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Cumulative Effects - Multiple Stressors in Cetacean Research

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Abstract
Due to an increasing number of anthropogenic threats in our marine environment, nature comes under pressure. Accordingly, cetaceans are exposed to multiple stressors which can result in adverse effects, such as decline in population size, health or body condition. Linking these responses of individual animals and populations to causal factors and possible interactions is highly complex and extremely challenging. The identification of stressors (active in a specific area and acting on a specific subpopulation/sex/life stage) hereby is equally important as is the mechanistic understanding of the underlying processes and their effect on the animal and the respective interactions between stressors.

This is a prerequisite for developing sustainable, effective and efficient management options to support population growth and individual's fitness. Here, we briefly outline the general context about (i) the approaches how to identify the stressors involved and (ii) the action and interaction of stressors on cetaceans, aiming at a basic understanding for non-specialists in this field. We focus particularly on cumulative effects of multiple stressors, where pollution is one of the stressors. We plead for more studies on the mechanism through which the single stressors act since this may help to predict when and where cumulative effects occur. We also suggest to further improve cross-cutting research, across disciplines, and with a multitude of methods, to achieve an integrative holistic picture of the animals in question and eventually be able to contribute to sustainable management options.

1. Introduction

Due to an increasing number of anthropogenic threats in our environment, "nature comes under pressure". Accordingly, cetaceans are almost always simultaneously subjected to multiple stressors which accumulate in their response. Their response is often hard to identify and to trace back to the causative factors, as (i) the easily observable responses are mostly nonspecific and (ii) the exposure to multiple stressors makes it difficult to identify the driving factors. As a consequence, cumulative effects are understudied.

Depending on the specific definition, 'cumulative' can be understood to result from repeated exposure to the same, or to different stressors. The situation in the environment is typically characterized by action of various factors, though, we understand cumulative here as the exposure to different stressors. Importantly, the stress response of a biological system, an organism, as well as a population, should not be seen as univariate but as multi-variate (Van Straalen 2003, Segner et al. 2014).

The term "stressor" refers to any external abiotic or biotic factor that moves a biological system out of its normal operating range (Van Straalen 2003). Stress is the internal response of the biological system to the stressor. The stressor impact depends on stressor intensity, timing and duration as well as on the physiological or ecological properties of the animal under stress. Usually, the stress response is transient and involves adaptive or compensatory mechanisms (e.g. physiological acclimation at the individual level). As adaptive or compensatory responses to stressors cost energy, stress means a chronic drain of metabolic energy from biological systems. Stress can be relieved by moving back to the original homeostatic state, or by establishing a new stable state. However, when

the system is passing a threshold, this can also result in aggravation of organ functions and eventually in a complete breakdown of the system. We distinguish natural and anthropogenic stressors. In addition, stressors can be intrinsic (internal, physiological factors challenging the animals homeostastis, e.g., fasting) or extrinsic (external factors, creating stress in an animal, e.g. pathogens, pollutants, noise), they can be biotic (e.g. pathogens, algal toxins) or abiotic (e.g. unphysiological salinity change, temperature increase).

2. Action and interaction of stressors involved

Even when looking at effects of a single stress factor, it has to be admitted that only for some stressors the molecular mechanisms and action pathways are understood. The starting point for stressors is always on the level of molecules and cells, and the responses might eventually be translated at individual or population levels. Some stressors, such as many pollutants, prey limitation and noise, act on the hypothalamic pituitary- adrenal (HPA) axis, which mediates the stress response and regulates many body processes in mammals (FIG. 1). Subsequently, all levels of the organism are affected along this axis, starting with the molecular mechanisms being translated on the higher organismal level.

The presence of other stressors modulates the response of the stressor in question. In the case of a pollutant, this can lead to significant shifts in chemical toxicity (Laskowski et al. 2010). As an example, climate change-related alterations of environmental temperatures influence environmental transport and persistence of chemicals, as well as chemical uptake and bioaccumulation, transfer along food webs, as well as sensitivity of species to the toxicants (Munro Jenssen 2006, and others). *Vice versa*, exposure to chemical stressors can modify the response of biological systems to additional biological or physical stressors (Hooper et al 2013). Marine mammals are vulnerable to infectious diseases, in particular when they are subjected to other stressors (Harcourt et al. 2019). For instance, previous exposure to PCBs increased the risk of death from infectious diseases in harbor porpoises (Hall et al. 2006).

