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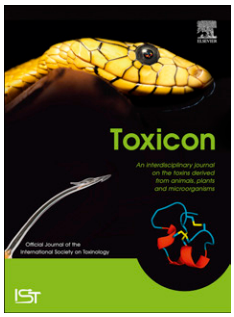

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Scott A. Weinstein, Julian White, Daniel E. Keyler, David A. Warrell

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Non-front-fanged colubroid snakes:

A current evidence-based analysis of medical significance

Scott A. Weinstein[1*], Julian White[1], Daniel E. Keyler[2],

David A. Warrell[3]

[1]Department of Toxinology, Women's and Children's Hospital, 72 King William St., North Adelaide, South Australia,

[2]Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, 308 Harvard Street, SE Minneapolis, MN 55455, USA

[3]Nuffield Department of Clinical Medicine, University of Oxford, United Kingdom

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[*]Corresponding author: phone 61-8-8-161-4088; e-mail herptoxmed@yahoo.com

Abstract

Non-front-fanged colubroid snakes (NFFC; formerly and artificially taxonomically assembled as "colubrids") comprise about 70% of extant snake species and include several taxa now known to cause lethal or life threatening envenoming in humans. Although the medical risks of bites by only a handful of species have been documented, a growing number of NFFC are implicated in medically significant bites. The majority of these snakes have oral products (Duvernoy's secretions, or venoms) with unknown biomedical properties and their potential for causing harm in humans is unknown. Increasingly, multiple NFFC species are entering the commercial snake trade posing an uncertain risk. Published case reports describing NFFC bites were assessed for evidence-based value, clinical detail and verified species identification. These data were subjected to meta-analysis and a hazard index was generated for select taxa. Cases on which we consulted or personally treated were included and subjected to the same assessment criteria. Cases involving approximately 120 species met the selection criteria, and a small subset designated Hazard Level 1 (most hazardous), contained 5 species with lethal potential. Recommended management of these cases included antivenom for 3 species, *Dispholidus typus*, *Rhabdophis tiginis*, *R. subminiatus*, whereas others in this subset without commercially available antivenoms (*Thelotornis* spp.) were treated with plasma/erythrocyte replacement therapy and supportive care. Heparin, antifibrinolytics and/or plasmapheresis/exchange transfusion have been used in the management of some Hazard Level 1 envenomings, but evidence-based analysis positively contraindicates the use of any of these interventions. Hazard Level 2/3 species were involved in cases containing mixed quality data that implicated these taxa (e.g. *Boiga irregularis*, *Philodryas olfersii*, *Malpolon monspessulanus*) with bites that caused rare systemic

effects. Recommended management may include use of acetylcholinesterase inhibitors (e.g. neostigmine) and wound care on a case-by-case basis. Hazard level 3 species comprised a larger group capable of producing significant local effects only, often associated with a protracted bite (eg *Heterodon nasicus*, *Borikenophis* (*Alsophis*) *portoricensis*, *Platyceps* (*Coluber*) *rhodoracis*). Management is restricted to wound care. Bites by Hazard level 4 species comprised the majority of surveyed taxa and these showed only minor effects of no clinical importance. This study has produced a comprehensive evidence-based listing of NFFC snakes tabulated against medical significance of bites, together with best-practice management recommendations. This analysis assumes increasing importance, as there is growing exposure to lesser-known NFFC snakes, particularly in captive collections that may uncover further species of significance in the future. Careful and accurate documentation of bites by verified species of NFFC snakes is required to increase the evidence base and establish the best medical management approach for each species.

Introduction

The majority of living snakes belong to the superfamily Colubroidea, the "advanced snakes" (e.g. those with derived anatomical traits), that evolved during the Oligocene-Miocene Periods of the Cenozoic Era [Table 1]. This group includes front-fanged snakes such as those of the families Viperidae (Old World vipers and Old and New World pit vipers), Elapidae (cobras, mambas, coral snakes, sea snakes and their allies) and two genera (*Atractaspis* spp. [mole vipers, burrowing asps or stiletto snakes] and *Homoroselaps* spp. [African dwarf garter or harlequin snakes]) of the Lamprophiidae, subfamily Atractaspidinae. All of the known front-fanged colubroids possess a canaliculated (hollow or lumenate) venom apparatus located on the anterior maxillae that is associated with a venom gland whose contents are ejected under high pressure by compression of the gland through contraction of skeletal muscle fibers inserted in the gland fundus. Approximately 350 species of front-fanged colubroids are known to inflict medically significant bites on humans (www.toxinology.com). Probably around 75% of these species may cause notable morbidity and/or mortality in humans. There are also a number of lesser-known front-fanged species of uncertain medical significance. This is partly due to the infrequent contact of these species with humans (e.g. many of these snakes are fossorial and/or are found in ecosystems in which contact with humans is rare), as well as the possible lack of formal medical review of bites that may occur in isolated locales among remote human populations.

The larger number of colubroid species are non-front-fanged species and many of these have been traditionally and inaccurately grouped in an artificial family, the Colubridae, a group first defined in 1758 by the Swedish natural historian and founder of systematic zoology/taxonomy, Carl Nilsson Linnaeus (Carl von Linné or Carolus Linnaeus; 1707-1778). The name, "Colubridae", is derived from the rather non-

descript Latin, “coluber”, the general term for “snake” or “serpent”. Of the approximately 3,350 species of extant snakes, the previous definition of the Colubridae included about 70% of these taxa (e.g. about 2,345 species). On the basis of several morphological and/or molecular systematics investigations (some conflicting), the number of previous sub-families included under the Colubridae has been re-defined. Several have been raised to full family status, while others have been retained within the original family that now comprises an estimated 1,750 species (about 74% of the previous assemblage). As currently defined, these snakes are represented by taxa with wide distribution, but geographically variable abundance in the Neotropics, North America, Mexico, Africa, Asia and Southeast Asia, the Indian subcontinent, New Guinea, Europe, and with the least representation in Australia. A general accounting of the Colubridae and newly defined families that previously were included as “colubrids” includes a diverse assortment of widely distributed species (Table 1). Some of these snakes have been variously called, “rear-fanged”, “opisthoglyphous”, or “aglyphous”, referring to their posterior or mid-maxillary dentition that may or may not be enlarged and/or quite variably modified with external grooves and/or lateral ridges, but are not hollow, and thus lack a fully enclosed internal lumen or canal (McKinstry, 1983; Weinstein and Kardong, 1994; Weinstein et al., 2011). In some species (the precise number is unclear), this dentition is associated with a gland (“Duvernoy’s gland”, or venom gland, depending on author and interpretation of glandular roles, or assignment of identity based primarily on phylogenetic relationships; see ahead) whose contents are evacuated under low pressure due usually to a general lack of any significant skeletal muscle fiber insertion in the gland fundus (Taub, 1967; Kardong, 1996; Fry *et al.*, 2008; Weinstein *et al.*, 2010). While the majority of these snakes are still in the family Colubridae, they are

now collectively, and more accurately, termed “non-front-fanged colubroids” (NFFC).

