Pharmaceuticals in the environment

An enormous range of pharmaceuticals, from painkillers to chemotherapy drugs, is entering our rivers and waterways via wastewater. The concentrations are tiny, but drug pollution has had unexpected and at times devastating impacts on plants and animals. Ecotoxicologists and health experts alike are calling for a concerted effort to better understand how pharmaceuticals behave in the natural environment.

This special *Health Report* program has been prepared by Corinne Podger.

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Transcript

Norman Swan: Hello and welcome to the *Health Report* with me Norman Swan. This week's program covers an issue that many of us probably haven't thought about that much - what happens to our medications once we've swallowed them or had them injected? They've got to go somewhere after all and often, to be crude, it's down the toilet and often that goes out into the environment and we're talking about antibiotics, anti cancer drugs, heart drugs and all sorts of things which could be quite toxic. And in fact there's been a letter published in the journal Nature from the European Centre for Environment and Human Health warning that pharmaceutical contamination in the environment has reached alarming levels. And it warns of worse to come as global population grows and ages and as cheap generic drugs become increasingly available.
Now they're not alone in calling for more attention to the issue, the Americans are worried about it too and the European environment agencies suggested tighter regulations and guidance on managing pharmaceutical waste. And it's also on the radar of the World Health Organisation. So how alarmed should we be? Corinne Podger has been investigating.

Corinne Podger: On average how often do you reckon you take drugs? Nothing illegal, I'm talking about the pills many of us use: painkillers, anti-inflammatories, contraceptives and antibiotics, tablets to control cholesterol or blood pressure, anti-depressants. Collectively, it's a lot. Close on 300 million community prescriptions a year in Australia in fact and on top of that drugs from supermarkets and over the counter. And those are just the run of the mill drugs. Thousands of Australians receive chemotherapy at any one time and those are some of the most toxic drugs imaginable. So what happens next?
SFX - Flushing Toilet

That's right, these chemicals land in our waste water via sewers, farm run-off and landfill. Water treatment removes a lot of drug pollution but minute concentrations remain and can be detected in rivers and waterways. Dr Stuart Khan heads the Trace Chemical Contaminants research team at the University of NSW.

Stuart Khan: Well if we have a look at chemicals that make their way through a waste water treatment plant we find a wide variety of different pharmaceutical substances, all sorts of hormones for example are probably the most famous and well studied pharmaceutical type chemicals in waste water, so lots of oestrogens and androgens, we can find antibiotics, many antibiotics, sulphonamides, trimethoprim, have been measured in fairly high concentrations in waste water. Analgesics and anti-inflammatory chemicals like paracetamol, ibuprofen, naproxen, insect repellents like deet, antiseptics, triclosan, are commonly found in waste waters. Even anticonvulsants, drugs that are used to control epilepsy, like carbamazepine and primidone, are commonly found and of course caffeine, caffeine we find in very high concentrations wherever we look for it in waste waters. And all of these things make it through the waste water treatment plant to some degree, depending on how well designed and operated that waste water treatment plant is. And then of course make it into the environment where we discharge waste water either into streams or in the case of Sydney and many large cities on the coast straight into the ocean.

Corinne Podger: What we'll mostly be talking about in this program is how drug pollution can affect animals and plants, but you might be wondering about drinking water. Well before you start looking suspiciously at the kitchen tap just hang on, the World Health Organisation asked exactly that question in a global report published in June called *Pharmaceuticals in Drinking Water* and it found that drug concentrations in the world's drinking water supplies are in the millionths, even trillionths of a therapeutic dose. At those levels any effect on human health is extremely unlikely. One of the report's advisors is Dr David Cunliffe, principal water quality advisor with the South Australian Department of Health.

David Cunliffe: Well the drugs going into the water cycle are quite broad because basically the source is human sewage and livestock waste, so whatever people take they'll excrete a certain amount, or they'll excrete metabolites so it ends up in sewage through its treatment and then can end up in water resources. The amounts we detect in drinking water tend to be a much narrower range simply based on concentration because the concentrations fall quite rapidly, they're removed in the environment and then they're removed by water treatment. So pharmaceuticals can be detected infrequently in drinking water supplies and when they are the concentrations are tiny.

