'One Toxicology', 'Ecosystem Health' and 'One Health'

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Summary

'One Health' as a discipline links human and veterinary medicine as co-equal partners in an increasingly efficient joint venture into health promotion and prioritised research. 'One Toxicology' is proposed as a way to reunify toxicology as a component of 'Ecosystem Health' and the encompassing 'One Health'. Ecotoxicology, which includes wild animal, plant and microbial communities, is a critical component of 'Ecosystem Health'. 'One Toxicology' is proposed to help hold toxicological sciences together and maintain intimate connections to medicine in general. 'One Toxicology' is efficient because biochemical systems are highly conserved and, thus, when one group of species is at risk, other groups of species are also often at risk. Fortunately, in the case of toxicological risk, problems can be avoided, because humans can minimise exposures. Historically, human health has benefited immensely from studies of the impacts of chemicals on laboratory animals and wildlife. Similarly, veterinarians and wildlife managers have learned from careless or accidental poisonings of humans to protect the health of both domestic and wild animals. Yet, newly discovered emerging toxicoses abound, and well-known toxicoses persist – to the detriment of all life forms, including our own. Thus, in the 'One Toxicology' of the future, disciplinary boundaries should more rapidly blur. If this is done well, physicians, various public health specialists, veterinarians of many disciplines, wildlife health specialists, ecologists and an array of toxicologists will share and rely upon disparate sources of information with increasing efficiency to facilitate diagnosis and management of poisoning; to prevent unwanted, unwise, and unnecessary toxic injury to human, animal, plant, and microbial components of biodiversity; to decrease nutrients available that enable toxigenic species; and to prevent releases of chemical contaminants that indirectly set the stage for infectious diseases.

Keywords

Ecosystem, Health, Medicine, One Health, Public health, Toxicology, Veterinary.

"Una sola tossicologia", "Salute dell'ecosistema" e "Una sola salute"

Riassunto

"Una sola salute", intesa come disciplina, racchiude in sé la medicina umana e veterinaria come componenti di pari livello di una "joint venture" sempre più efficiente tesa alla promozione della salute e alla visione prioritaria della ricerca. "Una sola tossicologia" è un approccio all'integrazione della tossicologia come componente di "Salute dell'ecosistema" e che racchiude il concetto di "Una sola salute". L'ecotossicologia che comprende le comunità della fauna selvatica, vegetali e microbiotiche, è un componente intrinseco di "Salute dell'ecosistema". Viene proposta "Una sola tossicologia" per riunire le tradizionali scienze tossicologiche preservando gli stretti legami con la medicina in generale. "Una sola tossicologia" è utile in quanto i sistemi biochimici sono caratterizzati da un elevato grado di conservazione, pertanto, quando un gruppo di specie è a rischio, il rischio investe spesso anche

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altri gruppi. Fortunatamente, per quanto riguarda il rischio tossicologico è possibile evitare problemi poichè l'uomo è in grado di ridurre al minimo l'esposizione. Nella storia, la salute umana ha tratto enormi benefici dallo studio dell'impatto degli agenti chimici su animali da laboratorio e fauna selvatica. Analogamente, veterinari ed esperti di fauna selvatica hanno imparato a proteggere la salute di animali domestici e selvatici da intossicazioni dovute a cause accidentali o comportamenti incauti. Tuttavia, si osserva un'abbondanza di tossicosi emergenti di recente scoperta, con la persistenza di quelle ben note, a scapito di tutte le forme di vita, compreso l'uomo. Pertanto, nel concetto futuro di "Una sola tossicologia" i confini tra le varie discipline dovranno svanire più rapidamente. Così facendo, medici, esperti di salute pubblica, veterinari di diverse discipline, professionisti nel campo della salute della fauna selvatica, ecologisti e una lunga schiera di tossicologi potranno condividere e impiegare in modo più efficiente le molteplici fonti di informazione per diagnosi e gestioni più agevoli delle intossicazioni che possono colpire i componenti della biodiversità; per evitare intossicazioni indesiderate, inopportune e inutili ai componenti umani, animali, vegetali e microbici della biodiversità; per ridurre i nutrienti che consentono la riproduzione delle specie tossicogene; e per evitare il rilascio di contaminanti chimici all'origine di malattie infettive.

Parole chiave

Ecosistema, Medicina, Salute, Salute pubblica, Tossicologia, Una sola salute, Veterinaria.

Introduction

This paper endeavours to illustrate how 'Ecosystem Health', 'One Health' and 'One Toxicology' can better support one another. It illustrates how 'One Toxicology' has existed and how it should evolve to do a far better job of controlling both direct and indirect toxicant-induced injury to human beings, other animals and other components of biodiversity.

