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Untersuchungen zu Anomalien in natürlichen Populationen von Amphibien

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A review of anomalies in natural populations of amphibians and their potential causes

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Abstract. Amphibian anomalies have been a source of curiosity for centuries and the literature on this topic is enormous. We provide a comprehensive overview of the anomalies that have been observed in natural populations of amphibians and discuss their suspected and demonstrated causes. We review the evidence for different sensitivity of species to acquire anomalies and the individual and population level consequences of anomalies as well as their conservation implications. We then go on to review the evidence for an increase in the prevalence of anomalies in natural populations of amphibians over recent decades. Finally, we provide recommendations for future studies and argue that in spite of knowledge gaps, we have sufficient information to reduce the anthropogenic contribution to the plights of amphibians for the sake of amphibian conservation and ecosystem and human health.

For our review we traced any publication on anomalies in natural populations of amphibians starting from our extensive literature collections. We compiled the published data in a database, treating each species from a particular location as a separate case. Likewise, we entered each population as a separate case, if population specific data were provided for at least one population. In such cases, we ignored additional data provided for lumped populations that included this population.

The earliest documents of amphibian anomalies are provided by the fossil record. Excluding fossils, we compiled data for 3517 natural populations from 98 countries for which anomalies have been reported. These belong to 6, 117 and 386 living species of Gymnophiona, Urodela and Anura, respectively. The oldest definite report of non-fossil anomalies dates back to 1554 and was a toad with malformed limbs. Since the 1860s publications on the topic have appeared almost every year and rapidly increased. Three major increments in the annual number of publications are noticeable, the first occurring after the Second World War, the second in the mid–1970s and the most recent one in 1996 (the year after which malformation hotspots were widely publicized in the USA).

Most published cases involve only one or two individuals (57% of 3034 cases with data). More than 1000 individuals were only affected in 11 cases (9 cases from single populations). Likewise, the vast majority (81% of 3238 cases with data) involved only one or two types of anomalies. Only six cases (four of them being single populations) comprise more than 15 types of anomalies. The highest number (32) was found in a population of the green toad (*Bufotes viridis*) in Roßwag, Germany.

Abnormal individuals have been reported on all continents, with the vast majority of reports from Europe and North America. The same applies to hotspots of anomalies. Hotspots differ strongly in the pattern of anomalies. Besides limb anomalies, tumours, edema, colour anomalies (especially albinism) and malformation of mouthparts in larvae were detected with high prevalences at hotspots. Only one hotspot (a population of *B. viridis* at Roßwag, Germany) showed a high prevalence of various skeletal anomalies, as well as several types of colour anomalies and edema and tumours. The different patterns of anomalies at different hotspots can only be explained by different causative factors or combinations thereof. Opinions on them vary among scientists and their relative importance differs from continent to continent but include chemical pollution, radioactivity, infection by the trematode *Ribeiroia ondatrae* and other parasites, predator attacks, diseases and various combinations of these factors.

We next review the occurrence of different types of externally visible anomalies: skeletal duplications (polymely, polydactyly, supernumerary bones at the jaw, tail bifurcation and duplication, dicephaly and Siamese twins), absence and reduction of skeletal elements (ectromely, phocomely, ectrodactyly, tail partially or completely missing, brachycephaly, microcephaly, pointed snouts, mandibular hypoplasia, absence of nostrils), other skeletal anomalies (clinodactyly, syndactyly, taumely including bony bridges, rotated limbs, truncated stiff vertebral column, torsion of the tail or body), non-skeletal morphological anomalies (duplication of the eyes and the spiraculum, absence of the tympanum, microphthalmy and anophthalmy, tail retention in anurans after metamorphosis, arm not emerging from the branchial cavity, skin webbing, abnormal spiraculum and ventral tube, malformed mouthparts in tadpoles, giant size and nan-

ism, edema and bloatedness, tumours and tumour-like structures) and colour anomalies (albinism, black-eyed and blue individuals, erythrism, flavism, melanism, translucent skin). For each type of anomaly we tallied the number of natural populations and species for which the anomaly had been reported. We discuss suggested and potential causes, focussing on cases, where more than ten individuals and more than 10% of the population had been affected.

Species may show very different degrees of sensitivity to the different environmental factors that cause anomalies, such as pollutants, predators or parasites. However, there is no evidence that urodeles are less sensitive than anurans. The factors determining differential sensitivity are still insufficiently understood. While phylogeny had no effect in the single study that has tested it so far, some studies indicated that more aquatic species are more sensitive (to water-born factors) than less aquatic species, whereas others suggest the opposite, proposing that rapidly developing species are the more sensitive ones.

Only a few experimental studies addressed individual level effects of anomalies. With few exceptions they showed adverse effects, such as failure to metamorphose, reduced mobility, growth, body condition and survival. The occurrence of an effect may depend on the environment, such as food type or the presence of predators.

At the population level, the effects of anomalies are less evident. Even though populations declined and species became extinct at several hotspots, this may not necessarily have been an effect of anomalies. Direct death and anomalies may have been caused by the same factor, and at some hotspots, anomalies and populations persisted for decades. Population effects need further study to understand the relevance of anomalies for amphibian declines.

It is widely believed that the prevalence of anomalies has increased over recent decades. Evidence from comparisons of historical museum collections and recent surveys as well as resurveys of former hotspot sites tend to support this assumption, although declines in the frequency of anomalies have also been observed and the few long-term monitoring studies available show that the frequency of abnormal individuals can fluctuate widely without an apparent trend. As further evidence for an increasing trend, mechanistic links between eutrophication and high rates of anomalies have been demonstrated and various chemical pollutants are also known to cause elevated rates of anomalies at environmentally relevant concentrations. Because environmental pollution increased since the Second World War, there should indeed have been an increase in anomaly prevalences over recent years. In addition, there is evidence that background rates of anomalies are about an order of magnitude lower than currently assumed.

We finish our review with recommendations for future directions in the research of anomalies in natural populations of amphibians. We conclude that in spite of gaps in our knowledge, sufficient information is available for use to reduce human-induced plights of amphibians.

Keywords. Amphibia, anomalies, hotspots, colour anomalies, disease, edema, individual effects, morphological anomalies, parasites, pollution, population effects, predators, radioactivity, skeletal anomalies, trends, tumours.

Zusammenfassung. Anomalien bei Amphibien haben seit Jahrhunderten die Neugier des Menschen geweckt. Entsprechend existiert eine sehr umfangreiche Literatur über dieses Thema. Wir geben einen umfassenden Überblick über im Freiland an Amphibien beobachtete Anomalien und deren vermuteten und nachgewiesenen Ursachen. Wir stellen Kenntnisse zu einer unterschiedlichen Empfindlichkeit von Arten, Anomalien zu entwickeln, sowie zu den Konsequenzen von Anomalien auf der individuellen und Populationsebene zusammen. Abschließend diskutieren wir Hinweise für eine Zunahme an Anomalien in natürlichen Populationen von Amphibien während der letzten Jahrzehnte und enden mit Empfehlungen bezüglich Forschungsfragen, die helfen können, die Entstehung von Anomalien bei Amphibien und deren Bedeutung für den Amphibienschutz und die Umwelt besser zu verstehen. Trotz Wissenslücken reichen unsere Kenntnisse aus, um den vom Menschen verursachten Anteil an hohen Raten von Anomalien bei Amphibien reduzieren zu können, wenn der Wille hierzu vorhanden ist.

Für unsere Übersicht haben wir, ausgehend von unseren umfangreichen privaten Literatursammlungen, jede uns zugängige Publikation ausgewertet, in der Anomalien für natürliche Populationen von Amphibien erwähnt werden. In der erstellten Datenbank betrachten wir jede Art und jede Population als separaten Fall, sofern populationsspezifische Daten publiziert wurden. Wenn gleichzeitig summarische Daten publiziert wurden, die populationsspezifische Daten einschließen, haben wir nur letztere berücksichtigt.

Fossiles Material liefert die frühesten Dokumente von Anomalien bei Amphibien. Ohne deren Berücksichtigung umfasst unsere Datenbank 3517 Populationen aus 98 Ländern. Diese stammen von 6, 117, und 386 Arten der Ordnungen Gymnophiona, Urodela bzw. Anura. Der älteste definitive Bericht stammt aus dem Jahr 1554 und betrifft eine Kröte mit missgebildeten Beinen. Seit dem frühen 18. Jahrhundert erschienen Publikationen, die sich spezifisch mit Anomalien von Amphibien in natürlichen Populationen beschäftigen, seit den 1860iger Jahren jährlich und in rasch wachsender Zahl. Dabei sind drei Stufen in der Anzahl jährlich erschienener Publikationen ersichtlich: nach dem Zweiten Weltkrieg, Mitte der 1970iger Jahre sowie im Jahr 1996, dem Jahr, in dem Missbildungen an Amphibien in den USA eine weite Aufmerksamkeit in der Öffentlichkeit erhielten.

Die meisten Fälle betreffen 1–2 Individuen (57% der 3034 Fälle mit Daten). Mehr als 1000 anomale Individuen wurden in elf Fällen (9 davon sind Einzelpopulationen) beobachtet. Ebenso umfasst die überwiegende Zahl der Fälle (81%, n = 3238) nur 1–2 unterschiedliche Typen von Anomalien. Nur in sechs Fällen (vier davon sind Einzelpopu-

lationen) traten mehr als 15 verschiedene Typen auf. Der extremste Fall waren 32 unterschiedliche Typen in einer Population der Wechselkröte (*Bufotes viridis*) in Roßwag, Deutschland.

Anomalien wurden auf allen Kontinenten festgestellt, am häufigsten in Europa und Nordamerika. Dasselbe gilt für deren massenhaftes Auftreten, sogenannte Hotspots. Hotspots zeigen sehr unterschiedliche Muster an Anomalien. Je nach Hotspot traten entweder Missbildungen der Gliedmaßen, Tumore, Ödeme, Farbanomalien (besonders Albinismus) oder Missbildungen der Mundpartien von Kaulquappen in großer Häufigkeit auf. Nur an einem Hotspot (einer Population von *B. viridis* bei Roßwag, Deutschland) wurden sowohl verschiedene Skelettmissbildungen als auch verschiedene Farbanomalien, Ödeme und Tumore in großer Anzahl festgestellt. Die unterschiedlichen Muster an Anomalien zeigen, dass es unterschiedliche (Kombinationen von) Ursachen für die Hotspots geben muss. Die Meinungen über deren Ursachen werden häufig kontrovers diskutiert, sie umfassen jedoch chemische Stoffe, Radioaktivität, Infektion durch den Saugwurm *Ribeiroia ondatrae*, andere Parasiten, Verletzungen durch Prädatoren, Krankheiten und verschiedene Kombinationen dieser Faktoren.

Wir geben anschließend eine Übersicht über das Auftreten verschiedener Typen von äußerlich sichtbaren Anomalien: Skelettanomalien (Polymelie, Polydactylie, zusätzliche Knochen am Kiefer, Bifurkation und Verdoppelung von Schwänzen, Doppelköpfigkeit und Siamesische Zwillinge), fehlende oder reduzierte Skelettteile (Ectromelie, Phocomelie, Ectrodactylie, reduzierte oder fehlende Schwänze, Brachycephalie, Microcephalie, abnormal zugespitze Schnauzen, reduzierte Kiefer, Fehlen von Nasenöffnungen), weitere Skelettanomalien (Clinodactylie, Syndactylie, Taumelie, Verdrehung von Knochen der Arme oder Beine, gestauchte steife Wirbelsäulen, verkrümmte Körper und Schwänze), andere morphologische Anomalien (Verdoppelung der Augen und des Spiraculums, Fehlen des Tympanums, Microcephalie, Anophthalmie, Beibehalten des Schwanzes nach der Metamorphose bei Froschlurchen, Arme, die unter der Kiemenfalte verbleiben, Hautfalten an Arm- oder Beingelenken, die die Beweglichkeit einschränken, missgebildetes Spiraculum und Afterröhre, missgebildete Mundfelder von Kaulquappen, Riesen- und Zwergwuchs, Ödeme und Aufblähungen, Tumore und tumor-ähnliche Strukturen) sowie Farbanomalien (Albinismus, anomale schwarze Augen, blaue Frösche, Erythrismus, Flavismus, Melanismus, durchscheinende Haut). Wir diskutieren Erklärungen für die Ursachen dieser Anomalien, wobei wir den Schwerpunkt auf Fälle mit mehr als zehn betroffenen Individuen und 10% der Population legen.

Die Empfindlichkeit gegenüber Umweltfaktoren, wie Chemikalien, Parasiten oder Prädatoren, die Anomalien hervorrufen können, kann artspezifisch sehr unterschiedlich sein. Die dafür verantwortlichen Faktoren sind noch ungenügend geklärt. Während Phylogenie in der einzigen Untersuchung, die deren Einfluss geprüft hat, keine Wirkung hatte, zeigten einige Studien eine höhere Empfindlichkeit stärker aquatischer Arten (gegenüber wassergebundenen Faktoren) als weniger aquatischer Arten. In anderen Studien waren dagegen die sich am schnellsten entwickelnden Arten am empfindlichsten. Es gibt keine Hinweise, dass Froschlurche generell empfindlicher sind als Schwanzlurche.

Die Auswirkungen von Anomalien auf Individuen wurde nur selten experimentell untersucht. Mit wenigen Ausnahmen hat sich eine nachteilige Wirkungen gezeigt, z.B. Verhinderung von Metamorphose oder eine reduzierte Beweglichkeit, geringere Körperkondition, langsameres Wachstum oder niedrigere Überlebenswahrscheinlichkeit. Das Auftreten negativer Wirkungen kann von der Umwelt abhängen, zum Beispiel der Art der Nahrung oder dem Vorhandensein von Fressfeinden.

Die Auswirkungen von Anomalien auf Populationsebene sind bisher wenig verstanden. Obwohl an einigen Anomalie-Hotspots die Abundanz der betroffenen Art(en) abgenommen hat und Populationen erloschen sind, bedeutet dies nicht, dass dafür die Anomalien verantwortlich gewesen sein müssen. Vielmehr kann einer oder mehrere Faktoren gleichzeitig hohe Raten von Anomalien und Mortalität verursacht haben. Die Bedeutung von Anomalien für die Populationdynamik bedürfen gezielter Untersuchungen, bevor deren Relevanz für den globalen Rückgang von Amphibien eingeschätzt werden kann.

Oft wird angenommen, dass die Häufigkeit von Anomalien in den letzten Jahrzehnten zugenommen hat. Vergleiche mit historischen Sammlungen sowie erneute Erfassungen an bekannten Hotspots geben dafür Anhaltspunkte, allerdings gab es auch Abnahmen in der Häufigkeit. Außerdem zeigen die wenigen Langzeiterfassungen, dass die Häufigkeit von Jahr zu Jahr sehr stark schwanken kann. Andererseits gibt es mechanistische Zusammenhänge zwischen der Häufigkeit von Anomalien und Eutrophierung und verschiedene Chemikalien können hohe Raten an Anomalien bei Konzentrationen bewirken, die umweltrelevant sind. Da die Eutrophierung und die Verschmutzung von Gewässern seit dem Zweiten Weltkrieg zugenommen hat, müsste als Konsequenz dieser Zusammenhänge auch die Häufigkeit von Anomalien zugenommen haben. Weiterhin scheinen die natürlichen Hintergrundraten an Anomalien etwa eine Größenordnung niedriger zu sein als oft angenommen wird.

Abschließend geben wir Empfehlungen für künftige Forschungen zum Auftreten von Anomalien bei Amphibien im Freiland und deren Ursachen. Trotz Forschungsbedarf besteht jedoch ausreichend Wissen zum Handeln, um den von Menschen verursachten Anteil am Auftreten von Anomalien bei Amphibien im Freiland zu verringern.

Schlüsselwörter. Amphibia, Anomalien, Auswirkungen auf Individuen, Auswirkungen auf Populationen, Farbanomalien, Fressfeinde, Krankheiten, morphologische Anomalien, Ödeme, Parasiten, Radioaktivität, Skelettanomalien, Trend, Tumore, Verschmutzung

1 Introduction

Amphibian anomalies have been a source of human curiosity for centuries (e.g., Wurffbain 1683, Vallisneri 1706, De Superville 1740, Geoffroy Saint-Hilaire 1832, 1836) to the extent that they have even become part of Chinese folklore and art (Fig. 1). Amphibian anomalies also played a pivotal role in the emerging of the science of developmental biology (e.g., Hertwig 1892, Brandt 1924, Woerdeman 1936) and they still have this function today (e.g., Gardiner & Bryant 1996, Kovalenko & Kovalenko 1996, Nye et al. 2003).

Increased environmental awareness, the global decline of amphibians (e.g., Henle & Streit 1990, Stuart et al. 2004) and the recent rediscovery of populations exhibiting mass anomalies (Burkhart et al. 2000, Souder 2002, Lannoo 2008, 2009) have instigated renewed interest in amphibian anomalies as potential indicators for environmental perturbations (e.g., Tyler 1983, Burkhart et al. 2000, Souder 2002, Vershinin 2002). In response to findings of mass anomalies in North America, the North American Reporting Centre for Amphibian Anomalies (NARCAM) was established (Lannoo 2008). Mass anomalies were also reported in other organisms from polluted environments, for example, plants (Hesse-Honegger 2008, Yablokov et al. 2009, Taira et al. 2014), invertebrates (Vuori & Parkko 1996), reptiles (Ernst 1995, Bishop & Gendron 1998), birds and humans (Hoffmann et al. 1988, Savchenko 1995, van der Schalie et al. 1999, Møller et al. 2007, Yablokov et al. 2009), but, so far only humans (e.g., Winter et al. 1988, Savchenko 1995, Feshchenko et al. 2002, Scherb & Weigelt 2003, Lannoo 2008, Yablokov et al. 2009) and domestic animals (Taruffi 1881–1886, Noden & de Lahunta 1985, Yablokov et al. 2009) have received similar attention to amphibians.

Not surprisingly, the literature on amphibian anomalies is enormous (Henle 2014). There is a considerable number of published reviews; the first comprehensive one appeared more than a century ago (Taruffi 1881–1886). Most reviews focus on rather specific topics and, with few exceptions (noticeably Rostand 1971), do not discuss to any extent the potential and limitations to infer causes from observed patterns of anomalies. Many factors have the potential to cause anomalies in amphibians (reviewed e.g., by Rostand 1971, Dubois 1979b, Tyler 1989, Ferraro & Burgin 1993, Ouellet 2000, Henle et al. 2017a), but the relevance for natural populations of many of them remains debated (compare Skelly & Benard 2010 and Sessions & Ballengée 2010). Linking cause to pattern is a central issue in ecology (Wiegand et al. 2003) and crucial for the use of amphibian anomalies as an indicator of the nature of an environmental perturbation that has occurred in a habitat.

Fig. 1: Chinese artwork figuring a toad with a single hindleg (ectromely) based on a Chinese legend. Photo: K. Henle.

The most recent comprehensive review by Ouellet (2000) addressed primarily skeletal anomalies. While he discussed a range of potential causes, no systematic evaluation of the known or suspected causes of mass anomalies or particular types of anomalies was made. Here we provide a comprehensive overview of the anomalies observed in natural populations of amphibians and discuss their suspected and potential causes. We cover mass anomalies on all continents as well as observations on single individuals. We focus (but do not limit) our review on external anomalies that have been frequently reported or observed in incidences of mass anomalies. We further assess the evidence for an increase in the prevalence of anomalies in natural populations of amphibians over recent decades and review the individual and population level consequences of anomalies as well as their conservation implications. Finally, we provide perspectives for future research.

2 Methods

2.1 Data collation

We attempted to find any citations made on anomalies in natural populations of amphibians starting with our own extensive literature collection, the literature on amphibian anomalies compiled by The North American Reporting Centre for Amphibian Malformations, the literature on field herpetology compiled by Schriftenschau für Feldherpetologie and a manual search for any anomaly-related key words in the Zoological Record for 1945–1985 and in Biosis for 1945–1985 and 1996–1999. More recent volumes were searched through the Web of Science using the headings of the results section of this publication as key words (latest access January 2017). In the review that follows we included only those publications that we could check ourselves except for a limited number of papers published more than 100 years ago. Such publications were included, when we recognized verbal citations of relevant parts of these publications, or if at least two later publications cited them consistently with different details provided so that these authors were likely to have examined the original source independently.

Reviewing the occurrence of anomalies poses major challenges. Even gross morphological anomalies in a given species may be the norm in another one; thus, spe-

cies in the genus *Brachycephalus* have only two or three fingers and three or four toes. This condition would qualify as ectrodactyly in most other anuran genera. In some salamanders, toe morphology is highly variable and it is difficult to set the limit between the range of normal and abnormal variation (Henle et al. 2017b). In *Plethodon cinereus*, a red colour morph is frequent in some regions but very rare in others (Lotter & Scott 1977) and thus might only classify as an anomaly in parts of its range. Particularly complex is the situation for *Salamandra salamandra.* It is a highly polymorphic species with some colour morphs, such as highly or completely yellow or highly black, being very common in some subspecies but a rare anomaly in other subspecies. Then again, there may be small areas within a subspecies, at which a colour morph that is a rare anomaly in other parts of the distribution area of the subspecies, is common, such as the highly yellow colour morph in *S. s. terrestris* near Holzminden, Germany (Seidel & Gerhardt 2016). In these cases we only considered data if the individuals were referred to as abnormal by the respective author(s).

Moreover, some authors included injuries (e.g. Reeves et al. 2013) in the figures for anomalies whereas others did not and even excluded ectrodactyly and amely because they regarded them as the result of injuries (e.g. Flindt 1985a). As injuries may develop into deformed bones (Magnusson et al. 1999) and may be difficult to differentiate from developmental anomalies, we also included injuries in our tallies of anomalies. However, we excluded superficial scars that are regularly found in some species that frequently fight in territorial disputes. Contrary to Reeves et al. (2013), we did not include injuries that resulted from capture. Whereas Reeves et al. (2013) scored the presence of parasites as abnormal, we only did this if the presence was accompanied by, explicitly mentioned, morphological (including lesions) or colour anomalies.

There is no generally accepted terminology for amphibian anomalies. Some of the early terms have changed in meaning over time, some are no longer used and others have been replaced by other terms by some but not all authors. Unfortunately, it is often the case that neither a definition of the terms used nor an explicit reference to a glossary is provided. Our definitions follow those suggested by Henle et al. (2017b). As far as possible we translated the terms used by others into these terms.

Data on anomalies are also provided in a highly inconsistent way. Sometimes data apply to the number of limbs that are affected or the number of anomalies observed and not to the number of abnormal individuals. In our database we only included numbers that refer to individuals. Some authors scored the same complex of anomalies, e.g., an incomplete duplication of a limb, as two anomalies. We follow Dubois & Henle (2017) and regard such cases as a single anomaly. Some publications provided sample sizes for each population but anomalies were merged across populations and vice versa. In such cases we merged all data for all populations. If authors provided overlapping data for specific populations and across sites, we only used data for specific populations. To enable comparisons with Ouellet (2000), we pooled data across years and authors for the same population(s), if the data did not overlap. If the degree of overlap remained uncertain, we only used the data from the most recent publication(s). However, for trend analyses, we split, when possible, data that covered more than 5 years of surveys into 5-years-intervals starting with the first survey year. Unless otherwise stated, frequencies are averages across samples weighed by sample size. If a publication contained information on several species, we regarded each species as a separate case.

Names and status of taxa have changed over time. With few exceptions, we follow Frost (2016). When easily possible, we updated names but we did not attempt to trace specimens and locations or morphological descriptions to revise species identities.

Currently, our database on amphibian anomalies covers 3341 publications, 1775 of them reporting anomalies from natural populations, 1046 publications presenting results from experiments and 247 reviewing specific topics within the field of amphibian anomalies.

2.2 Causal inference

Causes for observed anomalies in natural populations are frequently suggested with limited knowledge of the relevant experimental literature. We therefore evaluated suggested causes of anomalies against a comprehensive assessment of experimental studies. Not all experimental studies provided test results that included controls and others lumped together different types of anomalies. Therefore, we accepted a suggested factor as a potential cause for a particular type of anomaly, if any of the following applied: (a) a mechanistic causative pathway between the factor and the anomaly in question was known, (b) at least one study showed a statistically significant difference between treatment and control, (c) there was a significant correlation between the rate of anomalies and the intensity of the causative factor even if no control data were provided, (d) more individuals were affected in the experimental treatment than in the control in more studies than expected at random, or (e) 100 % of individuals were affected and more than 50 individuals were examined, if no data on controls were provided.

Whereas some authors (e.g., Reaser & Johnson 1997) suggested that, albeit limited, inferences can be made from the percentage of individuals affected, others (e.g., Kovalenko 2000) believed that there was no relationship between the frequency of anomalies and environmental quality. Numerous experimental studies have shown that the strength of a teratogenic factor can have a strong influence on the incidence of anomalies. This applies in many but not all cases involving chemicals, irradiation, parasite abundance (e.g., Nishioka et

al. 1981, Power et al. 1989, Zavanella et al. 1989, Johnson et al. 1999), egg retention time and temperature (Briggs 1941, Witschi 1952, Mikamo & Hamaguchi 1973). High incidences of anomalies can also be caused by several other factors, such as disease (e.g., Bradford 1991), predators (e.g., Caldwell 1982, Veith & Viertel 1993), hybridization (e.g., Delarue 1982, Mable & Rye 1992) and inbreeding (e.g., Humphrey 1948, Droin & Fischberg 1984).

Sensitivity also differs among stages. Gene expression – gastrulation is the first stage at which parental genes become active (Davidson 1976) – as well as structural, physiological and biochemical transformations are particularly intensive during the rapid transition of stages (i.e., embryogenesis and metamorphosis) (Duellman & Trueb 1986), explaining why in general, but not invariably, sensitivity is higher at these stages compared to stasis (Tschumi 1954). For example, factors that can cause skeletal deviations are most effective when they act before the aggregation of skeletal mesenchyme at stage 40–42 (Kovalenko 2000) [i.e., approx. stage 30 of Gosner (1960)]. Likewise, osteolathyrogenic compounds are most effective during the stages of limb development and have no effect on earlier or later stages (Riley & Weil 1987). Furthermore, the same chemical may cause polydactyly only early on in limb regeneration but oligodactyly across a longer period of development or regeneration (Gebhardt & Faber 1966b). Effects of exposure to the trematode parasite *Ribeiroia ondatrae* may also be stage dependent, both in the percentage of individuals affected and the dominant types of anomalies (Johnson et al. 2011).

As a consequence, the percentage of affected individuals does not provide information about the cause of the observed anomalies. The only certain inference that can be made from a high incidence of anomalies is that the factor must have been strong and most individuals of the population must have been exposed to it.

3 Occurrence of anomalies in natural populations

The earliest documents of amphibian anomalies are provided by the fossil record. Wang et al. (2016) described 14 salamanders of the species *Chunerpeton tianyiensis* that showed abnormal polydactyly. Polymely, polyphalangy and brachydactyly were present in two, two, and four, respectively, of these individuals. Mlynarski (1961) observed an asymmetric urostyle in fossil *Rana* sp. and Ippen & Heinrich (1977) described abnormally healed broken bones with a callus in three fossil *Rana* sp. Fejérváry (1916) discovered a fossil *Rana mehelyi* with a fractured ilium. The oldest fossil record of skeletal anomalies in amphibians known to us is a capitosauroid, presumably *Eocyclotosaurus wellesi,* from the Middle Triassic of Arizona (Witzmann 2007).

Excluding fossils, our database covers 3517 natural populations from 98 different countries for which anomalies have been reported. These belong to 6, 117 and 386 living species of Gymnophiona, Urodela and Anura, respectively. The oldest definite report of non-fossil anomalies dates back to 1554 and was a toad, possibly *Bufo bufo*, with malformed limbs that Gesner (1554) observed in Zurich, Switzerland. He also discussed bicephalic salamanders supposedly depicted in hieroglyphs that have been referred to by ancient Greek writers. He regarded them, presumably correctly, as misinterpretations. A century later, Aldrovandi (1645) reported on an earlier mentioning of melanistic toads from Italy but he was also sceptical about its reliability. A few decades later, Wurffbain (1683) again mentioned occasional stories involving bicephalic salamanders and provided a first concrete example: a two-headed salamander that was exhibited by Mercerus. He further illustrated an albino *Salamandra s. salamandra* from Italy (Plate II, Fig. 1) that later was described as *Salamandra candida* by Laurenti (1768). Another figure (Plate I, Fig. 2) may be a flavistic individual faintly showing a pattern.

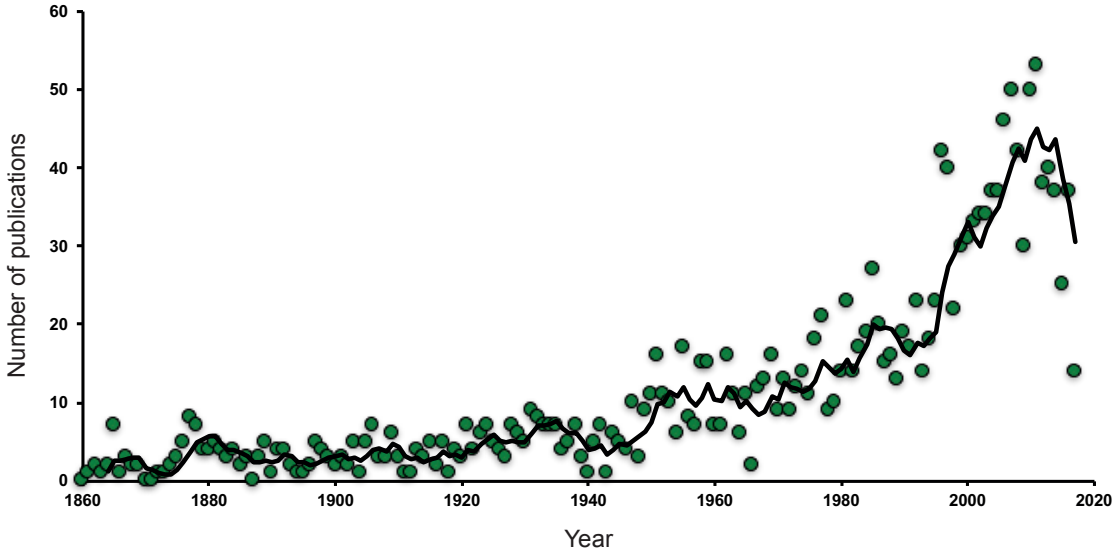

Fig. 2: Temporal pattern of publications reporting or reviewing anomalies in natural populations of amphibians since 1860, with 5-years running average. Source: our database as of 7.6.2017.

Publications that explicitly targeted abnormal amphibians started to appear from the early 18th Century (Vallisneri 1706). In the 18th Century and the first half of the 19th Century ten and 16 publications, respectively, addressed abnormal amphibians in natural populations. Since the 1860s, publications on abnormal amphibians appeared almost annually and rapidly increased in numbers (Fig. 2). Three major increments in the number of annual publications are noticeable: the first occurring after the Second World War, the second in the mid-1970s and the most recent in 1996 (the year after which malformation hotspots had been widely publicized in the USA). Whereas the first increment is also apparent in the graph presented by Johnson & Chase (2004), the second one occurred earlier than indicated in their graph and the last one occurred too late to be assessed by them.

Most published cases involve only one or two individuals (57% of 3034 cases with data; Fig. 3) and background rates are usually around or well below 1% (Tab. 1; see also Henle et al. 2017a). More than 1000 individuals were only reported for 11 populations (9 of them being from single populations), with the largest number for a single population being 2458 adult *Ambystoma tigrinum* with tumours (approx. 0.2% also had edema) living in a sewage pond contaminated by polycyclic hydrocarbons (Rose 1976, 1977, 1981, Rose & Harshbarger 1977). Likewise, the vast majority (81% of 3238 cases with data) involved only one or two types of anomalies (Fig. 4). Only six cases (four of them being from single populations) comprised more than 15 types of anomalies. The highest number of different types of anomalies (32) was exhibited by a population of the green toad (*Bufotes viridis*) in Roßwag, Germany (Henle et al. 2017a).

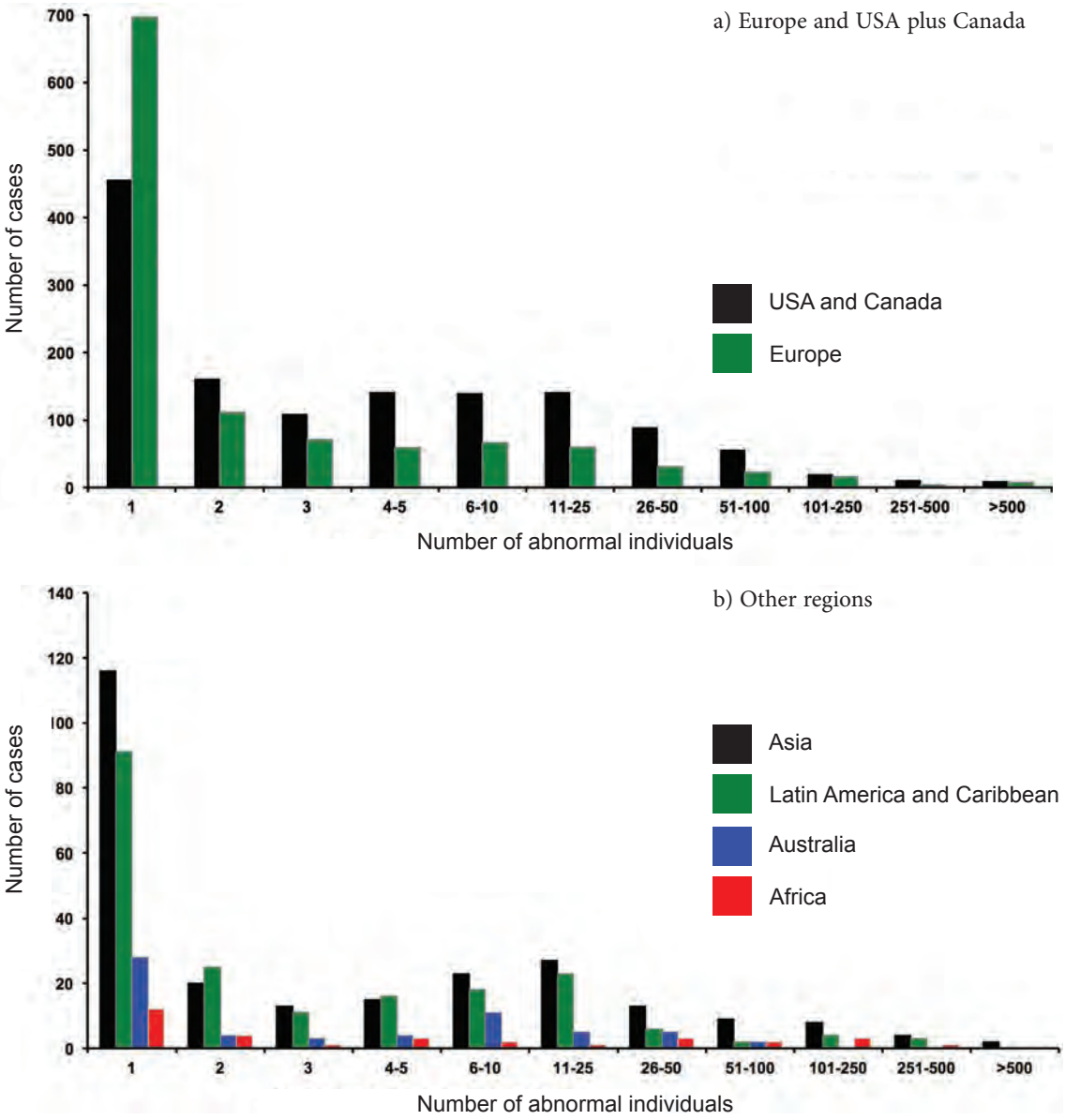

Fig. 3: Frequency distribution of the number of abnormal individuals observed in natural populations; a) Europe and USA plus Canada and b) other regions. Source: our database as of 7.6.2017.

Abnormal individuals have been reported on all continents with the vast majority of cases from Europe and North America (Fig. 3), which is likely to be due to the higher number of naturalists in these regions combined with easier access to locally published observations and the large survey program of amphibian anomalies across U.S. wildlife refuges (Reeves et al. 2013). The frequency distribution of the number of abnormal individuals observed per case (Fig. 3) differs highly significantly among continents (Europe, USA-Canada, remaining parts of America, Asia, Australia+Africa; categories > 500 affected individuals combined) (χ^2_{40} = 216; α = 0). The significance is primarily due to an overrepresentation of cases involving a single individual in Europe and USA-Canada relative to the other groups. Contrary to the opinion of Lannoo (2008) the number of affected individuals does not show a bimodal distribution with most cases either being a single individual or ten or more individuals; rather the distribution follows a steady decline. An exponential decline was also observed in the largest spatial survey that covered 135 wildlife refuges in the USA, in which 48,081 individuals were assessed (Reeves et al. 2013).

On all continents, observations of a single type of anomaly clearly dominate (Fig. 4). The frequency distribution differs highly significantly among continents (Europe, USA-Canada, remaining parts of America, Asia, Australia, Africa; categories > 5 types of anomalies combined) (χ^2_{20} = 227 α = 0). Cases with a single type of anomalies are overrepresented in Europe and cases with more types of anomalies are underrepresented, whereas it is the opposite in North America. In Asia cases with two types of anomalies are underrepresented. For all other categories and continents the frequencies are similar to the global average.

In the following, we first review hotspots of anomalies that involve several types of anomalies or several species, followed by a review of specific types of anomalies.

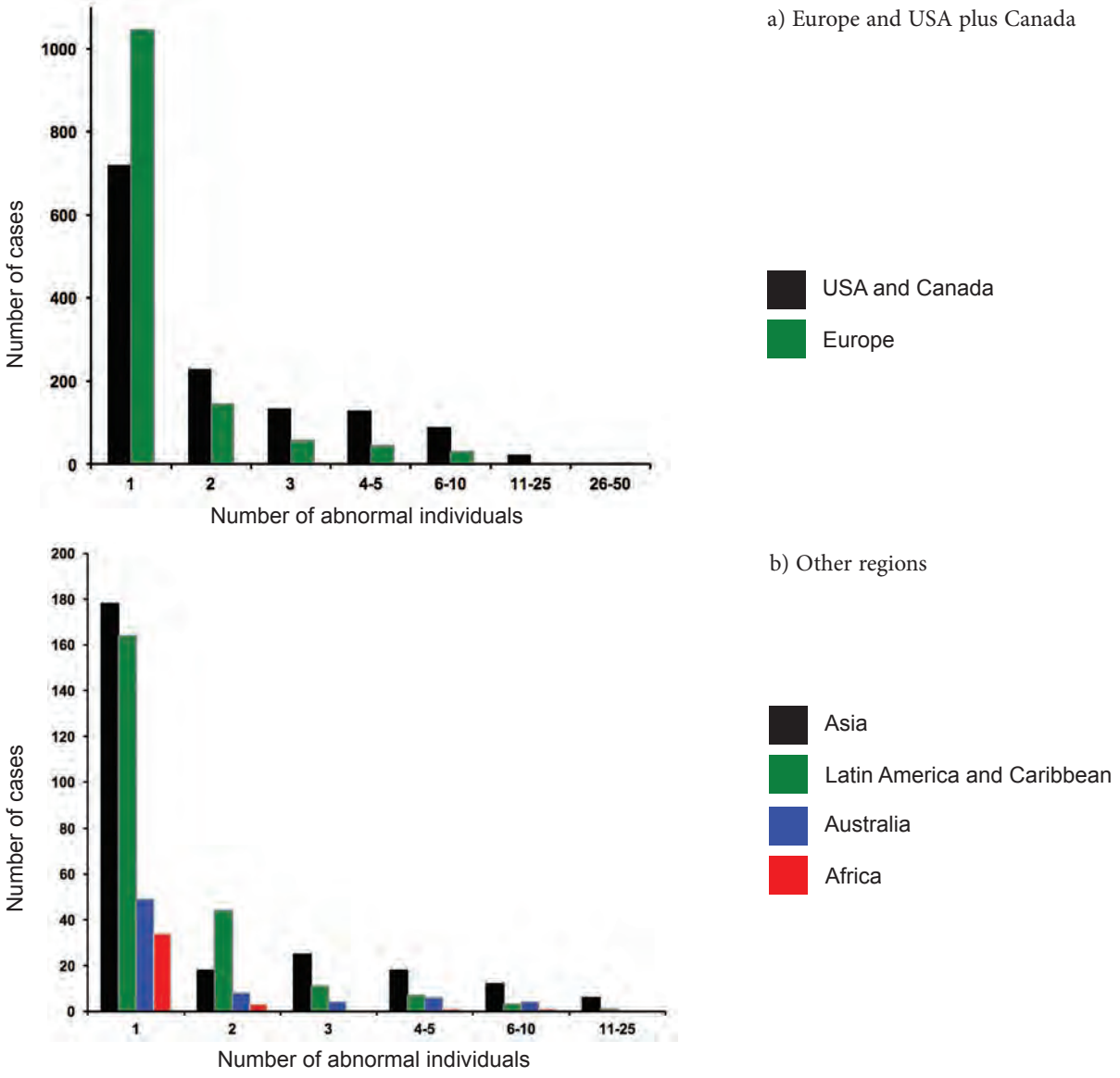

Fig. 4: Frequency distribution of the number of different types of anomalies observed in natural populations of amphibians; a) Europe and USA plus Canada and b) other regions. Source: our database as of 7.6.2017.

Table 1: Background rates of specific types of anomalies in amphibians from presumably "healthy" environments; only studies with samples sizes $N > 5{,}000$ included.

Anomaly	Frequency	*N*	Species	References
Abnormal limbs	2.5%	14,962	*Bufo bufo*	Gittins 1983
Albinism	0.000005%	219,269	*Bufo bufo*	Oerter & Kneitz 1994
Albinism	0.006%	15,657	*Ambystoma opacum*	Mitchell & Church 2002
Albinism	0.006%	16,147	*Necturus maculosus*	Hutt 1945
Albinism	0.008%	25,000	*Necturus maculosus*	Hutt 1945
Albinism	≈ 0.01%	Several 10,000	*Rana temporaria*	Kordges 2002
Albinism	0.01%	9,387	*Ambystoma opacum*	Campbell 2011
Albinism	0.01%	9,000	*Eurycea cirrigera*	Miller & Braswell 2006
Albinism	0.35%	13,852	*Clinotarsus curtipes*	Desai & Pancharatna 2003
Albinism	1%	6,500	*Scaphiopus holbrooki holbrooki*	Johnston & Johnston 2006
Anophthalmy	0.036%	99,992	*Bufo bufo*	Wolf 1994
Anophthalmy	0.07%	7,260	*Lithobates sylvaticus*	Eaton et al. 2004
Anophthalmy	0.15%	5,243	*Lithobates sylvaticus*	Eaton et al. 2004
Blue colouration	0.2–0.3%	1,000–7,000	*Lithobates clamitans*	Berns & Uhler 1966
Clinodactyly	0.23%	44,000	*Bufo bufo*	Rostand 1949a, 1951a,b
Clutch anomaly: eggs without membranes; membranes without eggs	0.08%	11,200	*Rana temporaria*	Vershinin 2002
Ectromely	0.24%	7,260	*Lithobates sylvaticus*	Eaton et al. 2004
Ectromely	0.29%	10,600	*Bufo bufo*	Van Gelder & Strijbosch 1995
Ectromely	0.38%	5,243	*Lithobates sylvaticus*	Eaton et al. 2004
Ectromely	2.4%	9,407	*Bufo bufo*	Wisniewski 1979
Edema	0.01%	7,175	*Pseudacris regilla*	Johnson et al. 2001a
Edema	0.04% (range 0–0.4%)	14,691	*Rana arvalis*	Vershinin 2005
Edema	0.09%	99,992	*Bufo bufo*	Wolf 1994
Flavism	0.007%	14,483	*Bufo bufo*	Thomas et al. 2002
Flavism	<0.02%	50.000	*Pelobates fuscus*	Bisping et al. 2016
Mandibular hypoplasia	0.03%	6,689	*Lithobates pipiens*	Hoppe 2000
Melanoid	<0.02%	50.000	*Pelobates fuscus*	Bisping et al. 2016
Oligodactyly	0.004%	25,000	*Necturus maculosus*	Hutt 1945
Oligodactyly	0.035%	99,992	*Bufo bufo*	Wolf 1994
Oligodactyly	0.34%	7,407	*Bufo bufo*	Rostand 1948
Oligodactyly	0.68%	44,000	*Bufo bufo*	Rostand 1949a, 1951a,b
Oligodactyly	0.82%	5,243	*Lithobates sylvaticus*	Eaton et al. 2004
Oligodactyly	1.32%	13,815	*Cynops pyrrhogaster*	Meyer-Rochow & Asashima 1988
Nasal bones destroyed by maggots of *Lucilia bufonivora*	0%	16211	*Bufo bufo*	Meisterhans & Heusser 1970

Table 1: Continuation.

Anomaly	Frequency	*N*	Species	References
Polydactyly	0%	7,260	*Lithobates sylvaticus*	Eaton et al. 2004
Polydactyly	0.007%	≈30,000	*Ichthyosaura alpestris*	Hachtel 2011
Polydactyly	0.02%	10,000	*Pelophylax lessonae*	Borkin & Pikulik 1986
Polydactyly	0.02%	5,243	*Lithobates sylvaticus*	Eaton et al. 2004
Polydactyly	0.11%	7,407	*Bufo bufo*	Rostand 1948, 1951a
Polydactyly	0.12%	44,000	*Bufo bufo*	Rostand 1949a, 1951a,b
Polydactyly	0.13%	5,350	*Rana temporaria*	Borkin & Pikulik 1986
Polydactyly	0.54%	5,215	*Rana arvalis*	Borkin & Pikulik 1986
Polydactyly	1.04%	13,815	*Cynops pyrrhogaster*	Meyer-Rochow & Asashima 1988
Polymely	0%	5,243	*Lithobates sylvaticus*	Eaton et al. 2004
Polymely	0.000005%	219,269	*Bufo bufo*	Oerter & Kneitz 1994
Polymely	0.002%	45,000	*Pelophylax* synkl. *esculentus*	Duméril 1865
Polymely	0.003%	29,730	*Xenopus laevis*	Hobson 1958
Polymely	0.006%	15,000	*Bufo bufo*	Johnson et al. 2001b
Polymely	0.006%	17,935	*Ambystoma talpoideum*	Semlitsch et al. 1981
Polymely	0%	5,567	*Cynops pyrrhogaster*	Fukui et al. 1996
Polymely	<0.01%	>9,600	*Hoplobatrachus tigerinus*	Mahendra 1936
Polymely	0.01%	10,000	*Lithobates pipiens*	Levey et al. 2003
Polymely	0.03%	7,260	*Lithobates sylvaticus*	Eaton et al. 2004
Polymely	0.025%	48,081	Average across 32 anuran species collected in 135 US national wildlife refuges	Reeves et al. 2013
Polymely	0.05%	13,815	*Cynops pyrrhogaster*	Meyer-Rochow & Asashima 1988
Syndactyly	0%	>50.000	*Bufo bufo*	Rostand 1951d
Syndactyly	0.04%	5,243	*Lithobates sylvaticus*	Eaton et al. 2004
Tail bifurcation	0.003%	≈30,000	*Ichthyosaura alpestris*	Hachtel 2011
Tail bifurcation	0.011%	17,935	*Ambystoma talpoideum*	Semlitsch et al. 1981
Transient albinism	0.5%	9,473	*Pelodytes punctatus*	Rivera et al. 2001
Tumour (skin)	1.8%	13,613	*Cynops pyrrhogaster*	Asashima & Komazaki 1980, Asashima et al. 1982

3.1 Hotspots of anomalies

The rediscovery of malformation hotspots by school children in Minnesota, USA, in 1995 (Helgen 2012) boosted renewed interest in malformation hotspots for amphibians, with most of the literature focussing on North America. However, hotspots are neither limited to North America nor are they only recent. Hotspots have been discovered on all continents.

Reviewing hotspots of anomalies presents several major challenges. First, the frequency of anomalies varies continuously from the single rare individual to

hundreds and even thousands of affected animals. Second, so far there is no common definition of a hotspot. Because of the large number of populations (72; cases that merged data from different populations not considered), in which at least 100 affected individuals were found, it is not possible to discuss each hotspot in detail. Therefore, we focus our review on cases, in which more than 10% of the sampled individuals were affected and additionally either several types of anomalies were observed or where several species exhibited anomalies at the same location. Additional cases in which the anomalies showed a strong correlation with a potential cause or in which the causes were experimentally tested are mentioned as well. This overview is structured on a geographical basis rather than on assumed causes or types of anomalies because causes were not always explored and are contentious in other cases and because too many different patterns of anomalies occur in hotpots.

3.1.1 Europe

One of the earliest report of a hotspot of anomalies comes from Europe. In 1929 Bonnet & Rey (1937) discovered 21 tadpoles of *Pelophylax* synkl. *esculentus* at Villars-les-Dombes, France, that exhibited polydactyly and schizodactyly. Because of the number affected they assumed a genetic cause but did not test this hypothesis. The same type of anomaly was rediscovered by Rostand and became one of the longest studied mass anomaly in amphibians (Rostand 1971). The anomaly now known as anomaly P appears in its benign form as simple polydactyly; its severe forms include schizodactyly, brachymely, inguinal tumours, bony excrescences and even polymely (Dubois 2014, 2017). In the most intensively studied population in Trévignon in France, prevalence varied from 0 to 80% in tadpoles and from 2.6 to 14.5% in adults (Rostand 1971, Dubois 2014, 2017). Anomaly P is characterized by several constant features, including a postero-anterior gradient and a good, although not always perfect, bilateral symmetry (Fig. 5). Mass occurrence of this anomaly is known for at least 13 locations in France (Rostand 1971, Dubois 1984). It affects only species within the *Pelophylax esculentus* complex. Rostand conducted comprehensive investigations on the cause testing experimentally, among others, various chemicals, UV, temperature, overripe eggs and a genetic basis (see Rostand 1971 and Dubois 1984, 2014, 2017 for a summary). It is caused by an unknown exogenous teratogenic factor, possibly a virus, transmitted by fish that acts very early in the development.

