Allegations of bias cloud conflicting reports on bisphenol A's effects

Bisphenol A is found in everything from plastic baby bottles to the liners of tin cans—and it may or may not be bad for you.

Since the mid-1990s, the estrogen-like chemical has been the focus of an escalating, ugly debate between two groups of scientists. One group has argued vehemently that the chemical is dangerous and must be banned even as the other, equally vigorously, has defended its safety.

In late July, a group of scientists published a report concluding that exposure to even low levels of bisphenol, particularly during development, can cause serious reproductive problems (*Reprod. Toxicol.*, doi:10.1016/j.reprotox.2007.07.005).

But less than two weeks later, an independent panel assembled to advise the US government expressed "negligible concern for adverse reproductive effects."

Damir Cudic

Hidden menace? Experts sharply disagree on whether bisphenol A, found in many consumer products such as baby bottles, is safe.

The public disagreement has incited accusations of bias on both sides and left consumers bewildered. Should they avoid the chemical? Or not?

"It's certainly confusing and I wish it weren't," says Michael Shelby, director of the US National Toxicology Program's (NTP) Center for the Evaluation of Risks to Human Reproduction, which convened the government panel. "According to the panel results, if there is concern, it's not great," Shelby says.

Critics have accused the government panel of industry bias, forcing the NTP in April to dismiss a contractor that had ties to the chemical industry. The US Environmental Protection Agency has also come under fire for considering scientists with conflicts of interest to assess the safety of acrylamide, a neurotoxin found in fried and baked goods.

Some experts also question the government panel's methods, in particular the decision to exclude as sources of information more than half of the 124 papers published on bisphenol A's effects on development.

"I was shocked," says Beverly Rubin, a bisphenol A expert at Tufts University in Boston. "[The review] was bizarre, sloppy and very arbitrary. They discounted a lot of very good work and then left in a lot of work that's not so good."

What's more, the panel accepted 70% of industry-funded papers, but only 30% of those from academia, notes Ana Soto, a developmental biologist at Tufts. "Why would they do that?" Soto asks. "It's mind-boggling."

Richard Chapin, a researcher at the pharmaceutical company Pfizer and chair of the advisory panel, denies allegations of industry influence. "We established scientifically valid criteria and then we held those up to each study in turn," he says.

Chapin says Soto and others may be too passionate to be scientifically rigorous. "This might be a case where people are putting advocacy before science," Chapin says.

Some of the uncertainty about bisphenol A is the result of a dearth of human studies, which have to last through the long lag time between exposure and any effects. The National Children's Study, scheduled to begin next year, aims to follow 100,000 American children from the womb until age 21, and will assess exposure to bisphenol A as well as to heavy metals, pesticides and other pollutants. But the first results won't emerge for at least five years.

The NTP is also not likely to have an official position on bisphenol A for at least six months. In the meantime, Shelby recommends that those consumers who are concerned should switch to bisphenol A–free alternatives, such as glass baby bottles instead of plastic, and fresh and frozen foods as opposed to canned goods.

Kimberly Thompson, a risk analysis expert at Harvard University, advocates that individuals become informed so that they can assess their own risk. "[But] it's very tricky," she says. "People really do rely on experts to understand whether they should or shouldn't be concerned."

Cassandra Willyard, New York

DDT's ability to repel mosquitoes trumps resistance, scientists say

The notorious pesticide dichloro-diphenyl-trichloroethane (DDT), maligned for decades because of its alleged effect on ecosystems, is highly effective at repelling mosquitoes that are resistant to it, according to a new study published in August.

Malaria prevention programs have chosen pesticides for their ability to kill—not deter—mosquitoes. But a pesticide that repels mosquitoes can also be used against those that are resistant to it, making it a more attractive option.

Faced with malaria's unrelenting death toll, particularly in Africa and in some parts of Asia, international agencies last year renewed support for DDT (*Nat. Med.* **12**, 870–871; 2006). The insecticide is now one of 12 recommended for indoor residual spraying by the World Health Organization's malaria program.

Anti-DDT campaigns launched by environmental groups in the 1970s had led the US and many European countries to ban the pesticide's use. Its return last year met with criticism from environmentalists and from scientists who noted that mosquitoes have developed resistance to the chemical.

The new study lays that latter criticism to rest (*PLoS ONE* **2**, e716; 2007).

"If the primary action of the insecticide is not to kill but to repel, then it can remain effective," says Richard Tren, director of Africa Fighting Malaria, a Washington, DC–based nonprofit health advocacy group that advocates DDT use and that publicized this study.

Based on the study, the researchers propose a new classification system for insecticides that considers their repellent, irritant and toxic effects.

In their work, the researchers studied DDT-resistant strains of *Aedes aegypti* mosquitoes, which transmit dengue and yellow fever, but not malaria. They looked at how the mosquitoes responded to three different insecticides: dieldrin, alphacypermethrin and DDT.

In huts sprayed with dieldren, 92% of mosquitoes that touched the chemical died. Mosquitoes exposed to alphacypermethrin became irritated after making contract with the chemical and quickly left the hut or died, effectively reducing the number of mosquitoes that can transmit disease by 61%.

Bone marrow transplant paper revives contentious debate on fertility

Are women born with a fixed supply of eggs that cannot be replenished? That is still an open question.

Scientists have sought answers with studies on mice, but after three years, the debate about whether mice can regenerate eggs is far from settled, and work from Jonathan Tilly's laboratory at Massachusetts General Hospital (MGH) continues to fuel disagreement in the field.

