| Table S1. Hypotheses for amphibian abnormalities (adapted from Johnson et al. 2010). |
| --- |
| Hypothesis Name | Summary | Background  |
| Null  | Abnormalities occur at low frequencies and are caused by random errors in development. | Abnormalities occur in all organisms, but what prevalence is considered “normal” for amphibians? In wild populations, this prevalence is low, generally less than 2% [[1](#_ENREF_1),[2](#_ENREF_2)]. Based on a literature review, others [[3](#_ENREF_3)] proposed a 5% threshold for baseline abnormality levels. Recent studies looking at large numbers of frogs across Canada and the United States support a threshold of 5% or lower: Minnesota (2.5% [[4](#_ENREF_4)], Michigan (0.14% [[5](#_ENREF_5)]), the midwestern and northeastern United States (1.4%-2.6% [[6](#_ENREF_6),[7](#_ENREF_7)]), western Canada (0.2% [[8](#_ENREF_8)]), Vermont (1.6% [[9](#_ENREF_9)]), and Illinois (0.4% [[10](#_ENREF_10)]). It is not clear what fraction of these "baseline" study abnormalities are due to developmental errors versus injuries. |
| Contaminants  | Chemicals in the environment cause errors in development that result in a broad spectrum of amphibian malformations.  | Amphibians are often cited as indicator organisms, showing heightened sensitivity to environmental conditions before they harm other taxa [[11-13](#_ENREF_11)] . Abnormalities in amphibians could represent a sublethal response to toxic chemicals in their habitat [[14](#_ENREF_14),[15](#_ENREF_15)]. Such contaminant-induced abnormalities have been associated with historic landfills, coal spoils, or other waste disposal areas [[15-21](#_ENREF_15)] or wetlands subjected to localized road or agricultural runoff [[1](#_ENREF_1),[21](#_ENREF_21)]. The teratogenic effects of a number of agricultural chemicals on amphibians have been investigated in controlled experiments [[11](#_ENREF_11),[22-48](#_ENREF_22)]. The effects of these chemicals vary; however, it is clear they can cause skeletal deformities in developing amphibians. A fundamental challenge in investigating the role of contaminants in causing amphibian limb malformations in nature is determining which chemical(s) (or combination thereof) to study. Testing for the full-suite of these compounds and their various breakdown products in wetlands is prohibitively expensive and can be methodologically challenging.  |
| Parasites | Parasites infect developing limbs of amphibian larvae causing a variety of abnormalities, commonly multiple limbs, bony triangles, and skin webbings. | This hypothesis was first suggested in 1990 [[49](#_ENREF_49)] when high frequencies of malformed amphibians in a California pond were found to have parasites encysted near the malformed limbs. Subsequent work identified the parasite responsible as *Ribeiroia ondatrae* [[50](#_ENREF_50),[51](#_ENREF_51)], a digenetic trematode with a multi-host life cycle. *Ribeiroia* moves sequentially among freshwater snails, larval amphibians, and finally, birds or, less frequently, mammals [[52](#_ENREF_52)]. Extensive evidence now supports a causal link between *Ribeiroia* infection and limb malformations in amphibians [[53-59](#_ENREF_53)]. Exposure to realistic numbers of *Ribeiroia* cercariae causes increased mortality and severe malformations in frogs, toads, and salamanders. The frequency of malformations induced is often high, and can reach 100% among surviving animals. Malformations and mortality are dose-dependent; higher levels of *Ribeiroia* exposure increase the risk and the severity of malformations produced, as well as the likelihood that the animal dies following exposure. Low levels of infection may or may not cause any obvious pathology.  |
| Predators | Predators bite the developing limbs off of amphibian larvae, leading to missing or partially-regenerated, but malformed limbs.  | Growing evidence suggests that predators may play an important role in causing certain types of abnormalities in amphibians. Predators like stickleback [[60](#_ENREF_60)], dragonfly larvae [[60](#_ENREF_60),[61](#_ENREF_61)], or leeches [[62](#_ENREF_62),[63](#_ENREF_63)] cause abnormalities by attacking developing tadpole hind limbs without killing the tadpole. In these cases, the abnormalities are dominated by partially and completely missing hind limbs. Predators may create an injury that either results directly in an abnormality (e.g., a missing limb) or creates a malformation during the regeneration process, often lacking obvious scar tissue and with some development of digits at the distal end.  |