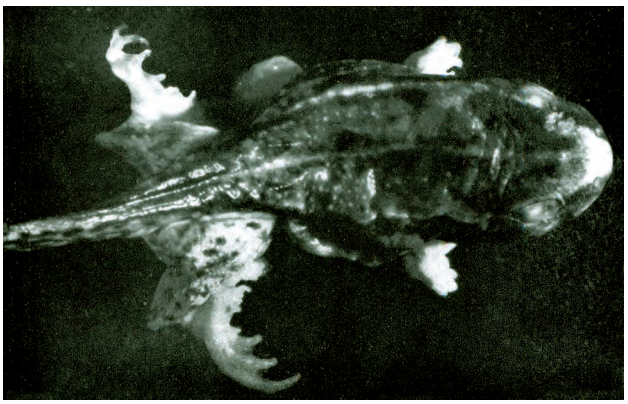

Fig. 5: Anomaly P in a metamorphosing *Pelophylax synkl. esculentus*. Source: Rostand (1971: Fig. 30).

Hillenius (1959) discovered a further hotspot for polydactylous *P. esculentus* in Amsterdam, The Netherlands. He assumed low-level radioactive contamination as the cause but because of a similar pattern of the anomalies Rostand (1971) assigned the case to anomaly P. In Belorussia, Borkin & Pikulik (1986) reported another case of mass polydactyly in the hindlimbs but not the forelimbs, which (based on morphological similarity) is another case of anomaly P. Of 114 juvenile *P. lessonae* (a few were possibly *P. esculentus*) collected at the Alba fishery ponds in the Minsk region, 42 individuals were affected. Furthermore, four out of 47 adults were affected.

Globally the most serious hotspot in terms of different types of anomalies observed was discovered in Europe: a population of *Bufotes viridis* in a quarry near Roßwag, Germany (Henle et al. 2017a). Over a five-year study period (1980–1984), 32 different types were registered, involving among others polymely (Figs. 6a, 10c), ectromely (Fig. 6b), phocomely, a range of further skeletal anomalies, edema, tumours, giant size and

Fig. 6: Examples of anomalies observed in the *Bufotes viridis* population at Roßwag, Germany, in October 1980; a) polymely (voucher: Museum National d'Histoire Naturelle 1984.2325). Photo: H. Steinicke; b) amely, Photo: K. Rimpp.

various colour anomalies including, abnormal yellow patches (Fig. 32), albinism and melanism. At least 245 toadlets and 1,000–2,500 tadpoles were abnormal. An official enquiry did not class ectromely as an anomaly because it was supposedly caused by predators (in spite of its occurrence in the absence of predators) and concluded that hybridization combined with atavism and inbreeding were the culprits for the remaining anomalies (Flindt 1985a). These explanations are incompatible with the range of anomalies observed that can only be explained by a strong mutagenic agent. As high levels of radioactivity were recorded at several places of an earthern deposit and no indication for chemical pollutants were found, radioactive pollution was the most likely cause. See the accompanying papers by Henle et al. (2017a,c) for a detailed documentation and discussion of this case.

In an Italian population of *Triturus carnifex* exposed to low doses of radiation from radon D'amen et al. (2006, 2008) observed eight different types of anomalies (primarily ectrodactyly, polydactyly and webbing between the toes) and a slightly elevated rate of anomalies (5.2%; $n = 1522$). At another site that was surrounded by fields with intensive agriculture and a wide range of pesticide applications, 8.5% ($n = 340$) and 5.6% ($n = 267$) of *T. carnifex* and *Lissotriton vulgaris*, respectively, were abnormal. In contrast, at a third, fully protected, non-polluted site 1.8% ($n = 114$) and 1% ($n = 96$) of *T. carnifex* and *L. vulgaris*, respectively, were found to be abnormal.

Further hotspots were discovered at several contaminated sites. In the Dnepropetrovsk Province in eastern Ukraine, Flax & Borkin (1997, 2004) sampled 1749 *P. ridibundus*, 766 *Bombina bombina* and 484 *Bufotes viridis* between 1991 and 1995. Of these 37.4%, 30.8% and 25.7%, respectively, were abnormal. Tumours, polydactyly, ectromely and ectrodactyly were the most common types of anomalies observed. In addition, 39.2%, 33.5% and 40.8% ($n = 400–500$), respectively, of the tadpoles exhibited anomalies, primarily asymmetric hindlimbs, body curvature and microcephaly. Flax & Borkin (2004) discussed the edge of the range, hybridization, infection and environmental pollution as possible causes. The latter was the most likely cause, with significant correlations found between the frequencies of anomalies and levels of environmental contamination (heavy metals and organic compounds). Likewise, in heavily polluted reservoirs in the vicinity of Kiev up to 42% ($n = 65$) of the sampled *P. ridibundus* exhibited polymely; the average frequency of anomalies (polymely and four other types of anomalies) for the years 2000–2003 and 2006 was 18% ($n = 190$) (Nekrasova et al. 2007). At sites of the Sviyaga and Usa rivers in Russia that were heavily polluted with metals, 61.5% ($n = 343$) and 30.2% ($n = 63$), respectively, of *P. ridibundus* were abnormal (Spirina 2009, Borkin et al. 2012). Of 2400 and 3600 tadpoles of *Rana arvalis* and *R. temporaria*, respectively, that were collected from six polluted sites (heavy metals, petroleum products and/or household waste in Moscow and its surroundings, 32% and 18% showed edema, torsion of the body, gill anomalies, light patches of skin, skin damage and retarded development (Aguillón Gutiérrez & Severtsova 2012).

Other European hotspots were likely to be due to predators and parasites. Malkmus (2008) collected 430 tadpoles of *R. temporaria* in a pond in Germany of which 18% lacked feet (some also lacked the tibia) and 99% lacked parts of the tail. He assumed that sticklebacks (*Gasterosteus aculeatus*) had inflicted these injuries but did not test this assumption experimentally. Veith & Viertel (1993) and Bohl (1997) reported a population of *Bufo bufo* in Rhineland-Palatinate and Bavaria, respectively, in which 15.5% ($n = 1689$) and 42.7% ($n \approx 500$) of the tadpoles and toadlets suffered anomalies (mainly ectromely, but also ectrodactyly). Veith & Viertel (1993) additionally found rare incidences of other skeletal anomalies, such as syndactyly and fusion of legs (skin webbing?). Transplant experiments in the field and laboratory tests demonstrated that these cases were due to predatory attacks from the leech *Erpobdella octoculata* and that the leeches did not inflict these anomalies on other syntopic frogs and newts. Another publication reporting more than 100 affected individuals and a slightly elevated frequency that was attributed to predators is known to us for Europe. Wisniewski (1979) observed 221 (2.4%) adult *B. bufo* with legs partially or completely missing. As metamorphs leaving the pond also exhibited ectromely, he assumed small predators (shrews or carabid beetles) to be the culprits. One frog (*R. temporaria*?) was also affected.

One case that could be attributed to the parasitic fly *Lucilia bufonivora* was recorded by Kordges (2000) from Germany. The fly deposits its eggs on anurans, especially *B. bufo*, and the larvae destroy the nasal bones leading to a wide opening of the narines, invariably leading to the death of the attacked individual (Neumann & Meyer 1994). Although only small numbers of infected individuals are usually observed (Tab. 1), 46% ($n = 260$) of the toads examined by Kordges (2000) at a drift fence in a former mining area in 1999 had destroyed narines.

On European mesic and moist grasslands a large number of frogs may fall victim to mowing machinery (Classen et al. 1996, Oppermann et al. 1997). The authors did not examine whether such injuries resulted in elevated rates of anomalies at breeding sites or whether most injured frogs died. In a population study of *P.* synkl. *esculentus* in an agricultural landscape in Northrhine-Westfalia, Germany, about 100 individuals showed toe injuries and 46 ectromely (*n* approx. 2500) and in total approx. 6.5% exhibited anomalies (Schmidt & Hachtel 2011) – note that the percentages published by the authors are too low for the sample size given. The authors stated that leg injuries had only healed superficially and attributed them to harvesting machinery. Van Gelder & Strijbosch (1995) counted 35 toads (*B. bufo*) ($n = 10,600$) with ectromely in a long-term study and also attributed them to mowing. In a large-scale study in Finland covering 26 farmland breedings sites (includ-

ing grasslands), anomalies in froglets of *R. temporaria* occurred at a low frequency (max. 4%; mainly ectromely and ectrodactyly) (Piha et al. 2006). Adults were not assessed. The effects of mowing and crop harvesting machinery on anomalies (especially ectromely and ectrodactyly) of amphibians at breeding sites still requires more experimental studies to understand whether (and if so, to which extent) agricultural machinery may contribute to the occurrence of mass ectromely.

Bezman-Moseyko et al. (2014) reported another case of mass anomalies affecting 62% (n = 235) and 75% (n = 212) of syntopic *P. ridibundus* and *P. esculentus,* respectively, from Bugornia in the Pridnestrovie District of Russia. At another location the rate of anomalies was also above 60% but sample sizes were much lower. Ectrodactyly and limb deformities were the most common anomalies but in *P. ridibundus* polydactyly was also frequent. In total 5–7 different types of anomalies occurred. The locations did not show any sign of human impact and the cause remains unclear. Lada (1999) reported a further case of mass polydactyly for two Russian populations of *B. bufo*, for which the cause also remains unclear.

3.1.2 Asia

Anomaly hotspots in Asia are known in Russia, India, Malaysia, Kazakhstan and Japan. The second highest incidence on a global scale in terms of different types of anomalies was discovered in Siberia. In 1993, an accident at the Siberian Chemical Combinate in Seversk (Tomsk) contaminated approx. 120 km² with Ruthenium-106, Niobium-95, Cerium-95, Plutonium and Uranium, with the total activity being 500–900 Curie (Saveliev et al. 1996, Kuranova 1998, 2003, Moskvitina et al. 2011). In 1993–1994, these authors observed a range of clutch and embryonal anomalies, including the complete disintegration of embryos of *Rana arvalis*. In surviving tadpoles and froglets, they found a range of internal anomalies, tumours, ectromely and brachymely. While they did not provide detailed information on tadpoles and froglets, they referred to a total of 21 different types of anomalies in embryos and in total to at least 25 different types. Whereas the rate of embryonal anomalies was only 0.9% in control areas, it reached 36.5% in the contaminated area and at least 49% of the embryos died (Moskvitina et al. 2011). Kuranova & Saveliev (1997, 1999) further examined *Salamandrella keyserlingi* from the same contaminated sites. This species also suffered from a range of severe embryonal and clutch anomalies, including the autolysis of bodies. Surviving larvae showed various colour anomalies, absence of a tail, anomalies of axial organs, among many other types of anomalies, most of them not specified. In total, 21 different types of anomalies were observed. Unfortunately, further details about the types and numbers of anomalies in larvae or metamorphs of the two species were only included in disclosed reports. Moskvitina et al. (2011) further reported that the rate of embryonal anomalies in small mammals was also 3.3 times higher in the contaminated area compared to control areas.

Hotspots due to radioactive pollution are known from two further locations in the former Soviet Union. In the East Uralian Radioactive Trace caused by the accident in Mayak, the rate of morphological anomalies in metamorphs of *R. arvalis* was also significantly higher (17%, n = 60) than in control populations (Pyastolova et al. 1996). At locations polluted by nuclear tests at Semipalatinsk, Kazakhstan, 16.3% of *Pelophylax ridibundus* showed ectrodactyly, syndactyly, asymmetrical limbs, melanism and dorsal pattern anomalies (Rakhimzanova & Khromov 1998). Unfortunately, no further details were provided.

In Japan, the region around Hiroshima is a hotspot for colour anomalies; most cases occurred within the immediate vicinity of 6000 km². Between 1963 and 1975 at least 152 (10.7%, n = 1422) albinistic tadpoles of *Dryophytes japonicus* were collected from 12 sites (Daito 1968, Nishioka & Ueda 1977b, 1983). Three different recessive albino genes and two kinds of dominant melanising genes, which affect parts of the albino body, were detected in the sample. At one location, a dominant gene for black-eyedness was linked to the albino gene. At another location a dominant colouring gene linked to the albino gene gives a light greenish colouration to frogs carrying the gene. Nishioka & Ueda (1985c) reported on three adult black-eyed individuals from a further location close to Hiroshima and at another location recessive black-eyedness was discovered in a female by applying gynogenetic techniques. Nishioka & Ueda (1985a) and Nishioka et al. (1987) also collected 428 albinistic tadpoles of *P. nigromaculatus* and two adult albinistic *P. porosus* from an area of < 250 km around Hiroshima. They detected five different recessive genes causing albinisms in these populations. In addition, one *P. porosus* with a transparent blackish back was found (Nishioka & Ueda 1985e) but the anomaly was not inheritable. Furthermore, one adult flavistic and more than 18 albinistic tadpoles of *Rhacophorus schlegelii* were discovered in four populations in the same region (Nishioka & Ueda 1985b). In all populations recessive inheritance was demonstrated. In addition, more than 42 black-eyed individuals were found, with the anomaly being inheritable. These accumulations of colour anomalies across species and the large number of genes controlling them are truly unique on a global scale (see the sections on "albinism, hypomelanism and depigmentation", "black eyes" and "flavism" below). In most species background rates of albinism do not exceed 0.01% (Tab. 1). The authors never discussed the potential cause(s) of this exceptional accumulation of mutations. Only a mutagenic factor operating across species and a large area can explain such an extreme elevation above background rates. Irradiation after the atomic bomb was dropped on Hiroshima could be one explanation.

Chemical pollution also created anomaly hotspots. In 1979, Mizgireuv et al. (1984) collected *Bufo gargarizans, Rana amurensis and R. pirica* (as *R. chensinensis*) of various age classes in three locations on Sakhalin Island in the Far East of Russia that were polluted

by the discharge from a paper mill (one location) and municipal sewage works (two locations). All three species suffered from ectromely and, in the larval stage, also from edema, microcephaly and unilateral anophthalmy. More detailed data were only provided for *R. pirica*. This species was additionally affected by bone tumours, with 2–3 weeks post-metamorphosis being the youngest age at which the tumours became macroscopically visible. At the discharge site of the paper mill, 42% showed abnormal limbs and 11.5% had tumours, whereas the frequencies were 31–39% and 0–5.5% for the sites polluted with municipal wastewater (all $n > 1000$). The level of organic contamination correlated with the frequencies of anomalies but the nature of the contaminants was not assessed. Although the effect of the polluted water was not tested against controls in the laboratory, the correlation suggests a causal relationship. In support of this conclusion it may be noticed that necrosis following disease, chemicals and irradiation are the only factors in experimental tests that induce high numbers and frequencies of both ectromely and tumours (Henle et al. 2017a). Mizgireuv et al. (1984) did not discuss diseases, but it is likely that they would have discovered and mentioned it given their detailed examination of abnormal *R. pirica*.

In the same region, Levinskaya & Barinova (1978) observed that 37.5% (*n* not provided) of immature *R. amurensis* in 1972 suffered from syndactyly, brachydactyly and clinodactyly. They also originated from a site that was polluted with the discharge from a paper mill, but it remains unclear as to whether it is the same paper mill as in the study conducted by Mizgireuv et al. (1984). While experimental tests were not carried out, these hotspots on Sakhalin Island, Russia, call for a systematic testing of the teratogenic effects of paper mill discharges in the field and in the laboratory.

In Ekaterinburg, Vershinin (2002) found significant difference in the frequency of anomalies of *R. arvalis* among different zones of urbanization (Fig. 7). Frequencies were highest in areas of multi-story buildings (juveniles: 4.2%, $n = 3422$; adults: 14.1%, $n = 170$) intermediate in areas of low-story buildings (juveniles: 2.7%, $n = 1004$; adults: 9.4%, $n = 53$) and urban forest parks (juveniles: 1.7%, $n = 5309$; adults: 4.4%, $n = 183$) and low in rural forest control sites (juveniles: 0.78%; $n = 2939$; adults: 1.8%; $n = 57$). In total, eleven different types of anomalies were observed, including abnormal limbs (Figs. 21, 25), digits (Fig. 8a, 12) and mouth (Fig. 17), black-eyes (Fig. 28a) and other eye anomalies, abnormal patterns (Figs. 8b) and edema. *Lissotriton vulgaris* showed the same tendency but sample sizes were much smaller and the difference to other zones was only significant for the low-story buildings zone (Vershinin et al. unpubl.). For *Pelophylax ridibundus*, which occured only in the multi-story buildings zone, the frequency of anomalies was also high (13.4%; $n = 2178$), with the frequency increasing over the last 15 years (Vershinin et al. 2002, unpubl.). Higher concentrations of sulphates, petrol and detergents were associated with these differences as well as a higher biological consumption of oxygen in the urban sites. However, pollution was not the only factor associated with anomalies in *R. arvalis*. Heavy infections by the trematode *Holostephanus volgensis* contributed to skeletal anomalies. although primarily to externally not visible anomalies of vertebrae and the urostyle (Vershinin & Neustroeva 2011).

In India, Gurushankara et al. (2007) compared the prevalence of anomalies in four frog species (*Fejervarya brevipalmata, F. keralensis, F. limnocharis, F. rufescens*) from rice paddy fields, coffee plantations and forests. Of 6303 frogs collected between 2001 and 2003 229 were abnormal (mainly ectrodactyly, ectromely and anophthalmy). The incidence was highest in coffee plantations (4.6%), followed by rice paddies (4%) and water bodies (3.9%). None of the 661 frogs collected in the forests displayed any form of anomaly. Prevalence also differed among species, with the highest rates (8.4–12%) occurring in *F. rufescens*. The authors assumed agricultural contaminants to be the culprits but noted that this hypothesis still needs testing as they did not measure the contamination of the sites surveyed. Likewise, Patel et al. (2008) found elevated rates of anomalies (10.8%; $n = 259$; ectromely, ectrodactyly, tumours) in adult *F. limnocharis* collected in rice paddy fields.

Mass occurrence of tumour-like lesions were reported in Malaysia. Of 471 *Duttaphrynus melanostictus* collected in the region of Kuala Lumpur, 218 were affected externally (Dhaliwal & Griffiths 1963). Attempts to infect toads with fungal mycelium through the epidermis failed but were highly successful after subcutaneous inoculation. The identity of the fungus was not provided and no investigations were made into the reasons for the high rate of infection.

An enigmatic malformation hotspot was discovered by Woitkewitsch (1955, 1959, 1961, 1964, 1965) in Kazakhstan. Between 1947 and 1962 he examined more than 6000 *P. ridibundus* from six water bodies in one particular area of the Ala-Tau Mountains, of which 546 were malformed. The average annual percentage of individuals affected was 12%. Strangely, in all affected individuals the right hindleg was duplicated and only in nine severe cases the left side was also polymelous. Some of the supernumerary legs additionally exhibited bony triangles, other forms of taumely, or polydactyly. Mainly tadpoles exhibited the anomaly, but a few subadults and adults also suffered. The duplication of legs already appeared at limb bud stages. Eighteen individuals (tadpoles; 1-year-old frogs) showed ectromely and at least one giant tadpole was found. Woitkewitsch (1959) provided a very detailed description of the development and morphology of the abnormal limbs. All supernumeray limbs were immobile. In some but not all individuals the supernumerary legs were mirror-image duplications.

A laboratory cross of two polymelous individuals resulted in 472 fertilized eggs of which 285 reached metamorphosis; none of them was abnormal. In addition, the original and the duplicated legs were able to regenerate normally after amputation in the early stages of limb differentiation. Therefore a genetic cause is unlikely. Woit-

Fig. 7: Types of monitoring sites for anomalies of amphibians in the region of Ekaterinburg, Russia; a) multi-story urban area; b) low-story urban area; c) urban forest park; d) rural forest control site. Photos: V. Vershinin.

Fig. 8: Examples of anomalies observed in *Rana arvalis* in Ekaterinburg, Russia; a) oligodactyly in a juvenile found in the multi-story building zone, 3.9.1986; b) abnormal pattern (spotted) in an adult female observed in the multi-story building zone, 4.7.2002. Photos: V. Vershinin.

kewitsch (1959, 1961) discussed traumatism, parasites, radioactivity, UV-irradiation, viruses, chemicals and temperature as potential causes. He considered cold temperatures to be the likely cause because all water bodies with malformed tadpoles were fed by cold mountain springs. However, this is inconsistent with the results of laboratory studies for other species. Low temperatures did not induce polymely in laboratory experiments using *Ambystoma mexicanum* and *Xenopus laevis* (Swett 1926, Detwiler 1938, Kovalenko 2000; see Henle et al. 2017a for a review of temperature effects on skeletal anomalies). Furthermore, the species also occurred in other water bodies in the same region but without any individual showing polymely. No detailed comparison of the temperature or chemistry of the water bodies was provided. Moreover, two other frog species (*Rana asiatica?* and a „green" frog) living in the same water bodies as the malformed *P. ridibundus* did not exhibit anomalies. Skin webbing and bony triangles that usually are associated with trematode infections (e.g., Johnson et al. 2001b) were absent and no parasites were discovered in spite of very detailed anatomical studies of the malformed limbs (Woitkewitsch 1959, 1961).

3.1.3 Australia and Oceania

We only know four hotspots of anomalies in Australia. In Jabiru, Northern Territory, Australia, Tyler (1989) collected 261 abnormal frogs belonging to 14 species, with the frequency of abnormal specimens ranging from 3.8% to 16.1% (n = 26–914). The most common type of anomaly was ectrodactyly, followed by syndactyly, mandibular hypoplasia and clinodactyly. At least four other types of anomalies were detected (but not specified). The largest series was taken from a small body of water from a radioactive source trapped within a retention pond of the uranium mine before its filling; pesticides and herbicides were also detected but at low levels (0.5 ppm), just above detection thresholds. Ten other species collected in Jabiru did not exhibit anomalies but it is not known whether they were collected at the same site and how many of them were sampled. There are no data available on the level of radioactivity nor are there any data available from when the retention pond went into operation.

At the Olympic Dam mine in South Australia, prevalence of limb anomalies (mainly ectrodactyly) in *Neobatrachus centralis* was as high as 9%, with a mean of 1.6% (Read & Tyler 1990, 1994). Levels of radionuclides in frogs and water were low and not related to the incidence of anomalies. However, the data and statistics used are unclear as the location where radionuclide measurements and abnormality assessments were carried out only marginally overlapped. It may be worth mentioning that at another location, Paralana Springs, Flinders Range, South Australia, that naturally exhibits a relatively high level of radon (2,000 pCi/l), 35% (n not given) of the froglets of *Crinia riparia* exhibited abnormal hands.

In contaminated rice paddies in New South Wales 7% of the examined frogs (n = 1209; three species combined) exhibited external anomalies (Spoylarich et al. (2011). *Limnodynastes fletcheri* (7.1%; n = 694) and *L. tasmaniensis* (8.2%; n = 428) had high rates of anomalies, whereas only one out of 87 *Ranoidea raniformis* was abnormal. Ectrodactyly was the most frequently observed anomaly in the former two species, with crooked dorsal stripes also being frequent in *L. tasmaniensis.*

3.1.4 Africa

Only a few anomaly hotspots are known in Africa. Hassine et al. (2011) discovered an anomaly hotspot in Tunisia. At the Lema Dam, 74 of 221 (33%) metamorphs of *Pelophylax saharicus* and 13 of 52 (25%) adult *Discoglossus pictus* were abnormal. We did not count incompletely reabsorbed tails in metamorphs as an anomaly because this is a common feature in *Pelophylax* species in various parts of their distribution. While the authors claimed in the legend to a photo that an adult specimen also had an incompletely reabsorbed tail, the error bar shows that this individual had approximately the average size of a metamorph. Unfortunately, the terminology used by Hassine et al. (2011) is, in part, difficult to convert to historically established terminology. Moreover, the authors sometimes counted the same anomaly as different types of anomalies, e.g., incomplete additional limbs as polymely, ectromely (as hemimely), ectrodactyly and brachydactyly. Therefore, it remains partly unclear as to which types and how many different types of anomalies were involved (approx. 10 and 5 different types for *P. saharicus* and *D. pictus*, respectively). However, skeletal anomalies dominated, with polymely, polydactyly and presumably also ectromely and ectrodactyly having been common. The location was ectremely eutrophic and impacted by pesticides; at a second location, the Oasis of Gabes, where agriculture recently became more intensive, Hassine et al. (2011) found 6 (13%; n = 47) abnormal *D. pictus*. Out of 386 *P. saharicus* and 384 *D. pictus* collected in non-agricultural areas, none exhibited any anomaly. Therefore the authors regarded contamination with herbicides and pesticides as the most likely explanation, with some anomalies presumably also having been caused by predation.

Rostand (1971) mentioned that 25% of a Moroccan *P. saharicus* population was affected by anomaly P (polydactyly). Unfortunately, no further details were presented.

Of 353 and 107 tadpoles of *Kassina* sp. and *Phrynomantis microps* tadpoles from two large temporary ponds in the Ivory Coast 85.8% and 78.8%, respectively, showed tail injuries (Rödel 1998). The rate of tail injuries was significantly correlated with the number of Anisoptera dragonflies and giant water bugs (*Bellostoma*) in the samples taken from different sections of the ponds.

In Comoé National Park, Ivory Coast, 65–80% of *Phrynobatrachus francisci* examined in three populations (n = 45–116) had orange cysts containing *Endotrombicula pillersi* but none of the other 33 sympatric species was affected, with the exception of a single individual of *Sclerophrys maculata* (Spieler & Linsenmair

1999). Spieler & Linsenmair (1999) regarded the mite as a host-specific parasite. More recently, Wohltmann et al. (2007) collected the same parasite from 235 (n = 1183) *P. alleni* in the Tai National Park, Ivory Coast. They also found cysts in four more *Phrynobatrachus* species, *Petropedetes natator* and a single *Ptychadena aequiplicata* but with a lower infection rate. None of the 34 other species examined had cysts.

In the northern Drakensberg of South Africa, Smith et al. (2007) sampled tadpoles of *Strongylopus hymenopus* at 13 sites. Of 256 individuals, 16% had abnormal mouthparts; 39 of these 41 individuals were infected with *Batrachochytrium dendrobatidis*. In a second species sampled at 19 different sites, only 1.7% (n = 294) showed abnormal mouthparts; all were infected with *B. dendrobatidis*.

3.1.5 South and Central America

Seven hotspots of anomalies are known in South and Central America. Three of the cases with more than 100 affected individuals and high frequencies involve tadpoles infected by *Batrachochytrium dendrobatidis*. In Costa Rica, 100% (n = 150) of the tadpoles of *Isthmohyla calypsa* were affected by the absence of dark keratinization of mouthparts and/or the absence of tooth rows (Lips 1998). In Guatemala, Mendelson et al. (2004) observed more than 1000 tadpoles of *Ptychohyla hypomykter* with malformed mouthparts; in moribund individuals tail tips were discoloured. In Argentina, pigmentation of mouthparts was absent in 46.5% (n = 243) of the tadpoles of *Hylodes* cf. *ornatus* (Vieira et al. (2013). Elevated rates of abnormal mouthparts also occurred in four anuran species in the Departamento Yerba Buena, Argentina, albeit with lower numbers of individuals affected. The frequency was highest in the species with a longer larval period (*Boana riojana;* 38.9%, n = 211; *Odontophrynus americanus*: 23.7%, n = 97) compared to the species with shorter larval periods (*Pleurodema borellii*: 19.4%, n = 67; *Rhinella arenarum*: 16.3%, n = 49) (Medina et al. 2013). Elevated prevalence of tadpoles with abnormal mouthparts and/or mass mortality due to *B. dendrobatidis* has been observed at other locations in South and Central America (e.g., Lips 1999) but anomalies usually were not recorded for individual locations and species.

A striking hotspot occurs on the oceanic island Fernando de Noronha, Brazil. In the introduced Cururu toad (*R. jimi*), 17% (n = 179) of the adult toads collected in 2009 and 2010 lacked one or both eyes (Tolledo & Toledo 2015). No other anomalies were reported. In 2008, only 8.2% (n = 159) of the individuals had anophthalmy but 44.6% of the sampled individuals were abnormal (Toldeo & Ribeiro 2009). Besides anophthalmy, ectrodactyly was very common (at least 23.3%). Tadpoles also exhibited a high rate of anomalies (52.5%; n = 413) in 2009 and 2010 (Tolledo et al. 2014). In total 18 different types of anomalies were observed (Toledo & Ribeiro 2009, Tolledo et al. 2014, 2015). The causes are unknown but could be a combination of inbreeding caused by founder effects, absence of competitors and predators, and other unknown factors (Toledo & Ribeiro 2009, Tolledo & Toledo 2014).

In Argentina Agostini et al. (2013) compared the prevalences of anomalies in five species from ponds in two farmland areas. Ponds in the area with intensive and extensive crop production and cattle breeding were contaminated by endosulfan, cypermethrin, and chlorpyrifos. No contamination was detected in the ponds in the reference area with cattle breeding at low density. The prevalences in the populations from cultivated and reference areas were as follows: *R. fernandezae* (37.1 and 10.2%, respectively), *Leptodactylus latrans* adults (28.1 and 9.2%) and juveniles (32.9 and 15.3%), and *H. pulchellus* (11.6 and 2.8%). *Scinax granulatus* populations did not show abnormalities. *Pseudis minuta*, which was only detected in the reference area, exhibited a prevalence of 13.3%. For the former three species prevalences were significantly higher at contaminated ponds than at ponds from the reference area. Ectrodactyly and ectromely were the most common anomalies, with abnormal eyes, pigment defects, microcephaly, and torsion of the vertebral column having also been found at elevated rates. In the laboratory endosulfan can cause ectromely at environmentally relevant concentrations (Rohr et al. 2003).

An enigmatic mass occurrence of polymely was observed by M. Copping in an Ecuadorian *Leptodactylus* species (Rostand 1958b) but unfortunately there is no further information available on the case.

At three locations in Panama, the rate of anomalies in adult *Dendrobates auratus* averaged 13.3% (n = 592) (Gray et al. 2002). At two of these locations an average of 4.3% (n = 230) adult *Physalaemus pustulosus* also exhibited anomalies and at one of them 2.7% of the juveniles of the latter species were abnormal. Ectrodactyly was found to be the main type of anomaly and attributed to attacks from ants and other invertebrates. Although this explanation is plausible, no study has been undertaken to test this hypothesis.

3.1.6 The Caribbean islands and Bermuda

Studies on amphibian anomalies are largely lacking for Carribean islands, but Patel et al. (2012) observed mass occurrence (62%; n = 645) of abnormal mouthparts in tadpoles of the introduced *Rhinella marina* that were associated with infections with *Batrachochytrium dendrobatidis.* The frequency of anomalies increased with development from stage 27 to 41 of Gosner (1960).

Mass anomalies in *R. marina* are also known from Bermuda. Bacon et al. (2006b) examined 13,856 toadlets, subadults and adults at 38 sites across Bermuda. Of these, 21% showed anomalies, with the incidence for some ponds reaching up to 58%. In total 20 different types of anomalies (skeletal, eye-anomalies) were detected, with ectrodactyly, syndactyly, polydactyly, other digital anomalies and ectromely being the most common ones. Run-off from roads and agricultural fields were assumed to be the cause. Surface water and sediments from four hotspots and one control pond showed

high concentrations of metals and petroleum hydrocarbons. In the laboratory these samples induced polydactyly, ectrodactyly, ectromely and abnormal mouths in toadlets of *R. marina* (Fort et al. 2006b, Bacon et al. 2013). The data indicated that metals and hydrocarbons were individually capable of inducing the observed anomalies but that they seemed to act synergistically.

3.1.7 North America

Even though the majority of hotspots in North America were discovered recently (since the 1990s), the earliest hotspot known was also found in North America. At Boulder Creek in California 98.6% (n = 74) of the *Taricha torosa* sampled between 1926 and 1942 had tumours (extreme proliferation of fibrous connective tissue) (Wolterstorff 1935, Twitty 1942, Brattstrom & Warren 1953). The frequency dropped to 10% in 1953. The cause of this anomaly is unknown.

The world's most comprehensive survey of amphibian anomalies was also carried out in the USA. Between 2000 and 2009 the Fish and Wildlife Service conducted a nationwide survey of amphibian anomalies in national wildlife refuges. The core dataset comprises 48,081 anurans, representing 462 sites, 32 species and 41 states. The nation-wide prevalence of morphological anomalies averaged 2.0%, which is consistent with expected background frequencies (Lunde & Johnson 2012, Reeves et al. 2013). From 675 collection events 152 yielded frequencies higher than the 5% that is generally used in the USA as the classification criterion for hotspots. Partially or completely missing limbs or digits clearly dominated; polymely and polydactyly together comprised only 1.7% of all anomalies registered. Up to 20 different types of anomalies were observed [a population of *Lithobates sphenocephalus* at Colin's Ditch, Great Swamp National Wildlife Refuge, in which 11% (n = 583) of the individuals sampled were abnormal]. Clusters of high-abnormality sites were found in the Mississippi River Valley, in California and Alaska (Reeves et al. 2013). In Alaska, 9269 metamorphosing *L. sylvaticus* were examined from 86 breeding sites in five National Wildlife Refuges (Reeves et al. 2008). Prevalence of skeletal and eye anomalies ranged from 1.5% to 7.9% and were as high as 20% at individual breeding sites. Ectromely, black eyes, micromely and brachydactyly were the most common types of anomalies. Polymely and polydactyly were rare.

Several other state-wide surveys were carried out in the USA. In randomly selected wetlands in north-central USA that were sampled between 1998 and 2000, 1.4–2.3% ($n \geq 389$) of the sampled individuals exhibited either skeletal or eye anomalies (Schoff et al. 2003). In Minnesota, out of 25,000 frogs that were sampled at 100 different ponds until the year 2000, 8.2% were malformed and more than 37 sites contained "significant" numbers of deformed frogs (Vandenlangenberg et al. 2003, Helgen 2012). The observed rate is well above the expected baseline of below 2% (Lunde & Johnson 2012, Reeves et al. 2013, Henle et al. 2017a). As in the nationwide survey, ectromely and ectrodactyly were the most common types of anomaly, whereas polymely was rare. Above baseline rates were also recorded at several sites in various other states (Helgen 2012). For example, Lannoo (2008) described 12 hotspot sites from Minnesota and mentioned a hotspot site each for Iowa, Wisconsin, Ohio, California and Indiana. Unfortunately, no quantitative data on observed anomalies or their frequencies were provided. Sessions & Ruth (1990) and Johnson et al. (2001a, 2006, 2013) reported other hotspot sites in California. Hotspots are also known in Vermont (Fort et al. 1999a, Burkhard et al. 2000, Levey et al. 2003) and British Columbia (Roberts & Dickinson 2012).

We found quantitative data for 19 sites, for which prevalence was at least 10% and at least 100 abnormal individuals of a single species were recorded (Tab. 2). Two of the sites harboured populations of larval amphibians that exhibited non-skeletal anomalies. Two hotspots were characterized by cysts caused by mites of the genus *Hannemania* and another one by pustules of unknown ethiology. At the remaining hotspot sites, mainly skeletal anomalies occurred. At most Californian sites, polymely dominated. Parasites were the most frequently assumed or experimentally demonstrated cause of the hotspots. At three sites chemical pollution and at two sites predators were experimentally identified as causes. Cannibalistic attacks presumably contributed to high frequencies of anomalies at two sites and the cause(s) for some or all anomalies remains unknown or controversial for six sites.

Hypothesized causes for skeletal anomalies at other hotspot sites include parasites, predators, chemicals, diseases, UV-irradiation and radioactivity and interactions among these factors, with the first three being the most frequent suspects (Johnson et al. 2004, Ballengée & Sessions 2009, Helgen 2012). Although several authors provided evidence that there are multiple causes and that the causes differ among hotspots (e.g., Meteyer et al. 2000a, Reeves et al. 2010, 2013, Lunde & Johnson 2012), there is still considerable disagreement (e.g., see Lannoo 2008 versus Sessions 2009; Ballengée & Sessions 2009, Ballengée 2010 and Sessions & Ballengée 2010 versus Skelly & Benard 2010). Opinions range from assuming direct effects of chemicals as the main cause at most hotspots (Lannoo 2008, McCoy & Guillette 2009, Mann et al. 2009, Helgen 2012) to the belief that chemicals only play an indirect role through immunosuppression, making tadpoles more sensitive to attacks from trematodes (e.g., Rohr et al. 2009), to an outright exclusion of chemicals and the assumption that all anomalies can be explained entirely by predators and parasites (e.g., Sessions 2009, Ballengée & Sessions 2009, Sessions & Ballengée 2010).

The CWB site in Minnesota, which sparked renewed interest in amphibian anomalies in the USA, is a prime example for the controversy and challenges for establishing the cause(s) of mass anomalies. Three species had high prevalences of anomalies, with cutaneous fusion, polymely, ectromely and anteversion having frequently been observed (Tab. 2). Another four spe-

cies were studied at the site that had much lower sample sizes and prevalences of anomalies. Water samples showed a deficit of micronutrients that caused anomalies in the laboratory (Garber et al. 2004) and lipophilic extracts from water solutions induced skin webbing in a high percentage of the tested individuals (Bridges et al. 2004). Based on the spectrum of anomalies but without studying water samples, Gardiner & Hoppe (1999) suggested that environmental retinoids were the cause of the anomalies. Stopper et al. (2002) disagreed and argued that cysts of the trematode *Ribeiroia ondatrae* induced the malformations as experimental infections of amphibians supposedly resulted in all of the anomalies reported by Gardiner & Hoppe (1999). However, Stopper et al. (2002) did not study the site and contrary to their statement, ectromely and ectrodactyly do not occur beyond background levels in experimental infections with *R. ondatrae,* except for *Pseudacris regilla* (see section 3.1.7.1). While *R. ondatrae* occurred at CWB (Vandenlangenberg et al. 2003), to our knowledge no experimental or correlational study addressed its association with the observed anomalies at the site. Notwithstanding, given that *R. ondatrae* has been shown to be the cause of polymely and cutaneous fusion at other hotspot sites and very few other factors have been shown experimentally to cause elevated rates of polymely (section 3.2.1.1), they presumably contributed to the anomalies observed at CWB. In conclusion, current evidence suggests that *R. ondatrae* and chemical pollution were the main causes for the hotspot. Whether other factors also played a role (see Helgen 2012 for a discussion) remains speculative in the absence of any relevant study at the site.

Studies to unravel the causes were only carried out at a few sites, primarily at the hottest hotspot sites listed in Table 2. Another drawback for inferences is that, as with CWB, most studies that attempted to reveal causes were limited to a single potential factor. Notwithstanding, given the large differences in the pattern of anomalies at North American hotspot sites, different causes must be responsible for the anomalies at different sites. Existing evidence suggests that most hotspots at which either polymely and cutaneous fusion or cysts dominated were caused mainly by parasites (compare Table 2 and the overview table of anomalies that have been produced experimentally published by Henle et al. 2017a), although polymely and cutaneous fusion may also be caused by chemical pollution (see sections 3.2.1.1 and 3.3.2.3). Hotspots at which ectromely and ectrodactyly dominated were likely to have been caused by chemical pollution or predators, including their interactions, and hotspots at which other types of anomalies dominated were likely to have been caused by chemical pollution or diseases. In the following we review the role of these factors for the hotspots in North America.

3.1.7.1 Parasites. Infection by cysts of the trematode *Ribeiroia ondatrae* is a comparably well-studied process that creates limb anomalies in some North American hotspots. Signalling molecules produced by cells set up the three primary limb axes by interacting with regulatory genes (Johnson & Tabin 1997, Martin 1998, Pearse & Tabin 1998, Chen & Johnson 1999). Any factor that disturbs the spatial organization of the cells and thus interferes with their positional values or disrupts the signalling pathways usually causes pattern duplication in a variety of organisms (Bryant et al. 1981, Wallace 1981, Chapron 1986). Cysts of *R. ondatrae* disturb this spatial organization. As a consequence, experimental infection of tadpoles produces polymely, with the frequency increasing with the number of cercariae of *R. ondatrae* in the water to which tadpoles are exposed. Cutaneous fusion and bony triangles also often appear in high frequencies (e.g., Johnson et al. 2001b, 2006, Schotthoefer et al. 2003). Ectromely and ectrodactyly are usually either absent or only occur at low frequency. The only exception is *Pseudacris regilla* (Johnson et al. 1999, Romansic et al. 2011), a species, which seems to be particularly sensitive to *R. ondatrae* infection. In this species, there is a narrow critical window, stages 24–28 of Gosner (1960), during which infection causes high rates of anomalies. Exposure at earlier stages resulted in high mortality and no limb anomalies. When individuals were exposed at stage 24, at which mortality was still high, ectromely occurred. Exposure after stage 26 never caused ectromely or ectrodactyly. In exposures at stages 26–28, bony triangles, skin webbing and polymely dominated (Fig. 9). After stage 28, only a few anomalies were induced (Johnson et al. 2011), explaining why not all infected individuals develop anomalies. Furthermore, effects are greater in small-scale (laboratory) experiments rather than in larger scale experiments using cages or full-scale lake manipulations (Lunde et al. 2012).

Cysts of *R. ondatrae* have been found in the limbs of amphibians at all but two North American hotspots, at which large numbers of individuals with polymely occurred (e.g., Johnson et al. 2001b, 2003, 2006). As *R. ondatrae* readily causes polymely in the laboratory in many frog species, it is plausible to assume that this trematode is (part of) the cause for these hotspots. However, this hypothesis has only been tested in the field once in a British Columbian hotspot (Roberts & Dickinson 2012). At this hotspot 23% of 521 *P. regilla*

Fig. 9: *Pseudacris regilla* with polymely that was induced by *Ribeiroia ondatrae* cysts. Source: Goodman & Johnson (2011a).

Table 2: North American hotspots of anomalies, with more than 100 individuals and 10% of the population of at least one species being affected. Data are sums (*N-abn*) and weighted averages (Freq) across cited references. Stage: ad: adult, juv: juvenile, l: larval, m: metamorphs, p: stages post metamorphosis; Freq: % of the population affected; *N*-abn: number of abnormal individuals; main type: types of anomalies that affected at least 10% of all abnormal individuals (at least 10% of a subsample of at least 50 individuals if data are not available for all samples); Cause: (e): the cause was supported by experimental studies, all other causes are assumptions.

Location	Species (Stage)	Freq	*N-abn*	Years	Main type	Cause	References
Aptos Pond, California	*Ambystoma macrodactylum croceum* (l, juv, ad) *Pseudacris regilla* (m)	14.8% 54.2%	1738 212	1986–1987+1998–2000 1986–1987, 1999	Polydactyly, polymely, ectromely Polymely, ectromely, cutaneous fusion	*Ribeiroia ondatrae,* trauma (conspecifics[3], predators, and their interactions) (e)	Sessions & Ruth 1990, Sesssions et al. 1999, Johnson et al. 2003, 2006
Hidden Pond, California	*Pseudacris regilla* (l, m) *Taricha torosa* (l, ad) *Anaxyrus boreas* (l, m)	12.3% 15.4% 3.3%	1097 148 18	1986, 1987, 2006–2009 1997–1998 1997–1998	Polymely Ectromely, ectrodactyly Ectromely, ectrodactyly	*Ribeiroia ondatrae* (e) Unknown[1] Unknown[1]	Johnson et al. 2001a, Lunde et al. 2012
Sheep Pond, California	*Pseudacris regilla* (m, ad)	43.4%	681	2009–2011	Polymely, cutaneous fusion	*Ribeiroia ondatrae*	Goodman & Johnson 2011a
Frog Pond, California	*Pseudacris regilla* (l, m) *Taricha torosa* (l) *Anaxyrus boreas* (l, m) *Lithobates catesbeianus* (l, m, ad)	25.2% 41.3% 3.1% 3.7%	578 267 51 32	1986, 1987, 2006–2009 1997–1998 1997–1998 1997–1998	Polymely, cutaneous fusion Ectromely, ectrodactyly Ectromely, ectrodactyly Polymely	*Ribeiroia ondatrae* (e) Unknown[1] Unknown[1] Unknown	Johnson et al. 2001a, Lunde et al. 2012
Fortynine Palms Oasis, Joshua Tree National Monument, California	*Pseudacris cadaverina* (p)	98.8%	253	1969–1970	Cysts	Mites: *Hannemania hylae* (histology)	Welbourn & Loomis 1975
Hog Lake, California	*Pseudacris regilla* (p)	26.2%	207	2006–2008	No site specific data available but presumably polymely, bony triangles, polydactyly, skin webbing	*Ribeiroia ondatrae* (e)	Lunde et al. 2012
CWB site, Minnesota	*Lithobates septentrionalis* (m) *Lithobates pipiens* (m) *Lithobates clamitans* (m) *Anaxyrus americanus* (m) 3 further species with sample size < 100	67.5% 12.8% 33.5% 6.7% 2.9%	587 253 82 8 4	1996–1999 1996–1999 1996–1999 1996–1999 1996–1999	Cutaneous fusion, polymely; presumably also torsion of limbs, ectromely Cutaneous fusion, polymely, ectrodactyly, anteversion Cutaneous fusion, polymely, anteversion, ectromely No data provided No data provided	Competing hypotheses[2]: *Ribeiroia ondatrae*, retinoids, micronutrient deficiency, and pollution	Vandenlangenberg et al. 2003, Hoppe 2005
ROI site, Minnesota	*Lithobates pipiens* (m) (5 further species were found but no data on anomalies were provided)	20.3%	283	1996–1999	Ectromely, ectrodactyly	Unknown; *Ribeiroia ondatrae* was not found but estrogenic substances and pesticides	Vandenlangenberg et al. 2003
Duck Pond, Minnesota	*Anaxyrus americanus* (m) *Dryophytes versicolor* (m)	59.5% 3.2%	368 8	2004 2004	Bony triangle, skin webbing, polymely, ectromely –	*Ribeiroia ondatrae* Unknown	Johnson & Hartson 2009
Dor site, Minnesota	*Lithobates pipiens* (m)	18.3%	115	1996–1997	No data provided	Unknown	Canfield et al. 2000, Helgen et al. 2000
Potholes, Oregon	*Ambystoma macrodactylum* (juv)	35%	141	2002, 2004	Ectromely, ectrodactyly	Trauma (conspecifics[3])	Johnson et al. 2006
Lake Aspen, Oregon	*Anaxyrus boreas* (l, m)	12.9%	1734	1998–2008	Ectromely, ectrodactyly, tail injuries	Injury from *Gasterosteus aculeatus* (e)	Bowerman et al. 2010, Johnson & Bowerman 2010
Jette Pond, Montana	*Pseudacris regilla* (l, juv) *Ambystoma macrodactylum* (l, ad)	47.6% 11.5%	161 60	1958–1959, 1999–2001 1998–2004[4]	Polymely, cutaneous fusion Brachymely, skin webbing, polydactyly, polymely	*Ribeiroia ondatrae* *Ribeiroia ondatrae* (but see sction 3.3.2.3)	Hebard & Brunson 1963, Johnson et al. 2003, 2006

Table 2: Continuation.

Location	Species (Stage)	Freq	*N-abn*	Years	Main type	Cause	References
Savannah River National Environmental Research Park (coal ash deposition swamp), Aiken, South Carolina	*Lithobates catesbeianus* (l) *Dryophytes cinereus* (l)	78.5% 0%	1171 0 of 32 tadpoles	1995, 1996 1995, 1996, 1998	Labial tooth rows partially missing, bent tails –	Coal combustion waste (e)	Rowe et al. 1996, Hopkins et al. 2000
Savannah River National Environmental Research Park (coal ash drainage swamp), Aiken, South Carolina	*Lithobates catesbeianus* (l)	34.8%	286	1995, 1996, 1998	Labial tooth rows partially missing, bent tails	Coal combustion waste (e)	Rowe et al. 1996, Hopkins et al. 2000
Rhine Pond, Orange County, North Carolina	*Lithobates palustris* (a, m)	12.6%	162	1961–1963	Cysts, faulty eruption of forelimbs	Mites: *Hannemania dunni* (histology) and unknown	Murphy 1965
Tunica, Mississippi	*Lithobates catesbeianus* (p)	?	350	1958	Polymely	Pesticides assumed	Volpe & Rosenbaum 2000
UPM02 site (Fish Farm Mounds), Upper Mississippi River National Wildlife and Fish Refuge, Iowa	*Lithobates pipiens* (l, m) *Lithobates clamitans* (l, m)	66.5% 4.9%	119 2	2002, 2003, 2006 2002	Small translucent pustules –	Unknown –	Reeves et al. 2013
Isobel Lake, British Columbia, Canada	*Pseudacris regilla* (m) *Rana luteiventris* (m)	23.0% 30.7%	120 86	2011	Polymely, cutaneous fusion Cutaneous fusion, rotation of limbs, ectromely	*Ribeiroia ondatrae* (e) Unknown (*R. ondatrae* assumed[5])	Roberts & Dickinson 2012

[1] The pattern is inconsistent with results from experimental infections with *Ribeiroia ondatrae* (see section 3.1.7.1).

[2] For competing hypotheses see Gardiner & Hoppe (1999), Stopper et al. (2002), Lannoo (2008), Helgen (2012) and section 3.1.7.

[3] Johnson et al. (2006) assumed cannibalism as the cause because when two individuals were housed together in 1.5 l containers without food high frequencies of limb injuries occurred. However, these conditions are very artificial and need to be corroborated under more natural conditions.

[4] No anomalies were observed in 1958–1961 (Hebard & Brunson 1963).

