
Erythrolamprus mimus
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Erythrolamprus aesculapii
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Xenodon semicinctus
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Xenodon neuwiedii
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Xenodon merremi
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Philodryas olfersii
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Clelia clelia
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Oxyrhopus formosus
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Hydrodynastes gigas
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Helicops angulatus
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Conophis vittatus
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Dipsas catesbyi
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Atractus flammigerus
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Leptodeira septentrionalis
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Hypsiglena torquata
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Farancia abacura
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Diadophis punctatus
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Carphophis amoenus
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Heterodon simus
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Thamnophis brachystoma
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Thamnophis elegans
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Nerodia cyclopion
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Regina grahamii
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Regina septemvittata
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Storeria occipitomaculata
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Regina alleni
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Regina rigida
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Natrix natrix
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Natrix tessellata
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Natrix maura
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Sinonatrix percarinata
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Sinonatrix annularis
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Xenochrophis piscator
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Amphiesma stolatum
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Rhabdophis leonardi
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Rhabdophis tigrinus
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Rhabdophis subminiatus
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Macropisthodon rudis
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Lampropeltis getula
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Lampropeltis calligaster
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Pantherophis obsoletus
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Pantherophis alleghaniensis
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Pituophis catenifer
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Elaphe quadrivirgata
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Euprepiophis conspicillatus
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Drymarchon corais
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Coluber constrictor
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Dasypeltis scabra
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QAVTEEDPAGDN
Boiga irregularis
Hydrophobicity
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QAGTEDDPAGDN
Lycodon rufozonatus
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Cyclophiops semicarinatus
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Dendrelaphis punctulatus
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Dendrelaphis subocularis
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Hemiaspis signata
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Pseudechis australis
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Acanthophis praelongus
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Naja nigricollis
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Naja melanoleuca
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Naja naja
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Naja atra
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Hemachatus haemachatus
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Dendroaspis angusticeps
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Dendroaspis polylepis
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Ophiophagus hannah
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Boaedon fuliginosus
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QAGTEDDPSGDN
Hypsiscopus plumbea
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Crotalus atrox
Hydrophobicity
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Sistrurus catenatus
Hydrophobicity
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QAGTEEDPAGDN
Agkistrodon contortrix
Hydrophobicity
PI
LAGTEEDPSRDN
Viridovipera stejnegeri
Hydrophobicity
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QVGTEEDPAGDN
Bitis nasicornis
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Bitis arietans
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Cerastes cerastes
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Causus maculatus
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Vipera berus
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Vipera aspis
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Acrochordus arafurae
Hydrophobicity
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QAGTEDDPAGDN
Morelia spilota
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Liasis fuscus
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Python regius
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Python molorus
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Epicrica albipuncta
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Figure S1. List of amino acid sequences for the H1-H2 extracellular loop of all species analyzed in this study, generated by Geneious v. 6.1.8 (Biomatters Ltd.). The hydrophobicity and isoelectric point (PI) of each residue is indicated below each sequence. The Q111L mutation results in increased hydrophobicity and the G120R mutation results in increased PI.

Table S1. Snake species included in this study, indicating the presence or absence of the resistance mutations of Na^+/K^+-ATPase and the presence or absence of toads in the diet. The dietary data are compiled almost exclusively from primary literature, a large portion of which includes comprehensive dietary studies rather than anecdotal observations. We considered most secondary literature to be unreliable for accurate dietary data. Due to the imperfect nature of dietary studies, we have taken a conservative approach and consider a species bufophagous if it is a generalist predator and there exists a record of at least one individual consuming a toad (i.e., marked "Yes" under "Toad in Diet"). Furthermore, we considered a bufadienolide-resistant snake bufophagous if it is a generalist predator with a high frequency of amphibians in the diet, even though there are no published records of toads. Bufadienolide-resistant species that are not considered bufophagous include primarily species with dietary specializations that do not include amphibians. Asterisks indicate species with diets including >80% toads or those that sequester dietary bufadienolides.

Species	Resistance Mutations	Toad in Diet	References
Erythrolamprus mimus	**Yes**	**No**	[1–2]
Erythrolamprus aesculapii	**Yes**	**No**	[1,3–8]
Xenodon semicinctus	**Yes**	**Yes**	[4]