For several compounds, such as PCB's and organochlorine pesticides (e.g DDT) endocrine-disrupting properties have been demonstrated. This means that they interfere with any aspect of hormone action (Zoeller et al., 2012). Due to their hormone mimicking properties and endocrine associations with cancer risk (co-cancerogenesis), these compounds including PAHs may increase the likelihood of cancer (Gulland et al. 2020, Poirier et al 2019). It has to be taken in consideration that not only the parent compound but also the metabolites can exert toxic effects, such as known for organochlorine compounds, e.g. DDT and its metabolites DDE, DDD, etc.

Stressor combinations can result in additive, synergistic (more than additive) or antagonistic (less than additive) effects. Multiple stressors might act via a common or via different physiological pathways. When acting through a common pathway, an interaction between the stressors is likely because they may provoke physiological perturbations within the same organ or the neuroendocrine system, the HPA. Accordingly, when stressors act through a common molecular mechanism it is assumed that their doses can be summed up to provide a cumulative dose, resulting in a single dose–response function (dose addition). Also, when stressors are acting through similar mechanisms response is found to be additive in most cases, while when stressors act through alternative but dependent pathways a synergistic response may result (Crain et al. 2008). However, many dose–response functions are nonlinear, e.g. most toxic chemicals cause responses which are sigmoidal in shape. This makes the prediction of the outcome of more stressors acting jointly more complex (NASEM 2017, Segner et al. 2014). An individual based model to assess the potential impact of PCB's on cetacean calf survival and immunity was developed and tested. It showed that achievable population growth rates were more affected by PCB's effects on immunity than on calf survival which

emphasize the relevance of multiple stressors, in this case, the exposure to pathogens (Hall et al. 2018).

Chemicals often act on multiple organismal targets (tissues, organs) and in this way open up the possibilities for multiple actions and pathways. Petroleum, for instance, causes acute and chronic toxicity in marine mammals such as adrenal toxicity, epidermal inflammation as well as externally visible oil fouling of body surfaces & sensory organs (Schultz et al. 2021, Schwacke et al. 2013). It also causes suppression of immune response, increased susceptibility to diseases, increased prevalence of organ lesions, impaired response to stress, and reduced reproductive success (Schultz et al. 2021). Chemicals which mainly act through immune suppression allow infection with oncogenic viruses (Robertson & Hansen, 2020). The best model to explain urogenital carcinoma occurrence in sea lions included herpesvirus status and organochlorine exposure (Gulland et al. 2020).

The cumulative effects can further depend on a variety of confounding factors, such as duration of exposure, life stage of exposure, sensitivity, vulnerability and others. For example, migrating animals might be exposed during a short time span; some life stages are extremely vulnerable (e.g. during lactation or when fasting). Timing of multiple stressors influence their combined effects (Cheng et al. 2015). Organisms, population and ecosystems can show threshold rather than linear responses to increasing anthropogenic stress (Groffman et al., 2006).

Cumulative effects can be the product (multiplicative) of individual stress effects or a single stressor is dominant and drives the cumulative outcome. It is evident that under a multiple stressor regime, additional pathways and mechanisms may be affected, leading to potential higher order interactions, such as the “ecological surprises” (Billick & Case 1994, Schindler 2006).

A meta-analysis of 171 studies provided strong evidence that multiple stressors generally interact synergistically in marine systems and indicate that cumulative effects of multiple stressors will often be worse than what is expected from single stressor impacts. More specifically, the interaction was mostly synergistic for heterotrophic organisms and in studies that measured population-level responses. Outcomes will vary in specific scenarios, so covariates and context dependency are important in driving multiple stressor effects (Crain et al. 2008).

