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Review

Mus spretus as an environmental sentinel: A review of 17 years (1998–2015) of research in Mediterranean Europe

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ABSTRACT

The Algerian mouse *Mus spretus* has been widely used as a biomonitor to assess environmental contamination, either *in situ* or *ex situ*. Knowledge on toxic effects of environmental pollutants on *M. spretus* greatly stems from multi-approach studies, in late 1990's and early 2000's, aiming at evaluating the acute and chronic environmental impacts generated by mining activities, in Spain and Portugal. These studies also identified several measures of overall fitness in mice as indicators of metal stress. More recent studies have pointed out for two promising pathways: the use of non-invasive and non-destructive endpoints aiming to protect wild populations; and the "omic" sciences. Overall, the set of studies carried out over the last 17 years (1998–2015) demonstrates the potential use of *M. spretus* as a sentinel species to detect environmental contamination, especially by mixtures of contaminants.

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1. Introduction

Several species of wild small mammals have been taken as suitable sentinels for environmental health assessment across the world, because of their usual wide distribution range, high abundance, ecological representativeness (Beardsley et al., 1978; Roberts and Johnson, 1978) and functional diversity. Moreover, the easy capture, handling and maintenance under laboratory conditions comprise other features making rodents excellent models in environmental monitoring surveys.

Free-living small mammals depend on the quality of their habitats, being greatly influenced by local environmental health conditions (biota, soil, water and atmosphere) (Tataruch and Kierdorf, 2003). In this sense, many studies have reported impacts of diminishing the environmental quality on rodents in Oceania (e.g. Knutt and Woinarski 2007; McLean et al., 2009), Africa (e.g. Attuquayefio and Wuver 2003; Eccard et al., 2000; Lagesse and Trondhlana 2016; Wallgren et al., 2009), North America (e.g. Mussali-Galante et al., 2013; Tovar-Sánchez et al., 2012), South America (e.g. da Silva Júnior et al., 2000; Tabeni and Ojeda, 2003) and Europe (e.g. Ieradi et al., 1996, 2003; Mitkovska et al., 2012), being the wild small mammals *Crocidura russula* (greater white-toothed shrew), *Apodemus sylvaticus* (wood mouse) and *Mus spretus*

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(Algerian mouse), the species in which environmental monitoring studies in Mediterranean Europe have foccused (e.g. Ieradi et al., 1998; Festa et al., 2003; Sánchez-Chardi and Nadal 2007; Sánchez-Chardi et al., 2007, 2013).

The free-living mouse *Mus spretus* is highlighted in these studies because it has proven to be a suitable biomonitor in contaminated sites. This species distributes mainly from the Southern France to Tunisia, but isolated populations are found in Libya and non-established populations in Egypt (Palomo et al., 2009) (Fig. 1).

The physiology and ecology of *M. spretus* are well-known. To mice in the southern Iberian Peninsula, there are two stages in their reproductive cycle, sexual inactivity during the wintertime (from November to January) and sexual activity in the remaining part of the year (reaching the maximum on April/May and September/October) (Table 1). Average lifespan is less than four months, with the utmost longevity of 13–14 months (Palomo et al., 2009).

Contrary to the house mouse *Mus musculus,* widely used as a biological model, the Alegrian mouse *M. spretus* avoids urbanized areas, and rather lives in different kinds of agroecosystems, including crops, orchards, grasslands, scrublands, young forests and post-fire habitats (Khidas et al., 2002; Torre and Diaz, 2004; Palomo et al., 2009), In its habitat, *M. spretus* builds tunnels for its protection from predators, using the available vegetation and tree branches. It feeds on seeds, fruits, cropped and non-cropped vegetables and insect larvae. And it is preyed upon by some carnivorous predators like owls and serpents. Its intermediate position in the food chain, associated with the high capacity of pollutants bioaccumulation (Pereira et al., 2006), makes this species a major player in the transfer of pollutants along the food web.

M. musculus and *M. spetrus* also differ from each other in their social behavior. While *M. musculus* is aggressive and intolerant to intruders, *M. spretus* uses odor trails (Hurst et al., 1997) and postural behaviors to establish dominance relationships among males (Palomo et al., 2009).

Over the last 30 years, this small rodent has been used in many fields of genetics studies. Extensive genetic polymorphisms might be employed as a suitable complimentary tool, regarding the limited genetic polymorphism exhibited by laboratory mice strains. The use of *M. spretus* can also contribute to advances in research on inflammatory response patterns, cellular cycle control, susceptibility to tumors, infertility and development (Dejager et al., 2009).

