Environmental Toxicants Under Scrutiny at Baltimore Meeting

A record-breaking 4800 toxicologists met in Baltimore earlier this month for the Society of Toxicology's 34th annual meeting. The newly clean waters of the nearby Inner Harbor offered proof of potential economic payoffs from toxicological research, and against that background, conventioneers discussed topics ranging from the hazards of wood smoke and water chlorination to how PCBs interfere with thyroid hormones to produce hearing loss and giant testes.

PCBs Pack Hormonal Punch

Studying the properties of polychlorinated biphenyls (PCBs) is like opening one of those neatly carved Russian dolls: The closer you look, the more faces you find. However, in this case the faces aren't pretty. At the Baltimore meeting, researchers working with rats reported that PCBs, by interfering with hormones released by the thyroid gland, can cause hearing loss and enlarged testes. But they caution that more work is needed to understand their effects on humans and the interaction between PCBs and other environmental toxicants.

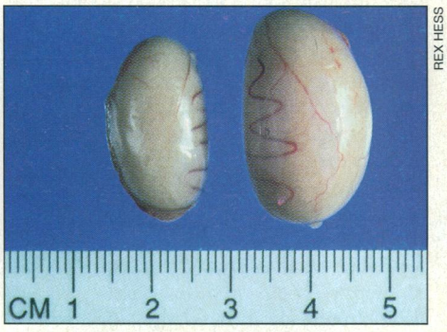
PCBs, a family of 209 related compounds, were widely used as industrial coolants before the 1970s, when they were found to cause liver cancer in lab rats. Despite a 20-year ban on their manufacture, these potent poisons remain in the food chain, where they have been accused of many deleterious effects, including mass deaths of harbor seals (*Science*, 18 November 1994, p. 1162).

Now scientists are probing how PCBs disrupt processes ranging from reproduction to cognitive development. University of Illinois researchers have found that, at least in rats, PCBs can act like a hormone—but with a surprising twist. Conventional wisdom says hormonelike pollutants suppress sperm production in lab animals and may have played a role in a global decline in human sperm count over the past half century (*Science*, 15 July 1994, p. 309). But some PCBs apparently don't fit this pattern. In a just-completed study, a commercial mix of PCBs fed to newborn rats actually boosted their sperm production and testes size. "It's an incredibly robust effect," says Environmental Protection Agency (EPA) reproductive toxicologist Earl Gray.

The unpublished Illinois findings, by reproductive biologists Paul Cooke and Rex Hess and colleagues at the College of Veterinary Medicine, grew out of an attempt to reconcile studies that found abnormally small testes in lab animals and humans suffering from persistent hypothyroidism with evidence from Illinois neurobiologist Esmail Meisami of extra-large testes in young rats with hypothyroidism. At first, PCBs weren't even on the researchers' radar screen. Cooke and Hess started out by spiking the drinking water of newborn pups with 6-propyl-2-thiouracil (PTU), a compound that induces goiter, an enlargement of the thyroid gland. They found that PTU rats grew testes twice as heavy as normal, and that daily sperm production during adulthood shot up 140%.

The researchers had assumed that levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH)—pituitary hormones crucial to secretion of testosterone and subsequent maturation of the testes—were rebounding after PTU treatment had stopped. But they were wrong. "To our great surprise, PTU caused a permanent decrease in FSH and LH levels," Hess says. Even more surprising, the animals had normal testosterone levels. "This was a very strange disturbance of the endocrine system," Hess says.

The Illinois group eventually identified the secret behind PTU's effects: Compared with controls, PTU-rat testes had 157% more Sertoli cells, a reservoir for germ cells that give rise to sperm. Still, there was a problem. Although previous studies found that Sertoli cells have a receptor for thyroid hormones, the PTU-treated rats were producing minimal amounts of thyroxin, the main thyroid hormone. So if thyroxin was important in sperm production, and Sertoli cells were getting so little of it, why were the rats churning out so many sperm?



REX HESS

Potent effect. Young rats injected with PCBs and the goiter-inducing chemical PTU grow extra-large testes and produce more sperm. Normal testis is shown at left.

Cooke and Hess hypothesize that thyroxin inhibits Sertoli cell proliferation during normal testes development. Although FSH levels are reduced in PTU-treated rats, lower levels of thyroxin allow Sertoli cells to proliferate, which ultimately boosts sperm production. But Hess admits there's plenty of room for other explanations.

The ramifications of this weren't lost on Hess's group. Chemicals that boost sperm production, they say, could become valuable fertility drugs to animal breeders, considering that 80% of U.S. dairy cattle and nearly 100% of turkeys in commerce are produced by artificial insemination. As a promising sign, says Hess, early results indicate PTU works in roosters.