Corinne Podger: Now they are tiny but the exposure is potentially across the lifespan and to an enormous range of substances even at the nano level. How confident is the WHO that the risks are minimal?

David Cunliffe: We're reasonably confident because the concentrations are so small. There's a widely cited study from the United States where they did detect some pharmaceuticals in US water drinking supplies. The maximum concentration they detected was 5 million times below the lowest daily therapeutic dose. One of the messages that got confused is that detection of a pharmaceutical automatically means danger while ignoring that dose is important. So a year or two ago we saw headlines in the United States about drugs in drinking water, that was the headline and that attracted a lot of attention. The US government had a hearing on pharmaceuticals in drinking water but the discussion about concentration tended to get pushed back and we

found evidence that pressure was being put on water utilities to take action against pharmaceuticals when there actually wasn't evidence of human health risk. But the danger was that this could distract people from micro organisms and chemicals that we know do pose a health risk.

Corinne Podger: Indeed I understand that one of the reasons why we're able to detect pharmaceuticals in drinking water or any form of water is because the analysis that we can subject water to is much better than it used to be.

David Cunliffe: That's correct. The chemists are just getting better and better. The reality is that we are going to detect more and more compounds in water in general and in drinking water in particular because the test methods are getting more and more sensitive. We're now detecting chemicals in the parts per trillion range and even lower than that. So at those concentrations they don't represent a risk to human health but they're there and that's why it's even more important now to make that distinction between detection and health risk.

Corinne Podger: At the same time the WHO report says that very few countries have routine screening programs to check for pharmaceutical pollution in drinking water including presumably the levels at which pharmaceutical pollution is occurring. Are screening programs needed do you think?

David Cunliffe: The evidence says that the concentrations we're finding are really low so even in sources such as sewage where you'll have the highest potential concentrations; concentrations are very low so the risk assessment actually says no, we don't need to do routine monitoring in most environments. Now exceptions could be where you've got large generic drug making factories that could be discharging large amounts of material into the environment. So if that's occurring then yes, there is a case to do some monitoring.

Corinne Podger: Dr David Cunliffe. But it does occur, not in Australia but in developing countries like India where many generic drugs are manufactured these days. Waste water from these drug factories can contain high concentrations of pharmaceuticals according to Professor Alistair Boxall at York University in Britain.

Alistair has been engaged in the study of environmental drug pollution from the discipline's early days just over a decade ago.

Alistair Boxall: There's an area in India called Hyderabad where a lot of pharmaceutical manufacturing now occurs. What's happened is that the pharmaceutical industry has exported their manufacturing out to some regions like India and China. In those areas the controls, the regulation controls are perhaps not quite as good as they are in Europe the US and as a result the treatment systems at the end of the manufacturing processes perhaps aren't as effective. What we're finding is when people are going out and taking samples from some of these areas we find very, very high levels of pharmaceuticals. So there's this Swedish study where they were looking at antibiotics for example and they found levels of antibiotics which were massive compared to what we would take as a human actually being released out into surface waters.

Corinne Podger: In settings like this where one might find pharmaceutical concentrations in water ways, water supplies far higher than typically in the west is there a concern if one is exposed directly to those waters?

Alistair Boxall: I think yes there is, I mean some of the levels that are being reported are sort of up to levels that would correspond to a dose that you would take as a pill or possibly more. They are levels where potentially you're going to see biological activity of the pharmaceuticals. I think issues around human health and human exposure are something we should be thinking about.

David Cunliffe: In countries such as Australia that doesn't occur. We have very tight controls on manufacturing, so we don't see a lot of that type of discharge, it doesn't warrant monitoring. We did a study, we commissioned a study as part of developing the Australian guidelines for water recycling because there have been proposals about adding recycled water to drinking water supplies. And one of the issues that were raised in public debate was what about the pharmaceuticals? So we looked at all the published reports on pharmaceuticals in sewage and in waters receiving sewage and that commissioned study found that concentrations were low, typically a thousandfold below the lowest daily therapeutic dose. So then when you take into account the fact that you get dilution because the way we do have sewage disposal there's mixing in the receiving water and then there's treatment before it goes into the drinking water supply so we get further reductions in concentration the risk is very low.

