Pat Thomas

When Tyrone B Hayes, an expert in amphibian biology and a popular professor at the University of California at Berkley, was asked by Syngenta to look into one of the world's most commonly used herbicide, Atrazine, he was excited. Until he discovered what it was doing to his beloved frogs and us. Pat Thomas meets Syngenta's worst nightmare

In 1997 Professor Tyrone B Hayes received an offer that would change his life. He was asked to examine the impact of atrazine, the most widely used herbicide in the US, on the hormonal systems of frogs. This invitation was made by environmental consulting firm Ecorisk on behalf of Syngenta, atrazine's manufacturer. At that time atrazine was one of five pesticides up for review and reapproval by the US Environmental Protection Agency (EPA) and Syngenta was keen to plug the holes in its existing research and thus help ensure atrazine's reapproval.

Hayes, an expert in amphibian biology and a popular professor at the University of California at Berkley, had already published 10 peer-reviewed papers on amphibian development. However, it was his field work in Africa studying the effects of hormone disruption in Hyperolius argus, a type of reed frog and his subsequent development of a screening test known as Hyperolius Argus Endocrine Screen (HAES) which can detect hormone disruption at low levels, that convinced the Syngenta-funded panel of researchers at Ecorisk that Hayes would be a valuable member of the team.

Syngenta was confident that atrazine, long believed to be non-toxic, would pass muster. Studies utilising large doses, which most animals would not encounter in the wild and which most humans would not be exposed to in their water supply, had been shown to have no effect on health or reproduction.

Hayes says he probably never would have begun looking at atrazine had Ecorisk not approached him. He knew very little about the herbicide at the time, but the work was prestigious and well funded and made perfect sense as a career move.

Research started in 1998 and by 1999, working with African clawed frogs that he had raised in his lab, Professor Hayes began testing the effects of various doses of atrazine on the animals'hormonal systems. Within months he was alarmed to fi nd that doses of atrazine in concentrations as low as one part per billion were inhibiting the growth of the larynxes of male frogs. He readily shared his findings with colleagues on the Ecorisk panel and with Syngenta. The effects were noteworthy, since under EPA guidelines, atrazine is considered safe in drinking water as long as it is found in levels no greater than three parts per billion.

Ecorisk responded cautiously, suggesting that the findings required confirmation with additional research, but the company made no moves to provide funding for further research and by controlling the money, says Hayes, 'they had control over the pace of the work'. Frustrated by the delay, Hayes eventually did the additional analysis with his own funds and with the help of students who happily volunteered their time to the project.

In 2000 a second series of studies, which looked not only at the larynxes but also at the sex organs of atrazinetreated frogs, showed that at levels as low as 0.1 parts per billion – one tenth the concentration of that affecting the larynxes – multiple non-functioning ovaries and testes appeared in the atrazine-treated male frogs. A closer look revealed that in these frogs the testes were producing eggs rather than sperm.

Atrazine triggers these changes by stimulating the activity of an enzyme called aromatase, which converts the male hormone testosterone into oestradiol, a form of estrogen and a female hormone. 'If this happens at the wrong time in young frogs' development,' says

Hayes, 'you end up with animals that look fine on the outside, but when you start to examine more closely whether or not they are functioning, they're clearly not fine.'

Source: ecologist.testing.net-genie.co.uk/investigations/health/83082/sex_lies_and_herbicides.html

Hayes kept the Ecorisk panel informed of his disturbing findings, and pressed for more research funding. But with funding still not forthcoming, late in 2000 he decided to quit the panel and complete the work on his own.

By now the penny was beginning to drop that Syngenta/Ecorisk were not interested in pursuing or publicising the bad news in Hayes' data. His resignation letter noted: 'It will appear to my colleagues that I have been part of a plan to bury important data… This fear will be particularly realized when independent laboratories begin to publish data similar to data that we (Novartis and my laboratory) produced together as early as 1999.'

Looking back Hayes recalls that after his field work in Africa and the subsequentdevelopment of the HAES test, a television reporter enquired whether the kind of results revealed by his screening test might one day make some big company shake in its boots. 'I told him that if a big company had a chemical that was potentially harmful, I think they would be happy to get the data. That's how naïve I was.'

