A potentially less costly approach, says Pirkle, is regular

biomonitoring of subsets of the population to measure the levels of dangerous chemicals in blood and urine, and link particular chemicals to specific health effects. Every two years since 2001, the US Centers for Disease Control has published data on the US population's exposure to a range of potentially harmful chemicals. In 2005 the agency released data for 148 chemicals; next year it plans to release a report covering 275. While that number falls far short of the number of new chemicals entering the fray each year, Pirkle says that technology is making it ever easier to monitor new substances. The reports do not consider specific mixtures but include exposure data for each individual chemical to make it easier to calculate the likely effects of mixtures.

The European Union, meanwhile, is taking steps to control the number of chemicals being released in the first place. On 1 June its REACH (registration, evaluation, authorisation and restriction of chemical substances) regulations became law. The aim is to cut health risks associated with everyday chemicals by forcing chemical manufacturers and importers to register their compounds and provide safety information to the new European Chemicals Agency, based in Helsinki, Finland. This information must be provided before the chemicals are sold. The new law shifts the burden of responsibility for the health effects of chemicals from government to industry and is also intended to encourage the use of less harmful alternatives for the more toxic chemicals.

Not everyone is so worried about the cocktail effect. Some researchers even find it reassuring -- or at least not as bad as it could be. Kevin Crofton, a neurotoxicologist at the EPA, explored how a mixture of 18 polyhalogenated aromatic hydrocarbons found in electrical equipment, flame retardants and paints could disrupt thyroid hormone levels in rats. At the lowest doses of the mixture the effect on the levels of the thyroid T4 hormone was what you would expect from the principle of dose addition; at the highest doses the effect was twice that. "Some people would call that synergy," says Crofton, "but it is not a very big synergistic effect. It was a twofold difference."

He adds: "These results are quite reassuring because EPA's default to calculate the cumulative risk of mixtures is dose addition." Only recently, however, have scientists like Crofton been able to prove that this default is correct. "If it had been a 20-fold difference I would have said, 'Boy, the agency needs to look into how it is doing things.'"

Kortenkamp says that regulatory bodies seem to be starting to acknowledge that chemical-by-chemical risk assessment provides a false sense of security. In November last year around 100 scientists and EU policy-makers at the "Weybridge +10" workshop held in Helsinki concluded that mixture effects must be considered during risk assessment and regulation. The European Commission plans to spend more on probing the effects of environmental chemicals on human health.

For now, though, chemicals are an inescapable part of life. And while high-profile campaigns by pressure groups like WWF seek to alert us to what they see as the dangers of artificial chemicals, some toxicologists warn that they

may be overstating the case. "I think you need to be careful about hyping the risk," says Crofton, referring to stories in which individuals have been screened for several hundred chemicals. "When you say I have 145 chemicals in my body, that in itself does not translate into a hazard. You have to know something about the dose, the hazard and how all these chemicals can add up." Olea, however, suggest that it is sensible to be cautious. "If you don't know it is good, assume it is bad," he says.

Like it or not, the chemicals are with us. "People can't keep phthalates [or other chemicals] out of their air, water or food," says Swan. "Most people don't have the information or money to do these things." A more productive approach might be to tell people how to limit exposure to harmful substances and request better labelling from manufacturers. "We need to put a lot of money into figuring out what these things do in real-world scenarios and take regulatory action," she says. "Just like we limited cigarette smoke exposure, we'll have to limit other exposures."

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