So again it's very difficult to make a case for routine screening for pharmaceuticals in drinking water supplies because again it diverts our attention away from those parameters that we know are important, that we know can have a health impact and that's where the focus should be.

Corinne Podger: Dr David Cunliffe. However the WHO is keeping a watching brief on drinking water because as you'll hear even low level drug pollution has had unpredictable and disturbing impacts on plants and animals. And there's a still a lot we don't know about the implications for us if not directly then via the environment, so drug pollution is an area of robust almost frantic research. One area of keen interest is whether pharmaceuticals can be absorbed by crops - Alistair Boxall.

Alistair Boxall: Five years ago we did a study looking at veterinary drugs, trying to understand whether veterinary drugs could be taken up from soils into crops and basically what we did was we added the compounds to soil, we grew different crops and then we measured the levels of the pharmaceuticals in the crops. And we did see uptake of a handful of drugs and since then actually that whole area has sort of bloomed and there's a whole range of studies being done looking at both human and veterinary pharmaceuticals being taken up from soils into plants.

Again I mean they're seeing similar results to what we saw, I mean they are seeing that some pharmaceuticals are taken up, others aren't.

Corinne Podger: We've seen with heavy metals that these can be concentrated as they move up the food chain. Is there any evidence of that happening with pharmaceutical products?

Alistair Boxall: Again we've been doing a little bit of work to try and understand that, so we've been working with some model communities where we try and simulate a food web in the laboratory and the drugs we've looked at actually we don't see by magnification through the food chain. What you tend to find is as you move up through the different levels, when you get to the higher levels of the food chain the concentrations are lower than the levels at the lower

end of the food chain. But we have only looked at a handful of drugs. There are probably other compounds out there that might be accumulative. This is something that I think we need to look at in a little bit more detail; it's an area where perhaps our understanding isn't quite as well developed as it is for some of the other areas in terms of drugs in the environment.

Corinne Podger: Now so far we've been talking about protecting human health and the risks for human health, people being exposed to minute quantities of drugs that they don't need. Much of your work has involved studying other non-target organisms like plants and animals and what do we know about the risks there?

Alistair Boxall: Obviously when you consider organisms in the environment they are being exposed directly to these things in the environment. The general message from the data that we're seeing again is that the levels in rivers are fairly low. For most pharmaceuticals the risk to aquatic systems are also quite low. There are probably a handful of drugs that the levels in the rivers are high enough where you do see effects on things like fish, invertebrates and algae in the laboratory.

Corinne Podger: And not just in the laboratory, Dr Stuart Khan from the University of NSW says drug pollution even in low concentrations is known to cause physical changes in animals and plants in the natural environment.

Stuart Khan: The main concerns is the toxicity to other environmental organisms and most famously the oestrogenic hormones, the natural hormones and also the synthetic hormones that are used in the contraceptive pill have been shown to have major impacts in some cases on aquatic species including fish. The most publicised of all is the feminisation of male fish in many rivers exposed to natural and synthetic oestrogens so that was something that was identified originally by people fishing and cutting open fish and if you know what you're looking for some people are able to tell the difference between a male fish and a female fish and they found that the male fish had many female characteristics and subsequent investigations led to demonstrating that that was a result of exposure to very low concentrations of these chemicals over a lifetime of a fish.