In the beginning Atrazine, manufactured by Syngenta (a subsidiary of pharmaceutical giant Novartis), was introduced into agriculture in 1958. It's most commonly used in the production of maize but is also used on sorghum, sugar cane, pineapples, chemical fallows, grassland, macadamia nuts, conifers and for industrial weed control. It is a selective systemic herbicide, absorbed mainly through the plant's roots, that inhibits photosynthesis and interferes with enzymatic processes of the plant. Like many pesticides, atrazine is strongly persistent in the environment and can be found in significant quantities in rain, fog, surface, marine and ground water.

By the 1980s atrazine had been identified as a potential carcinogen associated with high rates of prostate cancer among workers at Syngenta manufacturing facilities. Because of this the company could hardly have been surprised at Hayes' data and yet the ferocity of its objections to Hayes' findings and refusal to even consider the data took the scientist by surprise.

According to Professor Hayes, the company sat on the data for a long time, failed to report it to the EPA and dragged its feet on funding new studies to confirm the results. For two years they maintained that the results were inconclusive and inconsistent with accepted beliefs about how toxic compounds behave. However Hayes, like many amphibian biologists, began nursing a growing concern that the documented and worldwide decline in frog populations might be a consequence of this low-level endocrine disruption.

In addition to burying his findings, Syngenta also tried to get him to change the way he assessed the results. 'For example,' says Hayes, 'with the voice box data they asked me to recalculate the data by dividing the size of the larynx by the body weight. And my response was, why would I do that? For example, my daughter was four years old at the time and using that kind of calculation I was able to show that if I measure my calf muscle and divide by my bodyweight and do the same for my daughter I could make my daughter look bigger than me! You would just never do that in a study of this kind, and at that point I began to ask are these guys that dumb or that unethical? Of course, these guys aren't dumb. They're actually quite smart, some of them are smarter than I am. So you know that they know this is an inappropriate thing to do and the results would be misleading.'

When Hayes quit the Ecorisk panel in 2000 to pursue his experiments independently, the confi dentiality agreement between Hayes and Ecorisk no longer applied. It was then, according to Hayes, that Ron Kendall, director of the Ecorisk panel, offered him $2 million to do the studies 'in a private setting' – an offer which Hayes took to mean in a setting where Ecorisk and Syngenta could control the release of the data. Kendall denies that such an offer was ever made.

Hayes maintains that when he refused, the character assassination began. In this respect Hayes is Syngenta's worst nightmare – youthful, handsome and black, an articulate, fastidious scientist and a dedicated family man so there is little to pick apart. Nevertheless, further scientifi c papers published in 2002 attacked Hayes' work as difficult to interpret and unreproduceable.

Source: ecologist.testing.net-genie.co.uk/investigations/health/83082/sex_lies_and_herbicides.html

'I would read these criticisms of me or of my work and invariably it would be by a scientist in the pay of Syngenta.' At this point Hayes began to realise just how deep scientific conflicts of interest can go, especially when huge profi ts are at stake. 'For example,' he says, 'Ron Kendall was working for Syngenta and running Ecorisk while chairing a scientific advisory panel to the EPA. He was also editing the journal that published a paper challenging my findings, written by one of his colleagues at Texas Tech University, who was also under contract to Ecorisk.'

Hiring academic scientists and portraying them as an independent panel creates a veneer of scientific respectability, but a closerlook atthe papers showed a clear schism between the results of the corporate funded data, which supported the safety of atrazine, and that of Hayes and other independent scientists which found evidence of harm.

But it wasn't just the conflicts of interest and questionable ethics of the scientists employed to discredit him. The science itself was poor. The more than a dozen studies funded by Ecorisk to discredit Hayes' findings were, he says, methodologically sloppy, often involving no control groups (that is, groups of unexposed frogs necessary for comparison purposes), and drew weak conclusions from data involving high death rates among test animals and contaminated samples. In one such study frogs were left in open tanks, able to hop freely between atrazine- and non-atrazine-containing containers. But the conclusion, that the study 'did not support Hayes' findings', was nevertheless reported to the EPA and in the press.

Remarkably Hayes remains largely pragmatic about the experience. 'To me the most important thing is to continue to be careful with my data because I know that there's always some body picking through every single line, every word, every statistic I publish. For instance, when I published a recent review in Pesticide News, the editors were concerned about the lengthof the references that were almost as long as the article. But I said no way am I putting myself out there without back-up. I like to be able to back up everything I say and yes,it's stressful, but in the end I think it also makes me a better scientist.'