Although a handful of toxins present in the oral secretions/venoms and glands of NFFC have been characterized, the majority of NFFC produce oral products that have unknown properties and/or functions (Weinstein et al., 2011, 2012). Consequently, a relatively small number of these snakes meet the traditional biological criteria defining them as “venomous”, although there is current debate concerning the definition of “venom” and the venomous condition (see ahead). It is important to recognize that the medical effects of snake venoms are a circumstantial result of the interaction of humans with snakes whose venoms or oral products coincidentally have a medically significant effect and therefore should not be used as criteria for defining snakes as “venomous” or not (Kardong, 1996; Weinstein and Keyler, 2009; Weinstein *et al.*, 2011, 2012).

There is much confusion and incorrect information in the scientific, medical and popular literature, and increasingly in Internet dialogues, about the possible medical risks posed by some NFFC. A few NFFC have caused multiple human fatalities, while others either inflict bites capable of causing severe systemic pathology, or cause only minor medically insignificant, local effects. However, most taxa are of unknown medical significance because there have been no adequately documented cases delineating the clinical symptoms and pathophysiological effects of their bites. Previously, only a limited number of published cases have been subjected to medically qualified review and these tended to be regionally focused (e.g. Minton, 1990; Warrell, 2004). A recent comprehensive analysis of the available evidence for medical significance of NFFC found a limited database with few well-documented

cases containing detail sufficient for assignment of risk to a relatively small number of NFFC (Weinstein *et al.*, 2011).

This report summarizes some of the results of evidence-based review of the body of literature concerning the medical risks of NFFC.

Methods

Published cases of NFFC bites were obtained by searching the literature available online using multiple search engines (scirus, pubmed, scopus, sciencedirect and others), institutional online archives and specific biomedical and life science journals. Archived print material was obtained through extensive searches conducted with the help of the authors' institutional libraries. Information was also obtained from private library holdings (including those of the authors). Cases that we personally treated or on which we were consulted were included and subjected to the same analytical criteria as those obtained from the published literature. Case assessment and subsequent Hazard Index assignment followed the methods of Weinstein *et al.* (2011) and considered multiple criteria including: number of cases and quality of documented information; level of clinical detail and support for reported symptoms/signs as indicated from examination and investigations included in the account; results of laboratory investigations when available; appropriate investigation and/or efforts to characterize the nature of reported sequelae; formal identification of the snake species involved, and consideration of any information about venom/oral secretion toxicity and yield (preferably obtained without parasympathomimetic stimulation), although this last criterion was found to be important only in the highly toxic (murine i.v. LD_{50} <0.5 mg/kg) dispholidine and natricine species. Available information collected using these methods was evaluated using a modification

(Weinstein *et al.,* 2011) of the Strength of Recommendation Taxonomy (SORT, Ebell *et al.,* 2004).

Overview of basic differences between Oral Gland Secretion and Associated Delivery Systems of NFFC and Front-Fanged Colubroids and their impact on possible medical risks (Table 2)

An unknown number of NFFC possess Duvernoy's glands that produce variably toxic secretions released under low pressure (due to a lack of muscular compression of the glands). This contrasts with the highly muscular and therefore compressible glands of front-fanged colubroids (Table 2). Compressed venom glands release a bolus of stored venom and facilitate its injection into prey or a human victim. The pressure of injection may exceed 30 psi similar to a typical automobile tire pressure (Kardong, 2009). In contrast, NFFC *inoculate* their secretions under low pressure (the few studied species produce ≤5 psi; Kardong, 2009) into wounds produced by maxillary teeth that may be variably grooved, but unlike those of front-fanged snakes, are not canaliculated. *Dispholidus typus* (boomslang), and possibly other members of the tribe, Dispholidini, as well as perhaps a few other unrelated taxa, have limited striated muscle insertion into the gland resulting in a partially pressurized venom delivery system. Several hypotheses have been considered that attempt to address the evolution of the venom apparatus, and the selection for venom delivery systems. The traditional consensus definition and use of the terms, "venom", and "venom gland", includes evidence of biological use of the oral secretion in prey subjugation and/or defense (Minton, 1974; Minton and Minton, 1980; Russell, 1980; Mebs, 2002). However, on the basis of shared toxins or their transcripts, common among ophidian venoms and other oral products, some authors' advocate redefined phylogenetically-based criteria for identifying a given squamate reptilian oral secretion as "venom" (Fry *et al.*, 2012).

NFFC Venoms, Secretions and Toxins

During the relatively short period (approximately 75 yr) encompassing modern snake venom research, attention has been almost exclusively focused on venoms from front-fanged snakes, especially those of recognized medical importance. The Duvernoy's secretions/venoms of NFFC have received far less attention. Interest in the life-threatening/fatal effects of bites by the African dispholidines (*Dispholidus typus* and the African twig, bird, tree or vine snakes, *Thelotornis* spp.) was stimulated by the tragic and publicized deaths of two distinguished herpetologists, Robert F.W. Mertens and Karl P. Schmidt. Although the potentially fatal effects of tiger keelback or, Yamakagashi (*Rhabdophis tigrinus*) bites were long known to some Japanese investigators, the life-threatening bite from a privately owned red-necked keelback, *Rhabdophis subminiatus,* in London in 1978 increased interest in other NFFC that might have medical importance. Contemporary biochemical and pharmacological investigations are greatly expanding knowledge of the Duvernoy's secretions and venoms of NFFC. However, advances in this sub-discipline are greatly hindered by an almost complete lack of active research funding and disinterest by relevant "mainstream" biomedical disciplines, as there is limited demonstrable medical importance attributed to most NFFC.

