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# Effects of widely used pharmaceuticals and a detergent on oxidative stress biomarkers of the crustacean *Artemia parthenogenetica*

B. Nunes [a,b,*], F. Carvalho [c], L. Guilhermino [a,b]

[a] *ICBAS, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Departamento de Estudos de Populações, Laboratório de Ecotoxicologia, Largo Prof. Abel Salazar, 2, 4099-003 Porto, Portugal*

[b] *CIIMAR, Centro Interdisciplinar de Investigação Marinha e Ambiental, Laboratório de Ecotoxocologia, Rua dos Bragas, 289, 4050-123 Porto, Portugal*

[c] *REQUIMTE, Departamento de Toxicologia da Faculdade de Farmácia da Universidade do Porto, Rua Aníbal Cunha, 164, 4099-030 Porto, Portugal*

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**Abstract**

Pharmaceuticals are continuously dispersed into the environment as a result of human and veterinary use, posing relevant environmental concerns. The present paper reports the acute toxic effects of three therapeutic agents (diazepam, clofibrate and clofibric acid) and a detergent, sodium dodecylsulphate (SDS), to the hypersaline crustacean *Artemia parthenogenetica*. This study specially focused on oxidative stress parameters, namely (1) total and selenium-dependent glutathione-peroxidase (GPx), (2) glutathione reductase (GRed), (3) total superoxide dismutase (SOD), and (4) glutathione-S-transferases (GSTs). The effects of tested substances on lipid peroxidation (thiobarbituric acid reactive substances, TBARS), and soluble cholinesterases (ChE) were also investigated. Diazepam caused a significant inhibition of ChE (LOEC = 7.04 mg/l) and total GPx activities. SDS was responsible for a decrease in the activity of both ChE (LOEC = 8.46 mg/l) and GRed (LOEC = 4.08 mg/l). Both fibrates (clofibrate and clofibric acid) were responsible for significant decreases in Se-dependent GPx, with LOEC values of 176.34 and 3.09 mg/l, respectively. Clofibrate also caused a slight increase of TBARS content of *A. parthenogenetica* homogenates. These results indicate that the exposure to all the tested compounds induced alterations on the cellular redox status in *A. parthenogenetica*. In addition, diazepam was shown to have the capability of interfering with *A. parthenogenetica* neurotransmission, through the inhibition of ChE.
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## 1. Introduction

The use of biomarkers in Ecotoxicology is becoming a useful routine, and various end-points have been proposed as valuable tools to assess the effects of environmental chemical contamination. Among the most used

* Corresponding author. Address: CIIMAR, Centro Interdisciplinar de Investigação Marinha e Ambiental, Laboratório de Ecotoxocologia, Rua dos Bragas, 289, 4050-123 Porto, Portugal. Tel.: +351 22 340 1828; fax: +351 22 339 0608.
*E-mail address:* brunonunes@cimar.org (B. Nunes).

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biomarkers, oxygen-related enzymatic alterations and cholinesterase inhibition assume the leading position, being frequently used both in environmental monitoring and laboratory assays. Several studies measuring oxidative stress biomarkers in a wide number of distinct organisms have been published. Livingstone (2001) reported the use of oxidative stress parameters in a vast number of situations and organisms. Using oxidative stress biomarkers, Pandey et al. (2003) assessed the effects of environmental pollution on several tissues of the fish *Wallaga attu* and Oakes and Van Der Kraak (2003) investigated the influence of pulp mill effluents on the fish *Catostomus commersoni*. The metals cadmium and mercury were also shown to interfere with oxidative related alterations on Nile tilapia, *Oreochromis niloticus* (Almeida et al., 2002) and salmon, *Salmo salar* (Berntssen et al., 2003).

