Chapter 19
Spider Venoms Potentially Lethal to Humans

Wolfgang Nentwig and Lucia Kuhn-Nentwig

19.1 Introduction

Spiders have one pair of venom glands, and only a few families have reduced them completely (Uloboridae, Holarchaeidae) or modified them to another function (Symphytognathidae or Scytodidae, see Suter and Stratton 2013). All other 42,000 known spider species (99%) utilize their venom to inject it into prey items, which subsequently become paralysed or are killed. Spider venom is a complex mixture of hundreds of components, many of them interacting with cell membranes or receptors located mainly in the nervous or muscular system (Herzig and King 2013). Spider venom, as it is today, has a 300-million-yearlong history of evolution and adaptation and can be considered as an optimized tool to subdue prey.

In Mesothelae, the oldest spider group with less than 100 species, the venom glands lie in the anterior part of the cheliceral basal segment. They are very small and do not support the predation process very effectively. In Mygalomorphae, the venom glands are well developed and fill the basal cheliceral segment more or less completely. Many of these 3,000 species are medium- to large-/very large-sized spiders, and they have created the image of being dangerous beasts, attacking and killing a variety of animals, including humans. Although this picture is completely wrong, it is persistent and contributes considerably to human arachnophobia. The third group of spiders, Araneomorphae or "modern spiders", comprises 93% of all spider species. The venom glands are enlarged and extend to the prosoma; the openings of the venom ducts are moved from the convex to the concave side of the cheliceral fangs and enlarged as well. These changes save the chelicerae from the necessity of being large, and hence, on the average, araneomorph spiders are much smaller than mygalomorphs. Nevertheless, they possess relatively large venom glands, situated mainly in the prosoma, and may also have rather potent venom.

W. Nentwig (✉) • L. Kuhn-Nentwig
Institute of Ecology and Evolution, University of Bern, Bern, Switzerland
e-mail: wolfgang.nentwig@iee.unibe.ch

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This evolutionary development leads to the strange situation that while most large mygalomorphs are rather harmless to humans, among the araneomorph spiders, there are some groups possessing venoms which may affect humans considerably.

Most spiders never attack or bite humans. Moreover, several conditions must be fulfilled to call a spider dangerous or harmful for humans. (1) Spiders must be able to survive in the human environment or somehow coexist with humans. (2) After contact with the human skin, spiders must be willing to bite, i.e. they need a minimum of aggressive or self-defence behaviour. (3) Only spiders with more than 8–10 mm body length can penetrate the relatively thick human skin with their chelicerae. Since most spiders are smaller than 8–10 mm, do not live in man-made habitats and do not intend to attack and bite, most species are absolutely harmless to humans.

Most spider bites are unintentional, because a spider is accidentally squeezed and forced to bite. Most bites are harmless and can best be compared to a mosquito or wasp sting. For some spider genera, however, severe responses of human victims have been reported, leading to serious medical problems and sometimes also to death. This group comprises five genera with a few dozen species "of medical importance for humans" which are the topic of this chapter.

The most dangerous venomous animals are snakes, causing at least 20 fatalities per million humans annually (Table 19.1). Among arthropods, scorpions are the most dangerous (0.1–1.4 deaths per million humans), but also bees and wasps (up to 0.2 deaths) are dangerous. Spiders are considered to be less dangerous, but there is only poor documentation of the frequency of spider bites. Russell (1991) assumes <200 fatalities, globally per year, due to spider bites and Langley (2005) gives an annual average of six fatal issues for the USA. These figures refer to 0.04 and 0.02 deaths per million people per year, but both reports are based on statistics where no spider species verification was required.

