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A review of multiple stressor studies that include ionising radiation

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ABSTRACT

Studies were reviewed that investigated the combined effects of ionising radiation and other stressors on non-human biota. The aim was to determine the state of research in this area of science, and determine if a review of the literature might permit a gross generalization as to whether the combined effects of multi-stressors and radiation are fundamentally additive, synergistic or antagonistic. A multiple stressor database was established for different organism groups. Information was collected on species, stressors applied and effects evaluated. Studies were mostly laboratory based and investigated two-component mixtures. Interactions declared positive occurred in 58% of the studies, while 26% found negative interactions. Interactions were dependent on dose/concentration, on organism's life stage and exposure time and differed among endpoints. Except for one study, none of the studies predicted combined effects following Concentration Addition or Independent Action, and hence, no justified conclusions can be made about synergism or antagonism.

1. Introduction

1.1. A multiple stressor environment

Increased industrialization and population densities have led to humans and the environment being exposed to a multitude of stressors, for which little is known about their combined health and ecological consequences. Some 82,000 chemicals are registered for commercial use in the USA alone (Duncan, 2006), and in Europe roughly 150,000 chemicals were preregistered for a later full registration within REACH (Backhaus et al., 2010). An estimated 2000 new chemicals are introduced annually for applications in everyday items such as foods, personal care products, prescription drugs, household cleaners, and lawn care products (Duncan, 2006). Mixtures of polychlorinated biphenyls (PCBs), pesticides, endocrine disruptors, fire retardants, heavy metals and radionuclides are now ubiquitous in our environment (Muir et al., 2005).

Although contaminants never occur in isolation, legislation (e.g., benchmarks, clean-up standards) is largely based on studies that examined the effects caused by single contaminants, not mixtures. Kortenkamp et al. (2009) reviewed the regulations concerned with chemicals and found that only four pieces of European legislation address mixture toxicity. One of those, REACH (Registration, Evaluation and Authorisation and Restriction of Chemicals), gives guidance on the assessment of substances that are in fact chemical mixtures. The task of assessing health risks from even single contaminants is overwhelming, with only a quarter of the chemicals used in the U.S. having been tested for toxicity (Suk and Olden, 2005; Duncan, 2006). Most chemicals on the European market today have never been tested for their effects on health and the environment. In the 12 years prior to the instigation of REACH only 140 chemicals have been subject to detailed risk assessment (European Commission, 2003).

REACH, however, does not include radioactive contaminants, and the derivation of environmental radiation protection criteria by international organizations (e.g., IAEA, 1992; ICRP, 2008; UNSCEAR, 2008) or the EURATOM projects ERICA (Larsson, 2008) and PROTECT (Howard et al., 2010) are based on studies that considered radiation as the sole contaminant, in isolation from other stressors, as there is a large void in our understanding of contaminant mixtures that include radiation. However, there is considerable evidence from research on non-radioactive contaminants that (1) effects induced by a combination of stressors can differ from the sum of the individual effects and (2) compounds can exert effects in mixtures at concentrations in which the single contaminants do not show effects (Kortenkamp et al., 2007; Baas et al., 2010).

Other contaminants commonly occur in situations where radionuclides are generally the focus. For example, routine liquid

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releases from nuclear power plants contain, apart from a number of radioactive substances (e.g., ^{110m}Ag, ^{58,60}Co, ^{134,137}Cs, ^{3}H, ^{131}I), a substantial array of chemicals (e.g., Cu, Zn, boric acid, ammonium, morpholine, lithine, hydrazine, Fe) (EDF, 2006; Garnier-Laplace et al., 2008). High-level radioactive waste disposal involves chemical contaminants in the zirconium alloys and spent fuel (with constituents that include virtually the entire periodic table), the waste containers (Cr, Ni, Zn), and the over-pack (Cr, Ni, Mn, Pd, To, Mo) which are released to the environment after disposal (Harju-Autti and Volckaert, 1995). Mixtures were also evident in an analysis of U.S. Superfund Waste Sites, in which it was found that radionuclides commonly existed together with other types of contaminants (e.g., metals, volatile organic compounds, inorganic compounds, PAHs, pesticides) (Hinton and Aizawa, 2007). Uranium mining and milling has resulted in an important legacy of contamination that includes ^{238}U-series radionuclides mixed with, among other components, heavy metals (e.g., Cd, Cu, Ni, Pb, Zn) (Carlsson and Büchel, 2005; Geletneky et al., 2002; Johnston and Needham, 1999; Pidsley, 2002). The NORM (Naturally Occurring Radioactive Materials) industry is also an important source of mixed contamination with U- and Th-series radionuclides and heavy metals (Müller et al., 2000; Tayibi et al., 2009; Yusof et al., 2001).

