Toxicity of Palytoxin After Repeated Oral Exposure in Mice

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Palytoxin (PLTX), a marine hydrophilic polyether, is a highly toxic compound detected in several edible marine organisms from intra-tropical areas, where seafood poisoning were reported. In the Mediterranean area, monitoring programs have detected PLTX-like molecules in edible mollusks and echinoderms along the Italian, Greek and French coasts. Although in Europe no human poisonings have been reported yet, epidemiological data suggest that consumption of PLTX-contaminated seafood can be of concern, potentially leading to lethal effects. Symptoms usually start with gastro-intestinal malaise, often accompanied by myalgia, muscular cramps, dyspnea and, sometimes, arrhythmias (Tubaro et al., 2011).
Despite this, the toxicological profile of PLTX is still an issue. *In vivo* acute oral toxicity studies on PLTX showed LD_{50} values in the range 510-767 μg/kg in mice (Munday, 2008; Sosa et al., 2009). Although repeated consumption of contaminated seafood, at least for a short period of time, can be representative of human exposure scenarios, PLTX-induced toxicity after repeated oral administration has never been investigated so far. The present paper present results obtained after daily PLTX oral administration to mice, for 7 days. PLTX caused toxic effects and lethality at doses ≥ 30 μg/kg/day, whereas no adverse effects were observed at 3 μg/kg/day. Macroscopic alterations at gastrointestinal level (gastric ulcers and intestinal fluid accumulation) were observed in mice dead during the treatment period. Histological analysis highlighted severe inflammation, locally associated with necrosis, at pulmonary level, as well as hyper-eosinophilia and fiber separation in cardiac muscle. Cardiac damage was supported by the *in vitro* effect of the toxin on cardiomyocytes.
The obtained results show that sub-acute PLTX treatment can cause lethality at doses 10-fold lower than lethal acute oral doses, with a quite steep dose-response curve. These results highlight the need of knowing the mode of action and the dose response relationship of sub-acute toxicity also for other PLTX analogues, in order to quantitatively evaluate the risk for the exposed population.

Munday (2008). In: Botana, L.M. (Ed.), *Seafood and Freshwater Toxins. Pharmacology, Physiology and Detection*. CRC Press, Boca Raton, pp. 693–713.
Sosa et al. (2009). *Toxicol. Lett*. 191, 253-9.
Tubaro et al. (2011). *Toxicon*. 57, 478-95.