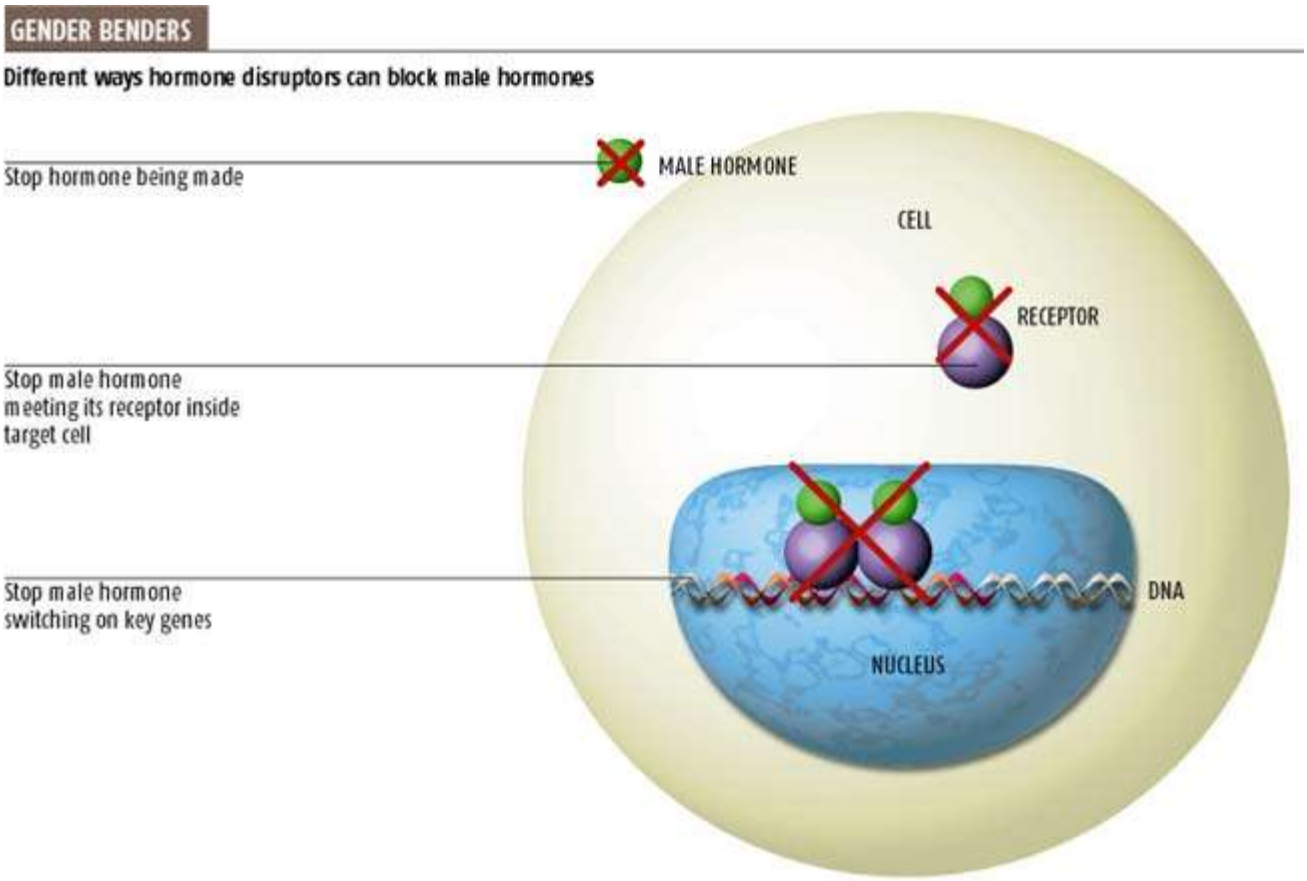
Boys won't be boys

29 June 2002
From New Scientist Print Edition. Subscribe and get 4 free issues.
Julie Wakefield
http://www.newscientist.com/article/mg17423495.300;jsessionid=JGIKANPNOJPP

PEOPLE don't quite know what to make of Theo Colborn. Is she the prophet of a new environmental threat or an errant alarmist? Hunched over a computer at the World Wildlife Fund in Washington DC, Colborn is amassing a database of chemicals she believes are hijacking our hormone systems, damaging men's fertility - even putting them at higher risk of developing testicular cancer. And what's more these chemicals are on the increase.



