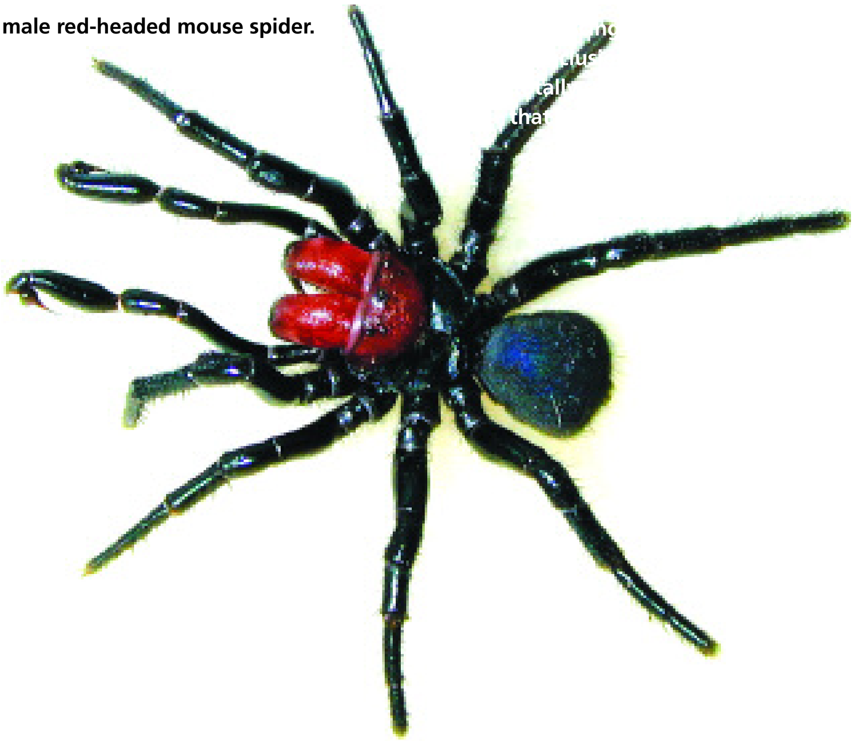


A male red-headed mouse spider.

Safe Pesticides from SPIDER VENOM

The venomous eastern mouse spider doesn't share the reputation of the infamous funnel-web, but it could change the future of insecticides. Youmie Chong puts its venom to the test.

On a cool autumn morning on the central coast of New South Wales, the air is crisp and moist from the rain of the previous night. A child playing in his suburban backyard discovers a big black spider among his toys. His parents, distressed at the funnel-web's "invasion", immediately douse the spider with enough fly spray to kill an entire species.

> **"Some of these compounds also have potential as therapeutic drugs, such as the anti-bloodclotting agents found in some snake venoms and the pain-killing properties of cone-snail toxins."**

Such scenarios are common, particularly in eastern Australia, where the density of funnel-webs is high. Fear of these spiders is no surprise given their bad publicity. What many people don't know is that funnel-webs aren't the only deadly ground-dwelling spiders in this part of Australia.

In early 2002 I joined the Neurotoxin Research Group headed by Graham Nicholson at the University of Technology, Sydney. I began my research on the eastern mouse spider (*Missulena bradleyi*), and as soon as I saw a live specimen I realised why I'd been unaware of this impressive-looking creature.

It is easily mistaken for a funnel-web as it shares some characteristics, such as a heavy-set body and a shiny black carapace. Like their feisty funnel-web cousins and unlike other spiders, which run and hide at the first sign of a threat, mouse spiders rear up on their hind legs and display large needle-sharp fangs. Yet mouse spiders are quite sluggish in their movement and are on average much smaller than funnel-webs: females grow to around 2.5 cm, while funnel-webs can be up to 5 cm.