Ecosystems are also clearly exposed to combinations of anthropogenic and natural stressors (e.g., excess UV, sub-optimal temperature, pH or nutritive status, predation). Ecotoxicological effect studies often expose test organisms under optimal environmental conditions. However, organisms in their natural settings rarely experience optimal conditions but are forced to cope with sub-optimal conditions or even with severe environmental stress. Whether interactive effects are common in natural settings and whether these are predominantly synergistic or antagonistic is a key unresolved question. Holmstrup et al. (2010) reviewed more than 150 studies to provide a synthesis of existing knowledge on the interactions between effects of “natural” and chemical (anthropogenic) stressors. Stressors considered in these studies included heat, cold, desiccation, oxygen depletion, pathogens and immunomodulatory factors combined with a variety of environmental pollutants. Synergistic interactions were reported in more than 50% of the available studies. Antagonistic interactions were also detected, but in fewer cases. Crain et al. (2008) conducted a synthesis of 171 factorial experimental studies in marine systems where two or more human-induced stressors (e.g., nutrients, temperature, sedimentation, disease, toxins) were manipulated and direct impacts measured. Cumulative effects found were more or less evenly distributed between additive (26%), synergistic (36%), and antagonistic (38%) (where synergism and antagonism were defined as deviations from an additive effect). A meta-analysis across all studies revealed a significant synergistic overall interaction effect. However, interaction type varied by response level (community: antagonistic, population: synergistic), trophic level (autotrophs: antagonistic, heterotrophs: synergistic), and specific binary mixtures. The addition of a third stressor changed interaction effects significantly in two-thirds of all cases and doubled the number of synergistic interactions. Darling and Côté (2008) performed a meta-analysis of 112 factorial experiments evaluating the impacts of multiple stressors on animal mortality in freshwater, marine and terrestrial communities. One third of the studies showed a truly synergistic effect on mortality (i.e., greater than what is expected from the simple addition of the effects of individual stressors), and this was consistent across studies investigating different stressors, study organisms and life-history stages. In more than 75% of the experiments, interactions were non-additive (i.e., synergies or antagonisms). They concluded that ecological surprises (i.e., deviations from effect addition) may be more common than simple additive effects.

A lack of knowledge about complex mixtures of pollutants is among the major challenges that environmental sciences face (Eggen et al., 2004). The long-term human and ecological risks from chronic exposures to contaminant mixtures are not known. In the framework of radiological risk assessments, data are needed to determine to what extent radiation should be considered in a multiple pollution context (Bréchignac and Doi, 2009). Thus, our aims were to (1) review studies in which combined effects of radiation and other stressors on non-human biota were evaluated and (2) determine if the effects observed were generally additive, synergistic or antagonistic. The findings from the review are important because they give guidance as to whether or not radiation needs to be considered within a multi-contaminant context, and they provide direction for current research needs.

To date, the only attempt to review the scientific literature on combined effects of radiation and other stressors has been that of UNSCEAR (2000), which focussed on cancer induction, mutation and possible prenatal effects in humans. Their aim was to elucidate the mechanisms of the interactions of other stressors in the development of radiation-induced cancer, particularly caused by chronic low-radiation doses. They reviewed the data on the effects of specific combined exposures on carcinogenesis (experiments with animal cells and animals), but interaction effects in humans other than cancer were also discussed. Many of the radiological experiments that UNSCEAR reviewed used acute, high radiation doses and high exposures to other agents. The general assumption about the dose-effect relationship for radiation and genotoxic chemicals was that these relationships are linear at low doses and quadratic at high doses. For non-genotoxic chemicals, non-linear dose-effect curves were the norm since higher order enzymatic reactions are involved in most cases (UNSCEAR, 2000). They concluded that although both synergistic and antagonistic combined effects are common at high exposures, there is no firm evidence of additivity at controlled occupational or environmental exposures.

1.2. Fundamentals of environmental multiple stressors

Although most scientists acknowledge that contaminant mixtures within the environment are the rule, rather than the exception, relatively few researchers properly study them. Instead, the vast majority of research is focused on single contaminants in isolation from all others. The study of a single stressor is infinitely easier than a multi-component mixture. However, the problem of conducting research solely on single contaminants is that it limits our knowledge of potential interactions.

Interactions between pollutants in a mixture may occur at three levels: (1) Pollutants may influence each other's mobility in the environmental media and hence, each other's availability to organisms; (2) different pollutants may block or enhance each other's uptake into the organism; (3) once inside the organism, pollutants may block or enhance each other's detoxification, alter the nature of their toxic actions, and/or impact repair capacities. The primary molecular and cellular effects of the many agents potentially involved in combined effects are extremely numerous and diverse (e.g., the mode of action may be genotoxic or non-genotoxic and they may interact via different pathways and through different mechanisms). Understanding the effects of chemical mixtures in real ecosystems requires knowledge of how biological and non-biological parameters may affect interactions at all three levels set out above.

1.2.1. Interactions affecting mobility or bioavailability of mixed contaminants

Few radioecological studies have been performed where the effect of mixed stressor or mixed contaminant conditions on