Tilly's group reported in 2005 that stem cells in the bone marrow replenish the egg supply in mice, suggesting adult females can make new eggs under the right conditions (*Nat. Med.* 11, 911; 2005). His results were met with widespread skepticism.

The following year, another group, also at MGH, showed that mice receiving bone marrow transplants failed to ovulate—or release from the ovary for fertilization—donor-derived eggs (*Nature* 441, 795; 2006), seemingly refuting Tilly's work.

Tilly's group has now come back with yet another study, reporting in August that bone marrow transplants restore fertility in chemotherapy–treated mice, but that the pups born are from the transplant recipient's own eggs (*J. Clin. Oncol.* 25, 3198–3204; 2007).

"I feel pretty darn comfortable that there is regeneration," says Tilly. "But the real point of this paper is to tell people that stem cell–based technologies do hold future promise for ovarian rescue."

A few formerly critical peers, such as Evelyn Telfer of the University of Edinburgh, concede that this work raises interesting questions, but note that how the transplanted stem cells might help ovaries without actually contributing functional eggs remains a mystery.

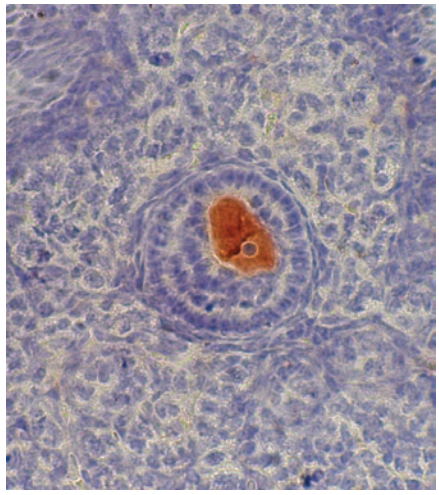
Critics chalk up the improved fertility to the transplanted cells restoring the recipient's overall health, or contributing a factor that helps eggs that survive the chemotherapy.

"[The new work] is inconsistent with Tilly's two prior papers, and there's no evidence that this idea [of regeneration] is not just a figment of one's imagination," says David Keefe, chair of obstetrics and gynecology at the University of South Florida in Tampa.

The high stakes—potentially overturning the long-held paradigm that female mammals are born with a fixed pool of eggs, and providing methods to preserve fertility—has led to particularly passionate arguments from both sides.

Tilly points to recent studies in mice that show no decline in egg numbers with age, and indicate that bone marrow–derived cells can generate sperm. Keefe and colleagues have in turn reported that adult human ovaries don't express genes involved in meiosis or oogenesis.

One finding from Tilly's work stubbornly remains unresolved: the identity of the donor-derived cells that make their way into recipient ovaries. Tilly argues that the cells are immature eggs that may somehow help support ovulation of the recipient's eggs.



Egg drop: A donor-derived cell (brown) is seen in the ovary of the bone marrow transplant, but it is unclear whether the cell is an oocyte.

Telfer agrees that the cells appear to be immature oocytes enclosed in a follicle structure, and that the 'helper cell' idea is plausible. But she stops short of supporting the idea of regeneration. "The [recipient eggs] are there from the start," she says.

Keefe contends that the donor cells may in fact be immune cells, cleaning up after chemotherapy-induced cell death, and have nothing to do with fertility.

Not surprisingly, Tilly rejects that suggestion. "The burden of proof our critics want is a moving target—it has morphed toward the point that unless we produce a baby, these cells aren't oocytes."

Still, Tilly admits that these cells may be peripheral to the restored fertility, and other transplanted cells could be involved in restoring signals that support the ovary's stem cell niche.

That's consistent with ovarian transplants that have restored natural fertility to the once-menopausal ovaries of human cancer survivors, says Kutluk Oktay, a reproductive endocrinologist at Weill Cornell Medical College in New York City.

"The ovarian transplant might provide the niche that the other ovary is lacking. A bone marrow transplant might be doing something similar," says Oktay. "This paper continues the discussion—it both confirms and refutes Tilly's earlier work. But that's how science works."

Kendall Powell, Denver

But DDT acted as a 'chemical screen', keeping 59% of mosquitoes out of the hut entirely. Combined with its moderate irritant and toxic properties, DDT reduced the number of mosquitoes that can transmit disease by 73%, the researchers found.

"If the house wall is sprayed with DDT, the mosquitoes will stop entering," says Donald Roberts, professor emeritus of tropical disease at the Uniformed Services University of the Health Sciences. "If they don't enter, they can't touch people while they sleep. In terms of disease control, it works beautifully."

Others, however, are skeptical.

The study did not measure how much DDT vaporizes, which would support the idea of its repellent power, says Gregory Lanzaro, director of the Mosquito Research Program at the University of California, Davis. DDT might keep mosquitoes out of some homes, Lanzaro adds, but they would still be able to transmit malaria in untreated houses or outside.

What's more, says Maureen Coetzee, chief of vector control research at South Africa's National Institute for Communicable Diseases, the researchers did not test mosquitoes that transmit malaria. "Mosquitoes will not all respond the same," Coetzee says.

Roberts says that DDT may be even more effective against *Anopheles* mosquitoes, which transmit malaria, because some studies have suggested that they are more sensitive to chemicals than are *A. aegypti*. "It's time to stop ignoring the repellent action of DDT," Roberts says.

Alisa Opar, New York