The problem with spiders is that people often tend to name any sting or bite as a "spider bite", irrespectively of the presence of a spider or not. Physicians and other health professionals tend to identify all kinds of creatures as spiders and even confirm "spider bites" without having seen any animal. Also the presence of two fang marks is no reliable indication of a spider bite. For a more detailed insight into these problems, see Isbister and Gray (2002a, b), Isbister and White (2004) and Vetter and Isbister (2008). Following these considerations, three prerequisites must be fulfilled to accept a spider bite as such: (1) evidence of a bite through symptoms such as pain or discomfort, (2) collection of the spider during or immediately after the bite and (3) identification of the spider by an expert.

19.2 Spiders Lethal to Humans

19.2.1 Australian Funnel-Web Spiders (Atrax and Hadronyche, Hexathelidae)

The only group of mygalomorph spiders of medical importance comprises about 40 species of *Atrax* and *Hadronyche* (Australian funnel-web spiders, Hexathelidae),

Table 19.1 Numbers of bites and stings and documented deaths per year for the two most venomous animal groups (snakes and scorpions), for bees and wasps and for spiders

Venomous animal group	Region	Bites or stings per year	Deaths per year	Human population (millions)	Death rate per million	Reference
Snakes	World	5,400,000	125,345	5,840	21.5	Chippaux (1998)
Scorpions	World	115,000 (recorded)	180	2,264	0.08	Chippaux and Goyffon (2008)
–	World	1,190,000 (recorded + estimated)	3,271	2,264	1.4	Chippaux and Goyffon (2008)
Bees and wasps	USA	NIA	48	265	0.18	Langley (2005)
–	Australia	NIA	0.35	18	0.02	McGain et al. (2000)
Spiders	World	NIA	<200	5,300	0.038 (1)	Russell (1991)
–	USA	NIA	6	265	0.023 (1)	Langley (2005)
–	World	NIA	0 to <5	6,200	0 to <0.001 (2)	This study

The human population refers to the considered region and time when data were compiled

(1) Data do not refer to verified spider bites only and thus are much too high and not reliable

(2) According to this study, no proven record of fatal issue due to spider bites has been recorded for the last 20 years. In some cases, however, documentation is poor; therefore, we conclude that at most, "a few" fatal issues may have happened which is here translated as "0 to <5". On the basis of the medium year 2000 of the considered period, this refers to 0 to <0.001 deaths per million

NIA no information available

most commonly *A. robustus*, *H. infensa*, *H. versuta*, *H. formidabilis*, *H. venenata*, *H. cerberea* and a few still undescribed *Hadronyche* species (Isbister et al. 2005). These are large to very large spiders with typical orthognath chelicerae, dark brown to black and 15–45 mm body length. Most species are terrestrial, some arboreal in hollow tree trunks. They build silken tubular retreats with irregular silk lines radiating from the entrance ("funnel"). Spiders may be concentrated in suitable habitats, thus forming "colonies". They usually sit in the entrance of their burrow and grasp prey items that touch the silken lines. Adult males usually leave their burrow to search for females.

Atrax and *Hadronyche* species are restricted to the south-eastern coast of Australia where they can be found in moist to dry woodland and semiopen habitats. They prefer sheltered microhabitats, and so urban areas offer ideal possibilities. Spiders are frequently found around stone walls, garden rocks, dead wood and logs or heaps of building materials. This high spider abundance in the densely populated parts of Australia causes regular bites by Australian funnel-web spiders, but the frequency of bites is unknown. White et al. (1995) give an estimate of 30–40 annual bites, of which only one tenth needs medical treatment since most bites are "dry" (no venom injected) or effects are so minor that no health institution is consulted. Most bites occurred at the extremities, usually on the fingers.

In the most comprehensive analysis of these species, Isbister et al. (2005) gathered information on 138 cases where the collected spider could be attributed to *Atrax* and *Hadronyche* species. In 88% of cases adult males caused a bite, obviously in their mate-searching phase. Severe symptoms occurred in 31% of cases and were only caused by male spiders, 69% were considered as minor or moderate and nearly half of the severe cases happened to children. Half of the severe cases were due to bites of *Atrax robustus*, and one seventh of all cases could be attributed to *Hadronyche formidabilis* and *H. cerberea*, respectively. Before the introduction of antivenom in 1981, 13 fatalities occurred, half of them in children. After 1981 no further death was recorded. In more than 90% of antivenom application, a complete positive response could be achieved, and so the antivenom therapy is considered to be safe (Isbister et al. 2005).