A stress made more dynamic, no doubt, over the last 10 years by the occasional film noir quality his life has taken on since challenging the might of Syngenta.

'After I published my initial data I had people from the Worldwide Fund for Nature (WWF) advising me that I should never go home the same way twice. When I testifi ed for the Environmental Protection Agency (EPA), I had to have a federal officer pick me up and take me to my hotel. I was advised to stay in a different hotel each night and call him and let him know where I was each day. And all the time I was thinking why? It was sometimes like being in a movie, but I think I didn't feel it as much as the people around me did. I mean I had a threat management officer assigned to me on campus and one day the fire department contacted my wife to reassure her that any 911 calls from my lab or from home would get an immediate full response from the bomb squad or whatever. That was pretty strange.'

Are frogs canaries?

The very public squabbles between Hayes and Syngenta were framed by the manufacturers as being little more than a simple academic disagreement. This had the effect of drawing attention away from the real significance of Hayes' findings and his growing concern that atrazine-induced hormone disruption was influential in the global decline of frog populations and may be implicated in human diseases as well.

The demasculinisation of frogs has many unhappy consequences for frog populations. With underdeveloped voice boxes the male frogs cannot call to prospective mates. With testicles full of oocytes (eggs) instead of sperm they cannot successfully mate. Without the right hormones released at the right time in their metamorphosis from tadpole to mature frog, the animals do not grow large enough or develop large enough mouths to eat their usual prey, and they do not know when to leave the pond and begin life as partly terrestrial beings.Drowning and starvation are common.

Source: ecologist.testing.net-genie.co.uk/investigations/health/83082/sex_lies_and_herbicides.html

The question is, can we expect to see the same effects in humans? Syngenta argues that even if frogs are affected by atrazine in the way Hayes says, evidence of harm in frogs does not automatically suggest that their herbicide is harmful to people, especially at the low levels being studied. Professor Hayes counters that whatever the outward differences between people and frogs, hormonally both species share significant similarities.

'Male frogs sing and females don't because testosterone makes their voice box grow. This is the exact same testosterone that makes the voice box and larynx grow in humans. Estrogen regulates their egg production and the reproduction. It's the exact same estrogen that regulates a woman's menstrual period and is involved in a woman's breast growth. Thyroid hormone regulates the frog's metamorphosis and development and it's the exact same thyroid hormone that regulates our metabolism, that is in part responsible for obesity and that is necessary for brain development and normal growth in humans.

'Stress hormones work the same way in frogs and people too. Our stress hormones can decrease human growth and cause trouble in pregnancy in the same way that stress hormones can decrease growth and immune function and cause trouble during a frog's metamorphosis. All these types of hormones in frogs, the glands that make them are precisely the same as those that we see in humans.'

The potential toxicity of a substance can usually be measured by whether or not it causes harm in more than one species, and indeed the data show that atrazine's toxic effects are not limited to frogs. It has been shown to feminise fish, amphibians and reptiles, birds and mammals. Available research shows that it inhibits immune function in carp. In mice, it reduces thymus weight and the normal cell count of the spleen. Atrazine significantly inhibits immune function in male rats exposed during fetal development and reduces the ability of human T and natural killer lymphocytes to destroy tumour cells.

Harmful effects in humans and linked to hormone disruption are already emerging.

Atrazine in well water, for example, is associated with a higher than normal risk of breast cancer among women. Also in the summer of 2001, the Natural Resources Defense Council (NRDC), which had been prodding the EPA for some time to ban atrazine, learned that Syngenta had been tracking prostate cancer in its employees. Only after the NRDC alerted the EPA did Syngenta submit reports to the agency of numerous cancer cases among employees at its St Gabriel, Louisiana atrazine plant. The data, which has since been published in the Journal of Occupational and Environmental Medicine, found that Syngenta employees had rates of prostate cancer more than three-and-a-half times higher than the Louisiana statewide average.

Other human data shows that levels of atrazine in the urine of men living and working in some agricultural areas, and who are experiencing fertility problems, are equivalent to the levels that chemically castrate frogs. In 2004 epidemiologists from the University of Missouri found reproductive consequences in humans associated with atrazine, including sperm counts in men in farm communities that are 50 per cent below normal. Iowa scientists are finding similar results in a current study.