Colborn is at the forefront of a 14-year debate on what are known as endocrine disruptors: pollutants that mimic or block the effects of human hormones. While some researchers argue there is no proven link between endocrine disruptors and reproductive problems in people, Colborn and her team believe these chemicals can have serious side effects even at low levels.

Until recently, the debate focused on oestrogen mimics - chemicals that behave like female hormones. Some researchers link these to falling sperm counts and increases in cancer rates, while others strongly dispute any link. This debate is still unresolved, but now the hot topic is a new class of chemicals called androgen disruptors, which either mimic or suppress the action of male hormones such as testosterone. In theory, they could have an even greater impact on male fertility than oestrogen mimics. How worried should we be?

The first hints that pollutants might be able to interfere with male hormones turned up over 20 years ago. Mike Howell, a fish biologist at Samford University, Alabama, discovered that female mosquitofish living in Florida rivers were starting to look like males. The fish, found downstream from a paper mill, had mysteriously developed an enlarged anal fin. This is normally a characteristic of male mosquitofish and it is used in mating. Since then masculinised females have turned up in other species of fish in American, Canadian and European waterways.

The answer to this particular mystery only emerged last year. Howell's team analysed samples of polluted water taken downstream from another paper mill. They found traces of several androgens, the first ever spotted in the environment. One of them was androstenedione, a precursor to testosterone and an anabolic steroid favoured by bodybuilders. This time, though, the hormone had appeared in the water because of the wood pulp churned out by the mill. Bacteria in the water were converting chemicals called sterols in the pine pulp into androstenedione. The team suspects that similar biological processes may be releasing many more androgens into the environment.

But it's not just androgens we have to worry about, it's also anti-androgens, chemicals that block the action of normal male hormones in the body. Anti-androgens could exert their effects in a number of ways: by stopping the production of testosterone, blocking its ability to signal to cells to switch on key genes, or even by directly quashing the activity of genes testosterone normally switches on (see Diagram). This is worrying, because testosterone is vital for the normal development of the male sex organs.

It's only eight years since Earl Gray and his team at the US Environmental Protection Agency, the EPA, discovered these anti-androgens in the environment. These chemicals can end up in our food in the form of fungicides that are commonly sprayed onto fruit and vegetables. The team found the fungicide vinclozin stunted the sexual development of male rat pups in the womb. The list of anti-androgens keeps growing, and includes some chemicals known for their effects as oestrogen mimics. Phthalates, used to soften plastics, can also act as anti-androgens, as can DDE, a metabolic breakdown product of the pesticide DDT.

Is there any evidence that anti-androgens could cause reproductive problems in humans? In theory at least they could, as animal studies show. The herbicide linuron, for example, is an anti-androgen that can cause sterility in male rats exposed to it in the womb. Paul Foster, then a researcher at the industry-funded CIIT Centers for Health Research in North Carolina, found that it impairs the development of the cells in embryos that go on to form sperm. Linuron can also damage the developing testis to such an extent that the adult rat can be sterile and have shrunken testes. Male rats exposed to phthalates also have low sperm counts and a higher risk of developing testicular cancer, says Foster, now a consultant with the EPA.

Trouble is, Foster's work has so far only involved using high doses of anti-androgens: in the case of phthlates, 300 times the amount to which people are normally exposed. And it's the question of dose that is central to the whole endocrine disruptor debate.

Few scientists would dispute that endocrine disruptors are bad news in high doses. One of the most infamous examples is diethylstilboestrol, a synthetic oestrogen prescribed to pregnant women up until the 1970s to reduce miscarriage. Women whose mothers took DES have fertility problems and a higher rate of gynaecological cancers.