The use of *M. spretus* in Environmental Toxicology studies is more recent and has been widely conducted in Portugal and Spain, where the Algerian mouse has been applied as a sensitive biosentinel to identify hazards and risks associated with environmental contamination by toxic substances. Table 2 lists the studies performed on the effects of environmental pollution using this species, discussed in the Sections below.

1.1. Mining area

Studies performed in mining fields in Portugal have used *M. spretus* as an environmental biomonitor. Nunes et al. (2001a) were the pioneers in analyzing morphological and hematological biomarkers to evaluate effects of environmental pollution on mice inhabiting an active tin-copper mine area in Central Portugal. Authors attributed changes in morphological and hematological parameters to

physiological stress caused by the reduced environmental quality. Other study performed in the same area (Nunes et al., 2001b) used the dental fluctuation asymmetry as a tool to determine ecological stress.

Biochemical responses associated with hepatic metal accumulation were also investigated in mice inhabiting mining areas (Viegas-Crespo et al., 2003). Results unveiled seasonal patterns in antioxidant enzyme activities and hepatic metal burdens, probably related to the sexual activity of mice or variation in the level of environmental contaminants over the year. Overall, these studies highlighted the relevance of the Algerian mouse as a metal bioaccumulator and contributed for the understanding of the toxic potential of mixtures of elements. In addition, reference values were attributed to several parameters and may drive future studies.

Other sets of studies were performed in abandoned mining areas. Despite inactive, injuries to the biota may persist in either recent (Marques et al., 2008) or long-term (Pereira et al., 2006) abandoned mines. Eroded soils, rainstorms and air drifts favor the remobilization of toxic substances that may harm terrestrial and aquatic organisms. In this context, the metal determination in tissues and hair, as well as the use of histopathological (Pereira et al., 2006) and biochemical (Marques et al., 2008) markers were suitable to confirm exposure to a persistent releasing of toxic metals from abandoned mines. These studies have confirmed that old mines may constitute sources of metal contamination and strongly support the need for environmental recovery and monitoring plans in these areas.

1.1.1. A case study: the Doñana National Park Disaster

On the 25 of April 1998, there was a rupture in a decanting dam of Azalcóllar pyrite mine, province of Sevilla, Spain. Approximately 4 million cubic meters of acidic water and 2 million cubic meters of mud containing high concentrations of toxic metals were released in the vicinity, including the area of the Doñana National Park. After the accident, an emergency plan to remove the mud and to treat the acidic waters was carried out (Grimalt et al., 1999). Taking into account that previous studies had pointed out the sensitivity of *M. spretus* to metal pollution, several new studies were conducted aiming to investigate the negative impacts originated from the Doñana National Park disaster and to monitoring the affected area.

A set of genotoxic biomarkers were investigated and several studies were reported. Among the widespread genotoxicity bioassays and used in various studies of this species are the comet assay and micronucleus test. The first bioassay evaluates the DNA fragmentation, while the second evaluates the loss of portions of chromosomes in the cell. The micronucleus test was applied by Tanzarella et al. (2001) to determine genotoxic effects in erythrocytes of peripheral blood of *M. spretus* captured six months after the disaster. Animals taken from areas whose mud was rich in metals and water was acidic, showed higher micronuclei frequencies than those collected in non-affected areas. Festa et al. (2003) also reported genotoxic damages in mice using the comet assay. These authors collected specimens of *M. spretus* in two consecutive years (October 1998 and 1999), and peripheral blood leucocytes were screened. Results showed high damages in animals collected shortly after the disaster (1998) and reduction of effects one year later. Similarly, Udroiu et al. (2008) identified sperm abnormalities in mice against metal accumulation in the liver and suggested the implementation of biomonitoring programs in order to determine long-term effects of the disaster, as well as biota recovery strategies.

Biochemical parameters were also investigated assess how the spill at Azalcóllar affected the biota. Ruiz-Laguna et al. (2001) studied the activity of antioxidant and biotransformation enzymes and oxidative damages on biomolecules to verify the effects of the disaster on the health of *M. spretus*. Similarly, Bonilla-Valverde et al. (2004) relied on biochemical biomarkers and tissues metal accumulation in mice to monitor selected areas of the Doñana National Park between 1999 and 2001. A more recent study investigated the proteins related to the cellular cycle control in the kidneys of *M. spretus* (Leoni et al., 2008). According to the results found, environmental pollution caused by the disaster in the pyrite mine led to the induction of cellular proliferation in the kidneys as a compensatory mechanism following tissue damage and apoptosis.