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# Ionizing radiation, antioxidant response and oxidative damage: A meta-analysis

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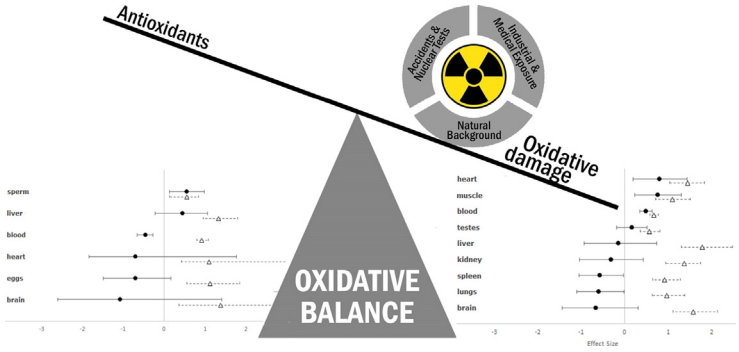
## HIGHLIGHTS

- There is interest in variation in metabolic effects of chronic low-dose ionizing radiation
- A random effect meta-analysis of effect sizes of radioactive contamination was performed
- We found significant effects of radiation on oxidative damage and antioxidant response
- We found significant heterogeneity among biological matrices, species and age classes

## GRAPHICAL ABSTRACT

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## ABSTRACT

One mechanism proposed as a link between exposure to ionizing radiation and detrimental effects on organisms is oxidative damage. To test this hypothesis, we surveyed the scientific literature on the effects of chronic low-dose ionizing radiation (LDIR) on antioxidant responses and oxidative damage. We found 40 publications and 212 effect sizes for antioxidant responses and 288 effect sizes for effects of oxidative damage. We performed a meta-analysis of signed and unsigned effect sizes. We found large unsigned effects for both categories (0.918 for oxidative damage; 0.973 for antioxidant response). Mean signed effect size weighted by sample size was 0.276 for oxidative damage and −0.350 for antioxidant defenses, with significant heterogeneity among effects for both categories, implying that ionizing radiation caused small to intermediate increases in oxidative damage and small to intermediate decreases in antioxidant defenses. Our estimates are robust, as shown by very high fail-safe numbers. Species, biological matrix (tissue, blood, sperm) and age predicted the magnitude of effects for oxidative damage as well as antioxidant response. Meta-regression models showed that effect sizes for oxidative damage varied among species and age classes, while effect sizes for antioxidant responses varied among species and biological matrices. Our results are consistent with the description of mechanisms underlying pathological

*Abbreviations:* LDIR, low-dose ionizing radiation; NCRP, National Council on Radiation Protection and Measurements; INES, International Nuclear and Radiological Event Scale; NPP, Nuclear Power Plant; ROS, reactive oxygen species; RNS, reactive nitrogen species.

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effects of chronic exposure to LDIR. Our results also highlight the importance of resistance to oxidative stress as one possible mechanism associated with variation in species responses to LDIR-contaminated areas.



## 1. Introduction

Low-dose ionizing radiation (LDIR) is the type of low-rate chronic irradiation that does not induce adverse toxic effects (National Council on Radiation Protection (NCRP), 1987). However, exposure to LDIR can accelerate cellular senescence via increasing activity of reactive oxygen species (ROS) and disruption of biopolymers (Loseva et al., 2014). Because the power of exposure decreases with the distance to the source, a bigger potential hazard comes from radiological agents being ingested or inhaled.

Industrial and military use of radioactive materials has led to their release to ecosystems. Early monitoring studies of humans and biota following atomic bomb testing as well as radiation-related accidents (e.g. in Kyshtym, Russian Federation), suggested elevated health risks and mortality rates in humans and some mammals associated with high acquired doses after chronic exposure to LDIR (Sakata et al., 2012; Lushnikova et al., 1997; Mozolin et al., 2008; Shoikhet et al., 1999; Grigorkina and Olenev, 2013; Grigorkina and Pashnina, 2007). These studies also suggested that the effects of direct exposure to ionizing radiation were exacerbated by incorporation of soluble radioactive elements (Ivannikov et al., 2002). Recent ecological studies of the Chernobyl and Fukushima catastrophes confirmed this, and demonstrated high variability in such effects among taxa. Along with a high frequency of morphological abnormalities (Akimoto, 2014; Hiyama et al., 2012, 2013; Møller et al., 2007) and tumors (Møller et al., 2013), and an overall decline in population abundances (Møller and Mousseau, 2007a, 2007b, 2009; Møller et al., 2012), these effects included high rates of genetic aberrations in somatic (Alamri et al., 2012; Bonisoli Alquati et al., 2010a; Møller et al., 2013) and germline cells (Ellegren et al., 1997). Moreover variation exists across species in their biochemical and genetic responses to increasing environmental radiation (Galván et al., 2014; Hinton et al., 2007).

