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

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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.

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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; Schieber, 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 ‘bioxin’.

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, exclusiveness, 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 poisonem (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

<table>
<thead>
<tr>
<th>Source of definition</th>
<th>Hierarchy and exclusiveness</th>
<th>Source of secretion</th>
<th>Delivery structure/system</th>
<th>Mode of transmission</th>
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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 (Ornithorhynus 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; Denil & 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.

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 cardiotxin, 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, 2000b). 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).

<table>
<thead>
<tr>
<th>Biological toxin</th>
<th>Delivery mechanism</th>
<th>Penetration wound</th>
<th>Mechanism of transfer or deployment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poison</td>
<td>No</td>
<td>No</td>
<td>Ingestion, inhalation, or absorption across body surface</td>
</tr>
<tr>
<td>Toxungen</td>
<td>Yes</td>
<td>No</td>
<td>Delivered to body surface without accompanying wound</td>
</tr>
<tr>
<td>Venom</td>
<td>Yes</td>
<td>Yes</td>
<td>Delivered to internal tissues via wound</td>
</tr>
</tbody>
</table>

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

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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 factually 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...
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(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) major biological effects; (v) primary cellular or tissue targets; (vi) molecular mechanisms of action; (vii) 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, 2009b; 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, toxungenous, 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 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

<table>
<thead>
<tr>
<th>Classification</th>
<th>Delivery mechanism</th>
<th>Wound</th>
<th>Synthesis</th>
<th>Storage gland</th>
<th>Representative examplea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoaglandular—poisonous</td>
<td>Absent</td>
<td>Absent</td>
<td>Autogenous</td>
<td>Absent</td>
<td>Meloidae beetles</td>
</tr>
<tr>
<td>Autoaglandular—poisonous</td>
<td>Absent</td>
<td>Absent</td>
<td>Autogenous</td>
<td>Present</td>
<td>Rhinocricidae millipedes</td>
</tr>
<tr>
<td>Heteroglandular—poisonous</td>
<td>Absent</td>
<td>Absent</td>
<td>Heterogenous</td>
<td>Absent</td>
<td>Pidulx birds</td>
</tr>
<tr>
<td>Heteroglandular—poisonous</td>
<td>Absent</td>
<td>Absent</td>
<td>Heterogenous</td>
<td>Absent</td>
<td>Dendrobaidae frogs</td>
</tr>
<tr>
<td>Autoaglandular—toxungenous</td>
<td>Present</td>
<td>Absent</td>
<td>Autogenous</td>
<td>Absent</td>
<td>None known</td>
</tr>
<tr>
<td>Autoaglandular—toxungenous</td>
<td>Present</td>
<td>Absent</td>
<td>Heterogenous</td>
<td>Absent</td>
<td>Myrmicaria ants</td>
</tr>
<tr>
<td>Heteroglandular—toxungenous</td>
<td>Present</td>
<td>Absent</td>
<td>Heterogenous</td>
<td>Absent</td>
<td>Phrynusoma horned lizards</td>
</tr>
<tr>
<td>Heteroglandular—toxungenous</td>
<td>Present</td>
<td>Absent</td>
<td>Heterogenous</td>
<td>Absent</td>
<td>Hapalochlana octopuses</td>
</tr>
<tr>
<td>Autoaglandular—venomous</td>
<td>Present</td>
<td>Present</td>
<td>Autogenous</td>
<td>Absent</td>
<td>Lonania caterpillars</td>
</tr>
<tr>
<td>Autoaglandular—venomous</td>
<td>Present</td>
<td>Present</td>
<td>Autogenous</td>
<td>Absent</td>
<td>Viperidae snakes</td>
</tr>
<tr>
<td>Heteroglandular—venomous</td>
<td>Present</td>
<td>Present</td>
<td>Heterogenous</td>
<td>Absent</td>
<td>Erinaceidae hedgehogs</td>
</tr>
<tr>
<td>Heteroglandular—venomous</td>
<td>Present</td>
<td>Present</td>
<td>Heterogenous</td>
<td>Present</td>
<td>Chaetognath worms</td>
</tr>
</tbody>
</table>

aCitations for representative examples are supplied in the text.
fungi (Buck, 1961; Vetter, 1998; Bennett & Klich, 2003; Rohlf et al., 2007; Reverberi et al., 2010), and plants (Harborne, 1999a; 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.

Autoaglandular—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; Optiz & 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, Kalaizis & 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).

Heteroaglandular—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; Pugenthi & 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.

Autoaglandular—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, catalasas, and peroxidases, and the exothermic reaction results in production of a scalding vapour, containing 1,4-benzoquinones, that is used to deter
Redefining toxic secretions and organisms

predators (Eisner et al., 1977, 2000a). Some evidence suggests that benzoquinones can exert toxic effects on predators (Eisner, 1958, 1960; Eisner et al., 2000b, 2005; Payssé, Holder & Coats, 2001; also see Souza & Willemart, 2011).

Heteroaglandular-toxogenous 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 \textit{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 & 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-toxogenous 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 toxogenous organism on the planet.

Heteroglandular-toxogenous 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 toxogenous and venomous. The tiger keelback (Rhhabdophis tigrinus), a colubrid snake found in eastern Asia, sequesters toxins (bufadienolides) from toads (like \textit{Bufo bankeiensis}) in its mucosal 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 toxogenous.

(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 (Mehs, 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 \textit{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 (Mehs, 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., 2009b), and we concur. Slow lorises (genus \textit{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 (Altenburg, 1995; Hagey, Fry & Fitch-Snyder, 2007).

Heteroglandular—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 (\textit{Erinaceus europaeus}) preys upon poisonous toads (\textit{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; Mehs, 2001). Certain crabs similarly co-opt the nematocysts of anemones by situating the entire anemone on their carapace or claws (Chintiroglou, Doumenc & Guimont, 1996; Karplus, Fiedler & Ramcharan, 1998). Even humans are facultatively heteroglandular—venomous organisms. The indigenous Embera Indians of Western Columbia, for example, used darts coated with poison (batrachotoxins) from a poison dart frog (\textit{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., 1973). 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, 2009a). 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 (Bes & 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., 2009b).

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, 1999b). 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 toxungogenous 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 cryptis rather than aposematism.

VII. CONCLUSIONS

(1) Toxins are substances that, when present in relatively minute physiological concentrations, cause dose-dependent pathophysiologically 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 venoms 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—toxungens. A toxungens 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, toxungogenous).

(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.

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