In terms of prevention of problems now and into the future, toxicology should be the easy component of health stewardship. After all, the solution is simple: decrease or prevent exposures of life forms to unwarranted concentrations of chemicals. Unfortunately, however, unnecessary chemically induced diseases remain commonplace today around the world. Direct poisonings involve all body systems, cause acute and chronic dysfunction and often induce lesions, malformations and death. When the immune system is directly involved – as in the case of many heavy metals and mycotoxins – or when it is indirectly involved – as in the case of toxicants that stress animals to prompt the chronic release of cortisol, the risks of infectious diseases increase.

Poisoning of predators at all scales of the ecosystem may aggravate infectious disease problems. Small invertebrates, such as hydra, copepods, damselfly larvae and dragonfly larvae eat trematode cercariae, reducing infective loads (45). Other predators eat snails, thereby reducing their role in the vast asexual reproduction of trematodes. Various small predators (e.g. fish) eat mosquito larvae and thus reduce the numbers of these vectors available to transmit viruses. Others eat rodents, birds and small predators, such as opossums, raccoons and cats that may also transmit diseases, especially when present in high numbers. Of course, large predators test herds of prey and the sick 'typhoid Marys' that tend to be slower and thus easy to catch are more likely to be removed from the population compared to those able to resist or rapidly recover from infection. Removal of predators from the small to the very large, through any means, including poisoning, may thus set the stage for increased risks of infectious diseases. The widespread contamination of the environment with nutrients – as well as the poisoning of organisms that would normally trap nutrients – are 'making life easy' for toxigenic species and they, in turn, poison humans, animals and other life forms on Earth. Examples of toxicoses are used below to illustrate how toxicant-induced problems come about and how a new, smarter, more efficient approach to 'One Toxicology' can contribute to both 'Ecosystem Health' and 'One Health' not only in the short term but also far into the future.

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'One Health' and 'One Toxicology' in context

'One Health' can be thought of as a *broad discipline* that relates to the understanding and care of human beings, domestic animals, wildlife and other life forms – as individuals and as populations. Hence, we have multiple health sciences and professions within the discipline of 'One Health'.

Of course, in regard to one or more humans or other animals, the word 'health' is used routinely not only in the disciplinary sense but also to describe the *overall condition* of the individual or group of individuals examined within a given time frame. *Without question, when we consider health as a condition, we have preferences; and the value judgment that we make in choosing among superb health, good health, average health, or poor health is not often debated.* Questions to the readers of this treatise arise.

Do 'Superb One Health' and 'Poor One Health' have a meaning as overall conditions and is one preferred over the other? Is 'Superb One Health' a logical, responsible, ethical and economically astute aim? If so, how might we get there; and just what is inferred in terms of ethical and professional responsibilities? Would 'Superb One Health' lead us in the direction of larger and significantly more effective collaborations? The author is of the opinion that the answer to the latter question is yes and that the daunting challenge faced by veterinarians – who assume some responsibility for the health of all animal species – is so great that it must increasingly be shared with many other medical professionals and other scientists and stewards.

Much of the effort directed towards the 'One Health' initiative to date has focused on potentially devastating emerging and re-emerging infectious diseases. This chapter focuses on critically important chemically mediated health problems and how they too are shared among humans, domestic animals and wildlife. Despite the importance of this disciplinary realm, it is necessary to prevent inadvertent 'toxicology blinders' or 'infectious disease blinders' from limiting our vision. Given current conditions and trends, even if people, animals and other components of biodiversity were no longer exposed to highly infectious agents, toxic doses of anthropogenic chemicals and human-induced elevations in natural toxins, *Homo sapiens* and other components of animal life would still be in peril. This is because it is essential to address not only these concerns but also the other 'big drivers' of ecosystem disease. To have a regulated climate, a breathable atmosphere, clean air and clean water, fertile soils, diverse organisms from which we may discover disease-resistant strains of existing food-producing plants and animals, and life forms from which we may derive new foods, medicines and other commercial products, as well as the natural biota whose lives stimulate the mental and emotional development and integrity of humans and other animals, we must allow for myriad other components of biodiversity to thrive. This means:

- controlling emissions of sub-toxic yet climate-altering quantities of carbon dioxide and methane into the atmosphere
- meeting the needs of wild plants and animals by counteracting habitat loss, reconnecting fragmented habitats, enlarging habitats and implementing rational buffers to offset the impacts of human urban, industrial and agricultural disturbance
- protecting the vertebrates, arthropods, annelids, fungi and bacteria of the soil not only in wild places but also in agriculture, forestry and lawns
- preventing invasions of exotic species.