The composition of NFFC venoms/Duvernoy's secretions is similar to that of venoms of viperids, elapids and *Atractaspis* spp. (Rosenberg *et al.,* 1985; Minton and Weinstein, 1987; Weinstein and Smith, 1993; Weinstein and Kardong, 1994; Hill and Mackessy, 2000; Mackessy, 2002; Fry *et al.*, 2003, 2008; Ching *et al.*, 2006; Weldon and Mackessy, 2010; Peichoto *et al.*, 2012), and probably reflects tissue-specific protein recruitment as seen in front-fanged colubroid venoms (Fry *et al.*, 2009). Recent proteomic, genomic and transcriptomic investigations have identified some of

the components detected during early chromatographic studies of NFFC venoms and secretions, and/or have reported the presence of previously undetected classes of biologically active constituents including cysteine-rich secretory proteins (CRISPs), multiple enzymes and isozymes (e.g. metalloproteases, phospholipases A2, fibrinogenases, Factor X and prothrombin-activators, and others), myotoxins, as well as post-synaptic neurotoxins (Fry *et al.*, 2003, 2008; Ching *et al.*, 2006, 2012; Estrella *et al.*, 2010; Weldon and Mackessy, 2010; Peichoto *et al.*, 2012; see Table 3 for representative examples). To date, the few well-characterized neurotoxins [three finger-fold toxins, FTX3] have shown greater specificity for the saurian and/or avian motor-end plate (Table 3). Some NFFC venoms/oral secretions are less complex than venoms of viperids and elapids (e.g. "venom" from the homolopsid, *Cerberus rynchops* [dog-faced watersnake], OmPraba *et al.*, 2010, and that of the dipsadine colubrid, Lichtenstein's racer [*Philodryas olfersii*], Ching *et al.*, 2006). The venoms/oral secretions of a relative handful of NFFC have received any substantial study.

EVIDENCE-BASED ASSESSMENT OF MEDICAL RISKS OF NFFC

(I) SOME IMPORTANT CONSIDERATIONS

The medical significance of the majority of NFFC taxa is unknown, and a recent comprehensive analysis of this question emphasized the paucity of well-documented medically significant bites, or "envenomings", inflicted by NFFC in the literature (Weinstein *et al.*, 2011). Aside from several NFFC that have been observed on a number of occasions to inflict serious, life-threatening and/or fatal envenomings (e.g. *R. tigrinus*, *R. subminiatus*, *D. typus*, *Thelotornis* spp.), bite cases ascribed to NFFC predominantly are poorly documented, rely on anecdotal information and/or are authored/analysed by non-medically qualified contributors often by the victim

him/herself with highly subjective impressions. Some previous authors have speculated about the possible medical importance of NFFC taxa that are popular in the commercial snake trade. Others have based their opinions entirely on chromatographic or spectroscopic profiles of NFFC venoms/oral secretions. As a result, a number of taxa have acquired an unwarranted reputation for inflicting potentially fatal bites, or have been prematurely viewed as hazardous (Weinstein *et al.*, 2011; Weinstein *et al.*, in press). Many NFFC are popular in private collections, and speculation about their possible ability to inflict medically significant bites is often replete with incorrect information and assumption. Mouse lethal potency studies of venom/oral secretions of NFFC have been used as a basis for such predictions, (e.g. that of the false water cobra, *Hydrodynastes gigas*; 2.0 [i.p.]-9.4 [s.c.)] mg/kg, Glenn *et al.*, 1992) by comparison with medically important front-fanged species such as the timber rattlesnake (*Crotalus horridus*) (2.63-3.31 [i.p.]-9.15 [s.c.] mg/kg, Russell, 1980; Minton, 1987; Weinstein *et al.*, 1992). On some Internet fora, neurotoxic potency based on *in vitro* nerve-twitch electrophysiological preparations testing powerful elapid venoms (e.g. that of the common death adder, *Acanthophis antarcticus*) has been compared with those of some NFFC. This is misleading as it simply relates the magnitude of antagonism observed from *in vitro* nerve-muscle preparation assays to potential lethal potency *in vivo.* Such observations can reflect the medical importance of highly potent venoms that contain a high proportion of medically important toxins in a potentially large volume of venom delivered under high pressure with canaliculated fangs, but it is misleading to compare these with NFFC toxins. Aside from the differences in delivery systems and glandular storage/secretion characteristics, another contributing factor to such an inappropriate comparison is the receptor specificity of some colubroid toxins (e.g. greater affinity

for avian- or lizard-specific cellular targets as mentioned previously). Most NFFC venoms/oral secretions assayed to date exhibit modal or low lethal potencies in the murine model (see Weinstein and Kardong, 1994, and Weinstein *et al.*, 2011, for comparison of lethal potencies), but do have high toxicity and potency in some avian and lizard models (Mackessy et al., 2006; Pawlak et al., 2006, 2008).

The explosion of popularity of reptiles (especially snakes) and amphibians in the pet industry, and among amateur enthusiasts increases the importance of these considerations. It is important that medical professionals are better informed about the potential clinical importance of NFFC termed "mildly venomous," or of those with unknown toxicity (Weinstein *et al.*, 2010, 2011). The medically relevant toxicity of oral secretions/venoms in the vast majority of NFFC remains unknown, but there are likely taxa of several subfamilies that secrete venoms of clinical importance. Some large adult NFFC with modal or low lethal potency may also pose a risk to pediatric or geriatric patients and to those with chronic illness and/or multiple co-morbidities (Weinstein *et al.*, 2010, 2011). Therefore, a medically qualified, patient-centered, evidence-based approach is crucial when conducting a medical risk assessment of NFFC based on published information, as well as personal clinical experience (Weinstein *et al.*, 2011).

(II) Overview of Evidence-Based Analysis of Medically Important NFFC and Management of Their Bites (Table 4)

A patient-centered critical analysis of bites inflicted by NFFC found that only a small number of species (around 120 taxa) have been documented with clinical content acceptable for qualified medical assessment. Most cases were of insignificant or mild local effects (puncture wounds, abrasions, lacerations, limited bleeding and mild edema). Only approximately 24 species inflicted bites that produced medically

significant effects, and bites from an additional 31 taxa produced non-progressive mild local pathology insufficient to be tabulated as "medically significant", but are included in Table 1 because of the near-significance of their respective presentations. A small number of reports described bites producing moderate local effects that occasionally resulted in persistent symptoms. In some cases unfortunately perpetuated in the literature, fatal consequences of bites inflicted by *Tachymenis peruviana* (Peruvian slender snake) or *Philodryas olfersii* (Lichtenstein's or South American green racer) were implied without providing any convincing data supporting these outcomes, or lacking any mention of specific bites inflicted on human victims (Weinstein *et al.*, 2011; Weinstein *et al.*, under review). The life threatening risks of venomous colubrine genera such as *Dispholidus typus* and *Thelotornis* spp. (African bird, twig, tree or vine snakes) and that of natricines such as two taxa of *Rhabdophis* (Asian keelbacks or flower snakes) are well established by unequivocal clinical evidence (Table 4). Bites from these species cause consumptive coagulopathy and hemorrhagic diathesis, complicated in some cases by acute kidney injury, and are designated "Hazard Level 1" (Weinstein *et al.*, 2011; Table 4). A single well-documented case of transient cranial nerve palsies that resulted from an envenoming by *M. monspessulanus* establishes the potential danger associated with bites from this species ("Hazard Level 2-3", Table 4). Although there is limited information about the epidemiology of bites by most NFFC, analyses of larger series of documented bites by some species (e.g. the South American racers, *Philodryas olfersii* and *P. patagoniensis*, as well as the brown tree snake, *Boiga irregularis*) have yielded some significant associations between specific circumstances and the incidence of medically significant bites by these species (see Table 4).