The cocktail effect

To date, the data amassed by Professor Hayes and his team at Berkeley has deeply challenged the accepted wisdom of toxicology – that the dose makes the poison. 'You cannot dissolve enough atrazine in the water to kill a tadpole,'comments Hayes, 'so it's "safe" – at least that's what the industry has been bragging about for 40 years. But really it's time to redefine our concept of non-toxic, because at levels that are equivalent to one one-thousandth of a grain of salt dissolved in a litre of water, atrazine can produce profound reproductive and developmental deformities.'

Like many endocrine disrupters, a mixture of atrazine and other hormone-disrupting pesticides can end up producing an additive or 'cocktail effect' where the damage caused becomes greater than could otherwise be predicted with each additional toxin in the mix. But even more revealing is the way that chemicals like atrazine can interact with stressful aspects of the animals' lifestyle to unpredictably and

profoundly alter levels of several key hormones. At a very primitive level the body does not distinguish between the stress of being exposed to an environmental toxin and the stress of being exposed to, say, a predator. The reaction on a chemical level is just the same and the release of stress hormones triggered by these stressors can produce a cocktail effect that profoundly disrupts the hormonal balance and immune function of the animal.

'The fact is no animal is exposed to only one stressor, to only one thing that we've done to the environment. The next challenge for researchers, and we are currently working on this in my lab, is to look at what happens when you mix one type of stressor with another set of stressors. What if you consider global warming? What if this mixture is now combined with the stress of higher temperatures? What if that stress of high temperature is now combined with the pond drying up, which increases the concentration of the pesticides in the water?

'So now there's interaction between three stressors: the pond drying up, increasing temperature and the pesticide. As the pond dries up the animals become more crowded, that's another stressor. Now we've got density, temperature, desiccation and pesticides, making it likely that the immune system is shot due to all this stress. Now throw in a parasite that's naturally there, which the immune compromised animal's body won't be able to fight off.'

'This is troublesome because it's going to take a lot of work to take all these pesticides that are currently on the market, that have been tested individually and at high doses only and start testing them in combination and at low doses and in real world situations. It's going to be a nightmare for regulators because they have to try and not only regulate a single compound, but regulate the mixtures as well. And even if they can regulate you as a farmer, how are they going to regulate what your neighbour is laying down that might mix with what you have used?'

Keeping it simple

Although the EPA espouses a 'weight of the evidence' approach to regulation, the real weight of the evidence for atrazine, according to Hayes, has never been fully reviewed. He notes that it was an act of Congress, not a regulatory agency like the EPA, which eventually banned DDT in the US; likewise it was Ronald Reagan who eventually banned tributyltin. In fact the EPA has never acted to ban a dangerous substance that it has previously approved and Hayes envisages that should atrazine ever be banned in US it would require a similar act of Congress or presidential intervention. In his view many regulatory agencies are simply unequipped to deal properly with the emerging science of endocrine disruption and low-dose effects. Further, there is an urgent need to address the impact of pesticide mixtures and how these mixtures interact with other environmental stressors. These issues need to be addressed separately from any bottom line concerns, and yet with a world market for atrazine worth over $400 million, the bottom line is never far from regulators' thoughts.

'I don't trust in government agencies to make good choices about what is safe and what is not. To me it's unforgivable when an agency that calls itself the

Environmental Protection Agency begins weighing the economic cost of banning atrazine against the public health cost of maintaining atrazine and giving economic considerations considerably more weight in the final analysis. And yet that is what is happening at the

moment. If that's the case, then don't call yourselves the Environmental Protection Agency, call yourself the Economic Protection Agency.

'It's the same thing with agencies like the FDA; Vioxx was approved right? In fact, I've often given a talk that I call "Is atrazine the EPA's Vioxx?" Have they allowed industry to influence their decisions and forgotten about what their mission is? I would say yes they have, and my role is to make sure that they know that all this data on adverse effects exists, rather than allowing them to get away with saying no such research exists – because that simply isn't true.'