Expanding on such considerations, Grifo and Rosenthal (18) published the book *Biodiversity and human health* which conveys messages of a conference jointly sponsored by the National Institutes of Health, the National Science Foundation and the Smithsonian Institution, that fostered a dialogue among experts in public health, biology, epidemiology, botany, ecology, demography and pharmacology. Therein, Thomas Lovejoy enumerated some of the ways that human health and biomedicine draw upon natural compounds and natural processes. More recently, Chivian and Bernstein (10) produced a book entitled

Sustaining life, how human health depends on biodiversity which discussed the dependence of humans on bacteria, fungi, plankton, arthropods and other organisms. Accordingly, it is stressed that the health and well-being of humans and non-humans rely upon hosts of organisms both in and apart from those members of the animal kingdom that are generally attended to by physicians and veterinarians. Not only vertebrates and other animals but also other life forms must be the focus of attention for 'Superb One Health' as a condition to be a plausible goal. Grouping biodiversity together, assessing the nature and quality of critical interactions among species, setting out that there are preferred states (e.g. robust biodiversity with redundancy and competition among organisms to regulate the climate, pollinate the plants, produce and purify the soil, water and air, provide the niches for a host of life forms, provide the food, building materials and medicines, and control the diseases) takes one squarely into the realm of 'ecosystem health' (5).

Thus to improve upon 'One Health' as a condition for the long term, collaboration among practitioners and researchers in ecology, wildlife biology and management, fisheries, toxicology, human medicine, veterinary medicine and 'Ecosystem Health' is essential and, in addition, these individuals should devise and refine research and management options in concert with non-biomedical and non-ecological experts as well as the society at large. Better public education, more participatory research, improved policies, smarter incentives and disincentives, and more astute regulations are all necessary (Fig. 1).

The breadth and depth of toxicology

As a former small animal practitioner, a clinical and diagnostic veterinary toxicologist, a researcher into the fate and mechanisms of mycotoxins and cyanobacterial toxins, a researcher on ecotoxicological problems of amphibians and other wildlife groups and a director of the Envirovet Program in Wildlife and Ecosystem Health, I have had relatively broad exposure to the boundaries of toxicology and its interactions with other disciplines. Toxicology, as I understand it, is the study of all the adverse biochemically mediated effects of all chemicals on all life forms. Ecotoxicology is even more complex in that it includes all of the above, plus the chemically induced disruption of all the interactions among organisms and their interactions with the air, minerals, soils and water of the planet. These

> Concepts of 'Ecosystem Health' were introduced beginning in the late 1970s (36) and the 1980s (43). They were developed further at a seminal workshop of ecologists, veterinarians, physicians, economists, and lawyers hosted at the University of Illinois in 1991 (38). As was recently reaffirmed by ecosystem economist, Robert Costanza, who was among the participants of that meeting, ecosystem services make life possible on this planet and they form the foundation of the bulk of human economic activity (13). In 1994, the International Society for Ecosystem Health was established and produced the journal *Ecosystem Health* for several years (37). Nevertheless, only a relatively small number of physicians or public health specialists became involved in the organisation, probably because many of these professionals did not recognise what was intended by the term 'Ecosystem Health' (i.e. that it included human health). In an effort to overcome this lack of understanding, in 2006, the International Society for Ecosystem Health changed its name to the International Association for Ecology and Health and elected Jonathan Patz (MD, MPH), a professor of environmental studies and population health and Director of Global Environmental Health at the University of Wisconsin-Madison, as its president. This Society hosted EcoHealth meetings in Madison, Wisconsin, in 2006 and again in Merída, Mexico, in 2008, that were attended by experts in human medicine, public health, veterinary medicine, wildlife health and ecology from around the globe. The official publication of the organisation is the journal *EcoHealth* (www.ecohealth.net/ aboutus.php). Among the hallmarks of the organisation and many of the articles published in its journal are 'One Health' themes and inclusive research in which people at risk of health problems and stewards of urban and rural resources come together to examine major threats and opportunities for health improvement through improved management and disease prevention.

Figure 1
Development of 'Ecosystem Health', magnitude of its importance and a leading 'One Health'/'Ecosystem Health' organisation

realms of study involve all elements and compounds, whether they occur naturally or whether they are concentrated or synthesised by human beings. Thus, they address oxygen, water, sodium chloride, other inorganic compounds and all biochemicals including, but not limited to, microbial toxins, plant toxins and zootoxins, and the products of chemical syntheses (produced deliberately and accidentally), as well as the products of spontaneous chemical reactions, combustion, biotechnology and nano-technology. Accordingly, because of the complexity and breadth of chemically induced injury, the limited knowledge generated to date about the myriad toxic agents and combinations thereof and the resultant need (and the genuine opportunity) to control toxic chemicals at the source, 'One Toxicology' is recommended to integrate human, veterinary, wildlife and ecological toxicology to support more rational choices as to what chemicals and what concentrations are allowed to come into contact with people and their domestic animals and the generally far more threatened wild animals, wild plants and ambient microbial communities. Indeed, it is the wild organisms that must perform optimally to survive and reproduce. In *their* lives, slight toxic effects are much more likely to be lethal or to prevent reproduction, in comparison with the generally more coddled lives of domestic animals or our fellow human beings (Fig. 2).