(III) Common Features of Well-Documented Bites By Non-Hazard Level 1 NFFC

NFFC genera such as the cat-eye snakes (*Boiga* spp.), hognose snakes (*Heterodon* spp.), several taxa split from the genus *Coluber* (e.g. *Hemorrhois, Platyceps, Hierophis*; "racers" or "whipsnakes"), and the common natricines, the garter snakes and their allies (*Thamnophis* spp.), occasionally inflict bites that cause mild-moderate local effects, but most of these species have no medical importance. Rarely, protracted bites from the Western hognose snake (*H. nasicus*; Weinstein and Keyler, 2009), the Puerto Rican racer (*Borikenophis* [*Alsophis*] *portoricensis* Hedges *et al.*, 2010), and some larger specimens of *Boiga* spp. may result in medically significant local effects of moderate severity (e.g. more evidence of higher modified objective pain scores, locally progressive edema, blistering, etc.). To date, aside from a handful of cases involving *B. irregularis* bites inflicted on neonates or infants in which the etiology of the clinical syndrome remains incompletely characterized, there is no evidence of systemic effects of bites from any of these taxa.

It is noteworthy that of the approximately 32 species of *Boiga* spp., only a few well-documented bites have been recorded involving 7 taxa (including Blanding's tree or cat-eyed snake, [*Toxicodryas blandingi* Ullenbruch *et al.*, 2010; www.reptile-database.com], previously *B. blandingi*, and provisionally re-assigned by some authors to *Boiga*, specifically, Segniagbeto *et al.*, 2011). Of these, only *B. irregularis* bites that caused serious effects in less than half a dozen pediatric victims have identified this species as a medically important member of the genus. During the last decade, an increased number of *Boiga* spp. have entered the commercial snake trade. Previously, mostly *B. dendrophila* ssp. (mangrove, or ringed cat snakes), and *B. cyanea* (green cat snake) were imported into the US, Western Europe and some Asian

countries. Although there is limited information about the possible effects of bites inflicted by other members of the genus, for reasons discussed earlier it is important not to prematurely base unproven medical significance of these on murine lethal potency data, non-clinically derived information such as chromatographic profiles, or by using purely *in vitro* observations obtained from studying their venoms/oral secretions.

Bites by Lichtenstein's or South American racer (*Philodryas olfersii*) may rarely cause systemic effects (widespread ecchymoses), but, to date, there is no documented evidence of coagulopathy or other life-threatening effects caused by bites of this species, or by bites of the Patagonian racer (*P. patagonienis*). Likewise, there is no clinical evidence of life threatening or fatal bites by *Tachymenis peruviana* (Peruvian slender snake, Colubridae, Dipsadinae), and yet wholly incorrect statements about these species are still perpetuated in the literature (Weinstein *et al.*, in press). Many published cases of bites by NFFC contain low quality evidence, and the poor documentation complicates the assessment of evidence-based risk of many species.

(IV) LITTLE-KNOWN NFFC

Recent proteomic and/or genomic-based studies have detected among the venoms/oral secretions of a few NFFC many classes of toxins and other biologically active proteins common in front-fanged snake venoms. However, the oral secretions/venoms of the vast majority of NFFC remain unstudied. Many of these snakes are fossorial or semi-fossorial, and thus are rarely encountered. Some of these occasionally enter the commercial snake trade (there are numerous examples of these; e.g. *Salvadora* spp. [patchnose snakes, Colubridae, Colubrinae; Southwestern USA to Mexico], *Chionactis* spp. [shovelnose snakes, Colubridae, Colubrinae; Southwestern USA to Mexico], *Pseudaspis cana* [African mole snake, Lamprophiidae, Pseudaspidinae;

central West Africa to East Africa, down to mid-South Africa]), while others (e.g. *Chilomeniscus* spp. [sand snakes; common names are frequently shared among many colubroid snakes], Colubridae, Colubrinae; Southwestern USA to Mexico], *Aparallactus* spp. [centipede-eating snakes, Lamprophiidae, Aparallactinae) East-Central to South Africa], *Stenorrhina* spp. [scorpion-eating snakes; blood snakes, Colubridae, Colubrinae; Mexico to Central America]) are uncommonly collected or maintained in captivity due to highly specialized prey preferences (as indicated by some of the common names listed above). Although in most cases, little or nothing is known of the oral secretion properties of the representative prey-specialized taxa mentioned above, they are likely to have likewise prey-specific secretion components, and their possible bites are unlikely to have any notable medical significance. However, this doesn't negate the possibility of isolated bites that may include some significant local effects, nor diminishes the possible biomedical value of investigating their oral products/venoms.

(VI) COMMENTS ABOUT SOME LITTLE-KNOWN FRONT-FANGED COLUBROID TAXA

In relation to the previous section regarding little-known NFFC that might be kept in captivity, some species of little-studied front-fanged colubroid taxa are frequently available in the commercial snake trade in Europe and the USA. Some of these such as the elapids, *Aspidelaps* spp. (the African shieldnose cobras), and the viperid, *Proatheris superciliaris* (African lowland or swamp viper), have caused fatal and/or life-threatening envenoming (e.g. see Keyler, 2008; van Egmond, 1984). The venoms of these representative species have received little attention and, to date, there are no antivenoms known that provide established paraspecific protection against these species. Therefore, whenever possible, medically significant bites from little-known

colubroids (non-front-fanged or front-fanged) should prompt admission to a Level I-II trauma facility and urgent consultation with an experienced clinical toxinologist.

SUMMARY

Only about 24 species inflicted bites that produced well-supported medically significant effects. Three species of dispholidines (*D. typus, T. kirtlandii, T. capensis*) and two species of natricines (*R. tigrinus, R. subminiatus*) have inflicted life threatening and/or fatal envenoming. These are all designated Hazard Level 1 NFFC (Weinstein *et al.*, 2011). Procurement and administration of antivenom is the cornerstone of management of bites from *D. typus, R. tigrinus and R. subminiatus*. Replacement therapy may be indicated per clinical need. There are no antivenoms available against *Thelotornis* spp., and treatment is limited to replacement therapy (Weinstein *et al.,* 2011).

The dipsadine colubrid, *P. olfersii* has inflicted a single well documented systemic envenoming (widespread ecchymoses) [Hazard Level 2/3, while the psammophine lamprophiid, *M. monspessulanus*, has inflicted at least one systemic envenoming (cranial nerve palsy) [Hazard Level 2/3]. Bites by *B. irregularis* uncommonly may produce systemic effects in infants, but the etiology of the effects may be related to trauma +/- introduced venom (Hazard Level 2/3). To date, there is no unequivocal evidence of neurotoxic envenoming by this species. Other NFFC may have the potential to inflict systemic envenoming, but most species assessed to date only produce mild local effects (Weinstein *et al.,* 2011).