Xenodon neuwiedii	**Yes**	**Yes**	[9–12]
Xenodon merremi	**Yes**	**Yes***	[9–10,13–12]
Philodryas olfersii	**Yes**	**No**	[7,14–18]
Clelia clelia	**Yes**	**No**	[19]
Oxyrhopus formosus	**Yes**	**No**	[17–18]
Hydrodynastes gigas	**Yes**	**Yes**	[20]
Helicops angulatus	**Yes**	**No**	[7,14,21–24]
Conophis vittatus	**Yes**	**No**	[25]
Dipsas catesbyi	**Yes**	**No**	[23,26–27]
Atractus flammigerus	**Yes**	**No**	[15]
Leptodeira septentrionalis	**Yes**	**Yes**	[28–30]
Hypsiglena torquata	**Yes**	**Yes**	[31]
Farancia abacura	**No**	**No**	[32–33]
Diadophis punctatus	**No**	**No**	[34–35]
Carphophis amoenus	**No**	**No**	[34]
Contia tenuis	**No**	**No**	[36]
Heterodon simus	**Yes**	**Yes**	[37–38]
Heterodon nasicus	**Yes**	**Yes**	[37–39]
Heterodon platirhinos	**Yes**	**Yes***	[37,40–41]
Thamnophis radix	**Yes**	**No**	[42–45]
Thamnophis butleri	**Yes**	**No**	[46–47]
Thamnophis brachystoma	**Yes**	**No**	[48–49]
Thamnophis elegans	**Yes**	**Yes**	[12,50–51]
Thamnophis atratus	**Yes**	**Yes**	[52–54]
Thamnophis couchii	**Yes**	**Yes**	[55–56]
Thamnophis ordinoides	**Yes**	**No**	[49,56]
Thamnophis marcianus	**Yes**	**Yes**	[57]
Thamnophis cyrtopsis	**Yes**	**Yes**	[58]
Thamnophis melanogaster	**Yes**	**No**	[59–63]
Thamnophis sauritus	**Yes**	**Yes**	[64]
Thamnophis proximus	**Yes**	**Yes**	[57,65–67]
Thamnophis sirtalis	**Yes**	**Yes**	[12,51,68–70]
Nerodia fasciata	**Yes**	**Yes**	[71–73]
Nerodia sipedon	**Yes**	**Yes**	[34–35,74]
Nerodia rhombifer	**Yes**	**No**	[71,74–76]
Nerodia cyclopion	**Yes**	**No**	[74–75]
Regina grahami	**Yes**	**No**	[71,74]
Regina septemvittata	**Yes**	**No**	[74,77–78]

Storeria occipitomaculata	**Yes**	**No**	[79–80]
Storeria dekayi	**Yes**	**No**	[79,81]
Regina alleni	**Yes**	**No**	[74,82–84]
Regina rigida	**Yes**	**No**	[74–75]
Natrix natrix	**Yes**	**Yes**	[85–88]
Natrix tessellata	**Yes**	**Yes**	[86,89]
Natrix maura	**Yes**	**No**	[90–91]
Sinonatrix percarinata	**No**	**No**	[92]
Sinonatrix annularis	**No**	**No**	[92]
Xenochrophis piscator	**Yes**	**Yes**	[93]
Amphiesma stolatum	**Yes**	**No**	[94]
Rhabdophis leonardi	**Yes**	**No**	[95]
Rhabdophis tigrinus	**Yes**	**Yes***	[96–98]
Rhabdophis subminiatus	**Yes**	**Yes**	[99]
Macropisthodon rudis	**Yes**	**Yes**	[100]
Lampropeltis getula	**No**	**No**	[66]
Lampropeltis calligaster	**No**	**No**	[35,66]
Pantherophis obsoletus	**No**	**No**	[35,66,101]
Pantherophis alleghaniensis	**No**	**No**	[102]
Pituophis catenifer	**No**	**No**	[103]
Elaphe quadrivirgata	**No**	**No**	[96–97,104]
Euprepiophis conspicillatus	**No**	**No**	[105]
Drymarchon corais	**Yes**	**Yes**	[106–107]
Coluber constrictor	**No**	**No**	[35,66,108–109]
Dasypeltis scabra	**No**	**No**	[110–111]
Boiga irregularis	**No**	**No**	[112]
Lycodon rufozonatus	**Yes**	**Yes**	[113]
Cyclophiops semicarinatus	**No**	**No**	[105]
Dendrelaphis subocularis	**No**	**No**	[114–115]
Dendrelaphis punctulatus	**No**	**No**	[116–118]
Hemiaspis signata	**No**	**No**	[119–121]
Pseudechis australis	**No**	**No**	[121]
Acanthophis praelongus	**No**	**No**	[122]
Naja nigricollis	**Yes**	**Yes**	[123]
Naja melanoleuca	**Yes**	**Yes**	[123–126]
Naja naja	**Yes**	**Yes**	[127–128]
Naja atra	**Yes**	**Yes**	[127–129]
Hemachatus haemachatus	**Yes**	**Yes**	[126]

Dendroaspis angusticeps	**No**	**No**	[130–131]
Dendroaspis polylepis	**No**	**No**	[131]
Ophiophagus hannah	**No**	**No**	[132]
Boaedon fuliginosus	**No**	**No**	[133]
Hypsiscopus plumbea	**No**	**No**	[134]
Crotalus atrox	**Yes**	**No**	[135–137]
Sistrurus catenatus	**No**	**No**	[138–140]
Agkistrodon contortrix	**Yes**	**No**	[66,141–143]
Viridovipera stejnegeri	**No**	**No**	[127,144]
Bitis nasicornis	**Yes**	**Yes**	[124,145]
Bitis arietans	**Yes**	**Yes**	[146]
Cerastes cerastes	**Yes**	**No**	[147–148]
Causus maculatus	**Yes**	**Yes**	[149]
Vipera berus	**No**	**No**	[150–151]
Vipera aspis	**No**	**No**	[152–154]
Acrochordus arafurae	**No**	**No**	[155–156]
Morelia spilota	**No**	**No**	[157–158]
Liasis fuscus	**No**	**No**	[159–161]
Python regius	**No**	**No**	[162]
Python molurus	**No**	**No**	[163–165]
Epictia albipuncta	**Yes**	**No**	[166–167]

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