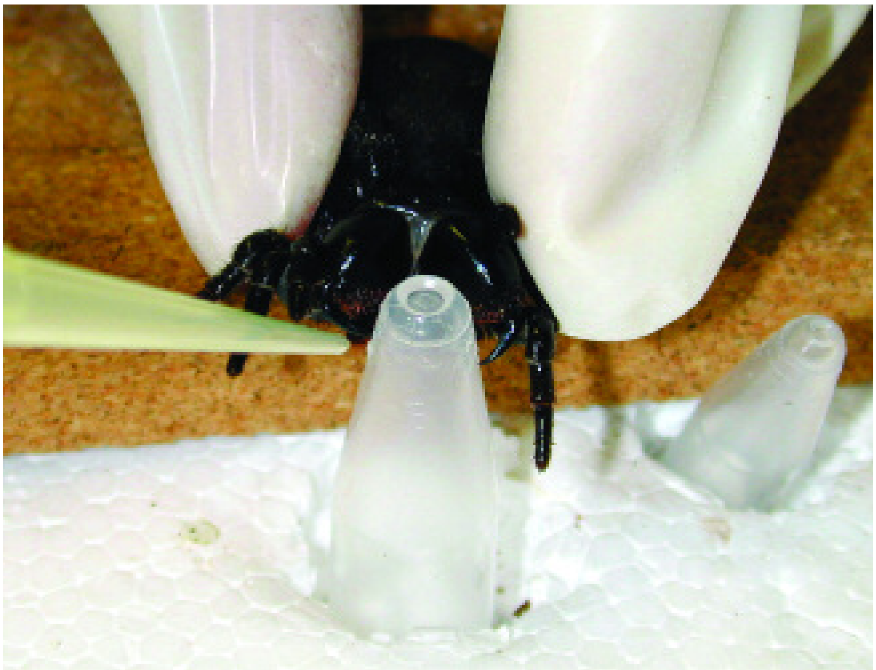
The venom of red-headed and male eastern mouse spiders appears to be as potent as the venom of male funnel-web spiders (*Atrax* and *Hadronyche* spp.) found in areas such as Sydney and the Blue Mountains. A small number of cases of male mouse spider bites to adults and children have been medically documented, with symptoms ranging from localised pain to uncontrollable muscle twitching, vomiting and profuse sweating.

Fortunately, funnel-web antivenom seems to reverse the neurotoxic effects of mouse-spider venom. It has been used on patients suffering bite symptoms with great effect, and experiments I have performed show that funnel-web antivenom is an effective antidote to mouse spider bites.

Indeed, the active component in mouse spider venom is very similar in structure to its equivalent in funnel-web venom. It is therefore possible that the number of mouse spider bites has been underestimated – a case of mistaken identity.

Interestingly, not all mouse spider venom is harmful to humans. The female eastern mouse spider, for example, produces about the same amount of venom as its male counterpart, but tests have shown no significant effect on vertebrate animals such

Top: A female mouse spider in her burrow.
Below: A female is milked.



as chicks, mice and rats. In other words, a bite from a female eastern mouse spider is unlikely to cause any serious side-effects other than perhaps some slight swelling and pain at the local bite site.

I had read this from previous reports, but to be certain I performed the same experiments on vertebrate nerves using female mouse spider venom as I did for male venom, and found that the female venom was innocuous.

So why the difference between male and female eastern mouse spider venom? The outdoor walking habits of the males exposes them to predation by birds, reptiles and mammals. Perhaps the males have responded by developing a defensive toxin that is effective against vertebrates. Or perhaps the toxins that evolved against prey insects were fortuitously active on mammals such as primates and rodents because of the conservation of targets in the nervous system of both invertebrate and vertebrates during evolution.

Female eastern mouse spiders spend most of their lives in the burrow, so there has been little pressure to evolve vertebrate toxins in their venom.

Meet the Mygalomorphs

Mouse spiders, along with funnel-webs and trapdoors, belong to a group of primitive spiders known as mygalomorphs, whose ancestry dates back some 300 million years before the evolution of flying insects. Rather than building webs to catch their next meal, these spiders have developed large heavy bodies, huge fangs and potent venom to paralyse and kill their arthropod prey.