A spider bite is usually very painful for about 30 min. Most cases are restricted to local symptoms (skin redness, sometimes piloerection, sweating and muscle fasciculation). Systemic symptoms usually appear 10 min to 1 h after the bite and are usually considered to be severe. They start with tongue spasms, followed by nausea and vomiting, abdominal pain, sweating and dyspnoea. Among the severe cases, about 75% showed sweating and hypertension, about 50% increased salivation, agitation, vomiting, tachycardia, fasciculation and pulmonary oedema. Recommended treatment of such cases is the use of funnel-web spider antivenom (Isbister et al. 2005).

The effective components of the venom of Australian funnel-web spiders are the δ-atracotoxins, 42 amino acid residue containing polypeptides with four disulphide bridges following the inhibitor cystine-knot motif. These neurotoxins bind with high affinity to mammalian sodium channels and cause a prolongation of the action potential duration, whereas binding to most invertebrate sodium channels is only with low affinity. The alerted neuronal excitability explains the intense muscle

fasciculation, which is seen clinically during systemic envenomation, whereas effects on the autonomic nervous system such as vomiting or salivation are probably due to an accompanying excessive neurotransmitter release (Nicholson et al. 2004).

19.2.2 Recluse Spiders (Loxosceles, Sicariidae)

The worldwide occurring genus *Loxosceles* contains about 100 species, 85 of which are native to the Americas, and some have been globally distributed as alien species (e.g. the European *L. rufescens*). Recluse spiders are small- to medium-sized spiders of 5–12 mm body length, often yellowish or reddish to brown, and they have only six eyes. Spiders hide in crevices under rocks or under bark, where they spin a retreat and add a few silk lines to the surrounding surface, which alert them when a prey entangles. Most species occur primarily in arid to semiarid areas, and some are therefore predestined to a synanthropic way of living, including inside buildings. Males live up to two years, females up to three years. Only a few species are of medical importance, e.g. *L. reclusa* in North America, *L. laeta*, *L. gaucho* and *L. intermedia* in South America, *L. parrami* in South Africa and *L. rufescens* in the Mediterranean area. Recluse spiders can survive several months without food, are relatively tolerant to each other, and can reach high densities inside buildings such as up to 1,250 in one barn or 2,055 in one home. Interestingly, in this house, no family member had been bitten for over six years. In houses, spiders typically can be found under the folded flap of card boxes, inside cupboards, behind pictures and furniture, in shoes and in clothes left on the floor (White et al. 1995; Vetter 2008). This also describes the possibilities of getting unintentionally in contact with a recluse spider, which may then in turn feel threatened and may bite to defend. Typically, this results in bites in the extremities or, when a person is asleep or is getting dressed, bites to other exposed body parts. *Loxosceles* bites and the associated syndrome are often called loxoscelism.

Vetter (2008) distinguishes four categories of *Loxosceles* bites: (1) unremarkable bites with very little damage and self-healing; (2) mild reaction with skin redness, itching, and slight lesion but typically self-healing; (3) necrotic skin lesion; and (4) systemic or viscerocutaneous, affecting the vascular system, very rare, and potentially fatal. In contrast to the public perception, most recluse bites belong to categories (1) and (2), thus typically heal without treatment. In severe cases, *Loxosceles* venom causes vascular constriction at the bite site. After 3 h leukocytes infiltrate the tissue, dermal oedema occurs or arises after 6 h and itching, inflammation and ischaemia develop. Now the affected tissue causes pain, and a characteristic blister appears with eschar formation, which falls off later. This exposes soft tissue, which may take months to heal. In category (3), two third of all cases heal without complication. However, the most severe cases may result in 40 cm large necrotic lesions, healing only after several months and leaving an ugly scar. In very rare cases of systemic reactions, *Loxosceles* venom may cause hemolysis, intravascular coagulation, sepsis, renal failure and possibly death (White et al. 1995; Vetter 2008).