Producing goods and services for humans has often resulted in industrial and agricultural pollution with untoward repercussions on wildlife and ecosystems. Given the degraded condition of the environment and the roles of chemical pollutants in the current ongoing sixth extinction (1, 32, 39), the ethical assignment now must be to produce goods and services using chemicals in ways that allow the many beleaguered native species to recover their numbers beyond, around and even within areas intensively managed to meet human needs. To be efficient, 'One Toxicology', in which different groups of toxicologists and other health specialists share knowledge – particularly in regard to preventive medicine – must purposefully and rapidly blur distinctions among human, veterinary, environmental and ecological toxicology so that the needs of 'Ecosystem Health' and 'One Health' are addressed simultaneously.

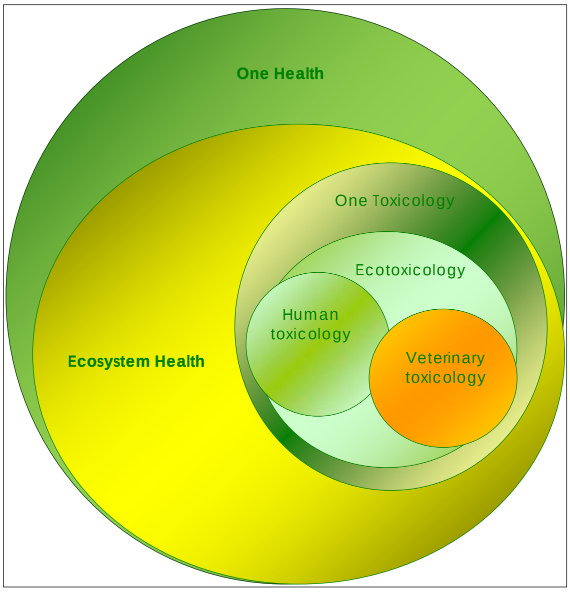

Figure 2
Inter-relationships among professionals who work in 'One Health', 'Ecosystem Health', 'One Toxicology', ecotoxicology, veterinary toxicology and human toxicology
All are working towards improving 'One Health'

It is stressed that 'One Toxicology' must extend beyond the developed world as a global investigative, clinical, diagnostic and preventive medicine endeavour that works with physicians, public health specialists, veterinarians, wildlife biologists, wildlife managers, animal scientists, livestock producers, agronomists, large- and small-scale farmers, forest managers, aquaculture specialists, other members of the business community, educators, journalists, government officials and the public to protect the human, animal, plant and microbial biodiversity of this planet.

Toxicology and regulatory toxicology are evolving sciences. Many types of individuals are involved with medical, veterinary medical and a host of other educational backgrounds. To many, the most revered voices in environmental toxicology have been Rachel Carson and her successor Theo Colborn.

Carson was a graduate of the Pennsylvania College for Women, which is now Chatham University, who studied at Woods Hole Biological Laboratory and completed a master of arts degree in zoology from Johns Hopkins. She worked as a writer for the United States Bureau of Fisheries and the United States Fish and Wildlife Service for fifteen years and then resigned in 1952 to focus on her writing (23). Carson's 1962 book, *Silent Spring*, warned of animal and human impacts in the 'One Toxicology' domain of emerging anthropogenic chemicals, especially pesticides, such as dichloro-diphenyl-trichloroethane (DDT) and other persistent organochlorines (8). That book is widely credited with launching the environmental movement that prompted such laws in the United States as the Clean Air Act, Clean Water Act and Superfund, as well as the withdrawals of DDT, polychlorinated biphenyls (PCBs) and other organochlorines.