Some species commonly maintained in private collections such as the dipsadine colubrids, *H. nasicus* and *Hydrodynastes gigas* rarely inflict bites, but when they occur may cause moderate local effects. These bites most often occur while the victim offers food manually to a captive specimen, or handles the snake after having contact

with a food item. Meticulous wound care is an important feature of management, and antibiotics should only be used when there is evidence of infection and/or there is notable predisposition to infection (e.g. interference with or contamination of the wound).

Private collectors may maintain NFFC or front-fanged species of unknown medical importance. Whenever possible, medically significant bites from these, whether from specimens in captivity or from those encountered in their natural habitat, should prompt qualified medical review at a critical care equipped medical facility and timely consultation with an experienced clinical toxinologist.

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Table 1. Overview of the superfamily Colubroidea[1] and their medical significance

Family (commonly used familial name)[2]	Subfamilies [Number of medically relevant NFFC species identified from evidence-based analysis[3]]	Approximate number of total genera and species[4]	Comments
Colubridae ("typical" snakes; "harmless egg laying snakes")	Colubrinae [12] Grayiinae [IC] Calamariinae [IC] Dipsadinae [28][5] Pseudoxenodontinae [IC] Natricinae [3] Scaphiodontophiinae [IC]	250 [1,750]	• Cases not included in the summarized tally here featured mild, transient local effects. • Five taxa have caused life-threatening effects or fatalities (see text). • There is a lack of any information about the possible medical risks posed by the potential bites of a number of species that are entering the commercial trade (e.g. bamboo snake, *Pseudoxenodon bambusicola*; Pseudoxenodontinae). • Some taxa are very rarely encountered (e.g. the two taxa of *Scaphiodontophis*, and many others), and in numerous cases, there is no substantial/reliable clinical information about the effects of bites from a given species.

Table 1. Overview of the superfamily Colubroidea[1] and their medical significance

Lamprophiidae (sometimes collectively called, "African nocturnal snakes")	Aparallactinae [1][6] Atractaspidinae [NA][7] Lamprophiinae [IC] Prosymninae [IC] Psammophiinae [6] Pseudaspidinae [IC] Pseudoxyrhophiinae [5]	61 [300]	• One species has inflicted a single well-documented case of systemic envenoming featuring cranial nerve palsies (see text). • To date, most well documented cases feature mild, transient local effects. However, bites from larger specimens of some species may be capable of producing more significant effects. • Currently, there is no clinical information that supports common speculation of the hypothetically more serious effects of bites from large specimens of *Psammophis* spp. ("sand snakes", Psammophinae). • Although envenoming cases are not included in the tally because they are front-fanged, all of the *Atractaspis* spp. must be considered medically important as their bites have caused fatalities and some species are significant causes of snakebite within their respective ranges.

Table 1. Overview of the superfamily Colubroidea[1] and their medical significance

Homalopsidae (Australasian mudsnakes)	---------- [IC]	11 [38]	• Mostly anecdotal information; the few medically well documented reports indicate mild, transient local effects. • Larger specimens of some species may be capable of inflicting a bite with more significant local effects.
Pareatidae (Asian slug-eating snakes)	---------- [IC]	3 [15]	Ibid
Xenodermatidae ("strange-scaled snakes", see comments)	---------- [IC]	5 [17]	• Rarely encountered and reportedly reluctant to bite, there is no available relevant clinical information. • Several specimens of these unusual snakes were briefly maintained by one of the authors (SAW), and none attempted to bite, but were rarely handled due to their fragile nature. These occasionally appear in the commercial trade, but their fragility often results in an early demise of the specimens.
Viperidae (vipers and pit vipers)	Azemiopinae Crotalinae Viperinae [NA]	39 [300]	• The medically serious, life-threatening and/or fatal bites of a large number of species have been

Table 1. Overview of the superfamily Colubroidea[1] and their medical significance

			thoroughly documented. However, the medical risks of some species are unestablished due to their remote habitats, infrequent contract with human populations and/or lack of medically qualified documentation of their bites.
Elapidae (sometimes collectively called, "fixed-front-fanged snakes", see comments)	Hydrophiinae[8] [NA]	65 [350]	Ibid • There is very limited or a lack of information about the medical risks that may be posed by some small fossorial species (see the previous entry).

[1]The taxonomy of the Colubroidea is fluid and under continuing review and re-assignment. The taxonomy included here follows that of Pyron *et al.* (2011).

[2]Traditionally used by some authors, these common names do not accurately encompass the diverse members of these families. For instance, the common names occasionally used for the Colubridae are imprecise because some are viviparous (some previously termed, ovoviviparous) and some are not "harmless", or "typical" (see text).

[3]Based on the critical analysis of Weinstein *et al.* (2011), and is limited to only those species for which available clinically relevant information is sufficient for risk assessment. Although only 24 species inflicted medically significant effects, an additional 31 taxa produced non-progressive mild local pathology insufficient to be tabulated as "medically significant", but are included here because these produced some degree of objectively recorded notable local effects during presentation. Therefore, this tally includes a summarized number of species that have inflicted bites causing some clinically significant pathological effects, and "medically significant" is defined after Weinstein *et al.* (2011), for example ranging from some locally progressive, but minor edema to bites with a fatal outcome. Bites resulting in simple puncture wounds and lacerations with reactive erythema are not included in the summarized figure. There are very likely a number of other NFFC that may have medical significance under some multifactorial circumstances.

[4]This approximate number estimates the number of genera and species (in brackets) contained in the family listed.

[5]This summarized number includes a single entry for some species such as the South American burrowing snakes, *Apostolepis* spp., a genus with some 26 taxa. The single number reflects the results of a collected series of reported bites that provide documentation of some significant uncomplicated local effects of bites from members of this genus without individual species identification.

[6]The single taxa included here is the Natal black snake, *Macrelaps microlepidotus*, a monotype that is considered a provisional member of either the Atractaspidinae or the Aparallactinae, depending on author. Therefore, the taxonomic status of this species remains unconfirmed. Purely for the sake of the medically relevant discussion here, it is included with the Aparallactinae in order to separate it from the front-fanged atractaspidines (see next footnote).

[7]This subfamily is provisionally recognized by some investigators, and not by others who still consider these as a full family (Atractaspididae). *Atractaspis* spp., and the other allied genus, *Homoroselaps*

Table 1. Overview of the superfamily Colubroidea[1] and their medical significance

spp., that is grouped with *Atractaspis* spp. on robust morphological grounds, are the only front-fanged colubroids assigned to what otherwise is a NFFC clade. See Pyron and Burbrink (2012), Vidal *et al.* (2007, 2010) and Zaher *et al.* (2009) for detailed information about the problematic taxonomy of some of these assignments.