[5] *Ribeiroia ondatrae* usually does not produce elevated rates of ectromely and other causes likely were more relevant for the hotspot (see section 3.1.7.1).

and 30.7% of 280 *Rana luteiventris* metamorphs but only a few *Ambystoma macrodactylum* and *Anaxyrus boreas* were affected. *Pseudacris regilla* and *R. luteiventris* primarily exhibited polymely and cutaneous fusion, respectively. When tadpoles were reared in closed cages that prevented the entry of *R. ondatrae*, no anomalies occurred. Roberts & Dickinson (2012) concluded that *R. ondatrae* caused the anomaly hotspot. A caveat remains as the authors did not provide any information as to whether the cages also excluded access to sediment and thus to pollutants that may have accumulated in the sediment, which could confound results (Helgen 2012). Moreover, predators likely were also excluded and, like chemicals, could be responsible for the elevated rates of ectromely in *Rana luteiventris* (compare section 3.2.2.1). Furthermore, no explanation has been provided why the other two species were only mildly affected in spite of them being highly sensitive to *R. ondatrae* infection in the laboratory (Johnson et al. 2001b, 2006).

In California and the northwestern states of the USA, a significant relationship between the number of *R. ondatrae* infections and the frequency of malformed *P. regilla* was discovered (Johnson et al. 2002, 2013, Lunde et al. 2012). However, such relationships do not exist for frogs in Alaska, Vermont and Michigan (e.g., Gillilland & Muzzall 2002, Levey et al. 2003, Skelly et al. 2007, Reeves et al. 2008, 2010); for Minnesota it still remains unclear whether such a relationship exists

(Helgen 2012). Further, at one of the hotspots with numerous polymelous individuals of *Lithobates catesbeianus* (Anonymous 1954), *R. ondatrae* was not detected in preserved polymelous frogs, nor in the resurvey, but anomalies were also absent in the resurvey (Johnson et al. 2003). The other exception (Volpe & Rosenbaum 2000) was discovered at a time when *R. ondatrae* was not yet known as a cause of limb anomalies. The anomaliy appeared only in one year. While the abnormality rate may vary from year to year (see section 6), to be absent in all years and very frequent in another year is at odds with the dynamics of *R. ondatrae*. Volpe & Rosenbaum (2000) assumed pesticides that were heavily used in the surrounding environment to be the cause.

Despite these exceptions and the fact that factors other than *R. ondatrae* have caused mass occurrences of polymely elsewhere (see 3.2.1.1), it is likely that *R. ondatrae* was one of the main causes in most North American hotspots in which polymely dominated, especially if bony triangles and/or cutaneous webbing were also prominent. At several of these hotspots other anomalies that are absent or very rare in experimental infections were also frequent, notably ectromely and ectrodactyly (e.g., Johnson et al. 2001b, 2006, Johnson & Hartson 2009). Thus, it is rather unlikely that trematodes were the only cause and trematodes cannot explain hotspots where ectromely and ectrodactyly were dominant but polymely was rare. This seems to be meanwhile consensus even among those scientists that otherwise have rather opposing opinions about the causes of amphibian anomalies.

Ribeiroia ondatrae is not the only parasite that may create anomaly hotspots. The database of Reeves et al. (2013) contains two populations of *L. clamitans*, in which 21 out of 53 and 52 out of 137, respectively, metamorphosing individuals had cysts. The trematode *Clinostomum* was the cause in the former population and unidentified metacercariae in the second population. High prevalences of individuals with cysts may also be due to chigger mites of the genus *Hannemania*. For example, prevalences well above 50% have been observed in *Desmognathus fuscus, Eurycea bislineata, Plethodon ouachitae, Anaxyrus punctatus, Dryophytes arenicolor, Pseud-acris cadaverina, L. berlandieri,* and *L. palustris* (Pope & Pope 1951, Murphy 1965, Duszynski & Jones 1973, Shoemaker & Clark 1975, Welbourn & Loomis 1975, Jung et al. 2001, Anthony et al. 2004, Westfall et al. 2008). Often reddening of the skin around the cysts is also observed (e.g. Pope & Pope 1951) and ectrodactyly may occur if digits are heavily infested (e.g. Winter et al. 1986 for *Desmognathus brimleyorum*).

Copepods are yet another group of parasites that are likely to have contributed to elevated rates of anomalies. Significantly more *Rana boylii* individuals with copepod parasites (*Lernaea cyprinacea*) were malformed at South Fork Eel River in California than those individuals without copepod parasites in 2006, but no difference occurred in 2008 (Kupferberg et al. 2009).

3.1.7.2 Chemical pollution. As an alternative explanation to infection by *R. ondatrae,* retinoids and the insecticide methoprene have been suspected as culprits for anomaly hotspots because retinoids play a major role in limb differentiation, can induce polymely in laboratory experiments and biologically active retinoids were detected by Gardiner et al. (2003) in water samples from sites where large numbers of malformed frogs were found. Other chemicals contributing to pollution have also been suggested as causes for anomaly hotspots.

Retinoids are metabolic derivatives of vitamin A. They are part of the thyroid hormone dependent system that activates the genes involved in limb differentiation (Kliewer et al. 1992, Maden & Corcoran 1996, Lee et al. 2004). Feeding retinoids to tadpoles can lead to ectromely and bony triangles (Degitz et al. 2000, Alsop et al. 2004). In regenerating limbs, the effects depend on the dose and duration of the application (Maden 1983b). At high and low doses polymely is not observed. High doses suppress regeneration completely and at low doses ectrodactyly occurs (Saxena & Niazi 1977, Maden 1983b, Thoms & Stocum 1984, Scadding & Maden 1986b).

Most authors observed polymely only in regenerating limbs but not in developing limbs (Scadding & Maden 1986a,b, Degitz et al. 2000) and in a review Niazi (1996) concluded that retinoids suppress differentiation in developing limbs. However, Das & Mohanty-Hejmadi (2000) obtained significantly elevated rates of polymely in the developing hindlimbs of *Duttaphrynus melanostictus* tadpoles raised in vitamin A solutions after the amputation of their tails. Moreover, Bruschelli & Rosi (1971) and Gardiner et al. (2003) observed polymely in developing limbs without surgical manipulation. No statistical comparisons were made with controls in both studies but the frequency was very high in the latter. Gardiner et al. (2003) emphasized that polymely only occurred when stage 52 tadpoles (*Xenopus laevis*, stages after Nieuwkoop & Faber 1994) were treated, which may explain the discrepancy with Degitz et al. (2000), who only treated tadpoles at stage 48 and 51. From studies on mice and rats it is also well known that the effects of retinoids are highly stage-specific (Lee et al. 2004).

On the other hand, embryos (of *Xenopus laevis*) are far more sensitive to retinoids than tadpoles and show 100% mortality at doses, which are ineffective in tadpoles (Degitz et al. 2003a). Degitz et al. (2003a) therefore concluded that retinoids and methoprene cannot play a significant role in malformation hotspots. However, this does not exclude a role of chemicals in the development of mass occurrences of polymely, since relevant chemicals may only contaminate water at times when tadpoles have reached later developmental stages. Moreover, recent research showed that various agrochemicals, including the widely used glyphosate, polychlorinated pollutants and persistent pharmaceuticals, influence retinoic acid activity at environmentally relevant doses or bind to retinoic acid receptors (Alsop et al. 2004, Lee et al. 2004, Mann et al. 2009, Paganelli

et al. 2010). Retinoid metabolism can be influenced by agricultural contamination (Bérubé et al. 2005, Boily et al. 2009) and one study showed that compounds in pulp mill effluent (probably originating from the wood used) bound to retinoid acid receptors (Alsop et al. 2004). Moreover, Wu et al. (2012) discovered that cyanobacteria blooms release teratogenic retinoic acids. Thus, one cannot dismiss *a priori* the direct effect of pollutants at hotspots with a duplication of limbs or digits. Notably, outside North America two cases are known in which a high number of polymelous frogs were found in polluted habitats where *Ribeiroia ondatrae* does not occur and no other potential cause has been found (see section 3.2.1.1). Notwithstanding, as yet there is no hard evidence that chemicals directly contributed to mass polymely at North American hotspots. However, field experiments with agrochemicals that influence retinoid activity and cyanobacteria are still in dire need. In any case, there is strong evidence of an indirect, meanwhile widely accepted, effect through eutrophication favouring snails that are intermediate hosts of *R. ondatrae* (see section 3.1.7.5).

In contrast to hotspots that are dominated by polymely, a direct chemical effect is likely to explain, at least in part, North American hotspots in Vermont, Minnesota, California, Alaska and Canada, where ectromely and ectrodactyly are frequent and where polymely is comparably rare or absent. Some authors reject such conclusions, putting all such cases down to predation attempts (e.g., Ballengée & Sessions 2009, Sessions 2009, Sessions & Ballengée 2010). Contrary to the statement made by Sessions & Ballengée (2010) there is strong evidence of a direct effect from chemicals for several sites.

In Minnesota and Vermont, water and sediment from hotspot sites caused high rates of anomalies in embryos but water from control ponds did not (Burkhart et al. 1998, Fort et al. 1999a,b). Garber et al. (2004) challenged these results because in their laboratory study an addition of sodium and potassium removed the teratogeneity of the water samples from three hotspot sites. However, later tests with laboratory prepared water of similar ionic strength as in the tested hotspots did not induce any anomalies (Burkhart et al. 2000). Thus, low ionic concentrations as such cannot explain the observed anomalies. Moreover, water from hotspot sites running through activated charcoal filters no more induced anomalies (Burkhart personal communication to Helgen 2012). Furthermore, fat-soluble extracts from water samples from malformation hotspots caused anomalies in tadpoles, including bony bridges, whereas those from a control pond did not (Bridges et al. 2004). Given these results and the fact that many biocides are capable of inducing ectromely and ectrodactyly at environmentally relevant concentrations (Tab. 3), it is very likely that chemicals were a main direct cause at the assessed hotspots. Note that *R. ondatrae* infection cannot explain most hotspots where ectromely or ectrodactyly dominate as so far only one species, *Pseudacris regilla*, has developed high rates of these anomalies in laboratory experiments, whereas other species affected in ectromely hotspots did not (see 3.2.2.1 for more details).

In Vermont, Taylor et al. (2005) examined 5264 metamorphs of six frog species collected in 42 wetlands for malformations. The rate of non-traumatic limb malformations varied by location from 0–10.2%. Ectromely and other limb anomalies were the most frequent types of anomalies, with only two individuals showing polymely. The proximity to agricultural land was associated with an increased risk of limb malformations, with an odds ratio of 2.26.

In California, Sparling et al. (2015) raised tadpoles of *Pseudacris regilla* in cages in three ponds each in the Yosemite, Sequoia and Lassen National Parks in 2001 and 2002. Volatile pesticides from the very agricultural Central Valley have been deposited in these ecosystems. Between 6.2% and 25.5% of the metamorphs exhibited brachymely (called hemimely by Sparling et al. 2015). Tissue concentrations of DDE, trans-nonachlor, cis-nonachlor, a-chlordane and polybrominated diphenyl ethers were significantly correlated with the percentage of malformed metamorphs. In 2002, when tissue loads were lower on average, no correlation was significant. Genotoxic effects were detected in tadpoles from all three parks.

For 21 sites in the Kenai Wildlife Refuge, Alaska, organic and inorganic pollutants in addition to predators (Odonata) best explained the probability of *L. sylvaticus* acquiring skeletal anomalies (Reeves et al. 2010). While water plus sediment from six of the ponds did not induce skeletal anomalies in the laboratory, pollutants at the site with the highest rate of anomalies exceeded toxic thresholds and Odonata were not abundant. This indicates that pollution was a direct cause of the anomalies.

In Quebec in Canada out of 853 metamorphosing anurans (*Anaxyrus americanus, Lithobates catesbeianus, L. clamitans, L. pipiens*) from 14 farmland habitats 106 (12%, range 0–69%) had severe ectromely or ectrodactyly compared to only two (0.7%, range 0–7.7%) out of 271 individuals from 12 control sites (Ouellet et al. 1997). Malformed frogs had chromosomal anomalies and flow cytometry revealed genomic disruption in adult and metamorphosing individuals from all farmland sites (Bonin et al. 1997, Lowcock et al. 1997). Water samples taken from these sites showed correspondingly high genotoxicity values – observations that cannot be explained by parasites or predators.

Sewage also created abnormality hotspots. Labial tooth rows were partially missing in 96.2% of 1048 *L. catesbeianus* tadpoles from a coal ash deposition pond and 85.1% (n = 208) in an associated drainage swamp but only 2.9% (n = 589) were affected in control ponds (Rowe et al. 1996). When eggs were transplanted 97–100% of the tadpoles that developed in the contaminated ponds suffered from the same anomalies (Rowe et al. 1998). In a sewage pond of the Reese Airforce Base adult *Ambystoma tigrinum* suffered from tumours, with the overall rate of anomalies being 6.6% (n = 37,143; range among years 0.04–50%) (Rose 1976, 1981). None

Table 3: Overview of chemicals that caused ectromely in experimental treatments.

Chemical	Species	References
a) Whole body application at environmentally relevant concentrations		
Carbaryl	*Ambystoma barbouri*	Rohr et al. 2003
Copper	*Xenopus laevis*	Fort & Stover 1996, 1997
Endosulfan	*Ambystoma barbouri*	Rohr et al. 2003
Malaoxon (organophosphate)	*Xenopus laevis*	Snawder & Chambers 1989
Maneb 80 (carbamate)	*Triturus carnifex*	Zavanella et al. 1984
Maneb (carbamate)	*Xenopus laevis*	Fort et al. 1999b
Methylmecury	*Lithobates sphenocephalus*	Unrine et al. 2004
Octylphenol	*Ambystoma barbouri*	Rohr et al. 2003
s-methoprene (field application as Altosid)	*Lithobates pipiens*	Sparling 2000
Retinoids (only if exposed after hatching)	*Ambystoma mexicanum, Xenopus laevis, Lithobates sylvaticus*	Scadding & Maden 1986a,b, Degitz et al. 2000
Seawater (8 ppm)	*Rhinella marina*	Rios-López 2008
b) Whole body application after limb or tail amputation		
Retinoids, vitamin A	*Ambystoma mexicanum, Xenopus laevis, Duttaphrynus melanostictus, Rana temporaria*	Jangir & Niazi 1978, Maden 1983a,b, Scadding 1983, Niazi & Alam 1984, Niazi & Ratnasamy 1984, Scadding & Maden 1986a,b, Das & Mohanty-Hejmadi 2000
c) Teratogeneity index low (i.e., mortality high in treatments causing anomalies) or conditions required that are unlikely in natural habitats		
Methoprene	*Lithobates pipiens*	Ankley et al. 1998
Nitrogen mustard	*Ambystoma maculatum, Taricha torosa*	Gillette & Bodenstein 1946, Bodenstein 1947
Thyroxine (after amputation)	*Notophthalmus viridescens*	Hay 1956
d) Test conditions environmentally not relevant or relevance not assessed		
Acetylhydrazide	*Xenopus laevis*	Fort & Stover 1997
Aflatoxine	*Rana temporaria*	Gabor et al. 1973
Atropine	*Notophthalmus viridescens*	Singer et al. 1960
Citral	*Eleutherodactylus coqui*	Lee & Elinson 2008
Colchicine (treatment of regenerating limbs)	*Xenopus laevis, Rana temporaria*	Bretscher 1949, Crézé 1950, Rostand 1950c, Tschumi 1954
Cyclophosphamide	*Xenopus laevis*	Dumont et al. 1983
Estradiol	*Pelobates cultripes*	Collenot 1965
Thalidomide and analogues EM_{12} and EM_{87}	*Notophthalmus viridescens, Xenopus laevis*	Bazzoli et al. 1977, Dumpert & Zietz 1984

of the 19,802 individuals examined from the non-sewage ponds suffered from tumours. Edema occurred at a frequency of 0.2% in the non-sewage ponds and at a similar frequency in the Reese Airforce Base sewage pond. The sewage sludge was contaminated by numerous polycyclic aromatic hydrocarbons (PAH), especially perylene. Physiological studies indicated that PAH derivatives induced the tumours.

In wetlands constructed with wastewater treatment in Georgia 20.9% (n = 833) of the sampled *L. catesbeianus* tadpoles showed anomalies, whereas in four control ponds only 1.6% (n = 190) were affected (Ruiz et al. 2010). Edema, scoliosis and nodules consisting of calcium phosphate were the most frequently observed anomalies. For the later two types of anomalies the frequency dropped substantially with the distance of the sampling site from the discharge point. These data strongly indicate that the anomalies were caused by chemicals that retained in the treated wastewater.

In floodplain ponds of a river contaminated with petroleum in the south central US, froglets from three out of four species (*L. sphenocephalus, L. blairi* and *L. clamitans*) had elevated rates of anomalies (> 11%; $n \geq 83$) (with face, eye, mouth and hindlimbs affected) compared to reference sites (≤ 0.7%; $n \geq 192$) (Fort & McLaughlin 2003). The spectrum of anomalies was similar to that obtained in in-situ caged tadpoles that excluded predators and in laboratory settings with water from the contaminated sites.

Anomaly hotspots in North America that are due to chemical pollution are not limited to amphibians but have also been reported for birds (Hoffmann et al. 1988) and reptiles (Ernst 1995, Bishop & Gendron 1998). There are also a number of publications that link increased rates of anomalies in humans in North America to chemical pollution, including those regions where amphibian anomaly hotspots also occur. However, such links have been even more rigorously rejected for humans than for amphibians (discussed by Lannoo 2008).

3.1.7.3 Predators. Predators were suggested as alternative explanation to chemicals for hotspots where ectromely and ectrodactyly were prevalent (Ballengée & Sessions 2009, Sessions 2009, Sessions & Ballengée 2010). Ballengée & Sessions (2009) derived their hypothesis from their own laboratory study with larval dragonflies of the genus *Sympetrum* and the European toad *Bufo bufo.* They cited several papers to support their claim that partial predation is common and the cause of anomalies at North American hotspots with ectromely. We have examined all the papers cited by them but none of them is relevant as none reported on staged predation experiments with amphibians; the large body of literature on that subject was ignored. In most staged predation experiments, including odonates and beetles, ectromely did not occur, and if it occurred, damage to the tails of tadpoles was also common (Henle et al. 2017a), which, unfortunately, is rarely assessed in the field. Moreover, ectromely was extremely rare (< 0.03%; n = 36,151) in eight anuran species examined from 37 ponds in Michigan in which larval *Sympetrum* achieved high densities (> 1 individual / m²) (Skelly & Benard 2010). This inconsistency between these field results and their laboratory study was rejected by Sessions & Ballengée (2010) as irrelevant for their conclusion that predator attacks are responsible for most cases of ectromely in natural populations of amphibians. However, inconsistencies between laboratory studies and field studies question the potential to extrapolate from laboratory conditions to field conditions.

Only three studies seem to have experimentally assessed the predator hypothesis for North American anomaly hotspots. One was negative (see the study above by Fort & McLaughlin 2003) and two were positive. At two hotspot sites in Oregon, Lake Aspen and two ponds on Broken Top volcano, the annual frequency of anomalies (mainly ectromely and ectrodactyly) in metamorphosed *Anaxyrus americanus* and *Lithobates cascadae* was as high as 35% (weighted mean 13%) n = 13,443) and 5–21% (n = ?), respectively (Bowerman et al. 2010). Tail damage was common in tadpoles at both sites. At Lake Aspen, annual rates of anomalies were related to stickleback (*Gasterosteus aculeatus*) abundance and at sites without sticklebacks less than 1% of the toadlets showed limb anomalies. Raising tadpoles in cages that excluded predators stopped the anomalies in tadpoles and toadlets but also excluded access to mud that could have contained teratogenic chemicals. Notwithstanding, laboratory experiments demonstrated that attacks from *G. aculeatus* were sufficient to explain the observed anomalies. Laboratory experiments also showed that nymphs of the dragonfly *Somatochlora albicincta* can inflict the same types of anomalies in *L. cascadae* as observed in the field while pond water and mud without predators resulted in normal froglets. As predators that are capable of inflicting ectromely also damage tails (Henle et al. 2017a), it is recommended that other studies testing the hypothesis of predators as a cause for hotspots dominated by ectromely also assess tail damage in tadpoles, which unfortunately is almost never done.

Although not severe hotspots, the prevalence of skeletal and eye anomalies at 38 sites of five Alaskan Wildlife Refuges ranged from 1.5–7.9% and was as high as 20% at one breeding site close to a former mine (Reeves et al. 2008). Ectromely, black eyes, micromely and brachydactyly were the most common types of anomalies. Polymely and polydactyly were rare and the trematode *Ribeiroia ondatrae* was absent. Proximity to roads significantly increased the risk of skeletal but not of eye anomalies. In a later study, Reeves et al. (2010) tested the association of anomalies with organic and inorganic contaminants, parasite infection, abundance of predatory invertebrates, UV-B and temperature for 21 wetlands in Kenai Wildlife Refuge, south-central Alaska. Logistic regression and model comparison using the Akaike information criterion (AIC) identified dragonflies and both organic and inorganic contaminants to be the best predictors for the probability of frogs acquiring skeletal

anomalies (individual frogs used as repeated measure). In predator exclusion experiments no tadpole had limb anomalies but 6.3% of the wild tadpoles at the same sites in the same years showed anomalies, which was significantly different. The cages also removed access of the tadpoles to mud so that two factors are confounded. Staged predation experiments were not carried out but limb amputation resulted in limb anomalies, which is an observation that has frequently been made before and depends on the stage, species and the degree of damage to the apical pit in the developing limb (see section 3.2.2.1). However, raising tadpoles in pond water with mud did not result in any limb anomalies, strongly supporting the hypothesis that predators were indeed responsible for the anomalies, except for the site with the highest rate of skeletal anomalies. At that site, several metals and organic contaminants exceeded toxic thresholds and odonate predators were not abundant, suggesting that pollution was a direct cause of the anomalies.

For eye anomalies, surprisingly, predatory beetles were the best predictors. Reeves et al. (2010) speculated that interaction with predators may induce tadpoles to take refuge in suboptimal habitats where they have to feed on a poor diet. However, while nutrition may change skin colouration and may cause limb anomalies, no effect on eye colouration has been discovered so far (reviewed by Henle et al. 2017a) and black-eyedness, which was the main eye anomaly observed by Reeves et al. (2010), is usually due to a recessive mutation (see section 3.3.5.2). The correlation may be spurious as predator exclusion did not change the frequency of eye anomalies and eye anomalies occurred when tadpoles were raised in the laboratory in pond water with access to mud. Also, temperature tested alone was found to be negatively associated with eye anomalies as well, although less strongly than predatory beetles. Interestingly, Vershinin (2004) noted in a long-term study that in years where no frosts occurred during the spawning period, no black-eyed *Rana arvalis* were discovered. Thus, a genetic basis with temperature acting epigenetically, may have been responsible for the black-eye anomalies.

The only other larger-scale correlational study using AIC model selection we know of found strong correlational evidence for predators (trouts – *Oncorhynchus mykiss*) and large conspecifics as cause for elevated rates of tail loss and ectromely (and other injuries?) in *Dicamptodon temebrosus* at 32 sites along the Fox Creek, Northern California (Munshaw et al. 2014). The average rate of injuries was 17% (n = 354) and increased with the size of individuals. Munshaw et al. (2014) found strong support for an effect of density of young-of-the-year *O. mykiss* and of the largest size class of the salamanders on the frequency of injuries. They explained the intraspecific effects with agonistic behaviour and not with attempted predation.

There are other North American studies that have implicated predators as the causes for ectromely and/or ectrodactyly (e.g., Martof 1956, Harris et al. 2001, Gridi-Papp & Gridi-Papp 2005, Kupferberg et al. 2009). Martof (1956) and Gridi-Papp & Gridi-Papp (2005) did not test their hypothesis. The percentage of abnormal individuals and/or sample sizes were low in the other two studies.

3.1.7.4 Disease and other causes. Diseases also caused anomaly hotspots in North America. At seven sites in Maine, Utah and North Dakota, hundreds and even thousands of dead larvae of *Ambystoma maculatum* and *A. tigrinum* were found. Sick individuals suffered from reddish skin and edema or swollen venter and legs (Worthylake & Hovingh 1989, Docherty et al. 2003). An iridovirus was isolated from sick larvae at six sites. At the 7th site (in Utah) no attempts to isolate viruses were made and anomalies were attributed to *Acinetobacter* bacteria (Worthylake & Hovingh 1989) but were most likely to be only secondary infections (Docherty et al. 2003).

In a population of *Rana muscosa* 41% (n = 387) of the tadpoles had depigmented and abnormal mouthparts and the anomalies were associated with *Batrachochytrium dendrobatidis* infection (Fellers et al. 2001). By comparison, in a study across 78 Californian ponds, the prevalence of the absence of dark keratinization of mouthparts in tadpoles of *Anaxyrus boreas, A. canorus, Pseudacris regilla* and *Lithobates catesbeianus* was not related to *B. dendrobatidis* infection (Padgett-Flohr & Goble 2007).

Finally, a hotspot of albinism is known. Childs (1953) discovered 298 (21%) albino tadpoles of *Spea hammondii,* which must have developed from 3–5 clutches.

3.1.7.5 Interactions among factors. It has been suggested that interactions among factors contribute to the appearance of hotspots of anomalies (e.g., Kiesecker 2002, Sessions 2009) but only two studies seem to have addressed this hypothesis in situ. Reeves et al. (2010) found that a significant negative interaction between odonate predators and metals best explained the probability of a frog having limb anomalies in *Lithobates sylvaticus* for 21 wetlands in Kenai Wildlife Refuge, Alaska. They came up with three possible explanations for this subadditive interaction. The one that was most compatible with the observed increased mortality rate of tadpoles raised in the laboratory with pond water and sediment was that in wetlands with high metal concentrations there was a higher mortality rate and thus fewer injured tadpoles survived to metamorphosis.

In field and laboratory experiments, Kiesecker (2002) discovered synergisms between anomalies caused by trematodes and water pollution. Larvae of *L. sylvaticus* were raised in enclosures in ponds that varied in exposure to agricultural run-off. In each pond, half of the enclosures prevented the cercariae of *Ribeiroia* from entering. The frequency of limb anomalies was higher in ponds exposed to contaminants than in those that had no detectable contaminants. No anomalies occurred in enclosures to which cercariae had no access and only 4% of the individuals in ponds without contamination but

exposed to cercariae were abnormal. Besides polymely, ectromely also accounted for a considerable number of the anomalies. This is surprising as in laboratory experiments polymely but not ectromely occurred when this frog species was exposed to *R. ondatrae* (Stopper et al. 2002). Either chemicals from agricultural run-off need not only have increased the susceptibility of the tadpoles to *R. ondatrae* but also changed the pattern of anomalies inflicted by them or the presence of the parasite made the tadpoles more sensitive to the effect of chemical pollution. In the laboratory, exposure to atrazine, malathion and esfenvalerate at low concentrations increased the rate of cercarial encystment and had a dramatic effect on immune response (Kiesecker 2002). However, currently no mechanism is known that could have caused a change in the types of anomalies produced by trematodes. This discrepancy requires further study. An increased sensitivity of tadpoles to agrochemicals in the presence of parasites might be related to the significant retardation of regeneration that was observed for larvae of *Ambystoma macrodactylum* with limb amputation exposed to *R. ondatrae* cercariae by Johnson et al. (2006). Furthermore, larvae with limb amputation developed 3–5 times more anomalies than those without amputation. Whether or not such a synergism also occurs when conspecifics or predators inflict injuries remains an open question.

Atrazine also increased the susceptibility of *L. pipiens* to infection by various trematode species in the field and a combination of atrazine concentration and phosphate accounted for 74% of the variation in trematode abundance across 18 wetlands in Minnesota, USA (Rohr et al. 2008). Unfortunately, the study did not quantify these associations for *R. ondatrae*, the only trematode known to cause mass anomalies in North America. Also, in a laboratory study, the infection rate of *L. sylvaticus* with the trematode *Echinostoma trivolvis* did not increase with atrazine treatment because both the host and the parasite were sensitive to atrazine (Koprivnikar et al. 2007). Notwithstanding, a relationship between eutrophication and anomalies induced by *R. ondatrae* is likely. Many of the hotspots described by Lannoo (2008) were strongly affected by eutrophication and nitrogen-based eutrophication has increased 20-fold in the USA over the past 50 years (Rouse et al. 1999). With increasing eutrophication shifts in snail communities occur and larger species, such as those that are intermediate hosts of *R. ondatrae,* increased in abundance (Johnson & Lunde 2005, Johnson et al. 2007). Furthermore, eutrophication enhances survival of infected snails, thereby increasing the period over which they release parasites. These changes can lead to higher infection rates in amphibians and consequently higher frequencies of anomalies.

Interactions among stressors, however, may also reduce the frequency of malformations, at least in mesocosms (Michel & Burke 2011). The presence of predators reduced the frequency of torsion of the tail in *L. sylvaticus* tadpoles, especially under low density.

3.2 Skeletal anomalies

3.2.1 Supernumerary elements

3.2.1.1. Polymely. Following Henle et al. (2017b), we include schizomely and polypody in the term polymely. Polymely is one of the most widely studied amphibian anomalies and a range of reviews on natural occurrences and/or potential causes is available (Taruffi 1880, 1881–1886, Ercolani 1881, Przibram, 1921, Guyénot & Schotté 1926, Guyénot et al. 1948, Butler & Schotté 1949, Rostand 1951b, Bennett 1957, Brunst 1961, Woitkewitsch 1961, Rose 1964, Thornton 1968, Scadding 1981, Tank & Holder 1981, Wallace 1981, Michael & Hassona 1982, Borkin & Pikulik 1986, Chapron 1986, Ouellet 2000). We found reports of 352 natural populations from 93 extant species. Two fossil *Chunerpeton tianyiensis* also showed abnormal polymely (Wang et al. 2016). Reported background rates are well below 0.1% (Tab. 1). Mass occurrence of polymely (at least 100 abnormal individuals, at least 10% of the abnormal individuals with polymely) was observed in 14 populations of seven species (*Ambystoma macrodactylum croceum, Anaxyrus americanus*, *Pseudacris regilla, Lithobates catesbeianus, L. clamitans, L. pipiens and L. septentrionalis*) in North America (Tab. 2). With six cases, *P. regilla* seems to be a particularly sensitive species. Outside North America, only six populations with high numbers or frequencies of polymely are known: a population of *Pelophylax* synkl. *esculentus* in Trevignon, France (Rostand 1952a,c, 1955b, 1958b, 1971, Dubois 1979b, 2014, 2017), a population of *P. ridibundus* near Almaty, Kazakhstan (Woitkewitsch 1955–1965), a Tunisian population of *P. saharicus* (Hassine et al. 2011), an Ecuadorian population of *Leptodactylus* sp. (Rostand 1958b) and a *Bufotes viridis* population in Roßwag, Germany (Henle et al. 2017a). In addition, 27 of 65 juvenile *P. ridibundus* sampled in two lakes in Kiev in 2001 were polymelous, but only a few individuals were affected in other years (Nekrasova et al. 2007). All cases, except *P. ridibundus* from Kazakhstan and *Leptodactylus* sp. from Ecuador, came from malformation hotspots, where various anomalies were observed.

The *B. viridis* case differs from all other cases of mass polymely because polymely is confined to the front legs as opposed to only or predominantly the hindlegs being affected in all other cases. The *P. ridibundus* population from Kazakhstan is unusual in that polymely always occurred on the right hindlimb with the left hindlimb being abnormal in only a few particularly severely malformed individuals (Woitkewitsch 1961). While supernumerary limbs in North American hotspots frequently show mirror symmetry (Rohr et al. 2009), this is usually not the case outside of North America (Figs. 6a, 10a,b). In fact, the supernumerary limb may develop incompletely and even be only a short stump as in some *B. viridis* from the Roßwag population mentioned above (Fig. 10c).

All North American cases, except for two populations of *L. catesbeianus*, with mass occurrences of polymely

Fig. 10: Different types of non-symmetrical duplications of limbs or parts thereof; a) asymmetric duplication of a hind limb in *Rana arvalis*, Chelyabinsk, Russia, 19.8.1981. Photo: V. Vershinin; b) incomplete duplication of the hand in a *Salamandra atra*, Hintersteiner Tal, Germany, July 2009. Photo: U. Schulte; c) rudimentary supernumerary limb in a juvenile *B. viridis,* Roßwag, Germany, October 1980. Photo: K. Henle.

were associated with high rates of infection with the trematode (*R. ondatrae*) and experimental infections invariably caused elevated rates of polymely (Johnson et al. 2001b). While only one field experiment identified *R. ondatrae* as the cause for a mass occurrence of polymely, there is strong evidence that it is the main factor for these mass occurrences in North America (see section 3.1.7.1 for further discussion and section 3.1.7.2 for an alternative explanation).

The cause for the hotspot in Kazakhstan remains unclear but is non-hereditary (see detailed discussion in section 3.1.2). The cause for the *Leptodactylus* sp. case from Ecuador (Rostand 1958b) also remains enigmatic. The French case is the most severe expression of anomaly P, which is characterized by severe polydactyly. Anomaly P is transmitted by fish; the causal factor remains to be identified but is most likely to be a virus (Dubois 1979b, 2014, 2017).

Hassine et al. (2011) and Nekrasova et al. (2007) assumed that pollution caused the anomalies, including polymely, in the Tunisian and Ukrainian populations, respectively, studied by them. Retinoids, vitamin A and colchicine are the only chemicals – save for surgically implanted crystals – for which the potential to induce polymely in regenerating limbs of amphibians has been repeatedly demonstrated (Tschumi 1954, Bruschelli & Rosi 1971, Maden 1982, 1983a,b, Syuzyumova 1985, Niazi & Ratnasamy 1984, Scadding & Maden 1986a,b, Bryant & Gardiner 1992, Gardiner & Bryant 1996). Colchicine treated amputated limbs produced polymely only at doses that were lethal when applied to the whole animal (Tschumi 1954). For a discussion of retinoids, agrochemicals and other pollutants that interact with the retinoid signalling pathway as a potential cause of polymely in natural populations of amphibians see section 3.1.7.2.

The cause for the *B. viridis* case in Germany was controversial. Flindt (1985a) linked it to hybridization and overripeness of eggs but only a strong mutagenic factor, most likely radioactivity, is consistent with the observations made for that case (Henle et al. 2017a). Contrary to the opinion of Flindt (1985a) polymely is an exception in hybrids. Only few, statistically insignificant cases of polymely have been observed in two independent crosses of *P. lessonae* × *P. esculentus* but not in 45 other crosses (Guex et al. 2001). In numerous crosses performed within *P.* synkl. *esculentus* by Berger (1971), only a single individual showed polymely.

Contrary to the belief of Flindt (1985a), polymely is not a characteristic developmental anomaly caused by overripe eggs. While Witschi (1920, 1922, 1925, 1952) reported polymely in *Rana temporaria* that were raised from overripe eggs (i.e., forced retention of the eggs in the uterus), he obtained only seven individuals in all his experiments (Witschi 1952). Five of these individuals originated from eggs from the same female and were raised at 28°C but none of 548 offspring of the same female raised at temperatures of 10–20°C were affected (Witschi 1920, 1925). Others (e.g., Bataillon & Tchou Su 1932, Briggs 1941, Rostand 1951c) did not succeed in inducing polymely in anurans, including *R. temporaria,* by the forced retention of eggs. Possibly, temperature exerted an epigenetic effect on a recessive mutation borne by the parental female.

Isolated cases of polymely are usually explained by hyperregeneration. Decades of research has shown that any mechanical perturbation that causes a physical rearrangement of cells in developing or regenerating limbs, such as the implantation of foreign tissue (Nassanov 1930, Bodemer 1959; reviewed by Ruben 1960), crystals of chemicals (Balls & Ruben 1964), or inert objects like resin beads (Sessions & Ruth 1990), cysts of

the trematode *Ribeiroia ondatrae* (Sessions & Ruth 1990, Johnson et al. 1999, Schotthoefer et al. 2003) and surgical rotation, ligature of legs, or cuts at an angle (e.g., Tornier 1901, Nassanov 1930, Scadding 1981, Tank & Holder 1981, Michael & Hassona 1982, Nye et al. 2003) can cause polymely. Injuries to the bones of the shoulder girdle or pelvis that cause a sliding partial separation of the injured parts may also lead to a duplication of the shoulder girdle or pelvis and associated limbs (Tornier 1901). However, simple amputation does not usually lead to a rearrangement of cells and thus does not usually induce hyperregeneration (e.g., Lecamp 1935, Holder et al. 1979, Stopper et al. 2002). Therefore, it is not surprising that polymely has never been reported in staged predation experiments. We only know three documented cases in which polymely developed after the partial loss of legs caused by conspecific attacks (Duméril 1867, Hellmich 1929a,b, Wolterstorff 1941).

Ming (2001) suggested that the ectroparasitic copepod *Lernaea cyprinacea* may also cause polymely by attaching deep in the dermis of the host. While such an attachment may cause a mechanical rearrangement of cells, it remains to be tested experimentally whether this parasite can actually induce polymely.

Two tadpoles of *Lithobates sylvaticus* that were exposed to a strong magnetic field (17,700 Gauss) at the egg stage developed supernumerary legs during the climax stage of metamorphosis (Levengood 1969) but the mechanism for this effect – and whether there is indeed a causal link – remains unclear.

Rostand (1951b) reviewed the genetic basis of polymely. The genetics of polymely has rarely been studied probably because such individuals are usually severely handicapped and only exceptionally survive to sexual maturity. Witschi & Chang (1954) demonstrated inheritance in a toad (species not provided) and Rostand (1958b) in a *Bufo bufo*. Polymely appeared in the first and second generation of irradiated eggs and sperm of *Pelophylax nigromaculatus* (Kawamura & Nishioka 1978).

3.2.1.2. Polydactyly and polyphalangy. Following Henle et al. (2017b), we include schizodactyly (split fingers) (Fig. 11) and polyphalangy (serial duplication of a phalange within a digit) in the term polydactyly. Cases in which the additional digit severely bends outwards (Fig. 12) were called clinodactyly rather than schizodactyly by some authors (e.g., Vershinin 2002). Here we include such cases under polydactyly, if we were confident that the anomaly in question was a split or additional digit, and restrict clinodactyly to the abnormal bending of a finger without any duplication.

Meteyer (2000) introduced a new terminology for polyphalangy and called all cases of polydactyly, in which the metatarsal or metacarpal is not duplicated, polyphalangy. However, absence or presence of these bones usually cannot be assessed in the field (see for example Fig. 13) and her definition deviates from the es-

Fig. 11: Schizodactyly, a specific form of polydactyly, in *Lissotriton vulgaris*, Ekaterinburg, Russia, 2002. Photo: V. Vershinin.

Fig. 12: Polydactyly, combined with brachydactyly (and lack of musculature), in a male *Rana arvalis*, Kalinovsky Forest Park, Ekaterinburg, Russia, 26.9.2009. This type of polydactyly is called clinodactyly by some authors because the additional finger is bent outwards. Photo: V. Vershinin.

Fig. 13: Symmetrical polydactyly in an adult *Pelophylax ridibundus*, Southern Ural, Russia, 2012. Photo: V. Vershinin.

tablished terminology (Henle et al. 2017b). Thus, one needs to be aware that recent publications mentioning polyphalangy may not actually be polyphalangy in our definition.

In urodeles abnormal polydactyly and polyphalangy may be difficult to distinguish from the normal pattern of variability in skeletal elements of the foot and hand. For example, in *Salamandrella keyserlingii,* in some but not all regions there is a high variation in digital bones, including polyphalangy and supernumerary digits (Fig. 34b), and only 30% or fewer of the animals may have the normal set of digits. Therefore, some authors (e.g., Borchvardt & Ivaschintsova 1993, Borkin 1999, Zmeeva 2014) regarded deviations from the normal number of digits as natural variation. However, others referred to such deviations as abnormal (e.g., Vershinin 2002, Kuzmin & Maslova 2003). Therefore, we included those cases classed as abnormal by authors in our database but not those cases classed as normal.

Excluding those publications where it remains unclear which definition of polyphalangy was used, polyphalangy has only been reported for 20 cases from 5 extant urodele and 7 extant anuran species, all except for one involving only a few specimens. In addition, Wang et al. (2016) reported it for the fossil *Chunerpeton tianyiensis*. Zamaletdinov (2014) reported polyphalangy for ten populations belonging to five species (*Bufo bufo, Bufotes viridis, Pelophylax lessonae, P. ridibundus, Rana arvalis*) in Tatarstan, Russia. In most locations, only a few individuals were affected but at Dogaya Polyana 47 out of 64 *P. ridibundus* exhibited it. Mikitinez (2014) observed polphalangy in Ukrainian *Pelobates fuscus, Pelophylax esculentus* and *P. ridibundus* and Svivin (2014) in Russian *P. lessonae* and *P. ridibundus*. Diego-Rasilla et al. (2007) described it for a male and an albinistic female *Triturus marmoratus* in Spain, D'Amen et al. (2006) for a *T. carnifex* in Italy, Hanken (1983) for one *Plethodon cinereus* ($n = 100$) in Canada and Chang & Boring (1935) for at least three Chinese *Batrachuperus pinchonii* (as *T. sinensis*) and one *Hypselotriton orientalis*. These cases are not included in the figures of polydactyly given below unless the duplication of digits was reported as well.

Several reviews of polydactyly in natural populations are available (Rostand 1951a, 1958b, 1971, Van Valen 1974, Dubois 1979, Borkin & Pikulik 1986, Ouellet 2000) but none on its potential causes. Our review resulted in 281 cases from 87 extant species. Wang et al. (2016) also observed abnormal polydactyly in 14 individuals of the fossil salamander *Chunerpeton tianyiensis*. Reported background rates ranged up to 1% (Henle et al. 2017a). The earliest illustration of a polydactylous frog is in Seba (1735: Tab. XIII, Fig. 3). However, it is unclear whether it is truly a polydactylous frog or the liberty of the artist because both front limbs have five fingers and symmetrical front limb polydactyly is very rare. On the other hand, all other amphibians illustrated show only four fingers. Virey (1819) was the first who explicitly mentioned polydactylous frogs.

Most cases of mass occurrences of polydactyly were reported either in green frogs of the genus *Pelophylax*, for North American malformation hotspots, or for polluted sites in Asia and Africa. Mass occurrence of polydactyly was first discovered in *P.* synkl. *esculentus* (Bonnet & Rey 1937) in France and termed anomaly P by Rostand (1952a). Anomaly P is characterized by, albeit not always perfect, symmetrical polydactyly that primarily affects the hindlimbs (Fig. 5). Anomaly P has been detected at 13 locations in France, with the frequency varying from 0 to 80% in tadpoles and from 2.6% to 14.5% in adults in different years (Bonnet & Rey 1937, Dubois 1968, Rostand 1952a-c, 1957, 1962, Rostand & Darré 1967, 1968, reviewed by Rostand 1958b, 1971 and by Dubois 1979, 1984, 2014, 2017). Mass occurrences that probably were related to anomaly P were further observed in one population of *P.* kl. *esculentus* in The Netherlands, with 45% of the sample being affected (Rostand 1957, Hillenius 1959), in populations of *P. esculentus* (7.9% affected; $n = 69$) and *P. lessonae* (27% affected; $n = 161$) at the Alba Fisheries in Byelorussia (Borkin & Pikulik 1986) and in *P. saharicus* (25% affected) in Morocco (Rostand 1971). At the hotspot site in Bugornia, Pridnestrovie district, Russia (section 3.1.1), 5% of the *P. ridibundus* individuals exhibited polydactyly. However, more than 40% showed ectrodactyly and most probably there is no relationship to anomaly P. In two populations of *Bufo bufo* from near Tambov, Russia, 24.9% ($n = 229$) of the adult toads showed symmetrical polydactyly of the hindlimb (Lada (1999). The symmetry of the anomaly is reminiscent of anomaly P although so far anomaly P is known only for green frogs of the genus *Pelophylax*.

Rostand and co-workers conducted a range of experiments to discover the cause(s) of anomaly P. It is not inherited and the causative factor is still unknown but likely to be a virus transmitted by fish (Rostand 1971; see Dubois 2014, 2017 for recent reviews). Rostand failed to evoke polydactyly in *P. esculentus* and/or *R. temporaria* by applying various physical stresses, such as thermic shocks, long exposure to high or low temperature, dehydration, long-term insolation (Rostand 1950a, 1959), or by overripeness of eggs (Rostand 1951c). Rearing eggs and tadpoles of *P. esculentus* in brackish water did not produce polydactyly (Rostand 1952b, 1958b). Rostand (1950b) also obtained negative results with various chemicals and this is also the case for all chemicals in our database except when combined with amputation (see below). We also failed to find a single published case of experimental hybridization that resulted in polydactyly. After irradiation of embryos, polydactyly occured in low numbers in *B. bufo* (Rostand 1955a, 1958a, Oerter 1985).

In North America, elevated rates of polydactyly have been observed in six populations of five species (Tab. 4). All of these cases were from hotspots where other types of anomalies were common as well. Apart from the population studied by Williams et al. (2008), for which there is no indication of a cause, these cases were associated with and presumably due, at least in part, to

Table 4: Elevated rates of polydactyly in North American populations of amphibians (≥ 5% of the population abnormal, ≥ 2.5% of the population with polydactyly, ≥ 10 polydactylous individuals). *N*: sample size; only cases with *N* ≥ 50 included; % polydactyly refers to the sample size. Cause: (e): the cause was supported by experimental studies; all other causes are assumptions.

Species	*N* (% abnormal)	% polydactyly	Location	Cause	References
Ambystoma macrodactylum	11,732 (14.8%)	≥4.4%	Aptos Pond, California	*Ribeiroia ondatrae* (e)	Sessions & Ruth 1990, Johnson et al. 2003, 2006
Ambystoma macrodactylum	520 (11.5%)	≥2.7%	Jette Pond, Montana	*Ribeiroia ondatrae* (e)	Johnson et al. 2003, 2006
Ambystoma tigrinum	1946 (8%)	4.5%	Wetland in Tippecanoe County, Indiana	Unknown	Williams 2007, Williams et al. 2008
Anaxyrus americanus	618 (59.5%)	3.4%	Duck Pond, Minnesota	*Ribeiroia ondatrae*	Johnson & Hartson 2009
Lithobates septentrionalis	869 (67.5%)	3.2%	CWB, Minnesota	Competing hypotheses[1]: *Ribeiroia ondatrae*, retinoids, micronutrient deficiency, and pollution	Vandenlangenberg et al. 2003, Hoppe 2005

[1] For competing hypotheses see Gardiner & Hoppe (1999), Stopper et al. (2002), Lannoo (2008), Helgen (2012) and section 3.1.7.

infections by the trematode *Ribeiroia ondatrae* (see section 3.1.7 for a discussion).

Chemicals have been suggested as an alternative explanation for mass anomalies observed in North American amphibians, not specifically for polydactyly, but rather for polymely (see section 3.1.7.2). As for polymely, retinoic acid (Scadding & Maden 1986b, Crawford & Vincenti 1998), colchicine (Tschumi 1954) and aminopterin (Gebhardt & Faber 1966a,b) treatments applied to amputated limbs caused polydactyly – aminopterin only, when amputation occurred proximally and only when applied at an early stage of limb regeneration. For thalidomide and its analogue EM_{12} inconsistent results have been published. Whereas Bazzoli et al. (1977) obtained increased rates of polydactyly, others did not report such an effect (Gebhardt & Faber 1966a, Dumpert & Zietz 1984). The difference may be due to stage-specific effects. Unfortunately, no North American study experimentally tested the hypothesis that mass occurrences of polydactyly may have been caused by chemicals.

While field tests on the possible effect of chemicals on the occurrence of polydactyly are lacking, a few studies showed an association of polydactyly with pollution of breeding sites, both in the Old and the New World. Bacon et al. (2006b) found at least 122 (approx. 1%) polydactylous *Rhinella marina* in Bermuda. Breeding ponds with elevated rates of anomalies were contaminated with petroleum hydrocarbons and metals at teratogenic concentrations (Fort et al. 2006a,b). Microcosm experiments with sediment and water from polluted sites also induced high rates of polydactyly (Bacon et al. 2013) and trematodes could be excluded as a cause (Bacon et al. 2006b).

In Tunisia, 19 of 221 *P. saharicus* metamorphs exhibited polydactyly (and various other skeletal anomalies) at the Lebna Dam, which is situated in intensively used agricultural area and contaminated by agrochemicals, whereas anomalies were absent in non-agricultural areas (Hassine et al. 2011). At polluted sites in Russia 18 (0.3%) *Rana pirica,* 230 (4.4%) *P. ridibundus and* 74 (2.5%) *Bombina bombina* exhibited polydactyly (Borkin & Pikulik 1986, Flax & Borkin 2004). In the latter two species, the frequency of limb anomalies (ectromely and ectrodactyly in addition to polydactyly) increased with the biological oxygen demand of the breeding sites. Whether chemicals played a direct or indirect role for these cases remains to be studied. The facts that retinoic acid can induce polymely and various agrochemicals (Mann et al. 2009, Paganelli et al. 2010), polychlorinated toxicants and estrogen may increase internally cycling levels of retinoic acids and that in one study compounds in pulp mill effluents (probably originating from the wood used) bound to retinoic acid receptors (Alsop et al. 2004), support the assumption of a direct effect.

Vershinin (2010) collected 10 (n = 294) *Bufotes viridis* with schizodactyly (he referred to it as clinodactyly) in presumably polluted sites in the vicinity of industrial premises in Magnitogorsk, South Ural (Russia); on the other hand, *Bufo bufo* from a relatively unpolluted site, Kuzino village (Sverdlovsk District, Russia), had similar

high rates (22 of 183 individuals). Slightly elevated rates of polydactyly (0.7–1.4%, n_{total} = 13,815) were further observed in *Cynops pyrrhogaster* from Honshu, Japan, in the years 1981–1985 (Meyer-Rochow & Asashima 1988). The rate dropped to less than 0.1% in 1995 (Fukui et al. 1996). The decline was explained by improved water quality – but no data on water quality were provided.