Corinne Podger: Are we seeing species here in Australia being affected by pharmaceutical exposure?
Stuart Khan: That's a good question. There has been research mainly on exotic species, in fact there's been quite a lot of work done at UTS, looking at mosquito fish and showing feminising effects to mosquito fish as a result of exposure to some of these same chemicals. But in terms of native Australian species no, there's been very little work done, there's been very few impacts identified and I would suggest it's because we really haven't spent the time and the energy and the money to go looking for them. And if we did that I don't see any reason that we wouldn't find the same types of impacts that have been observed in Europe and the USA.
Corinne Podger: The effect of oestrogen in fish was totally unexpected, equally unexpected the carnage in South Asia's vulture populations due to the veterinary use of diclofenac, an anti-inflammatory drug or NSAID that you might know off the shelf as Voltaren. It's used to treat ailing cattle in India, Pakistan and Nepal as Dr Richard Cuthbert from Britain's Royal Society for the Protection of Birds explains.
Richard Cuthbert: It's used as a human drug in India, it's also used as a veterinary drug in India and it's often given to cattle to treat them for pain or inflammation, if they're lame, if they have mastitis, it's also used because the animals aren't slaughtered and they are often worked to quite an old age. Unfortunately the drug is lethally toxic to vultures and they have a very high sensitivity to this drug, they only have to be exposed to a fraction of a milligram and that's enough to kill a vulture within a couple of days. There have been devastating impacts on populations, we've literally lost millions, tens of millions of vultures across India and Asia and for one species, the oriental white-backed vultures, declines over a 12 year period were more than 99.9%, so they were going down at 50% a year and they've continued to do that.
Corinne Podger: Looking specifically at diclofenac, different types of vultures react differently to it don't they and so do other carrion eating birds like crows, can you tell me a bit about that and why those differences are seen?

Richard Cuthbert: Yes there seems to be very marked species differences in the vulnerability and toxicity to NSAIDs and that is seen in mammals as well. I think a lot of people know that paracetamol is very toxic to cats. If you give your cat a human dose of paracetamol you've got a very good chance of killing it, whereas paracetamol is safe for most other mammals. Diclofenac and NSAIDs seem to have the same species-specific differences in birds, so diclofenac, as I said, is extremely toxic to Gyps vultures, which are the old world vultures, but it doesn't affect new world vultures, so your condors and turkey vultures in North and South America are able to tolerate diclofenac, as are crows. So we are still learning and still finding out which species are vulnerable and which species are unaffected, but we know for certainty that the old world vultures, the Gyps vultures are extremely vulnerable to this drug.

Corinne Podger: In South Asia there is the potential for an indirect effect on human health in settings where vultures have a role to play in cleaning up rotting material. Is that something that's been noticed in areas where there's been a drop off in vulture populations?

Richard Cuthbert: Yes, there's certainly a big worry and vultures clean up, or used to clean up tens of millions of tons of meat each year so that was cattle and other livestock that have died and been put out to be consumed. And in some parts of India and Asia human bodies are put out for vultures and with the loss of vultures that's no longer happening and we're seeing a rise in other scavengers particularly feral dogs, that obviously brings other risks and other zoonosis diseases that might be of severe risk to human health including rabies in particular and as well as the impact of dogs potentially spreading rabies, there are other diseases. There's TB, there's brucellosis, there's anthrax. That can all be spread by rotting cattle carcasses, so vultures used to play a huge eco system service by cleaning up all these carcasses and that's no longer the case.

Corinne Podger: Richard when you look at the broad range of pharmaceutical pollutants entering the natural environment from chemotherapy drugs, to birth control pills, to painkillers, to drugs to lower cholesterol - this huge range of products that are entering the environment by various ways, does that concern you with regard to non-target organisms, plants and animals?

Richard Cuthbert: Yes, that's of great concern and I think it's something that biologists and scientists are really just becoming aware of and the pharmaceutical industry is becoming aware of. So the whole concept of pharmaceuticals in the environment is a growing field, certainly the effects of pharmaceuticals on vultures was totally unexpected and very, very profound and these acute effects I think are probably quite unusual but it's become a classic conservation casebook study now, vultures and pharmaceuticals, but the broader implications of what other compounds may be doing in the environment are certainly profound. They might be much more chronic and long term in their effects but nonetheless they can have a great deal of influence.