In addition, also ecological drivers are affecting the cetaceans – and contribute directly or indirectly to the cumulative response. An ecological driver is defined as a biotic or abiotic feature of the environment that affects multiple components of an ecosystem directly and/or indirectly (NASEM 2017). They include loss of keystone or foundational species, variations in ocean climate (such as El Niño events) and climate change. Exploring these drivers can help to better predict the interaction of specific stressors (Crain et al. 2008).

3. Approaches how to identify the stressors involved

To test for interactive effects of multiple stressors, factorial experiments under controlled conditions (each stressor tested individually, then in mixtures, in different concentrations and over different time spans) would be needed. However, for practical and ethical reasons a paucity of such experiments exists for marine mammals. The ways to overcome this challenge is, on one hand, to extrapolate from experiments conducted with other species or from in-vitro studies, and, on the other hand, receive data from dedicated field studies on cetaceans. The latter will be shortly outlined here.

If the action of multiple stressors is suspected, first, a stressor inventory should be established. Data on the stress factors under suspect, such as pollutants, prey abundance, noise, entanglement rates, etc. have to be collected. A quantification of the stressors is of advantage for further evaluation.

To receive information about the stress status of the animals, and early warning indicators of risk, suites of physiological measures can be collected, including body condition, hematological and serum biochemical markers, stress hormones, reproductive hormones, immune markers, and oxidative stress markers. Modern tools, including remote sampling of animal tissue can be used to determine exposure and/or effect concentrations of stressors (e.g. Harcourt et al. 2019, NASEM 2017). Weight of evidence approaches are helpful in identifying which of the likely stressors have to be further considered (Forbes & Calow, 2002; Burkhardt-Holm & Scheurer 2007). In this approach, a check for plausibility for each of the stressors could be the next step. The intent is to preclude consideration of relations that clearly have a spurious basis. Documentation may include the description of a specific causal mechanism linking the stressor. Understanding the mechanism by which each individual stressor acts and drives population consequences facilitates predicting when and where cumulative stressors interact (Crain et al. 2008), however, as discussed above, is rarely available. Certainly, the most crucial point is to identify 'ecological surprises' (Schindler 2005).

This is then followed by the question on evidence that the population is, or has been, exposed to one or more of the suspected stressors. Analyzing spatial coincidence of multiple stressors in areas of species distribution is the next step forward to identify areas of potential for a high risk of cumulative effects (Andersen et al. 2017). Accordingly, areas with both high stressor intensities and core areas of species distribution identified deserve further attention. For most potential causes, evidence of exposure will come from monitoring programs, site surveys, or historical data. Such kind of data were used to develop a global contaminant mapping tool which display published data on the concentration of persistent organic pollutants and mercury in cetacean tissues (https://iwc.int/chemical-pollution; IWC/SC/68A/E01).
Next, a formal relation between the stressor and adverse effects are asked for. Ideally, the answer to this question will involve a statistical correlation or regression analysis. Stepwise multivariable logistic regression to investigate the relationship between factors under consideration can help to elucidate potential causing stressors. However, at best, correlations can be drawn, while elucidating cause-effect relationships is rarely possible.

It is assumed that most stressors have a threshold level, below which adverse effects on a population are unlikely. Accordingly, it is recommended to check whether the measured or predicted exposure levels exceed quality criteria or biologically meaningful thresholds. It is also possible that the population may exhibit adverse effects resulting from past exposures at critical levels that are no longer present, thus, historical data should also be evaluated. Next, it should be analyzed whether there is an effect in the population known to be specifically caused by exposure to the – presumably dominant – stressor. Some stressors are known to elicit specific responses in the target populations (e.g. activation of detoxification enzymes, metallothionein induction, etc.) and some diseases have very specific symptoms. However, it should also be noted that specific responses are not only the result of chemical exposure or disease.

Case-control approaches are applied with subsequent multifactorial analyses to explore the relative importance of distinct factors identified to date. A case control study provided evidence that urogenital carcinoma in California sea lions is a multifactorial disease whereby herpesvirus infection and exposure to organochlorine contaminants, are positively associated with cancerogenesis (Gulland et al. 2020).