Ten species of *Missulena* have been described, but only three of the larger species are commonly seen. The eastern mouse spider (*M. bradleyi*) is found on the east coast and highland regions of Australia, the red-headed mouse spider (*M. occatoria*) inhabits most of the continent west of the Great Dividing Range, while the northern mouse spider (*M. pruinosa*) lives in the tropical north. The males of these species have unique colour markings, a feature rarely seen in mygalomorph spiders.

The "mouse spider" epithet comes from the mistaken belief that these spiders either lived in mouse burrows or built deep hollow burrows like mice. Female eastern mouse spiders do spend most of their lives underground but they build a tight and narrow burrow lined with web, with two flaps that function as doors. For this reason the females are rarely seen, unless they are forced out of their burrows by disturbances such as flooding, building or gardening activities. The smaller males, however, are often spotted because of a characteristic bluish-white patch on the front of the abdomen and a tendency to roam in daylight in search of a mate. The male red-headed mouse spider is even more distinct due to the bright red colouring of its jaws and head region, and an iridescent gun-metal blue abdomen.

The venom of female mouse spiders is not toxic to vertebrates.

But they still need venom to disable and kill their crawling insect prey.

Insect-selective Toxins

Venomous animals are a perfect source of novel compounds for innovative and environmentally friendly pesticides. Some of these compounds also have potential as therapeutic drugs, such as the anti-bloodclotting agents found in some snake venoms and the pain-killing properties of cone-snail toxins.

Current technology allows these compounds to be synthesised in the laboratory using the original molecules as blueprints, which means that no animals need to be killed in the process.

My task was to identify the insect-selective toxins and what they were made of. I knew from previous research on spiders that venom often contained many different small-molecule proteins, or peptides. So I began by purifying the venom using a method known as high-pressure liquid chromatography, to get an idea of the composition of the venom. I isolated many peptides and, after testing on house crickets, found that most were not directly involved in paralysing or killing insects. Some of the peptides may have been enzymes used to digest the prey. But I came across one specific peptide that was quite different in its structure and primary sequence of amino acids (the building blocks of proteins) from others found in spiders like the funnel-webs, and this one was insecticidal.

The next step was to find out how the peptide toxin targets the insect nervous system. I tested the venom on cultured nerve cells from adult cockroaches. So far I have discovered that the toxin targets highly specific structures – known as voltage-gated calcium channels (VGCCs) – on the nerve. VGCCs play a critical role in nerve-signal transmission. Currently, none of the available pesticides kills insects using VGCCs as the target site, making this a promising new area of insecticide research.

The use of spider-based biopesticides for mainstream insect control is yet to happen, but this area of research has revealed much about insect physiology and the ways in which the nervous systems of vertebrates and invertebrates differ. During my time in the arachnid world I have developed a great respect for spiders in general. They live in our homes and backyards, quietly catching the bugs we love to hate, and we rarely give them the credit they deserve.

Youmie Chong is a PhD student researching the effects of toxins in spider venom at the Neurotoxin Research Group, University of Technology, Sydney.

The Search for New Biopesticides

At present, tonnes of chemicals are sprayed on crops and in homes and water supplies to get rid of pest insects. These chemicals contaminate the environment, including groundwater and rivers, and accumulate in more concentrated levels through the food chain. Recent studies have linked heavy pesticide use to a number of neurological diseases in humans. If we can harness the naturally occurring insect-selective toxins found in the venom of animals such as spiders, it may be possible to engineer a form of insecticide that has no deleterious effects on humans and other animals, and that does not persist in the environment.

This type of biopesticide is widely being used in the form of genetically modified plants that produce toxins in their leaves from a naturally occurring soil bacterium (Bacillus thuringiensis, Bt). These Bt plants are lethal to insects but relatively harmless to mammals. However, with mounting public concerns about genetically modified organisms, as well as the inevitable development of insect resistance to these plants, new avenues to beat these pests are needed.