[8]Most taxonomists no longer recognize this subfamily, or several others that were previously proposed, or used (e.g. Micrurinae, Laticaudinae, Elapinae, etc.). The Hydrophiinae is included only because it appears in some of the relevant literature.

Abbreviations: NFFC-Non-front-fanged colubroid snakes; NA-not applicable; IC-insufficient information.

Table 2. Summarized Comparison of the Major Features of Duvernoy's Glands of Non-Front-Fanged Colubroid Snakes (NFFC) and "True" Venom Glands of Viperids, Elapids, *Atractaspis* spp. and *Homoroselaps* spp. (Front-Fanged Colubroids, FFC)

NFFC	FFC	Comments
Variable gland morphology, but typically located temporally	Variable morphology, but some taxa uncommonly have markedly elongated venom glands (sometimes up to or greater than 1/3 the snout-vent length, e.g. *Causus* spp. [night adders]; Asian long-glanded coral snakes [*Calliophis* spp.]; *Atractaspis* spp. [mole vipers, burrowing asps])	In most species of NFFC, morphological diagnosis of Duvernoy's glands ("venom glands") highlights the distinctive qualities of the glands
The vast majority of species exhibit absence of any significant muscle attachment to fundus of gland	Notable attachment of muscle fibers on the fundus of the gland	Only a handful of NFFC (e.g. *Dispholidus typus*, boomslang) have some limited muscle fiber attachment
Dentition (enlarged mid- or posterior maxillary teeth) associated with Duvernoy's glands is always non-canaliculate (solid and without a lumen); may or may not possess an external groove or varying depth and length (e.g. *Rhabdophis tigrinus* has enlarged posterior maxillary teeth that lack grooves, while *Dispholidus typus* has markedly enlarged posterior maxillary teeth with grooves)	Dentition ("fangs") associated with venom glands always canaliculated (hollow; with a lumen; analogous to a hypodermic needle)	Due to the common lack of muscular attachment and canaliculated dentition, Duvernoy's glands are low-pressure systems ("low pressure venom glands"), while "true" venom glands are high-pressure systems
Most species lack any appreciable storage capacity; secretion is typically produced by cholinergic stimulation of the glands and is likely initiated by pterygoidal mobilization	Most species have significant venom storage capacity; glands have large reservoir for ready delivery of a stored venom bolus	Although protracted bites by NFFC are generally potentially more significant, some species may still deliver clinically significant volumes of secretion/venom in brief bites

Table 3. Representative components isolated from venoms/oral secretions of non-front-fanged colubroid snakes (NFFC)

NFFC Taxa[1]	Isolated/Characterized component(s)	Reference	Comments
Family, Subfamily[1]			
Colubridae, Colubrinae			
Mangrove snake, or ringed cat snake, *Boiga dendrophila*	Three-finger fold postsynaptic neurotoxin [3FTX] ("denmotoxin")	Pawlak *et al.* (2006); Pawlak and Kini (2008)	• Primarily avian-specific postsynaptic neurotoxin; M*r* 8.5 kDa that contains five disulphides. • Aside from a conserved leader signal sequence, its basic genetic organization (e.g. arrangement of untranslated and translated sequences) differs from that of elapid three-finger toxins. • This toxin is unlikely to have clinical importance.
Brown tree snake, *Boiga irregularis*	Unusual three-finger fold postsynaptic neurotoxin ("irditoxin")	Pawlak *et al.* (2009)	• Novel 17.1 kDa disulphide-linked, heterodimeric structure. • Approximately three-fold more active *in vitro* at the avian neuromuscular junction than in the rat phrenic nerve preparation. • Selective toxicity for lizards and birds. • This toxin is unlikely to have clinical importance.
Brown tree snake, *Boiga irregularis*	"Myotoxic fraction" (containing 2 proteins)	Weinstein *et al.* (1991)	• Fraction contained two proteins, 14.5 kDa and 17 kDa. • i.p. injection into mice caused myoglobinuria due to multifocal myofiber degeneration and necrosis.

[1]The taxonomy of the Colubroidea is fluid and under continuing review and re-assignment. The taxonomy included here follows that of Pyron *et al.* (2011).

Table 3. Representative components isolated from venoms/oral secretions of non-front-fanged colubroid snakes (NFFC)

			• There is currently no evidence supporting medical importance of these proteins.
Radiated ratsnake, copperhead ratsnake, *Coelognathus radiatus*	Three-finger fold postsynaptic neurotoxin ("colubritoxin")	Fry *et al.* (2003)	• An 8.5 kDa 3FTX; notable structural homology with elapid 3FTX. • Produces reversible antagonism in the chick biventer cervicis muscle preparation. • There is currently no evidence supporting medical importance of this toxin.
Boomslang, *Dispholidus typus*	"Coagulant principle"	Hiestand and Hiestand (1979); Guillin *et al.* (1980)	• The ≈67kDa "procoagulant principle" reported by Hiestand and Hiestand (1979) is probably the same or a similar molecular species noted by Guillin *et al.* (1980) with powerful prothrombin-activating activity. • This toxin very likely plays an important role in the life threatening clinical envenoming that can follow bites by this species.
Boomslang, *Dispholidus typus*	P-III/P-IV snake venom metalloprotease [SVMP] ("dispholysin A")	Kamiguti *et al.* (2000)	• The 65kDa species cross-reacted with the P-III hemorrhagic SVMP from *Bothropoides* (*Bothrops*) *jararaca* (Oliveira *et al.*, 2010) venom. • This toxin very likely plays an important role in the life threatening clinical envenoming that can follow bites by this species (see the previous entry).
Kirtland's twig,	Procoagulant	Kornalik *et*	• The ≈85 kDa

Table 3. Representative components isolated from venoms/oral secretions of non-front-fanged colubroid snakes (NFFC)

vine or bird snake, *Thelotornis kirtlandii*		*al.* (1978)	procoagulant (pI 5.25) was partly characterized from a "venom gland" extract, and found to be a direct prothrombin activator. • This fraction, as well as other similar procoagulant components in combined action with metalloproteinases, causes the life threatening clinical effects in patients after being bitten by this species.
Sonoran lyre snake, *Trimorphodon biscutatus lambda* [*Trimorphodon lambda* DeVitt *et al.*, 2008]	Phospholipase A_2 [PLA2] ("trimorphin")	Huang and Mackessy (2004)	• Some conserved structural features of the Group IA PLA2 were present in this 13.99 kDa PLA2, and suggested that there was a close relationship with some hydrophiine elapid PLA2. • There is currently no evidence supporting medical importance of this PLA2, but, to date, there are also very few well-documented bites by this species, and none are medically significant.
Colubridae, Dipsadinae			
Puerto Rican racer, *Borikenophis* [*Alsophis*] *portoricensis*	P-III metalloproteinase ("alsophinase")	Weldon and Mackessy (2012)	• α-fibrinogenolytic 56 kDa polypeptide with hemorrhagic activity in mice that has 67% primary sequence homology with metalloproteinase from *P. olfersii* venom. • Unknown clinical significance.
Mountain keel back, *Helicops angulatus*	Cysteine-rich secretory protein [CRISP] ("helicopsin")	Estrella *et al.* (2010)	• The 20 kDa CRISP was toxic to mice. • There is currently no