It is helpful when the suspected stressor has been applied in a controlled way (possibly in other species) which could have led to similar effects as those observed in the situation of interest.
Also of interest is the question whether the removal of the stressor led to an amelioration of effects in the population. If possible factors are known or suspected, their intentional removal may provide

an opportunity to help identify an associated effect. Such situations may result from a controlled experimental program or the implementation of a management mitigation measure.

To assess the consequences of multiple stressors on populations, further steps have to be considered. Demographic parameters are needed to assess the population status and to decide whether carrying capacity has been reached (NASEM 2017).

Population Viability Analyses (PVA) are based on a demographic model and are used to assess the relative importance of multiple anthropogenic threats on a population, single or in combination. They are also applied to evaluate how efficient recovery measures would be. For example, the PVA vortex model can be applied (i) to compare the relative importance of each stressor by projecting the population growth across the possible range of each stressor and (ii) to explore the degree to which threats would have to be mitigated, alone or in combination, to reach a quantitative recovery target. Cumulative threats can be assessed by combinations of threats which are then examined for sample scenarios (Lacy et al. 2017).

Conceptual models are developed, which are dependent on a series of transfer functions that describe how exposure to stressors affects individual health or behaviour. The PCoMS framework (population consequences of multiple stressors) (Fig. 1) documents the pathways from exposures to stressors through their effects on physiology, behavior, and health to their effects on vital rates and population dynamics. The relationships between the different compartments, as well as the integration across all the individuals in the population that are exposed to the stressor has to be translated into mathematical functions and parameterized to be utilized for assessing population consequences. Parameterizing any model of population consequences requires information on sensitivity (the degree to which the organism responds to a stressor, e.g. proportional reduction of vital rates) and vulnerability (probability of exposure to a stressor to which the animal is sensitive).

The PCoD model (population consequences of disturbance; New et al. 2014) proposes a bioenergetics model to detect biologically meaningful population responses, where disturbance costs are linked to lost energy (Villegas-Amtmann et al. 2015). Bioenergetic models are used to understand life history requirements and quantitatively assess the effort animals spend acquiring resources, and how they allocate those resources (Villegas-Amtmann et al. 2015). The model comprises transfer functions describing how exposure to stressors affects individual behavior, and these behavioural changes can affect health, subsequently affecting individual vital rates (probability of survival, growth, attaining sexual maturity (NASEM 2017). Variation in the level of exposure to the stressor experienced by different individuals can be used to scale up the anticipated changes in vital rates so that they can be used to predict population level effects (New et al, 2014). However, to predict effects of stressors on a population of cetaceans, extensive data sets are necessary, which are rare, since they require decades of data collection. Long-term epidemiological studies that control for multiple factors and use large sample sizes are a need (Gulland et al. 2020).

When data are limited, individual-based models, such as bioenergetic models, can be used and a hypothetical relationship between energy reserves and survival can be established to calculate population-level responses (e.g. Christiansen & Lusseau 2015). In cases where even such kind of data are missing, expert knowledge elicitation is helpful, as it is a formal and transparent process of quantification where experts predict populations consequences of different scenarios, based on their experience and knowledge (Runge et al. 2011).

4. Case studies on multiple stressors in cetaceans

The extremely complex issue makes it difficult to propose a 'one-fits-all' concept, rather, each situation might profit best from targeted, individual approach, depending on the data available, the suspected stressors, confounding factors, drivers, etc. Thus, we present exemplarily two cases here:

There is consensus among north american whale biologists that multiple stressors are acting on the North Atlantic right whales: Although under international protection since 1931 they barely recover, while other right whale species and populations are now recovering at 7% per annum at key sites around the Southern Hemisphere (IWC, 2013; Tulloch et al. 2018; Harcourt et al. 2019). It is assumed that this may be linked to the combination of changing food resources, entanglements, ship strikes, harmful algal blooms and marine pollutants. The impact of marine pollutants is not well understood but exposure to low, but chronic levels is considered to be of concern (Harcourt et al 2019).