Elevated rates of polydactyly were further reported for a population of *Triturus pygmaeus* (2.3%, *n* = 557) in Portugal (Caetano 1999), *B. bufo* (5%, *n* = 317) in Russia (Borkin & Pikulik 1986) and *R. arvalis* (2.6%, *n* = 464) in Byelorussia (Borkin & Pikulik 1986). The cause for these cases is unknown.

Isolated cases of polydactyly are most frequently explained by hyperregeneration. As for polymely (see section 3.2.1.1), polydactyly can be induced by mechanical perturbation that causes a physical rearrangement of cells in the developing or regenerating digits, such as the surgical implantation of inert objects such as resin beads (Sessions & Ruth 1990), surgical rotation (Lecamp 1935) and cell death caused by irradiation (Rieck 1954). In contrast to polymely, polydactyly (schizodactyly) can occur in high numbers after amputation without further manipulation as observed after toe-clipping in *Ambystoma talpoideum* (Semlitsch et al. 1981). Experimental infections with the trematode *Ribeiroia ondatrae* also caused significantly elevated rates of polydactyly in *Pseudacris regilla* and *Lithobates pipiens* (Johnson et al. 1999, Schotthoefer et al. 2003) but experiments with the trematode genus *Alaria* were negative (Johnson et al. 1999). In experiments with Sri Lankan monostome-type trematodes, three *Polypedates crucifer* (*n* = 218) developed polydactyly (Rajakaruna et al. 2008) but this was not significantly different from controls (χ^2= 1.084; $\alpha > 0.2$).

Dubois (1974) observed polydactyly, linked to clinodactyly, in a population of *Rana graeca* for which he hypothesized a genetic cause, based on crossing experiments in *B. bufo*. He reported recessive genetic transmission of polydactyly linked to clinodactyly in *B. bufo*. Genetic transmission of polydactyly is well-documented in *B. bufo*. Rostand (1949a) detected 53 polydactylous adult male *B. bufo* among the 44,000 that were examined. The breeding experiments conducted by him revealed that at least some of them were of genetic origin, being caused either by a dominant or recessive allele (Rostand 1947, 1949b, 1950d, 1951a, 1958b). Inheritance of polydactyly was further demonstrated in *Xenopus laevis* (Uehlinger 1969, Droin & Fischberg 1980). Hereditary polydactyly is also well known in mice and humans (Cohn & Bright 1999, Gurrieri et al. 2002).

3.2.1.3. Supernumerary bone at lower jaw. Christaller (1983) described a single individual of *Bufotes viridis* collected at Roßwag in Germany with a supernumerary bone at the lower jaw and regarded it as an extension of the lower mouth. Flindt (1985*a*) suggested that this anomaly was an additional limb and not a jaw malformation. This may be the case but the printed photograph is inconclusive. In the same population, a toadlet had a very short bony protuberance present at the angle of the left yaw and an additional protuberance on the right side of the head (Henle et al. 2017a). A supernumerary limb originating from the jaw was illustrated for a *Pelophylax nigromaculatus* by Iwasawa & Takasu (1985) and for an experimentally produced adult hybrid *Ceratophrys cranwelli* × *C. ornata* by Miranda (1989).

3.2.1.4. Tail bifurcation and duplication. Tail duplications have rarely been reported from natural populations (reviewed by Henle et al. 2012). They listed 11 publications that mentioned a total of 22 affected larval amphibians belonging to 15 species. Twenty publications described the incidence for 36 individual postlarval urodeles from 13 species. In experiments, the duplication of tails was induced by destroying parts of the chorda dorsalis, by injecting tar into the tail or by irradiating the lumbar region.

We found eight additional papers on this topic, adding seven more species. One *Ichthyosaura alpestris* from approx. 30,000 individuals examined in an area near Bonn, Germany (Hachtel 2011), and one adult female *Taricha torosa* among 22 adults examined from Boulder Creek, California (Wolterstorff 1935), had a split tail. Smirnov (2014) reported one male *Lissotriton montandoni* with tail bifurcation. Reeves et al. (2013) listed one (*n* = 52) *Pseudacris triseriata,* one (*n* = 121) *Lithobates pipiens,* one (*n* = 53) *L. sphenocephalus* and seven tadpoles of *L. sylvaticus* originating from six populations (10,345 individuals and > 100 populations exmined) in US national wildlife refuges. Levey et al. (2003) also reported one *L. pipiens* with a forked tail. Finally, Medina et al. (2013) listed one tadpole (*n* = 211) of *Boana riochana* from Argentina. Two papers added observations for species, for which tail bifurcation or duplication was already reported. Fukui et al. (1996) printed a photo of tail bifurcation in a *Cynops pyrrhogaster*. Up to four individuals may have been affected. Hiller (1986) observed two lateral tail appendages in a *Pelobates fuscus* tadpole.

3.2.1.5. Dicephaly and Siamese twins. Externally visible duplications of body parts other than limbs seem to be very rare in amphibians and were observed mainly in captivity. While there are various ancient but unreliable stories (discussed by Gesner 1554), Wurffbain (1683) was presumably the first to report a reliable observation: a two-headed salamander that was exhibited by Mercerus. Funk (1827) provided the first more detailed description of a dicephalic embryo of *Salamandra salamandra*. Jourdain (1877) briefly mentioned an individual with two heads that were almost completely fused but exhibited two faces and a Siamese twin that was fused at the sternum and umbilical scar. Furthermore, Braun (1875), Susebach (1941) and Wolterstorff & Freytag (1941) reported further dicephalic larvae and/or Siamese twins of the same species. While most if not all of these observations derived from individuals born

in captivity, the following observations presumably apply to individuals caught in the wild: a twin embryo (Lébédinsky (1921) and a dicephalic tadpole of *Rana temporaria* (Loyez 1897) and a *Bufo bufo* tadpole with a partially duplicated head (Canella 1935).

The following observations were definitely from natural populations. Schwind (1942) reported a total of 5 and 29 eggs with twin embryos of *Ambystoma maculatum* and *Lithobates sylvaticus*, respectively (plus further ones that were manipulated before the twins were detected). Lynn (1944) found one egg with twin embryo of *Eleutherodactylus alticola* among 20 eggs examined, Lindberg (1995) three eggs (n = 7846) with twin embryos of *Ambystoma tigrinum* and Hamed et al. (2015) one egg (n = 14,379) with twin embryos of *Hemidactylium scutatum*. Dragoiu & Busnitza (1927) detected a dicephalic embryo in a clutch of *Bombina bombina*. Donaire (2016) found a Siamese a twin larvae of *S. algira* and Rivera et al. (1993) collected a larval *S. salamandra* with two heads near Barcelona, Spain, which metamorphosed successfully in captivity. Marvin & Hutchison (1997) found a *Plethodon kentucki* with two heads, Pereira & Rocha (2004) found one such larval *Chioglossa lusitanica* and Schmidt (1930) found one such tadpole of *R. arvalis*. Fernández-Álvarez et al. (2011) collected a dicephalic embryo of *Lissotriton boscai*, which soon died. Bei et al. (2011) discovered a dicephalic larval *Ichthyophis bannanicus*.

Tornier (1901) suggested that the duplication of heads and Siamese twins result if the vertebrae and the adjacent skin are ruptured in embryos He further suggested that only supernumerary vertebrae will develop if the adjacent skin does not rupture as well. He did not provide any experimental evidence for his hypothesis. Experimental splitting of the head in young tadpoles did not result in head duplications. Rather, the injury healed normally (Vulpian 1862).

3.2.2 Absence and reduction of skeletal elements

3.2.2.1 Ectromely. The term ectromely is not used consistently in the literature. Following Henle et al. (2017b), we define ectromely as the partial or complete absence of a limb from distal to proximal. The term thus includes apody, hemimely and amely but neither phocomely nor brachymely.

So far, ectromely in natural populations has only been reviewed by Ouellet (2000). Our database contains 666 cases from 129 species. Reported background rates reach up to 2.4% (Tab. 1). Most mass incidences of ectromely have been observed in North America but cases are also known from Europe and Asia. From North America at least 15 cases belonging to 11 species are known, in which at least 5% of the population were abnormal and at least 2.5% of the population and ten individuals were affected by ectromely (Tab. 5). For regions outside of North America there are ten cases from six species. There are other cases with high numbers of ectromelous individuals but either insufficient data were provided to include them in Table 5 or they were summed across several populations. Suggested causes were parasitism, trauma due to attacks from predators or conspecifics and chemicals for the North American cases and trauma, chemicals and radioactivity for the remaining cases.

The cause(s) of the North American cases are controversial. Most frequently, infection from the trematode *Ribeiroia ondatrae* has been assumed as the cause (Tab. 5). However, in experiments, such infections did not result in elevated frequencies of ectromely and ectromely was even absent in some experiments: *Ambystoma macrodactylum* (Johnson et al. 2006), *Anaxurus americanus* (Johnson & Hartson 2009), *A. boreas* (Johnson et al. 2001b), *Dryophytes versicolor* and *D. cinereus* (Johnson & Hartson 2009, Johnson et al. 2012), *Lithobates pipiens* and *L. sylvaticus* (Stopper et al. 2002, Schotthoefer et al. 2003). The only known exception is *Pseudacris regilla* (Johnson et al. 1999, Romansic et al. 2011). Thus, *R. ondatrae* is unlikely to be a cause of elevated rates of ectromely, except perhaps for the one case involving *P. regilla*. Notwithstanding, *R. ondatrae* may have contributed to other anomalies observed in the same populations – see section 3.1.7.1 for further discussion).

Parasites other than *R. ondatrae* have been suggested once for a North American case of elevated rates of ectromely (not listed in Table 5). Kupferberg et al. (2009) reported a significantly higher percentage of abnormal *Rana boylii* (ectromely and other anomalies combined) in 2006 that were carrying parasitic copepods *Lernaea cyprinacea* attached to their limbs compared to those individuals that were free of the parasite. However, this was not the case in 2008 and the cause was not tested experimentally.

Trauma as an alternative explanation was only tested experimentally for the two German populations of *Bufo bufo* listed in Table 5. These exeriments demonstrated respectively made it very likely that the leech *Erpobdella octoculata* was the culprit (Bohl 1987, Veith & Viertel 1993). For the German population of *Rana temporaria* in Table 5, observations in aquaria supported the hypothesis that attacks from sticklebacks (*Gasterosteus aculeatus*) were the cause (Malkmus 2008). In addition, for two North American cases with elevated rates of ectromely, *A. boreas* in Lake Aspen and *Lithobates cascadae* at Broken Top, that are not listed in Table 5 because insufficient data were published, in-situ and laboratory experiments identified trauma inflicted by *G. aculeatus* and dragonfly larvae (*Somatochlora albicincta*) as the cause (Bowerman et al. 2010). While the exclusion experiments in the field also removed the contact with mud and thus results cannot unequivocally be attributed to the exclusion of predators, laboratory experiments, in which *L. cascadae* tadpoles had access to mud, did not produce elevated rates of ectromely or ectrodactyly whereas nymphs of *S. albicincta* did.

Sessions (2009) and Ballangée & Sessions (2009) attributed all cases of ectromely in natural populations to such failed predation attacks. However, one must be

Table 5: Elevated rates of ectromely in natural populations of amphibians (≥ 5% of the population abnormal, ≥ 2.5% of the population with ectromely, ≥ 10 ectromelous individuals). *N*: sample size; only cases with *N* ≥ 50 included; % ectromely refers to the sample size. Cause: (e): the cause was supported by experimental studies, (c): correlational evidence; all other causes are assumptions.

Species	*N* (% abnormal)	% ectromely	Location	Cause	References
North American cases					
Cryptobranchus bishopi	96 (39.6%)	≈ 6%	Eleven Point River, Arkansas	Trauma (fishing and conspecifics)	Hiler et al. 2005
Ambystoma macrodactylum croceum *Pseudacris regilla*	11,732 (14.8%) 391 (54.2%)	≥2.8% 11.3%	Aptos Pond, California	*Ribeiroia ondatrae*[1] *Ribeiroia ondatrae* (e)	Sessions & Ruth 1990, Johnson et al. 2003, 2006
Ambystoma macrodactylum	183 (15.3%)	≥10.4%	Toolman, Montana	Trauma (conspecifics), *Ribeiroia ondatrae*[1]	Johnson et al. 2006
Ambystoma macrodactylum	403 (35%)	≥18.1%	Potholes, Oregon	Trauma (conspecifics)	Johnson et al. 2006
Taricha torosa	647 (41.3%)	≥5.7%	Frog Pond, California	Unknown	Johnson et al. 2001a
Taricha torosa	961 (15.4%)	≥7.5%	Hidden Pond, California	Unknown	Johnson et al. 2001a
Anaxyrus americanus	618 (59.5%)	≥5.8%	Duck Pond, Minnesota	Unknown (*Ribeiroia ondatrae* assumed[1])	Johnson & Hartson 2009
Dryophytes cinereus	100 (17%)	12%	Dahomey National Wildlife Refuge (DHM03), Mississippi	Unknown	Reeves et al. 2013
Dryophytes chrysoscelis or *D. versicolor*	50 (24%)	24%	Oil pit, D'Arbonne National Wildlife Refuge (DRB03), Louisiana	Contamination by petrochemicals	Reeves et al. 2013
Lithobates clamitans *Lithobates septentrionalis*	245 (33.5%) 869 (67.5%)	6.1% 4.3%	CWB site, Minnesota	Competing hypotheses[2]: *Ribeiroia ondatrae*, retinoids, micronutrient deficiency and pollution	Vandenlangenberg et al. 2003, Hoppe 2005
Lithobates pipiens	1394 (20.3%)	8.8%	ROI site, Minnesota	Unknown; *Ribeiroia ondatrae* was not found but estrogenic substances and pesticides	Helgen et al. 2000, Garber et al. 2001, Vandenlangenberg et al. 2003
Lithobates pipiens	2493 (7.4%)	≈ 5%	NEY pond, Minnesota	Competing hypotheses: *Ribeiroia ondatrae*[1], chemical pollution	Canfield et al. 2000, Vandenlangenberg et al. 2003, Lannoo 2008
Rana luteiventris	280 (30.7%)	3.2%	Isobel Lake, British Columbia, Canada	Unknown (*Ribeiroia ondatrae* assumed[1])	Roberts & Dickinson 2012

Table 5: Continuation.

Species	*N* (% abnormal)	% ectromely	Location	Cause	References
Other regions					
Salamandra salamandra terrestris	456 (13.4%)	9%	Hummingenbach, Harburg, Germany	Trauma [conspecifics, dragonfly larvae (*Cordulegaster boltoni*)]	Giesenberg 1991
Salamandra salamandra terrestris	768 (11.8%)	11.6%	Künningbach, Niederbergisches Land, Germany	Trauma (conspecifics, *Neomys fodiens*)	Thiesmeier-Hornberg 1988, Thiesmeier 1990, 2004
Bufo bufo	≈ 500 (42.7%)	Most[3]	Fish pond, Aufseß, Germany	Trauma [leeches (*Erpobdella octoculata*)] (e)	Bohl 1997
Bufo bufo	2480 (14.8%)	≈ 10%[4]	Fish pond, Remagen-Oedingen, Germany	Trauma [leeches (*Erpobdella octoculata*)] (e)	Veith & Viertel 1993
Bufotes viridis	675 (7.4%)[5]	3.7%[5]	Roßwag, Germany	Radioactivity (e)	Henle et al. 2017a
Hyla arborea	87 (18.4%)	17.4%	Schmielteich near Wurzen, Germany	Trauma or chemical pollution	Grosse & Bauch 1988
Rana temporaria	430 (99.1%)	18%	Spring fed pond, Lehngrund, Spessart, Germany	Trauma (*Gasterosteus aculeatus*)	Malkmus 2008
Rana pirica	1095 (≥ 42%)	42%	Point A, South Sakhalin Island, Russia	Sewage effluent of paper and pulp mill (c)	Mizgireuv et al. 1984
Rana pirica	1614 (≥ 31%)	31%	Point B, South Sakhalin Island, Russia	Pollution from municipal sewage (c)	Mizgireuv et al. 1984
Rana pirica	3651 (≥ 39%)	39%	Point C, South Sakhalin Island, Russia	Pollution from municipal sewage (c)	Mizgireuv et al. 1984

[1] Experimental infections with *Ribeiroia ondatrae* do not result in elevated frequencies of ectromely, except for *Pseudacris regilla* (see section 3.1.7.1).
[2] For competing hypotheses see Gardiner & Hoppe (1999), Stopper et al. (2002), Lannoo (2008), Helgen (2012) and section 3.1.7.
[3] No figure provided but most individuals from a separate experiment with caged individuals showed ectromely.
[4] Calculated based on a subsample for which numbers of abnormal individuals were provided for different types of anomalies.
[5] Data for 1983, similar in 1980 but no exact counts available, lower in 1982 and 1984

careful when extrapolating from staged predation experiments under laboratory conditions to the field because whether predators amputate (parts of) legs or not depends on the predator and prey species and details of the experimental set-up (Henle et al. 2017a). Therefore, the hypothesis needs testing under field condition to demonstrate that it is the cause of an observed mass occurrence of ectromely (see section 3.1.5.3 for further discussion).

Meteyer et al. (2000a), Ouellet (2000) and Lannoo (2008) suggested that ectromely caused by predators can be differentiated from malformation during

limb development by disruption of the pigment pattern or the appearance of a regenerative spike but no study has tested this hypothesis explicitly. However, in *Pelobates fuscus* and *L. sylvaticus* the wound healed without the development of a spike and rapidly returned to a normal colour pattern after amputation (Kammerer 1905, Reeves et al. 2010). Similar observations were made in amputation studies by Lannoo (unpublished, fide Levey et al. 2003). On the contrary, a spike was observed in several hemimelous individuals of *Bufotes viridis* from the hotspot at Roßwag in Germany that developed in a predator-free pond. The spikes must therefore have originated from abnormal development, most likely due to radioactive contamination (Henle et al. 2017a). Likewise, legs may atrophy and the pigment pattern may be disrupted in diseased individuals, as reported by Wisniewski (1984) for *Cynops ensicauda popei* and *Paramesotriton chinensis* that were infected by *Saprolegnia*. Further, correlational evidence exists that infection from the pox virus may lead to ectromely with a disrupted colour pattern due to necrosis (Cunningham et al. 1993). Thus, ectromely can only be attributed with certainty to trauma if the wound is fresh.

Besides conspecifics and predators, trauma may be caused by machinery. Storer (1925) attributed a case to lawn mowing, in which approximately 50% of the sampled *A. boreas* lacked (parts of) limbs. In Poland Classen et al. (1996) found that large numbers of anurans were injured or killed during grassland mowing with the impact depending on the type of mowing machines used; however, they did not provide figures about the number of ectromelous anurans surviving. Injuries from agricultural machinery was also the likely cause for a case of mass occurrence of ectromely in waterfrogs (*Pelophylax* synkl. *esculentus*) living in an agricultural landscape dominated by crop fields in Germany, as in many of the individuals their wounds had only partially healed (Schmidt & Hachtel 2011).

Amputated limbs may regenerate in amphibians, with urodeles retaining this capacity more widely and for later stages in ontogeny than anurans (Sánchez Alvarado & Tsonis 2006)). In anurans it is a complex phenomenon (Bryant et al. 1987, Gardiner & Bryant 1996) that depends, among other factors, on the level of amputation, severity and the larval stage (Muneoka et al. 1986, Girvan et al. 2002, Ballengée & Sessions 2009). In early larval stages ectromely requires the removal of the apical ectodermal ridge of the amputated limb or cell death in the apical 200 mm of the mesenchyme (reviewed by Nye et al. 2003). Only structures distal to the amputation plane are formed. Late stage tadpoles have reduced ability and adults lose the ability of limb regeneration in most anuran species (Thornton 1968, Scadding 1981, Girvan et al. 2002) but some species are still able to produce cones or rods (reviewed by Kurabuchi & Inoue 1982).

Pollution by chemicals has also been suggested as a cause for the mass occurence of ectromely but is debated for North American hotspots. Whereas tadpoles raised in water samples from the CWB site in Minnesota developed elevated rates of anomalies, those raised in unpolluted controls did not (Volpe & Rosenbaum 2000, Bridges et al. 2004). However, ectromely was not among the types of anomalies reported at an elevated rate. Notwithstanding, there is evidence of chemical contamination from agricultural run-off as cause for elevated rates of ectromely in some regions of Minnesota, Alaska and Canada (Ouellet et al. 1997, Burkhart et al. 1998, 2000, Fort et al. 1999a, Bridges et al. 2004, Lannoo 2008, Reeves & Trust 2008). For example, Fort et al. (1999b) demonstrated for a Minnesota case that only some fractions of the water and sediment samples were able to induce anomalies and these contained a mixture of herbicides and pesticides, of which maneb is capable of causing ectromely (Zavanella et al. 1984, Fort et al. 1999b).

In addition to maneb, various other chemicals are capable of inducing ectromely at environmentally relevant doses, including some widely used pesticides, such as the mosquito-control agent s-methoprene (commercially known as Altosid) and malaoxon (a metabolite of the insecticide malathion) (Tab. 3). The effects of retinoids differ among species, are limited to a narrow window of development (Degitz et al. 2000) and might not even have an effect with continuous flow exposure (Degitz et al. 2003a for *Xenopus laevis*). Only those limb elements are suppressed that start differentiation when retinoids are administered (Niazi 1996). Thus, rather specific conditions would be required for them to contribute to mass occurences of ectromely in natural populations of amphibians.

Outside of North America four cases of mass occurrence of ectromely were associated with polluted sites (Tab. 5). The globally most severe cases were reported by Mizgireuv et al. (1984) for three points on southern Sakhalin Island, Russia. They discovered almost 2000 *R. pirica* (as *R. chensinensis*) (31–42% of the samples) with ectromely in ponds contaminated with municipal and paper and pulp mill sewage. The frequency of ectromely correlated with the oxygen demand of water samples from the breeding sites. For two respectively one Ukrainian district(s) mass occurrence of ectromely of *P. ridibundus* (535 individuals; 10% of the samples; several populations combined) and *Bombina bombina* (280 individuals; 10% of the samples; several populations combined) was reported by Flax & Borkin (1997, 2004). The frequency was also strongly correlated with oxygen demand and was significantly higher in the districts heavily polluted by heavy metals and organics compared to the area with lower contamination (all $\chi^2 > 4.5$, $\alpha < 0.05$). In Ekaterinburg, Russia, ectromely was significantly more common in *R. arvalis* from contaminated ponds compared to control sites (Vershinin 2002) ($\chi^2 = 4.02$, $\alpha < 0.05$), although the percentage of individuals affected was not high. In Argentina, 9% ($n = 124$) of the *Rhinella fernandezae* and 17% ($n = 785$) of the juvenile *Leptodactylus latrans* collected at ponds in cultivated areas that were contaminated by endosulfan,

cypermethrin, and chlorpyrifos, were ectrodactylous (Agostini et al. 2013). In the laboratory, endosulfan has been shown to cause ectromely at environmentally relevant concentrations (Rohr et al. 2003).

One case of elevated levels of ectromely, a population of *Bufotes viridis* in a quarry at Roßwag, Germany (Tab. 5), was associated and most likely due to radioactive pollution (Henle et al. 2017a). Ectromely frequently appears in anurans that develop from irradiated sperm, eggs and/or embryos (*Bufo bufo, Rana temporaria*: Rostand 1955a, 1958a, Oerter 1985; *P. nigromaculatus*: Kawamura & Nishioka 1978; *R. japonica*: Nishioka 1978). In *P. nigromaculatus* and *R. japonica* ectromely still occurred in the second and third generation, respectively. Inheritance of ectromely has further been shown in laboratory strains of *Ambystoma mexicanum* (Humphrey 1973), *Pleurodeles waltl* (Lauthier 1971, Dournon 1983) and *X. laevis* (Droin & Fischberg 1980). In the case of *P. waltl,* temperature acted epigenetically with the highest penetration when larvae were raised under high temperature before the development of limb buds (Dournon 1983). Heritable ectromely is also known in humans (Cohn & Bright 1999).

Ankley et al. (1998) observed high rates of ectromely in *Lithobates pipiens* tadpoles that were exposed to UV-B throughout hind-limb development. Pahkala et al. (2001) also found ectromely when embryos of *R. temporaria* were exposed to increased UV-B irradiation but the frequency was not different to that occurring under natural UV-B irradiation and Smith et al. (2000) did not report this effect in *L. blairi*.

Other factors exist that may cause ectromely but so far have not been suggested for mass occurrences of ectromely in natural populations. Ectromely appeared in metamorphs of experimental hybrids within the *Pelophylax esculentus* complex (Berger 1971, Berger & Uzzell 1977, Günther 1982, 1990, 1996b), in crosses of *Incilius bocourti* males with females of *Anaxyrus speciosus* and *A. cognatus*, in a cross between a male *A. nelsoni* with a female *A. punctatus* (9 of 11 metamophs) (Blair 1972) and among *Triturus* sensu lato species (Hamburger 1935), with only the latter case probably being significant (data however are insufficient for conclusions). None of the 54 hybridization experiments involving European bufonid species in our database reported any offspring with ectromely.

Rearing conditions may also cause ectromely (Meijer 1962, Dournon 1983). Christmann (1995) reported it for tadpoles that were fed on food tablets. A diet consisting only of enchytraea had the same effect in *Ambystoma mexicanum* and *Pleurodeles waltl* but not in *Triturus* (sensu lato) species (Reinhardt 1939, Vogt 1939). Witschi (1952) mentioned atrophied legs in *R. temporaria* developing from overripe eggs but does not provide any details.

3.2.2.2. Phocomely. Following Henle et al. (2017b) we define phocomely as the absence of the proximal long bones of limbs whereby the distal part of the limb is directly attached to the shoulder, pelvic girdle, elbow, or knee. So far there have not been any reviews of phocomely and it is rare in natural populations of amphibians. Our database contains 15 cases from at least ten species. The only mass incidence for a natural population was discovered by Kurtyak (2010), who found 31 (n = 89) individuals of *Pelophylax esculentus* with phocomely in the Transcarpathian lowlands of the Ukraine. He assumed hybridization as the cause but did not test his hypothesis. Except for one individual in each of the crosses of *Triturus cristatus* × *Lissotriton helveticus* and *T. cristatus* × *L. vulgaris* (Hamburger 1935), phocomely was never recorded from artificial hybridization experiments, including among *Pelophylax* species.

At least five phocomelous individuals were observed in a population of *Bufotes viridis* with the cause very likely being radioactive contamination (Henle et al. 2017a). Phocomelous individuals have been repeatedly observed after experimental irradiation of tadpoles, eggs or sperm (Rostand 1958*a*, Kawamura & Nishioka 1978, Nishioka 1978). The anomaly was still present in the second generation of *P. nigromaculatus* and the third generation of *Rana japonica* (Kawamura & Nishioka 1978, Nishioka 1978). A recessive gene *ph* causes phocomely in *Ambystoma mexicanum* (Humphrey 1975, Malacinski 1978).

In natural populations, phocomely has further been reported for four *Lithobates sphenocephalus* and one *L. sylvaticus* from three and one sites, respectively (Reeves et al. 2013), and two and one *L. pipiens* at a site in Minnesota (Meteyer 2000, Meteyer et al. 2000a,b) and Wisconsin (Lannoo (2008), respectively. Phocomely also occurred in *L. pipiens* in Douglas County, Minnesota, but the number of individuals remains unclear (Helgen 2012). It was further observed in one *A. tigrinum* (Williams et al. 2008), a larval *T. marmoratus* from Spain (Diego-Rasilla et al. 2007a), two albino *Bufo bufo* tadpoles in the Czech Republic (Wenig (1913), a metamorph of *Epidalea calamita* from Spain (Garin et al. 2009) and a *Hyla meridionalis* from the Canary Islands (Luis & Baez 1987). In addition, Peltzer et al. (2011) observed three phocomelous individuals in Argentina but did not provide the identity of the species.

The most extreme forms of anomaly P may also involve phocomely (Surlève-Bazeille et al. 1969b) but no concrete data for natural populations were given. Picariello et al. (2006) published a figure of *R. dalmatina,* which could possibly be phocomely but it is not certain. Bacon et al. (2006a) reported ≥ 26 (n = 13,856) metamorphs of *Rhinella marina* with "phocomely" from across Bermuda but they were not phocomelous in our definition because their definition of phocomely as "complete but malformed limbs" deviates from the general use of the term phocomely.

A few cases of mass incidences occurred in captivity. These were *P. ridibundus* that were fed on fish food as tadpoles but the causative mechanism remains unknown (Schchupak, pers. comm.). Another mass incidence occurred in the offspring of neoteneous *L. vulgar-*

is, with a few phocomelous individuals also occurring in the offspring of normal parents (Hartwig & Rotmann 1940), All offspring that developed from a single F_3-generation clutch of *Discoglossus pictus* were phocomelous, whereas all individuals from the remaining clutches were normal (Glaw 1987). Glaw (1987) assumed nutritional deficiencies of the parents to be the cause. Vogt (1939) showed that feeding on a pure diet of enchytraea caused phocomely in *Pleurodeles waltl* but not in *Triturus* (sensu lato) spp.

Thymus oil (Wink & Wurmbach 1967) and colchicine (Tschumi 1954) are known to cause phocomely in *Xenopus laevis*. Retinoids and vitamin A also caused phocomely when given for the short sensitive period when the thigh and shank start to differentiate but foot differentiation has not yet started (Liotti & Bruschelli 1969, Niazi 1996). Fort & McLaughlin (2003) reported that a diesel fraction of petroleum hydrocarbons induced phocomely in *Lithobates sphenocephalus* but no details were provided.

3.2.2.3. Ectrodactyly. The term ectrodactyly is not used consistently in the literature (Henle et al. 2017b). We follow the definition of these authors and include any complete (oligodactyly; Fig. 14) or partial absence (brachydactyly; Fig. 15) of one or more digits in the term ectrodactyly. Some salamander species show a high variability in foot and hand morphology, e.g., *Salamandrella keyserlingii* (Fig. 16) and *S. tridactyla* (Basarukin & Borkin 1984, Borkin 1999, Vershinin 2002, Zmeeva 2014), *Ambystoma maculatum* (Worthington 1974), *Batrachuperus pinchonii* (Chang & Boring 1935), *Lissotriton vulgaris* (Roberts & Verrel 1984), *Taricha granulosa* (Shubin et al. 1995), *Triturus carnifex* (Paces-Zaffaroni et al. 1992, 1996) and *T. marmoratus* (Caetano 1991). Brachydactyly is common in these species and even more than 50% of the individuals may show deviations from the normal number of digits, for example in *S. tridactyla* on Sakhalin Island, Russia (Basarukin 1984). In *S. keyserlingii* the percentage of individuals whose digit morphology deviates from the normal pattern may be small in some regions but high in others (Borkin 1999). As it is difficult to decide which cases are normal or abnormal, we only included the loss of phalanges or complete digits in urodeles if the individuals observed were regarded as abnormal in the assessed publication.

Fig. 14: Oligodactyly in a juvenile *Pelophylax ridibundus*, Kosolapowo, Oka, Russia, 30.8.2011. Photo: K. Henle.

Fig. 15: Brachydactyly in *Rana arvalis*, Tschekalin, Russia, 29.8.2011. Photo: K. Henle.

Fig. 16: Subadult *Salamandrella keyserlingii,* a species with a high variability of the number of phalanges: oligodactyly (right front limb), brachydactyly (left front limb) and shortened tail; depending on location and author the digital variability may be regarded as part of the normal variation or as abnormal. Note that four toes are the normal phenotype; Ekaterinburg, Russia, 29.7.2009. Photo: V. Vershinin.

So far, only Ouellet (2000) has reviewed the occurrence of ectrodactyly in natural populations. Our database contains 697 cases from 145 extant species. Wang et al. (2016) also observed abnormal brachydactyly in the fossil salamander *Chunerpeton tianyiensis.* Reported background rates reach up to 0.68% (Tab. 1). Elevated rates of ectrodactyly were recorded across several regions of North America (Bonin et al. 1997, Ouellet et al. 1997, Burkhart et al. 2000, Hoppe 2000, Sower et al. 2000, Johnson et al. 2003, Guderyahn 2006, Reeves et al. 2008, 2010, Bowerman et al. 2010) and at least eight cases belonging to six or seven species are known, in which at least 5% of the population were abnormal and at least 2.5% of the population and ten individuals were affected by ectrodactyly (Tab. 6). For regions outside North America the figures are 12 cases from ten species. Trauma inflicted by conspecifics and small invertebrates or parasites were suggested as causes for the North American cases and trauma inflicted by small invertebrates, chemical pollution, radioactivity, and unknown for the remaining cases but these hypotheses were not tested for any of these cases.

For one case not listed in Table 6, elevated rates of ectrodactyly in adult *Cryptobranchus alleganiensis*

Table 6: Elevated rates of ectrodactyly in amphibian populations (≥ 5% of the population abnormal, ≥ 2.5% of the population with ectrodactyly, ≥ 10 ectrodactylous individuals). *N:* sample size; only cases with *N* ≥ 50 included; % ectrodactyly refers to the sample size.

Species	*N* (% abnormal)	% ectrodactyly	Location	Cause	Reference
North American cases					
Ambystoma macrodactylum	403 (35%)	≥8.9%	Potholes, Oregon	Trauma (conspecifics)	Johnson et al. 2006
Ambystoma tigrinum	1926 (8%)	2.7%	Tippecanoe County, Indiana	Unknown	Williams et al. 2008
Taricha torosa	961 (15.4%)	≥3.9%	Hidden Pond, California	Unknown	Johnson et al. 2001a
Taricha torosa	647 (41.3%)	≥11.4%	Frog Pond, California	Unknown	Johnson et al. 2001a
Anaxyrus americanus	618 (59.5%)	≥3.2%	Duck Pond, Minnesota	*Ribeiroia ondatrae*[1]	Johnson & Hartson 2009
Anaxyrus species	170 (14.7%)	10.0%	Bald Knob National Wildlife Refuge (BLD-09), Arkansas, USA	Unknown	Reeves et al. 2013
Pseudacris streckeri	437 (11.4%)	≈ 11.4%	Barton Creek Habitat Preserve, Texas	Trauma (terrestrial invertebrates)	Gridi-Papp & Gridi-Papp 2005
Lithobates pipiens	1394 (20.3%)	7.7%	ROI site, Minnesota	Unknown; *Ribeiroia ondatrae* was not found but estrogenic substances and pesticides	Helgen et al. 2000, Garber et al. 2001, Vandenlangenberg et al. 2003
Other regions					
Bufo bufo	183 (30.1%)	25.7%	Kuzno village, Svertlowsk District, Russia	Unknown	Vershinin 2010
Bufotes viridis	294 (7.8%)	4.1%	Severnyi Plyazh beach, Magnitogorsk, Russia	Unknown	Vershinin 2010
Rhinella jimi	159 (44.6%)	>23.3%	Fernando de Noronha	Unknown	Toledo & Ribeiro 2009
Cyclorana australis *Cyclorana longipes* *Litoria rubella* *Platyplectrum ornatum*	914 (7%) 522 (7.5%) 479 (8.1%) 467 (13.5%)	5.9% 4.8% 4% 5.6%	Jabiru, Australia	Radioactivity, pesticides	Tyler 1989
Dendrobates auratus	231 (14.7%)	13.4%	Isla Tobago, Panama	Trauma (ants, other small invertebrates)	Gray et al. 2002
Dendrobates auratus	274 (10.4%)	9.9%	Cerro Ancon, Panama	Trauma (ants, other small invertebrates)	Gray et al. 2002
Dendrobates auratus	87 (19.5%)	14.9%	Cerro Bruja, Panama	Trauma (ants, other small invertebrates)	Gray et al. 2002
Pelophylax esculentus *Pelophylax ridibundus*	212 (62.3%) 235 (75.9%)	40.6% 65.5%	Bugornia, Russia	Unknown	Borkin et al. 2012, Bezman-Moseyko et al. 2014, pers. comm.

[1] Inconsistent with results from experimental infections with *Ribeiroia ondatrae* (see text).

(Miller & Miller 2005), the hypothesis of trauma as the cause is supported by observations in captivity. Captive *C. alleganiensis* do bite off the limbs and digits of conspecifics during the breeding time. Similar observations were made for larval *A. talpoideum* in laboratory experiments (Semlitsch & Reichling 1989). Cannibalism caused significantly elevated rates of lost digits (or feet – not specified), which increased with density.

Agricultural machinery has been suggested as another source of trauma. Schmidt & Hachtel (2011) attributed a case of mass ectrodactyly in waterfrogs (*Pelophylax* synkl. *esculentus*) in Germany to it. No tests were made to support the hypothesis.

For one case listed in Table 6, *Anaxyrus americanus*, infection with cysts of the trematode *Ribeiroia ondatrae* has been suggested as cause. However, ectrodactyly was absent or occurred at low, statistically insignificant numbers in most amphibian species that were experimentally infected with *R. ondatrae* (Johnson et al. 1999, 2001b, Stopper et al. 2002, Schotthoefer et al. 2003, Johnson & Hartson 2009). The only exception was *Pseudacris regilla* in the study of Romansic et al. (2011) in which ectrodactyly was slightly (5%) elevated. However, in another study of the same species, it was absent in most treatments and rare in the treatment with the highest number of cercariae (Johnson et al. 1999). Experiments with the trematode *Alaria mustelae* did not cause any limb anomaly (Johnson et al. 1999). In contrast, experimental infections of limb bud stage tadpoles (Gosner stage 27 and 28) of the Sri Lankan rhacophorid frog *Polypedates crucifer* with monostome-type cercariae (*Acanthostomum burminis* according to Jayawardena et al. 2013) caused significantly elevated levels of ectrodactyly (Rajakaruna et al. 2008). Limb anomalies did not occur when pre-limb bud stage tadpoles (Gosner stage 25 and 26) were exposed (Jayawardena et al. 2010). Clearly, more systematic studies across larval development with different amphibian and trematode species are needed before the potential of trematodes to induce high levels of ectrodactyly in natural populations can be understood.

Another parasite, chigger mites of the genus *Hannemania*, can cause ectrodactyly, if infestation of feet is heavy. Winter et al. (1986) and Brown et al. (2006) observed this effect in wild *Desmognathus brimleyorum* and *Plethodon metcalfi*, respectively.

For the four cases listed in Table 6 from retention ponds at the Jabiru Uranium mine in Australia, pesticides and/or radioactivity have been suggested as the cause. Ectrodactyly was observed in ten additional species from the same area (Tyler 1989). The extent to which the biocides or radioactivity were responsible could not be established. Ectrodactyly developed at low frequency in *Bufo bufo* and *Rana temporaria* that were irradiated as hatchlings (Rostand 1955a, 1958a) – for chemicals, see the next paragraph. At another uranium mine, the Olympic Dam in South Australia, Read & Tyler (1990, 1994) collected 19 *Neobatrachus pictus* (as *N. centralis*) with ectrodactyly at sites with very low radionuclide concentrations. The malformation rate did not differ significantly from areas outside the mine but the radioactivity level at one control site (and its frequency of ectrodactyly) was higher than for the mine sites (Read & Tyler 1990). Radioactivity was most likely to be the cause of several individuals of *Bufotes viridis* exhibiting ectrodactyly in a quarry at Roßwag in Germany (Henle et al. 2017a).

While not suggested for any other case listed in Table 6, evidence exists for chemical pollution as the cause for elevated rates of ectrodactyly from studies in Russia and Tunesia. Ectrodactyly in *Pelophylax ridibundus* and *Bombina bombina* was significantly more common (all $\chi^2 > 56$, $\alpha < 0.001$) in two and one Ukrainian area(s), respectively, strongly polluted by heavy metals and organics compared to an area with lower contamination (Flax & Borkin 1997, 2004). In Sakhalin (Russia), 37.5% of immature *R. amurensis* showed ectrodactyly (together with syndactyly and clinodactyly; sample size and number affected by ectrodactyly not given) in a habitat polluted by a paper and pulp mill but none in other populations (Levinskaya & Barinova 1978). In Ekaterinburg, Russia, ectrodactyly was significantly more common in *R. arvalis* from contaminated ponds than in control sites ($\chi^2 = 8.3$ $\alpha < 0.01$) (Vershinin 2002). In Indian rice paddies that were heavily contaminated by pesticides 6% (n = 259) of the collected *Feyervarja limnocharis* were ectrodactylous (Patel et al. 2008). In Argentina, 12% (n = 124) of the *Rhinella fernandezae* and 11% (n = 785) of the juvenile *Leptodactylus latrans* collected at ponds in cultivated areas that were contaminated by endosulfan, cypermethrin, and chlorpyrifos, were ectrodactylous (Agostini et al. 2013). The frequency of all anomalies was significantly higher than for individuals collected at control ponds without detectable pollution. Finally, ectrodactyly was one of the most common anomalies (exact figures not clear because of partial double counting) in *P. saharicus* metamorphs collected at the Lemna Dam in Tunisia, which is contaminated by agricultural run-off, whereas indivduals from non-agricultural areas did not exhibit any anomaly (Hassine et al. 2011).

Several chemicals are known to cause ectrodactyly in developing limbs: the fungicide maneb at environmentally relevant concentrations (Fort 1999b), the antifouling agent tributyltin oxide but only at concentrations that cause high mortality (Scadding 1990), retinoids (Scadding & Maden 1986a,b), citral (an inhibitor of retinoic acid synthesis) when treatment started at late neurulation (Lee & Elinson 2008), thymus oil and other seed oils (Wink & Wurmbach 1967), estradiol (Takahashi 1957, 1958, Collenot 1965) and trypoflavin (in *R. temporaria* but not in *P. esculentus*: Rostand 1950c).

Besides the factors discussed above, several others have experimentally been shown to cause ectrodactyly. A significantly elevated frequency of ectrodactyly has been observed in *R. temporaria* tadpoles treated with the mucus from the skin of fish from ponds in which anomaly P occurred (Surlève-Bazeille et al. 1969a).

The causative factor is still not clear but is assumed to be a virus (Dubois 2014, 2017). Correlational evidence exists that infection by poxvirus, *Aeromonas hydrophila* and *Batrachochytrium dendrobatidis* may cause oligodactyly due to necrosis in various species (Hine et al. 1975, Frye 1985, Cunningham et al. 1993, Brodman & Briggler 2008). Approximately 4% of 377 metamorphosed individuals of crosses within *P.* synkl. *esculentus* showed ectrodactyly (Berger 1971) and Hamburger (1935) obtained two such individuals in crosses between *Triturus* species.

Ankley et al. (1998, 2000, 2002) observed high rates of ectrodactyly in *Lithobates pipiens* tadpoles exposed to UV-B (full sunlight) throughout hind-limb development but exposure conditions were not natural. Under more realistic exposure conditions, Pahkala et al. (2001) obtained significantly elevated rates in *R. temporaria* metamorphs that were exposed to enhanced UV-B as embryos.

Inheritance of ectrodactyly has been demonstrated in *Ambystoma mexicanum* (Humphrey 1966, 1967b, Martin & Signoret 1968, Malacinski 1978), *Pleurodeles waltl* (Lauthier 1971, Dournon 1983), *Xenopus laevis* (Droin & Fischberg 1980) and *R. temporaria* (Dubois 1977). In the case of *P. waltl* temperature acted epigenetically with the highest penetration when larvae were raised under high temperature before the development of the limb buds (Dournon 1983). Heritable ectrodactyly is also known in humans (Cohn & Bright 1999).

3.2.2.4. Tail completely or partially missing. Tail autotomy occurs naturally in various plethodontid salamanders (Wake & Dresner 1967). Such cases are not included in this review. Our database contains 140 cases of partially (Fig. 16) or completely missing tails from 56 species.

Tail loss has rarely been reported for juvenile, subadult or adult urodeles. Our database contains 18 cases, involving ten species. In most cases only a few individuals were found and the cause remained unclear. The largest number reported was seven out of eight abnormal (n = 681) *Plethodon* individuals [as *P. glutinosus* (Highton 1956), but fide Hayslett et al. (1998) *P. grobmani*], although presumably more individuals were affected in a population of *Dicamptodon tenebrosus* (Munshaw et al. 2014). The cause in the former species remains unknown but was conspecifics and steelhead trouts (*Oncorhynchus mykiss*) for the latter species. Reported causes for partially or completely missing tails in adult urodeles were injuries from cars (for *Salamandra salamandra*: Feldmann & Klewen 1981, Klewen 1988), a bird attack (*S. atra*: Klewen 1986) and injuries from a spate (for *Triturus cristatus*: Böhm 2013).

In tadpoles frequencies are often high. For example, Bleakney (1958) reported that in a sample of hundreds of tadpoles of *Lithobates sylvaticus* all lacked parts of the tail. He assumed cannibalism under high density to have been the cause of this mass occurrence. In the same species and in *L. catesbeianus* Blair & Wassersug (2000) found that in samples of 98–100 tadpoles from six different ponds 37–87% of the tadpoles had shortened tails. They assumed predators to be the cause. In a population of *L. sylvaticus* sampled at the Great Bay National Wildlife Refuge 11.1% (n = 90) of the tadpoles lacked parts of their tails (Reeves et al. 2013).

Rates of tadpoles with shortened tails may differ among habitat types. For example, in *Acris crepitans* 38–51% of the tadpoles had damaged tails, with the frequency being significantly lower in lake habitats compared to creek and pond habitats (Caldwell 1982).

Most cases of mass occurrences of shortened or missing tails outside of North America were also attributed to either cannibalism or predation attempts. Bruch (1864) collected more than 100 tadpoles of *Bufotes viridis* with partially missing tails. He attributed the damage to gnawing by other tadpoles. In a sample of 430 tadpoles of *Rana temporaria*, 99% lacked parts of their tails; sticklebacks (*Gasterosteus aculeatus*) were assumed to be the cause (Malkmus 2008). Kordges et al. (2013) discovered tail damage in 93% of 83 *Pelobates syriacus* tadpoles examined and regarded predation attempts by fish and larvae of the dytiscid beetle *Cybister tripunctatus lateralis* to have been the cause. For one case, a population of *T. cristatus*, in which 9.7% (n = 179) of the tadpoles had partially or completely missing tails, cannibalism and attempted predation were suggested as the causes (Kupfer & von Bülow 2011).

None of the studies cited above tested their hypotheses experimentally or statistically but correlational evidence for predators as culprits of high rates of tail loss was provided by Rödel (1998) for two African species. Of 353 and 107 tadpoles of *Kassina* sp. and *Phrynomantis microps*, respectively, from two large temporary ponds in the Ivory Coast 85.8% and 78.8%, respectively, showed tail injuries. The rate of tail injuries correlated significantly with the number of Anisoptera larvae and giant water bugs (*Bellostoma*) in the samples taken from different parts of the ponds.

Only one study, Bowerman et al. (2010), experimentally tested the hypothesis of predator attacks being the cause of elevated rates of partially lost tails in tadpoles. At Lake Aspen, central Oregon, *Anaxyrus boreas* tadpoles typically lacked small pieces of their tails and at Broken Top in central Oregon less than 20% of the *L. cascadae* tadpoles had incomplete tails. The exclusion of predators effectively eliminated tail injuries in *Anaxyrus boreas* and laboratory experiments showed that sticklebacks (*Gasterosteus aculeatus*) inflict tail injuries at significantly elevated rates.

In another laboratory study, the mosquito fish (*Gambusia holbrooki*) injured tails of *L. capito* at a mean rate of 50% but rarely in *L. sphenocephalus* (Gregoire & Gunzburger 2008). Laboratory tests further showed that nymphs of various Odonata species frequently cause tail injuries or loss in tadpoles of all tested species (reviewed by Henle et al. 2017a). Salamanders are also known to inflict tail injuries in tadpoles (Parichy & Kaplan 1992) and staged interspecific interactions of

Ambystoma talpoideum and *A. mavortium nebulosum* also resulted in high rates of tail injuries or partial tail loss (Semlitsch & Reichling 1989, Harvey 2003). Likewise, fighting among courting male urodeles may lead to tail loss (*Eurycea cirrigera*: Halliday & Tejedo 1995; *Ommatotriton ophryticus*: Raxworthy 1989).

Radioactive contamination following a nuclear accident caused tail agenesia in *Salamandrella keyserlingii* embryos and larvae (Kuranova & Saveliev 1997, 1999). Tail loss after irradiation has been demonstrated experimentally for *A. mexicanum* and *Salamandra salamandra* (Luther 1939).

Besides the causes suggested for natural populations, feeding paraquat to tadpoles of *L. berlandieri* resulted in high rates of individuals with shortened tails (Bauer Dial & Dial 1995). Beetschen & Jaylet (1965) discovered a recessive mutant for short tails in *Pleurodeles waltl.*

3.2.2.5. Brachycephaly, microcephaly and pointed snouts. Microcephaly and other reductions of the head are extremely common anomalies in amphibian embryos resulting from experimental hybridization (Delarue 1974, 1982), chemical treatment (e.g., Brachet et al. 1964, Pérez-Coll et al. 1986) and irradiation (e.g., Kawamura & Nishioka 1978, Nishioka 1978) and may have a genetic basis (e.g. Beetschen & Jaylet 1965). However, they are rarely observed in natural populations. Several toadlets of *Bufotes viridis* from a quarry in Roßwag, Germany, exhibited both pointed snouts and brachycephaly, presumably due to radioactive contamination (Henle et al. 2017a). In Argentina, Agostini et al. (2013) observed microcephaly in 10 (n = 329) *Rhinella fernandezae* and in 6 (n = 2116) *Leptodactylus latrans.* Brachycephaly without pointed snouts was also discovered in ten out of 781 juvenile *Rana arvalis* from Ekaterinburg (Vershinin & Neustroeva 2011, Vershinin unpubl.), in one adult female *Rhinella jimi* out of 159 individuals sampled (Toledo & Ribeiro 2009) and in a recently metamorphosed *Bufo bufo* from Sagra, near Ekaterinburg (Vershinin, unpubl.), as well as in three metamorphs of *Lithobates pipiens* (Meteyer 2000, Reeves et al. 2013).