Corinne Podger: Dr Richard Cuthbert from the Royal Society for the Protection of Birds in Britain. Another instance of environmental damage has been observed in bird populations in Spain. This time it's believed that antibiotics are to blame - Professor Alistair Boxall from York University has been monitoring that research.

Alistair Boxall: There was some interesting work a couple of years ago actually where scientists in Spain were looking at red kites and vultures and they were detecting antibiotics, these were fluoroquinolone antibiotics, in the eggs of the red kites and the vultures. And in the samples where they were seeing the presence of the antibiotics they were seeing effects on the embryos.

Corinne Podger: When you say effects do you mean deformity?

Alistair Boxall: Yes, absolute deformities of the embryo and I think in the paper they say that safety studies that were done on these drugs, studies with dogs, showed similar types of effects. But it's an area that's been quite heavily debated at the moment.

Corinne Podger: Another area of debate is the possible contribution antibiotic pollution might be making to the problem of antibiotic resistance. In recent years there's been plenty of discussion on this front about the use of antibiotics in chickens. But drugs going into sewers and waterways are also under suspicion. Dr Stuart Khan at the University of NSW.

Stuart Khan: We know that bacteria develop resistance to antibiotics when they are exposed to low non-lethal concentrations of those antibiotics and it happens

in the human gut, it happens in animal guts all the time. When we take antibiotics it's a major problem for human health and medication. But we started to realise well actually we're measuring low, constant concentrations of these same antibiotics in sewage treatment plants and all of our sewage treatment plants are designed to be biological processors and we encourage the growth of bacteria in those treatment processes. We rely on the bacteria to break down other chemicals and so the question is could our sewage treatment plants actually be a source of a selective pressure for the development or proliferation of antibiotic resistant strains of bacteria.
And there are many groups around the world currently tackling that question. We put together a review which was published this year. That review looked at the available evidence, it looked at what questions would we need to ask, what observations would we need to make in order to conclusively show that antibiotic resistance was being developed as a result of exposure to antibiotics in sewage treatment plants. And so in our study we found suggestions that this could be occurring however the evidence is still not conclusive and so further work is still required to really nail down that question.

Corinne Podger: One of the challenges in understanding pharmaceutical pollution is that drugs can behave unpredictably during water treatment, both individually and as elements in the greater mix of waste water contaminants. Dr Khan's team has had some unsettling results here. One study involved naproxen, another non-steroidal anti-inflammatory drug which is widely used to relieve menstrual pain.
Stuart Khan: Naproxen was a big surprise to us. Naproxen comes in two different forms and we refer to those as (S)-Naproxen and (R)-Naproxen and one of them, (S)-Naproxen, is a very effective pharmaceutical drug. (R)-Naproxen is toxic and highly toxic to the liver. So when you take Naproxen it's purely (S)-Naproxen and most analytical methods, when you go and measure Naproxen in waste water you can't tell the difference between the two - you get one peak in your chromatogram and that's Naproxen. We went to a lot of extra trouble to develop a new analytical method that could distinguish between (S)-Naproxen

and (R)-Naproxen and after doing that we found out that during the waste water treatment process (S)-Naproxen can be converted by the micro organisms, the bacteria in the waste water, into (R)-Naproxen, so even though the total concentration of Naproxen is decreasing we're actually forming a much more toxic product as a result. So this has led us to all sorts of questions about transformation products and it's currently a very active area of research, people thinking about how does one chemical break down and what does it form as a result of breaking down and here we find this very subtle change potentially leading to a quite significant change both in human toxicity and potentially in environmental toxicity as well.

Corinne Podger: Another big unknown that is the target of a lot of emerging research is mixtures of chemicals, what happens when different chemicals mix together in waste water and soil. And the outcomes there in terms of toxicity can be unpredictable can't they?

