BIOLOGICAL REVIEWS

Cambridge Philosophical Society

Biol. Rev. (2014), **89**, pp. 450–465.
doi: 10.1111/brv.12062

Poisons, toxungens, and venoms: redefining and classifying toxic biological secretions and the organisms that employ them

David R. Nelsen[*], Zia Nisani[†], Allen M. Cooper, Gerad A. Fox, Eric C. K. Gren, Aaron G. Corbit and William K. Hayes

Department of Earth and Biological Sciences, Loma Linda University, 11065 Campus Street, Loma Linda, CA 92350, U.S.A.

ABSTRACT

Despite extensive study of poisonous and venomous organisms and the toxins they produce, a review of the literature reveals inconsistency and ambiguity in the definitions of 'poison' and 'venom'. These two terms are frequently conflated with one another, and with the more general term, 'toxin.' We therefore clarify distinctions among three major classes of toxins (biological, environmental, and anthropogenic or man-made), evaluate prior definitions of venom which differentiate it from poison, and propose more rigorous definitions for poison and venom based on differences in mechanism of delivery. We also introduce a new term, 'toxungen', thereby partitioning toxic biological secretions into three categories: poisons lacking a delivery mechanism, i.e. ingested, inhaled, or absorbed across the body surface; toxungens delivered to the body surface without an accompanying wound; and venoms, delivered to internal tissues *via* creation of a wound. We further propose a system to classify toxic organisms with respect to delivery mechanism (absent *versus* present), source (autogenous *versus* heterogenous), and storage of toxins (aglandular *versus* glandular). As examples, a frog that acquires toxins from its diet, stores the secretion within cutaneous glands, and transfers the secretion upon contact or ingestion would be heteroglandular–poisonous; an ant that produces its own toxins, stores the secretion in a gland, and sprays it for defence would be autoglandular–toxungenous; and an anemone that produces its own toxins within specialized cells that deliver the secretion *via* a penetrating wound would be autoaglandular–venomous. Adoption of our scheme should benefit our understanding of both proximate and ultimate causes in the evolution of these toxins.

Key words: definition, classification, toxin, venom, poison, toxungen.

CONTENTS

---

[*] Author for correspondence (Tel: +1 909 558 4530; Fax: +1 909 558 0259; E-mail: dnelsen@llu.edu).

[†] Antelope Valley College, Biology, Division of Math, Science & Engineering, 3041 West Ave K, Lancaster, CA 93536, U.S.A.

I. INTRODUCTION

Poisonous and venomous organisms have generated both fascination and loathing since the beginning of recorded history. They have also inspired considerable research across a broad range of disciplines. Despite the extraordinary attention given to these animals and the toxins they produce, substantial confusion remains regarding the distinction between 'poison' and 'venom'. Even a cursory review of the scientific literature reveals inconsistencies and ambiguities in definitions of these terms, as well as frequent conflation with the more general term, 'toxin'. Furthermore, the definition for venom, which has the most precise meaning, is often excessively narrow and excludes many toxic secretions classically thought of as venoms.

Despite this long and continuing history of conflation (e.g. Osterhoudt, 2006; Gibbs, 2009), biologists and toxicologists alike have gradually forged an important distinction, primarily in mechanism of delivery: poisons are typically ingested or encountered passively, whereas venoms are typically injected by means of a specialized device (Mebs, 2002). This distinction, though based on proximate causation, can help to clarify the evolution of these toxins in terms of ultimate causation (*sensu* Ayala, 1999). The mechanisms by which organisms deliver toxins relate to how the toxins function and their evolution. Toxins delivered by passive contact or ingestion function best for defence, whereas those delivered *via* a penetrating wound are especially well suited for predation, and therefore are often under different selective pressures (Mebs, 2002; Brodie, 2009). Understanding such distinctions can inform our efforts to develop applications for biotechnology and pharmaceutical purposes.

Herein, we first clarify the distinctions among three major classes of toxins (biological, environmental, and anthropogenic), but limit further consideration to a single group—the biological toxins. Second, we review the literature to evaluate critically prior definitions of venom which set it apart from poison, and assess which components of the definitions work better than others. Third, we propose more rigorous definitions for poison and venom based on readily defined differences in mechanism of delivery, and introduce a new term, 'toxungen' (pronunciation: tox-unj'-en), further to reduce ambiguity. Accordingly, we partition toxic biological secretions into three categories: poisons, toxungens, and venoms. Fourth, we develop a classification system for toxic biological secretions that specifies not only mechanism of delivery (absent *versus* present), but also source of toxins (autogenous *versus* heterogenous) and storage (aglandular *versus* glandular).

As a result of our efforts, we seek: (*i*) to develop a more rigorous and comprehensive terminology and classification of toxic biological secretions, thereby facilitating consistency in usage and discussion; (*ii*) to unify and place in better context a diverse and fractured body of literature; and (*iii*) to develop an improved framework for studying the evolution of these toxins, including their biochemical structure, associated structures (for synthesis, storage, and application), mechanism of delivery, functional roles in nature, and biodiversity.

II. TOXINS

To clarify the definitions of venom and poison, we first discuss a common feature of both: they are comprised of one or more toxins. Toxins are substances that, when present in biologically relevant quantities, cause dose-dependent pathophysiological injury to a living organism, thereby reducing functionality or viability of the organism. Onset of effects may be immediate or delayed, and impairment may be slight or severe. Relative quantity, or dose, is important because many ordinarily innocuous substances, including water, can become toxic to organisms at abnormally high levels, and many highly toxic substances can be harmless in minute quantities. As Theophrastus of Hohenheim (Paracelsus), the Swiss-German physician and 'Father of Toxicology', put it, 'All things are poison and nothing (is) without poison. Only the dose makes a thing not to be poison' (Poerksen, 2003). This axiom of toxicology posits that the effects of substances can vary depending on dose, which is a shared property of the substance and the target organism, including its receptors (Stumpf, 2006).

Little agreement exists on how toxins are classified (Hodgson, Mailman & Chambers, 1988; Schiefer, Irvine & Buzik, 1997; Eaton & Klaassen, 2001; Hayes, 2001). Based on perusal of the literature and on internet sources, which reflect common usage, we categorize toxins into three general classes:

Biological toxin—a substance produced by a living organism that is capable of causing dose-dependent pathophysiological injury to itself or another living organism; sometimes called a 'biotoxin'.

Environmental toxin—a naturally occurring substance in the environment that is not produced by an organism but is capable of causing dose-dependent pathophysiological injury to a living organism. Examples include arsenic, mercury, and lead.

Anthropogenic toxin—a substance produced by humans that does not otherwise occur in the environment which is capable of causing dose-dependent pathophysiological injury to a living organism; often called a 'man-made toxin' and sometimes called a 'toxicant'. Examples include DDT, dioxin, and polychlorinated biphenyls (PCBs).

Toxins are not in themselves living, replicating organisms, nor are they contagious, as in certain biological or chemical 'agents' used in biological warfare (e.g. bacteria, viruses, prions, or fungi). The term toxin is most appropriately applied to a single chemical substance (Mebs, 2002; Menez, Servent & Gasparini, 2002). Thus, complex mixtures of toxins, such as the venoms of snakes, should not be labeled a toxin in the singular sense. The term poison is often used to describe toxins of all three classes, whereas venom normally encompasses only biological toxins. However, humans may be uniquely capable of employing all three toxin types as venoms—*via* deliberate injection into tissues—for research and development purposes (e.g. biotechnology and medical applications), or for more nefarious objectives (e.g. harming other organisms, including humans). Other animals can accumulate environmental or anthropogenic toxins, and could conceivably use them for venom.

Hereafter, we restrict consideration largely to biological toxins, and within this context we show that poison and venom can and should be readily distinguished.

III. EXISTING DEFINITIONS

To understand better the distinction between poison and venom, we reviewed the multiple definitions of venom found in the primary and secondary literature. Definitions were found by reading through numerous venom-related articles, toxicology or toxinology textbooks, scientific dictionaries, and books dedicated to venom or venomous animals. This review allowed us to consolidate the most essential components into a single, more concise definition of venom. In the process, however, we have better defined the term poison as well, because many definitions of venom relate it to poison. Moreover, our review convinced us that, for added clarity, a new class of toxins should be recognized that is distinct from poisons and venoms.

Our review of the literature revealed a handful of shared components, or properties, among existing definitions of venom (Table 1). These included: (1) hierarchy and exclusiveness; (2) source of secretion; (3) mode of transmission, often including a specialized delivery structure or delivery system; (4) purpose (i.e. biological role or function); and (5) method of delivery being either active or passive. We examine each of these in turn.

(1) Hierarchy and exclusiveness

Hierarchy and exclusiveness should be expected in definitions of venom. By hierarchy, toxins are properly understood to be singular substances, toxic secretions deployed against other organisms are often comprised of multiple toxins (and often include non-toxic constituents as well), and organisms can possess multiple toxic secretions. As alluded to above, exclusivity, particularly between a poison and a venom, has also been deemed desirable in classifying toxins.

Of the 28 venom definitions gleaned from the literature, 5 classified venom as a toxin, 10 as a poison, and 1 of these as both a toxin and a poison. Fourteen did not specify a hierarchical classification in their definition. Lack of hierarchy is evident in statements such as, 'venoms are most commonly produced by the organisms that possess them, while toxins are often sequestered from an outside source or modified from external building blocks' (Brodie, 2009). Lack of exclusiveness is evident in, 'all venoms are poisons, but not all poisons are venoms' (Halstead, 1965). Clearly, toxin, poison, and venom are frequently conflated even by knowledgeable sources.

The Onions, Friedrichsen & Burchfield (1966) describes the origin of the word venom as being derived from the Latin word *venenum*, meaning 'poison', 'drug', or 'potion'. The origin of poison derives from the Latin *potionem* (nom. potio), meaning 'potion', or a 'poisonous drink' (Onions *et al.* 1966). Venom and poison are clearly related to each other in that they are both comprised of one or more biological toxins, as generally defined. However, the terms venom and poison, although linked in origin, have now taken on different connotations within the context of biological secretions, which 18 of 28 definitions attempted to make clear (i.e. the consensus position) and which we support. Accordingly, authors often and appropriately refer to a puffer fish (Tetraodontidae) as poisonous because of the toxic tissues which cause pathophysiological problems for predators upon consumption, and rattlesnakes (Viperidae) as venomous because they inject toxins into their prey *via* hollow fangs.

If toxicologists persist in an effort to create mutually exclusive categories for poisons and venoms, then both hierarchy and exclusiveness are appropriate for defining venom. Thus, poisons and venoms should be formally recognized as substances comprised of one or more toxins, and they should be defined so as to maintain their distinctiveness. However, two caveats merit mention: (*i*) a poison or venom can be composed of a single toxin, in which case the toxin would be equivalent to a poison or venom; and (*ii*) because poison and venom will ultimately be defined by how they are deployed, a single substance can be used as both a poison and as a venom, even by the same organism.