Compared to Rachel Carson, Theo Colborn was a 'late bloomer'. She was a practising pharmacist for many years and, at 58 years of age, completed a PhD at the University of Wisconsin in zoology and toxicology. After her 'One Toxicology' contributions to the book, *Great Lakes, Great Legacy?* (11), she enlisted a range of scientists in symposia that produced additional books directed not only to other scientists but also to the public about ubiquitous endocrine disruptors. Most notable among these is '*Our Stolen Future*' (12). As Colborn correctly illustrated, endocrine systems evolved as sensors of minute amounts of endogenous hormones that could readily be influenced not only by these compounds but also by hormone mimics, agents that are inhibitory at hormone receptors and compounds that influence endogenous hormone concentrations (e.g. through altered synthesis or degradation). From PCBs that were produced beginning in the 1930s that contaminated fish which became recognised as risk factors for infertility in piscivorous mammals, such as mink as early as 1971 (2) to the thyroid disrupting flame-retardant polybrominated diphenyl ethers (PBDEs) that are present in alarmingly high concentrations in orcas (41) and foam rubber, fabrics, house dust and house cats (D.A. Mensching, D.C. Ferguson and V.R. Beasley, unpublished data) today, animals have proven to be important sentinels of toxic threats to human populations.

Given that many toxic compounds cause harm after chronic exposure through bioaccumulation (e.g. PCBs) or via recurrent yet subtle incremental 'hit and run' toxicity with delayed outcomes (e.g. mutagens that cause carcinogenesis), human and veterinary clinicians may fail to recognise the relationships between disease outcomes and chemical threats. It becomes necessary, therefore, for the physician, the veterinarian, the environmental toxicologist and the epidemiologist, with other specialists to undertake and support the role of citizen scientists. For research funding to be available, the message of the citizen scientist is extremely important. Through the translations provided by citizen scientists, ordinary citizens and their representatives in government can more readily learn to understand the scientific process, scientific uncertainty, the need for research and the need to take judicious actions based on incomplete knowledge. However, taking the case and the uncertainty to the public is threatening to many scientists, in part because of potential counter-attacks by industry and industry-affiliated scientists, who may insist on incomplete knowledge to get products on the market and virtually complete knowledge to get them off the market. When regulatory bodies fail to do their work because of either a lack of funding or a lack of will, and when the need is to lessen the impacts of toxic chemicals on animal and human health, involving the public may be the only way to prompt industry and governing bodies to make changes that reduce or terminate exposures to toxic contaminants.

The benefits of modern environmental toxicology in recognising and reducing risks, and in addressing the ongoing dilemma of knowledge gaps on one hand and such expensive regulatory testing that safer products can never be produced on the other hand, were described by Anne Fairbrother, when she was president of the Society of Environmental Toxicology and Chemistry (16).

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To her credit, Fairbrother pointed to the fact that many potential products are never introduced to the marketplace because of concerns regarding toxic outcomes. She also described the opportunity afforded by adaptive management, such that we can make informed decisions and try new formulations when they seem to be safe enough to do so – provided that we also recognise the limits of our knowledge, that we subsequently monitor for adverse outcomes and that we respond when warranted to reduce or prevent further use by withdrawing products that are associated with unexpectedly serious toxic outcomes. Thus, we can reduce risks from anthropogenic chemicals by making informed choices: by choosing the chemicals that we use and release more astutely, releasing them in smaller quantities and in more controlled ways and not releasing some of them at all (e.g. ceasing synthesis of problem compounds).

To counter the race to the bottom, in which industries and agriculture migrate to and profit in areas of the globe with the least control of and liability for pollution, it is essential to have global laws, regulations, incentives and disincentives that limit harm from chemical contamination of the workplace, the home and the outdoor environment. While different needs and different economic resources cause variability in the chemicals that can be obtained to solve problems around the world, the globalising 'flatter' economy is undermining the argument that older, more toxic products are acceptable for the developing world.

Harmonisation of laws and regulations has been moving forward, especially in the pharmaceutical and pesticide industries with leadership from the United States, Japan and the European Union (EU). In recent years, the EU has shown additional leadership, relative to the United States and other parts of the world, in imposing stronger regulations with regard to regulatory toxicology. In particular, the EU regulatory framework for the Registration, Evaluation and Authorisation of Chemicals (REACH), which went into effect in 2007, will necessitate the re-examination of a wide array of products that are currently marketed in the EU in quantities $\geq$10 metric tons per year (17, 46). Thus, to continue sales of products into European markets will require new research to assess their physical hazards, acute and chronic toxicity and ecotoxicity. The REACH programme illustrates the potential to fill knowledge voids by setting more stringent, science-based standards to protect humans, animals and ecosystems from toxic injury. In turn, through modern communications and political pressure, discoveries found through the research required under REACH may also result in safer products around the world.

An ongoing challenge will be to ensure that knowledge from government-mandated and other toxicology testing is consistently made available in the public domain. Keeping such knowledge under wraps as a part of intellectual property and patent protection deprives physicians, veterinarians and ecosystem managers of needed diagnostic criteria.