Phospholipase D (also known as sphingomyelinase D) is the major active compound in the venom of *Loxosceles* spiders. It is a rare enzyme in organisms, mainly known from sicariid spiders and microorganisms (see also Binford 2013). Depending on the species, phospholipases D are 31–34 kDa enzymes which hydrolyse sphingomyelin and lysoglycerophospholipids at the outer surface of cell membranes, thus destroying the membranes. Obviously, *Loxosceles* rely to the highest degree among spiders on the activity of such enzymes when subduing a prey. Humans are extraordinary sensitive to phospholipase D, as rabbits and guinea pigs also are, but unlike rats and mice (Vetter 2008). Damage is greater in obese victims because the enzyme readily destroys poorly vascularised adipose tissue. Terms such as necrotic skin lesion, dermonecrosis, skin ulcerations or even necrotic araneism have been used to describe the clinical picture of severe recluse bites.

For most non-necrotic forms of *Loxosceles* bites, no specific therapy is needed besides rest and some cooling. Antivenom therapy is frequently used against loxoscelism, but its efficacy is controversial. Since a recluse bite causes no pain, which is quite unusual for spiders, patients often search medical help only after the first day and if the wound worsens. Therefore, no reliable data on the frequency of bites is available. Analyses of such patients with confirmed *Loxosceles* bites indicated an average of 40–60% of cases with necrosis and 2–16% of severe or systemic cases (Vetter 2008). For South America, White et al. (1995) reviewed several studies prior to 1988 with a total of 25 fatalities, collected over more than 30 years. While loxoscelism is the most frequently diagnosed cause of spider bites in the USA and in South America, *Loxosceles* species do not seem to be of major medical concern in other continents.

In addition to such figures, several studies showed that *Loxosceles* bites are overdiagnosed by physicians. Specifically in the USA, thousands of recluse bites were diagnosed from regions where *Loxosceles* did not occur or where they were extremely rare. Also misdiagnosis is frequent, as re-examinations showed that up to 80% of diagnosed recluse bites were caused by other agents, usually other arthropods, Lyme borreliosis, *Streptococcus* or *Staphylococcus aureus* infections or other pathogens (Vetter 2008).

19.2.3 Black Widow Spiders (Latrodectus, Theridiidae)

The worldwide-distributed genus *Latrodectus* contains 31 species, usually called (black, brown, grey, etc.) widow spiders. Widows are small- to medium-sized spiders of 8–18 mm body length, often black with characteristic red marks but also brown or grey. They build irregular cobwebs with sticky threads and a tubular retreat. Typically, widow spiders inhabit arid to semiarid habitats but are capable of invading a variety of different habitats, including rural and urban areas. Though widows are not aggressive, contact with humans can lead to bites, which may cause serious symptoms so that widows are regarded as the spiders with the highest medical importance. Most relevant species are the South American black widow

Fig. 19.1 *Above*: *Latrodectus geometricus* and *L. tredecimguttatus* (Theridiidae), © Barbara Thaler-Knoflach at www.araneae.unibe.ch. *Below*: *Phoneutria* sp. (Ctenidae), © Matjaz Kuntner

L. curacaviensis (Central and South America), the brown widow *L. geometricus* (Africa but introduced as alien species to all other continents) (Fig. 19.1), the redback *L. hasseltii* (Asia to Australia), the North American black widow *L. mactans* (North America but introduced as alien species elsewhere), the African black widow *L. indistinctus* (southern Africa) and the European black widow *L. tredecimguttatus* (Europe to China) (Fig. 19.1). Due to their affinity for human buildings and goods such as containers, widows are predisposed for easy spread by cargo transport. Widow bites and the associated syndrome are often referred to as latrodectism. Since the bites of different *Latrodectus* species, when analysed under comparable medical standards, cause very similar symptoms, latrodectism is considered as the same clinical syndrome worldwide (Isbister and White 2004).