(2) Source of secretion

Our use of the term 'secretion' is predicated on recognition that tissues, glands, cells, and even subcellular structures can produce secretions. Venoms typically consist of a secretion containing one or more toxins. Many existing venom definitions specified whether the secretion is glandular (produced in a gland) or glandular/sub-glandular (produced within either a gland, a collection of specialized cells, or a single cell) in origin. Indeed, 11 definitions specified that venoms are glandular, 5 allowed venoms to be glandular or sub-glandular, and 12 did not specify the origin (most of these were from secondary sources). All biological toxins must be made and/or stored somewhere in the organism; therefore, it is redundant to specify in the definition that the secretion

Table 1. Six frequent components of definitions of venom from various literature sources, illustrating the remarkable lack of consensus

	Hierarchy and exclusiveness		Source of secretion			Mode of transmission			Purpose		
Source of definition	Toxin	Poison	Gland	Sub-gland	Delivery structure/ system	Injection	Wound	Contact	Predation	Defence	Active application
Primary literature											
Roth & Eisner (1962)					×	×			×	×	
Beard (1963)		×			×	×	×				
Welsh (1964)			×	×	×	×	×	×	×	×	
Halstead (1965)		×			×	×	×				
Russell (1965)		×	×	×	×						
Freyvogel (1972)	×		×		×	×	×	×	×	×	
Oehme *et al.* (1975)			×			×			×		×
Bettini & Brignoli (1978)						×	×				
Mebs (1978)			×		×	×			×	×	
Schmidt (1982)			×		×				×	×	
Sharma & Taylor (1987)	×		×								
Auerbach (1988)	×		×		?	×		?			
Meier & White (1995)			×	×	×	×			×	×	
Russell (2001)		×	×	×	×						
Mebs (2002)			×	×	×	×			×	×	×
Kuhn-Nentwig (2003)			×			×					×
Eisner *et al.* (2005)			×			×					
Brodie (2009)			×		×	×					×
Fry *et al.* (2009*b*)			×		×		×		×	×	
Mackessy (2009)			×		×	×	×				
Wuster (2010)						×			×	×	
Secondary literature											
Morris (1992)	×					×					
Garcia (1998)		×			×						
Hodgson, Mailman & Chambers (1999)	×	×			×	×					
Youngson (2005)		×									
Dorland (2007)		×									
Parker (2003)		×									
Venes (2009)		×			×						

is glandular or sub-glandular. Moreover, if the definition of venom includes the stipulation that it must be glandular in origin, then cnidarians would not be considered venomous, as the toxins are produced by and stored within a single specialized cell called a cnidocyte or nematocyte (Lotan *et al.*, 1995; Ozbek, Balasubramanian & Holstein, 2009). Yet cnidarians, which do not possess a true gland for venom production or storage, are universally regarded to be venomous—a point surprisingly overlooked by many authorities on venom. Thus, we agree with the consensus position (if secondary sources are included) that specifying the source or storage site for the secretion need not be included in the definition of venom, and the same is true for poison. The term secretion should also be avoided in the definition of venom because humans, at least, are capable of deploying toxins that would not be secretions of biological origin (e.g. injecting refined toxic chemicals into other organisms; Mebs, 2002).

(3) Mode of transmission, including a delivery structure or delivery system

The mode of transmission refers to how a biological toxin is delivered to the recipient. Venom was most often defined as being delivered specifically *via* injection (12 definitions), with other definitions specifying more generally injection or delivery *via* a wound (seven definitions). Two definitions included delivery *via* mere external contact. Eight definitions did not specify mode of transmission (the majority of these were secondary references).

The word 'injection' has the connotation of introducing a substance relatively deep into the tissues of the target through an often highly specialized structure, such as a medical syringe, rattlesnake fang, or scorpion stinger. This is, indeed, the most common method that venomous animals use to deliver their toxic secretions. However, there are many animals that deliver toxins through less-specialized methods. Gila monsters (*Heloderma suspectum*) and many colubrid snakes possess teeth that are grooved rather than hollow (in contrast to viperid and elapid snake fangs), and their toxic secretion must be chewed rather than injected into the target organism, with the toxins penetrating the wound *via* surface tension and diffusion (Fry *et al.*, 2006; Young *et al.*, 2011). Members of the Formicidae ant family deliver piercing bites with their mandibles, and spray venom from their abdominal storage glands into the wound (McGain & Winkel, 2002; Eisner, Eisner & Siegler, 2005). Similarly, the soldier castes of some termite species inflict damage with their mandibles while simultaneously secreting toxins from their frontal glands onto their victims (Prestwich, 1979, 1984; Quennedey, 1984; Schmidt, 1990). Larvae of the beetle *Phengodes lateicollis* subdue millipedes by puncturing the prey's body with the mandibles, and then injecting fluids from the gut that paralyzes the millipede (Eisner *et al.*, 2005). Thus, delivery of venom *via* a wound comprises a more general and applicable description of envenomation, and we therefore reject the consensus criterion of delivery by injection.

We propose that any definition of venom should stipulate that the biological toxin is delivered *via* mechanical trauma produced by some kind of structure that results in a wound. Because a structure, whether specialized (e.g. fang) or general (e.g. unmodified tooth), is necessary to create the wound, we find it sufficient for the definition to require toxin delivery *via* a wound and redundant to specify how the wound is created other than by an assumed mechanism.

Two definitions (Welsh, 1964; Freyvogel, 1972) allowed for the topical application of venom. There are a host of biological toxins that are applied externally by means of a sometimes elaborate mechanism, but the inclusion of these would require serious changes to the current understanding and usage of the term venom. Nevertheless, it is understandable why Freyvogel (1972) and Welsh (1964) included the topical application of biological toxins as venoms. Spitting cobras (genera *Naja* and *Hemachatus*), for example, can introduce their biological toxins to an enemy *via* injection by fangs, or by spraying it, aiming at the recipient's face and eyes. Both delivery mechanisms result in pathophysiological injury, so why would we refer to the secretion as a venom in one usage and not in the other? Inclusion of topical application of a biological toxin in the classification of venoms would necessitate inclusion of a host of other organisms as venomous that are not commonly thought to be so, thus defeating the purpose of this paper: greater clarity in a definition. We will discuss the special case of topically applied biological toxins shortly, but for now we return to the features of a classically defined venom.

(4) Biological role(s)

Numerous definitions of venom focused on its biological role(s), or purpose(s), with one stipulating that venom is used only for predation, and nine stating that venom is used for either predation or defence. In many cases (18 definitions), however, no distinction regarding the role of venom was made. Is it important to specify within a definition the purpose of venom?

Most venomous animals, such as viperid and elapid snakes, employ their toxins for predation and defence. However, venomous animals may use their venoms for a range of other purposes. Male duck-billed platypuses (*Ornithorhyncus anatinus*), for example, use their toxins and delivery apparatus primarily in the context of mate competition, using it against male conspecifics during mating and territorial disputes (Torres *et al.*, 2000). This use should qualify as a venom regardless of whether it can also be used for defence. Scleractinian coral colonies and many actiniarians (anemones) use venom for predation and defence, but also possess specialized tentacles to attack other nearby colonies, thereby protecting and expanding their own territory in the context of intraspecific and interspecific competition for space (Williams, 1991). Again, use of toxins for competition should qualify as a venom regardless of whether it is also used for predation and defence. In addition to the use of venom for self and/or colony defence (generally by injection), some hymenopterans also spray their 'venom' to keep their broods free of parasites in the context of hygiene (Oi & Pereira, 1993), and some ants spray the same secretion that is used as a venom for trail marking in the context of communication (Blum, 1966; Mashaly, Ali & Ali, 2010). Clearly, venoms can be co-opted or exapted for other purposes, just as secretions serving other purposes can be co-opted or exapted to become a venom.

Because venom can be used for more than predation and defence, the stipulation that venom must serve a defensive or predatory role seems excessive and unnecessary. Thus, we agree with the consensus position in omitting a biological role from the definition. Further, the fact that a single secretion may be delivered in multiple ways (e.g. biting and spraying) and serve multiple functions (e.g. defence, predation, competition, communication) means that individual secretions may be categorized in multiple ways simultaneously. We will revisit this notion.

(5) Active application

Four authors specified that venom is 'actively applied', whereas the remainder made no such specification. Although the behavioural act of delivering venom was not common among the definitions surveyed, we should consider its merits. As Mebs (2002, p. 1) stated, 'venoms are actively applied for both prey acquisition, which may include predigestion, and as a defense against predators . . . ' This language implies a deliberate or reflexive act on the part of the venomous animal in response to an external stimulus. But is this true for organisms that are commonly considered venomous, and what level of 'activity' is necessary to be considered active application?

Numerous widely accepted examples of envenomation obfuscate the meaning of active application. Snakes, of course, deliver their venom by biting, and scorpions and bees deliberately sting their victim. Many fish (e.g. stone fish, genus *Synanceia*, and lionfish, genus *Pterois*), however, have venomous spines that deliver toxins only defensively when the recipient (victim) initiates contact. Likewise, the toxin-bearing, harpoon-like cnidocytes of cnidarians (corals, anemones, jellyfish) are often fired due to incidental contact by recipient organisms. Do these involve 'active' participation by the venomous animal? One could argue that venomous fish must erect their toxin-laden spines, or that the cnidocytes have cnidocil triggers, and these qualify as active application. However, caterpillars of the genus *Lonomia* have stiff, permanently erect, urticating hairs that penetrate tissue and deliver venom upon contact initiated by the recipient. In this latter case, the caterpillar requires no active participation to defend itself *via* injection of toxins. A freshly deceased caterpillar could also do this every bit as effectively as a live specimen.

Thus, we agree with the consensus position that active application of toxins involving a specific behaviour or intention should not be a part of the definition of venom, as its inclusion would not result in further clarity.

IV. THREE CLASSES OF TOXIC BIOLOGICAL SECRETIONS: POISONS, TOXUNGENS, AND VENOMS

From our critical assessment of existing definitions of venom, we propose the following mutually exclusive definitions for three major classes of toxic biological secretions, with distinctions delineated in Table 2:

Poison—a toxic substance (comprised of one or more toxins) causing dose-dependent physiological injury that results in self-induced toxicity (e.g., bacterial endotoxins) or is passively transferred without a delivery mechanism from one organism to the internal milieu of another organism without mechanical injury, usually through ingestion, inhalation, or absorption across the body surface.

Toxungen—a toxic substance (comprised of one or more toxins) causing dose-dependent physiological injury that is actively transferred *via* a delivery mechanism from one organism to the external surface of another organism without mechanical injury.

Venom—a toxic substance (comprised of one or more toxins) causing dose-dependent physiological injury that is passively or actively transferred from one organism to the internal milieu of another organism *via* a delivery mechanism and mechanical injury.

Although our interest here is in toxic biological secretions (i.e. what animals normally possess), which are ordinarily comprised of one or more biological toxins, we render our definitions more general by simply including the essence of a toxin: ‘a toxic substance causing dose-dependent physiological injury’. Poison has a widely accepted usage that encompasses environmental and anthropogenic toxins in addition to biological toxins. Self-induced toxicity is included in the definition of poison because a dysfunction of metabolism can result in poisoning of the individual. Moreover, environmental and anthropogenic toxins can be diffusely distributed among the tissues of an organism, rendering it toxic, and therefore comprising a poison. Thus, our definitions are general enough to include environmental and anthropogenic toxins as poisons, toxungens, and venoms.

We propose with these definitions a new class of toxins, the toxungens, to provide greater clarity to the distinction between poisons and venoms. Numerous animals deliver their toxins by spraying, spitting, or smearing, including representatives among flatworms, insects, arachnids, cephalopods, amphibians, and reptiles (Sutherland & Lane, 1969; Koopowitz, 1970; Brodie & Smatresk, 1990; Deml & Dettner, 1994; Eisner *et al.*, 2005). These modes of delivery do not fit well within the traditional meaning of either a poison or a venom. We therefore propose the term toxungen, a new word derived by combining two Latin nouns: *toxicum*, meaning toxic, and *unguentum*, meaning balm or ointment. Thus, this word has the connotation of a toxic ointment, or a toxin that is applied to the outside of the victim’s body. We realize that this combination of toxicum and unguentum does not follow proper Latin grammar, but we feel that the combination adequately refers to the original roots while being combined in a way to produce a meaningful word with semblance to venom and poison.

Table 2. Critical components and features that distinguish the three major categories of biological toxins

Biological toxin	Delivery mechanism	Penetration wound	Mechanism of transfer or deployment
Poison	No	No	Ingestion, inhalation, or absorption across body surface
Toxungen	Yes	No	Delivered to body surface without accompanying wound
Venom	Yes	Yes	Delivered to internal tissues *via* wound

Although toxungens could be classified with poisons, there are reasons to consider them distinct. In addition to the difference in delivery, selection has often acted uniquely on the secretions of animals that spray, spit, or smear their toxins. Spitting cobras, for example, lack a subunit in their venom that in other cobras binds the cardiotoxin, rendering the unbound cardiotoxin more injurious to the eye membranes (Ismail *et al.*, 1993). Several arthropods that spray or smear their toxin incorporate a spreading agent with their secretion that increases penetration through the target animal’s cuticle and enhances toxicity (e.g. whip scorpions: Eisner *et al.*, 1961; termites: Prestwich, 1984; earwigs: Eisner, Rossini & Eisner, 2000*b*). By lumping toxungens and poisons together, important details regarding evolution of the toxins and their deployment may be overlooked. The term ‘contact poison’ exists in the literature, particularly for insecticides of anthropogenic use, but also for arthropod smearing of toxins (Prestwich, 1984; Heredia, de Biseau & Quinet, 2005). With our terminology, toxungens would be a subclass of contact toxins. Toxins passively transferred to surfaces represent contact poisons, whereas those actively delivered to surfaces comprise toxungens.