Table 3. Representative components isolated from venoms/oral secretions of non-front-fanged colubroid snakes (NFFC)

			evidence supporting medical importance of this toxin, but there are also very few well-documented bites by members of this genus.
Lichtenstein's racer, *Philodryas olfersii*	Myotoxin	Prado-Franceshi *et al.* (1998)	• The 20 kDa (pI 4.8) toxin produced myolysis and extensive widening of the intercellular spaces with partial or total loss of transverse muscle striations in the muscle periphery. • Although several authors relate these and similar toxins of *Philodryas* spp. to clinical effects in bitten victims, to date, there is no clear evidence of this linkage.
Patagonian racer, *Philodryas patagoniensis*	Haemorrhagic, α-fibrinogenolytic metalloprotease ("patagonfibrase")	Peichoto *et al.* (2007)	• An acidic 53.2 kDa SVMP that can directly cleave fibrinogen. The venom/oral secretion of this species also contains other metalloproteases, CRISPs, 3FTX, and a rich complement of other biologically active proteins. • See previous entry for comments regarding possible medical importance of this toxin.
Colubridae, Natricinae			
Tiger keel back, or Yamakagashi, *Rhabdophis tigrinus*	Metalloproteinase ("38 kDa metalloproteinase")	Komori *et al.* (2006)	• The authors noted that the regulatory mechanism of this novel proteinase suggested that it was more likely a matrix metalloproteinase, rather than a SVMP. • The venom of this

Table 3. Representative components isolated from venoms/oral secretions of non-front-fanged colubroid snakes (NFFC)

			species and that of the congener, *R. subminiatus* (red-necked keel back) has several medically important toxins such as prothrombin activators, and these combined with the action of metalloproteinases likely result in the life threatening haemorrhagic effects observed in patients after being bitten by these species.
Homalopsidae			
Dog-faced watersnake, *Cerberus rhynchops*	"ryncolins" (unconfirmed/unknown function)	OmPraba *et al.* (2010)	• Based on their structural homology with mammalian ficolins, OmPraba *et al.* (2010) hypothesized that ryncolins may act as platelet aggregators and/or complement activators. • Of unknown function. • To date, bites from this species and other homolopsids have been medically insignificant.
Lamprophiidae, Psammophinae			
Montpellier snake, *Malpolon monspessulanus*	Haemorrhagic toxin (" Fraction CM-6")	Rosenberg *et al.* (1985)	• This 24 kDa component produced pulmonary haemorrhage in mice, but did not cause local haemorrhage when administered intradermally. • Currently, there is no evidence that this toxin is medically important.
African beaked snake, *Rhamphiophis oxyrhynchus*	Postsynaptic neurotoxin, 3FTX ("rufoxin")	Lumsden *et al.* (2007)	• Novel toxin (molecular mass ≈10-12 kDa) lacking N-terminus homology with elapid 3FTX. • Produces reversible

Table 3. Representative components isolated from venoms/oral secretions of non-front-fanged colubroid snakes (NFFC)

			antagonism in the chick biventer cervicis muscle preparation. • As with most NFFC toxins characterized to date, there is currently no evidence that "rufoxin" has any medical importance, but there are also no well-documented clinically significant bites by this species.

Table 4. The medical significance of some representative non-front-fanged colubroid snakes (NFFC) [1]

NFFC Taxa (Family, Subfamily), [General geographic range]	Hazard Index[2]	Basic medical management strategy[3]
Boomslang, *Dispholidus typus* (Colubridae, Colubrinae) [East Africa to South Africa, through Central Africa to disjunct distribution in West Africa] Cape twig or vine snake, *Thelotornis capensis* (Colubridae, Colubrinae) [Southern East Africa to Central Africa and north-eastern South Africa] Kirtland's twig or vine snake, *T. kirtlandii* (Colubridae, Colubrinae) [East Africa through Central Africa to south-central West Africa] Tiger keel back or Yamakagashi, *Rhabdophis tigrinus* (Colubridae, Natricinae) [Japan, Eastern Russia {limited distribution}, Vietnam, North and South Korea, Taiwan, China {broad distribution in Central and mid-Southern provinces}] Red-necked keel back, *R. subminiatus* (Colubridae, Natricinae) [Indonesia (precise distribution unclear), most of southeast Asia, Western Malaysia, Singapore, north-eastern India, Nepal, Bangladesh, Southern China]	1	• Effective antivenoms are available for *D. typus* and *R. tigrinus*. • Antivenom raised against *R. tigrinus* venom should be used to treat serious envenoming by *R. subminiatus* as it probably provides paraspecific protection. • There is no antivenom for envenoming by *Thelotornis* spp. and there are no antivenoms that provide paraspecific protection (including those mentioned above). Treatment consists of replacement therapy[4] only. • Replacement therapy may also be needed for the aforementioned species in addition to antivenom on a case-by-case basis. • Significant bites from any of these species must be considered life threatening. • *The use of heparin, anti-fibrinolytics, vitamin K, corticosteroids, etc. is positively contraindicated due to an unfavourable risk vs. benefit profile.*
Monpellier snake, *Malpolon monspessulanus* (Lamprophiidae, Psammophinae) [Southern France, Spain, Portugal, Turkey, Greece, Albania; North Africa to Egypt and the Middle East] Brown tree snake, *Boiga irregularis*[5] (Colubridae, Colubrinae) [See footnote #5]	2-3	• Closely monitor neurological signs in those bitten (especially pediatric patients) by *M. monspessulanus* and *B. irregularis*, and coagulation panels in those bitten by *Philodryas* spp. • Consider the use of neostigmine if paralytic features (e.g. ptosis, dysphagia) develop. • *Do NOT give antivenom of any*

Table 4. The medical significance of some representative non-front-fanged colubroid snakes (NFFC) [1]