Bites usually occur on the extremities (70–80%), less frequently on the trunk (20%) and rarely on the head or neck. In many cases, a bite causes significant effects, with severe and long-lasting pain in two-thirds of cases, and prevented patients from sleeping in one-third of cases. As in most other comparably small spiders, puncture marks or bleeding is rarely observed. Pain increases in more than half of the cases within the first hour and mostly radiates into the limbs or

abdominal pain develops. According to a meta-analysis of Isbister and White (2004), the typical symptoms include sweating in about 70% of cases and systemic effects in 20–30% of cases (nausea and vomiting in less than 20%, raised temperature and neuromuscular effects in about 10%, hypertension in less than 10% of cases). Pain usually lasts 1–2 days and the other symptoms 1–4 days.

Nevertheless, many widow bites do not need any treatment because no symptoms appear or local pain disappears after some hours (White et al. 1995). The treatment of the more serious widow bites may be performed symptomatically (i.e. pain relief medicine, antispasmodic and relaxant drugs), but also antivenom is frequently applied if available and/or if the case seems to justify it. There is increasing discussion on the effectiveness of antivenom therapy, and there is considerable reluctance to administer it due to the frequency of allergic reactions. Nevertheless, given the potentially fatal consequences, Isbister and White (2004) conclude that antivenom may be justified in up to two third of cases.

The most active components in the venoms of *Latrodectus* are latrotoxins, of which α-latrotoxin is active against vertebrates. This is a 131 kDa protein which composes two tetramers in the neuronal membrane, thus forming a pore which allows mono- and bivalent cations, neurotransmitters, ATP and water to influx into the cell. This permanent firing blocks synapses and provokes cramps, it may cause cardiac disturbance and renal damage, and finally, it may even lead to a fatal outcome due to heart failure, myocardial ischaemia or renal failure.

The frequency of fatal issues with humans is highly debated since all latrodectism studies are considerably biased. They usually start with patients asking for medical help or often include only severe or hospitalised cases and therefore have a strong bias. Nevertheless, it is believed that 15% of *Latrodectus* bites do not lead to envenomation (Peterson 2006) and that many bites cause only minor effects, thus requiring no treatment or hospitalisation (White et al. 1995; Isbister and Gray 2003). Furthermore, it has often been mentioned that the frequency of widow bites is seriously overestimated since many diagnoses of latrodectism are wrong. There are no positive tests available, no single symptom supports such a diagnosis and only a spider collected while biting and subsequent identification by an expert can guarantee that it is a "verified *Latrodectus* bite". The fatalities attributed to latrodectism as reviewed in White et al. (1995) must be seen in this light. For Australia, no fatal case has been reported since 1956 when antivenom therapy became available, and also for the USA, no fatal case is listed in their annual reports among ten thousands of widow bites from the last years (American Association of Poison Control Centers 2012). Nevertheless, there are a few publications of fatal incidents of *Latrodectus* bites (e.g. Hoxha 2006; Gaisford and Kautz 2011), but all refer to non-verified spider bites.

19.2.4 Armed Spiders (Phoneutria, Ctenidae)

Eight species have been described for the Central and South American genus *Phoneutria*, all large spiders with body lengths between 20 and 45 mm (Fig. 19.1). Body colouration is usually grey to brown with reddish chelicerae and a black-striped

pattern on the underside of the first two pairs of legs. *Phoneutria* species do not build webs but search at night for prey. These tropical species live primarily in the rainforest but invade rural and urban areas and are able to habitate human buildings. When disturbed, these spiders show a typical defensive behaviour in which the body is in an erect position, the first two pairs of legs raised up, thus showing the conspicuous striped pattern on their underside, while the spider sways from side to side. Common species are *P. nigriventer*, *P. keyserlingi*, *P. fera* and *P. reidyi*.