Our definitions for three distinct biological secretions incorporate just two of the five components, or properties, that we identified as common among prior definitions of venom: (*i*) hierarchy and exclusiveness (each secretion type is comprised of one or more toxins, but defined to maintain exclusiveness); and (*ii*) mode of transmission (the primary means of distinction among the three toxic secretion classes). We argue that mode of transmission alone is both critical and sufficient for distinguishing these toxic secretions, depending on whether a delivery structure or delivery system exists (satisfied by toxungen and venom, but not by poison), and whether a penetration wound is created (satisfied only by venom). Further, our definitions explicitly reject the following components, or properties, that many authors have used to define a venom: (*i*) type of secretion (glandular synthesis and/or storage is irrelevant); (*ii*) biological role (restriction to defensive or predatory function is irrelevant); and (*iii*) active delivery (whether the organism employs a specific behaviour or action to deliver the secretion is irrelevant). Interestingly, our definition of venom matches the consensus position for 4 of the 5 components among the 28 published definitions we considered, but rejects the consensus view that venom must be injected (a wound is necessary, but the toxins may be delivered into the wound without injection). We believe our definitions are both robust and succinct.

As we will elucidate further, organisms that employ these three major classes of toxic secretions can be recognized as 'poisonous', 'toxungenous', or 'venomous', respectively. Some organisms exhibit more than one of these characteristics. We emphasize that while our definitions are mutually exclusive, individual secretions and the animals that rely on these toxins should not necessarily be constrained within one of these three toxic secretion classes.

To illustrate the adequacy and utility of our definitions, we offer three examples within a single vertebrate class: Amphibia. Toxins in the skin secretion of the golden dart frog (*Phyllobates terribilis*) can be transferred through recipient-initiated ingestion and possibly direct skin absorption resulting from contact (Myers, Daly & Malkin, 1978). Because the frog lacks a distinct mechanism for delivering the toxins to the surface of the recipient, or through a wound created in the recipient, we consider the secretion to be a poison and the frog to be poisonous. The toxins of the fire salamander (*Salamandra salamandra*) can be sprayed at potential predators up to 2 m away, and can be aimed in the direction of the attacker, which presumably can be deterred by the secretion (Brodie & Smatresk, 1990). Because the salamander has a distinct delivery mechanism which does not involve production of a wound, we consider the secretion to be a toxungen and the salamander to be toxungenous. The Brazilian casque-headed tree frog (*Corythomantis greeningi*) possesses specialized ossified spicules on the top of its skull, with toxin-containing glands in the overlying skin. When disturbed, the frog thrashes the top of its head toward the recipient. The spicules can puncture the frog's skin and associated glands, and cause mechanical damage to the recipient as well, thereby delivering the toxins to the recipient's internal tissues (Jared *et al*., 2005). In this case, the secretion is a venom and the frog is venomous because it delivers the toxins by means of tissue injury. These examples also illustrate how a secretion and the animal that produces it may be classified in at least two categories. If the toxin delivery mechanisms of the fire salamander (deployed as a toxungen) and casque-headed tree frog (deployed as a venom) fail to foil a predator, these and other skin toxins may still function as a poison against a predator that licks or consumes the amphibian. Thus, the fire salamander would be both toxungenous and poisonous, and the casque-headed tree frog would be both venomous and poisonous.

Our definition of venom, taken to its logical conclusion, recognizes that organisms other than animals can be venomous. Venoms, as generally recognized, have evolved across a diverse range of animals, varying in complexity from single-celled cnidarians to multicellular mammals (Mebs, 2002). Must we arbitrarily restrict the term 'venom' to a single clade or kingdom, Animalia? If so, then why? Is such an argument based on complexity? Organisms in other kingdoms—including many that rival or exceed the complexity of cnidarians—solve problems in remarkably analogous or even identical ways using biological toxins delivered *via* the creation of wounds. Phage viruses, for example, employ sophisticated injection systems that deliver lytic proteins and DNA into their victims, resulting in unambiguous pathogenesis (Rossmann *et al*., 2004). Bacteria similarly use sophisticated injection systems to introduce toxic proteins into their victims with devastating consequences (Kenny & Valdivia, 2009; Beeckman & Vanrompay, 2010). Among protists, the ciliate *Dileptus gigas* discharges harpoon-like, toxin-filled projectiles called toxicysts when pursuing prey, which rupture the victim's cell membrane and deliver the toxins, resulting in paralysis or death of the target (Visscher, 1923; Miller, 1968). Fungi produce a dizzying assortment of penetration structures to penetrate host cells and deliver toxins that can incapacitate their victims (Luo *et al*., 2007; Liu, Xiang & Che, 2009). Among plants, many members of the genus *Urtica* (nettles) possess specialized trichomes that penetrate the tissues of other organisms and deliver toxic substances such as oxalic acid, tartaric acid, acetylcholine, serotonin, and histamine (Fu *et al*., 2006). Without a cogent argument for restricting venom to a single kingdom, these examples of convergent evolution could rightfully be considered venomous organisms that deliver venom by means of venom delivery systems.

Returning to humans, we emphasize that they can be facultatively poisonous, toxungenous, and venomous. Humans can become poisonous, potentially, by accumulating toxic substances in their tissues. They can apply toxins by spraying or smearing them on other organisms. And they can inject toxic substances into other organisms. Some may object to any consideration of humans being toxic, but a simple example illustrates how profound their use of toxins can be. Humans have acquired the technology to spray toxins across vast swathes of the planet (Pimentel, 2009; Brookes & Barfoot, 2010), largely directed toward plants (herbicides) and insects (insecticides). In so doing, humans may now be the most ecologically relevant toxungenous organism on the planet.

V. CLASSIFYING ORGANISMS THAT USE POISONS, TOXUNGENS, AND VENOMS

Apart from the general (and frequently botched) distinction between poisons and venoms, biological toxins have been categorized by previous workers in a variety of ways

(Bonventre, Lincoln & Lamanna, 1967; Army, 1998; Ogata & Ohishi, 2002; Hewlett & Hughes, 2005; Pimenta & De Lima, 2005; Vetter & Schmidt, 2006; Calvete, Juárez & Sanz, 2007). These include, at the organismal level, the (*i*) organisms that produce them; (*ii*) anatomical source; and (*iii*) organisms susceptible to them. They also include, at the suborganismal level, their (*iv*) chemical structures; (*v*) major biological effects; (*vi*) primary cellular or tissue targets; (*vii*) molecular mechanisms of action; (*viii*) sub-molecular binding sites; and even (ix) levels of toxicity. In contrast to the toxins, classifying the organisms that produce these toxins has lacked a formal structure. In general, many toxic organisms are referred to as poisonous or venomous, but there has been disagreement and confusion here as well (Brodie, 1989; Rodríguez-Robles, 1994; Kardong, 1996).

We argue that organisms which use biological toxins should be classified to highlight the evolutionary and proximate source of their chemical armament. Different selective pressures have influenced whether an organism sequesters toxins from its diet, co-opts its own proteins for use as toxins, or appropriates toxins synthesized by another species. Since poisons, toxungens, and venoms all exhibit a high degree of variability with respect to source, storage, and delivery, we propose a binomial nomenclature to identify each of these attributes for any given organism. Given recent interest in the diversification and biological roles of these toxins (Fry *et al.*, 2008, 2009*b*; Vonk *et al.*, 2011), and the acute need for detailed toxin databases driven by recent technological advances and bioprospecting interests (He *et al.*, 2008; Jungo *et al.*, 2010; Herzig *et al.*, 2011; Kaas *et al.*, 2012), a classification scheme at the organismal level that combines the origin, storage, and deployment of such toxins becomes pragmatic. Further, the classification scheme we propose distinguishes whether the organism uses its toxins as a poison, toxungen, or venom (or in multiple ways).

Table 3 summarizes our binomial classification scheme based on delivery mechanism, source of acquisition, and storage of toxins. Our scheme yields 12 categories, including 4 within each group of poisonous, toxungenous, and venomous organisms. The first term in the binomial is a contraction that combines the distinction between intrinsic (autogenous) *versus* extrinsic (heterogenous) acquisition of venom, and whether the organism stores its toxins within a specialized structure (glandular or aglandular). The second term in the binomial indicates whether the organism is poisonous, toxungenus, or venomous, depending on use of a delivery mechanism and generation of a wound. Table 3 also includes examples of organisms in each of the 12 groups, and these are discussed in the sections that follow.

(1) Poisonous organisms

Poisonous organisms lack a specialized structure for delivery of their toxins. Thus, delivery of toxic secretion is normally a passive strategy. Although transfer of poison relies on ingestion or contact, poisonous organisms may still employ adaptive tactics to deploy or otherwise enhance the anti-predator efficacy of their toxins. These tactics include enhanced skin secretion in the presence of a predator (Saito *et al.*, 1985) and specific postures used to present toxin-dense regions of the body toward would-be molesters (Toledo & Jared, 1995; Lenzi-Mattos *et al.*, 2005; Mori & Burghardt, 2008; Kingdon *et al.*, 2011; Toledo, Sazima & Haddad, 2011). Unfortunately, deciphering whether the source of toxin is autogenous or heterogenous can sometimes be difficult. Further, some organisms fall into several classes because a portion of their toxins are stored in glands while the remainder are more widely distributed in other tissues.

Autoaglandular–poisonous organisms produce their own toxins but lack a storage gland and a delivery apparatus. The toxins are often widely distributed among their tissues. Numerous organisms can be identified within this group, including examples among bacteria (Bonventre *et al.*, 1967; Amano, Takeuchi & Furuta, 2010; Linhartova *et al.*, 2010; Aktories, 2011), protists (Sykes & Huntley, 1987; Turner, Tester & Hansen, 1998; Wolfe, 2000; Ianora *et al.*, 2006),

Table 3. Classification of toxic organisms based on delivery (presence of delivery mechanism, wound), source of acquisition (synthesis), and storage (gland) of toxin

Classification	Delivery mechanism	Wound	Synthesis	Storage gland	Representative example[a]
Autoaglandular–poisonous	Absent	Absent	Autogenous	Absent	Meloidae beetles
Autoglandular–poisonous	Absent	Absent	Autogenous	Present	Rhinocricidae millipedes
Heteroaglandular–poisonous	Absent	Absent	Heterogenous	Absent	*Pitohui* birds
Heteroglandular–poisonous	Absent	Absent	Heterogenous	Present	Dendrobatidae frogs
Autoaglandular–toxungenous	Present	Absent	Autogenous	Absent	None known
Autoglandular–toxungenous	Present	Absent	Autogenous	Present	*Myrmicaria* ants
Heteroaglandular–toxungenous	Present	Absent	Heterogenous	Absent	*Phrynosoma* horned lizards
Heteroglandular–toxungenous	Present	Absent	Heterogenous	Present	*Hapalochlaena* octopuses
Autoaglandular–venomous	Present	Present	Autogenous	Absent	*Lonomia* caterpillars
Autoglandular–venomous	Present	Present	Autogenous	Present	Viperidae snakes
Heteroaglandular–venomous	Present	Present	Heterogenous	Absent	Erinaceidae hedgehogs
Heteroglandular–venomous	Present	Present	Heterogenous	Present	Chaetognath worms

[a] Citations for representative examples are supplied in the text.

fungi (Buck, 1961; Vetter, 1998; Bennett & Klich, 2003; Rohlfs *et al.*, 2007; Reverberi *et al.*, 2010), and plants (Harborne, 1999*a*; Acamovic, Stewart & Pennycott, 2004; Winde & Wittstock, 2011). Examples among animals appear to be scarce. Blister beetles (family Meloidae), as a potential example, accumulate highly toxic cantharidin in their haemolymph and bleed reflexively from their leg joints when disturbed, thereby facilitating contact with the toxin (Carrel & Eisner, 1974; Dettner, 1987). Although the cantharidin is produced in the accessory glands, and is likely employed as a mate attractant (Carrel *et al.*, 1993; Nikbakhtzadeh *et al.*, 2012), its use for defensive purposes clearly functions within an autoaglandular context.