Among biomarkers of oxidative stress, enzymes such as superoxide dismutase, glutathione peroxidase and glutathione reductase are of special importance. Superoxide dismutase is responsible for the detoxification of the short-lived, highly reactive oxygen species superoxide anion. Glutathione peroxidase exerts its protective role by acting as scavenger for high concentrations of hydrogen peroxide; during this process, glutathione is oxidized and loses its protective capability. Glutathione reductase is the enzymatic species responsible for the reversion of the oxidized form of glutathione, thus leading to the formation of two molecules of glutathione, which can perform again their natural detoxification role. In spite of the existence of the before-mentioned physiological mechanisms of control of reactive oxygen species, oxidative damage is sometimes likely to occur, due to extensive production/reduced protective capacity of the organism. In the case of free radical attack of biological structures, some compounds, such as malondialdehyde (MDA), may be formed, as a consequence of degradation of initial products. The extent of lipid peroxidation can be measured through the evaluation of the levels of thiobarbituric acid reactive substances (TBARS), which are mostly comprised by MDA. Other biomarkers are also of great interest, such as the ones related to the detoxification potential of the studied organisms; glutathione-S-transferases (GSTs) are a group of widely distributed enzymes that catalyze the conjugation of xenobiotics with glutathione. Furthermore, this conjugation is followed by transfer of the glutamate by γ-glutamyltranspeptidase, by loss of glycine through cysteinyl glycinase, and finally by acetylation of the cysteine amino group. The toxicological importance of the conjugation process is very high, since the removal of reactive electrophiles allows the protection of vital nucleophilic groups in macromolecules such as proteins and nucleic acids. The mercapturic acids formed can be excreted either in the bile or in the urine (Hodgson, 2004).

Therapeutic agents and personal care products have a widespread distribution in the environment, as a consequence of its continuous use by human populations. These chemicals are used due to their biological activity, which is the most important parameter to be considered when evaluating their toxicological impact in the wild (Halling-Sörensen et al., 1998; Daughton and Ternes, 1999; Jones et al., 2002; Miao et al., 2002). Besides biological activity, these compounds are also designed to be resistant to metabolic degradation, and, usually, their lipophylicity is a basic requirement to be well absorbed by the organism. These factors contribute for the overall importance of their persistence in the environment. Other aspect to take into account when studying the environmental fate and effects of pharmaceuticals and personal care products is related to the variety of metabolites formed and to possible toxicological interactions (e.g., synergistic, additive, antagonistic effects) among pharmaceutical residues in the wild (Cleuvers, 2003). Therefore, a considerable part of pharmaceuticals and personal care products may be considered as active, effective and persistent environmentally unfriendly compounds. Furthermore, Kümmerer (2001) reported high contamination values for several classes of therapeutic agents, which can consequently lead to acute effects over organisms.

Diazepam is a benzodiazepine used in human therapeutics due to its anxiolytic, sedative and muscle relaxant effects. This pharmacological activity is consequent to the enhancement of GABAergic transmission at benzodiazepine-sensitive $GABA_A$-receptors (Mohler et al., 1996). The presence of diazepam in concentrations up to 0.04 μg/l in effluents from German sewage treatment plants (Ternes, 1998), and in concentrations ranging from 0.7 to 1.2 ng/l in River Po, Italy (Zuccato et al., 2000) has been reported. Diazepam was shown to possess the capacity of altering cellular redox systems (Musavi and Kakkar, 1998, 2003) an effect that remains to be elucidated.

Fibrates are used in human therapeutics due to their blood lipid regulation properties. This pharmacological activity is consequent to the activation of peroxisome proliferation and consequent increase in fatty acids peroxisomal β-oxidation, which occurs through activation of the nuclear peroxisome proliferator activated receptors (PPARs). The activation of PPARs causes a transcriptional activation of the genes encoding for the peroxisomal oxidation system (specially of hydrogen peroxide-generating peroxisomal fatty acyl-CoA oxidase) and cytochrome hydrogen peroxide-generating P450 CYP 4A isoforms (especially CYP4A1 and CYP4A3). Consequently, a hyperproduction of hydrogen peroxide is favoured. A compensatory mechanism of increase in the activity of the hydrogen peroxide-degrading enzymes (catalase) also occurs in peroxisomes, albeit not as much as it would be needed to cope

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