The main sticking point is whether endocrine disruptors can cause problems at low doses. Sceptics argue that the levels of endocrine disruptors we normally experience are too low to have a serious effect. What's more, our food contains many natural compounds that mimic or suppress the action of hormones, and this doesn't seem to harm us. "Almost everything we eat is hormonally active," says Stephen Safe, a toxicologist at Texas A&M University in College Station. "Just because something has an activity doesn't mean that the world shuts down. Let's see if there are any adverse effects first."

But the mere fact that endocrine disruptors play havoc with hormones in lab animals is enough for some to seek action. And researchers such as Foster believe that developing fetuses and infants are likely to be more sensitive due to their smaller size. What's more, if the development of the sex organs is disrupted at a crucial stage, the effects will be permanent. "Why play that kind of Russian roulette in our bodies?" says Sheldon Krimsky, an urban and environmental policy professor at Tufts University in Massachusetts, and author of the book Hormonal Chaos.

And there's another problem: many of these compounds aren't excreted by the body. Instead, they gradually build up inside tissues. For instance, levels of phthalates in American women of childbearing age are higher than those in any other age or gender group, according to the US Centers for Disease Control and Prevention in Atlanta. Most of us are carrying hundreds of assorted synthetic chemicals in our tissues, particularly in body fat. It really becomes an issue when body fat breaks down, releasing the accumulated chemicals into the blood. This can happen during early pregnancy and when a woman is breastfeeding. And no one understands how the chemicals in this cocktail might interact with one another to increase or reduce the overall effect on our health.

Researchers have done some low-dose experiments on animals, but the results are hotly contested. University of Missouri biologist Fred vom Saal, who has long been involved in the low-dose debate, feels the evidence is clear: even doses in the parts per billion range can cause reproductive and developmental abnormalities. He claims to have demonstrated such effects in mice using bisphenol-A, a polycarbonate that appears in everything from plastic wrap to baby bottles. "This is the next tobacco," he says.

The chemicals industry, which funds its own research in this area, disputes these findings. It insists that bisphenol-A is safe. Gray points out that other researchers have yet to reproduce the results vom Saal found in this particular study. But he acknowledges that the results of different experiments in a similar vein are consistent with vom Saal's low-dose hypothesis.

Gray is trying to study the effects on lab animals of known anti-androgens, including vinclozolin, other fungicides and phthalates. His team is currently looking at the effect on rat fetuses of giving high doses in short bursts. "It's clear that these chemicals are producing cumulative effects," Gray says. The team hopes to tackle low dose levels of a variety of mixtures next.

So far, however, no one has produced low-dose evidence that can convince the sceptics. But while the scientists wrangle over the methodologies of their experiments, is there any evidence that the human population is being affected by endocrine disruptors?

Perhaps the strongest evidence comes from the finding that testicular cancer rates have doubled in the Western world since the 1960s. The rate is especially high in Denmark, where Niels Skakkebaek and his colleagues at the National University Hospital in Copenhagen are researching male fertility.

Skakkebaek points out that a number of male reproductive problems, including testicular cancer, malformed genitals and reduced sperm counts, are all increasing together and says they are therefore linked. The team believes this is the result of abnormal development of the testes, which they call testicular dysgenesis syndrome or TDS. "It reflects the existence of a common underlying cause resulting in a maldeveloped testis," he says.

TDS starts, Skakkebaek believes, with disruption of testicular development in the womb. If hormone disruptors interfere with the cells which develop into sperm, this could predispose individuals to cancer and infertility later in life, he says.

But if endocrine disruptors were to blame, you would expect a fairly consistent rise in reproductive problems in the countries where these chemicals are common. That hasn't happened. Instead there are large regional differences in rates of testicular cancer. "If fertility is declining, it's not due to some global contaminant," Safe says. Denmark, for example, has one of the highest recorded rates of testicular cancer - four times that of nearby Finland, which has the lowest. What's more, experts are still divided on the issue of whether sperm counts really are declining. A team at the University of Minnesota is now collecting data that will allow them to estimate differences in semen quality between countries.