Autoglandular–poisonous organisms produce their own toxins and store them within a gland, but lack a delivery apparatus. Unicellular organisms lack glands, and therefore are excluded from this category. Examples abound, however, among plants and animals. Many plants, such as those in the nightshade family (Solanaceae), secrete and store toxins within glandular trichomes on their surface for protection against insects (Eigenbrode, Trumble & White, 1996; Maffei, 2010). Among animals, the tropical millipede *Rhinocricus padbergi* possesses a pair of repugnatorial glands that secrete toxic benzoquinones directly to the surface of its body when threatened (Valderrama *et al.*, 2000; Arab *et al.*, 2003). Amphibians, having an abundance of toxin-laden cutaneous glands, may be the best-studied group in this category (Daly, 1995; Toledo & Jared, 1995; Brizzi & Corti, 2007).

Heteroaglandular–poisonous organisms cannot produce their own toxic secretion, so they must acquire their toxins from other organisms. Lacking glands for storage, the toxins are often widely dispersed among the tissues. Exogenous toxins can be acquired in at least four ways: *via* ingestion (bioaccumulation), symbiotic bacteria, copulation, and maternal transfer to gametes and young. Several marine invertebrates and fishes appear to sequester toxins from their diet (Kvitek, 1991; Becerro, Starmer & Paul, 2006; Derby & Aggio, 2011), as do some insects (Nishida, 2002; Opitz & Muller, 2009) and several birds (Dumbacher, Spande & Daly, 2000; Dumbacher *et al.*, 2004; Dumbacher, Menon & Daly, 2009). Human-released toxins can also accumulate in animals, rendering them toxic (Mebs, 2002). Symbiotic bacteria can synthesize toxins for their metazoan host, as documented in some marine invertebrates and fishes (Chau, Kalaitzis & Neilan, 2011). Perhaps most remarkable, males of several beetle species transfer toxins to females *via* copulation, whereupon the toxins disperse in haemolymph (Holz *et al.*, 1994; Nikbakhtzadeh *et al.*, 2007, 2012). Maternal transfer of toxins to eggs, presumably conferring protection to the eggs and/or larvae, has been documented in marine invertebrates and fishes (Pawlik *et al.*, 1988; Lindquist, Hay & Fenical, 1992; Noguch & Arakawa, 2008), terrestrial invertebrates including insects (Schroeder *et al.*, 1999; Bezzerides *et al.*, 2004; Nikbakhtzadeh *et al.*, 2012), and amphibians (Akizawa *et al.*, 1994).

Heteroglandular–poisonous organisms similarly acquire their toxins from other organisms, but store the toxins within glands. Examples involving acquisition by food exist among marine invertebrates (West *et al.*, 1996) and abound in insects (Blum, 1981; Pugalenthi & Livingstone, 1995; Morgan, 2010). Several amphibians also fall into this category. Frogs of the family Dendrobatidae, for example, acquire batrachotoxins from their arthropod food source (Saporito *et al.*, 2009, 2011), and secrete the toxins through skin glands to the surface of their body (Daly *et al.*, 1994; Daly, 1995; Saporito *et al.*, 2010). Although most snakes possessing toxins are venomous, several species sequester diet-derived toxins within their nuchal glands, and maternally transfer the toxins to offspring (Williams & Brodie, 2004; Hutchinson *et al.*, 2008; Mori *et al.*, 2011). We are unaware of toxin production by symbiotic bacteria within this group, although examples can be anticipated.

(2) Toxungenous organisms

Toxungenous organisms possess the capacity to deliver their toxic secretion by means other than mere contact, but do not inflict a wound to introduce the toxins. Whereas poison delivery is essentially passive and relies primarily on the actions of the victim to introduce the toxins, toxungen delivery depends on actions taken by the toxic organism. Toxungen delivery often involves a specialized delivery apparatus, though this is not always required.

Autoaglandular–toxungenous organisms produce their own toxins, but do not store them within glands. This combination of features, apparently, is exceptionally rare, as we were unable to find any examples. Nevertheless, there may be organisms that satisfy the characteristics of this category.

Autoglandular–toxungenous organisms synthesize their own toxins and sequester them within glands. Many examples can be identified within this group. *Parabuthus* scorpions, the fire salamander (*Salamandra salamandra*), and spitting cobras (*Naja* spp. and *Hemachatus haemachatus*), for example, can spray their glandular secretions, which are toxic when contacting the eyes of mammalian predators (Newlands, 1974; Brodie & Smatresk, 1990; Chu *et al.*, 2010). Most toxungenous organisms use their secretion for defence. However, whereas numerous ant and wasp species spray their glandular secretions for defensive purposes (Kenne *et al.*, 2000), some ant species cooperatively seize, spread-eagle, and then smear toxins onto their prey to subdue them (e.g. Richard, Fabre & Dejean, 2001; Dejean & Lachaud, 2011). In these examples, the fire salamander is both poisonous (toxic *via* consumption) and toxungenous, and the cobras, scorpions, ants, and wasps are both toxungenous and venomous because they not only spray but also inject their toxic secretions. Insects that spray benzoquinones, such as bombardier beetles (family Carabidae), may represent additional examples. These beetles store hydroquinones and hydrogen peroxide in a two-chambered gland. When threatened, the beetle combines these two chemicals in a mixing chamber along with water, catalases, and peroxidases, and the exothermic reaction results in production of a scalding vapour, containing 1,4-benzoquinones, that is used to deter predators (Eisner *et al.*, 1977, 2000*a*). Some evidence suggests that benzoquinones can exert toxic effects on predators (Eisner, 1958, 1960; Eisner *et al.*, 2000*b*, 2005; Paysse, Holder & Coats, 2001; also see Souza & Willemart, 2011).

Heteroaglandular–toxungenous organisms acquire their toxins from other organisms but do not store them in a gland. Finding examples proved to be difficult, but the Texas horned lizard (*Phrynosoma cornutum*) may fit this category. Several studies reported that the blood-squirting response of *P. cornutum*, directed primarily toward canids, elicits a strong aversion response, particularly when blood is directed at the oral cavity; however, the chemical that acts as the deterrent has not been isolated, and whether it causes a pathophysiological response remains unclear (Sherbrooke & Middendorf, 2004; Sherbrooke & Mason, 2005). Further experimentation is needed to determine if the blood of the Texas horned lizard has a toxic effect, and thus truly represents a heteroaglandular-toxungenous organism. Humans, however, make abundant use of exogenously acquired toxins, especially for weed and insect control (Pimentel, 2009; Brookes & Barfoot, 2010). By dramatically altering the environment through toxin application, humans have become the most influential toxungenous organism on the planet.

Heteroglandular–toxungenous organisms also acquire their toxins from other organisms, but sequester them within glands. Tetrodotoxin, for example, is produced by bacteria in the Vibrionaceae family and acts by selectively blocking the activity of certain subtypes of voltage-gated sodium channels in nerves and cardiac and skeletal muscle (Watters, 2005). Some animals possess channels that are resistant to these toxins, which allows them to accumulate tetrodotoxin either in their tissues or within specialized glands. The ringed octopus (*Hapalochlaena maculosa*) harbours these bacteria in its salivary gland, and possesses a venom comprised largely, but not exclusively, of tetrodotoxin. In addition to introducing tetrodotoxin during a bite, it can eject saliva into the water around a crab, move a distance away, and wait for the toxin to take effect (Sutherland & Lane, 1969). Thus, this species is both toxungenous and venomous. The tiger keelback (*Rhabdophis tigrinus*), a colubrid snake found in eastern Asia, sequesters toxins (bufadienolides) from toads (like *Bufo bankorensis*) in its nuchal glands (Chen *et al.*, 2012). Under pressure during physical contact, these glands can spray the toxic secretions up to a meter, whereupon contact with the eye causes acute burning pain and tissue injury (Chen *et al.*, 2012). Tiger keelbacks also possess venom glands associated with enlarged maxillary teeth (Ferlan *et al.*, 1983), making them both venomous and toxungeous.

(3) Venomous organisms

Venomous organisms deploy their toxins by introducing them *via* mechanical trauma to the internal milieu of other organisms. The scope of venomous organisms is vast, not just among animals, but also among bacteria, protists, fungi, and plants, as mentioned previously. Delivery structures or delivery systems are nearly as diverse as the organisms possessing them, ranging from the intricate design of hypodermic viper fangs to the hollow spines employed by certain caterpillars (Mebs, 2002). In this section, we provide examples only from animals.

Autoaglandular–venomous organisms synthesize their own venom but do not store it within glands. Numerous examples exist, including the aforementioned cnidarians, which produce and store their toxins within individual cells. The caterpillar *Lonomia oblique* comprises a good metazoan example. These caterpillars possess no gland that produces the venom; instead, secretory epithelium that underlies the tegument and spines secretes the toxins, which are concentrated at the tips of the spines. When contact is made with the spine, the tip containing the venom breaks off and causes a cutaneous reaction in the victim (Veiga, Blochtein & Guimarães, 2001).

Autoglandular–venomous organisms possess the most sophisticated toxin-delivery systems, including venom glands and usually an elaborate delivery apparatus. This group has garnered more attention from researchers than any other. Representatives include numerous marine and terrestrial invertebrates, many fishes, several amphibians, several lizards, numerous snakes, and several mammals (Mebs, 2002). Some authorities consider haematophagous (blood-sucking) organisms (e.g. mosquitoes, tsetse flies, fleas, leeches), which secrete injurious enzymes, to be in this group (Fry *et al.*, 2009*b*), and we concur. Slow lorises (genus *Nycticebus*) represent an unusual case in which the secretion from the brachial gland, when combined with saliva from licking of the gland, becomes toxic, and can be used defensively when biting conspecifics or potential predators (Alterman, 1995; Hagey, Fry & Fitch-Snyder, 2007).

Heteroaglandular–venomous organisms procure their toxins from other organisms and lack glands for storage. In Section V.1 on poisonous animals, we described four sources of exogenous toxins: ingestion (bioaccumulation), symbiotic bacteria, copulation, and maternal transfer to gametes and young. In this group, we find a fifth source: deliberately co-opting the toxins or venom apparatus of another organism. Several examples illustrate this group. The hedgehog (*Erinaceus europaeus*) preys upon poisonous toads (*Bufo* sp.), and anoints its spines with the toxic secretion of its prey by rubbing or licking the toxins onto its spines (Brodie, 1989). The spines may then puncture a would-be attacker, delivering the toxins through a wound. Nudibranchs feed on hydrozoans and then store the undischarged hydrozoan nematocysts on their external surface for protection (Greenwood & Garrity, 1991; Mebs, 2001). Certain crabs similarly co-opt the nematocysts of anemones by situating the entire anemone on their carapace or claws (Chintiroglou, Doumenc & Guinot, 1996; Karplus, Fiedler & Ramcharan, 1998). Even humans are facultatively heteroaglandular–venomous organisms. The indigenous Embera Indians of Western Columbia, for example, used darts coated with poison (batrachotoxins) from a poison dart frog (*Phyllobates* sp.) for hunting (Myers *et al.*, 1978). The Indians would collect the poison by impaling or restraining a poison dart frog with a stick, rub their darts on the frog's back, and then dry the toxins on the dart over a fire (Myers *et al.*, 1978). How is this different than a hedgehog spreading toxins on its spines, or a crab using an anemone for protection? Indeed, as Mebs (2002) observed, *Homo sapiens* has become one of the most dangerous venomous animals, utilizing natural toxins (e.g. batrachotoxins) and manufactured 'toxicants' (e.g. chemical warfare) for both defence and predation. We have also co-opted toxins for more benevolent purposes, such as use in human and veterinary medicine (Reisner, 2004; Chaddock & Acharya, 2011; King, 2011).

Heteroglandular–venomous organisms store the toxins acquired from other organisms in one or more glands. Accumulating evidence suggests that a number of marine worms, including chaetognath (Thuesen & Kogure, 1989), nemertean (Ali *et al.*, 1990; McEvoy, Rogers & Gibson, 1998), and platyhelminth (Planoceridae) (Ritson-Williams, Yotsu-Yamashita & Paul, 2006) representatives, sequester tetrodotoxin produced by symbiotic bacteria within their glands, and deliver it through a wound for predation and possibly defence (Williams, 2010). Several species of blue-ringed octopus (*Hapalochlaena lunulata*) represent another example, having a highly toxic secretion containing tetrodotoxin, apparently produced by *Vibrio* bacteria within its posterior salivary glands (Hwang *et al.*, 1989), which can be injected into prey and predators, although other autogenous toxins appear to be present (Fry, Roelants & Norman, 2009*a*). These octopuses can also transfer the toxin maternally to their offspring (Williams *et al.*, 2011).