Especially in the large urban areas of the Brazilian east coast, spiders frequently encounter humans. Though the spiders are nocturnal, most bites occur during the day and in houses, mainly in the mating season (January to April) when the spiders are more active. *Phoneutria* spiders are frequently encountered in shoes, among rubbish and construction material and in banana bunches, which explains the high frequency of bites to the hands and feet. *Phoneutria* bites are very common and accompanied by strong pain. Almost all patients complain about burning pain, often spreading over the affected limb. Further local symptoms are swelling and a dilatation of blood vessels (hyperaemia). Children and young people are more sensitive to *Phoneutria* venom than older people. Mild envenomation is observed in 90% of cases and includes accelerated cardiac rate as a systemic symptom. Moderate cases (further 9%) are characterised by nausea, vomiting and sweating. Severe cases (less than 1%) show a reduced cardiac rate, hypotension, cardiac arrhythmia and acute pulmonary oedema. Symptomatic treatment includes analgesics to relieve pain as a standard treatment in >75% of cases. In some severe cases, antivenom is given, but nearly 20% receive no treatment at all (White et al. 1995; Bucaretchi et al. 2000).

During the last 100 years, 10 fatal cases have been reported from Brazil for *Phoneutria*. Most cases, however, are poorly documented, and only two meet today's standards, and the last fatal case occurred in 1985. Death is considered to be extremely rare and seems to be restricted to small children (Bucaretchi et al. 2000).

The venom of *Phoneutria* spiders contains several components, which may explain its toxic effects. Histamine causes pain, and a variety of ion-channel active peptides (in the size range of 3.5–8.6 kDa) inhibit or delay inactivation of Ca^{2+}, K^+ and Na^+ channels. This leads to a depolarization of muscle fibres and nerve terminals at the neuromuscular junction. Also several tachykinin peptides with molecular masses between 0.9 and 1.7 kDa could be identified from the venom of *P. nigriventer*. They are characterized by vasodilatory and neurohormonal activities and probably provoke the observed release of acetylcholine and catecholamines, which is responsible for some systemic effects (White et al. 1995; Kuhn-Nentwig et al. 2011).

19.2.5 Other Spider Species Which Are Considered to Be Dangerous

Large mygalomorph spiders ("tarantulas") are feared because of their size and the overall Hollywood image of being very dangerous. The reality, however, is different. Bites of Australian mygalomorph spiders other than the hexathelids mentioned

in Sect. 19.2.1 (such as Theraphosidae, mouse spider *Missulena* and trap-door spiders of the families Idiopidae and Nemesiidae) cause local pain, skin redness and sometimes bleeding due to the size of the wound, but no severe effects (Isbister and Gray 2002b). A comparable result was attained in a major Brazilian study with 91 identified cases. Theraphosid bites were considered to be rare (<1% of spider bites), and envenoming is described as mild with main symptoms of local pain and minor skin redness (Lucas et al. 1994).

Other large spiders, such as huntsmen (usually sparassids of the genera *Heteropoda* and *Neosparassus*), are feared because of their size and leg span, because of their ability to climb walls and ceilings and because of their synanthropic way of life. These spiders flee from humans already when they are a long distance away, but when people try to catch them, they may get bitten. Clinical effects are described as an immediate and transient pain, disappearing already after a few minutes. Systemic effects are rare and minor; thus, sparassids are regarded as very harmless spiders (Isbister and White 2004).

Yellow sac spiders of the genus *Cheiracanthium* comprise about 180 species, but only a few species exert a synanthropic way of living and encounter humans more frequently, mostly *C. inclusum* and *C. mildei* in North America and *C. punctorium* in Europe to Central Asia. These medium-sized spiders (body length mostly below 10 mm) have relatively long chelicerae and can bite humans, outdoors or at home or also at night when sleeping while unintentionally squeezing the spider. The bite provokes pain and discomfort in all cases, lasts typically for less than 2 h and leads to local redness (85% of cases), swelling (30%) and itchiness (30%). Systemic effects were observed in 15% (headache, vomiting). Complete recovery occurred fast, and no long-lasting effects were observed, so that *Cheiracanthium* species can be categorized as rather harmless (Vetter et al. 2006).