Bt this effect may have a dark side. One area the Illinois group is pursuing is to look at the effect on the testes of environmental toxicants that alter thyroid metabolism. PCBs are known to suppress thyroxin levels, so last year Cooke and Illinois toxicologist Larry Hanson injected newborn rat pups with a commercial PCB mix. The PCBs packed a wallop: At 15 days after birth in

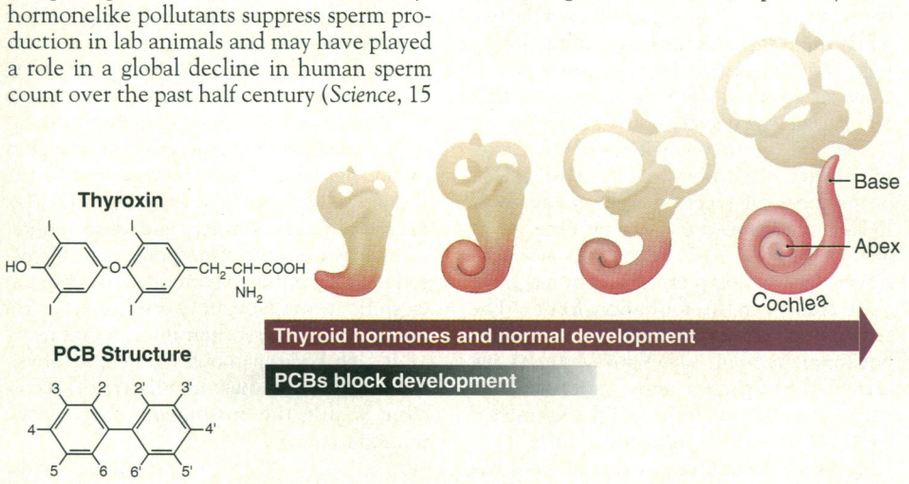


ILLUSTRATION: K. SUTLIFF

Sound barrier. Offspring of rats exposed to PCBs have underdeveloped cochlea apexes and suffer a low-frequency hearing loss linked to hypothyroidism. PCBs may compete for thyroxin receptor.

the treated rats, Sertoli cells were still dividing, while division had stopped in control rats. Overall, PCBs increased sperm production by 26%.

Guzzling PCBs may not be the best route to greater virility, of course, given the range of harmful effects from these chemicals. "It's an interesting example of the challenge of studying complex mixtures," says EPA's Gray, who points out that it's unlikely that the different PCBs would cancel each other out.

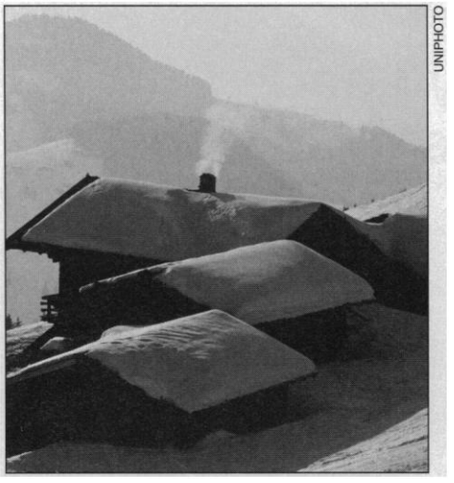
Thyroid hormones also play a critical role in the development of hearing, and new findings presented at the meeting show that PCBs can derail this process. The studies, by EPA neurotoxicologists Ellen Goldey and Kevin Crofton, set out to test whether PCB exposure might cause hearing problems. They sought to expand links found previously between hearing deficits and hypothyroidism in young animals and people. Goldey and Crofton exposed pregnant, lactating rats to PCBs, in doses of from 0 to 8 milligrams per kilogram of body weight per day. Thyroxin levels were greatly reduced in the offspring for the first several weeks after birth; levels of another thyroid hormone, triiodothyronine, began to drop a few weeks after birth. PCBs may compete for the receptor for thyroid hormones because their structures, sharing a dibenzene backbone, are so similar (see diagram on p. 1770).

Next the researchers tested the ability of the offspring to respond to tones. Offspring of treated and untreated dams responded equally well to high-pitched tones, but not to 1-kilohertz tones. According to Goldey and Crofton, the problem may arise during a period a few weeks after birth when both thyroxin and triiodothyronine levels are depressed. During this time the cochlea's apex—responsible for low-frequency hearing—develops. In a follow-up study, low-frequency hearing was partially restored in pups given thyroxin replacement therapy.