Source: ecologist.testing.net-genie.co.uk/investigations/health/83082/sex_lies_and_herbicides.html

'Beyond that I have avoided getting too involved in the politics, because I don't want to lose my objectivity as a scientist. I want to be able to do my research and present my data in as unbiased a way as possible.' Increasingly Hayes is placing his faith in the public to press for and achieve lasting change, and as his work has progressed has become acutely aware that the things that mean the most to scientists mean nothing to 99 per cent of the public. In keeping with the human touch displayed at his many lectures, Hayes' says his ultimate goal is to make his work more accessible to people who are not scientists but who nonetheless could be on the receiving end of any health effects from atrazine exposure.

Prostate and breast cancer, for instance, are two of the top causes of death in Americans age 25-40, but Black and Hispanic Americans in particular are several times more likely to die from these diseases.

'As scientists we're arguing in front of the EPA, but the farm workers and the public don't ever know about it. Ethnic minorities and people of low income are most likely to hold the "unskilled" labourer positions in agriculture and pesticide production that would put them at higher risk of exposure. They are also least likely to have access to the emerging science demonstrating the dangers of that exposure. So this environmental and public health issue is also a racial/ social justice issue because minority and working class people are the primary targets of pesticide exposure.'

'I'm past the point of believing that you have to use big words to sound smart and one of the catalysts for this was when my first Nature paper was published. Nature is considered the gold standard for scientists and I was fairly young when this paper came out and I remember talking to my mom, who is not a scientist and not an academic. I was trying to explain to her why this particular was so important and she was having difficulty understanding because I already had several papers published by that point. Anyway, the next day she calls me up and says, you know I'm really sorry and I know you said it was really important, but I went to Barnes and Noble and they've never heard of Nature. Immediately it struck me, just how important is it that we are holding this journal up as a kind of Holy Grail of science when my mom can't buy a copy of it.'

Hayes' faith in average people to get the point and take up the campaign to ban atrizine for themselves is noble, but it doesn't solve the immediate problem of continued and widespread use of this toxic herbicide. Although it has been banned in the EU due to concerns over groundwater contamination, the full ban will not come into effect until December 2007. Elsewhere in the world its use is largely unrestricted. For instance, while the EPA acknowledged that the Ecorisk studies presented to it were flawed, it nonetheless reapproved atrazine for use in the US in 2003. No new restrictions were placed on atrazine's use; the ruling called only for Syngenta to monitor the herbicide's levels in drinking water – and certainly if levels rose this could lead to more stringent regulatory action. The EPA also called for more studies. 'And guess who's going to do those studies?' Hayes asks. 'Syngenta.'

According to Hayes, these industry studies can go on for years with results never being reported to the EPA because they have no end point. That way, if they find something bad, the company buys time with these 'unfinished' studies to look for a replacement product. Syngenta has already offered such replacement products to farmers in the EU. In time they will surface in the US and elsewhere.

Hayes is, of course, continuing to develop his own research in this area. But with little commitment from industry to researching the human fall-out from 45 years of widespread atrazine use, Syngenta may well end up escaping litigation by the skin of its teeth; and if atrazine does cause cancer in humans, parent company Novartis has conveniently developed a breast cancer drug Letrozole to help. With doleful irony Hayes comments, 'they give it to you and then, for a price, they offer to take it away.' But there's a catch. Letrozole is another hormone disrupter, and works by blocking the effects of estrogen in the body. It is also associated with birth defects.

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The story of atrazine is a modern cautionary tale that asks us to decide just how far corporate responsibility stretches and how bullish and outspoken are we prepared to be to protect ourselves and our children from the devastating longterm consequences of hormone disruption.

Sperm counts are declining, breast cancer is on the rise. Reproductive abnormalities in boys such as hypospadias (the urethra opening on the underside of the penis) and cryptorchidism (undescended testicles) have become so commonplace that in some places physicians are no longer required to report them as abnormalities. The generational effects of known hormone disrupters such as diethylstilboestrol (DES), which is still causing cancer and reproductive devastation in the granddaughters of women who took it to prevent miscarriage 60 years ago, present a horrific picture of how damaging and how long term the effects of chronic exposure to 'weak' xenoestrogens – that is estrogens that originate outside the body – can be.

Because these changes have occurred over a relatively short period, environmental rather than genetic factors are the most plausible explanation. The question is do we sit back and chalk it up to life in the modern world or do we press to draw a line under the use of this clearly toxic herbicide? If the Precautionary Principle is going to be anything other than hollow rhetoric, then coordinated worldwide action to remove atrazine from the marketplace isn't just desirable, it is necessary, urgent and long overdue.

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