Despite frequent citation in the medical literature and in newspapers, hobo spiders (this term refers only to the alien introduction of the European *Tegenaria agrestis* (Agelenidae) into Pacific United States) do not cause painful bites or necrosis to humans (Vetter and Isbister 2008). Also bites by other agelenids (*Agelena*, *Agelenopsis*, *Hololena* species) are very rare events and usually harmless (Vetter 2012). Wolf spiders (Lycosidae) are distributed worldwide, and some genera comprise species of medium body size (e.g. *Hogna* and *Lycosa*), but nevertheless, their bites cause only medium pain and generally mild, transient symptoms. Details can be found in reviews by Isbister and White (2004) and Vetter and Isbister (2008).

19.3 Necrosis After a Spider Bite?

The term necrotic arachnidism refers to the fact that the bite of several spider species may induce skin necrosis. Especially in the older literature, often uncritically referred to, there is no clear differentiation between a direct venom effect and

potential secondary infections. Moreover, cases of unverified spider bites are included in such statistics. The non-scientific classification of spider bites ("putative, presumptive, probable, documented") as listed in the medical education literature (Sams et al. 2001) unfortunately suggests that it could be possible to identify spider bites and even the spider species according to symptoms. There is no way of correct spider identification without a specimen; thus, it is indispensable of keeping the gold standard of verified bites as described above. Such nebulous definitions of spider bites are probably the basis for frequently encountering necrotic arachnidism as being attributed to many spider species still today in the literature.

According to current knowledge, necrosis following a spider's bite is only caused by *Loxosceles* species (and the small genus *Sicarius*, endemic to South African deserts, both in the same family, Sicariidae). The venom contains phospholipase D (also known as sphingomyelinase D), an enzyme which destroys membranes, thus causing necrosis (see Binford, 2013). Careful analysis of other spider venoms proved the unique case of sicariids. Especially *Cheiracanthium* venom, for a long time also considered to cause necrosis, definitely does not cause necrosis (Vetter et al. 2006; Vetter and Isbister 2008). Necrotic arachnidism induced by sicariids must clearly be distinguished from secondary infections which may be caused by a variety of different agents, usually initiated by a physical injury or forms of skin blistering and ulceration (White et al. 1995).

19.4 Conclusions

Spiders from four families (*Atrax* and *Hadronyche* (Hexathelidae), *Loxosceles* (Sicariidae), *Latrodectus* (Theridiidae) and *Phoneutria* (Ctenidae), with several species each) may cause severe symptoms when biting humans. This is mainly due to a combination of factors: (1) synanthropic way of living (all taxa), (2) high densities in urban areas (*Latrodectus*, *Loxosceles*, *Phoneutria*), (3) large body size (*Atrax, Hadronyche, Phoneutria*), (4) ion-channel targeting neuropeptides or other venom compounds which are very potent and/or to which vertebrates/humans are very sensitive (*Atrax*, *Hadronyche*, *Latrodectus*, *Phoneutria*), (5) a venom enzyme causing necrosis (*Loxosceles*), and (6) aggressive behaviour towards humans (*Phoneutria*). Several decades ago, fatal incidents were reported for all four groups, but medical documentation as well as medical standards in many countries were poor. In the last 2–3 decades, no fatalities were reported for *Atrax, Hadronyche, Latrodectus* and *Phoneutria*. The situation with *Loxosceles* is less clear, but on a global scale, it is obvious that fatalities due to spider bites are now close to zero, which refers to an annual mortality of <0.001 per million humans. Thus, spiders are by far less dangerous than bees and wasps (Table 19.1).

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