For tadpoles, most observations of microcephaly were made at heavily polluted sites in Sakhalin, Russia [*B. gargarizans, Rana amurensis and R. pirica* (as *R. chensinensis*): Mizgireuv et al. 1984] and the Ukraine [18 (4.5%) *Bombina bombina,* 9 (1.8%) *Bufotes viridis* and 34 (6.8%) *Pelophylax ridibundus*: Flax & Borkin 2004]. Additionally, Reeves et al. (2008, 2013) found four microcephalic individuals of *Lithobates sylvaticus* when sampling 38 breedings sites in the Kenai Wildlife Refuge, Alaska. Reeves et al. (2013) further listed one metamorphosing individual of *R. aurora*, Levey et al. (2003) one tadpole of *L. pipiens*, and Bregulla (1987) and Veith (1988) each reported a *Salamandra salamandra* larva with microcephaly.

In the laboratory, microcephaly is occasionally retained in early tadpole stages in individuals developing from overripe eggs (Briggs 1941). Pisanets (1992) reported that 100% of the metamorphs from crosses between 11 male *B. danatensis* and 8 female *Bufotes viridis* (from the Ukraine) were brachycephalic but none were found in other crosses with the two species from other geographic origins. Brandt (1933) observed a young larval *Triturus marmoratus* × *T. karelini* hybrid with microcephaly and the only surviving adult hybrid *Ceratophrys cranwelli* × *C. ornata* had a shortened snout (Miranda 1989). Kawamura & Nishioka (1978) observed microcephaly in tadpoles developing from irradiated eggs or sperm. Heritable brachycephaly was discovered by Lipsett (1941) in one strain of *Ambystoma mexicanum*. Tetraploid or pentaploid larval *Notophthalmus viridescens* and *Cynops pyrrhogaster* usually show pointed snouts (Fankhauser 1945) similar to the *B. viridis* individuals with pointed snout in the Roßwag population.

3.2.2.6 Mandibular hypoplasia. No review exists for this type of anomaly. Mandibular hypoplasia (Fig. 17) has been reported for 70 natural populations of amphibians. Twenty-six species were affected. Background rates are very low: 0.03% (n = 6,689) in *Lithobates pipiens* (Hoppe 2000) and 0.1% (n = 12,674) in juvenile *R. arvalis* in Ekaterinburg and its vicinity in Russia (Vershinin 2002). Only three cases involved more than ten individuals: 33 out of 13,856 *Rhinella marina* from 38 sites across Bermuda, of which many were polluted with petroleum hydrocarbons and metals (Bacon et al. 2006b), 15 (n = 479) *Litoria rubella* (plus one *L. caerulea*) that developed in ponds contaminated with pesticides and radioactivity from the Jabiru Uranium Mine in Australia (Tyler 1989) and more than ten out of 295 toad-

Fig. 17: Mandibular hypoplasia, juvenile *Rana arvalis*, Ekaterinburg, Russia, 3.7.1997. Photo: V. Vershinin.

lets of *B. viridis* sampled in a quarry in Roßwag, Germany, in 1980, in which radioactive contamination was found (Henle et al. 2017a). *Litoria rubella* shared mass ectrodactyly and several other skeletal anomalies with the Roßwag population but not polymely; non-skeletal anomalies were not listed in the study by Tyler (1989).

In laboratory experiments, a few chemicals and radioactivity turned out to be potent causes of mandibular hypoplasia: 2-methyl-4-chlorophenoxy acetic acid in *Triturus carnifex* (Zavanella et al. 1989), corticosterone in *Kassina senegalensis* (Hayes et al. 1997, Hayes 2000), jodothyrin (Romeis 1918), thymus oil, various seed oils that inhibit the growth of the thyroid gland and the sulfonamids aristamid and nadisan (they inhibit sugar and energy metabolism) in *Xenopus laevis* (Wurmbach et al. 1964) and possibly diquat in *Rana temporaria* (Gelnarova 1987a,b). DDT induced hyperactivity in tadpoles of *R. temporaria,* which resulted in the lower jaw colliding with the inner surface of the upper jaw and eroding the jaw (Osborn et al. 1981). DDT treatment also caused mandibular hypoplasia in *Spea hammondi, Pseudacris regilla* and *Lithobates catesbeianus* (Hayes 1997).

Many *R. japonica* originating from irradiated sperm or eggs developed mandibular hypoplasia and other anomalies of the jawbones (Nishioka 1978). An inherited mandibular hypoplasia was found in *Pleurodeles waltl* (Jaylet 1971). Deformed lower jaws, which may include mandibular hypoplasia, were also observed in haploid larvae of urodeles (Fankhauser 1945).

3.2.2.7. Monorhyny and obscure or lacking nostrils or nasals. Apart from parasitism by the fly *Lucilia bufonivora* (Figs. 18&19) only very few cases are known in which nostrils or nasals were obscure or lacking. Kolobaev (2000) reported the absence of nostrils in *Rana dybowskii;* it remains unclear whether one or two individuals were affected. Rostand (1955b) raised 567 tadpoles of *Bufo bufo* collected in the wild to metamorphosis; 27 of them exhibited monorhyny. He published photographs of two individuals (Rostand 1958b). The cause remains unclear but might be genetic. One tadpole of *Rhinella jimi* from the island of Fernando de Noronha lacked one nostril and another one (n = 413) had a shortened nostril (Tolledo et al. 2014). In an experimental cross between *Pelophylax lessonae* and *P. esculentus* 4.1% (n = 491) individuals exhibited fused nostrils (Guex et al. 2001).

All other cases in our database apply to the destruction of nasal openings and bones by maggots of *L. bufonivora.* It is a wellknown phenomenon in *B. bufo* (Fig. 19) but the percentage of individuals affected usually is low (Meisterhans & Heusser 1970). Our database contains reports from at least 111 populations of *B. bufo* from Belgium (Preudhomme de Borre 1876, Lestage 1926), the Czech Republic (summaried by Zavadil et al. 1997), Denmark (Mortensen 1892, Kryger 1921), France (Moniez 1876, Brumpt 1934, Rostand 1947), Germany (e.g., Kordges 2000, Sowig & Laufer 2007), Poland (Sandner 1955), Russia (Kuranova 1998, Kuzmin 2013), Sweden (Löwegren 1939), Switzerland (Meisterhans & Heusser 1970), the Netherlands (Strijbosch 1980) and the UK (Richards 1926). In most cases only a few individuals with parasites were observed but the reported parasitization rate was up to 50% (Brumpt 1934). It usually increased with the size of the toads and juveniles were never infested (Strijbosch 1980). Infested toads always die but recovery was usually observed if all maggots were removed (Neumann & Meyer 1994).

Destruction of nasal bones by maggots of *L. bufonivora* occurs rarely in other species (Zumpt 1965, Neumann & Meyer 1994). Two exceptions are 20–25% and 4.5–9.5% of the *R. arvalis* sampled being infested in the Wolga-Kama region of Russia in 1972 (Garanin & Shaldybin 1976) and in Siberia in different years (Kuranova 1998), respectively. Rare cases have been observed in the following species: *Salamandra salamandra* (1 case; Keilin 1915), *Alytes obstetricans* (Meisterhans & Heusser 1970, Kordges 2003), *Bombina variegata* (Veith

Fig. 18: *Lucilia bufonivora* depositing eggs on an adult *Bufo bufo,* Botanical Garden, Munich. Photo: S. Swoboda.

Fig. 19: Adult *Bufo bufo* with the nasal openings destroyed by maggots of the fly *Lucilia bufonivora*; the fly on the head is not the culprit. Photo: R. Stawikowski.

1996), *Pelobates cultripes* (Taton 1877), *Pelobates fuscus* (Silantev 1898, Sigov 1936), *Bufo verrucosissimus* (Kidov 2010), *Bufotes viridis* (Mertens 1921, Garanin & Shaldybin 1976), *Epidalea calamita* (5 cases; reviewed by Zavadil 1996), *Pelophylax* synkl. *esculentus* (Sandner 1955, Albrecht et al. 1996, Schmidt & Hachtel 2011), *R. amurensis* (Kuranova 1998, Kuzmin 2013) and *R. temporaria* (Brumpt 1934, Sandner 1955, Koskela et al. 1974, Riedel 1988). Goverse (2009) further reported one case in *Hyla arborea,* despite eggs usually easily dropping off of *H. arborea* (Meisterhans & Heusser 1970).

In earlier publications the species *Lucilia splendida* and *L. silvarum* were also implicated as relevant parasites (e.g., Hesse 1906, Stadler 1930) but these were likely to be mis-identified (Zumpt 1965, Neumann & Meyer 1994). Eberle (1937) further reported one case in which *Muscina pabulorum* but no *L. bufonivora* hatched from the deceased toad. However, it cannot be excluded with certainty that this was a secondary infestation, as the deceased toad was not immediately placed securely under a mesh.

3.2.3 Other externally visible skeletal anomalies

3.2.3.1 Clinodactyly. Clinodactyly is an abnormal bending of a toe caused by the presence of an intercalary little asymmetrical bone between two phalanges. Note that when toes are split (schizodactyly, a specific form of polydactyly) the supplementary phalanges often bend away from the other phalanges (see Fig. 12). Therefore, and as an illustration (but not the definition) given by Tyler (1989) can easily be confused with schizodactyly, some authors used the term clinodactyly for such cases (e.g., Vershinin 1991, 2002). Where obvious from illustrations or photographs, we excluded such cases from the review of clinodactyly.

Clinodactyly has not yet been reviewed for amphibians. Our database contains 70 cases from natural populations of 38 species, all but two involving only a few individuals. The exceptions are 100 (n = 44,000) adult male *Bufo bufo* from France, for which the cause is unknown (Rostand 1949a). In addition, high frequencies of clinodactyly (37.5% but including syndactyly and ectrodactyly; the sample size and the number affected by clinodactyly were not given) were reported for *Rana amurensis* breeding in sites polluted by the discharge of a paper and pulp mill in Sakhalin (Russia) (Levinskaya & Barinova 1978). It is possible that the anomalies observed might have been schizodactyly rather than clinodactyly. Tyler (1989) reported low rates of clinodactyly for seven species collected in retention ponds of the uranium mine at Jabiru, Australia, that were additionally polluted with herbicides and pesticides.

Laboratory experiments demonstrated that several chemicals induce clinodactyly at elevated rates (often together with other limb anomalies): the antifouling agent tributyltin oxide (Scadding 1990), thiosemicarbacide, which is a potent osteolathyritic chemical (Riley & Weil 1986, 1987), thymus oil (Wink & Wurmbach 1967) and estradiol (Takahashi 1958, Collenot 1965). Percutaneous treatment of amputated legs of *Triturus carnifex* with the fungicid maneb also caused clinodactyly (Arias & Zavanella 1979, Zavanella et al. 1984). Clinodactyly further developed in hatchery raised *Pelophylax perezi* tadpoles fed on artificial diets but not when they were fed on fresh lettuce (Martínez et al. 1992). It was also observed in a few *B. bufo* tadpoles developing from irradiated embryos (Rostand 1958a, Oerter 1985).

Dubois (1977) discovered a heritable form of clinodactyly in *R. temporaria* that occurred together with other anomalies of the digits. Clinodactyly is also part of another syndrome of limb anomalies in the same species, the so-called anomaly E, which has a dominant inheritance (Rostand 1956a,b, 1958b). Temperature may act epigenetically to induce clinodactly, as Muto (1969a,b, 1970) observed (in some experiments, but not in others) that clinodactyly developed in *B. formosus* reared at 30°C, but not in controls reared at 20°C.

3.2.3.2 Syndactyly. So far, no review exists for syndactyly. In our database we have reports for 137 natural populations from 64 species. The number of affected individuals was low except for three, possibly four cases. Eleven *Lithobates sylvaticus* with syndactyly (0.2%; n = 5716) were found in a survey of 38 sites in the Kenai Wildlife Refuge in Alaska (Reeves et al. 2008, 2013). Out of 467 *Limnodynastes ornatus* collected in a water body derived from a radioactive source that was additionally polluted by herbicides and pesticides 32 (6.9%) exhibited syndactyly; several other species were also affected but at a lower rate (Tyler 1989). At least 191 out of 13,856 individuals of *Rhinella marina* sampled across Bermuda showed syndactyly, with the pollution of breeding ponds resulting from the run-off from roads and agricultural fields, and the spraying of pesticides presumably being the cause (Bacon et al. 2006b, Fort et al. 2006a). In a *Rana amurensis* population living in the wastewater from a paper and pulp mill in Sakhalin, Russia, 37.5% of immature frogs exhibited syndactyly, clinodactyly or ectrodactyly (the sample size and the number affected by syndactyly were not specified) (Levinskaya & Barinova 1978).

Various chemical treatments have caused syndactyly in laboratory experiments. All *Pelodytes punctatus* treated with testosterone developed syndactyly (Collenot 1965). Likewise, chloraethylamin treatment of limb buds and feeding retinoic acid to tadpoles caused a very high rate of syndactyly in *Xenopus laevis* (Tschumi 1954, Alsop et al. 2004). Limb amputation together with vitamin A treatment caused syndactyly in 5–7.5% (n = 40) of the treated larval *Duttaphrynus melanostictus* (Das & Mohanty-Hejmadi 2000). However, seemingly inconsistent results were reported for several other chemicals. Trypaflavine caused syndactyly in *R. temporaria* but not in *Pelophylax esculentus* (Rostand 1950b,c). For colchicine, syndactyly was noted in *X. laevis* by Tschumi

(1954) but not by Bretscher (1949), Crézé (1950) and Rostand (1950b,c); estradiol was effective in *R. pirica* but not in *Bufo formosus* (Takahashi 1957, 1958). According to Tschumi (1954), syndactyly is a mild expression of a syndrome that is caused by a reduction in cell numbers of the blasteme, which causes brachydactyly, ectrodactyly, or ectromely with an increased reduction of the number of living cells. Thus, these seemingly inconsistent results may be due to different degrees of damage of the blasteme, perhaps combined with a varying degree of sensitivity of species.

A high frequency of syndactyly has further been observed in *R. temporaria* tadpoles treated with the skin mucus of fish from ponds in which anomaly P occurred (Surlève-Bazeille et al. 1969a) but not in *P.* synkl. *esculentus* (Surlève-Bazeille et al. 1969a, Rostand 1971). Low to high rates were also found in *B. formosus* reared at 30°C, but none in controls reared at 20°C (Muto 1969a,b, 1970). It was further observed in several species after limb or toe amputation, especially under higher temperatures (e.g., Bonnet 1779, Schmalhausen 1925, Tschumi 1954, Dearlove & Dresden 1976, Semlitsch et al. 1981).

Syndactyly rarely occurs in anurans infected with the trematode *Ribeiroia ondatrae* (Johnson et al. 1999, 2001b, Schotthoefer et al. 2003). Hamburger (1935) obtained one syndactylous individual in experimental crosses of *Triturus cristatus* × *Lissotriton helveticus*. Syndactyly occurred rarely in *B. bufo* tadpoles developing from irradiated embryos (Rostand 1958a, Oerter 1985).

Dubois (1977) demonstrated the dominant inheritance of a syndrome of digital anomalies that included syndactyly in one *R. temporaria* individual. Syndactyly is also part of another dominant syndrome of limb anomalies in the same species, the so-called anomaly E (Rostand 1956a,b, 1958b). In humans and mice, several mutations of single regulatory genes are also known to cause syndromes of limb anomalies involving syndactyly (Cohn & Bright 1999, Gurrieri et al. 2002).

3.2.3.3 Symmely and related anomalies. Apart from the fusion of supernumerary limbs, we know this type of anomaly only from *Bombina bombina* (n = ?) in Hungary (Puky & Fodor 2002) and from a single individual of *Pelophylax esculentus* (Bruch 1864). In an individual of *Lithobates pipiens* the tibiofibula, the femur and the tail were fused together (Reeves et al. 2013).

3.2.3.4 Bony bridges, bony triangles and other forms of taumely. Taumely is a gross disturbance of the bauplan of the limb (Fig. 20), with a long bone being out of alignment (Henle et al. 2017b). The degree of misalignment may vary and some authors (e.g., Gardiner & Hoppe 1999) included any degree of bending back in the term taumely, whereas others restrict it to a misalignment of at least 90° (e.g., Tyler 1989, Meteyer et al. 2000a, Henle et al. 2017b). We additionally include cases in which the mis-alignment is smaller but the bauplan of the limb is grossly disturbed. Bony bridges,

Fig. 20: Taumely, *Rana arvalis*, Berdanish Lake, Ural, Russia, 6.9.1993. Photo: V. Vershinin.

and its synonym bony triangles, are a specific form of taumely in which the bent long bones have a sharp midshaft angle and form a triangle or pyramid. In spite of being called "bony", these anomalies are variably either ossified or chondrified (Gardiner & Hoppe 1999).

Our database contains 55 cases from natural populations of 27 species. Most of the cases from North America relate to bony triangles. High numbers and frequency of individuals with bony triangles have been reported for a population of *Anaxyrus americanus* (33%, n = 618) from Duck Pond, Minnesota (Johnson & Hartson 2009) and a population of *Lithobates clamitans* (≤ 9.8%, n = 245) and *L. septentrionalis* (≤ 5%, n = 869) from the CWB site, Minnesota (Vandenlangenberg et al. 2003, Hoppe 2005), respectively. Individuals of *A. americanus* were parasitized by the trematode *Ribeiroia ondatrae* and *R. ondatrae* also occurred at the CWB site. Johnson & Hatrson (2009) assumed *R. ondatrae* as the cause for bony triangles in the population studied by them. In contrast, Vandenlangenberg et al. (2003) and Hoppe (2005) regarded pollution as the cause for the cases at the CWB site. Likewise, Gardiner & Hoppe (1999) and Gardiner et al. (2003) assumed that retinoids were the cause of mass occurrences of bony bridges in natural populations, whereas Stopper et al. (2002) dismissed this explanation and assumed that infection with *R. ondatrae* caused elevated rates of bony triangles in natural populations.

Bony triangles are often regarded as being characteristic of *R. ondatrae* infection since they appeared frequently in experimental infections of anurans (*A. americanus, A. boreas, Pseudacris regilla*) with this trematode (Johnson et al. 2001b, 2006, 2010, Johnson & Hartson 2009). However, in other experimentally infected species they were only observed rarely or were even ab-

sent (e.g., in *Ambystoma macrodactylum croceum, Dryophytes versicolor* and *L. pipiens* Schotthoefer et al. 2003, Johnson et al. 2006, Johnson & Hartson 2009).

In a laboratory setting, bony triangles were found when rearing *L. pipiens* in a lipophilic water sample from a malformation hotspot and treating them with carbaryl in combination with atrazine (Bridges et al. 2004). Feeding retinoic acid to tadpoles of *Xenopus laevis* caused high rates of bony triangles (Degitz et al. 2000, Alsop et al. 2004). It should be noted that the effects of chemicals can be highly stage specific. For example, the synthetic retinoic acid receptor-specific activator TTNPB caused primarily bony triangles when *X. laevis* was treated at stage 52 but other anomalies or no anomalies appeared at other stages (Gardiner et al. 2003). In conclusion, both *R. ondatrae* and chemical pollution may have directly contributed to North American malformation hotspot at which bony triangles occurred with high frequencies.

In regions outside of North America, it is usually unclear as to what type of taumely had been observed. Rostand (1949a) reported about the rare occurrence of a hump-shaped tarsus in *Bufo bufo* and Brandt (1933) published a drawing of a *Pelophylax esculentus* that indicates a bony bridge. Landois (1882) described bony triangles in two ranid frogs from Germany. Woitkewitsch (1959) reported at least 47 individuals with bony bridges; however, most or even all affected limbs were supernumerary legs or legs with duplications of the foot. The causes for the cases outside North America remain unknown but in single individuals may be due to traumatism, as experimental rotation of the limb buds can cause high rates of bony triangles (Hecker & Sessions 2001, Stopper et al. 2002).

3.2.3.5 Rotation and curvature of bones; torsion and stiffness of limbs. Various terms have been used for these types of anomalies (see Henle et al. 2017b). Rotation of limbs is an anomaly in which limbs are twisted and the foot (hand) is not in a plain with the surface but the limb is not grossly malformed. Rotation may be caused by an abnormal joint or by a distortion of the direction of bone growth. Following Henle et al. (2017b) we regard torsion of the limbs as a synonym and anteversion as a specific form of rotation but note that some authors include bony bridges or all forms of taumely under the term anteversion (e.g., Hoppe 2005). We exclude studies from this section in which it is unclear as to whether authors used the term anteversion in such a broad meaning. In addition, the term curved long bones has been used as a synonym in cases where bones are curved but not more than 90° out of alignment (Sanchiz & Pérez 1974).

Rotation of limb bones is always combined with stiffness of limbs. However, limbs may be stiff without rotation, e.g., in the case of polymely, cutaneous fusion, or when the musculature is reduced or disfunct; the latter is often referred to as "Streichholzbeinchen" (Fig. 21) in the German literature. Here, we only consider forms of stiffness that are not linked to cutaneous fusion, polymely, or taumely (the latter being discussed in the previous section).

No review exists for rotation or for stiffness of the limbs. We found reports of rotation for 50 populations. These cases involve one urodele (*Notophthalmus viridescens*: Collins 1932) and 22 anuran species. In addition, Sanchiz & Pérez (1974) described three abnormally curved urostyles among 497 that were examined from a population of *Discoglossus pictus*. Further, Fodor & Puky (2002) and Puky (2006) mentioned clinomely for *Bombina bombina* and *Pelophylax* synkl. *esculentus* from two different respectively one location(s) at the Danube River. It is unclear as to whether these anomalies are the same as what we refer to as rotation and we do not know of others that have used the term clinomely for abnormal limbs.

Most of the studies that reported rotation for natural populations mentioned only few individuals but in a population of *Rana luteiventris* from British Columbia, Canada, 4.3% (n = 280) of the metamorphs had stiff limbs (Roberts & Dickinson 2012). All abnormal individuals carried cysts of *Ribeiroia ondatrae* in their limbs. Individuals reared in closed cages did not develop any anomaly. Therefore, Roberts & Dickinson (2012) concluded that *R. ondatrae* was the cause for the anomalies. In experiments with the trematode, rotation of limbs occurred as a rare anomaly in *Anaxyrus boreas* and *Ambystoma macrodactylum* (Johnson et al. 2001b, 2006). In spite of this rarity in experiments, *R. ondatrae* infection is a parsimonious explanation. However, a caveat re-

Fig. 21: Stiff front legs with disfunct musculature (called Streichholzbeinchen in the German literature) in a juvenile *Rana arvalis*, Rezhevskoy road, non-urban natural habitat near Ekaterinburg, Russia, 23.7.2003. Photo: V. Vershinin.

mains as no information was provided as to whether access to mud and predators was also excluded. Chemical pollution and/or predation and once a virus (anomaly P) have been assumed to be the cause(s) for rotation in other studies. However, no attempts have been made to test these assumptions in any of the cases. Whereas we do not know any staged predation experiment resulting in elevated rates of rotation, it was reported once (two tadpoles of *Hymenochirus boettgeri*) after experimental limb amputation (Girvan et al. 2002). In contrast, various chemicals are known to cause rotation and/or stiffness of limbs (see below).

In five of the cases of rotation, stiffness has also been mentioned explicitly and in two of them also atrophied musculature (Canfield et al. 2000, Helgen et al. 2000, Vandenlangenberg et al. 2003, Reeves et al. 2013, Henle et al. 2017a). We suggest that it is likely that in most cases of rotation stiffness was simply not mentioned. In one of the five cases, a *Bufotes viridis* population in a quarry at Roßwag, Germany, in more than 25 out of 295 toadlets sampled in 1980 the limbs were rotated and stiff; the anomalies were most likely induced by radioactive pollution (Henle et al. 2017a). In a population of *Lithobates sphenocephalus* from Goose Pond, Patuxent Research Reserve, one of 33 (sample size 595) abnormal individuals had a twisted bone and another one a stiff limb. In populations of *L. pipiens* at the NEY and the ROI hotspot site in Minnesota, respectively, approximately 35 (n = 2493) and 4 (n = 1394) individuals exhibited rotation of long bones and approximately 38 and 29–30 individuals showed muscle atrophy (Helgen et al. 2000, Vandenlangenberg et al. 2003).

In addition to the cases in which stiff limbs and torsion of legs co-occurred, we found 27 cases of stiff limbs covering 13 anuran species, in which rotation was not mentioned. All of these cases involved only a few individuals or stiff limbs occurred in low frequency.

In contrast to the scarce observations in natural populations, torsions and stiffness of limbs have been observed repeatedly in captive raised offspring of many anurans and urodelans, especially in Dendrobatidae (e.g., Klatt 1927, Krefft 1938, Ensinck 1978, Heselhaus 1983, Conaghan 1987, Cummins 1987, 1989, Glaw 1987, Krintler 1988, Birkhahn 1991, Meyer 1996, Zimmermann & Aeschbach 2005). Nutritional deficiencies, especially in Ca^{2+}, inbreeding and too high temperatures were frequently assumed to be the causes but were rarely addressed experimentally. Marshall et al. (1980) and Leibovitz et al. (1982) showed that diets low in calcium or vitamin C, respectively, caused twisted limbs in cultured *L. catesbeianus* larvae and that an enrichment of the diet with these nutrients significantly reduced the rate of deformities. Similarly, hatchery reared *P. perezi* tadpoles developed elevated rates of stiff legs and torsions of the vertebral column and tail when fed on artificial diets but no anomalies appeared when they were fed on fresh lettuce (Martínez et al. 1992). Likewise, stiffness and rotation of the legs developed after hatching in all *Lissotriton vulgaris* fed on a diet of mussle meat as larvae but not in controls (Klatt 1927, Krefft 1938). Both anomalies also occurred in *A. mexicanum* and *Pleurodeles waltl* fed on a pure enchytraea diet; however *Triturus* (sensu lato) spp. were insensitive to such a diet (Reinhardt 1939, Vogt 1939). Stiff legs also appeared in more than 50% of metamorphosing *Gastrotheca marsupiata* from two clutches that were raised at 26°C but none in 11 clutches of the same parents that were reared at lower temperatures (Ensinck 1978). However, the clutches were deposited at different times so that confounding factors cannot be ruled out completely.

Stiffness of legs was very frequent in hybrids of *T. cristatus* × *L. helveticus* and *T. cristatus* × *L. vulgaris* (Hamburger 1935). Stiffness and torsion of legs also occurred often in experimental hybrids within the *Pelophylax esculentus* complex (Berger 1971, Günther 1990, Berger & Berger 1992). Flindt & Hemmer (1967) and Hemmer (1973) reported stiffness of limbs (frequency not given) in one, but not in a second, experimental cross of *Epidalea calamita* × *Bufotes viridis*. As other authors never observed it in any experimental hybridization among European bufonid species, a causal relationship with hybridization is questionable.

Chemical treatment can also induce stiffness and torsion of legs. Stiffness is induced frequently when tadpoles are reared in hydrogen-enriched tapwater (Sladden 1932), water contaminated by petroleum (Danilova 1992), hydrocarbons (Fort et al. 2006a) and sugar cane solutions (Tornier 1908, Sladden 1932, Piiper 1933). It also appeared in a few individuals that were exposed as tadpoles to DDT, DDE (Cooke 1971, 1973), or endosulfan (Gelnarova 1987a,b). Various PCBs that act as endorcrine disruptors (Qin et al. 2005) as well as thymus oil, various other oils that inhibit the growth of the thyroid gland, the sulfonamids nadisan and aristamid that interfere with sugar and energy metabolisms (Wurmbach et al. 1964, Wink & Wurmbach 1967) and estradiol (Takahashi 1958) can cause stiffness and torsion of legs.

These anomalies also appeared in tadpoles of *Rana temporaria* reared in pH 4 under low to medium density (4–8 tadpoles/l) but not under high density (16 tadpoles/l) (Cummins 1987). However, the effect of pH could not be isolated from that of the diet. Indeed, no anomalies appeared when the diet was changed. While low pH itself probably does not cause torsion of legs, it enhances the effect of vitamin C deficiency in the diet on the appearance of twisted legs in *Lithobates catesbeianus* (Leibovitz et al. 1982).

Bent knees appeared in metamorphs as a carry-over effect when embryos of *R. temporaria* were exposed to enhanced UV-B, with doses still within natural variation (Pahkala et al. 2001). Irradiation of eggs, sperm, or embryos caused torsion of legs in a few to many metamorphs of *Xenopus laevis* (Schinz & Fritz-Niggli 1954), *B. bufo* (Oerter 1985), *P. nigromaculatus* (Kawamura & Nishioka 1978) and *R. temporaria* (Rostand 1955a, 1958a, Roth 1988). For *P. nigromaculatus* stiff legs without rotation were also reported and both types

of anomalies still occurred in the second generation (Kawamura & Nishioka 1978).

Inheritance of stiff legs was further shown by Krotoski et al. (1985), Kovalenko (2000) and Kovalenko & Kovalenko (2000) in inbred *X. laevis*. In some laboratory stocks of *Pleurodeles waltl,* anteversion of the knee joint seems to be inherited, with temperature acting epigenetically (Dournon 1983). In humans, bent bones may also be due to mutations and may appear as a syndrome together with brachymely, brachydactyly and knee joint anomalies (Cohn & Bright 1999).

3.2.3.6 Stiff and truncated vertebral column and torsion of the vertebral column. We only know four populations in which truncated stiff vertebral columns were observed: more than ten toadlets of *Bufotes viridis* in a quarry near Roßwag, Germany (Henle et al. 2017a), with radioactive contamination most likely being the cause. Jarvis (2011) and Raichoudhury & Das (1931) found one adult male *Triturus cristatus*, and one adult *Duttaphrynus melanostictus*, respectively, in which the lower vertebral column was fused and stiff; in the latter case, the anomaly was not visible externally. Schmelcher & Hellmich (1951) reported one larval *Salamandra salmandra* with a truncated body that was born by a recently captured female.

While fusion of vertebrae has been reported for various species, generally no information is given as to whether fusion resulted in a truncated stiff vertebral column (e.g., Benham 1894, Grewal & Dasgupta 1967, Worthington 1974, Prigioni & Langone 1985, Gollmann 1991, Vershinin & Neustroeva 2011). In some species (e.g., *B. bufo, Pelophylax esculentus*) fusion of some vertebrae is regarded as normal variation (e.g., Adolphi 1893, 1895).

The oldest record of torsion of the vertebral column is a capitosauroid, presumably *Eocyclotosaurus wellesi* from the Middle Triassic of Arizona (Witzmann 2007). For extant amphibians, only one study reported elevated rates of torsion of the vertebral column. Agostini et al. (2013) observed it in 73 (n = 2030) juvenile *Leptodactylus latrans* and 13 (n = 427) *Boana pulchella*. It has also been observed in two *Eurycea junaluska* (Ryan 1998), one *Plethodon idahoensis* (Peterson et al. 1999), two *P. glutionosus,* two *P. kentucki* (Marvin 1995, Marvin & Hutchison 1997), one *Pseudotriton ruber* (Haines-Eitzen 2016), in *Notophthalmus viridescens* (Collins 1932), one adult female *Lissotriton vulgaris* (D'amen et al. 2006), one metamorph of *Pseudacris regilla (*Reeves et al. 2013), one *Pelobates fuscus* (Nöllert 1990), *Bufo bufo* (Weddeling & Geiger 2011), one *Trachycephalus typhonius* (as *Pseudohyas hebes*: Vizotto et al. 1977), one female each of *Sphaerotheca breviceps* and of *Fejervarya kirtisinghei* (De Silva 2009), in at least five *Lithobates pipiens* (Levey et al. 2003, Lannoo 2008, Reeves et al. 2013), one *L. sylvaticus* (Reeves et al. 2013), one *L. septentrionalis* (Schoff et al. 2003) and in an unstated number of *Pelophylax ridibundus* (Spirina 2009). Lannoo (2008) assumed pollution to be the cause for the case observed by him but this assumption was not tested. Other authors did not discuss potential causes.

Irradiation of the eggs of *Pleurodeles waltl* and the sperm of *Xenopus laevis* resulted in offspring with a truncated vertebral column (Labrousse 1967, Hart & Armstrong 1984). Malformed backbones were further reported by Nishioka (1978) in the offspring produced by irradiating eggs or sperm of *Rana japonica*.

Using gynogenesis, Krotoski et al. (1985) discovered a case of inherited truncated vertebral column in *X. laevis* and Kovalenko (1994) observed vertebral fusion, together with asymmetry of the vertebral column, in an inbred line of the same species. Dasgupta & Grewal (1968) revealed a single dominant gene responsible for the fusion of vertebrae in five populations of *Euphlyctis cyanophlyctis* around Dehli.

The cause(s) of torsion of the vertebral column has been neglected so far in amphibians. In humans, it may be due to trauma, cancer, neuromuscular disease, inflammation of the vertebral column, oxygen deficiency and in rare cases mutations (McMaster 2001, Asher & Burton 2006).

3.2.3.7 Torsion of the tail or body in tadpoles and torsion of the tail in adult urodeles. In natural populations torsion of the tail and/or body has been noticed in 57 populations of 22 anuran and two urodele species but probably often remains undetected or unreported. Only two cases are known for urodele larvae: one *Salamandra salamandra longirostris* with a shortened bent tail from Spain (Escoriza & Garcia-Cardenete 2005) and one *S. salamandra* with a bent tail from Germany (Henle unpubl.). The latter lost the torsion during metamorphosis. Only Collins (1932) reported bent tails in adult newts: one male *Notophthalmus viridescens* with marked lateral undulatory twists in the tail.

Elevated rates of bent tails or bodies in tadpoles were reported from several sites. In a population of *Lithobates pipiens* from Maryland, 28.4% (n = 74) were affected (Hardy (1964). Bruch (1864) found 39 tadpoles of *Pelobates fuscus* with bent tails among more than 1000 individuals examined. In both cases the cause remains unknown. In a population of *Bufotes viridis* from a quarry in Roßwag, Germany, in which elevated levels of radioactivity were measured, 35–55% of the tadpoles had bent tails (total tadpole population size 2000–5000) (Henle et al. 2017a). In tadpoles of *L. catesbeianus* from wetlands constructed with treated wastewater in Georgia 54 out of 833 individuals were affected but none out of 190 individuals from reference sites (Ruiz et al. 2010). Also, the frequency dropped substantially with the distance from the discharge point. At the Savannah River National Research Park, 17.7% and 36.8% of the *L. catesbeianus* tadpoles sampled in two water bodies polluted by coal combustion waste were affected by torsion of tails whereas only 0% and 4.4% were affected at two control sites (all $n \geq 350$) (Hopkins et al. 2000). In water bodies of the Nikopol District, Ukraine, that were polluted by chemical and metallurgical discharge from factories,

5.8% (n = 400), 2.6% (n = 500) and 7.2% (n = 500) of the *Bombina bombina*, *Bufotes viridis* and *Pelophylax ridibundus* tadpoles, respectively, had torsions of the body (Flax & Borkin 2004). In Sakhalin, Russia, the percentage of recently hatched tadpoles of *Bufo gargarizans, Rana amurensis* and *R. pirica* with torsions of the body or tail increased with a decrease of water temperature and pH (Flax 1986). In the city of Moscow, 10% of the tadpoles of *R. temporaria* were affected by torsion of the body, whereas this was only the case in 4% in a pond at the Biological Station of the Lomonosov University 50 km west of Moscow (Aguillón Gutiérrez & Severtsova 2012). The cause for the difference is unknown.

Torsion of the body and/or tail is a very common anomaly in experimental studies of amphibian embryos, but much less is known for tadpoles. In embryos it develops, for example, after mechanically induced defects and constrictions (reviewed by Shen 1938), under malnutrition (Krefft 1938), after high intensity ultrasound treatment (Bonhomme & Pourhadi 1957, Bonhomme et al. 1960, Pourhadi et al. 1968), from overripe eggs (Briggs 1941) and in experimental hybridization, including all European bufonid species (Hertwig et al. 1959, Flindt & Hemmer 1967, Flindt et al. 1968, Schipp et al. 1968, Delarue 1974, 1982), within the *P. esculentus* complex (Berger 1967, Berger & Uzzell 1977, Tunner 1980) and in crosses of *Pseudophryne corroboree* from different geographic origins (Osborne & Norman 1991). Hybrid tadpoles of tetraploid *Bufotes viridis* × *B. pewzowi* may also show bent tails and curvature of the body (according to photographs in Stöck 1998). Tadpoles that developed from a clutch of a *R. arvalis* female that mated with a *R. temporaria* male in nature showed bent tails and all died before hindlimbs emerged (Luttenberger 1976).

A wide range of chemicals also causes torsions of the tail or body in embryos and some of them also in tadpoles (partially reviewed by Power et al. 1989). Among these are DDT and other organochlorides (e.g., Cooke 1971, Marchal-Ségault & Ramade 1981), carbamate insecticides (e.g., Rzehak et al. 1977, Cooke 1981, Raj et al. 1988, Bridges 2000), nitrate and nitrite (Hecnar 1995, Marco et al. 1999), some metals (Plowman et al. 1994), excess Vitamin A (e.g., Syuzyumova 1985) and low or high pH (Ferraro & Burgin 1993). These experimental studies corroborate the conclusion of pollution being the cause for the elevated rates of torsion of the tail or body in the field studies of polluted sites mentioned above.

When reared at elevated temperature (18°C), a high proportion of the larvae of *Euproctus asper* developed bent tails (Clergue-Gazeau 1971). Likewise, some larvae of *Lissotriton helveticus* hatching from eggs that were kept at a high temperature (22°C) showed a curvature of the tail, whereas those hatching from eggs maintained at 18°C or 14°C did not (Galloy & Denoël 2010). Unfortunately, the difference was not tested statistically. Notwithstanding, these observations and those of Flax (1986) mentioned above suggest that both too high and too low temperatures may result in increased frequencies of bent tails or bodies.

Exposure to radium bromide, γ- and X-rays very frequently result in torsions of the bodies or tails in embryos and tadpoles (e.g., Hertwig, O. 1911, Hertwig, G. 1913, Stachowitz 1914, Labrousse 1967, Nishioka 1977, 1978, Kawamura & Nishioka 1978, Oerter 1985, Trux 1985). The same applies for high intensity light (Ruehmekorf 1958) and unnaturally high doses of UV-B (e.g., Worrest & Kimeldorf 1975, Kashiwagi 1980, Grant & Licht 1995). Hays et al. (1996) found elevated rates of torsion of the tails in *Pseudacris regilla* when treated with moderate UV-A+UV-B, but not when treated only with UV-A. Furthermore, the treatment was only effective if tadpoles were kept in dim laboratory light but not under moderate light; the dim light may have inhibited photo-induced repair mechanisms of UV damage.

Besides the factors suggested for natural populations, amputation of tails at an angle may cause regeneration that leads to bent tails in various anurans and urodeles (Barfurth 1891).

Bent tails in tadpoles and bent bodies of metamorphosed individuals also occurred after experimental infection at the pre-limb bud stage (Gosner stages 25 and 26) tadpoles of the Sri Lankan *Polypedates crucifer* with *Acanthostomum burminis* cercariae (Jayawardena et al. 2010, Jayawardena & Rajakaruna 2013) but not in controls (difference not tested statistically). Only other types of anomalies were observed when limb bud stage tadpoles (Gosner stages 27 and 28) were exposed to the cercariae (Rajakaruna et al. 2008).

A genetic basis of torsion of the tail was discovered in a laboratory strain of *Pleurodeles waltl,* with temperature acting epigenetically (Fernandez & Beetschen 1975), in tadpoles of *Lithobates pipiens* (Browder 1972), in *Xenopus borealis* (Droin 1985) and in *X. laevis* (Elsdale et al. 1958, Droin & Chavane 1976, Hart & Armstrong 1984). *Rana japonica* and *Pelophylax nigromaculatus* originating from irradiated eggs or sperm maintained torsion of bodies and tails and other anomalies up to the third generation; in the fourth generation the frequency was similar to controls (Nishioka 1977, 1978, Kawamura & Nishioka 1978). Torsion of tails may have a genetic basis in other species as well (Freytag 1955, Sládecek 1964).

3.3 Non-skeletal morphological anomalies

3.3.1 Duplications and absence of structures

3.3.1.1 Duplication of eyes or spiraculum. Héron-Royer (1884) discovered an embryo of *Alytes obstetricans* with four eyes. He also observed a *Pelobates fuscus* tadpole with two spiracula instead of one.

3.3.1.2 Tympanum absent. While several amphibian species and genera lack an externally visible tympa-

num (Passmore & Carruthers 1995), i.e., absence is the normal condition, we found only five publications that mention an abnormal absence of the tympanum. Martof (1956) detected one *Lithobates clamitans* that lacked a tympanum and four more individuals in which the tympanum was ruptured. He assumed attacks by rock bass (*Amblopites rupestris*) to be the cause. Grosse (2015) published a photo of an adult *Rana temporaria* that lacked an externally visible tympanum. Reeves et al. (2013) listed one metamorph of *L. pipiens* and of *L. sphenocephalus* with the tympanum lacking. Bleakney (1963) discovered an *Anaxyrus americanus*, whose tympanum, and parotoid glands, had been destroyed by maggots of *Lucilia silvarum*. Finally, Peltzer et al. (2011) reported the absence of the tympanum in a sample of 12 Argentinian anuran species, without providing numbers or the species affected; they illustrated the anomaly for one *Leptodactylus mystacinus*.

3.3.1.3 Macrophthalmy, microphthalmy, anophthalmy and cyclopy. Macrophthalmy, microphthalmy (Fig. 22), anophthalmy (Fig. 23) and cyclopy in natural populations of amphibians have not yet been reviewed. Our database contains eight individuals with macrophthalmy: an adult *Bufo bufo* from Russia (Korzikov & Alekseev 2014) and one metamorphosing individual of *Acris* species, *Lithobates blairi, L. palustris*, *L. pipiens*, *L. sphenocephalus,* as well as two individuals of *L. sylvaticus* from the USA (Reeves et al. 2013).

Our data base further contains 53 cases of microphthalmy involving 20 species. Most of them are from surveys across many sites, involving only a few individuals. Bacon et al. (2006b) observed 18 and 21 *Rhinella marina* (n = 13,856) with microphthalmy and anophthalmy, respectively, in a survey of 38 sites in Bermuda and assumed pollution (metals and pesticides) to be the cause. To test this hypothesis, Fort et al. (2006b) exposed embryos to sediments from contaminated sites and raised them until metamorphosis had been completed in laboratory microcosms. This treatment resulted in elevated rates of eye anomalies (12.1%; n = 272) whereas no control individual showed any anomaly.

For individual populations, Haensch (1985), Harris et al. (2001) and Burton et al. (2008) each reported a single *Salamandra salamandra, L. pipiens* and *L. catesbeianus*, respectively. Maruschak & Muravynets (2013, unpubl.) further reported it for adult *Pelobates fuscus* and *Pelophylax ridibundus*. Burton et al. (2008) suggested ranavirus FV3 to be the cause, as they observed FV3 particles in the granuloma. Experimental studies assessing the potential of virus to cause microphthalmy or anophthalmy are still lacking.

Anophthalmy is known from 159 cases, involving 55 species. Only eight of these species are urodeles. The rarity of anophthalmy in natural populations of urodeles can be explained by their high capability of regeneration. In *Cynops pyrrhogaster,* extirpation of the eye lens 18 times within 16 years was followed each time by regeneration (Eguchi et al. 2011).

All but three publications mentioned less than ten affected individuals. A striking hotspot occurs on the oceanic island Fernando de Noronha, Brazil. In the introduced Cururu toad (*Rhinella jimi*) 17% (n = 179) of the adult toads collected in 2009 and 2010 lacked one or both eyes (Tolledo & Toledo 2015). In 2008, only 8% (n = 159) of the toads showed anophthalmy (Toledo & Ribeiro 2009). The cause is unknown but could be the result of inbreeding caused by founder effects (Tolledo & Toledo 2015). Gurushankara et al. (2007) collected 12 (n = 1670) *Fejervarya keralensis* with anophthalmy in contaminated rice paddies in India, whereas not one of the 239 individuals collected in forests was abnormal. Three further species (*F. brevipalmata, F. limnocharis, F. rufescens*) were also affected by anophthalmy or microphthalmy but at slightly lower frequencies.

Reeves et al. (2008) found 12 (n = 5716) *L. sylvaticus* with anophthalmy in a survey of 38 sites in Kenai Wildlife Refuge, Alaska. They also assumed that pollution, together with predators, were the cause of the eye anomalies observed. While many chemicals cause eye anomalies in embryos, much less is known of their effects on tadpoles. Tadpoles developing from clutches of *Dryophytes chrysoscelis* that invaded mesocosms contaminated with atrazine and chlorpyrifos developed anophthalmy (Britson & Threlkeld 1998). Feeding *Xenopus laevis* tadpoles with retinoic acid resulted in high rates of anophthalmy and microphthalmy (up to 45.5%), with stage 46 tadpoles being more sensitive than later stages (Alsop et al. 2004).

Fig. 22: Microphthalmy in an adult male *Rana arvalis*, Verhnaya Serga village, Russia, 21.4.2012. Photo: V. Vershinin.

Fig. 23: Unilateral anophthalmy in *Bombina bombina*, Morava-Dyje floodplains, Austria, 6.8.2012. Photo: U. Nüsken.

Klewen (1986) mentioned a *S. atra* that lost its eyes and received tail injuries due to the attack of a bird. Attacks from predators and injuries were also suggested for several other cases involving single individuals (e.g., Martof 1956, Gollmann & Gollmann 2012). Anophthalmy occurred occasionally in *B. bufo* tadpoles that were experimentally exposed to dragonfly nymphs (Ballengée & Sessions 2009). Taton (1877) and Grosse & Simon (2015) each reported a case in which the eyes of a *B. bufo* had been destroyed by maggots of the parasitic fly *Lucilia bufonivora*. In captivity, one *D. versicolor* lost its eye due to infestation with maggots of *L. illustris* (Anderson & Bennett 1963). Mitchell et al. (2004) suggested a genetic origin for anophthalmy in a single *Plethodon cinereus* that they found but they did not test their hypothesis. However, Jaylet (1971) and Krotoski et al. (1985) demonstrated the heritability of microphthalmy in *Pleurodeles waltl* and *X. laevis*, respectively.

Besides the factors suggested for observations in natural populations, hybridization may also result in microphthalmy or anophthalmy. Natural hybridization of a *R. ictericus* male with a *R. crucifer* female resulted in four individuals with anophthalmy and three with microphthalmy out of eight individuals that had successfully metamorphosed (Haddad et al. 1990). Anophthalmy may also be common in hybrids of *D. versicolor* × *D. cinereus* (Mable & Rye 1992) and in offspring of *Pelophylax lessonae* × *P. esculentus* (Berger & Uzzel 1977).

Whereas cyclopy is a rather common anomaly in embryos (Tornier 1908, Shen 1938), for postembryonic stages from natural populations, it was reported only for one albinistic larval *S. salamandra* (Cabela 1987).

3.3.2 Other non-skeletal morphological anomalies

3.3.2.1 Retention of tail in anurans after metamorphosis. Only a few observations have been made for natural populations. Olivier (1893) reported it for the first time in an adult *Bufo bufo* (see also photograph in Dubois 1979a). This remains the only publication for an adult anuran but De Silva (2009) mentioned an extension of the spine beyond the rump in an unidentified adult(?) *Philautus* species from Sri Lanka that may also be an incomplete resorption of the tail. Note that the figures of two adult toads with tails published by Aldrovandi (1645) are based on fake specimens. In addition, Hassine et al. (2011) labelled a photograph of a *Pelophylax saharicus* with incomplete tail retention as adult but this age class is inconsistent with the size bar and recently metamorphosed *Pelophylax* spp. may retain their tail for some time (Fig. 24).

All other observations relate to juveniles. Lannoo (2008) reported two recently metamorphosed *Lithobates catesbeianus* as well as *L. pipiens* and one recently metamorphosed *Acris blanchardi* with incompletely resorpted tails. He assumed, but did not test, that chicken waste fertilizer and other chemicals were the cause and suggested that unresorbed tails are common. Likewise, Helgen et al. (2000) collected one recently metamorphosed *L. pipiens* with a very long tail and McCallum & Trauth (2003) reported 37 *A. crepitans* with retained tails. García-Muñoz et al. (2010) collected a metamorphosed *Bufotes boulengeri* with an almost complete tail. Eikamp (1980) discovered a 28 mm long metamorphosed juvenile *Pelophylax esculentus,* which retained a long tail with tail fins still present and Hassine et al. (2011) four such *P. saharicus*. These observations may not be abnormal. In various frog species [e.g., *Bufo bufo, Osteocephalus elkejungingerae, P. ridibundus* (Fig. 24), *Rana temporaria*] metamorphosing individuals may leave the water with long tails that will be resorbed later (Henle & Vershinin, unpubl.). On the other hand, treating larval stages of *Xenopus laevis* with substances that interfere with the thyroid axis (rape-seed oil, wheat-germ oil, sesame-seed oil, cottonseed oil, thymus oil, labrafil, methimazole, or pentachlorophenol) does result in incomplete or delayed tail resorption (Pohland 1962, Wurmbach et al. 1964, Wink & Wurmbach 1967, Fort & Stover 1997).

To enable a more certain conclusion that retained tails in metamorphs are abnormal and not within the normal variation of a species, we recommend comparing and reporting the distribution of tail length relative to snout-vent length for sufficiently large samples across several sites.