Overall, attempts to rigorously monitor human populations in Ukraine, Belarus and Russia following the Chernobyl accident have been scattered at best (Edwards et al., 2004; Yablokov et al., 2009). Nonetheless, these studies showed that workers involved in the cleanup operations (the so-called 'liquidators'), who were exposed to much higher doses than evacuated civilians, demonstrated elevated frequencies of genetic abnormalities (Moysich et al., 2002; Sevan'kaev et al., 2005), solid cancers and cardio-vascular diseases (Cardis and Hatch, 2011; Serdiuk et al., 2011). An elevated fraction of evacuated adolescents and young adults suffered from thyroid cancer (Demidchik et al., 2007). At the same time, epidemiological studies with small cohorts and small and non-representative control groups carried out years after the catastrophe did not yield sufficient evidence to support the hypothesis of radiation-associated mortality linked to the Chernobyl accident (Serdiuk et al., 2011; Weinberg et al., 2001).

These findings emphasize the need to study variation in health effects in the context of chronic exposure to LDIR. Results of such studies are important and may be used in radiation protection and for defining safety requirements, particularly given the current debates about the shape of dose–response curves describing radiation-related effects and the severity of radiation injury (Ryan, 2012).

When absorbed by living cells, ionizing radiation can induce direct breakage in the chemical bonds of biological macromolecules. Ionizing radiation can also affect proteins, nucleic acids and complex lipids as a result of the generation of reactive oxygen species (ROS) via radiolysis of water or alteration of mitochondrial functions (Kam and Banati, 2014). ROS are a diverse group of chemical species, which naturally occur in cells, where they perform important signaling functions (Azzam et al., 2011; Murphy et al., 2011). ROS activity is controlled by a number of enzymatic and non-enzymatic antioxidants. The inability to balance the increased generation of ROS by antioxidant mechanisms results in oxidative stress, a complex stressor for cells that manifests as increased oxidative molecular damage to biomolecules, e.g. oxidation of lipids, oxidative modification of nitrogenous bases etc. (Halliwell and Gutteridge, 2007; Jones, 2006). In turn, oxidative damage may promote the emergence of pathological states, accelerated cell aging and apoptosis (Halliwell and Gutteridge, 2007; Spitz et al., 2004). In numerous invertebrate and vertebrate species, oxidative damage may result in reduced growth, fertility and survival (Costantini, 2014).

The association between LDIR and the generation of reactive species has been widely described (Azzam et al., 2011; Smith et al., 2012). The role of ionizing radiation in generation of ROS is well explained as the correlation between genetic damage and oxidative damage (e.g. Costantini, 2014; Galván et al., 2014). Oxidative damage might be one mechanism underlying several of the detrimental effects of radiation. The root of the controversy relates to the manifestation of a given symptom or morbidity as a consequence of the three-way interaction of increased concentrations of ROS, decreased activity of antioxidant enzymes, and genetic damage associated with increased background radiation (Spitz et al., 2004), especially when disease is followed by another medical condition, like malnutrition, inflammatory disease or respiratory malfunction. However, it is important to note that radionuclides do not only generate damage through radiation, but also through their catalytic activity (the Fenton reaction) (Halliwell and Gutteridge, 2007). In addition, while several studies have documented increased oxidative damage and reduced antioxidant defenses in humans and wild populations of animals chronically exposed to LDIR (e.g. Bonisoli Alquati et al., 2010b), other studies have shown the potential for animals to adapt their antioxidant system to chronic exposure to LDIR (Galván et al., 2014). In addition, theoretical calculations and lack of accurate dosimetry have called into question findings of increased oxidative stress from exposure to LDIR (Smith et al., 2012).

Here we assess the effects of chronic exposure to LDIR from radioactive contamination. We aim at exploring the insights of long-term metabolic processes, such as antioxidant function and oxidative damage, of individuals affected by chronic irradiation caused by radioactive contaminants. We collected exhaustive data from radiobiological studies in the Russian and the English language scientific literature, and combined published evidence into a meta-analysis of the effects of chronic radiation exposure on markers of oxidative damage and antioxidant protection. Our aim was to test whether high environmental radioactivity would lead to higher oxidative damage and lower antioxidant defenses in exposed organisms. Meta-analysis is a powerful tool for quantitatively summarizing research, especially when there is apparent heterogeneity in research findings (Arnqvist and Wooster, 1995; Hedges and Olkin, 1985; Koricheva et al., 2013).

We expected factors related to study design, age and model organism to explain variation across studies and species in the relationship between LDIR exposure and oxidative damage. Hence, we also tested whether different biological matrices and species differed in their response to radiation. Different organs and tissues can be differentially exposed and/or sensitive to radiation exposure, depending on the metabolic fate of radionuclides. Juveniles and adults can also differ in their sensitivity, with individuals at early developmental stages generally being more sensitive to increased radiation because of their immature antioxidant system (Costantini, 2014; Lu and Finkel, 2008) and due to potential hazardness of the damage being accumulated in their stem cell progeny (Liu et al., 2014). Finally, variation across species in