Examples of the need for 'One Toxicology' interactions

A recent analysis indicated that the medical profession does not often recognize environmental hazards despite their impacts on other species (35). Considering not only toxic but also infectious environmental health hazards, these authors examined reports selected from the National Library of Medicine's Medline database and concluded that, with the exception of well-known potentially lethal zoonoses, such as rabies, Venezuelan, Eastern and Western equine encephalitides, avian influenza, or West Nile virus infections, most physicians considering environmental health risks to their patients do not routinely rely on data from animal sentinels. They listed potential barriers to the integration of data from sentinel animals, including insufficient understanding of relationships among animal, human and ecosystem health, inadequate understanding of veterinary medicine, protocols that fail to incorporate animal data into public health surveillance and relative obscurity of scientific literature about animal sentinels (e.g. articles in journals not often read by physicians).

In a randomly selected set of 50 reports of chemical or physical hazards, these authors found that wildlife species accounted for 94% of the associations deemed relevant to human health, livestock accounted for 6%, and companion animals accounted for 0%. For these hazards, a wide array of wildlife taxa were involved, including several studies each that involved invertebrates, fish, herpetofauna, birds and mammals. However, in the 50 reports on chemical or physical hazards, only four confirmed both animal and human exposure to chemicals and none of the reports provided data on specific human outcomes. While 50 randomly selected reports on the animal sentinel concept from Medline comprised a small investigation, the study nevertheless reflected the urgent need to link animal and human studies through concurrent assessments of:

- exposures
- residues of parent compounds and active metabolites in body fluids and tissues
- biomarkers of effect (e.g. changes in haematology, serum biochemistry, biochemical and physiological changes in organs and tissues, and lesions) in both animals and human beings.

Breaking down the barriers to address this need would be a distinct benefit of a 'One Toxicology'/'One Health' approach.

Urgency of diagnosing poisonings of aquatic animals

In 1949, dead fish were noted floating in Minamata Bay in Japan. Catches by fishermen began to decline (27). By 1953, cats 'danced in circles' and 'cat suicides' were noted when they fell into the bay and drowned. Seabirds and crows were observed to spiral unexpectedly into the sea. It was shortly after this that the first cases of human sickness were noted, but the industry leaders and government officials at the national level did not directly confront the pollution for years thereafter. Part of the problem was intimidation by industrial polluters and politicians of the area. The polluting industry was a major employer in the area and fear of loss of employment curtailed public pressure.

Apparent neurotoxicity in children in association with fish and shellfish of Minamata Bay was reported in 1956 and, in 1957, the syndrome in cats was reproduced by feeding the animals a diet made from fish and shellfish from Minamata Bay. The syndrome in humans was specifically recognised as methyl mercury poisoning in 1959, but the point source of the methylmercury was not identified until 1961 (31). Wastewater from a chemical factory belonging to Chisso (translated as 'Nitrogen') Corporation had released methylmercury into the Bay at least as early as 1932 and it was allowed to continue until 1968. The reaction used to produce commercially marketed acetaldehyde relied upon a mercury catalyst and produced the methylmercury. By March 2001, a total of 2 265 human victims were counted (29). Had there been an effective system of environmental monitoring, coupled with a fish diagnostic capability and a responsive stewardship programme at the outset, piscine, avian, feline and human victims, as well as the economic vitality of the region could have been protected. Even now, however, routine monitoring of wild fish health in relation to environmental pollution is largely on an *ad hoc* basis. For fish to serve as sentinels of aquatic pollution and toxic as well as ecotoxic impact, a sustained, active 'One Toxicology' approach to monitoring, diagnosis and research is essential.

Concern for wild animals in a 'One Toxicology' world

Polyaromatic hydrocarbons (PAHs), such as benzo[a]pyrene, are among the most studied of carcinogens in human beings and the central role of laboratory animal research in deducing mechanisms of carcinogenesis, including through studies of purified PAHs and mixtures of such compounds, is well recognised (34). The scrotal cancers in chimney sweeps that were described by English physician and surgeon Percival Pott in 1775 (and later prevented by thorough washing not in England but in such countries as Denmark) were associated with soot and ultimately PAHs. Even today, lessons remain to be learned, as exposures to PAHs in cereals, fire-broiled foods, and smokes from tobacco, fossil fuels, and other sources remain ubiquitous causes of human cancer (33). Nevertheless, documenting exposures of charismatic animals may play a role – not only in the protection of such species, but also in the protection of human health.