3.3.2.2 Arms not emerging from the branchial cavity. We found reports of 48 individuals from natural populations in which one arm remained hidden within the branchial cavity: 13 *Rhinella marina* (n = 13,856; Bacon et al. 2006b), ten tadpoles of *Bufotes viridis* in the final stages of metamorphosis in a quarry in Roßwag, Germany (Henle et al. 2017a), three individuals in Argentina (one *Leptodactylus latrans*, identity not provided for

Fig. 24: Juvenile *Pelophylax ridibundus*, with tail still very long; additionally, the opecular chamber is still open, Ekaterinburg, Russia, 17.8.2005. Photo: V. Vershinin.

the other two individuals) (Peltzer et al. 2001), three *Lithobates pipiens* (Meteyer 2000, Levey et al. 2003, Lannoo 2008) and one individual each of *Bombina bombina* (Fayzulin 2011), *B. variegata* (Dubois 1979a), *Ranoidea aurea* (Richardson & Barwick 1957), *Pseudacris regilla* and *Lithobates sylvaticus* (Reeves et al. 2013). Annandale (1905) reported a tadpole of *Clinotarsus alticola* in which both forearms remained hidden beneath the skin; the individual also lacked both hindlimbs. Murphy (1965) collected 12 *L. palustris* (n = 990) in which one or both forelegs only partly emerged. In addition, we have a photograph of a juvenile *Rana arvalis* (Fig. 25) from Russia in which one foreleg did not erupt.

The cause of the *B. viridis* case was most likely to be radioactive pollution (Henle et al. 2017a). Murphy (1965) considered a genetic cause; no cause has been suggested for the remaining cases.

Failure of forelimbs to emerge from the branchial cavity occurred in several offspring of *Incilius valliceps* whose parents descented from the cross of an irradiated male and a control female (Blair 1960).

Several factors not considered for natural populations had been associated with the failure of a limb to emerge from the branchial cavity in experiments and in husbandry. Günther (1990, 1996b) occasionally observed it in experimental crosses within the *Pelophylax esculentus* complex. In tadpoles of a F_3 clutch of *Discoglossus pictus auritus* that developed thin and stiff front legs, these also occasionally remained covered by the opercular fold (Glaw 1987). Likewise, in captive *Gastrotheca riobambae,* the front legs often had difficulties to break through the skin and the skin had to be opened surgically (Hammermeister 1991). In some *Pleurodema cinereum* that were fed with food tablets the front leg remained hidden within the branchial cavity (Christmann 1995). After termination of the feeding of food tablets, the remaining tadpoles developed normally.

Fig. 25: One arm remaining covered underneath the opercular fold of skin in a juvenile *Rana arvalis*, Ekaterinburg, 8.7.1987. Photo: V. Vershinin.

Disruption of the thyroid axis often leads to one arm remaining within the branchial cavity. When tadpoles are fed with mammalian thyroids (Romeis 1914/15, 1918, Kahn 1916) or thymus oil extracts (Wink & Wurmbach 1967), one arm often fails to break through the skin that covers the branchial cavity, presumably due to a thickening of the skin (Romeis 1918). Many tadpoles of *Dryophytes versicolor* treated with perchlorate from the early larval stages onwards and iodine added after 70 days died during metamorphosis, often with only one arm having emerged (Sparling et al. 2003). Perchlorate strongly competes with iodine for storage in the thyroid and thus interferes with thyroid hormone production. When larval *Hoplobatrachus tigerinus* were treated with the pesticide methyl parathion, front legs also failed to break through the branchial cavity (Kennedy & Sampath 2001) but no data were presented; thus, the frequency and whether the effect was significant or not cannot be assessed.

In one individual of *L. sylvaticus* exposed to a strong magnetic field at the egg stage (17,700 Gauss), the arm did not emerge from the branchial cavity (Levengood 1969).

3.3.2.3 Skin webbing. Although skin webbing (synonym: cutaneous fusion), together with bony triangles, has been regarded as diagnostic for abnormal development induced by infection with the trematode *Ribeiroia ondatrae* (Johnson & Hatrson 2009), neither a review of its occurrence in natural populations nor in experimental teratogenesis exists. We collated 41 cases in our database, all but one from anurans. Except for seven, all originated from North America, involving the species *Ambystoma macrodactylum croceum* (Johnson et al. 2006), *Anaxyrus americanus* (Johnson & Hartson 2009), *A. boreas* (Johnson et al. 2001b), *Lithobates blairi, L. palustris, L. sphenocephalus, L. sylvaticus* (Reeves et al. 2013), *L. clamitans, L. pipiens* (Vandenlangenberg et al. 2003, Hoppe 2005, Reeves et al. 2013), *Rana luteiventris* (Johnson et al. 2002, Richards & Dickinson 2012), *L. septentrionalis* (Gardiner & Hoppe 1999, Vandenlangenberg et al. 2003, Hoppe 2005), *L. sylvaticus* (Reeves et al. 2008), *Pseudacris regilla* (Sessions & Ruth 1990, Johnson et al. 2003, Roberts & Dickinson 2012), *R. aurora* (Johnson et al. 2002) and *R. pretiosa* (Bowerman & Johnson 2003).

The seven cases outside North America are a ranid frog from Germany (Landois 1882), in which skin webbing extended along the entire upper and lower shank, up to twelve *Bufo bufo* – it is unclear how many of them had skin webbing and how many syndactyly – from Germany (Veith & Viertel 1993), one adult each of *B. bufo* and *Hyla arborea* from the Ukraine (Maruschak & Muravynets 2013), one *Hyla meridionalis* from France (Delcourt 1963), three individuals of *Rhinella marina* from Bermuda (Bacon et al. 2006b) and a juve-

nile *R. jimi* from a population introduced to the island of Fernando de Noronha (Toledo & Ribeiro 2009). In the German *B. bufo* the anomaly was likely due to limb damage from leeches (*Erpobtella octoculata*).

While the cause(s) of the North American cases has been controversial (Sessions & Ruth 1990, Gardiner & Hoppe 1999, Stopper et al. 2002, Bridges et al. 2004, Lannoo 2008), many of these cases were associated with *Ribeiroia ondatrae.* Skin webbing is a frequent anomaly in experimental infections with *R. ondatrae* (e.g., Johnson et al. 1999, 2001b), albeit not always. For example, experimental infection of *Ambystoma macrodactylum* did not produce a single individual with cutaneous fusion but the anomaly was common in a field site (Jette Pond), in which the parasite was present. In spite of this inconsistency all anomalies were explained by infection with *R. ondatrae* (Johnson et al. 2003, 2006). It should be noted that, while chemicals have been rejected categorically as an explanation for mass anomalies (e.g., Stopper et al. 2002, Sessions 2009), a lipophilic extract of a water sample from the CWB hotspot site, where *L. pipiens, L. septentrionalis* and *L. clamitans* exhibited skin webbing (Vandenlangenberg et al. 2003, Hoppe 2005), induced the same anomaly in the laboratory (Bridges et al. 2004). Notably, two commonly used agricultural chemicals, carbaryl in combination with atrazine, significantly increased the frequency of skin webbing in *L. pipiens* (up to 80% of the treated individuals) (Bridges et al. 2004).

In some locations in which skin webbing was detected, e.g., in the Kenai Wildlife Refuge in Alaska, *R. ondatrae* could not be found and pollution is a more likely explanation (Reeves et al. 2008). Moreover, *R. ondatrae* is absent from Bermuda (Bacon et al. 2006b) and Europe. The Bermuda cases have been explained by pollution (Bacon et al. 2006b) and the German cases by damage inflicted by leeches (Veith & Viertel 1993). Thus, skin webbing can be caused by factors other than infection by *R. ondatrae* and both *R. ondatrae* and pollution were likely to have contributed to the reported cases.

3.3.2.4 Misplaced or abnormal spiraculum, ventral tube, or operculum. We only know of three publications that mention this anomaly for natural populations. In a tadpole of *Pelobates fuscus* the spiraculum was situated on the wrong side of the body (Héron-Royer 1884). In one out of 47 *Leptobrachium pullum* the spiraculum was dextral instead of sinistral (Sunderasan & Rowley 2012). Additionally, the ventral tube was sinistral instead of dextral and various internal organs also showed reversed positions. One albinistic tadpole of *Bufotes viridis* collected in a quarry near Roßwag, Germany (an anomaly hotspot most likely due to radioactive contamination), had a mid-ventrally instead of laterally placed spiraculum (Henle et al. 2017a).

Only in two experimental studies a misplaced or abnormal spiraculum was mentioned. Berger (1967) detected two tadpoles with the spiraculum on the left instead of the right side and one on the belly among approximately 3000 individuals obtained in experimental crosses among the species *Pelophylax esculentus, P. lessonae* and *P. ridibundus*. In addition, Oerter (1985) noted one individual with a malformed operculum in a *B. bufo* that had been irradiated as an embryo.

3.3.2.5 Mouthparts abnormal in tadpoles. We do not know of any review of this type of anomaly. Our database contains 94 cases covering at least 74 anuran species. In 37 out of 72 cases with a sample size of at least 50, more than 10% and up to 100% of the individuals were affected and Mendelson et al. (2004) reported that 60–70% of several thousand tadpoles of *Ptychohyla hypomykter* showed abnormal mouthparts.

Of the cases with abnormal mouthparts 59% were attributed to infection by the chytrid fungus *Batrachochytrium dendrobatidis.* Infected individuals typically showed absence of dark keratinization of mouthparts, had missing, misshaped or interrupted labial tooth rows, swollen oral papillae or malformed jaw sheaths (e.g., Lips 1998, 1999, Fellers et al. 2001, Lips et al. 2004, Rachowicz & Vredenburg 2004, Knapp & Morgan 2006, Felger et al. 2007, Patel et al. 2012, Vieira et al. 2013). Therefore, malformation and absence of dark keratinization of mouthparts were used as characteristics to diagnose this disease in early studies. However, this is not possible. Infected tadpoles may appear normal and depigmentation can have other causes. For example, 27–94% of the tadpoles of four Californian anurans had malformed mouthparts without an infection with *B. dendrobatidis* (Padgett-Flohr & Goble 2007). Similarly, Drake et al. (2007) counted mouthpart anomalies relating to labial papillae, tooth rows and keratinized jaw sheaths in 13 populations of North American anurans belonging to the genera *Anaxyrus, Hyla* and *Lithobates*. Malformed mouthparts were common in all populations (13.5–98%) but *B. dendrobatidis* was only found in three of them. Some anomalies were minor and would probably be regarded as normal natural variation by others, such as Nichols (1937) in his study of *A. fowleri, Pseudacris triseriata* and *L. pipiens.* Rachowicz (2002) showed experimentally for *Rana muscosa* that pigmentation of mouthparts changes seasonally, with an absence of pigmentation under cold temperatures and reversibility of depigmentation when tadpoles were transferred to higher temperatures.

In a population of *Rhinella jimi* introduced to the oceanic island Fernando de Noronha 52.5% (n = 413) of the tadpoles collected from 2009 to 2010 had abnormal mouthparts, including missing tooth rows and lack of dark keratinization of mouthparts (Tolledo et al. 2014). Likewise, 45% out of 113 tadpoles of *Peltophryne fustiger* collected on Cuba had abnormal mouthparts including lack of dark keratinization (Alfonso Bosch et al. 2017). The cause for these high rates of anomalies remains unknown.

Abnormal mouthparts are often observed in captive raised tadpoles, e.g., in *A. americanus* (Tubbs et al.

1993), *Sclerophrys gutturalis* (Wager 1986) and *R. arvalis* (Grillitsch & Grillitsch 1989, Trubetskaya 2006). They appear frequently when tadpoles are raised at high but rarely when they are raised at low temperatures (Bresler 1954), which is opposite to what Rachowicz (2002) observed for the presence of dark keratinization of mouthparts.

Abnormal mouthparts were twice as common in the hybrid zone of *Bombina bombina* and *B. variegata* compared to populations from both species (Szymura & Barton 1986), but statistical tests were not presented.

Two cases of abnormal mouthparts were due to chemical pollution. In *L. catesbeianus* living in a pond contaminated by coal combustion waste, mouthparts lacked dark keratinization and labial tooth rows in 96% of the tadpoles (n = 1048). Rowe et al. (1998) showed experimentally that the pollution was responsible. In a *Bufotes viridis* population from a quarry in Roßwag, Germany, more than 250 (n = 2000–5000) tadpoles showed malformed mouthparts that were most likely due to radioactive contamination (Henle et al. 2017a).

Chemicals and irradiation also frequently induce abnormal mouthparts in experimental exposure studies, e.g., aminocarb in *L. clamitans* (Lyons et al. 1976 fide Power et al. 1989), DDT and DDE in *Bufo bufo* and *R. temporaria* (Cooke 1971, 1972, 1973), Zn in *Xenopus laevis* (Dawson et al. 1988), jodothyrin and thyroid extracts in *R. temporaria* (Romeis 1918). Oerter (1985) and Trux (1985) observed missing and interrupted labial tooth rows, partial absence of denticles and the keratinized beaks and lack of labial papillae in tadpoles developing from irradiated embryos of *B. bufo*. Moreover, *R. japonica* and *Pelophylax nigromaculatus* raised from irradiated eggs or sperm transmitted malformation of the labial teeth to the second generation (Nishioka 1977, 1978, Kawamura & Nishioka 1978). In one F_3 cross of *X. laevis,* Droin & Beauchemin (1975) detected a recessive genetic degeneration of the lower jaw in tadpoles. Rostand (1947) and Volpe & Dasgupta (1962) obtained gynogenetic tadpoles with missing or poorly developed denticles in *B. bufo* and *L. pipiens*, respectively.

3.3.3 Abnormal size

3.3.3.1 Giant larvae and adults. It is often difficult to decide whether large size is still within the expected normal range of size or abnormal. We include cases in which the author(s) referred to their observation(s) as gigantism or talked about abnormal size. We further include cases in which the reported size was at least 25% larger than the maximum size reported in other studies for the species.

Giant adults have been reported for one *Speleomantis flavus* (Lanza et al. 1986), two *Ichthyosaura alpestris* (Arribas 2008), two *Pleurodeles waltl* (Wolterstorff 1925b), one female *Anaxyrus terrestris* (Means & Richter 2007) and one female *Rana luteiventris* (Hayes & Cassidy 2013).

Various urodeles exhibit neoteny, in which larvae grow to adult size and reproduce without metamorphosis (e.g., Henle 1983). We exclude such cases from this review. Anuran larvae, in contrast, generally do not reach sexual maturity as larvae, although there are two reports of giant tadpoles of *Pelophylax ridibundus* and *P. esculentus*, in which one individual of the former species had eggs in the oviducts and three individuals developed testes; of the latter species one individual had well developed paired gonads (Lusis & Tsaune 1984, Milto 2009). Likewise, giant *Xenopus laevis* tadpoles may develop fully differentiated gonads but do not reproduce (Rot-Nikcevic & Wassersug 2004).

Gigantism in tadpoles was reviewed for green frogs (genus *Pelophylax*) by Borkin et al. (1981, 1982) and for European anurans by Günther (1990). However, there have been no reviews of other anurans or urodeles. Giant larvae were found in 78 natural populations of 23 anuran species and 9 urodele species. They have been reported most frequently in tadpoles of the *P. esculentus* complex (Borkin et al. 1981, 1982, Günther 1990, 1996b, Atakhanova & Bigaliev 1995, Fagotti et al. 2005). Mass incidences with at least ten giant larvae in samples of at least 50 individuals and an abnormaility rate of at least 2.5% were observed three times: 95.8% (n = 166) *Lissotriton helveticus* from Belgium (Giltay 1932), 33.2% (n = 177) *L. vulgaris* in Germany (Kordges et al. 2008), and at least 5–12.5% (n = 2000–5000) *Bufotes viridis* in Germany (Henle et al. 2017a). The latter case was most likely due to radioactive pollution (Henle et al. 2017a). Whereas 31 other types of anomalies occurred in this population, only a few other anomalies (if at all) were observed in all other cases in which giant tadpoles or larvae were discovered.

One other case, 30 (n = ?) giant tadpoles of *P. ridibundus*, originated from fishponds in Kazakhstan. The fishponds were probably contaminated by an emergency chemical discharge from a copper combinate (Atakhanova & Bigaliev 1995), which likely was the cause for the giant larvae.

Borkin et al. (1981, 1982) discussed the hypotheses suggested to explain giant tadpoles and concluded that only a disruption of the hypothalamus-pituitary-thyroid axis evoked by genetic factors and the continued presence of larval growth hormones could explain their occasional occurrence. However, it is also conceivable that external factors or disease could cause a disruption to the hypothalamus-pituitary-thyroid axis.

Laboratory studies corroborate that any disruption of the endocrine thyroid axis, which regulates metamorphosis (Kaltenbach 1996, Hayes 2000), can cause giant larvae. Thyroid ectomy (Allen 1917), mutations and other factors that block or modulate the effects of thyroid hormones or the enhancing effects of corticosterone on thyroid hormones as well as a lack of thyroid receptors will lead to the failure of metamorphic changes (Kobayashi & Gorbman 1962, Galton 1992, Hayes 2000) and continued growth (e.g., Pohland 1962, Wink & wurmbach 1967). Thus, hypophyseal hypertrophy (Hahn 1912, Dodd

& Dodd 1976), low light intensity, which inhibits the development of the thyroid gland (Toivonen 1952), and various chemicals can cause giant larvae. For example, perchlorate inhibits iodide uptake by the thyroid gland at environmentally relevant concentrations (Goleman et al. 2002) and may lead to giant tadpoles (Coleman et al. 1968) and estradiol blocks the conversion of thyroxine into the more potent triiodothyronine (Nishimura et al. 1997). Feeding tadpoles on defenuron (Paulov 1977), thymus oil (Pohland 1962, Wink & Wurmbach 1967), labrafil and oils prepared from plants (rape seed, cotton seed, sesame seed, wheat germ) (Pohland 1962, Wink & Wurmbach 1967) also results in giant individuals. Administration of thyroid hormone to giant tadpoles can induce metamorphosis (Guex et al. 2001).

Occasionally, giant albinistic tadpoles were observed in experimental crosses within the *P. esculentus* complex (Tunner 1980, Guex et al. 2001), in *Epidalea calamita* × *Bufo bufo* and *Bufotes viridis* × *Bufo bufo* (Hertwig & Weiss 1955, Hertwig et al. 1959, Weiss 1960).

Ponse (1941a,b) obtained giant tadpoles of *B. bufo* from eggs that were taken from Bidder's organ in castrated females but the mechanism for this result is unclear.

A genetic origin for giant growth has frequently been assumed (e.g., Ponse 1941a,b, Freytag 1956, Borkin et al. 1981, 1982, Tarkhnishvili & Serbinova 1998) – a plausible explanation given the tight genetic control of the thyroid axis and its pivotal role in metamorphosis (Hayes 2000). While congenital absence or reduction of the thyroid has been observed several times (Toivonen 1952, Saxén 1957, Rot-Nikcevic & Wassersug 2003), so far a genetic origin for gigantism in larval amphibians has only been demonstrated in a female *Xenopus laevis* obtained from nuclear grafting (Uehlinger 1965).

3.3.3.2 Nanism. It is difficult to judge whether small individuals found in natural populations can be classified as abnormal dwarf specimens or whether they are still growing (e.g., tadpoles derived from late clutches or individuals that underwent an early metamorphosis) and will eventually reach a normal size. Reports of small individuals from natural populations generally do not allow a clear differentiation among these alternative explanations, except for in a few cases.

Ippisch (1928) collected an unstated number of dwarf tadpoles of *Bombina variegata* that did not grow when transferred to an aquarium with ample food. Lenk (1995) reported on an abnormally small leucistic tadpole of *Pelobates fuscus*. Meteyer (2000) illustrated two emaciated dwarf postmetamorphic *Lithobates pipiens*. Metamorphosed *Rana arvalis* in the Uralian radioactive trace of the Chelabynsk oblast, Russia, were significantly smaller than individuals from non-contaminated control sites (Pyastolova & Vershinin 1999, Vershinin & Seredyuk 2000). In a population of *Bufotes viridis* from a quarry in Roßwag, Germany, more than 100 dwarf tadpoles were observed in 1980. All dwarf individuals also showed various anomalies of the mouthparts, which probably reduced their ability to ingest food. The combination of small size and abnormal mouthparts puts forward a case for a developmental anomaly in this case. The ultimate cause was presumably radioactivity (Henle et al. 2017a).

Experimental studies have shown that many factors can cause growth retardation or nanism in amphibian larvae or metamorphs. For example, dwarf metamorphs result if the dorsal chorda is injured or the tail amputated in embryos of *R. temporaria* (Aron 1929). Dwarf tadpoles occasionally occur in experimental crosses between *Epidalea calamita* × *Bufo bufo, E. calamita* × *Bufotes viridis* and *Bufotes viridis* × *Bufo bufo* (Hertwig & Weiss 1955, Hertwig et al. 1959, Delarue 1982), in crosses within the *Pelophylax esculentus* complex (Berger 1967) and in crosses of *Pseudophryne corroboree* from different geographic origins (which most likely represent different species) (Osborne & Norman 1991).

Almost any chemical in high enough concentration will reduce, retard, or stop the growth in amphibian larvae and for many chemicals, effects on growth start well below lethal concentrations (e.g., Marian et al. 1983, Power et al. 1989, Materna et al. 1995). Irradiation of embryos also frequently inhibits growth (e.g., Brunst & Figge 1951, Gallien 1969b, Oerter 1985). Heritable recessive dwarfism has been discovered by Lipsett (1941) in an inbred line of *Ambystoma mexicanum,* by Kaylor (1940) in *Cynops pyrrhogaster* and by Droin (1988) in *Xenopus laevis.*

3.3.4 Edema and bloatedness, tumours and nodules, cysts and swellings

3.3.4.1 Edema and bloatedness. The literature on amphibian anomalies often does not differentiate between edema (Fig. 26), i.e., intercellular accumulation of fluids and inflation of the body from gas. Bloatedness is often used for both types of anomalies, sometimes only for the latter one. Thus, some of the cases included here under edema may actually be cases of the accumulation of gas in the body cavity rather than edema.

Fig. 26: Edema in a metamorph of *Pelophylax ridibundus,* Ekaterinburg, Russia, 16.9.1980; Photo: V. Vershinin.

We found 158 cases of bloatedness (edema or gas accumulation), covering 51 species. Reported background rates of edema are very low (0.01–0.4%; Tab. 1) and we only know of four cases in which at least 5% of the population were abnormal and at least 2.5% of the population and ten individuals were affected by edema. In three out of ten years, Wittouck (1980) detected a total of 50 edemateous *Pelophylax esculentus* with an average frequency of 17% in those three years. He suggested a genetic cause. In a population of *Bufotes viridis* in a quarry near Roßwag, Germany, more than 250 tadpoles (n = 2000–5000) and more than 30 (n = 1630) toadlets exhibited severe edema (Flindt 1985a, Henle et al. 2017a), with radioactivity being the most likely cause (Henle et al. 2017a). In wetlands constructed with treated wastewater in Georgia, 39 (n = 833) tadpoles of *Lithobates catesbeianus* exhibited edema, whereas none out of 190 individuals from reference sites was affected (Ruiz et al. 2010). Slightly elevated rates of edema occurred in tadpoles of *Bombina bombina* (1.5%, n = 400), *Bufotes viridis* (0.8%, n = 500) and *P. ridibundus* (2.2%, n = 500) collected in polluted habitats in the Ukraine (Flax & Borkin 2004). Finally, O'Connor et al. (2016) observed at least 100 tadpoles of *Lithobates sylvaticus* with swollen – presumably edemateous – hindlimbs floating on the surface. Ten of the sampled tadpoles were infected with *Ranavirus*.

In cases where only a few individuals were affected by edema, a range of causes have been suggested, most often disease (e.g., Densmore & Green 2007), pollution (e.g., Mizgireuv et al. 1984), or hybridization (e.g., Hemmer 1973, Gollmann et al. 1984). Occasionally, edema was also observed in toads (*Bufo bufo*) parasitised by the maggots of *Lucilia bufonivora* (Stadler 1930, Neumann & Meyer 1994) and in *Pseudacris regilla* parasitized by the trematode *Ribeiroia ondatrae* (Johnson et al. 2001a). In all of these cases no attempts have been made to test the cause experimentally. A causal relationship is unlikely in the case of *R. ondatrae* infection, since it generally does not appear in experimental infections.

Six cases were definitely gas accumulations. Guderyahn (2006) discovered ten tadpoles/recently metamorphosed *Lithobates sylvaticus* with gas accumulation when surveying four national wildlife refuges in Alaska (n = 164). Reeves et al. (2013) additionally listed two tadpoles of *Rana aurora* from one site and three tadpoles of *L. sphenocephalus* from two sites that exhibited gas accumulations. In rare cases, the pulmonary nematode *Rhabdias tokyoensis,* a parasite of *Cynops pyrrhogaster,* penetrates the lungs of the infected individuals allowing the peritoneal cavity to fill with air while inhaling; individuals affected are greatly distended and float at the surface (Pfeiffer-Asashima 1997). Mutschmann (2010) found a greatly distended adult *B. bufo* that died after three days. He assumed injuries from predator attacks as cause.

Laboratory experiments have shown that many factors can cause edema: e.g., bacterial and viral infections, pronephric defects, degenerative and toxic kidney and liver diseases, heart and lymph heart insufficiencies (e.g., Granoff et al. 1969, Wolf et al. 1969, Newcomer et al. 1982, Olson et al. 1992, Green 2001, Ny et al. 2005, Lee & Elinson 2008), unbalanced nutrition and deprivation of food (Reinhardt 1939, Grimm 1953, Reichenbach-Klinke 1961, Jara 1963), which in some cases is reversible (Mangold 1955), forced overripeness of eggs (Witschi & Chang 1954), chilling of embryos in a refrigerator (Coghill 1936), temperature shock (Fischberg 1948), rearing at high temperature (Muto 1969a; but see Muto 1969b) and treatment with high intensity of light (Ruehmekorf 1958) or ultrasound (Pourhadi et al. 1968). It also becomes frequently manifest in experimental hybridizations (e.g., Berger 1967, Berger & Uzzell 1977 Kuramoto 1983), including experimental crosses of European species of toads (e.g., Pflüger & Smith 1883, Born 1886, Montalenti 1933, Hertwig & Weiss 1955, Hertwig et al. 1959, Kawamura et al. 1980, Delarue 1974, 1982). Edema also occurred in tadpoles of *Polypedates crucifer* when they were exposed at the pre-limb bud stage (Gosner stage 25 and 26) to *Acanthostomum* cercariae (Jayawardena et al. 2010, Jayawardena & Rajakaruna 2013) but not when limb bud stage tadpoles (Gosner stage 27 and 28) were exposed (Rajakaruna et al. 2008).

A very wide range of chemicals can cause edema in embryos or tadpoles, often at very high rates. These include various organochlorine, organophosphate, carbamate (reviewed by Power et al. 1989) and pyrethroid insecticides (e.g., Fort et al. 1999b), various herbicides and fungicides (e.g., Harris et al. 1998; partly reviewed by Power et al. 1989), atrazine (Morgan et al. 1996), hydrazine and derivates (e.g., Greenhouse 1976, 1977), vitamin A and retinoids (e.g., Syuzyumova 1985, DeYoung et al. 1991), various metals (e.g., Pérez-Coll et al. 1985), low pH (e.g., Haidacher & Fachbach 1991), nitrates and nitrite (e.g., Hecnar 1995, Marco et al. 1999), as well as PCBs (Birge et al. 1978).

Exposure to X-rays, γ-rays, or neutron irradiation of any developmental stage of amphibians induces severe edema often at high frequency (e.g., Stachowitz 1914, Rugh 1950, Labrousse 1967, Nishioka 1977, Kawamura & Nishioka 1978, Oerter 1985, Trux 1985; partly reviewed by Ahmad 1976). High intensitiy UV-B irradiation also causes severe edema (e.g., Kashiwagi 1980, Nishioka et al. 1981, Grant & Licht 1995) but whether or not natural levels can induce elevated rates is still unclear. Hays et al. (1996) attributed high rates of edema in metamorphs of *Lithobates cascadae* and *Pseudacris regilla* and in tadpoles of the latter species to treatment with moderate levels of UV-B. However, the main difference in the appearance or frequency was related to light levels in the laboratory, with dim lights having more severe effects than moderate lights. This finding may be related to the need for light as the most important repair mechanism of UV-B damage: the photoreactivation with the help of the enzyme photolyase (Sinha & Häder 2002). In the study by Pahkala et al. (2002) UV-B was only effective at low pH, which can

cause edema on its own (e.g., Haidacher & Fachbach 1991) and, unfortunately, their figures combine edema with kinky tails. In any case, most authors (e.g., Calfee et al. 2006) did not report edema under natural UV-B levels (but see e.g., Blaustein et al. 1997 for *Ambystoma macrodactylum*).

Several studies demonstrated – usually recessive – heritability of edema in *A. mexicanum* (e.g., Humphrey 1964, 1972, Smith & Armstrong 1990; reviewed by Malacinski 1978), *Pleurodeles waltl* (Gallien & Collenot 1964, Signoret et al. 1966) and in *Xenopus borealis, X. laevis, X. muelleri* and *X. tropicalis* (e.g., Uehlinger & Reynaud 1965, Droin & Colombelli 1982, Hart & Armstrong 1984, Krotoski et al. 1985).

In conclusion, edema is a very general expression of a developmental disorder and, in the field, does not pinpoint to a specific cause.

3.3.4.2 Tumours and nodules. A tumour is an abnormal mass of tissue resulting from excessive cell division. Tumours can affect all organs. We restrict this review to externally visible tumours. Nodules are swellings that contain lipids or particles of microorganisms (Henle et al. 2017b). They often are initial stages in the formation of tumours (Lucké & Schlumberger 1949). Some authors (e.g. Ruiz et al. 2010) call swellings caused by atypical deposition of chrystals nodules and some (e.g., Green et al. 2002) call swellings caused by parasites nodules whereas we treat them under the heading "cysts and other forms of swellings" (chapter 3.3.4.3). Where possible, depending on the information provided by the authors, we adjusted terminology to the one used here.

The occurrence of tumours in amphibians has been repeatedly reviewed (Schlumberger & Lucké 1948, Willis & Collins 1948, Lucké & Schlumberger 1949, Balls 1962a, Balls & Ruben 1964, Mizell 1969, Balls & Clothier 1974, Balls et al. 1978, Asashima et al. 1987, Green 2001). These reviews did not differentiate between internal and externally visible tumours. Balls & Clothier (1974) cited more than 100 reports involving 53 species. Our review covers 95 cases of externally visible tumours from 35 species and 21 cases of nodules from 11 species.

Most cases of mass occurrence or elevated rates of tumours are from polluted sites (Tab. 7). Between 1970 and 1980 Rose (1976, 1991) and Rose & Harshbarger (1977) collected more than 2458 (annual mean 6.6%, range 0.04–50%; n = 37,143) *Ambystoma tigrinum* in a sewage pond at the Reese Airforce Base, Texas, that were affected by tumours. At 19 non-sewage ponds, by contrast, no tumours were detected (n = 19,802). The pond was contaminated by polycyclic aromatic hydrocarbons, especially perylene, and physiological studies indicated that metabolic derivatives of polycyclic aromatic hydrocarbons were the most likely inductor for the tumours. Flax & Borkin (1997, 2004) found 20 (n = 1980) *Bombina bombina* and 117 (n = 3505) *Pelophylax ridibundus* with tumours at sites in eastern Ukraine that were polluted by sewage and Mizgireuv et al. (1984) counted 126 (n = 1095) and 202 (n = 3651) *Rana pirica* with tumours at sites in Sakhalin, Russia, that were polluted with the wastewater of a paper and pulp mill and municipal sewage, respectively. Patel et al. (2008) reported 11 *Fejervarya limnocharis* with tumours from contaminated agricultural sites. In a polluted site in Horicon National Wildlife Refuge, USA, 16 of 125 tadpoles and recently metamorphosed *Lithobates pipiens* had small translucent pustules (Reeves et al. 2013); in four other National Wildlife Refuges 22–83% ($n \geq 86$) of the tadpoles had pustules or nodules. In a quarry near Roßwag, Germany, 10–25 (n = 295) toadlets of *Bufotes viridis* with tumours were encountered in 1980, with radioactivity being the most likely cause (Henle et al. 2017a).

Besides pollution, microorganisms, fungi, and virus have been found or suggested as cause for elevated rates of tumours. In Malaysia, Dhaliwal & Griffiths

Table 7: Elevated rates of tumours in amphibian populations (≥ 5% of the population abnormal, ≥ 2.5% of the population and ≥10 individuals with tumours. *N:* sample size; only cases with $N \geq 50$ included; % tumours refers to the sample size. Cause: (e): the cause was supported by experimental studies; all other causes are assumptions.

Species	*N* (% abnormal)	% tumours	Location	Cause	References
Ambystoma tigrinum	37,143 (6.6%)	(mean 6.6%, range 0.04-50%)	Reese Airforce Base, Texas, USA	Polycyclic aromatic hydrocarbons (e)	Rose 1976, Rose & Harshbarger 1977
Duttaphrynus melanostictus	471 (46.3%)	46.3%	Kuala Lumpur, Malaysia	Fungus (e)	Dhaliwal & Griffiths 1963
Pleurodema cinereum and/or *Pleurodema marmoratum*	663 (9.7%)	19.5%	La Paz, Bolivia	Unknown (bacilli assumed)	Machicao & La Paca 1954
Lithobates pipiens	74 (28.4%)	28.4%	Long Beach, Maryland, USA	Unknown	Hardy 1964

(1963) discovered 218 *Duttaphrynus melanostictus* with tumour-like lesions. An unidentified fungus caused the lesions, which were transmissible. In Bolivia Machicao & La Paca (1954) found tumours in 19.5% (n = 663) of the *Pleurodema cinereum* and/or *Pleurodema marmoratum* collected in the vicinity of La Paz. Bacilli were associated with the lesions.

Pfeiffer et al. (1979), Asashima & Komazaki (1980) and Asashima et al. (1982) collected 286 (n = 12,167) *Cynops pyrrhogaster* with skin papilloma in Japan, with the frequency varying geographically between 0% and 6.3%. Tsonis (1984) reported another 22 individuals with the same type of tumour. A virus was the cause for these cases, with temperature influencing its expression (Asashima et al. 1987). Since then Meyer-Rochow & Asashima (1988) and Fukui et al. (1996) collected another 170 (1.2%) and 67 (1.6%) affected individuals, respectively, from regions that overlapped with the sampling areas of these earlier publications. However, whether the same type of virus was involved or not is not mentioned.

Experimental studies showed that in many different organisms, including amphibians (Asashima et al. 1987), several forms of tumours have a viral ethiology (Gross 1961). Bacteria of the genus *Mycobacterium* can also lead to visceral tumour-like nodules (Inoue & Singer 1970, Hardwick & Philpott 2015). However, they do not have a neoplastic nature (Green 2001). In rare cases, the fungus *Mucor amphibiorum* induced tumour-like skin nodules and ulceration in *Rhinella marina* (Speare et al. 1997) and in one free-ranging *Ranoidea caerulea* (Berger et al. 1997), and in Africa, the fungus *Rhinosporidium rwandae* caused similar pathologies in *Hyperolius viridiflavus* and *H. lateralis* (Scheid et al. 2015). See Hardwick & Philpott (2015) for an overview of the developmental pathways that are involved in the proliferation of tumours.

Embryos from overripe eggs show abnormal ectodermal growth, some of them resembling papilloma (Briggs 1941). At later developmental stages, no tumours were observed.

Early reviews (e.g., Balls & Ruben 1964) stated that many attempts to induce tumours chemically failed because of rapid removal of tumourous tissue and the ability of amphibians to regenerate damaged tissue. While amphibians are relatively resistant to spontaneous and transplanted tumours (Hardwick & Philpott 2015), a range of chemicals is known to induce tumours in amphibians, such as tar, benzopyrene, dibenzanthracene, methylcholanthrene, fluorenacene, fluoraphene, diethylnitrosamine, potassium perchlorate and various aldehyde blocking agents, such as semicarbazides, hydrazines, nitriles and urea (Koch et al. 1939, Levy 1958, Pflugfelder 1959, Neukomm & Luder-Huguenin 1960, Arffmann & Collatz Christensen 1961, Balls 1962b, Seilern-Aspang & Kratochwil 1962, Ingram 1971, Khudoley et al. 1979). Therefore, newts are used as a standard test system for carcinogenic substances in Russia (Pliss & Khudoley 1979).

Irradiation can also induce tumours. Tumours developed in most adults of *Triturus carnifex* after intensive (1.3×10^5 J/m^2) UV-B irradiation (Zavanella & Losa 1981). Solid tumour-like swellings appeared on the back of some metamorphosed *Pelophylax nigromaculatus* developing from irradiated eggs or sperm (Kawamura & Nishioka 1978). The anomaly was still present in the second generation. Oerter (1985) observed tumour-like proliferation of the epidermis in early developmental stages of *Bufo bufo* that were irradiated as embryos.

3.3.4.3 Cysts and other forms of swellings. Cysts are swellings to encapsulate parasites. Some authors (e.g., Green et al. 2002) call swellings caused by parasites nodules. We include these anomalies under the term cysts, except for when the parasites are microorganisms. Our review covers 180 cases of cysts from 87 species (21 Urodela, 66 Anura) and 50 cases of other forms of swellings in 22 different species (2 Urodela, 20 Anura).

Reeves et al. (2013) listed two populations of *Lithobates clamitans*, in which 21 (n = 53) individuals in the final stages of metamorphosis had cysts. Trematodes (*Clinostomum*) were the cause. Trematodes presumably were also the cause in a population of *L. palustris,* a population of *L. pipiens* and two populations of *L. sphenocephalus*, in which 16 (n = 166), 54 (n = 67), 16 (n = 88) and 31 (n = 124), respectively, individuals showed small cysts. In two populations of *L. pipiens* and *L. clamitans* 46 (n = 52) and 52 (n = 137) individuals, respectively, had cysts but potential causes were not mentioned.

Infection by *Amphibiocystidium ranae* induced cysts in 12 out of 200 Swiss *Rana temporaria* and several *Triturus cristatus* sampled (Guyénot & Naville 1922), in 23 out of 43 Italian *Pelophylax bergeri* and eight out of 50 *P. hispanicus* (Pascolini et al. 2003). Several other cases involving fewer individuals exhibiting cysts were also attributed to infection with *Amphibiocystidium* spp. (e.g., Carini 1940) or to trematode parasites (e.g., Green et al. 2002).

Trombiculid mites of several genera usually, but not always, bury within the skin of their amphibian hosts, inducing the development of externally visible cysts. Some authors mentioned in addition a red or orange colour of the cysts (e.g., Pope & Pope 1951, Regester 2001, Anthony et al. 2004, Westfall et al. 2008). Heavy infection of the digits can result in ectromely (reported for *Desmognathus brimleyorum* by Winter et al. 1998). Species of the genus *Hannemania* parasitize anurans and urodeles in North, Central and South America (e.g., Sambon 1928, Duszynski & Jones 1973, McAllister et al. 1995, Jung et al. 2001, Regester 2001, Bradley et al. 2002, Hatano et al. 2007, Westfall et al. 2008). We found 80 published cases, involving 11 urodelan and 39 anuran host species, in which externally visible cysts caused by species of *Hannemania* were explicity mentioned.

Prevalences well above 50% have been repeatedly observed, e.g., in *D. fuscus, Eurycea bislineata, Plethodon ouachitae, Anaxyrus punctatus, Dryophytes arenicolor, Pseudacris cadaverina, Hylodes phyllodes*, *Lithobates*

berlandieri and *L. pipiens* (Pope & Pope 1951, Loomis 1956, Duszynski & Jones 1973, Shoemaker & Clark 1975, Welbourn & Loomis 1975, Jung et al. 2001, Anthony et al. 2004, Hatano et al. 2007, Westfall et al. 2008). Prevalences may vary substantially among years (Welbourn & Loomis 1975) and among host species (Jung et al. 2001, Regester 2001, Anthony et al. 2004, Hatano et al. 2007, Westfall et al. 2008). Primarily, terrestrial species are infested (Hatano et al. 2007). Aquatic and arboreal species usually do not harbour encysted mites (Wohltmann et al. 2007) but Quinzio & Goldberg (2015) also observed cysts in the aquatic *Telmatobius atacamensis*. Prevalences also differ among habitats. For example, significantly more *Leptodactylus chaquensis* were infected in rice and soybean fields than in native forests (Attademo et al. 2012).

Some but not all species of the genus *Vercammenia* also induce cysts (Domrow et al. 1983). For example, *V. hasseltii* induced tiny cysts in three terrestrial Malaysian frog species (Audy & Nadchatram 1958). *Vercammenia zweifelorum* caused externally visible orange cysts in the Australian microhylid *Cophixalus neglectus* but did not protrude above the skin level in *Taudactylus acutirostris* (Domrow et al. 1983). Likewise, larvae of *V. gloriosa* did not protrude beyond the lesion they created in *Taudactylus* spp. (Domrow et al. 1983).

In Africa and Madagascar *Endotrombicula* spp. induce orange cysts in the skin of terrestrial anurans, especially in species of the genus *Phrynobatrachus* (5 species, for which externally visible cysts were explicitly mentioned: Spieler & Linsenmair 1999, Wohltmann et al. 2007). Spieler & Linsenmair (1999) further mentioned a single infected individual of *Sclerophrys maculata*. On Madagascar, tiny cysts caused by *E. madagascariensis* were found in *Gephyromantis luteus* (Sambon 1928).

Larvae of the dipteran *Batrachomyia krausi* caused skin swellings in five populations of four frog species from Papua New Guinea (Kraus 2007). In one population of *Papurana supragrisea* 13 out of 16 examined individuals were parasitized.

Most other forms of swellings reported from wild populations were caused by parasites or fungal or viral infections. Many adult *Notophthalmus viridescens* with plaquelike swellings of the caudal half of the body, the rump and the proximal half of the body caused by a fungal disease (*Ichthyophonus*-like) were found in Virginia and Vermont (Herman 1984, Green 2001). In *L. clamitans* from Vermont an *Ichthyophonus* infection was associated with the swelling of the dorsal pelvic musculature (Green et al. 2002). A similar swelling was found in five recent metamorphs of *L. catesbeianus* from Massachusettes (Goodchild 1953). Whereas Goodchild (1953) regarded *Amphibiocystidium ranae* to be the cause, Green (2001) argued that *Ichthyophonus* also was the cause in this case.

The ciliate *Tetrahymena pyriformis* caused a swelling of the head and chest in larvae of *Ambystoma maculatum* that hatched in the laboratory from eggs collected in ponds with the ciliate present but not from eggs collected in a pond without the ciliate (Ling & Werner 1988). Swelling was followed by rapid death, usually within 24 h. A *Ranavirus* infection caused ulcers and swellings of the head, limbs and ventral surface in 61% (n = 570) of farmed *Andrias davidianus* (Geng et al. 2011).

Of 833 tadpoles of *L. catesbeianus* collected in wetlands constructed with treated wastewater in Georgia, USA, 110 had swellings that were completely filled with calcium phosphate (Ruiz et al. 2010).

Five publications mention abnormally swollen (but not clearly edemateous) digits. A juvenile *Bufotes viridis* from a quarry near Roßwag, Germany, in which radioactive pollution was discovered, had an abnormally swollen finger and another one showed an abnormally swollen shank (Henle et al. 2017a). Two *Anaxyrus canorus* in a population presumably suffering from immuno-depression due to an unknown factor had swollen toes (Green & Kagarise Sherman 2001). One recently metamorphosed *Rana muscosa* infected with *Batrachochytrium dendrobatidis* exhibited a thickened epidermis of the toe pad (Fellers et al. 2001) but none of the numerous other studies on chytrid infections of anurans mentioned the same kind of anomaly. One *R. amurensis* had a (several?) thickened phalange(s) (Gurvich 2014). In an Argentinian collection examined by Medina et al. (2013), four, five, and two individuals of *Leptodactylus chaquensis, Pleurodema borellii* and *Rhinella arenarum*, respectively, had swollen parts of digits.

In humans broadened thumbs and big toes are well-known clinical manifestations of the Rubinstein-Taybi-syndrome, which is caused by a mutation of the gene encoding the CRB-binding protein – a co-activator of cyclic AMP-regulated gene expression (Gurrieri et al. 2002). Whether swellings of digits in amphibians can also have a genetic cause is unknown.

3.3.5 Colour anomalies

The colours and patterns of amphibians are produced by the relative densities and arrangements of three basic types of pigment cells (melanophores, iridophores and xanthophores) and the types, presence, abundance and distribution of pigments within them (Frost-Mason et al. 1984). Any mutation or exogenous factor, which affects the distribution or abundance of any type of chromatophores, the distribution of the pigments within the chromatophores, or the synthesis chain of any kind of pigment, either totally or partially, will result in a "pigment pattern variant" or "colour variant". As most patterns are species specific so are colour anomalies and thus require a sufficient knowledge of the species in question to decide whether a particular phenotype is still within the "expected" normal variation or should be scored as an anomaly. Therefore, we limit our review to types of colour anomalies that occur across different species.

Most colour anomalies are due to genetic factors. However, depigmentation and paling may be due to temperature, disease, or chemicals. Likewise, darkening may be due to chemicals, UV-irradiation, or diseases.

Reddening in the form of haemorrhage may be caused by disease or injury and cysts produced by parasites may also have red or orange colour (e.g. Domrow et al. 1983, Westfall et al. 2008).

3.3.5.1 Albinism, hypomelanism and depigmentation. The terminology for whitish amphibians is inconsistent in the literature and the term albinism is either used in a narrow or a broader sense (Dyrkacz 1981, Henle et al. 2017b). Unfortunately, it is often impossible to know whether a particular publication used the term in the narrow or the broader sense. Consequently, in this section, we use the term in the broader sense but exclude cases that clearly belong to flavism or erythrism (see below). Thus, we include in this section any individual that completely or partially lacks pigmentation resulting in a white (complete albinos when eyes are red; leucism when eyes have normal colour), whitish, light pinkish (due to blood vessels) or paler than normal appearance. We further include individuals in which melanophores or melanin are absent (amelanistic) or strongly reduced (hypomelanistic), i.e., individuals, in which the body parts that are normally black appear abnormally faded to whitish but in which other types of pigments are present (Fig. 33b). We further review factors that can cause discolouration or depigmentation if the affected individuals show a whitish or pale colouration.

For some species, e.g., *Proteus anguinus*, albinism is the normal phenotype. Likewise, amphibian species that deposit their eggs in concealed sites tend to have white eggs but larvae or froglets that emerge from them are pigmented (Duellman & Trueb 1986, Passmore & Carruthers 1995). Such cases are not covered in the following review and the latter cases are usually not called transient albinism.

Albinism has received great attention and several reviews exist, most of them with a regionally limited coverage and/or restricted to specific taxa (Noble 1931, Rostand 1946, 1955b, Brame 1962, Gilboa & Dowling 1974, Hensley 1959, Dubois 1979b, Dyrkacz 1981, Frost et al. 1984a, 1986a,b, Klemz & Kühnel 1986, Klewen 1988, Günther 1996a, Rivera et al. 1993, Schlüpmann et al. 1995, Thiesmeier & Schulte 2010, Seidel & Gerhardt 2016). Browder (1975), Bagnara et al. (1978), Malacinski (1978), Dubois (1979b), Nishioka & Ueda (1985a,b), Sumida & Nishioka (2000), and Seidel & Gerhardt (2016) reviewed the heritability of albinism in selected taxa of amphibians. To our knowledge neither transient albinism nor discolouration has been reviewed.

Albinism is one of the most commonly reported anomalies in Amphibia. Our database contains 595 cases from 150 species (86 Anura, 64 Urodela) with partial or complete albinism. These include 15 cases that were termed depigmentation or discolouration, implying that pigmentation initially was normal but was lost later on. However, only in three cases a cause was suggested: skin discolouration in *Lithobates pipiens* presumably due to *Aeromonas hydrophila* infection (Hine et al. 1975), pale skin patches in *L. sylvaticus* due to infection with a ranavirus (Krynak & Dennis 2014) and discoloured tail tips in *Ptychohyla hypomykter* due to infection with *Batrachochytrium dendrobatidis* (Mendelson et al. 2004).

The earliest report of albinism dates back to Wurffbain (1683) who illustrated an albino *Salamandra salamandra.* Background rates of albinism are up to 1% but usually much lower (Tab. 1). The most exceptional case occurred in Japan where albinism was found in several species in an area of up to 250 km around Hiroshima, with most of them in the immediate vicinity of 6000 km². In this region, two albinistic adult *Pelophylax porosus* and 428 albinistic tadpoles of *P. nigromaculatus* were discovered (Nishioka & Ueda 1985a, Nishioka et al. 1987). Five different recessive genes caused albinism in these populations. In addition, at least 152 albinistic tadpoles (10.7%, $n = 1422$) of *Dryophytes japonicus* were collected at 12 sites from 1963 to 1975 (Daito 1968, Nishioka & Ueda 1977b, 1983). Nishioka & Ueda (1977b, 1983) identified three different recessive albino genes and two kinds of dominant melanising genes, which affected parts of the albino body. Moreover, one flavistic adult and more than 18 albinistic tadpoles of *Rhacophorus schlegelii* were found (Nishioka & Ueda 1985b). In all four populations, from which these individuals originated, recessive inheritance was demonstrated.

Another exceptional case is the finding of 100–250 ($n = 2000–5000$) albinistic tadpoles of *Bufotes viridis* in a quarry near Roßwag, southern Germany, which was most likely caused by irradiation from radioactive pollution (Henle et al. 2017a). It is interesting to note that a considerably elevated frequency of partial albinism (13–15%) that was caused by an increased rate of germline mutations was also observed in barn swallows (*Hirundo rustica*) from the contaminated area of Chernobyl (Ellegren et al. 1997).