Lichenstein's green racer, *Philodryas olfersii* (Colubridae, Dipsadinae) [Venezuela, French Guiana, Brazil, Bolivia, Paraguay, Uruguay and Argentina] [6]		*kind.* • Carefully scrutinize the wound and provide early wound treatment if clinically indicated.
False water cobra, *Hydrodynastes gigas* (Colubridae, Dipsadinae) [Surinam, Brazil, eastern Bolivia, Paraguay, northern Argentina, coastal French Guiana] Western hognose snake, *Heterodon nasicus* (Colubridae, Dipsadinae) [South-central Canada, broad US distribution from Montana down to Arizona and New Mexico; east to Illinois; Mexico] Mangrove snake, *Boiga dendrophila* (Colubridae, Colubrinae) [Wide distribution in Indonesia, Malaysia, Southeast Asia, Singapore, Philippines]	3	• Any patient presenting with a clinically significant bite should be observed in a well-equipped facility. • *Do NOT give antivenom of any kind.* • Carefully scrutinize the wound and provide early wound treatment if clinically indicated. • There is no current convincing evidence of systemic effects occurring after the bites of any of these taxa, but patients should be carefully assessed and bites from large specimens may produce moderate local "envenoming".
Garter and ribbon snakes, *Thamnophis* spp. (Colubridae, Natricinae) [this genus ranges furthest north of all North American snakes and is widely distributed in North America from south-eastern Alaska and Canada to Central America] and many other taxa of diverse taxonomic affinities[7]	4	• Minor local wound care only.

[1]This list contains only some representative species, and risk assignment can only be accomplished for relatively few NFFC. This is due to the absence of acceptably documented clinical information, species identification and/or other criteria that would constitute a basis for accurate assessment and Hazard Index assignment, as suggested by Weinstein et al. (2011). The presence in ophidian oral secretions/venoms of toxins, and/or their transcripts are insufficient criteria for assessment of possible medical significance of a given species as these may be prey-specific and/or may have no medical relevance due to multifactorial influences relevant to both the snake and human victim. There are very likely a number of other NFFC that may have medical significance under some multifactorial circumstances.

[2]Hazard index is defined as: Level 1-Serious and potentially fatal envenoming is possible; Level 2-Systemic envenoming is possible, but uncommon; Level 3-Usually mild-moderate local effects and usually associated with a protracted bite; Level 4-Most commonly medically insignificant; larger specimens may inflict minor local effects (Weinstein *et al.*, 2011).

[3]This only lists the essential basic management approach; specific cases may require additional interventions. See Weinstein *et al.* (2011) for a detailed discussion of diagnosis, laboratory investigations and management of medically significant NFFC bites.

Table 4. The medical significance of some representative non-front-fanged colubroid snakes (NFFC) [1]

[4]Replacement therapy consists of provision of packed erythrocytes, platelets, cryoprecipitate or fresh frozen plasma, etc. The use of these in coagulopathic envenoming carries risk and remains controversial. Therefore, this should be considered per clinical need on a case-by-case basis.

[5]This hazard assignment applies only to the non-native *B. irregularis* populations that were introduced on Guam and several other Micronesian islands during World War II. These snakes generally reach larger size than that of most *B. irregularis* found in their natural range (coastal New South Wales, Queensland and Northern Territory, Australia; New Guinea; Indonesia [Sulawesi, Togian Islands]).

[6]There is a substantial evidence-base that suggests that the Patagonian racer (*Philodryas patagoniensis*) is a medically important species in Brazil and several other South American locales. To date, well-documented cases of bites from this species have been limited to only local effects (Hazard Level 3), but systemic effects may be possible as noted from bites of the congener, *P. olfersii*.

[7]This table contains only summarized information about important representative species. See Weinstein *et al.* (2011) and references cited therein for more detailed information about bites from these and numerous other taxa, as well as the distribution, basic dietary preferences and available toxinology data for these species.

Highlights

- Non-front-fanged colubroid snakes (NFFC; formerly and artificially taxonomically assembled as “colubrids”) comprise about 70% of extant snake species and include several taxa now known to cause lethal or life threatening envenoming in humans.
- Cases involving approximately 120 species contained well-documented clinical detail sufficient for evidence-based analysis, and a small subset designated Hazard Level 1 (most hazardous), contained 5 species with lethal potential.
- Other NFFC species that inflicted bites causing either systemic (but not life threatening) or local effects only were assessed and categorized as Hazard 2/3-4.
- Considered are problems present in a large volume of the literature containing descriptions of NFFC bites, incorrectly formulated or premature perceptions of medical hazards posed by little studied NFFC, and evidence-supported management strategies for medically significant NFFC bites.

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Highlights

- **Non-front-fanged colubroid snakes (NFFC) include taxa known to inflict fatal envenoming**
- **There are relatively few well documented; those describing bites by ≈120 species were analysed**
- **NFFC species were classified as Hazard Levels 1 (lethal potential) to 4 (minor local effects only)**
- **Deficiencies in reported cases and management of medically significant bites by NFFC are discussed**

References ("uncited")

Estrella et al 2011

Correction: There cited reference is correct in Bibliography (as written above it is 2011, not 2010). It requires correction in Table 3 and on pg. 10 of the manuscript text.

Fry et al. 2006

Correction: This reference was errantly included in the Bibliography and should be deleted.

Guillin et al. 1978

Correction: The cited reference is correct in the Bibliography (as written above it is 1978, not 1980). It requires correction in Table 3.

Hedges et al. 2009

Correction: The cited reference is correct in the Bibliography (as written above it is 2009, not 2010). It requires correction on pg.14 of the manuscript text.

Kardong 2012

Correction: The cited reference was errantly included in the Bibliography and should be deleted.

Lawson et al. 2005

Correction: The cited reference was errantly included in the Bibliography and should be deleted.

Wiens et al. 2008

Correction: The cited reference was errantly included in the Bibliography and should be deleted.

References ("unmatched")

Kardong 2009

Correction: The following citation should be added to the Bibliography:

Kardong, KV. 2009. Presentation at Venom Week 2009 (Albuquerque, New Mexico).

Weinstein et al. in press

Correction: The cited reference is correct in the manuscript text, but incorrect in the Bibliography. It should be corrected in the Bibliography to:

Weinstein, SA, White, J, Westerström, A, Warrell, DA. 2012. Anecdote vs substantiated fact: the problem of unverified reports in the toxinological and herpetological literature describing non--front-fanged colubroid snakebites. Herpetol. Rev. (in press).

Hedges et al. 2010

Correction: See above; the cited reference is correct in the Bibliography (it is 2009, not 2010). It requires correction on pg.14 of the manuscript text.

Weinstein et al. under review

Correction: As noted above, the cited reference is correct in the manuscript text, but incorrect in the Bibliography. It should be corrected in the Bibliography to:

Weinstein, SA, White, J, Westerström, A, Warrell, DA. 2012. Anecdote vs substantiated fact: the problem of unverified reports in the toxinological and herpetological literature describing non--front-fanged colubroid snakebites. Herpetol. Rev. (in press).