Stuart Khan: This is one of the big issues at the moment. So we can look at the toxicity of individual chemicals and that's what we've done for decades now and that's how we know which chemicals are toxic and how toxic they are. But all of those tests are done on high concentrations of single chemicals. One of the areas that we don't cope with very well at the moment is this issue of low concentrations of complex mixtures of chemicals. What we do know is that the toxicity of a mixture can be very different to what we might expect from the sum of its parts. If we look at the toxicity of all of the individual components and we add them up, often we find we have much more toxic solutions and that's because of what we call agonistic effects, the chemicals interact with each other in a way that one chemical causes another chemical to be more toxic than it otherwise would have been on its own.

Alternatively and perhaps even more commonly we find antagonistic effects where the presence of one chemical I guess softens the toxicity of another chemical. Predicting those effects, assessing those effects, measuring those effects with mixtures is a current area of research, it's currently a little bit beyond us in a regulatory level, it's not something that we can impose for routine water quality analysis but there's a lot of research going on and particularly the National Water

Commission has invested millions of dollars in addressing some of these issues. First of all creating mixtures, synthetic mixtures to try and understand the types of impacts and the types of effects that can occur but perhaps more importantly developing tools to be able to go out and measure a water sample, a natural water sample directly. So whatever chemicals are in that water, even if we don't know what they are and in most cases we have no idea what they are and the way that we do that is by developing what are called biological assays. So it might be an assay where we grow human cells in a laboratory in a petri dish and we expose those cells to these complex mixtures and we can look at the impacts to those cells in terms of carcinogenicity, immunogenicity, just general cell toxicity etc.

Corinne Podger: Dr Stuart Khan. Earlier this year in a bid to identify the big unknowns of pharmaceutical pollution Alistair Boxall arranged a meeting of stakeholders, academics, drug company representatives and government officials. They put forward more than 400 questions covering human, animal and plant health, questions about impacts on genomes and biodiversity and how long different drugs can survive in water and soil. The questions were narrowed down into a top 20 priority list with the participants calling for concerted work over the next decade to find answers.

Alistair Boxall: If you look at the number of compounds that are in use, I think more than 4,000 pharmaceuticals are used around the world, it's obviously impossible to consider all of those and test all of those and monitor them in the environment. One of the questions is how you can sort of identify which of those are likely to be causing the real problems in the environment, so that you can then target your research work on the top priority substances. There are questions around movement of drugs into organisms and up through the food chains, there are a couple of questions around antibiotic resistance, there are a few questions about risk management, so obviously as a society pharmaceuticals are essential for our everyday life. If there are drugs that are causing a risk in the environment then we need to look at ways in which we can manage those risks and also how you evaluate whether a particular management system is effective or not.

Corinne Podger: In the meantime Australian advisor to the WHO report Dr David Cunliffe says he wants more of a focus on doctors' prescribing habits.
David Cunliffe: There isn't a great deal that we can do about pharmaceuticals getting into sewage in terms of directed use, we can stop discharge into sewage so we don't want people pouring excess pharmaceuticals down their sink or flushing it down the toilet. But in terms of the pharmaceuticals that we take I mean they are going to end up in sewage. The best thing is trying to prevent as many of the hazards actually getting to your treatment plant in the first place so with pharmaceuticals that should be directed at good prescribing, good disposal of unwanted pharmaceuticals and there are a lot of take back programs that have been developed to try and keep pharmaceuticals out of the environment and they have been quite successful. They have taken out tons and tons of pharmaceuticals that may have ended up in the environment so just by good management you can reduce the concentrations that get into our water resources. And that just makes good sense, you reduce the waste, you reduce the concentrations that just don't need to be in our water resources.
Norman Swan: That special *Health Report* on pharmaceuticals in the environment was made by Corinne Podger, I'm Norman Swan and you can hear the *Health Report*again by going to ABC Radio National's website.

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Further Information

Professor Alistair Boxall - website
Dr Richard Cuthbert - website
Dr Stuart Khan - website
Australian Drinking Water Guidelines (October, 2011)
Pharmaceuticals in Drinking Water - Technical Report WHO, June 2011
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Vulture Rescue - A conservation and awareness raising initiative
Drugs in Drinking Water - JAMA, October 12, 2011, Vol. 306, No. 14, page 1535

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