Large numbers of albinistic tadpoles were also observed by Childs (1953), Johnston & Johnston (2006) and Hensley (1959): 298 (21%), 65 (1%) and 65 *Spea hammondi, Scaphiopus holbrooki* and *Gastrophryne carolinensis*, respectively. Martof (1962) collected 43 albinistic *Desmognathus marmoratus* between 1954 and 1960, with the frequency increasing from 0.7% to 8.9%. In 1963, the percentage had increased to 15% (Martof & Walton 1965). In the years 1997, 1998, 2000 and 2001 Nijs & Keller (2002) detected between 9 and 109 albinistic *Rana temporaria* tadpoles. While it is not rare that larvae that hatch from white eggs acquire pigmentation during larval development (see below), their observation is the only one known to us in which all eggs from clutches deposited were black and some larvae became gradually pale after some weeks. Dandová et al. (1995) and Kotlík & Zavadil (1997) observed 71 albinistic *P. lessonae* tadpoles. They assumed that chemical pollution had induced mutations that resulted in albinism.

While a genetic origin is likely for all the cases compiled, except the 15 cases termed discolouration and perhaps for the case reported by Nijs & Keller (2002), heritability has been demonstrated only for the Japanese

species studied by Nishioka and colleagues. For *P. nigromaculatus* heritable albinism has also been detected by Tokunaga (1949). In addition to these Japanese species, heritable albinism – always recessive – has been demonstrated in individuals collected in the wild from at least 11 further species: *Ichthyosaura alpestris* (Parent & Thorn 1983), *Triturus carnifex* (Capanna 1967, Capanna & Foresti 1974), *Salamandra salamandra* (Concaro 2004, Seidel et al. 2012), *Alytes obstetricans* (Héron-Royer 1886), *Bombina orientalis* (Ellinger 1980), *B. variegata* (Genthner & Hölzinger 2007), *Bufotes viridis* (Boschwitz 1963), *Pseudacris maculata* (Corn 1986), *Phrynobatrachus* sp. (Oeser 1952), *Lithobates pipiens* (Gibbs et al. 1971, Browder 1972) and *R. temporaria* (Smallcombe 1949). Only a single study failed to demonstrate a genetic origin (Nishioka & Ueda 1985e for partial albinism in *Pelophylax porosus*).

Albinistic individuals sometimes appeared in low numbers in experimental hybrids, probably due to gynogenesis (which results in haploid individuals), e.g., in crosses of *Epidalea calamita* × *Bufo bufo* (Hertwig et al. 1959), *E. calamita* × *Bufotes viridis* (Siboulet (1971), *B. viridis* × *B. bufo* (Born 1883, 1886, Hertwig & Weiss 1955, Hertwig et al. 1959), within the *P. esculentus* complex (Tunner 1980, Pabijan et al. 2004) and in *Geocrinia laevis* × *G. victorina* (Littlejohn et al. 1971, Gollmann 1991). In crosses within the *P. esculentus* complex transient albinism has also occasionally been discovered (Ogielska-Nowak 1985, Pabijan et al. 2004).

Mutations leading to albinism have been induced by treating adults with ethyl methanesulfonate and ethyl nitrosurea (Hart & Armstrong 1984) and by irradiation of eggs and sperm (Nishioka 1977, Nishioka & Ueda 1977a, 1985a, Kawamura & Nishioka 1978). In *P. nigromaculatus* these mutations were still retained in the 10th generation (Nishioka & Ohtani 1986). Genes controlling the expression of albinism may operate at different levels (Bagnara et al. 1978, Nishioka & Ueda 1985a). Some are involved in the production of tyrosinase, while others affect the melanosomal matrix.

While most attempts to establish heritability of albinism in individuals collected in the wild were successful, other factors may also cause whitish individuals. Experimental infection with Sri Lankan monostome-type trematode cercariae caused partial or complete lack of pigmentation in metamorphs of *Polypedates cruciger* (Rajakaruna et al. 2008) (significantly different to controls: $\chi^2 = 12.4$; $\alpha < 0.001$) but the mechanism for this effect and whether it is truly depigmentation remains obscure. Colour anomalies were not reported in experiments with the North American trematodes *Ribeiroia ondatrae* and *Alaria* sp. (Johnson et al. 1999, 2001b, Stopper et al. 2002, Schotthoefer et al. 2003). Disease (psittacosis, bacterial infection, frog virus 3 and *Batrachochytrium dendrobatidis*) can also cause (partial) depigmentation (Granoff et al. 1969, Newcomer et al. 1982, Nichols et al. 2001, Wright & Whitaker 2001).

Tornier (1907) observed that a diet consisting mainly of algae (with a minimum amount of meat required to allow growth) caused albinism in *Pelobates fuscus*. Though his observations have been questioned (see Freytag 1952a), bleaching due to nutritional deficiencies has been shown repeatedly for *Lissotriton vulgaris* (Klatt 1927, Krefft 1938) and an appropriate diet reverses it (Klatt 1927). Presumably, nutrition interfered with melanin synthesis in these cases.

There is a range of chemicals that are able to cause depigmentation or bleach amphibian skin: ammonium nitrate (Hecnar 1995), the insecticides aldrin (Rane & Mathur 1978), endosulfan (Brunelli et al. 2009), fenitrothion, benzene hexachloride, carbofuran (Pawar & Katdare 1983) and karbatox 75 (Rzehak et al. 1977), the herbicides maneb, nabam (Pawar et al. 1983) and their metabolite ethylene-thiourea (Ghate 1986) and coal gasification effluents (Dumont & Schultz 1980). Malathion strongly reduced pigmentation in *Microhyla ornata* and *Xenopus laevis* (Pawar et al. 1983), but no such effect was reported in *Rhinella arenarum* (Rosenbaum et al. 1988). Depigmentation is transient for sodium diethyldithiocarbamate treatment (Bancroft & Prahlad 1973, Ghate & Mulherkar 1980). S-methoprene might also cause amelanism but it was not significantly more frequent than in controls (Sparling 2000). Depigmentation also commonly develops when embryos receive high doses of irradiation: e.g., *Pleurodeles waltl* (Labrousse 1967), *I. alpestris* (Mangold & Peters 1956, Sanides 1956), *X. laevis* (Hart & Armstrong 1984) and *B. bufo* (Oerter 1985, Trux 1985).

Transient albinism is an anomaly in which some or all eggs are abnormally white and pigmentation is acquired during development (Henle et al. 2017b). Note that many amphibian species that deposit their eggs in concealed sites have white eggs as the normal phenotype and the larvae get increasingly pigmented. Such cases are usually not called transient albinism and not covered in our review. Our database contains 32 cases of transient albinism from 18 species. Most cases are white clutches (Fig. 27b) from which tadpoles hatched that increasingly acquired pigmentation soon after hatching. Most of these observations are based on single clutches; the maximum concrete number reported are three clutches in a population of *Bufotes viridis* (Christaller 1983, Flindt 1985b).

Completely white larvae of *S. salamandra* frequently develop the yellow colour pattern after metamorphosis (e.g., Opatrny 1979, Pastors & Greven 2016). There are only four other cases in which pigmentation was acquired at later developmental stages. In a *Pelodytes punctatus* population in Spain, 48 individuals were completely white as tadpoles, with red eyes, but acquired pigmentation after metamorphosis (Rivera et al. 2001). One adult female *T. cristatus* collected in the wild had a pigmentless chin and reduced pigmentation on the belly. It turned whitish within a few months in captivity; two years later it regained increasingly normal pigmentation (Freytag 1947). A cause was not provided but nutritional deficiency is known to be able to cause reversible albinism (Klatt 1927). From laboratory stocks

two further exceptions are known. A female *Ambystoma mexicanum* from a cross between a white and a black parent was initially white but became pigmented within 1.5 years (Häcker 1906). In a laboratory strain of *Dryophytes japonicus* a dominant colouring gene was only activated after metamorphosis (Nishioka & Ueda 1977b).

A genetic basis of transient albinism has also been demonstrated in laboratory strains of *A. mexicanum* (Humphrey 1975) and *X. laevis* (Hoperskaya 1975, 1981, MacMillan 1979, Droin & Fischberg 1984) and in *Pelophylax nigromaculatus* that were derived from irradiated eggs or sperm (Nishioka 1977, Nishioka & Ueda 1977a, Kawamura & Nishioka 1978). Heritability for albinism has further been demonstrated for *A. mexicanum* (e.g., Humphrey 1967a,b, Gallien 1969a, Malacinski & Brothers 1974; reviewed by Frost et al. 1984, 1986a,b), *A. tigrinum* (Humphrey 1967a), *Pleurodeles waltl* (Lacroix & Capuron 1970) and *X. laevis* (Krotoski et al. 1985, Droin 1992). Albinism (silvery tadpoles) in tadpoles of *L. pipiens* with congenital absence of the pituitary and/or the infundibulum and normal colouration in sibs that had both also indicates a genetic origin (Underhill 1967). These effects can be explained by the central role of melanotropic substances and tyrosine in melanin synthesis (Allen 1916, Smith 1916, Frost-Mason et al. 1984).

3.3.5.2 Black eyes. In black-eyed amphibians the eyes may either be completely or partially black. However, phenotypically all share a lack of the glittering iris (Nishioka 1977). A black iris is the normal phenotype in some species of anurans, e.g., in some species of the families Pelobatidae, Microhylidae, Bufonidae, Leptodactylidae, Hylidae, Dendrobatidae, Brachycephalidae and Ranidae (Glaw & Vences 1997).

Nishioka (1977), Dubois (1979b) and Richard & Nace (1983) reviewed the black-eyed anomaly focussing on ranid frogs. Our database contains data for 123 natural populations belonging to 29 species in which black-eyed individuals were observed; all but a single individual of *Lissotriton helveticus* (Dubois et al. 1973) were anurans. In most cases the number of individuals and frequencies were very low and only six publications reported more than 10 individuals from natural populations. Nishioka & Ueda (1985b) detected more than 42 black-eyed tadpoles in one population of *Rhacophorus schlegelii*, with the anomaly being heritable. Among 13,856 toadlets, juvenile and adult *Rhinella marina* examined in Bermuda Bacon et al. (2006b) discovered 19 with a dark brown or missing (i.e. black) iris. Within four years Rostand & Darré (1970) found approximately 60 *Pelophylax esculentus* with black eyes in the West of France.

Within 23 years Vershinin (2004) discovered 194 black-eyed *Rana arvalis* (Fig. 28a) among 15,803 individuals examined from four different environmental zones in Ekaterinburg and its vicinity. The frequency was higher in juveniles than in adults and in urban populations compared to populations from forests. He assumed that inbreeding, together with a higher mutation rate in polluted urban habitats, was responsible for the elevated frequency. In years in which no black-eyed individuals were discovered, no frosts occurred during the spawning period. This indicates that temperature possibly acted epigenetically on the expression of a mutation.

Reeves et al. (2008) found 154 black-eyed individuals among 9268 *Lithobates sylvaticus* examined in a four-years survey of 86 Alaskan breeding sites. They also regarded pollution to be the likely cause. In a later study (Reeves et al. 2010), they surprisingly found that the abundance of predatory beetles was the best predictor for the probability that *L. sylvaticus* exhibited eye anomalies, mainly black eyes, at a site. However, the anomaly was also negatively associated with temperature, which, as in *R. arvalis* in Ekaterinburg, was most likely to be the proximate factor responsible, acting either through differential survival or epigenetically (see section 3.1.7.3 for further discussion).

Most cases of black-eyedness are likely to be due to recessive mutations but in one breeding stock of *Dryophytes japonicus* the mutation was dominant. Inbreeding in a captive group of *Osteocephalus elkejungin-*

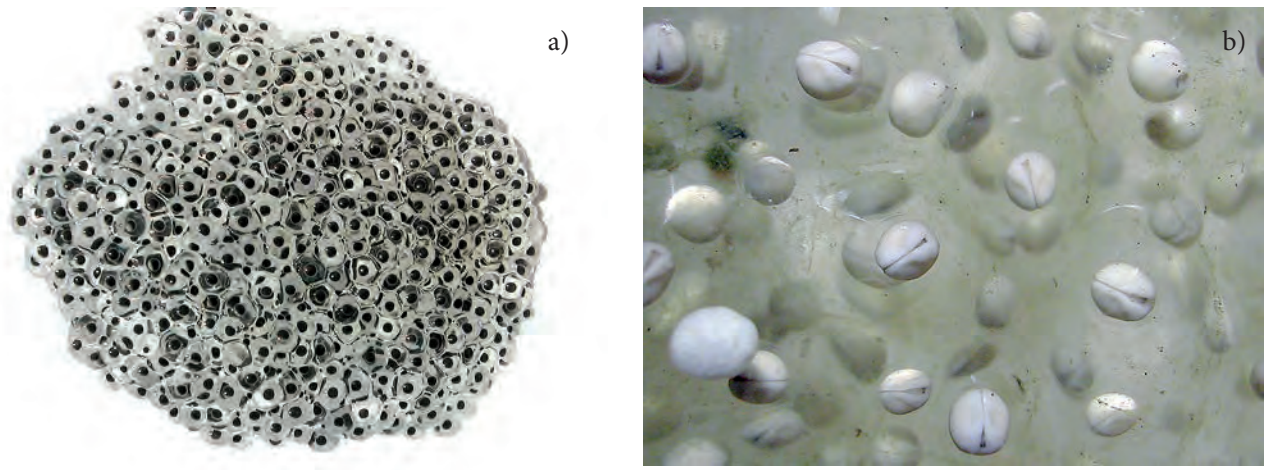

Fig. 27: a) Normal and b) abnormal white clutch (transient albinism) of *Rana arvalis*; the tadpoles that hatched from the white eggs acquired pigmentation during the larval stages; Ekaterinburg, Russia, 2005. Photos: V. Vershinin.

Fig. 28: a) Black-eyed adult female *Rana arvalis,* Polevskoi, Russia, June 2004. Photo: V. Vershinin; b) normal eye colour in an adult female *R. arvalis*, Tschekalin, Russia, 5.8.2008. Photo: K. Henle.

gerae revealed a recessive mutation for black-eyedness (Henle 1992). Nishioka (1977) obtained three recessive black-eyed mutations from 64 irradiated gametes of *P. nigromaculatus;* all mutations occurred at the same locus. Genetic studies in other species, however, showed that mutations leading to black-eyedness usually are non-homologous, which explains the differences in the morphological expression of the anomaly among species (*D. japonicus*: Nishioka & Ueda 1977b, 1985c; *L. clamitans, L. pipiens, L. sylvaticus*: Richards et al. 1969, Richards & Nace 1983; *Rhacophorus schlegelii*: Nishioka & Ueda 1985b).

Only in three cases involving *P. porosus* and *P. nigromaculatus* heritability could not be demonstrated (Nishioka & Ueda 1985d,e). In addition, Günther (1996c) wrote, without presenting details, that occasionally *P. ridibundus* acquires black-eyedness after long periods of captivity. Also, UV-irradiation produced a greatly increased number of melanophores in the cornea of *L. catesbeianus* and *L. pipiens* but only when tadpoles were kept in dark after irradiation (Zimskind & Schisgall 1956).

Fig. 29: Male *Ichthyosaura alpestris*, one of the few urodele species in which the normal phenotype is blue (only in males), Naturtheater Renningen, Germany, May 2005. Photo: K. Henle.

3.3.5.3 Blue, bluish and bluish-grey colour. Blue is a structural colour in most animals and occurs only in a few amphibian species as normal phenotype, such as male *Ichthyosaura alpestris* (Fig. 29). In addition, male *Rana arvalis* may turn blue during the breeding season. Such cases are not reviewed here.

Berns & Uhler (1966), Dubois (1979b) and Murphy (1980) reviewed the occurrence of blue individuals in the genera *Pelophylax* and *Lithobates.* Most cases involved only few specimens. Rivera et al. (1993) and García-Paris et al. (2004) reviewed the occurrence of blue frogs in Spain; most cases were observed in *Hyla meridionalis.*

Our database contains 92 cases covering either completely or mottled green / blue individuals from 20 species. Except for seven individuals, all belong to the genera *Hyla* (3 species) (Fig. 30) *Dryophytes* (1 species), *Lithobates* (5 species) or *Pelophylax* (6 species). The ex-

Fig. 30: *Hyla arborea;* a) abnormal colouration (blue), Saxony, 1980s. Photo: L. Berger; b) normal phenotype of an adult male, Waldsteinberg, Germany, April 2006. Photo: K. Henle.

ceptions are a single bluish-grey (axanthic) toad (*Anaxyrus fowleri*) (Bechtel 1995), a mottled green / blue *Acris crepitans* (Niccoli 2013), three juvenile *Pseudarcis regilla* (Altig & Brodie 1968), a *P. cultripes* with a bluish eye (Gonzáles-Fernández & Valladolid 2004), two bluish-grey *Pelobates fuscus* tadpoles (Sacher 1985), and an adult female *Ichthyosaura alpestris* with a greyish blue venter (Dandová & Zavadil 1993).

Most cases involve only a few individuals and the prevalence of blue frogs is usually low although it can reach higher rates in some populations. Berns & Uhler (1966) and Uhler (1971) obtained 69 blue *L. clamitans* among 2 million individuals from suppliers in Wisconsin and Minnesota; they further obtained 15 individuals from Barre, Massachusetts. Rivera et al. (1993, 2001) and Arribas et al. (1996) found 51 (2%) and 28 (4%) blue *H. meridionalis* in different populations near Barcelona, Spain. Furthermore, Dubois (1979b) observed 27 (4.5%) and 23 (4.0%) blue *P.* synkl. *esculentus* in two French populations and Nekrasova (2014) ten (16.7%) blue individuals in a mixed population of *P. lessonae/P. esculentus/P. ridibundus* in the Ukraine.

Bagnara et al. (1978) reviewed the genetic and physiological basis of blue colouration in frogs. Blue mutants either lack partially or totally the xanthophore cell type (Nishioka & Ueda 1985d) or show a diminuation or complete absence of pigments in xanthophores (Bagnara et al. 1978). Presumably, most blue frogs carry recessive mutations for this type of anomaly. For example, up to 40% of the offspring of a female *P. nigromaculatus* whose eggs were irradiated or fertilized with irradiated sperm were blue (Nishioka 1977, Nishioka & Ohtani 1986). Blue frogs were homozygous for a recessive gene coding for the absence of carotenoid vesicles in the xanthophores and possessed a dominant allele for the expansion of all three kinds of chromatophores. However, one case is known in which blue colouration was not heritable: two juvenile female *Dryophytes japonicus* that lacked xanthophores (Nishioka & Ueda 1985d). Although the cause remains unclear, a somatic mutation could explain it.

3.3.5.4 Erythrism. In many amphibian species red colouration belongs to the normal phenotype. Whether a red colour morph is regarded as normal or abnormal may depend on the origin of the individual. For example, in *Plethodon cinereus* an erythristic morph exists, which is rather common in some regions (Lotter & Scott 1977), yet very rare in others (Thurow 1961). Here we include only species or individuals in which red colouration was regarded as abnormal by the author(s). It is caused either by yellow pigment being replaced by red or orange pigment (e.g., in *Salamandra salamandra*), by a reddish brown colour replacing normal brown colouration, e.g., in *Rana temporaria* (Fig. 31; Rösel von Rosenhof 1758, Deichsel 2013) and *Discoglossus* spp. (Vences et al. 1996), or by widely expanded red spots, e.g., in *Bufotes viridis* (Schreiber 1912, Bons & Geniez 1996, Lanza & Canestrelli 2002).

Our database contains 58 cases involving 11 species – excluding an individual of *S. salamandra* that was orange in a reprint published by Schmidtler (2016), as the individual is yellow in the original publication by Meyer (1748–1756). Except for a population of *S. salamandra* near Barcelona, Spain, where 14 (5%; $n = 286$) individuals were erythristic (Rivera et al. 2001) and a population of *R. dybowskii* in the Far East of Russia, in which 14 (5.6%; $n = 250$) adults had an abnormal reddish colouration (Kolobaev 2000), all cases involved only few individuals. Apart from the species already mentioned, erythrism has been discovered in *Ichthyosaura alpestris* (Hachtel 2011), *S. corsica* (Michelot 1980), *R. arvalis* (Schreiber 1912, Henle unpubl.) and *Bufo bufo* (Luef 2009).

Tornier (1907) stated that *Pelobates fuscus* tadpoles fed on a diet rich in meat turned an orange colour. While his observations need confirmation, it is known that food rich in carotinoids intensifies orange colours in newts (*Triturus* s.l.) (Wolterstorff 1924 fide Freytag 1952) and red colour in other taxa (e.g., Chatzifotis et al. 2011).

Wolf (1994) observed that *B. bufo* migrating across a field that was treated with N-fertilizer developed reddish bellies. Reddish skin patches due to hemorrhage is a commonly observed pathology in diseased individu-

Fig. 31: Juvenile *Rana temporaria;* a) with normal colouration, Samarowo, Russia, September 2012; b) erythristic individual, Samarowo, Russia, 16.9.2013. Photos: K. Henle.

als, especially after *Aeromonas hygrophila* infection (see Henle et al. 2017a for a short overview). These types of reddening can easily be differentiated from an erythristic colour pattern.

Heritability of erythrism has been demonstrated in populations of *Salamandra salamandra* (Schweizerbarth 1909, Rivera et al. 2001, Seidel & Gerhardt 2016). No other causes have been suggested for erythrism in natural populations.

3.3.5.5 Flavism and abnormal yellow patches. Yellow pigmentation that is not part of the normal colouration is called flavism. Very few species are entirely yellow but in many species yellow colouration belongs to the normal phenotype, e.g. *Salamandra salamandra* (Fig. 33a). In addition, males of several species, notably in the genus *Scinax,* become completely yellow during the breeding season. Such cases are usually not called flavism and are not reviewed here.

Parent & Thorn (1983) reviewed the occurrence of flavism in amphibians. They listed ten species for which it had been reported. Our database contains 134 cases involving 26 urodelan and 20 anuran species. The earliest report of flavism is by Wurffbain (1683) for a *Triturus cristatus* and presumably also a *Salamandra salamandra*. Natural background rates are below 0.1% (Tab. 1) and only two cases cover more than ten specimens: 26 (sample size not provided) *Lithobates catesbeianus* (Peters 1962) and 12 *Lissotriton helveticus* and/or *L. vulgaris* (Smith 1950).

We know of only one case of transient flavism. A yellowish-beige paedomorphic larva of *L. vulgaris* was reddish-brown when recaptured two years later (Thiesmeier 2014). In addition a yellow adult female *T. cristatus* that was almost completely yellow in spring developed increasingly large black patches till October (Reichenbach 1865).

Flavism usually affects the whole body. However, in an adult *Pseudopaludicola mystacalis* only the anterior dorsal surface was yellow. Similarly, in a *Lithobates clamitans* flavism was restricted to those body parts that are normally green (Pinder 2010) and Guttmann (1972) published a photo of an individual of the same species with a yellow saddle-back. Rimpp (2007b) and Sewell (2007) each also reported a partially flavistic *T. cristatus*.

The affected bodyparts may be further reduced to small yellow, orange-yellow, or golden-yellow patches while the rest of the body has the normal colour: for example, more than ten metamorphs and tadpoles of *Bufotes viridis* from Roßwag, Germany, with yellow or ocre patches on different parts of the body (Fig. 32) (Henle et al. 2017a), two male *Chioglossa lusitanica* with an irregular yellow dorsal patch (Sequeira et al. 1999), an adult *Salamandrina perspicillata* with yellow spots on the back (Lanza & Canestrelli 2002), golden-yellow dorsal spots on a melanistic *Hyla arborea* (Bitz & Schader 1996), an adult female *L. clamitans melanota* (Vorps 1976) and an adult male *Rana temporaria* with sulphur-coloured patches on the back (Goethe 1972). Yellow spots on the back also occur occasionally in *Bombina variegata* (Pracht & Rogner 1987, Herrmann 1990, Gollmann & Gollmann 2012), a species that has a bright yellow venter. In one of the *Bufotes viridis* individuals from Roßwag the anomaly was heritable (presumably dominant) and the mutation was most likely caused by irradiation (Henle et al. 2017a).

In *Salamandra salamandra* yellow is part of the normal pattern (Fig. 33a) and in some subspecies a substantial expansion to almost completely yellow belongs to the normal range of patterns; in the subspecies *S. s. terrestris* a substantial extension of the yellow pattern has been observed often in a small area near Holzminden, Germany (Seidel et al. 2012) but we know only one publication that mentioned a single individual for another locality, Ludwigsburg, in southern Germany (Klewen et al. 2016).

Recessive mutations coding for flavism have been discovered in *Ambystoma mexicanum* (Bagnara & Obika 1964), *Ichthyosaura alpestris* (Parent & Thorn 1983), *S. salamandra* (Nath 1940, Seidel et al. 2012) and *T. carnifex* (Capanna & Foresti 1974). Wolterstorff (1925a) obtained an albinistic larva from a cross between two flavistic *S. salamandra.*

3.3.5.6 Melanism and darkening. A few species, such as *Salamandra atra* (but not the subspecies *S. a. aurorae*) and *S. lanzai,* are completely black in the normal phenotype; these species are not reviewed here. Some species, e.g., *Salamandrella keyserlingii* (Fig. 34), may physiologically change to complete black under dark and cold conditions. If returned to light and warm condition, their colouration reverses to the normal pattern. Such physiological changes are not considered in this review.

Browder (1975), Bagnara et al. (1978), Malacinski (1978), Richards & Nace (1983), Frost et al. (1984, 1986a), Klewen (1988) and Seidel & Gerhardt (2016) reviewed abnormal melanism and its genetic origin in *Ambystoma mexicanum, S. salamandra*, ranid frogs and other amphibians. Richard & Nace (1983) additionally suggested a classification for different types of melanism. Schlüpmann et al. (1995) reviewed melanism in amphibians from Northrhine-Westphalia, Germany.

Fig. 32: Abnormal ocre patch in a juvenile *Bufotes viridis*, Roßwag, Germany, September 1980. Photo: K. Henle.

Fig. 33: *Salamandra salamandra;* a) normal pattern of the subspecies *S. s. salamandra*, individual born in captivity, parents from Austria; b) albinistic individual, collected as larva in Wuppertal, Germany; c) melanistic individual born in captivity. Photos: B. Trapp.

Our database contains data from 111 natural populations of 24 urodelan and 25 anuran species, in which individual(s) were completely or partially black or abnormally dark. The earliest mentioning of melanistic individuals (*Bufo* species from Italy) was by the poet Guntheus (Aldrovandi 1645). However, Aldrovandi (1645) slightly doubted this claim as no other author had ever mentioned toads that were completely black. We were unable to track the original source. Completely black individuals are rare exceptions (e.g., Rivera et al. 2001, Manenti 2006) and only five cases comprise more than ten partially or completely melanistic individuals for a single population: a population of *Pelodytes punctatus* from France, in which thousands of tadpoles were almost black on the back (Boulenger 1891), a high altitude population of *Bufotes viridis* in the Alps, in which most tadpoles were black (Andrä & Deuringer-Andrä 2011), and two German populations of *Bufo bufo,* in which 27 out of 386 and 13 out of 26 individuals, respectively, had large black spots on the back or belly (Mattes 2013). In another population of *B. bufo*, only 4 out of 1121 individuals were affected. Mattes (2013) assumed that a fungal disease was the cause. Kliemt (2017) observed black spots on 15 (n = several thousands) juvenile *B. bufo* that were caused by a fungus of the genus *Cladosporium*. In addition, Richards et al. (1969) and Richards & Nace

Fig. 34: *Salamandrella keyserlingii;* a) normal phenotype, Nishni Angarsk, Lake Baikal, Russia, 26.7.2014. Photo: K. Henle; b) physiological colour change to black in an individual kept under dark and cold conditions, Ekaterinburg, Russia, May 2003; this individual also shows polydactyly (left front leg), which sometimes is regarded as part of natural variation in this species. Photo: V. Vershinin.

(1983) received 32 melanistic *Lithobates pipiens* from various dealers (sample size and locations not given).

A genetic origin is assumed for most cases but has rarely been tested, except in laboratory stocks of commonly maintained species. In melanistic laboratory stocks of *A. mexicanum,* at least 16 different recessive genes cause dark pigmentation (Malacinski 1978). Melanoid mutants are characterized by an overproduction of eumelanin, usually through the differentiation of an excessive number of melanophores. Melanoid mutants exhibit a great diminuition in xanthophore and iridophore number and it is assumed that this is caused by a genetic defect involving the xanthine dehydrogenase (Bagnara et al. 1978). Inheritance of melanism has also been shown in laboratory stocks of *L. pipiens* (Gibbs et al. 1971, Richards & Nace 1983). Moreover, gynogenesis revealed mutations that caused darkening of tadpoles in *Xenopus laevis* (Krotoski et al. 1985) and melanism in *L. clamitans* (Richards & Nace 1983). Heritability of melanism has also been demonstrated in captive stocks of *S. salamandra* (Freytag & Susebach 1942, 1949, Freytag 1955, Seidel & Gerhardt 2016; Fig. 33c).

Apart from mutations, a few other factors may be considered as causing an abnormal black colouration. Tornier (1907) observed that feeding *Pelobates fuscus* tadpoles on a diet consisting exclusively of meat and ant eggs resulted in a very dark, almost black colouration. According to Freytag (1952) the dark colouration may have been due to reversible physiological changes. However, rare cases of darkening to almost completely black have been observed in captivity also for *Speleomantes flavus, Salamandra a. aurorae* (Steinfartz 1998), *Triturus carnifex* and *T. cristatus* (Werner 1930, Mertens 1941, Mutz 1999). Reichenbach-Klinke (1956) reported increased melanisation of necrotic tissue in *Pleurodeles waltl* and Cummer et al. (2005) and Bachhausen (2016) observed the same in an individual of *Plethodon neomexicanus* infected with *Batrachochytrium dendrobatidis* and *S. salamandra* infected with *B. salamandrivorans*, respectively. An infection may also have been the cause in a *B. bufo* in which the head showed pathologically altered black skin (Glaw et al. 2014).

Two (frequency < 1%) darkened individuals appeared from experimental crosses between *Pelophylax esculentus* and *P. lessonae* (Tunner 1980). Their uniqueness questions the relationship with hybridization.

Several chemicals may cause darkening of tadpoles by affecting melanophore number, distribution, size or contraction or melanin synthesis (Pogonowska 1914, Pohland 1962, Pandey & Tomar 1985). Tadpoles of *Euphlyctis hexadactylus* develop abnormal black spots when treated with the pesticide carbamate (Raj et al. 1988). Furthermore, dichlorvos, an organophosphorous insecticide, may cause the release of the hypophyseal melanocyte-stimulating hormone, which results in darkening at low doses but lightening at high doses (Tomar & Pandey 1988). Lindane causes darkening by dysfunction of the intermediate lobe of the hypophysis that controls pigmentation (Marchal-Ségault & Ramade 1981).

Unnaturally high doses of UV-B irradiation will lead to enhanced pigmentation and darkening of tadpoles (Worrest & Kimeldorf 1976, Grant & Licht 1995). At ambient levels of UV-B, darkening has been observed in *Hyla arborea* tadpoles but not in *T. cristatus, Bufo bufo, Epidalea calamita* or *Rana temporaria* (Langhelle et al. 1999). Tadpoles that develop from irradiated eggs, sperm or embryos often show high rates of melanism (e.g.: *Bombina orientalis*: Ueda 1980; *Glandirana rugosa*: Kashiwagi 1980; *P. nigromaculatus*: Nishioka 1977, Nishioka & Ueda 1977a).

3.3.5.7 Translucent skin. While a translucent skin on parts of the body is the natural condition for some species, notably in the family Centrolenidae, translucent patches of skin may also be an abnormal condition. An abnormal absence of the epidermis or lack of pigmentation giving the affected skin patch a grey to blackish translucent appearance has rarely been observed in amphibians collected from the wild. Our database contains 26 cases from 18 species, all but four involving a single individual. Absence of the epidermis due to injury was the likely cause in three out of 24 *Rana arvalis* examined by Henle (unpubl.; see Fig. 47 in Henle et al. 2017b) in Samarowo, Russia, that had a translucent patch of skin on the belly, head and back, respectively. Dubois (1968) described a translucent ventral skin for four *Pelophylax esculentus* affected by anomaly P and Rostand & Darré (1970) mentioned several tadpoles from another population that were also affected by anomaly P. The fourth case is several *Bufotes viridis* metamorphs in the Roßwag population in Germany that showed translucent blackish patches of skin; the anomalies were presumably due to irradiation (Henle et al. 2017a).

A translucent blackish female *Pelophylax porosus* collected in the wild ($n = 29$) lost its pattern over the course of two years (Nishioka & Ueda 1985e). Among its 36 gynogenetic and F_2 offspring, one acquired a blackish colouration one year after metamorphosis and the anomaly was not heritable. The involvement of phagocytes in the formation of these colour anomalies was indicated by their contact with xanthophores and melanophores and pieces of melanophores in their cytoplasm. No causes for the remaining cases of singular individuals observed were suggested.

Out of 218 Sri Lankan *Polypedates crucifer* experimentally infected with monostome-type cercariae (species not identified) nine exhibited translucent skin but none of the 78 controls did (Rajakaruna et al. 2008) ($\chi^2 = 3.32$; $0.1 > \alpha > 0.05$). Such anomalies were not reported in experiments with the North American trematodes *Ribeiroia ondatrae* and *Alaria* sp. (Johnson et al. 1999, 2001b, Stopper et al. 2002, Schotthoefer et al. 2003).

In experimental crosses within the *Pelophylax esculentus* complex, tadpoles and metamorphs showed patches of translucent skin (Berger 1971, 1976, Günther 1990). Similarly, the posterior body part was translucent in 30 surviving tadpoles from a clutch obtained from natural hybridization between a *Rhinella icterica* male and a *R. crucifer* female.

Translucent patches of skin further appeared in *Bufo bufo* tadpoles raised from irradiated embryos (Oerter 1985, Trux 1985) and in *P. nigromaculatus* raised from irradiated eggs or sperm (Nishioka 1977, Nishioka & Ueda 1977a, Nishioka & Ueda 1985a, Nishioka & Ohtani 1986). In the latter species, it was always combined with the black-eye anomaly.

In laboratory stocks of *Lithobates pipiens* translucent patches of skin occur occasionally and the anomaly has an incomplete dominant inheritance (Browder 1968). Recessive inheritance of translucent grey body colour has also been discovered in a *B. bufo* (Rostand 1951e) and in *Rana temporaria* raised from clutches of females affected by anomaly E (Rostand 1956a, 1958b).

4 Species differences in sensitivity

Several suggestions of differences in the sensitivity of species and between anurans and urodeles to develop anomalies have been made. For example, occasionally it has been suggested that the phenomenon of mass occurrence of anomalies is limited to the Temperate Zone of the Northern Hemisphere and absent from tropical areas. However, the few studies with large sample sizes available for tropical areas show that this is not the case. Mass occurrences have been observed in Malaysia, India, northern Australia, the Ivory Coast, Costa Rica, Guatemala, Panama and Ecuador. These involved skeletal and other morphological anomalies and were associated with disease, predators, parasites as well as chemical and radioactive pollution (see section 3.1 for further details).

Ankley et al. (2004) and Lannoo (2008) suggested that anurans are more prone to acquire limb anomalies than urodeles. Lannoo (2008) derived his conclusion from the higher percentage of North American anuran species for which limb anomalies have been reported compared to urodele species. In contrast, Litvinchuk (2014) stated that urodeles are more sensitive. He derived his ideas from a limited set of data on the percentage of individuals observed with anomalies. Globally, anomalies are known for a higher fraction of the total number of species of Urodela than for Anura or Gymnophiona (Fig. 35; ($\chi^2_2 = 126$; $\alpha = 0$). Borkin (2014) noticed a similar pattern in Russian amphibians but asked whether this may not be a sampling effect. Indeed, such inferences depend on the strong assumption that both anuran and urodele species were exposed to the same teratogenic factors and that the same percentage of species and the same (average) number of populations have been assessed with sufficiently large sample sizes. These assumptions are certainly violated. For example, our global comparison rather reflects the fact that a larger percentage of urodele species are found in Europe and North America than is the case for anuran species and Gymnophiona (Duellman 1999), i.e. for regions that have a much longer and broader natural history tradi-

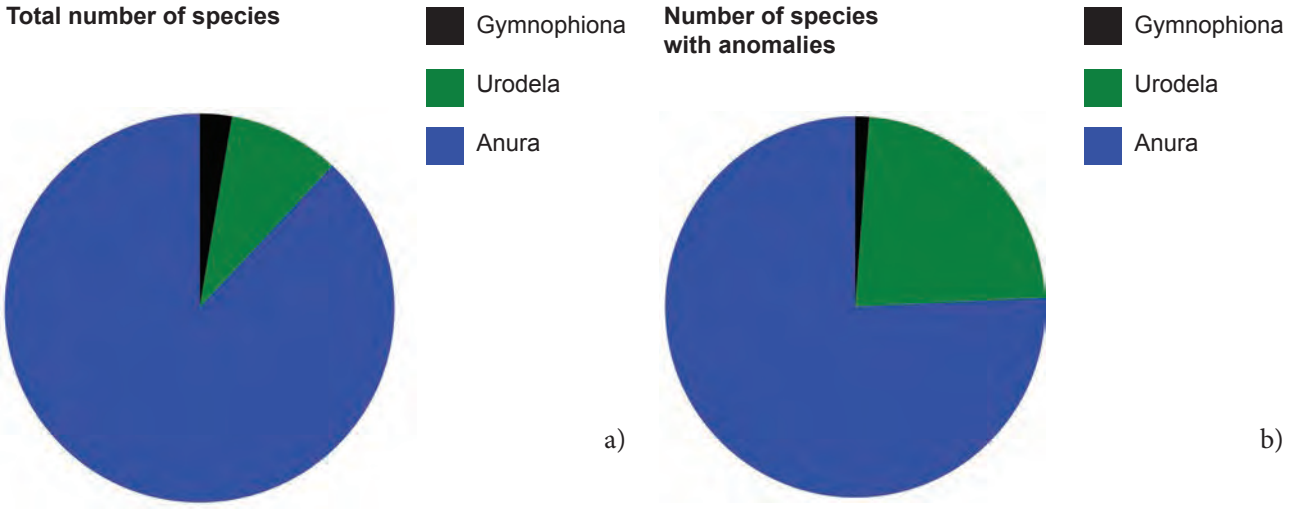

Fig. 35: Comparison between extant amphibian orders for a) global number of species (Frost 2017) and b) the number of species for which anomalies have been reported. Source: our database as of 7.6.2017.

tion than other regions of the world. To obtain reliable inferences surveys are required that assess all urodele and anuran species for anomalies across a larger set of sites.

One of the authors of this paper (Vershinin 2002) conducted such a study that allows comparisons of the sensitivity between anurans and urodeles. Since 1977 all amphibians found in three zones of urbanization within the city of Ekaterinburg, Russia, and rural areas 23 km away from the city were scored for anomalies. In the most urbanized zone the frequency of abnormal *Lissotriton vulgaris* was intermediate between *Rana arvalis* (the most affected species) and *R. temporaria*. It was higher compared to adult but lower than for juvenile *Pelophylax ridibundus*. In the second most urbanized zone, *L. vulgaris* was also less affected than *R. arvalis* but similar to *R. temporaria*. In the forest park zone *Salamandrella keyserlingii* was the most severely affected species, followed by *R. arvalis, L. vulgaris* and *R. temporaria*. In the rural area *S. keyserlingii* was most frequently affected followed by *Rana arvalis*. Thus, sensitivity apparently was consistent when comparing the same species declining from *S. keyserlingii* to *R. arvalis* to *L. vulgaris*, with *R. temporaria* being the least sensitive species. In the Danube floodplains at Gemenc, Hungary, *L. vulgaris* scored intermediately between six anuran species in terms of the number of types of anomalies (Puky & Fodor 2002). These data indicate that neither anurans nor urodeles as a group were more prone to have anomalies but that there may be a consistent ranking of species.

At two sites in California, Johnson et al. (2001) surveyed all amphibians. The newt *Taricha torosa* exhibited the highest rate of anomalies, followed by *Pseudacris regilla, Anaxyrus boreas* and *Lithobates catesbeianus*. Anomalies were probably caused by the trematode *Ribeiroia ondatrae*. At Duck Pond, Minnesota, the prevalence of anomalies was high for *A. americanus* (60% abnormal; n = 618) and *L. pipiens* (~50%) but low for *Dryophytes versicolor* (3%; n = 251) (Johnson & Hartson 2009). The results from another study across 345 Californian wetland sites were only partially consistent with these results. Whereas *P. regilla* showed on average the highest frequency of anomalies, it was followed by *Rana draytonii* and *L. catesbeianus*, but *A. boreas* had only a low (2.6%) average frequency of anomalies (Johnson et al. 2013).

The sensitivity ranking obtained in laboratory experiments that compared the effects of the trematode *Ribeiroia ondatrae* on anomalies in 13 amphibian species agreed only weakly with the ranking from field sites. The two urodele species tested (*Ambystoma macrodactylum, T. torosa*) were intermediate in sensitivity between the most sensitive species (*Anaxyrus* spp., *Pseudacris* spp., *L. cascadae*, *Rana pretiosa*) and *D. cinereus, D. versicolor*, *L. catesbeianus* and *Xenopus laevis*, which were immune (Johnson et al. 2012). Moreover, mesocosm studies showed that the infection of *P. regilla* with *Ribeiroia ondatrae* depended on amphibian species composition (Johnson et al. 2013). Whereas the addition of *L. catesbeianus* tadpoles significantly reduced infection this was not the case when adding *L. cascadae* tadpoles.

Across 462 wetland sites in US wildlife refuges, anuran species were not differentially sensitive to obtain anomalies (Reeves et al. 2013). This is to be expected as the factor(s) that caused anomalies are likely to differ considerably across the USA.

In the laboratory study of Johnson et al. (2012) discussed above, species that develop quickly and metamorphose at a small size were most prone to develop anomalies but phylogeny had no effect on sensitivity. In contrast, the rapidly developing Asian *Duttaphrynus melanostictus* was less prone to develop anomalies when experimentally exposed to cercariae of the trematode *Acanthostomum burminis* compared to *Polypedates cruciger*, which has a long developmental time (Jayawardena et al. 2013). The types of anomalies were also less severe. Other studies, in contrast, suggested that aquatic species are more sensitive than semi-aquatic and terrestrial species (Borkin 2014). At the CWB hotspot site in

Minnesota, for example, the two most aquatic species with the longest larval period exceeded by far the remaining species in terms of the frequency of anomalies (Hoppe 2005). These contradictory observations among studies and locations can be explained best by different causal factors occurring in the field and species-specific differences in the susceptibility to different teratogenic factors. The different sensitivity ranking of species at CWB compared to sites at which *R. ondatrae* likely was the main causative factor of anomalies (see previous paragraph) supports the conclusion of Helgen (2012) that parasites at most played a minor role at the CWB site.

A higher sensitivity of those species that have longer larval periods compared to those with shorter larval periods to anomalies caused by pollution is corroborated by amphibians at breeding sites contaminated by sewage in the Ukraine (Flax & Borkin 1997, 2004). The most aquatic species, *Pelophylax ridibundus* showed the highest rate of anomalies, *Bombina bombina* was intermediate and the most terrestrial species, *Bufotes viridis,* was least affected. Likewise, 96% of the tadpoles of *L. catesbeianus* partially lacked labial tooth rows in a coal ash deposit pond, whereas *D. cinereus* was not affected (Rowe et al. 1996). The former species has a much longer larval period than the latter (Lannoo 2005). At a site in Argentina, tadpoles of the two species with the longest larval period, *Boana riojana* and *Odontophrnus americanus*, had higher rates of anomalies than the two species with a shorter larval period, *Pleurodema borellii* and *Rhinella arenarum* (Medina et al. 2013).

Another suggestion is a difference between urodeles and anurans in their proneness to show different types of anomalies. For example, Asashima et al. (1987) assumed that anurans are more prone to develop tumours than urodeles. They based their proposition on the higher regeneration capacity of urodeles compared to anurans. However, there is a lack of comparative studies in the laboratory or the field in which anurans and urodeles were exposed to the same carcinogenic factors. A corollary of this hypothesis is that tumours should be found less frequently relative to other types of anomalies and in a smaller percentage of sampled populations of urodeles compared to anurans. Similarly, because of the high regeneration capacity of urodeles for the eye (Eguchi et al. 2011), anophthalmy should be observed less frequently relative to other types of anomalies in urodeles than in anurans. Extending the argument about the regeneration capacity, one should find the same relationships for ectromely and ectrodactyly, which are often assumed to be primarily caused by trauma (but see section 3.2.2.1).

Excluding populations for which the types of anomalies found was not specified, there is a striking highly significant difference (χ^2-Tests) between urodeles and anurans in the percentage of populations for which these four types of anomalies were reported (Tab. 8). As predicted anophthalmy, ectromely and ectrodactyly were reported for a much smaller fraction of the surveyed urodele populations compared to anuran populations. Contrary to prediction, the opposite was the case for tumours.

The reporting patterns, assessed as the relative numbers of populations for which particular types of anomalies were reported, also differed strongly between urodeles and anurans (Figs. 36–38). These differences are not rigorous tests of a different sensitivity of urodeles and anurans to develop a particular type of anomaly, as other factors than a different sensitivity (e.g. sampling in different regions and habitats that differ in teratogenic agents, types of anomalies targeted in one but not the other taxonomic group) might have contributed to these differences. Notwithstanding, they are indicative of the types of anomalies that are promising to target in a well-designed study that compares the sensitivity of urodeles with that of anurans.

In terms of limb anomalies ectromely has been reported much less frequently relative to other types of anomalies in urodeles compared to anurans and the opposite is the case for polydactyly (Fig. 36). For polydactyly this parallels the much higher natural variability in the phalangeal formula of urodeles compared to anurans (Alberch & Gale 1985). The relative frequency of other limb anomalies is similar in urodeles and anurans, with a slightly higher rate for syndactyly in uordeles.

In terms of non-skeletal morphological anomalies, anophthalmy has been reported less frequently and tumours more frequently relative to other types of anomalies in urodeles compared to anurans (Fig. 37). Giant larvae were also reported relatively more frequently and microphthalmy, skin webbing and bloatedness less frequently in urodeles compared to anurans. Oral anomalies in larval amphibians have only been studied for anurans.

Albinism is by far the most frequently reported type of colour anomaly for natural populations of Urodela and Anura and the only one reported for Gymnophio-

Table 8: Comparion between Anura and Urodela of the number of populations with and without a particular type of anomaly having been reported. Bold: amphibian order with the higher percentage of populations for which the respective type of anomaly was reported.

Type of Anomaly	Urodela		Anura		Significance
	with	without	with	without	
Anopthalmy	13	806	**145**	**2531**	$\alpha < 0.0001$
Tumours	**38**	**781**	57	2617	$\alpha < 0.001$
Ectromely	53	766	**609**	**2066**	$\alpha = 0$
Ectrodactyly	103	716	**589**	**2086**	$\alpha = 0$

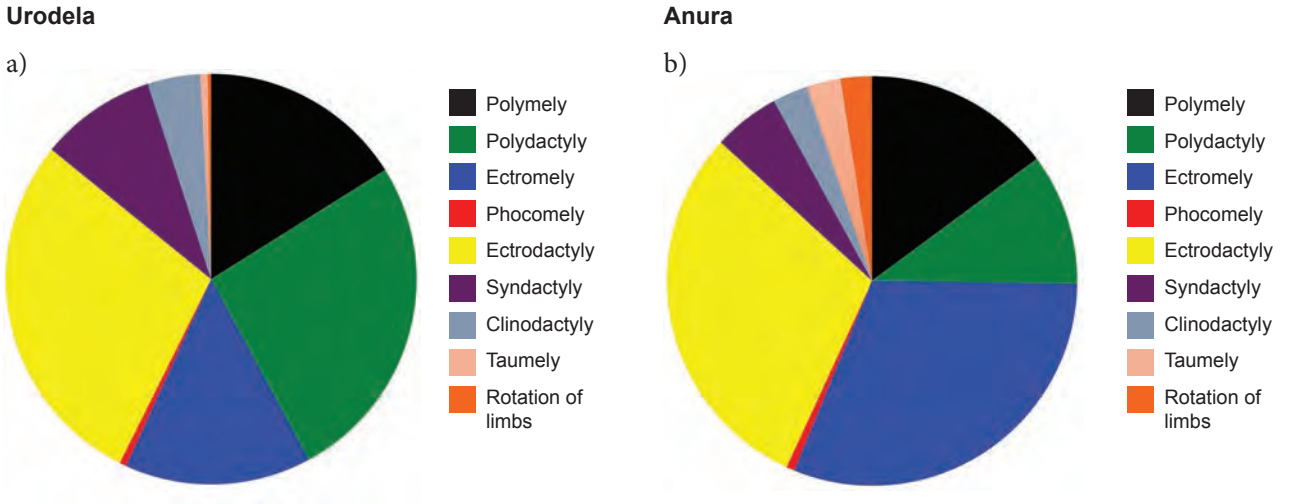

Fig. 36: Comparison of the reporting frequency of different types of skeletal anomalies for a) urodeles (n = 361) and b) anurans (n = 1981). Source: our database as of 7.6.2017.