Skakkebaek's team is now trying to find out why there is such a difference in testicular cancer rates between Denmark and Finland. They are looking into differences in exposure to endocrine disruptors and cancer-causing chemicals in the two countries. For almost four years now, the team has been measuring the concentrations of these chemicals in breast milk and pregnant women's blood, and studying these women's babies once they are born. So far, the team has surveyed several thousand newborns, but has yet to analyse their findings.

Another possible line of evidence comes from hypospadias. This is a common birth defect in boys in which the penis doesn't develop properly and the urethral opening may appear anywhere along the shaft - even within the scrotum. In the US, 1 in 125 boys are born with varying degrees of hypospadias. And the prevalence of hypospadias has increased in recent decades. According to the Centers for Disease Control and Prevention, the rate among Americans nearly doubled between 1968 and 1993, the same period when the suspect anti-androgens entered periods of higher production. Seven European countries, including Norway, Sweden, England and Wales, Hungary, Denmark, Italy and France, also reported increasing rates of hypospadias in the 60s, 70s and 80s, according to the International Clearinghouse for Birth Defects Monitoring Systems.

But again regional differences complicate the picture. Outside the US, increases were most notable in Norway and Denmark while rates levelled off in Britain, Canada and the northern Netherlands after 1985.

"We still don't have any idea what causes hypospadias in 95 per cent of children," says Larry Baskin, a urologist at the University of California at San Francisco. But he believes that a majority of the defects are caused by exposure to anti-androgens during pregnancy, and perhaps also to oestrogen mimics. The researchers suspect anti-androgens may also cause undescended testicles. For Safe, however, regional differences are enough to let endocrine disruptors off the hook. In fact, he points to one study that found fewer babies were being born with undescended testicles.

Making a concrete link between a given disease and an individual endocrine disruptor may be impossible, Colborn admits, given the large number of industrial compounds out there and individual variations in exposures. Not to mention the long interval between exposure in the womb and effects which may only appear at sexual maturity.

But without convincing evidence, it will be hard to persuade policy makers and industry to take action. So far, very few of the 15,000 chemicals produced in the highest volume in the US have been tested for any endocrine-disrupting effects. Testing costs, and a blanket ban on all these chemicals, would be unworkable, not least because we are so dependent on the products they are used to make.

How are we to resolve this impasse? Sceptics like Safe are calling on Colborn and her like-minded colleagues to come up with precise, testable hypotheses on how endocrine disruptors work and what their effects are.

Proponents such as vom Saal say current toxicology methods just aren't up to the job of detecting the subtle low-dose effects of endocrine disruptors. Some of these show an unusual relationship between dose and effect,they argue. Unlike many chemicals, which have stronger effects as the dose increases, hormone disruptors could have their strongest effect at low dose, and no effect at high dose. This makes it difficult to use traditional toxicology models to predict how they could affect people.

Foster, on the other hand, thinks that toxicologists already know how to deal with unusual dose-effect relationships. The biggest problem, he says, is that when scientists test endocrine disruptors on experimental animals, normally only a few of them develop any reproductive changes. We need to develop new toxicological methods that can reveal these subtle, unpredictable effects, he argues.

The EPA has created a screening programme to figure out how best to evaluate low-dose reproductive and developmental effects and dose-response relationships for endocrine disrupting chemicals. Environmentalists welcome the development, but say that studies have not progressed far because the governing panel can't agree on how best to proceed. As a result, it has yet to come up with a solution that satisfies everyone.

In the meantime, Colborn keeps collecting information for her Internet database, in the hope that the weight of accumulated data will sway opinion in her favour. Despite the difficulties in

proving a link with human disease, Colborn advocates a precautionary approach. It's time we stopped arguing and started being much more cautious about what we release into the environment, she says. "Every generation we wait, that's one more grandchild, daughter, or son."

Julie Wakefield is a science writer based in Washington DC
From issue 2349 of New Scientist magazine, 29 June 2002, page 41