A group at the St Hyacinth veterinary faculty of the University of Montreal led by veterinary pathologist Daniel Martineau has built on an initial encounter of a lethally stranded beluga whale, which was found to have cancer, on the shores of the St Lawrence estuary. The St Lawrence forms the outlet of the Great Lakes of North America. Ultimately, when Martineau and co-workers continued monitoring this endangered population of belugas for years thereafter, they found a much higher incidence of cancer than would normally be expected in free-ranging wildlife (14, 25, 26). The belugas, which feed on benthic organisms, were being exposed to hydrophobic PAHs that were delivered to the sediment largely from the emissions of hundreds of tons of the chemicals from the nearby aluminum company. Confirming the exposure was a report that illustrated marked differences in benzo[a]pyrene adducts to DNA of brains of the beluga whales of the contaminated region and the brains of the same species from a reference region (47).

In parallel, cancers were found at elevated rates in the aluminum plant workers and local residents (reviewed in 26). In both the humans and the belugas, the cancers were consistent with what would be expected from exposures to polyaromatic hydrocarbon emissions. Martineau's group also found a high incidence of cancers as well as evidence of endocrine disruption in another bottom-feeding species of the St Lawrence estuary, specifically the lake whitefish (28). Eventually, the aluminum manufacturing plant ceased using the most polluting technology and thus reduced regional inputs of PAHs. Media attention about the plight of the belugas which are a focus of ecotourism in the region (7, 49) may have contributed to the decommissioning of the obsolete technology that released PAHs. That the widespread recognition of the mutagenicity and carcinogenicity of PAHs did not greatly limit the emissions of these pollutants before they harmed the whales and the people reflects on some of the recent historical attitudes of certain business leaders, not only with regard to wildlife health but also human health as well.

The ongoing problems with PAHs around the world today, not only in relation to the Soderberg method of aluminium production that was used in Quebec, but also fossil fuel burning cannot be excused given currently available alternative technologies. Industry leaders, energy generators, engineers, political leaders, government regulators, health and environmental non-governmental organisations and consumers have the opportunity to contribute to vast risk reductions in exposures to PAHs. Around the world, a reduced reliance on fossil fuels and more widespread and efficient pollution-control technologies offer a genuinely important 'One Toxicology'/ 'One Health' opportunity to reduce human and animal suffering and death.

Free nutrients, climate change, phycotoxins and 'One Health'

Free nutrients in the environment from improperly treated human and animal wastes, fertilizers applied for food-producing plants and lawns and air pollution (e.g. ammonia that arises from concentrated animal feeding operations and is detected in atmospheric deposition, namely in dry particulates and rainfall) contribute to blooms of phytoplankton that may be toxigenic, as in the case of cyanobacteria, and to deaths of algae that contribute to dead zones in large lakes and at the mouths of rivers around the world. Domoic acid originates primarily from diatoms of the genus *Pseudo-nitzschia* (3). As silicon, phosphorus, nitrogen and iron availability have been linked to the growth of *Pseudo-nitzschia* and given that the subsequent depletion of phosphorus and silicon by these organisms stresses them so that they produce domoic acid (51), it has been suggested that an increase in toxic blooms of *Pseudo-nitzschia* might be occurring as a consequence of increased nutrient and desert dust pollution. In some cases, the planktonic diatoms expand their numbers in the zones of shellfish and fish in relation to upwellings spurred by currents prompted by global climate change (51). Moreover, global warming may prolong the seasonal growth of *Pseudo-nitzschia* and expand its global range. Accordingly, pollution from animal agriculture, sewage effluents, crops and lawns, and silica dust from desertification, as well as carbon dioxide and methane that contribute to global warming may all play a role (30). The toxins passed from the plankton to shellfish and fish are transferred to predators that eat them. The syndrome of domoic acid toxicosis was first recognised in relation to what became known as amnesic shellfish poisoning in the area of Prince Edward Island in Canada, when three elderly people died and over 100 individuals developed various poisoning symptoms after eating mussels contaminated by the diatoms (4). Humans with domoic acid toxicosis experience vomiting, diarrhoea, abdominal pain, confusion, permanent short-term memory loss, disorientation, seizures and coma. Only after domoic acid toxicosis was recognised in people was the syndrome discovered in marine vertebrates. In recent years, large numbers of multiple species of marine mammals (grey whales, dolphins, sea lions, seals, sea otters) as well as fish-eating birds (e.g. pelicans) have been found to be poisoned off the coasts of California, Oregon, Washington and Alabama.

It is now believed that seals and sea lions sometimes become aggressive due to poisoning by domoic acid. Retrospective assessments have suggested that, in 1961, altered bird behaviour and deaths in the region of Monterey, California, gave Alfred Hitchcock the idea for the movie 'The Birds' (15). Perhaps if those birds had been adequately studied, toxicosis from domoic acid (a simple molecule that was previously used at lower doses as an anthelmintic) could have been recognised sooner and assays of seafood might have been available to protect against human toxicoses. Overall, respecting the precautionary principle (21) and ecosystem services, the control of carbon dioxide and methane emissions, as well as better sewage, agricultural, forest, and lawn management to keep nutrients in higher plants and silicon in soils may contribute to reductions in this syndrome thereby protecting human and wildlife alike. This is another 'One Health' and 'One Toxicology' concern in which stewardship of ecosystems may have prevented – and may yet prevent – an emerging toxicological disease.