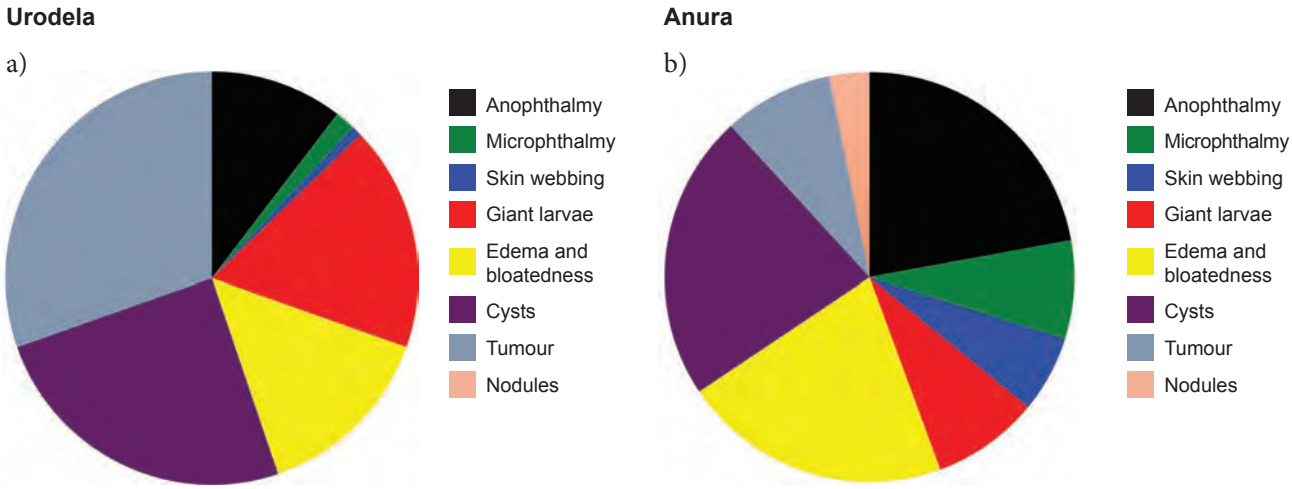

Fig. 37: Comparison of the reporting frequency of different types of non-skeletal morphological anomalies for a) urodeles (n = 125) and b) anurans (n = 660). Source: our database as of 7.6.2017.

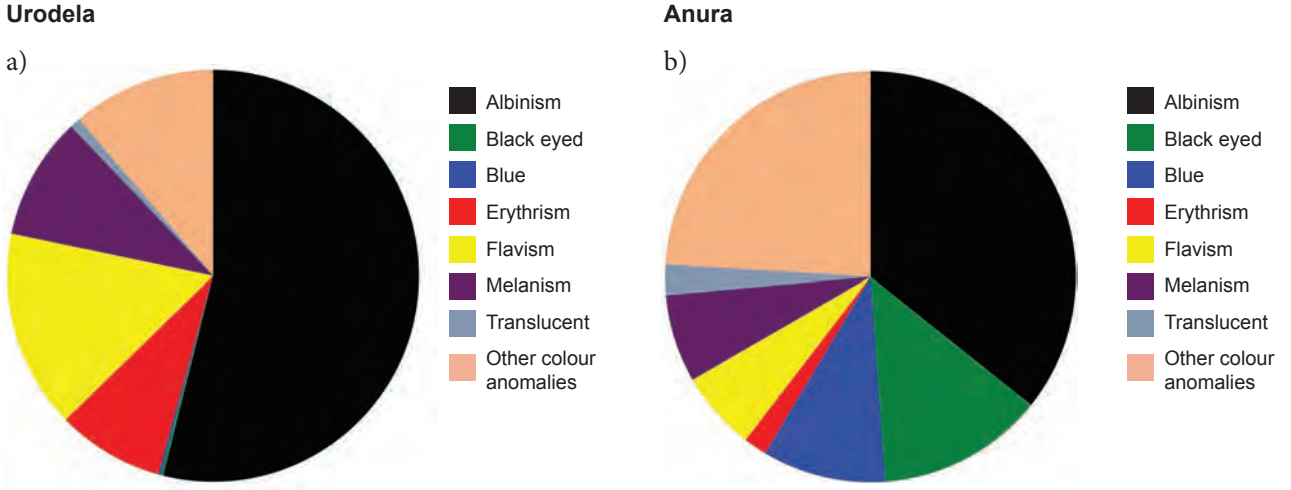

Fig. 38: Comparison of the reporting frequency of different types of colour anomalies for a) urodeles (n = 456) and b) anurans (n = 954). Note: albinism does not include flavism and erythrism. Source: our database as of 7.6.2017.

na. For urodeles it dominates much more strongly than for anurans (Fig. 38). Likewise, relative to other types of colour anomalies, erythrism, flavism, and to a lesser extend melanism have been reported more frequently in urodeles compared to anurans, whereas the opposite is the case for abnormal black-eyedness and blue colour.

Some anomalies are rather species-specific, with syntopic species not being affected at all. Such species-specific reactions seem to take place primarily if parasites or diseases are involved. For example, anomaly P only affects species within the genus *Pelophylax* (Dubois 2014, 2017). Similarly, *P. ridibundus* was the only species suffering from mass polymely at the Kazakh locations studied by Woitkewitsch (1959, 1965), whereas two other syntopic ranid species did not exhibit any anomaly. Maggots of the fly *Lucilia bufonivora* destroy the nasal bones of *Bufo bufo* but other species are rarely parasitized. Similarly, at six sites in Maine, USA, *Ambystoma maculatum* and *A. tigrinum* were infected by an iridovirus and suffered from edema, while non-ambystomatid urodeles and anurans were not affected (Docherty et al. 2003). The reasons for these highly species-specific reactions are still unknown.

As for predators, the leech *Erpobtella octoculata* causes ectromely in *Bufo bufo* but not in syntopic *Rana temporaria* (Bohl 1997); it can also damage limbs in *Ichthyosaura alpestris* (Hachtel 2011). Laboratory experiments demonstrated further that predator effects on tail injuries and/or ectromely of larval amphibians is often rather specific to the combination and size of the species involved and the larval stage (reviewed by Henle et al. 2017a).

In summary, species may show very different sensitivities to particular environmental factors that cause anomalies, such as pollutants and biological agents, with the latter sometimes being rather species-specific. However, there is no evidence that urodeles are less sensitive than anurans or vice-versa and phylogeny had no effect in the only study that has tested it so far. While several studies have indicated that more aquatic species are more sensitive (to water born factors) compared to less aquatic species, others have suggested the opposite with rapidly developing species being the more sensitive ones. These seemingly contradictory observations may be explained by different causal factors in the field. Analyses that simultaneously assess different potential causes and differentiate different types of anomalies are in dire need to better understand the differential sensitivity of species to teratogenic factors in the field.

5 Individual and population level effects

Concerns have been voiced that increased incidences of anomalies contribute to the global decline of amphibians (Lannoo 2008, Helgen 2012) but only a few studies have attempted to assess the impacts of anomalies at the individual or population level. As expected, most of these show adverse effects on the individual level, which may or may not translate to population level effects.

5.1 Individual level effects

Helgen et al. (2000) found a significantly smaller snout-vent-length (SVL) of *Lithobates pipiens* metamorphs at malformation hotspot sites in Minnesota in 1996 compared to reference sites. However, this does not necessarily mean that anomalies were responsible for the smaller mean SVL. It could have simply been that a noxious factor caused both anomalies and the smaller SVL. In 1997, they compared the SVL of abnormal and normal individuals within seven sites. At three sites the former were significantly smaller and at two other sites the mass was significantly lower. At a sixth site, the Ney pond, the difference was significant for mass on one but not on another sampling date.

Between 1997 and 1999, Canfield et al. (2000) also compared SVL and mass of *L. pipiens* metamorphs at seven sites in Minnesota. Three of these sites were the same as those used in the study by Helgen et al. (2000). In this study, abnormal metamorphs were smaller than normal ones at four sites but larger at three sites. The difference was significant for two of the latter sites (CWB, NEY). An ANOVA showed that most of the variance was explained by the sites and not by the status of being normal or abnormal. Abnormal metamorphs had a lower mass at six sites and a higher one at one site (CWB). The differences were only significant for one site (ROI). Canfield et al. (2000) explained the difference at the ROI site with mass loss from missing limbs and the handicap in capturing prey for affected individuals. An ANOVA showed that most of the variability was explained by site effects, followed by the interaction of sites and the logratio of mass of abnormal / mass of normal metamorphs. While there is an overall tendency of abnormal froglets to have a lower mass compared to normal froglets, the assessments of SVL do not provide a consistent picture. More studies are needed that also include the main types of anomalies observed and the sampling dates, and also on tadpoles before metamorphosis took place, before we can better understand the effects that anomalies have on the size and mass of metamorphs.

In a larval guild of *Ambystoma opacum, A. tigrinum* and *A. maculatum,* in which invertebrate predators were rare, severely injured individuals of *A. opacum* (partially missing gills, digits, and/or limbs) had smaller snout-vent-lengths than individuals that were not injured and individuals only suffering from tail injuries (Mott & Steffen 2014). They also showed an increased use of benthic microhabitats, a higher risk of intraspecific aggression and reduced agonistic displays. However, foraging success was not reduced. Similarly, *Dicamptodon tenebrosus* that lacked limbs or tails or parts thereof had a significantly lower mass compared to individuals that had not been injured, but only in the largest size class (Munshaw et al. 2014). In recently metamorphosed individuals from a population of *Lissotriton vulgaris* in Romania SVL was very similar between animals that had not been injured and animals with ectromely, ectrodactyly or injured tails (Nemes 2005).

Early stage larvae of *Ambystoma jeffersonianum* with torsion of the body caused by boron treatment had substantially reduced swimming speed compared to normal larvae (Laposata & Dunson 1998).

Blind Cururu toads (*Rhinella jimi*) on the oceanic island Fernando de Noronha, Brazil, where the species is invasive, have significantly lower body condition than individuals with two functional eyes (Tolledo & Toledo 2015). Half blind toads were intermediate. Moreover, the number of oocytes and reproductive effort were lowest in blind individuals, intermediate in half blind individuals and best in normal toads, with the difference being significant.

The few studies available that were either conducted in the laboratory or using enclosures indicate that anomalies often but not always reduce growth and development in tadpoles and may reduce survival. For example, tadpoles of *Rhinella jimi* with oral anomalies foraged less efficiently than tadpoles without oral anomalies (Tolledo et al. 2014). *Rana arvalis* tadpoles with numerous anomalies of the mouthparts were sluggish, had reduced growth and reached Terent'ev (1950) stage 29 6–12 days later than normal tadpoles (Trubetskaya 2006). Most of them died during metamorphosis and surviving postmetamorphic juveniles differed from their siblings in morphophysiological parameters. Tadpoles of *L. sylvaticus* with bent tails had lower survival than normal individuals when exposed to a beetle (*Dytiscus*) predator while the presence of predators reduced the percentage of tadpoles that developed bent tails (Michel & Burke 2011).

Effects may depend on the environment. Tadpoles of *L. catesbeianus* that suffered from deformed labial teeth rows and papillae were less able to graze on periphyton compared to normal tadpoles, when tested in the laboratory (Rowe et al. 1996). They had lower (negative) growth rates compared to those with normal teeth rows when periphyton was the only food source. However, when particulate food was also available, tadpoles grew well regardless of their deformities. When exposed together to juvenile snapping turtles (*Chelydra serpentina*) in outdoor tanks (Raimondo et al. 1998), survival was lower in individuals with abnormal mouth parts compared to normal individuals. In the absence of predators, however, survival was similar.

Pelobates cultripes tadpoles with tail injuries had a marginally lower survival rate than uninjured tadpoles, with the difference increasing with the number of times that the tail had been injured (Nunes et al. 2010). The effects did not dependent on food availability and development and growth were not affected. In *Dryophytes chrysoscelis*, swimming performance (sprint speed and distance swum) and the ability of tadpoles with damaged or incomplete tails to escape the attacks of dragonfly larvae (*Tramea lacerata*) was significantly reduced (Semlitsch 1990, Figiel & Semlitsch 1991). In *D. versicolor,* maximum speed and minimum escape time were also impaired but only if at least 30% of the tail was removed (Van buskirk & McCollum 2000). As an exception to the increased sensitivity of abnormal tadpoles to predation, there was no statistical difference between the prevalence of deformities and the median time to predation of *L. cascadae* tadpoles by the newt *Taricha torosa* under laboratory conditions (Romansic et al. 2009).

Whereas the survival of albino tadpoles of *Spea hammondii* to metamorphosis did not differ from normal tadpoles when predators were excluded, it was only one third of that of normal tadpoles in a natural pond to which predators had access (Childs 1953). While several albino tadpoles metamorphosed successfully, albeit later than normal ones, all albino froglets died soon after metamorphosis. Albinism also prolonged the time required for development and metamorphosis in *Phrynohyas mesophaea* (Sazima 1974); such prolongation usually increases the mortality of amphibians in natural populations (e.g., Semlitsch et al. 1988).

Anomalies can also reduce survival rates in the absence of predators. For example, in a *Bufotes viridis* population in Roßwag, Germany, none of the more than 100 albinistic tadpoles metamorphosed despite the absence of predators (Henle et al. 2017a). Notwithstanding, albinism is not always lethal and in captivity albinistic individuals have been raised through many generations (e.g., *Ambystoma mexicanum*: Malacinski & Brothers 1974; *Salamandra salamandra*: Concaro 2004). Whereas albinistic tadpoles may complete metamorphosis, giant tadpoles do not metamorphose nor do they reproduce.

Ambystoma larvae infected by an iridovirus and suffering from edema were lethargic and slow moving. They swam in circles with obvious buoyancy problems (Docherty et al. 2003). Larvae of *A. maculatum* with swellings due to infection from the ciliate *Tetrahymena pyriformis* died within 24 hours (Ling & Werner 1988). Likewise, edemateous tadpoles in a population of *B. viridis* had obvious buoyancy problems and soon died (Flindt 1985a, Henle et al. 2017a). Moreover, incidences of anomalies in tadpoles often decrease with season (e.g., Flindt 1985a, Burkhart et al. 2000), indicating decreased survival. Likewise, a decrease in the spectrum of anomalies during development, indicating the elimination of (sub-)lethal types of anomalies, was observed in several cases (e.g., Flindt 1985a, Kuranova 1997, Pyastolova & Vershinin 1999, Vershinin 2004).

Limb anomalies caused by *Ribeiroia ondatrae* did not affect the development rate of *Pseudacris regilla* tadpoles; however, the infection itself retarded development irrespective of the malformation status (Romansic et al. 2011).

Frogs with supernumerary or missing limbs often fall on their back when attempting to jump (Woitkewitsch 1959, Helgen 2012). *Pseudacris regilla* that were malformed due to *R. ondatrae* infection (mainly polymely or skin-webbing) allowed simulated predators to approach more closely than did normal frogs (Goodman & Johnson 2011b). They had reduced jumping distances (41% reduction), slower swimming speed (37% reduction), decreased endurance (66% reduction), low-

er body condition and poorer foraging success, which resulted in a 22% lower biweekly survival rate relative to infected frogs without malformations (Goodman & Johnson 2011a). By contrast, in enclosures without predators, survival was similar to normal frogs. Moreover, malformed individuals selected warmer microhabitats than normal frogs, which resulted in higher body temperatures of the malformed frogs (Goodman & Johnson 2011b). They were more likely to use open ground microhabitats relative to vertical refugia and selected less-angled perches closer to the ground compared to normal frogs. This altered habitat selection is likely to expose them more to avian predators, which should facilitate the transmission of the parasite to its definitive host and thus can be regarded as an extended phenotype of the parasite that facilitates transmission to the definitive host. Selection of warmer sites may also increase the risk of desiccation and overheating but this risk has not yet been assessed in the field.

Lower survival rates of abnormal individuals are reflected in higher percentages of abnormal juveniles compared to adults. Johnson et al. (1999), Goodman & Johnson (2011a) and Lunde et al. (2012) found less than 5% abnormal adult *P. regilla* at ponds in California even after years in which up to almost 60% of the metamorphosing frogs were abnormal. Black-eyed *Rana arvalis* were significantly more frequent among juveniles than adults in Ekaterinburg, Russia (Vershinin 2006). In three Australian frog species in Jabiru the frequency of abnormal individuals was 2–8% lower in adults than in juveniles (Tyler 1989). In a population of *Bufo bufo* from Rhineland-Palatinate, Germany, only 1% of the adults but 15.5% of tadpoles and toadlets suffered from ectromely or oligodactyly (Veith & Viertel 1993). Likewise, in a Californian population of *A. macrodactylum* infected by *Ribeiroia ondatrae* only 4.6% of the adults but 38.5% of the juveniles showed limb anomalies (Sessions & Ruth 1990). In populations of *Pelophylax* synkl. *esculentus* affected by anomaly P (Dubois 1979b) and the *P. ridibundus* populations studied by Woitkewitsch (1959, 1965), the frequency of anomalies was much higher in tadpoles than adults; Woitkewitsch (1959, 1965) even had difficulties finding any affected adults. These differences indicate that most abnormal individuals died before reaching sexual maturity. However, when anomalies are due to abnormal regeneration or injuries, then they sometimes accumulate with age (Vershinin 2002, Gridi-Papp & Gridi-Papp 2005).

5.2 Population level effects

Because anomalies are usually detrimental at the individual level, one might expect that anomalies contribute to the global decline of amphibians (Dubois 1979b, Lannoo 2008, Helgen 2012). For example, a population of *Anaxyrus americanus* failed to breed after years of high rates of malformations (Johnson & Hartson 2009) and in some wetlands 90–100% of the larval *Pseudacris regilla* were abnormal leading to an almost outright recruitment failure (Lunde et al. 2012). At Veteran's Park, Idaho, and Muskee Lake, California, *P. regilla* and *Ambystoma tigrinum*, showed high rates of anomalies (albeit sample size was low for the latter species) in 1988 and 1946–1951, respectively, and were extirpated in 1999. Similarly, at Morgan Pond in Texas *Lithobates catesbeianus* had an abnormality rate of approx. 5% in 1961 and was extinct in 2001 (Johnson et al. 2003). A neotenic population of *A. tigrinum* from the Reese Air Force Base, Texas, USA, in which up to 45% of the individuals developed tumours between 1970 and 1980 rapidly declined from approx. 18.000 mature individuals in 1976 to around 3.000 in 1980 (Rose 1981). However, similar declines also occurred in populations from non-polluted sites and might have been due to low rainfall rather than the anomalies.

Mass mortality and declines, however, are not necessarily due to anomalies. For example, at the CWB malformation hotspot in Minnesota, *L. sylvaticus* and *L. pipiens* became extinct and *Anaxyrus americanus* seriously declined (Hoppe 2005, Lannoo 2008). Concomittantly, increasing numbers of dead and dying tadpoles and frogs of several species were found in the lake (Hoppe 2002). It should be noted that the frequency of abnormal individuals was the same in dead and living samples, indicating that mortality was irrespective of the abnormality status. Moreover, dead fish were observed as well. This indicates that anomalies may not have been the direct cause of decline. Rather, one (or multiple) factor(s) probably simultaneously caused anomalies and directly killed the frogs and fish.

Mass occurrence of anomalies linked to major mortality events caused by infection with *Ranavirus*, an iridiovirus, *Areomonas hydrophila*, or *Batrachochytrium dendrobatidis* have been discovered in various amphibian species in different regions of the world (e.g., Cunningham et al. 1993, 1996, Lips 1999, Docherty et al. 2003, Lips et al. 2004, Berger et al. 2009, Teacher et al. 2010). Infections with *Ranavirus* and *B. dendrobatidis* have been implicated in the long-term decline of populations and even the extinction of species (Berger et al. 2009). However, in all of these cases, the observed anomalies, such as edema or hemorrhage, are rather an epiphenomenon than the cause of the mortality. For example, *B. dendrobatidis* infection causes mortality by disrupting cutaneous functions in sensitive species (Voyles et al. 2009).

In spite of observed declines and extinctions, evidence exists that some anomalies may be maintained in a given population over rather long periods of time, at least for 27 years (Rostand 1971, Dubois 1984, Vershinin 2002) and even longer (Dubois, unpublished data). Anomaly P, for example, was retained in several populations of *Pelophylax* synkl. *esculentus* in France for more than a decade (27 years at Champdieu) at variable, often high rates (up to 80% in tadpoles) (Rostand 1971, Dubois 1979b, 1984, 2014, 2017). At Seascape, California, and Jette Pond, Montana, for example, *P. regilla* showed high rates of anomalies 1986–1987 and

1958–1959 and were still extant one and four decades later, respectively, again exhibiting high rates of anomalies (Johnson et al. 2003). The reason why populations remained extant over years despite high frequencies of anomalies may be explained by a combination of several factors. First, there may be an overestimation of the percentage of abnormal metamorphs as these may be easier to observe and may disperse less from breeding locations than normal individuals. The extent to which dispersal differs in abnormal individuals from normal ones has not been studied and only Goodman & Johnson (2011a) seemed to have addressed catchability: there was no difference between malformed and normal *P. regilla*. Secondly, mortality may be compensatory, which is common in larval and recently metamorphosed amphibians (e.g., van Buskirk & Smith 1991, Patrick et al. 2008). Therefore, mortality in post-metamorphic stages of pond breeding amphibians is more likely to contribute to declines rather than the mortality of eggs, larvae and recently metamorphosed individuals (Biek et al. 2000, Salice 2012). While it is clear that many types of anomalies incur costs to the abnormal individual, the population level effects are less clear and urgently need to be addressed to understand the role of anomalies for the conservation of amphibians.

6 Temporal patterns in the occurrence of anomalies and their reporting

In the North American literature it is generally assumed that the occurrence of anomalies has increased considerably since the 1990s, (e.g., Blaustein & Johnson 2003, Sessions 2003, Hoppe 2005, Johnson & Chase 2004, Johnson & Lunde 2005, Lannoo 2008; Anderson & Hoppe 2010, Helgen 2012). Several pieces of evidence were advocated to support these conclusions, such as lower rates of anomalies in historical museum collections and in early surveys at locations that have been resurveyed more recently. Also, average rates of anomalies above the baseline rates in several recent large-scale surveys and the appearance of hotspots have been regarded as evidence of an increase in the frequency of anomalies over recent decades. Finally, mechanistic arguments that link an increase in anomalies to the eutrophication of ponds and lakes have been put forward.

To evaluate whether an increase in the occurrence and frequency of anomalies has occurred over time, and if so, when and how strongly, is challenging because of the almost complete absence of standardized monitoring programs with an appropriate site selection design. Moreover, greater public awareness following the rediscovery of anomaly hotspots in North America (Souder 2002) and concomitantly substantially increased survey efforts likely contributed to the considerable increase in publications reporting anomalies from natural populations since the 1990s (see Fig. 2). In addition, populations without anomalies are rarely reported and in spite of guidelines for data collecting (Meteyer 2000, Lunde & Johnson 2012) anomalies are still examined, scored and reported in inconsistent ways.

In the following we discuss what can be inferred despite these challenges. We first summarize the results from comparisons of recent data with historical museum collections. We then evaluate trends from resurveys and long-term monitoring of sites and analyse whether there is evidence for an increase in the prevalence of anomalies in recent large-scale surveys and from the record of publications. Finally, we outline mechanistic arguments that link an increase in anomalies to environmental change over recent decades.

6.1 Historical collections

The few comparisons of more recent and historical museum collections provide some support for the notion of increased frequencies of abnormal amphibians over recent decades. In recent (1993–1999) collections of tadpoles of *Rana muscosa* from the Sierra Nevada, California, 18% of the individuals showed oral anomalies but none of those collected between 1955–1976; the difference was highly significant (Fellers et al. 2001). The anomalies were caused by infection with *Batrachochytrium dendrobatidis*.

Of the museum specimens of *Acris crepitans* housed at the University of Arkansas, 3.3% were scored as abnormal (mainly ectrodactyly and syndactyly and retained tails) for the period 1957–1979 (McCallum & Trauth 2003). In the 1980s, the rate was 5.5%, increasing to 6.9% in the 1990s and to 8.5% by 2000. This increase was statistically highly significant. There are two caveats for inferences from these data that must be mentioned. Firstly, frequencies of abnormal frogs were not uniformly distributed across Arkansas; they were rather high at locations in the Ozark highlands and no data were given whether the percentage of examined individuals that originated from these highlands were the same in all compared periods. Secondly, one third of the abnormalities were retained tails and presumably occurred in recently metamorphosed individuals – tail retention in adults has been reported only extremely rarely and retarded tail resorption is a normal feature in some anuran species (see section 3.3.2.1). Unfortunately, McCallum & Tauth (2003) did not provide the age of these individuals nor whether age distribution was constant across the periods under comparison.

Juvenile and adult amphibians of 19 species collected at six localities in Tucumán Province, Argentina, between 1940 and 2010 also did not show uniform distributions of the prevalence of anomalies across decades (Medina et al. 2013). The highest prevalence was observed in the decade 1960–1969. Similar caveats as for the study by McCallum & Trauth 2003) apply. Prevalences differed (marginally significant) among sites and it was not assessed whether all sites were equality represented in all decades. In addition, digital amputations were considered as toe-clipping and not as anomalies but criteria how amputations by toe-clipping and natural loss of digits could be

differentiated in museum specimens were not provided – and is unlikely to be possible (see section 3.2.2.1).

6.2 Resurveys

Resurveys and monitoring of sites showed mixed results. Resurveys conducted within a few years most frequently showed limited differences in the percentage of individuals affected between the survey and the resurvey (e.g., Canfield et al. 2000, Levey et al. 2003, Vandenlangenberg et al. 2003, Johnson et al. 2001, 2003). In a nation-wide survey of US wildlife refuges the differences among surveys was most frequently below 10% but reached more than 30% at one site, with the variability being higher at sites within hotspot clusters compared to outside of hotspot clusters (Reeves et al. 2013). This is not too surprising as hotspot clusters include more hotspots that by definition have higher prevalences of anomalies and thus can vary more than those areas outside hotspot clusters.

At a few sites, the percentage of abnormal frogs had declined considerably in the resurveys (Canfield et al. 2000, Lunde et al. 2012) or even completely disappeared. For example, at Granite Falls, Minnesota, many malformed frogs were observed in 1993 but none were discovered among hundreds examined in a resurvey the following year (Helgen 2012). At Hog Lake in California the percentage of abnormal *Pseudacris regilla* was approximately 50% in the 2006–2007 and 2007–2008 breeding seasons and then dropped to approx. 5% in the 2008–2009 and 2009–2010 breeding seasons (Lunde et al. 2012). At Muskee Lake, Colorado, a high prevalence of polydactyly suddenly appeared in *Ambystoma tigrinum* in 1945 and disappeared again after 1953 (Bishop 1947, Bishop & Hamilton 1947).

Surveys that were made more than a decade apart showed a similar mixed picture. At Macinaw River, Illinois, for example, no abnormal *Acris crepitans* was found in 1968–1971 ($n = 345$) but in a resurvey in 1998 three out of 140 individuals had a missing digit (Gray 2002). The increase is statistically significant (Fisher's exact test: $P = 0.02$), albeit small. Field surveys at nine sites in Minnesota sampled between 1975 and 1992 revealed three abnormal *Lithobates pipiens* out of the 1772 examined. A resurvey in 1996–1997 resulted in 2.3% of 2548 frogs being abnormal, which is a small but significant increase (Hoppe 2000). Unfortunately, no data were provided as to whether the earlier surveys comprised the same percentage of juveniles as the later resurveys.

Of 276 juvenile *L. pipiens* specimens collected from 1958 to 1963 by Merrell and stored at the Bell Museum of Natural History, University of Minnesota, from five sites, at which the species was still found in 1997, one was abnormal (0.4%). In 1997, 15 out of 611 individuals were malformed; the increase is significant (Hoppe 2000). A limitation of the study is that Hoppe (2000) did not include individuals of the historic collection with missing body parts (limbs?) in the number of abnormal individuals because he regarded them to be due to predators. However, trauma as cause can be identified with certainty only if wounds are still fresh, which is not the case in old collections (see 3.2.2.1). Notwithstanding, further surveys during 1998–1999 yielded frogs at four more sites at which museum specimens were available for comparison. Across the nine sites, the frequency of abnormal individuals was higher than the historic frequency when individulas with amputations were included in the number of abnormal specimens (2.4 % versus 0.7%) (Hoppe 2005, Anderson & Hoppe 2010). At one of these sites, in Douglas County, none of the museum specimens collected between 1958 and 1963 was abnormal ($n = 40$), only a single one ($n = 85$) was abnormal in a resurvey from 1996 to 1999 (Hoppe 2005) but 14 ($n = 147$) were abnormal in 2011 (Helgen 2012). Moreover, the malformation risk in the 1990s was about six times that of the historical period (calculated without counting individuals with amputations as abnormal) (Anderson & Hoppe 2010)

At Frog Pond, California, 15% and 25% of the *P. regilla* were abnormal in 1997 and 1998, respectively (Johnson et al. 2003). A decade later (2006–2009), the frequency was slightly higher (25–35%). At Jette Pond, Montana, the anomaly rate increased in three species (*Ambystoma macrodactylum* from 0% to 11%, *Anaxyrus boreas* from 0% to 6%, *P. regilla* from 20% to 46%) between 1958 and 2002 (Johnson et al. 2003). A very strong increase of the abnormality rate also occurred in *Cryptobranchus bishopi* in the Spring River, Arkansas: from 12.5% ($n = 45$) in museum specimens collected between 1970 and 1975 to 90% ($n = 10$) in field samples in 2003–2004 (Hiler et al. 2005). The difference is highly significant ($\chi^2 = 25.4$, $\alpha < 0.0001$). Tumours, ectromely, ectrodactyly and necrotic limbs were the most common anomalies.

Four declines in abnormality rates were detected in resurveys. At Ripley Pond, Ohio, 8% of *L. catesbeianus* suffered from polymely, polydactyly, ectromely, or ectrodactly in 1954 (Anonymous 1954) but only a single abnormal individual (with schizodactyly) was found in a resurvey in 2001 (Johnson et al. 2003). At Seascape, California, the abnormality rate in *P. regilla* and *Ambystoma macrodactylum croceum* dropped substantially (from 72% to 13% and from 28% to 0.9%, respectively, between 1986 and 2000 (Johnson et al. 2003). Slightly elevated rates of polydactyly (0.7–1.4%) were observed in *Cynops pyrrhogaster* from Honshu, Japan, in the years 1981–1985 (Meyer-Rochow & Asashima 1988), which fell to less than 0.1% in 1995 (Fukui et al. 1996). The fall was explained by improved water quality – but no explicit data on water quality were provided.

In summary, resurveys tend to indicate a slight dominance of increases in abnormality rates. However, from eight increases only four were strong and four declines occurred as well, two of which were very severe. Given the very high year-to-year fluctuations that have been reported for several populations, little can be inferred about historic trends from these resurveys until more resurveys become available to enable assessments about whether increases occurred significantly more often than declines.

6.3 Long-term monitoring of sites

Very few long-term monitoring studies of the same site(s) are available. Most of them did not show a clear trend of the prevalence of anomalies through time. For example, at Hidden Pond in California the percentage of abnormal *Pseudacris regilla* was approximately 10% in 1997 and 1998 (Johnson et al. 2001a), increased to 58% in 2006 and then fell to 28–36% in the years 2007–2009 (Lunde et al. 2012). Between 1997 and 2001 the perecentage of abnormal *Lithobates pipiens* metamorphs fluctuated between 1% and 20% at one site (Otter Creek) in the Lake Chamberlain Region of Vermont, showed little fluctuations at three sites, and declined from 35% to 1% at one Site (Wards Marsh) (Levey et al. 2003). Between 1949 and 1967, the frequency of *Pelophylax* synkl. *esculentus* suffering from anomaly P at Trévignon in France varied from 0% to 80% in tadpoles and from 2.6% to 14.5% in adults (Dubois 1979b, 2014, 2017). In another population from central France, Champdieu (Loire), the frequency varied from 0% to 6.3% between 1950 and 1976, whereas in a third one, Lingé (Indre), from 1961 to 1970 the frequency in tadpoles fluctuated between 14% and 70% (Dubois 1979b, 1984, 2014, 2017). At the same time in Champdieu the frequency of black-eyed individuals ranged from 0% to 0.7%; black-eyedness is not related to anomaly P. The percentage of black-eyed individuals of *Rana arvalis* in Ekaterinburg, Russia, fluctuated between 0% and 10% in 1980–1998, with the fluctuations being highest in the multistory urban zone and lowest in rural forest areas (Vershinin 2002, 2004, 2005). It is noteworthy that even for the same type of anomaly and the same cause the interannual variability in the frequency of anomalies may differ considerably among sites and may be huge.

Besides the one site in Vermont mentioned above, only five studies witnessed a clear trend in the percentage of abnormal individuals for a specific location. Martof (1962) collected 43 albinistic *Desmognathus marmoratus* between 1954 and 1960, with their frequency increasing from 0.7% to 8.9%. In 1963, the percentage had increased to 15% (Martof & Walton 1965). Rose (1976, 1981) monitored an *Ambystoma tigrinum* population in a sewage pond at the Reese Airforce Base, Texas, that suffered from tumours. Polycyclic aromatic hydrocarbons were identified as the cause of the anomalies. In 1970, only one larva out of 2430 was abnormal. The anomaly rate rose continuously to approx. 50% in 1975 and then fell again to approx. 20% in 1980, with the fall happening simultaneously with a strong decline in abundance.

In two Russian populations of *Bufo bufo* the incidence of polydactyly dropped from 29.8% in 1990 to 0% in 1997 (Lada 1999). From 1926 to 1934 all 46 individuals of *Taricha porosa* that were sampled at Boulder Creek, California, exhibited a pathological warty skin (Brattstrom & Warren 1953) that Twitty (1942) identified as an extreme proliferation of fibrous connective tissue, i.e., tumour. In 1942, this was the case for 27 out of 28 individuals sampled. Prevalence had dropped to 26% (n = 19) in 1948 and to 10% (n = 148) in 1953 (Brattstrom & Warren 1953). The anomaly was not transmitted among individuals maintained in captivity nor influenced by the maintenance temperature and the cause of the anomaly remains obscure.

6.4 Prevalence of anomalies in large-scale surveys and background rates

Following the re-discovery of anomaly hotspots in Minnesota, a range of large-scale surveys on abnormal frogs was carried out in various states of the USA and nationwide in wildlife refuges (Helgen 2012, Reeves et al. 2013). The nation-wide frequency of anomalies across 135 national wildlife refuges was 2% (Reeves et al. 2013). In the surveys outside national wildlife refuges in various states, anomaly rates well above this rate were repeatedly found (reviewed by Helgen 2012). Unfortunately, some of these surveys also targeted known anomaly hotspots and thus may not have provided data for unbiased comparisons (Reeves et al. 2013). Also, a considerable number of surveys resulted in anomaly prevalences around the presumed baseline level (Lunde & Johnson 2012), which would weaken the conclusion that contemporary rates of anomalies are elevated. On the other hand, Table 1 indicates that true baseline rates might even have been an order of magnitude lower than the 2% calculated in the nation-wide survey in wildlife refuges (see Tab. 1 and Henle et al. 2017a), which would strengthen the conclusion about an elevated frequency of anomalies over recent decades. It is worth noting, however, that, although not targeted, the survey of Reeves et al. (2013) included some hotspots. One third of the sites did not reveal any anomaly and at about 50% of the sites the frequency of anomalies was below 2%. This further strengthens the results from Table 1 on true baseline rates of well below 1%. In the absence of comparative data from the past uncertainty remains about true baseline rates.

Based on an analysis of the compilation of data from publications of skeletal anomalies by Ouellet (2000), Lannoo (2008) argued that the frequency of anomalies increased in recent decades. He coded all records in a binary fashion, with "fewer than ten individuals" as one category and "ten or more individuals" as the second category. A plot of these data against publication date indicated that the category "more than ten" started to appear around 1950 and became increasingly more prevalent. He concluded that these reports of "ten or more" constitute the malformed frog problem and that this problem started to appear from about 1950.

There are several caveats with this conclusion. Firstly, the number of publications has strongly increased (Fig. 2) creating a strong overlap of dots on his graph for recent decades. Therefore, it is not really clear as to whether the percentage of surveys that resulted in "ten or more" has indeed increased over recent decades. Lannoo (2008) did not test for a temporal trend in this percentage. Secondly, several cases of the category "ten or more" that were recorded for the first half of the last

century were missing in the compilation of Ouellet (2000).

We redraw the graph based on our more comprehensive database that includes all types of externally visible anomalies (Fig. 39). If sampling covered more than one year, we used the median survey year (the earlier year in cases of equal numbers of sampling years). To reduce noise created by long time spans, we divided the data, if possible, into 5-years-intervals, starting with the first year that the site was sampled. Figure 39 clearly shows that there is a considerable number of "ten or more" cases that occurred in the first half of the 20th Century.

Lannoo's (2008) conclusion further requires the assumption that sample sizes did not increase over time as this would bias trend analyses based on the number of abnormal individuals observed. Elsewhere we will show that the median value of the percentage of abnormal individuals observed per case increased with the year of observation (Henle et al. submitted).

6.5. Mechanistic explanations linking an increased frequency of anomalies to environmental changes

Mechanistic links of anomalies to environmental factors that have changed over recent decades provide the best evidence that the frequency of anomalies has indeed increased over recent decades. One comparably well understood link is to eutrophication. Many of the North American hotspots occur in highly eutrophic water bodies (Lannoo 2005) and eutrophication has substantially increased in North America (Rouse et al. 1999) and in many other parts of the world (Ellenberg 1991). This increase already started many decades ago, well before the 1990s, and thus is in line with Lannoo's (2008) suggestion that the the malformed frog problem already started to appear around the 1950s (or even slightly earlier – see Figure 39; and not only in the 1990ies as assumed by many authors, see introduction to section 6) and that the collapse of wetlands caused by eutrophication and other pollutants was a key driver of the malformed frog problem.

The eutrophication of ponds fosters planorbid snails that are intermediate hosts to the trematode *Ribeiroia ondatrae* (Johnson & Chase 2004). Eutrophication further enhances the survival of infected snails, thereby increasing the period over which they release cercariae of the parasite. A higher abundance and an enhanced survival of infected snails will increase the number of cercariae in a pond that can infect amphibian hosts. These changes should lead to higher infection rates in amphibians and as a consequence higher frequencies of anomalies. While a range of observational and experimental studies support these mechanisms (Johnson & Chase 2004, Johnson & Lunde 2005, Johnson et al. 2007), it can only explain an increase in anomalies that are typical for an infection with *R. ondatrae*, such as polymely, polydactyly, bony triangles and skin webbing. Several of the hotspots in the northwestern states of the USA and California are characterised by these types of anomalies (Johnson et al. 2002) but in many other re-

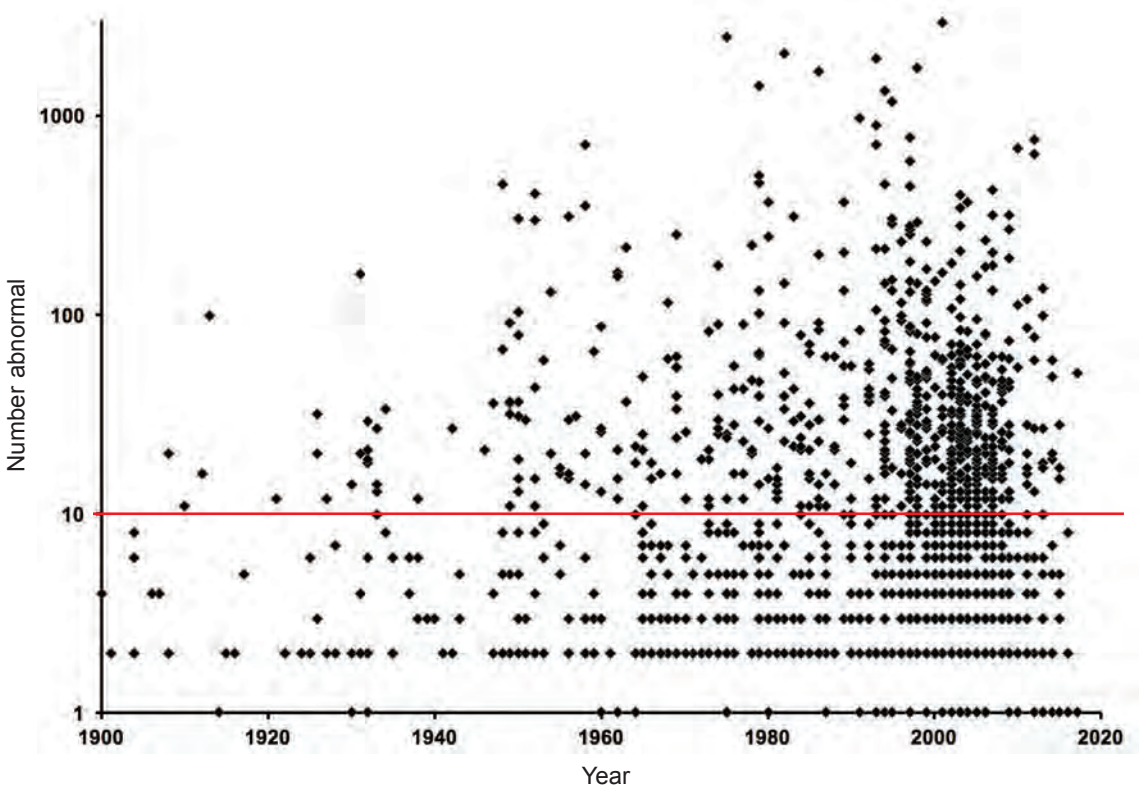

Fig. 39: Plot of the number of anomalous individuals reported per case against year of observation. Note the logarithmic scale. The red line separates the two categories used by Lannoo (2008) for inferring an increase in the frequency of abnormal individuals since about 1950.

gions of the USA and in all other parts of the world the spectrum of anomalies does not fit the pattern typical for this parasite (see section 3.1).

Lannoo (2008) suggested that eutrophication and the resulting collapse of wetland ecosystems is also a direct cause for increased frequencies of anomalies, independent of the presence of *R. ondatrae*. While fertilizers are not known to cause most of the anomalies observed in hotspots, eutrophication is an indicator of intensive agricultural practices. Intensive agriculture in turn is characterised by an intensive use of pesticides (Henle et al. 2008, Lannoo 2008) that can contribute to an increase in the prevalence of anomalies through at least two mechanisms. Firstly, they may enhance infection rates of tadpoles by *R. ondatrae* (Kiesecker 2002). Secondly, various pesticides are teratogenic for larval amphibians at environmentally relevant concentrations. Among other anomalies, they can induce ectromely and ectrodactyly (see e.g. Table 3 and section 3.1.7.2), which are dominant at many North American hotspot sites.

Recently, a further mechanism that may link eutrophication to increased frequencies of anomalies was discovered. Eutrophication may cause blooms of cyanobacteria that produce teratogenic retinoic acids (Wu et al. 2012). Together, these mechanisms should have contributed to an increase in the prevalence of anomalies in landscapes dominated by intensive agriculture that relates to the intensification of agriculture. While historical comparisons are not available to document such a temporal correlation, comparisons of sites close to intensively used agricultural fields with control sites away from intensive agriculture tend to support such a causal relationship; for examples from Europe, Asia, Africa, North and South America see section 3.1. Moreover, several of the hotspot clusters identified in the USA are located in areas with intensive agriculture, particularly in the Midwest (Lannoo 2008, Helgen 2012, Reeves et al. 2013). However, quantitative assessments that relate abnormality prevalences to land cover types are rare and the few existing ones used only crude proxies for the intensity of agriculture (e.g., Ouellet et al. 1997, Piha et al. 2006), with measures of eutrophication or the use of pesticides missing in large-scale assessments. Because agricultural land use is spatially and temporally heterogeneous, showing strong non-linearity across scales (Tzanopoulos et al. 2013), results may also differ, depending on the scale of assessment. This heterogeneity in time and space may further explain why historical comparisons and resurveys show both increases and decreases in the percentage of abnormal individuals.

If pollution associated with more intensive land use has contributed significantly to an increased prevalence of anomalies at a large scale (be it directly or indirectly), then prevalences of anomalies should be higher outside compared to inside national parks, wildlife reserves and forest reserves, which generally have a lower land use intensity. Elsewhere we show that this is the case for North America (Henle et al. submitted).

Some hotpots of anomalies in Europe, Asia, Australia, Bermuda and North America were linked to industrial pollution (see section 3.1). A wide range of anomalies can be caused in amphibians by industrial chemicals (Henle et al. 2017a) and the causal relationships have been documented experimentally for several hotspot sites. Like eutrophication, the pollution of water bodies from industrial sources has also increased substantially worldwide after the Second World War (e.g., Widener 1970, Koch & Vahrenholt 1983, Dubois 2012) and this should also have contributed to an increase in the prevalence of amphibian anomalies since then. On the other hand, progress in water protection in some countries should have also reversed the trend of the prevalence of anomalies. Indeed, Fukui et al. (1996) related a decline in the rates of polydactyly in *Cynops pyrrhogaster* in Honshu, Japan, from 0.7% to 1.4% in the years 1981–1985 to less than 0.1% in 1995 to improved water quality. Unfortunately, he did not provide data on water quality and data that relate changes in the frequency of anomalies to changes in water quality are generally lacking. In any case, progress in water protection is limited in many regions of the world. Even in Europe with its very stringent legal requirements, water pollution still jeopardizes the health of freshwater ecosystems on a continental scale (Malaj et al. 2014) – but note that no large-scale data are available for small, especially ephemeral water bodies that are preferred breeding sites for many amphibians.

7 Conclusion and perspective

Since the first reliable report of an observed malformed amphibian in 1554 (Gesner 1554) a considerable number of publications and observations have accrued. Much of this literature is widely dispersed and addresses anectodal observations of 1–2 individuals and types of anomalies. Anomalies have been reported from all continents and from more than 400 species. Large numbers and percentages of affected individuals (so-called hotspots) are also known from all continents. The largest number of reports originates from Europe and North America, likely due to a much higher number of naturalists being active in these countries and greater chances of finding their publications.

A considerable number of causes have been suggested for observed anomalies but attempts to unravel them have only been undertaken in a minority of cases. This also applies to hotspots and much of the inferences rely on correlations and extrapolations – which may be indicative but have limitation – and less on experiments conducted for specific hotspots. Nevertheless, it is clear that a range of different factors is involved. This also applies to hotspots in North America (Reeves et al. 2013) in spite of the still existing controversy. Demonstrated causative factors are parasites, chemical pollution, predators, disease, injuries from mowing and radioactive pollution, with the relative importance differing among regions. All but the last were demonstrated for at least one hotspot site in North America as well. These factors may not only

co-occur at a particular hotspot site but may interact with each other, even though co-occurrences and interactions are still insufficiently understood.

It is widely assumed that prevalences of anomalies have increased over recent decades. Evidence from museum collections and resurveys tend to support this assumption, although declines were observed over recent decades as well and the few long-term monitoring studies available show that the frequency of abnormal individuals can fluctuate widely without an apparent trend. Despite these fluctuations, across all published cases, there is a significant increase over time in the percentage of individuals that are abnormal and this is especially apparent in the most severe cases (Henle et al. submitted). However, in the absence of large-scale long-term monitoring programs these patterns are only indicative but cannot prove a change over time. Initiation of well-designed long-term monitoring studies and resurveys of sites where anomalies were assessed in the past are urgently needed.

Notwithstanding, the revelation of mechanistic relationships does support an increase in the prevalence of anomalies over the last 50 years. Mechanistic links of eutrophication with high rates of anomalies have been demonstrated and various chemical pollutants are also known to cause elevated rates of anomalies. Because pollution increased in many parts of the world since the Second World War and still jeopardizes the health of freshwater ecosystems on a continental scale (USEPA 2009, Malaj et al. 2014), it is likely that the prevalence of anomalies has indeed had an increasing tendency over recent decades. Further, there is evidence that background rates of anomalies are about an order of magnitude lower than currently assumed. However, in the absence of repeated standardized large-scale surveys based on sampling design theory, in which potential causative factors and also absences of anomalies are reported, it is difficult to establish baseline rates and to quantify the role different factors play in increased rates of anomalies.

Little is also known about the population level consequences of elevated rates of anomalies. Even at the individual level, few studies quantitatively addressed the effects of particular types of anomalies. Although most types of anomalies hamper performances of affected individuals, this often depend on other environmental factors, such as presence or absence of predators and food availability. Also, decreased performance, including reduced survival, does not necessarily translate into population level effects because of compensatory mortality. Moreover, anomalies may not be the direct cause of an observed increase in mortality and population decline; rather the same factor may cause the anomalies and directly kill normal and abnormal individuals. Therefore, it is currently not possible to know whether elevated rates of anomalies contribute to the decline of amphibians and studies that unravel population level effects are urgently needed. Likewise, studies on other organisms in regions where several hotspots of amphibian anomalies occur could be enlightening to better understand the relevance of amphibian anomalies for ecosystem and human health.

In conclusion, while studies on single individuals or types of anomalies are still valuable, especially for countries and species for which only limited observations have been published, one should always examine all individuals, report sample sizes and the number of abnormal individuals, and describe the anomalies using a clearly defined terminology. In population studies, anomalies should be routinely assessed in such a way that they can be used in rigorous meta-analyses and it should be reported if none were detected.

In addition, long-term monitoring studies across larger regions based on sampling design theory that include the monitoring of potential causative factors need to be established to better understand trends. Such studies should not only assess populations in wildlife areas (as e.g. Reeves et al. 2010, 2013) but should include other land use types. Evaluating the correlation between anomaly prevalences and land cover type and quantitative indicators of land use intensity, such as indicators of agricultural intensity (Ouellet et al. 1997, Taylor et al. 2005), urbanization (Vershinin 2002) or industrialization (Mizgireuv et al. 1984), across large scales would further allow major progress in identifying likely causative factors of elevated rates of anomalies. Hypotheses derived from such studies could then be tested experimentally for targeted sites or landscapes. Experimental studies to unravel potential causes should not be limited to a single factor; rather they should address all of those factors that are consistent with the pattern of anomalies observed in the targeted natural population and thus possible candidates as culprits. In this respect the work of the amateur biologist Jean Rostand to elucidate the cause(s) of anomaly P (summarized in Rostand 1971 and Dubois 2017) still remains a highly recommendable example.

Finally, studies are needed that unravel the population level consequences and the consequences for amphibian declines and ecosystem and human health of elevated rates of anomalies. Whether or not, and if so to which extent, they contribute to amphibian declines, it is an ethical obligation to minimize eutrophication and pollution of wetlands to reduce the anthropogenically driven plight of amphibians. This, at the same time, will benefit many other organisms, ecosystem services to humans, reduce human health risks, and improve the quality of human life.

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http://www.fws.gov/contaminants/amphibian/PictureThumbs.html.

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