VI. TOXIN EVOLUTION: THE INFLUENCE OF DELIVERY MECHANISM

In the ongoing co-evolutionary arms races between organisms that employ toxins and those affected by them, continual toxin variation is often important for keeping the toxic organism one step ahead of its competitors (Kordis & Gubenek, 2000). Toxic organisms employ a wide range of different toxins, which vary from small secondary metabolites to larger peptides and proteins (Mebs, 2001, 2002). Different taxonomic groups of toxic organisms generally employ different classes of toxins. Poisonous animals generally possess toxins that are small secondary metabolites, whereas venomous organisms generally produce toxic secretions that contain peptide or protein toxins (Mebs, 2002). These differences may result largely from the interaction of the evolutionary drive towards increased toxin variation with the functional constraints of the toxin delivery mechanism.

The major constraint on poisons stems from their passive route of delivery. These toxins must be resistant to digestion if delivered *via* ingestion, or must have properties that enable them to penetrate the external surface of the organism they come into contact with. Protein toxins will generally not work for this kind of application, since most proteins are readily broken down by digestive action (Mebs, 2002) and are generally too large to be absorbed across a body surface (Bos & Meinardi, 2000). The use of secondary metabolites overcomes these constraints; however, because secondary metabolites are produced *via* complex metabolic pathways employing many different chemical reactions catalyzed by multiple enzymes (Mebs, 2001; Wright, 2002), they may be less able to undergo rapid evolution.

Venom toxins bypass these constraints because they are delivered directly to the tissues. This may mean that the major factor that governs venom effectiveness over time, considering the evolution of venom resistance, is its ability to generate significant variation. Having direct genetic control over toxin production, rather than indirect control *via* modification of one or more enzymes (as secondary metabolites require), allows for the creation of a significantly more diverse array of toxins (Mebs, 2001). Indeed, most genes coding for venom protein toxins are a part of large multigene families, suggesting significant gene duplication and subsequent modification, thereby promoting rapid evolution (Kordis & Gubenek, 2000; Fry *et al.*, 2009*b*).

The difficulty in evolving new secondary metabolite toxins may also influence whether an organism acquires its toxins autogenously or heterogenously. Despite the fact that evolving resistance to a toxin involves significant costs (Brodie & Brodie, 1999; Mebs, 2001), it may be, in some circumstances, easier to evolve resistance to a toxin and then sequester that toxin than it is to evolve a new secondary metabolite *de novo*. This may be one reason why most examples of heterogenous acquisition of toxins come from poisonous animals that sequester secondary metabolite toxins, whereas nearly all venomous animals employ autogenous toxins. Toxin availability may also be an issue, as primary consumers generally have greater access to the protective toxins synthesized by producers (cyanobacteria, autotrophic protists, algae, plants) than do predators. Thus, although bioaccumulation can occur up the trophic ladder (Wang, 2008; Miller *et al.*, 2010), heterogenous acquisition of toxins is more frequent among invertebrates than vertebrates.

Whether toxin delivery is active or passive can impact how selection acts. Poisonous organisms primarily use their toxins for defence (Meier & White, 1995; Mebs, 2002). In animals, effective use of the poison for defence is often closely linked to the animal's aposematic adaptations (Sherratt, 2002; Blount *et al.*, 2009), which can take the form of colouration, behaviour, or olfactory cues (Eisner & Grant, 1981). Potential predators must acquire the capacity, through innate recognition or learning, to avoid these toxic animals in order for the toxins to be employed as part of an effective defence. This need may set up a situation where selection acts to prevent the development of overly toxic poisons, since a potential predator cannot learn anything if the poison results in its death (Mebs, 1994).

Another consideration is that poisons, by virtue of their passive transfer, may not necessarily act to preserve the life of the individual. In poisonous plants, this is not much of a problem, since these plants can afford to lose many leaves and branches to consumption without risk of the whole plant dying. Animals, by contrast, generally cannot survive when a significant portion of their body is consumed; however, this is often what must happen if an attacker is to consume a significant dose of the animal's poison. This means that selective pressures pushing animals towards being poisonous sometimes act at a level above that of the individual. This may be why many poisonous arthropods tend to be found in aggregations of closely related individuals, suggesting that their toxicity evolved through kin selection (Pasteels, Gregoire & Rowell-Rahier, 1983).

Organisms that more actively or more precisely control their toxins may begin to shift the level of selection back to the individual. Control of toxin deployment can evolve in multiple ways. First, some organisms concentrate their toxins in strategic places and utilize behaviour to place higher concentrations of their toxins in the path of their attacker (Toledo & Jared, 1995; Lenzi-Mattos *et al.*, 2005; Mori & Burghardt, 2008; Kingdon *et al.*, 2011; Toledo *et al.*, 2011). Second, some organisms employ toxins that are inducible rather than constitutive, enabling them to increase their secretion of toxins when an attacker is present (Harborne, 1999*b*). Plants, for example, often increase toxin production following browsing, and more so in tissues subject to the highest rates of browsing (Zangerl & Rutledge, 1996). Pufferfish can increase toxin release when a predator approaches (Saito *et al.*, 1985). Third, because toxin production and storage entails both energetic and ecological costs, selection has favoured judicious use of toxin in a number of venomous animals, ensuring optimal venom expenditure during defensive or predatory contexts (i.e. venom metering or venom optimization; Wigger, Kuhn-Nentwig & Nentwig, 2002; Hayes, 2008; Herbert & Hayes, 2008). Judicious toxin use occurs in toxungenous delivery as well (Obin & Vander Meer, 1985). Finally, selection has further refined the delivery systems of some animals so that toxins can be deployed as toxungens *via* spitting, spraying, or squirting, thereby avoiding the risk of physical contact with a potentially dangerous enemy.

Active delivery of toxins to the attacker, rather than the attacker coming to get the toxins, allows the toxins to be used not only for defence, but also for predation. Thus, in contrast to poisons (and most toxungens), venoms often serve a predatory function. For species that rely on venom for subduing and procuring prey, the toxins are under intense selection to paralyze quickly, kill, and even digest the victim. Although defensive use of toxungens and venoms benefits from aposematism and predator recognition, active delivery of toxins for predation, by contrast, is generally more effective with crypsis rather than aposematism.

VII. CONCLUSIONS

(1) Toxins are substances that, when present in relatively minute physiological concentrations, cause dose-dependent pathophysiological injury to a living organism, thereby reducing functionality or viability. Toxins may be categorized into three general classes: biological, environmental, and anthropogenic.

(2) Venom and poison are functionally distinct, and should not be conflated.

(3) A detailed literature review of the definitions of venom reveals several features in common: hierarchy and exclusiveness, source of secretion, mode of transmission, purpose, and active/passive delivery. Our revised definition includes hierarchy and exclusiveness and mode of transmission, but excludes source of secretion, purpose, and active delivery.

(4) A poison is defined as a toxic substance (comprised of one or more toxins) causing dose-dependent physiological injury that results in self-induced toxicity (e.g., bacterial endotoxins) or is passively transferred without a delivery mechanism from one organism to the internal milieu of another organism without mechanical injury, usually through ingestion, inhalation, or absorption across the body surface.

(5) A venom is defined as a toxic substance (comprised of one or more toxins) causing dose-dependent physiological injury that is passively or actively transferred from one organism to the internal milieu of another organism *via* a delivery mechanism and mechanical injury.

(6) We argue for the creation of a new category of toxic biological secretions—toxungen. A toxungen is defined as a toxic substance (comprised of one or more toxins) causing dose-dependent physiological injury that is actively transferred *via* a delivery mechanism from one organism to the external surface of another organism without mechanical injury.

(7) We argue that organisms which use biological toxins should be classified to highlight the evolutionary and proximate source of their chemical armament. We propose a classification scheme that distinguishes organisms based on three attributes of the toxin: its production or acquisition (autogenous, heterogenous), storage (glandular or aglandular), and nature (venomous, poisonous, toxungenous).

(8) The themes argued in this paper may be novel, and some readers may counter that they are unwarranted, but we believe that they will better organize and unify a fractured body of literature. The improved definitions and classification scheme should make these terms more accessible to and better understood by both researchers and the general public.

VIII. REFERENCES

Acamovic, T., Stewart, C. S. & Pennycott, T. (2004). *Poisonous Plants and Related Toxins*. CABI, Wallingford.

Akizawa, T., Mukai, T., Matsukawa, M., Yoshioka, M., Morris, J. & Butler, V. Jr. (1994). Structures of novel bufadienolides in the eggs of a toad, *Bufo marinus*. *Chemical & Pharmaceutical Bulletin (Tokyo)* **42**, 754–756.

Aktories, K. (2011). Bacterial protein toxins that modify host regulatory GTPases. *Nature Reviews Microbiology* **9**, 487–498.

Ali, A. E., Arakawa, O., Noguchi, T., Miyazawa, K., Shida, Y. & Hashimoto, K. (1990). Tetrodotoxin and related substances in a ribbon worm *Cephalothrix linearis* (Nemertean). *Toxicon* **28**, 1083–1093.

Alterman, L. (1995). Toxins and toothcombs: potential allospecific chemical defenses in *Nycticebus* and *Perodicticus*. In *Creatures of the Dark: The Nocturnal Prosimians* (eds L. Alterman, G. A. Doyle and M. K. Izard), pp. 413–424. Plenum Press, New York.

Amano, A., Takeuchi, H. & Furuta, N. (2010). Outer membrane vesicles function as offensive weapons in host-parasite interactions. *Microbes and Infection* **12**, 791–798.

Arab, A., Zacarin, G., Fontanetti, C., Camargo-Mathias, M., Dos Santos, M. & Cabrera, A. (2003). Composition of the defensive secretion of the Neotropical millipede *Rhinocricus padbergi* Verhoeff 1938 (Diplopoda: Spirobolida: Rhinocricidae). *Entomotropica* **18**, 79–82.

Army, U. (1998). *Medical Response to Chemical Warfare and Terrorism*. Chemical Casualty Care Division, USAMRIID, Aberdeen Proving Ground, MD.

Auerbach, P. (1988). Clinical therapy of marine envenomation and poisoning. In *Handbook of Natural Toxins: Marine Toxins and Venoms* (Volume **3**, ed. A. T. Tu, pp. 493–565). Marcel Dekker, New York.

Ayala, F. J. (1999). Adaptation and novelty: teleological explanations in evolutionary biology. *History and Philosophy of the Life Sciences* **21**, 3–33.

Beard, R. L. (1963). Insect toxins and venoms. *Annual Review of Entomology* **8**, 1–18.

Becerro, M. A., Starmer, J. A. & Paul, V. J. (2006). Chemical defenses of cryptic and aposematic gastropterid molluscs feeding on their host sponge *Dysidea granulosa*. *Journal of Chemical Ecology* **32**, 1491–1500.

Beeckman, D. & Vanrompay, D. (2010). Bacterial secretion systems with an emphasis on the chlamydial type III secretion system. *Current Issues in Molecular Biolology* **12**, 17–41.

Bennett, J. W. & Klich, M. (2003). Mycotoxins. *Clinical Microbiology Reviews* **16**, 497–516.

Bettini, S. & Brignoli, P. M. (1978). Review of the spider families, with notes on the lesser-known poisonous forms. In *Arthropod Venoms: Handbook of Experimental Pharmacology* (Volume **48**, ed. S. Bettini), pp. 101–120. Springer-Verlag, Berlin.

Bezzerides, A., Yong, T. H., Bezzerides, J., Husseini, J., Ladau, J., Eisner, M. & Eisner, T. (2004). Plant-derived pyrrolizidine alkaloid protects eggs of a moth (*Utetheisa ornatrix*) against a parasitoid wasp (*Trichogramma ostriniae*). *Proceedings of the National Academy of Sciences of the United States of America* **101**, 9029–9032.

Blount, J. D., Speed, M. P., Ruxton, G. D. & Stephens, P. A. (2009). Warning displays may function as honest signals of toxicity. *Proceedings of the Royal Society of London, Series B: Biological Sciences* **276**, 871–877.

Blum, M. S. (1966). Source and specificity of trail pheromones in *Termitopone monomorium* and *Huberia* and their relation to those of some other ants. *Proceedings of the Royal Entomological Society of London, Series A: General Entomology* **41**, 155–160.

Blum, M. S. (1981). *Chemical Defenses of Arthropods*. Academic Press, New York.

Bonventre, P. F., Lincoln, R. E. & Lamanna, C. (1967). Status of bacterial toxins and their nomenclature: need for discipline and clarity of expression. *Bacteriological Reviews* **31**, 95–109.