| UV-B | UV-B radiation causes bilateral and symmetrical shrunken limb abnormalities when larvae are exposed during development. | Declines in the earth’s ozone layer have caused seasonal increases in the level of UV-B penetration, which is suspected to have deleterious effects on aquatic systems [[64-70](#_ENREF_64)] . Because many amphibians deposit their eggs in shallow water, they are perhaps particularly vulnerable to changes in UV-B [[65](#_ENREF_65),[71-73](#_ENREF_71)]. Laboratory and outdoor studies have established that exposure to ambient UV-B can cause high frequencies of limb reductions or deletions in amphibians [[74-76](#_ENREF_74)]. However, the resulting abnormalities were generally bilaterally symmetrical, unlike most field observations, causing the authors to question a direct role of UV-B in explaining recently observed malformations in amphibians [[77](#_ENREF_77)]. Additionally, field studies and risk assessment analyses suggest that the levels of UV-B exposure to which amphibians are exposed in natural wetlands is usually insufficient to induce abnormalities [[78](#_ENREF_78)]. In nature, UV-B is often rapidly attenuated in aquatic ecosystems, owing to dissolved organic carbon in water, and maternal behavior can further buffer offspring from UV-B effects by laying eggs in the shade [[78](#_ENREF_78)]. |
| Multiple Stressors | Multiple stressors (often a combination of biotic and abiotic) like nutrients and parasites, chemicals and predators, or chemicals and UV-B, must co-occur to cause abnormalities, sometimes by complex mechanisms.  | Several recent studies have shown abnormalities in nature to have complex chains of causation, that several things must go wrong at once to cause high abnormality frequencies [[14](#_ENREF_14),[79](#_ENREF_79),[80](#_ENREF_80)]. In some cases, chemicals associated with agricultural runoff have increased levels of parasite infection [[79](#_ENREF_79),[80](#_ENREF_80)]. In other cases, relatively constant contamination combines with variable effects due to the timing of other more dynamic stressors like parasites or predators [[14](#_ENREF_14),[81-83](#_ENREF_81)]. In a third example, chemical pollutants may vary in toxicity when they are irradiated with UV-B, which may activate toxic compounds and increase their toxicity, causing increased frequencies of abnormalities [[15](#_ENREF_15),[84-86](#_ENREF_84)]. |
| Species | Either genetics or life historical factors make some species more susceptible to abnormalities than others. | Susceptibilities to limb abnormalities may differ among species and could be related to such genetic or life history characteristics as frog or toad size [[21](#_ENREF_21)], habitat preference [[87](#_ENREF_87)], or susceptibility to parasite infection [[88-90](#_ENREF_88)], or contaminant toxicity [[91-94](#_ENREF_91)], or predator attack [[60](#_ENREF_60),[61](#_ENREF_61),[95](#_ENREF_95)]. |
| Time | Some studies have shown North American abnormality frequencies to be increasing through time.  | Historically, severe malformations were uncommon in amphibian populations. Museum studies and resurveys of historic field sites suggest that, in some regions, abnormalities have increased [[10](#_ENREF_10),[96-98](#_ENREF_96)]. Accounts in which >5% of the amphibian population exhibited limb malformations, are extraordinarily rare in the historical literature (1900-1990; [[97](#_ENREF_97)] for review). Collectively, these findings support the hypothesis that recently observed patterns of amphibian malformations deviate from the historical precedent. |
| Climate | Climatic changes like excessive rainfall or drought may cause abnormalities through temperature extremes or increased tadpole densities.  | Abnormal amphibian development has been observed when larvae are exposed to extremely high or low temperatures either directly [[99-103](#_ENREF_99)] or through interactions with other stressors [[83](#_ENREF_83),[103-107](#_ENREF_103)].  |
| Cyanobacteria | Harmful bacteria that occupy eutrophic habitats can produce malformation-causing retinoic acids | Retinoic acids are teratogens known to cause malformations in amphibians and other species [[91](#_ENREF_91),[92](#_ENREF_92),[108](#_ENREF_108),[109](#_ENREF_109)]. Recent research has shown that cyanobacteria associated with toxic algal blooms in artificially eutrophic habitats produce retinoic acids which may cause malformations in aquatic species inhabiting these affected areas [[110](#_ENREF_110)].  |

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