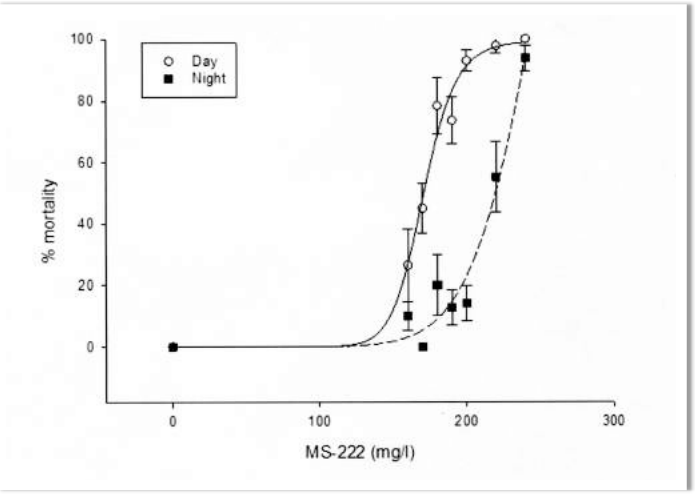
Chronotoxicity

During evolution, fish have developed biological clocks that are synchronised to the geophysical cycles that originate from the alternation of day and night, lunar phases and seasons. These internal clocks play a key role in controlling biological rhythms since they help fish to adapt their daily and seasonal activities to the environmental cycles. Light information is perceived and transduced by the pineal organ in the brain, which produces the hormone melatonin during the night. In this manner fish receive information about the time of day and year and their physiological functions, such as feeding or reproduction, are entrained.

Chronotoxicity tackles the study of temporal variation in the presence and severity of adverse effects of chemical substances when administered to an organism at different times of the day. Aquaculture fish species are exposed to a great number of xenobiotic substances in routine procedures (e.g. antibiotics, antifungals, parasiticides, disinfectants, vaccinations, anaesthetics). Most of these compounds are used to guarantee fish health and welfare but drug efficacy and toxicity may vary with time of the day. Knowing the time at which drug effectiveness is optimal and side effects minimal will improve fish welfare and reduce economic costs. The toxicity rhythm of therapeutants can be due to the existence of rhythmicity at different levels. First of all, the uptake from the aquatic environment might differ depending on the time of the day, which would determine the final dose absorbed and therefore, a higher uptake may cause more severe side effects. On the other hand, the enzymes involved in the metabolism and detoxification of toxic compounds can present circadian rhythmicity too and thus affecting the time span from the uptake until the neutralisation and/or elimination. And finally, the excretion mechanisms could be also subjected to daily variations.

Tricaine methanesulphonate (MS-222) is an anaesthetic commonly used in aquatic organisms. The toxicity and effect of anaesthetics is of special interest since they are frequently used in research and routine aquaculture procedures to immobilise fish and minimise their stress responses. Previous investigations showed that exposure to sublethal concentrations of MS-222 affected the swimming patterns of gilthead seabream (*Sparus aurata*) and zebrafish (*Danio rerio*) in a different manner, depending on the time of exposure. The time required to induce anaesthesia was shorter during daytime than during night time, whereas the recovery period was longer during the day, underlining that the toxicity and effectiveness of MS-222 is highest during daytime, coinciding with the active phase of these fish, and suggesting a link between the daily rhythms of behaviour and toxicity. Moreover, the acute toxicity of MS-222 exerted strikingly different effects depending on the time of exposure. Thus, in zebrafish a given concentration (190 mg/L) resulted in a mortality rate of 82% when fish were exposed during the day but only 14% during the night (Fig. 1). Besides, in seabream, different feeding schedules were able to modify the day-night variations of effectiveness, suggesting that feeding time could be used to manipulate toxicity rhythms which may help to establish optimum protocols for application in the aquaculture industry.

Dr. Luisa Vera recently joined the Genetics and Reproduction Group at the IoA to develop this new line of research. Currently, new projects and experiments are being designed to determine the existence of daily variations in the lethal and sublethal effects of several therapeutants commonly used in Atlantic salmon aquaculture in the UK. Ultimately this research has the potential to optimise the administration protocols of these chemicals and improve fish welfare during treatments which may result in lower mortalities.



Mortality rate of zebrafish exposed to eight concentrations of MS-222 during the day and night