Bos, J. D. & Meinardi, M. M. H. M. (2000). The 500 Dalton rule for the skin penetration of chemical compounds and drugs. *Experimental Dermatology* **9**, 165–169.

Brizzi, R. & Corti, C. (2007). Cutaneous antipredatory secretions and pheromones in anurans and urodeles. *Marine and Freshwater Behaviour and Physiology* **40**, 225–231.

Brodie, E. D. (1989). *Venomous Animals*. St. Martin's Press, New York.

Brodie, E. D. III (2009). Toxins and venoms. *Current Biology* **19**, R931–R935.

Brodie, E. D. III & Brodie, E. D. Jr. (1999). Costs of exploiting poisonous prey: evolutionary trade-offs in a predator-prey arms race. *Evolution* **53**, 626–631.

Brodie, E. D. & Smatresk, N. J. (1990). The antipredator arsenal of fire salamanders: spraying of secretions from highly pressurized dorsal skin glands. *Herpetologica* **46**, 1–7.

Brookes, G. & Barfoot, P. (2010). Global impact of biotech crops: environmental effects, 1996–2008. *AgBioForum* **13**, 76–94.

Buck, R. W. (1961). Mushroom toxins: a brief review of literature. *New England Journal of Medicine* **265**, 681–686.

Calvete, J. J., Juárez, P. & Sanz, L. (2007). Snake venomics. Strategy and applications. *Journal of Mass Spectrometry* **42**, 1405–1414.

Carrel, J. E. & Eisner, T. (1974). Cantharidin: potent feeding deterrent to insects. *Science* **183**, 755–757.

Carrel, J., McCairel, M., Slagle, A., Doom, J., Brill, J. & McCormick, J. (1993). Cantharidin production in a blister beetle. *Cellular and Molecular Life Sciences* **49**, 171–174.

Chaddock, J. A. & Acharya, K. R. (2011). Engineering toxins for 21st century therapies. *The FEBS Journal* **278**, 899–904.

Chau, R., Kalaitzis, J. A. & Neilan, B. A. (2011). On the origins and biosynthesis of tetrodotoxin. *Aquatic Toxicology* **104**, 61–72.

Chen, Y. C., Yen, D. H. T., Chen, Y. W., Huang, M. S., Huang, C. I. & Chen, M. H. (2012). Toxin ophthalmia caused by nuchal gland secretion of the Taiwan tiger keelback (*Rhabdophis tigrinus formosanus*). *Journal of the Formosan Medical Association* **56**, 1–4.

Chintiroglou, C. C., Doumenc, D. & Guinot, D. (1996). Anemone-carrying behaviour in a deep-water homolid crab (Brachyura, Podotremata). *Crustaceana* **69**, 19–25.

Chu, E. R., Weinstein, S. A., White, J. & Warrell, D. A. (2010). Venom ophthalmia caused by venoms of spitting elapid and other snakes: report of ten cases with review of epidemiology, clinical features, pathophysiology and management. *Toxicon* **56**, 259–272.

Daly, J. W. (1995). The chemistry of poisons in amphibian skin. *Proceedings of the National Academy of Sciences of the United States of America* **92**, 9–13.

Daly, J. W., Garraffo, H. M., Spande, T. F., Jaramillo, C. & Rand, A. S. (1994). Dietary sources for skin alkaloids of poison frogs (Dendrobatidae). *Journal of Chemical Ecology* **20**, 943–955.

Dejean, A. & Lachaud, J. P. (2011). The hunting behavior of the African ponerine ant (*Pachycondyla pachyderma*). *Behavioural Processes* **86**, 169–173.

Deml, R. & Dettner, K. (1994). *Attacus atlas* caterpillars (Lep., Saturniidae) spray an irritant secretion from defensive glands. *Journal of Chemical Ecology* **20**, 2127–2138.

Derby, C. D. & Aggio, J. F. (2011). The neuroecology of chemical defenses. *Integrative and Comparative Biology* **51**, 771–780.

Dettner, K. (1987). Chemosystematics and evolution of beetle chemical defenses. *Annual Review of Entomology* **32**, 17–48.

Dumbacher, J. P., Menon, G. K. & Daly, J. W. (2009). Skin as a toxin storage organ in the endemic New Guinean genus *Pitohui*. *Auk* **126**, 520–530.

Dumbacher, J. P., Spande, T. F. & Daly, J. W. (2000). Batrachotoxin alkaloids from passerine birds: a second toxic bird genus (*Ifrita kowaldi*) from New Guinea. *Proceedings of the National Academy of Sciences of the United States of America* **97**, 12970–12975.

Dumbacher, J. P., Wako, A., Derrickson, S. R., Samuelson, A., Spande, T. F. & Daly, J. W. (2004). Melyrid beetles (Choresine): a putative source for the batrachotoxin alkaloids found in poison-dart frogs and toxic passerine birds. *Proceedings of the National Academy of Sciences of the United States of America* **101**, 15857–15860.

Dorland, W. A. N. (2007). *Dorland's Illustrated Medical Dictionary*. Venom. Elsevier Health Sciences, New York.

Eaton, D. L. & Klaassen, C. D. (2001). *Casarett and Doull's Toxicology: The Basic Science of Poisons*. Sixth Edition. McGraw-Hill, New York.

Eigenbrode, S., Trumble, J. & White, K. (1996). Trichome exudates and resistance to beet armyworm (Lepidoptera: Noctuidae) in *Lycopersicon hirsutum f. typicum* accessions. *Environmental Entomology* **25**, 90–95.

Eisner, T. (1958). The protective role of the spray mechanism of the bombardier beetle, *Brachynus ballistarius* Lec. *Journal of Insect Physiology* **2**, 215–220.

Eisner, T. (1960). Defense mechanisms of arthropods. II. The chemical and mechanical weapons of an earwig. *Psyche* **67**, 62–70.

Eisner, T., Aneshansley, D. J., Eisner, M., Attygalle, A. B., Alsop, D. W. & Meinwald, J. (2000*a*). Spray mechanism of the most primitive bombardier beetle (*Metrius contractus*). *Journal of Experimental Biology* **203**, 1265–1275.

Eisner, T., Rossini, C. & Eisner, M. (2000*b*). Chemical defense of an earwig (*Doru taeniatum*). *Chemoecology* **10**, 81–87.

Eisner, T., Eisner, M. & Siegler, M. (2005). *Secret Weapons: Defenses of Insects, Spiders, Scorpions, and Other Many-Legged Creatures*. Belknap Press of Harvard University Press, Cambridge.

Eisner, T. & Grant, R. P. (1981). Toxicity, odor aversion, and olfactory aposematism. *Science* **213**, 476.

Eisner, T., Jones, T., Aneshansley, D., Tschinkel, W., Silberglied, R. & Meinwald, J. (1977). Chemistry of defensive secretions of bombardier beetles (Brachinini, Metriini, Ozaenini, Paussini). *Journal of Insect Physiology* **23**, 1383–1386.

Eisner, T., Meinwald, J., Monro, A. & Ghent, R. (1961). Defence mechanisms of Arthropods. I. The composition and function of the spray of the whipscorpion, *Mastigoproctus giganteus* (Lucas)(Arachnida, Pedipalpida). *Journal of Insect Physiology* **6**, 272–298.

Ferlan, I., Ferlan, A., King, T. & Russell, F. E. (1983). Preliminary study on the venom of the colubrid snake *Rhabdophis subminatus* (red-necked keelback). *Toxicon* **21**, 570–574.

Freyvogel, T. A. (1972). Poisonous and venomous animals in East Africa. *Acta Tropica* **29**, 401–451.

Fry, B. G., Roelants, K. & Norman, J. (2009*a*). Tentacles of venom: toxic protein convergence in the kingdom animalia. *Journal of Molecular Evolution* **68**, 311–321.

Fry, B. G., Roelants, K., Champagne, D. E., Scheib, H., Tyndall, J. D. A., King, G. F., Nevalainen, T. J., Norman, J. A., Lewis, R. J. & Norton, R. S. (2009*b*). The toxicogenomic multiverse: convergent recruitment of proteins into animal venoms. *Annual Review of Genomics and Human Genetics* **10**, 483–511.

Fry, B. G., Scheib, H., Van Der Weerd, L., Young, B., McNaughtan, J., Ramjan, S. F. R., Vidal, N., Poelmann, R. E. & Norman, J. A. (2008). Evolution of an arsenal. *Molecular and Cellular Proteomics* **7**, 215–246.

Fry, B. G., Vidal, N., Norman, J. A., Vonk, F. J., Scheib, H., Ramjan, S. F. R., Kuruppu, S., Fung, K., Hedges, S. B., Richardson, M. K., Hodgson, W. C., Ignjatovic, V., Summerhayes, R. & Kochva, E. (2006). Early evolution of the venom system in lizards and snakes. *Nature* **439**, 584–588.

Fu, H. Y., Chen, S. J., Chen, R. F., Ding, W. H., Kuo-Huang, L. L. & Huang, R. N. (2006). Identification of oxalic acid and tartaric acid as major persistent pain-inducing toxins in the stinging hairs of the nettle, *Urtica thunbergiana*. *Annals of Botany* **98**, 57–65.

Garcia, B. (1998). *Mosby's Emergency Dictionary*. Venom. Elsevier Health Sciences, New York.

Gibbs, F. W. (2009). *Medical understandings of poison circa 1250–1600*. Unpublished PhD Dissertation: University of Wisconsin, Madison.

Greenwood, P. G. & Garrity, L. K. (1991). Discharge of nematocysts isolated from aeolid nudibranchs. *Hydrobiologia* **216**, 671–677.

Hagey, L. R., Fry, B. G. & Fitch-Snyder, H. (2007). Talking defensively: a dual use for the brachial gland exudate of slow and pygmy lorises. In *Primate Anti-Predator Strategies* (eds S. L. Gursky and K. A. I. Nekaris), pp. 253–272. Springer, New York.

Halstead, B. W. (1965). *Poisonous and Venomous Marine Animals of the World: Invertebrates* (Volume **I**). U.S. Goverment Printing Office, Washington.

Harborne, J. B. (1999*a*). Plant chemical ecology. In *Comprehensive Natural Products Chemistry* (ed. K. Mori), pp. 137–196. Pergamon Press Inc., Oxford.

Harborne, J. B. (1999*b*). Recent advances in chemical ecology. *Natural Product Reports* **16**, 509–523.

Hayes, A. W. (ed.) (2001). *Principles and Methods of Toxicology*. Fourth Edition. Taylor & Francis, Ann Arbor.

Hayes, W. K. (2008). The snake venom-metering controversy: levels of analysis, assumptions, and evidence. In *The Biology of Rattlesnakes* (eds W. K. Hayes, K. R. Beaman, M. D. Cardwell and S. P. Bush), pp. 191–220. Loma Linda University Press, Loma Linda.

He, Q. Y., He, Q. Z., Deng, X. C., Yao, L., Meng, E., Liu, Z. H. & Liang, S. P. (2008). ATDB: a uni-database platform for animal toxins. *Nucleic Acids Research* **36**, D293–D297.

Herbert, S. S. & Hayes, W. K. (2008). Venom expenditure by rattlesnakes and killing effectiveness in rodent prey: do rattlesnakes expend optimal amounts of venom?. In *The Biology of Rattlesnakes* (eds W. K. Hayes, K. R. Beaman, M. D. Cardwell and S. P. Bush), pp. 221–228. Loma Linda University Press, Loma Linda.

Heredia, A., De Biseau, J. C. & Quinet, Y. (2005). Toxicity of the venom in three neotropical *Cromatogaster* ants (Formicidae: Myricinae). *Chemoecology* **15**, 235–242.

Herzig, V., Wood, D. L. A., Newell, F., Chaumeil, P. A., Kaas, Q., Binford, G. J., Nicholson, G. M., Grose, D. & King, G. F. (2011). ArachnoServer 2.0, an updated online resource for spider toxin sequences and structures. *Nucleic Acids Research* **39**, D653–D657.

Hewlett, E. L. & Hughes, M. A. (2005). Toxins. In *Principles and Practice of Infectious Diseases*. Sixth Edition (eds G. L. Mendell, J. E. Bennett and R. Dolin), pp. 24–33. Churchill Livingstone, New York.

Hodgson, E., Mailman, R. B. & Chambers, J. E. (1988). *Dictionary of Toxicology*. McMillan Reference, London.