A second case is presented by the Southern Resident killer whale (Orcinus orca) population in the northeastern Pacific Ocean. This one of the most critically endangered populations of marine mammals in the USA and Canada and it declined in the last two decades (Lacy et al. 2017). Three threats were identified, decline in prey abundance, noise and persistent pollutants (PCB's and others, such as polybrominated flame retardants) (Lacy et al. 2017). The reduction in Chinook salmon abundance, the preferred prey of these killer whales, was the single factor having the largest effect on the decline in population size. The causal mechanism behind this phenomenon is suggested to be due to nutritional stress in periods of lower abundance of salmon, resulting in fewer successful pregnancies. The effect of PCB's was considered with respect to influencing the calf mortality while other potential impacts, such as impaired immune response and the potentially resulting consequences, were not incorporated into the model, due to a lack of data (Lacy et al. 2017).

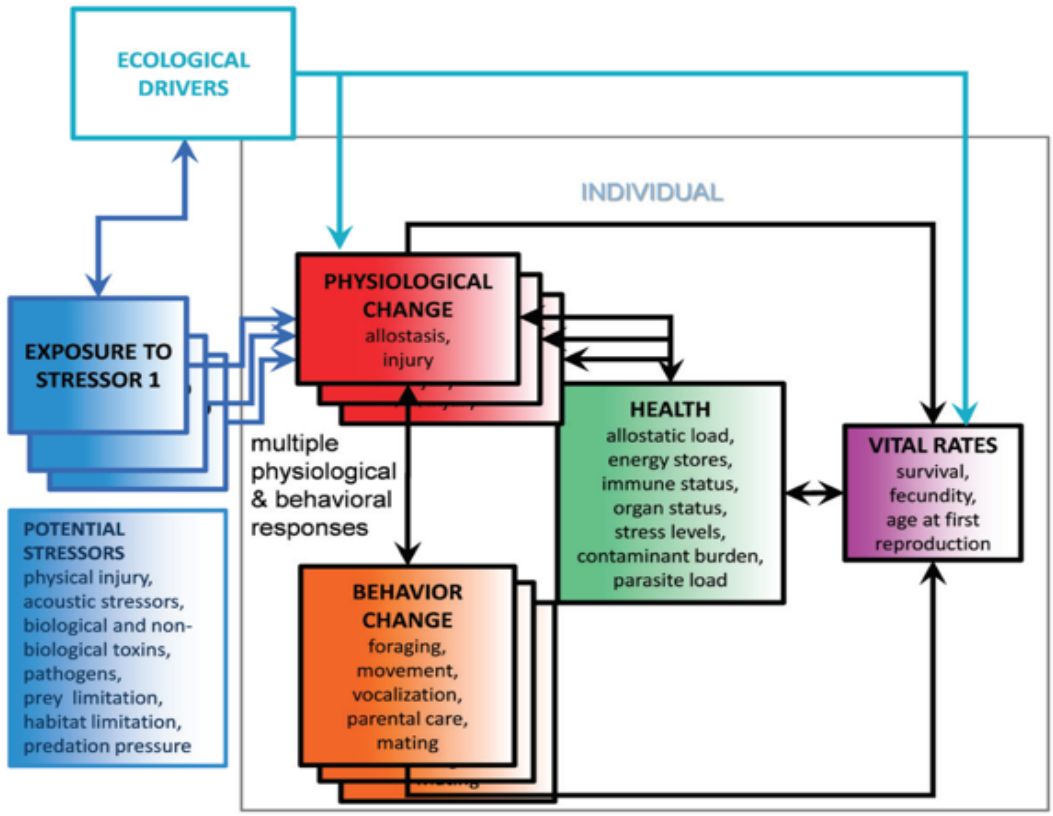

Fig. 1: The Population Consequences of Multiple Stressors (PCoMS) framework for a single individual exposed to multiple stressors. Arrows present causal flows. Changes in physiology may result in changes in behavior (such as movement away from a sound source and cessation of feeding), which may in turn affect physiology (NASEM 2017).

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