Goldey and Crofton say further studies are needed to sort out the impact of environmental levels of PCBs on hearing in wildlife and humans. People won't necessarily show the same effect, they say, because human cochleas, unlike rat cochleas, develop before birth. And any follow-up inquiry should be broader than just PCBs, says Goldey, who points out that several pesticides are toxic to the thyroid.

Wood Smoke Fires Infections

The crackle of flames from a fireplace may warm the heart and kindle romance. But among those fuzzy feelings by the fireside might also be something not as nice—the beginnings of a nasty lung infection, caused by particles in wood smoke that appear to suppress the immune system. The reason for concern stems from two studies presented at the meeting linking exposure to wood smoke to an increased susceptibility to lung infections in rodents.



Smoldering problem. Wood smoke is implicated in lung infections.

Part of the problem is that wood smoke is a witch's brew of carcinogens, including aldehydes and polycyclic aromatic hydrocarbons, carbon monoxide, and organic particles less than 10 microns in diameter, called PM_{10}. PM_{10}s have been implicated in increased morbidity and mortality on days of heavy air pollution. Epidemiological studies have also linked wood smoke to respiratory illness in preschoolers.

Two new studies lend biological credence to this statistical association. In one, immunotoxicologist Mary Jane Selgrade of the Environmental Protection Agency (EPA) found that mice breathing wood smoke were more susceptible to a flu bug than those exposed to emissions from an oil furnace, which releases fewer pollutants and less of them. After the mice spent 6 hours inhaling various combustion products, Selgrade exposed them to an aerosol of the bacterium *Streptococcus zooepidemicus*, which causes severe respiratory infections. After 2 weeks, 5% of the mice in the control group exposed to air and bacteria had died, along with a similar percentage of the mice breathing the oil fumes. But 21% of the wood-smoked mice were felled.

To measure the potency of the smoky pollutants, another group, led by New York University School of Medicine immunotoxicologist Judith Zelikoff, made use of a unique furnace developed by colleague Lung Chi Chen. Chen's furnace delivers known amounts of wood-smoke constituents directly to a rat's nose. Using the homemade furnace, Zelikoff's team exposed rats to small amounts of red-oak smoke, maintaining concentrations of particulate matter at 800 micrograms per cubic meter for one hour—levels "relevant to home burning," Zelikoff says.

NYU immunotoxicologist Mitchell Cohen then exposed some rats to *Staphylococcus aureus*, another respiratory pathogen. Although the rats' lungs showed little inflammation or other signs of insult, the bacteria were more virulent in the smokers than in the nonsmokers. Researchers attribute the result to a suppression in activity of the rats' macrophages, immune cells that roam the body, looking to engulf and destroy foreign particles. "It's really good data," says EPA toxicologist Gary Hatch.

Zelikoff says her findings emphasize the importance of inspecting wood-burning units for leaks and making sure rooms are properly ventilated. As for herself, Zelikoff says she and her husband intend to continue using their fireplace—unless, of course, they think they're coming down with something.

Ozonation Leaves a Hole

Water treatment is a challenge, because it's necessary to get rid of disease-causing microbes without leaving nasty byproducts. Chlorination, the standard method, has been linked to elevated rates of some cancers, and last year the Environmental Protection Agency (EPA) proposed that water treatment facilities reduce levels of chlorinated byproducts in drinking water. One way would be to switch to ozonation, in which ozone is bubbled through the water (*Science*, 24 June 1994, p. 1835). But some toxicologists now believe ozonation may pose its own threats to health.

The problem is that ozone reacts with bromine in drinking water to form unstable compounds that latch onto organic matter, producing an array of potential carcinogens. Studies over the past several months, says EPA toxicologist Rex Pegram, indicate that these compounds have "significantly more ability" to bind DNA than does chloroform (a byproduct of chlorination). At the same time, Pegram added, many brominated disinfectant byproducts need more testing, and others remain untested.

Any problems with ozonation would create a public policy dilemma by presenting the government with an unsavory choice. The EPA draft regulation was spurred by epidemiological studies linking chlorinated drinking water to cancers of the bladder, colon, and rectum. Indeed, in a study under review by the National Cancer Institute of 655 cases of rectal cancer in Iowa residents, NCI epidemiologist Kenneth Cantor reported that people who had imbibed chlorinated water for more than 40 years were twice as likely as controls to develop rectal cancer.

For the moment, says University of Washington pharmacologist Richard Bull, who co-chaired the symposium, the chlorination-cancer problem isn't going away. "It's not obvious that going to ozone is going to save us."

–Richard Stone