Hodgson, E., Mailman, R. B. & Chambers, J. E. (1999). *MacMillan Dictionary of Toxicology*. Venom. Macmillan Publishers Ltd, New York.

Holz, C., Streil, G., Dettner, K., Dutemeyer, J. & Boland, W. (1994). Intersexual transfer of a toxic terpenoid during copulation and its paternal allocation to developmental stages: quantification of cantharidin in cantharidin-producing oedemerids (Coleoptera: Oedemeridae) and *Canthariphilous pyrochroids* (Coleoptera: Pyrochroidae). *Zeitschrift Fur Naturforschung C: Journal of Biosciences* **49**, 856–864.

Hutchinson, D. A., Savitzky, A. H., Mori, A., Meinwald, J. & Schroeder, F. C. (2008). Maternal provisioning of sequestered defensive steroids by the Asian snake *Rhabdophis tigrinus*. *Chemoecology* **18**, 181–190.

Hwang, D., Arakawa, O., Saito, T., Noguchi, T., Simidu, U., Tsukamoto, K., Shida, Y. & Hashimoto, K. (1989). Tetrodotoxin-producing bacteria from the blue-ringed octopus *Octopus maculosus*. *Marine Biology* **100**, 327–332.

Ianora, A., Boersma, M., Casotti, R., Fontana, A., Harder, J., Hoffmann, F., Pavia, H., Potin, P., Poulet, S. A. & Toth, G. (2006). New trends in marine chemical ecology. *Estuaries and Coasts* **29**, 531–551.

Ismail, M., Al-Bekairi, A. M., El-Bedaiwy, A. M. & Abd-El Salam, M. A. (1993). The ocular effect of spitting cobras: II. Evidence that cardiotoxins are responsible for the corneal opacification syndrome. *Clinical Toxicology* **31**, 45–62.

Jared, C., Antoniazzi, M., Navas, C., Katchburian, E., Freymüller, E., Tambourgi, D. & Rodrigues, M. (2005). Head co-ossification, phragmosis and defence in the casque-headed tree frog (*Corythomantis greeningi*). *Journal of Zoology* **265**, 1–8.

Jungo, F., Estreicher, A., Bairoch, A., Bougueleret, L. & Xenarios, I. (2010). Animal toxins: how is complexity represented in databases? *Toxins* **2**, 262–282.

Kaas, Q., Yu, R., Jin, A. H., Dutertre, S. & Craik, D. J. (2012). ConoServer: updated content, kowledge, and discovery tools in the conopeptide database. *Nucleic Acids Research* **40**, D325–D330.

Kardong, K. V. (1996). Snake toxins and venoms: an evolutionary perspective. *Herpetologica* **52**, 36–46.

Karplus, I., Fiedler, G. & Ramcharan, P. (1998). The intraspecific fighting behavior of the Hawaiian boxer crab, *Lybia edmondsoni*: fighting with dangerous weapons? *Symbiosis* **24**, 287–302.

Kenne, M., Schatz, B., Durand, J. L. & Dejean, A. (2000). Hunting strategy of a generalist ant species proposed as a biological control agent against termites. *Entomologia Experimentalis et Applicata* **94**, 31–40.

Kenny, B. & Valdivia, R. (2009). Host-microbe interactions: bacteria. *Current Opinion in Microbiology* **12**, 1–3.

King, G. F. (2011). Venoms as a platform for human drugs: translating toxins into therapeutics. *Expert Opinion on Biological Therapy* **11**, 1469–1484.

Kingdon, J., Agwanda, B., Kinnaird, M., O'Brien, T., Holland, C., Gheysens, T., Boulet-Audet, M. & Vollrath, F. (2011). A poisonous surprise under the coat of the African crested rat. *Proceedings of the Royal Society of London, Series B: Biological Sciences* **279**, 675–680.

Koopowitz, H. (1970). Feeding behaviour and the role of the brain in the polyclad flatworm, *Planocera gilchristi*. *Animal Behavior* **18**, 31–35.

Kordis, D. & Gubenek, F. (2000). Adaptive evolution of animal toxin multigene families. *Gene* **261**, 43–52.

Kuhn-Nentwig, L. (2003). Antimicrobial and cytolytic peptides of venomous arthropods. *Cellular and Molecular Life Sciences* **60**, 2651–2668.

Kvitek, R. G. (1991). Paralytic shellfish toxins sequestered by bivalves as a defense against siphon-nipping fish. *Marine Biology* **111**, 369–374.

Lenzi-Mattos, R., Antoniazzi, M. M., Haddad, C. F. B., Tambourgi, D. V., Rodrigues, M. T. & Jared, C. (2005). The inguinal macroglands of the frog *Physalaemus nattereri* (Leptodactylidae): structure, toxic secretion and relationship with deimatic behaviour. *Journal of Zoology* **266**, 385–394.

Lindquist, N., Hay, M. E. & Fenical, W. (1992). Defense of ascidians and their conspicuous larvae: adult vs. larval chemical defenses. *Ecological Monographs* **62**, 547–568.

Linhartova, I., Bumba, L., Masin, J., Basler, M., Osicka, R., Kamanova, J., Prochazkova, K., Adkins, I., Hejnova-Holubova, J., Sadilkova, L., Morova, J. & Sebo, P. (2010). RTX proteins: a highly diverse family secreted by a common mechanism. *FEMS Microbiology Reviews* **34**, 1076–1112.

Liu, X. Z., Xiang, M. C. & Che, Y. S. (2009). The living strategy of nematophagous fungi. *Mycoscience* **50**, 20–25.

Lotan, A., Fishman, L., Loya, Y. & Zlotkin, E. (1995). Delivery of a nematocyst toxin. *Nature* **375**, 456–457.

Luo, H., Liu, Y. J., Fang, L., Li, X., Tang, N. H. & Zhang, K. Q. (2007). *Coprinus comatus* damages nematode cuticles mechanically with spiny balls and produces potent toxins to immobilize nematodes. *Applied and Environmental Microbiology* **73**, 3916–3923.

Mackessy, S. P. (2009). The field of reptile toxinology: snakes, lizards, and their venoms. In *Handbook of Venom and Toxins of Reptiles* (ed. S. P. Mackessy), pp. 3–23. CRC, Boca Raton.

Maffei, M. E. (2010). Sites of synthesis, biochemistry and functional role of plant volatiles. *South African Journal of Botany* **76**, 612–631.

Mashaly, A. M. A., Ali, A. S. & Ali, M. F. (2010). Source, optimal dose concentration and longevity of trial pheromone in two *Monomorium* ants (Formicidae: Hymenoptera). *Journal of King Saud University Science* **22**, 57–60.

McEvoy, E. G., Rogers, A. & Gibson, R. (1998). Preliminary investigation of *Vibrio alginolyticus*-like bacteria associated with marine nemerteans. *Hydrobiologia* **365**, 287–290.

McGain, F. & Winkel, K. D. (2002). Ant sting mortality in Australia. *Toxicon* **40**, 1095–1100.

Mebs, D. (1978). Pharmacology of reptilian venoms. In *Biology of the Reptilia* (eds C. Gans and K. Gans), pp. 437–560. Academic Press, New York.

Mebs, D. (1994). The strategic use of venoms and toxins by animals. *Universitas* **3**, 213–222.

Mebs, D. (2001). Toxicity in animals. Trends in evolution? *Toxicon* **39**, 87–96.

Mebs, D. (2002). *Venomous and Poisonous Animals: A Handbook for Biologists, Toxicologists and Toxinologists, Physicians and Pharmacists*. CRC Press, Boca Raton.

Meier, J. & White, J. (1995). *Handbook of Clinical Toxicology of Animal Venoms and Poisons*. CRC Press, Boca Raton.

Menez, A., Servent, D. & Gasparini, S. (2002). The sites by which animal toxins bind to their targets involve two components: a clue for selectivity, evolution and design of proteins?. In *Perspectives in Toxinology* (ed. A. Menez), pp. 171–200. John Wiley & Sons, Ltd, West Sussex.

Miller, S. (1968). The predatory behavior of *Dileptus anser*. *Journal of Eukaryotic Microbiology* **15**, 313–319.

Miller, M. A., Kudela, R. M., Mekebri, A., Crane, D., Oates, S. C., Tinker, M. T., Staedler, M., Miller, W. A., Toy-Choutka, S. & Dominik, C. (2010). Evidence for a novel marine harmful algal bloom: cyanotoxin (microcystin) transfer from land to sea otters. *PLoS ONE* **5**, 214–220.

Morgan, E. D. (2010). *Biosynthesis in Insects: Advanced Edition*. Royal Society of Chemistry, Cambridge.

Mori, A. & Burghardt, G. M. (2008). Comparative experimental tests of natricine antipredator displays, with special reference to the apparently unique displays in the Asian genus, *Rhabdophis*. *Journal of Ethology* **26**, 61–68.

Mori, A., Burghardt, G. M., Savitzky, A. H., Roberts, K. A., Hutchinson, D. A. & Goris, R. C. (2011). Nuchal glands: a novel defensive system in snakes. *Chemoecology* **22**, 187–198.

Morris, C. G. (1992). *Academic Press Dictionary of Science and Technology*. Venom. Academic Press, SanDiego, CA.

Myers, C. W., Daly, J. W. & Malkin, B. (1978). A dangerously toxic new frog (*Phyllobates*) used by Embera indians of western Colombia, with discussion of blowgun fabrication and dart poisoning. *Bulletin of the American Museum of Natural History* **161**, 307–366.

Newlands, G. (1974). The venom-squirting ability of *Parabuthus* scorpions (Arachnida: Buthidae). *South African Journal of Medical Sciences* **39**, 175–178.

Nikbakhtzadeh, M. R., Dettner, K., Boland, W., Gade, G. & Dotterl, S. (2007). Intraspecific transfer of cantharidin within selected members of the family Meloidae (Insecta: Coleoptera). *Journal of Insect Physiology* **53**, 890–899.

Nikbakhtzadeh, M., Vahedi, M., Vatandoost, H. & Mehdinia, A. (2012). Origin, transfer and distribution of cantharidin-related compounds in the blister beetle *Hycleus scabiosae*. *Journal of Venomous Animals and Toxins including Tropical Diseases* **18**, 88–96.

Nishida, R. (2002). Sequestration of defensive substances from plants by Lepidoptera. *Annual Review of Entomology* **47**, 57–92.

Noguch, T. & Arakawa, O. (2008). Tetrodotoxin—distribution and accumulation in aquatic organisms, and cases of human intoxication. *Marine Drugs* **6**, 220–242.

Obin, M. S. & Vander Meer, R. K. (1985). Gaster flagging by fire ants (*Solenopsis* spp.): functional significance of venom dispersal behavior. *Journal of Chemical Ecology* **11**, 1757–1768.

Oehme, F., Brown, J. & Fowler, M. (1975). *Toxins of Animal Origin*. Macmillan Publishing, New York.

Ogata, N. & Ohishi, Y. (2002). Molecular diversity of structure and function of the voltage-gated Na + channels. *Japanese Journal of Pharmacology* **88**, 365–377.

Onions, C. T., Friedrichsen, G. W. S. & Burchfield, R. W. (1966). *Oxford Dictionary of English Etymology*. Oxford University Press, London.

Oi, D. H. & Pereira, R. M. (1993). Ant behavior and microbial pathogens (Hymenoptera, Formicidae). *Florida Entomologist* **76**, 63–74.

Opitz, S. E. W. & Muller, C. (2009). Plant chemistry and insect sequestration. *Chemoecology* **19**, 117–154.

Osterhoudt, K. C. (2006). The lexiconography of toxicology. *Journal of Medical Toxicology* **2**, 1–3.

Ozbek, S., Balasubramanian, P. G. & Holstein, T. W. (2009). Cnidocyst structure and the biomechanics of discharge. *Toxicon* **54**, 1038–1045.

Parker, S. P. (2003). *McGraw-Hill Dictionary of Scientific and Technical Terms*. Venom. McGraw-Hill, New York.

Pasteels, J. M., Gregoire, J. C. & Rowell-Rahier, M. (1983). The chemical ecology of defense in arthropods. *Annual Review of Entomology* **28**, 263–289.

Pawlik, J. R., Kernan, M. R., Molinski, T. F., Harper, M. K. & Faulkner, D. J. (1988). Defensive chemicals of the Spanish dancer nudibranch *Hexabranchus sanguineus* and its egg ribbons: macrolides derived from a sponge diet. *Journal of Experimental Marine Biology and Ecology* **119**, 99–109.