Nutrients, pesticides, parasites, frogs, and people

Since the 1990s, myriad news stories, books (22, 48), field studies, and laboratory research have focused attention on outbreaks of limb abnormalities in frogs. Extra limbs as well as malformed and missing limbs are involved. Ultimately, it was deduced that at least most of the extra limb phenomena and many of the malformed limbs were attributable to infections with trematodes of the genus *Ribeiroia* (19). The amphibians in this case are a second intermediate host and metacercariae form in the limb bud areas after cercariae penetrate the skin. High level infections of frogs with the trematodes can be lethal to tadpoles (19), especially when early life stages are involved (44). Johnson *et al.* (20) showed that nutrient pollution, which fed periphyton, the predominant algal food of snails (species in which vast asexual reproduction of the trematodes takes place) contributed to the problem. In an earlier field study, Beasley *et al.* (6) linked another trematode of frogs with the same type of life cycle to herbicide impacts on aquatic plant communities. By impairing the metabolism of, or killing, the macrophytes (higher plants), herbicides prevent their uptake of nutrients, leaving them to be used by periphyton. The greater species and strain diversity, and the shorter generation time of periphyton organisms gives them an advantage in terms of recovery after herbicide insult in comparison to the macrophytes. In addition, herbicide-induced elimination of the macrophytes reduces physical structure in wetlands, potentially facilitating completion of

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the complex life cycle of the trematodes (easier for miracidia to find snails, for cercariae to find tadpoles and for definitive hosts [birds] to find infected tadpoles). Moreover, Schotthoefer *et al.* (45) recently showed that a number of invertebrate predators found in waters with cercariae of *Ribeiroia* readily ingest and digest the parasites. Accordingly, pesticides or other chemicals that may selectively eliminate these micropredators may also increase risks of trematode infections.

After examining more than 200 potential contributing factors from a large field study in an agricultural area of Minnesota, Rohr *et al.* (40) implicated not only a fertilizer (phosphate) but also the ubiquitous agricultural herbicide atrazine in the trematode infection loads of frogs. That report also described controlled studies in which atrazine indirectly increased snail populations and was immuno-suppressive to tadpoles. Accordingly, it seems that common nutrients, herbicides and any contaminant that impairs the survival of small predators that eat either motile stages of trematodes, or for that matter snail intermediate hosts, would tend to increase risks of trematode impacts on frogs. Other authors noting some of the discoveries about trematodes in amphibians have also drawn attention to the need for nutrient management to protect human health (24). Given that the trematodes that cause schistosomiasis in human beings rely on a life cycle also involving asexual reproduction in snails, it seems to follow that nutrient, herbicide and other chemical contamination that directly or indirectly feeds periphyton and thus snails or that reduces predation on trematode miracidiae or cercariae, or on snail intermediate hosts would increase risks of this human disease. Thus, in addition to recognising risks of flooding snail habitat, prevention of human schistosomiasis should likely involve much more than moluscicides (a common approach at present). Research is warranted to explore the potential merits of re-establishment of biodiverse life forms in water courses, including on species that feed on cercariae and snails. Considering that schistosomiasis infects about 200 million people, especially in developing countries (50) with debilitating effects on about 20 million of them (9) and it commonly affects ecotourists (42, 50), it seems that prevention of pollution with nutrients and pesticides should be a component of disease prevention. Perhaps a more expansive 'One Health' and 'One Toxicology' approach may help protect frogs, humans and other species that endure the impacts of trematode infections.

Concluding remarks

Toxicology is an extraordinarily complex endeavour, but it is only one component of 'One Health'. Even more challenging perhaps than 'One Toxicology' are 'Ecosystem Health' and 'One Health'. 'One Health' professionals must recognise the need for recovery of depleted biodiversity if ecosystems are to offer a better quality of life for human beings and less suffering of domestic and wild animals for the long term. Controlling and preventing unwarranted contamination of the environment is therefore a central component of 'One Health'. Interfacing with the public so that they understand the complexity of current threats to health and biodiversity, including how chemicals can cause direct and indirect harm to health and ecological sustainability is a part of this endeavour. If human medical, veterinary medical, wildlife and ecological professionals understand one another's challenges and skill sets, and if they work together to set in motion programmes towards the synchronous recovery of human, domestic animal, wildlife and ecosystem health, they may play a central role in sustaining life on Earth.

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