Paysse, E. A., Holder, S. & Coats, D. K. (2001). Ocular injury from the venom of the southern walkingstick. *Ophthalmology* **108**, 190–191.

Pimenta, A. M. C. & De Lima, M. E. (2005). Small peptides, big world: biotechnological potential in neglected bioactive peptides from arthropod venoms. *Journal of Peptide Science* **11**, 670–676.

Pimentel, D. (2009). Environmental and economic costs of the application of pesticides primarily in the United States. In *Integrated Pest Management: Innovation-Development Process* (eds R. Peshin and A. K. Dhawan), pp. 89–111. Springer, New York.

Poerksen, G. (2003). *Paracelsus. Septum Defensiones. Die Selbstverteidigung eines Aussenseiters*. Schwabe AG Verlag, Basel.

Prestwich, G. D. (1979). Chemical defense by termite soldiers. *Journal of Chemical Ecology* **5**, 459–480.

Prestwich, G. D. (1984). Defense-mechanisms of termites. *Annual Review of Entomology* **29**, 201–232.

Pugalenthi, P. & Livingstone, D. (1995). Cardenolides (heart poisons) in the painted grasshopper *Poecilocerus pictus* F. (Orthoptera: Pyrgomorphidae) feeding on the milkweed *Calotropis gigantea* L. (Asclepiadaceae). *Journal of the New York Entomological Society* **103**, 191–196.

Quennedey, A. (1984). Morphology and ultrastructure of termite defense glands. In *Defensive Mechanisms in Social Insects* (ed. H. R. Hermann), pp. 151–200. Praeger, New York.

Reisner, L. (2004). Biologic poisons for pain. *Current Pain and Headache Report* **8**, 427–434.

Reverberi, M., Ricelli, A., Zjalic, S., Fabbri, A. A. & Fanelli, C. (2010). Natural functions of mycotoxins and control of their biosynthesis in fungi. *Applied Microbiology and Biotechnology* **87**, 899–911.

Richard, F. J., Fabre, A. & Dejean, A. (2001). Predatory behavior in dominant arboreal ant species: the case of *Crematogaster* sp. (Hymenoptera: Formicidae). *Journal of Insect Behavior* **14**, 271–282.

Ritson-Williams, R., Yotsu-Yamashita, M. & Paul, V. J. (2006). Ecological functions of tetrodotoxin in a deadly polyclad flatworm. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 3176–3179.

Rodríguez-Robles, J. A. (1994). Are the Duvernoy's gland secretions of colubrid snakes venoms? *Journal of Herpetology* **28**, 388–390.

Rohlfs, M., Albert, M., Keller, N. P. & Kempken, F. (2007). Secondary chemicals protect mould from fungivory. *Biology Letters* **3**, 523–525.

Rossmann, M. G., Mesyanzhinov, V. V., Arisaka, F. & Leiman, P. G. (2004). The bacteriophage T4 DNA injection machine. *Current Opinion in Structural Biology* **14**, 171–180.

Roth, L. M. & Eisner, T. (1962). Chemical defenses of arthropods. *Annual Review of Entomology* **7**, 107–136.

Russell, F. E. (1965). Marine toxins and venomous and poisonous marine animals. *Advances in Marine Biology* **3**, 255–384.

Russell, F. E. (2001). Toxic effects of terrestrial animal venoms and poisons. In *Casarett and Doullís Toxicology: The Basic Science of Poisons* (ed. C. D. Klaassen), pp. 945–964. McGraw Hill, New York.

Saito, T., Noguchi, T., Hashimoto, K., Harada, T. & Murata, O. (1985). Tetrodotoxin as a biological defense agent for puffers (*Fugu niphobles*, *F. vermicularis vermicularis* and *F. pardalis*). *Bulletin of the Japanese Society of Scientific Fisheries* **51**, 1175–1180.

Saporito, R. A., Isola, M., Maccachero, V. C., Condon, K. & Donnelly, M. A. (2010). Ontogenetic scaling of poison glands in a dendrobatid poison frog. *Journal of Zoology* **282**, 238–245.

Saporito, R. A., Norton, R. A., Andriamaharavo, N. R., Garraffo, H. M. & Spande, T. F. (2011). Alkaloids in the mite *Scheloribates laevigatus*: further alkaloids common to oribatid mites and poison frogs. *Journal of Chemical Ecology* **37**, 213–218.

Saporito, R. A., Spande, T. F., Garraffo, H. M. & Donnelly, M. A. (2009). Arthropod alkaloids in poison frogs: a review of the "dietary hypothesis.". *Heterocycles* **79**, 277–297.

Schiefer, H. B., Irvine, D. & Buzik, S. C. (1997). *Understanding Toxicology: Chemicals, Their Benefits and Risks*. CRC Press, Boca Raton.

Schmidt, J. O. (1982). Biochemistry of insect venoms. *Annual Review of Entomology* **27**, 339–368.

Schmidt, J. O. (1990). *Insect Defenses: Adaptive Mechanisms and Strategies of Prey and Predators*. State University of New York Press, New York.

Schroeder, F. C., Gonzàlez, A., Eisner, T. & Meinwald, J. (1999). Miriamin, a defensive diterpene from the eggs of a land slug (*Arion* sp.). *Proceedings of the National Academy of Sciences of the United States of America* **96**, 13620–13625.

Sharma, R. P. & Taylor, M. J. (1987). Animal toxins. In *Handbook of Toxicology* (eds T. J. Haley and W. O. Berndt), pp. 439–470. Hemisphere Publishing, New York.

Sherbrooke, W. C. & Mason, J. R. (2005). Sensory modality used by coyotes in responding to antipredator compounds in the blood of Texas horned lizards. *Southwestern Naturalist* **50**, 216–222.

Sherbrooke, W. C. & Middendorf, G. A. (2004). Responses of kit foxes (*Vulpes macrotis*) to antipredator blood-squirting and blood of Texas horned lizards (*Phrynosoma cornutum*). *Copeia* **2004**, 652–658.

Sherratt, T. N. (2002). The coevolution of warning signals. *Proceedings of the Royal Society of London, Series B: Biological Sciences* **269**, 741–746.

Souza, E. S. & Willemart, R. H. (2011). Harvest-ironman: heavy armature, and not its defensive secretions, protects a harvestman against a spider. *Animal Behavior* **81**, 127–133.

Stumpf, W. E. (2006). The dose makes the medicine. *Drug Discovery Today* **11**, 551–555.

Sutherland, S. & Lane, W. (1969). Toxins and mode of envenomation of the common ringed or blue-banded octopus. *Medical Journal of Australia* **1**, 893–898.

Sykes, P. F. & Huntley, M. E. (1987). Acute physiological reactions of *Calanus pacificus* to selected dinoflagellates: direct observations. *Marine Biology* **94**, 19–24.

Thuesen, E. V. & Kogure, K. (1989). Bacterial production of tetrodotoxin in four species of Chaetognatha. *Biological Bulletin* **176**, 191–194.

Toledo, R. C. & Jared, C. (1995). Cutaneous granular glands and amphibian venoms. *Comparative Biochemistry and Physiology A: Physiology* **111**, 1–29.

Toledo, L. F., Sazima, I. & Haddad, C. F. B. (2011). Behavioural defences of anurans: an overview. *Ethology Ecology & Evolution* **23**, 1–25.

Torres, A., De Plater, G., Doverskog, M., Birinyi-Strachan, L., Nicholson, G., Gallagher, C. & Kuchel, P. (2000). Defensin-like peptide-2 from platypus venom: member of a class of peptides with a distinct structural fold. *Biochemical Journal* **348**, 649–656.

Turner, J. T., Tester, P. A. & Hansen, P. J. (1998). Interactions between toxic marine phytoplankton and metazoan and protestan grazers. In *Physiological Ecology of Harmful Algal Blooms* (eds D. M. Anderson, A. D. Cembella and G. M. Hallegraeff), pp. 452–474. Springer-Verlag, Heidelberg.

Valderrama, X., Robinson, J. G., Attygalle, A. B. & Eisner, T. (2000). Seasonal anointment with millipedes in a wild primate: a chemical defense against insects? *Journal of Chemical Ecology* **26**, 2781–2790.

Veiga, A., Blochtein, B. & Guimarães, J. (2001). Structures involved in production, secretion and injection of the venom produced by the caterpillar *Lonomia obliqua* (Lepidoptera, Saturniidae). *Toxicon* **39**, 1343–1351.

Venes, D. (2009). *Taber's Cyclopedic Medical Dictionary*. Venom. F. A. Davis Company, Philadelphia.

Vetter, J. (1998). Toxins of *Amanita phalloides*. *Toxicon* **36**, 13–24.

Vetter, R. S. & Schmidt, J. O. (2006). Semantics of toxinology. *Toxicon* **48**, 1–3.

Visscher, J. P. (1923). Feeding reactions in the ciliate, *Dileptus gigas*, with special reference to the function of trichocysts. *Biological Bulletin* **45**, 113–143.

Vonk, F. J., Jackson, K., Doley, R., Madaras, F., Mirtschin, P. J. & Vidal, N. (2011). Snake venom: from fieldwork to the clinic. *Bioessays* **33**, 269–279.

Wang, D. Z. (2008). Neurotoxins from marine dinoflagellates: a brief review. *Marine Drugs* **6**, 349–371.

Watters, M. R. (2005). Tropical marine neurotoxins: venoms to drugs. *Seminars in Neurology* **25**, 278–289.

Youngson, R. M. (2005). *Collins Dictionary of Medicine*. Venom. Collins, New York.

Welsh, J. H. (1964). Composition and mode of action of some invertebrate venoms. *Annual Review of Pharmacology* **4**, 293–304.

West, D. J., Andrews, E. B., Bowman, D., McVean, A. R. & Thorndyke, M. C. (1996). Toxins from some poisonous and venomous marine snails. *Comparative Biochemistry and Physiology C: Toxicology & Pharmacology* **113**, 1–10.

Wigger, E., Kuhn-Nentwig, L. & Nentwig, W. (2002). The venom optimisation hypothesis: a spider injects large venom quantities only into difficult prey types. *Toxicon* **40**, 749–752.

Williams, R. (1991). Acrorhagi, catch tentacles and sweeper tentacles: a synopsis of 'aggression' of actiniarian and scleractinian Cnidaria. *Hydrobiologia* **216**, 539–545.

Williams, B. L. (2010). Behavioral and chemical ecology of marine organisms with respect to tetrodotoxin. *Marine Drugs* **8**, 381–398.

Williams, B. L. & Brodie, E. D. (2004). A resistant predator and its toxic prey: persistence of newt toxin leads to poisonous (not venomous) snakes. *Journal of Chemical Ecology* **30**, 1901–1919.

Williams, B. L., Hanifin, C. T., Brodie, E. D. & Caldwell, R. L. (2011). Ontogeny of tetrodotoxin levels in blue-ringed octopuses: maternal investment and apparent independent production in offspring of *Hapalochlaena lunulata*. *Journal of Chemical Ecology* **37**, 10–17.

Winde, I. & Wittstock, U. (2011). Insect herbivore counteradaptations to the plant glucosinolate-myrosinase system. *Phytochemistry* **72**, 1566–1575.

Wolfe, G. V. (2000). The chemical defense ecology of marine unicellular plankton: constraints, mechanisms, and impacts. *Biological Bulletin* **198**, 225–244.

Wright, J. L. C. (2002). Attack and defend: the function and evolution of bioactive or toxic metabolites. In *Proceedings of the Xth International Conference on Harmful Algae* (eds K. A. Steidinger, J. H. Landsberg, C. R. Tomas and G. A. Vargo). Florida Fish and Wildlife Conservation Commission, St. Petersburg, FL.

Wüster, W. (2010). What's your poison? *Heredity* **104**, 519.

Young, B. A., Herzog, F., Friedel, P., Rammensee, S., Bausch, A. & Van Hemmen, J. L. (2011). Tears of venom: hydrodynamics of reptilian envenomation. *Physical Review Letters* **106**, 198103.

Zangerl, A. R. & Rutledge, C. E. (1996). The probability of attack and patterns of constitutive and induced defense: a test of optimal defense theory. *American Naturalist* **147**, 599–608.

(*Received 26 November 2012; revised 15 August 2013; accepted 16 August 2013; published online 17 September 2013*)