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# Human risk associated with palytoxin exposure

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ABSTRACT

Palytoxin (PTX) was first isolated from the zoanthid *Palythoa toxica*. Evaluation of PTX toxicity using various animal models determined that PTX was extremely potent through intravenous, intraperitoneal, and intratracheal exposure. PTX was less potent by direct intragastric exposure. PTX also caused significant, non-lethal effects through dermal and ocular exposure. PTX and PTX-like compounds have now been found in additional zoanthid species, red alga, a sea anemone, and several dinoflagellates. PTXs are found throughout certain reef associated food webs, including in fish and crabs responsible for human illness and death. Many of the organisms found to contain PTXs in the environment are also sold in the home aquarium trade, and recent evidence suggests poisonings have occurred through exposure to these organisms. Due to co-occurrence with other seafood toxins, such as ciguatoxins, saxitoxins, and tetrodotoxin, it has been difficult to assess the true risk of PTX poisoning through seafood consumption in humans, but limited cases have been well documented, some involving human fatalities. Recent evidence also suggests that humans are negatively impacted through PTX exposure by inhalation and dermal routes. Continued research into the distribution and occurrence of PTX and PTX-like compounds both in seafood and marine organisms sold in the aquarium trade appears warranted.

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## 1. Introduction

Palytoxins (PTXs) are a group of complex, extremely potent, marine natural products first described from tropical Cnidarian zoanthids (a type of colonial anemone). PTXs have been found throughout the food web including in fish and crabs responsible for human illnesses. PTXs target membrane sodium–potassium pumps responsible for maintaining ionic gradients critical to cellular function ($Na^+/K^+$-ATPase), essentially converting these ion-specific pumps into non-selective cationic pores (Artigas and Gadsby, 2003; Hilgemann, 2003). Disruption of these pumps results in a myriad of organism level effects, some life threatening. Characteristic aspects of PTX activity include delayed hemolysis with a large pre-lytic loss of potassium (Habermann et al., 1981). The cardiac glycoside ouabain specifically inhibits the action of PTX on certain, but not all, $Na^+/K^+$-ATPases (Habermann et al., 1989). For example, rat and mouse erythrocytes are the most sensitive to PTX induced hemolysis but are the least sensitive to the inhibitory effects of ouabain (Habermann et al., 1989; unpublished data).

Several recent reviews have described in detail the occurrence (Mundy, 2008), chemistry (Katikou, 2008; Kita and Uemura, 2008), and pharmacology (Vale, 2008) of PTXs. Provided here is a brief review of the toxins involved in the syndrome palytoxicosis, including their biological origin and symptoms reported in exposed animals and humans. The primary focus of this article are the potential routes and risks of human exposure to PTXs including two new accounts of poisonings following exposure to marine aquarium zoanthids; one involving dermal exposure and the other detailing an unusual case of inhalational toxin exposure.

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## 2. Toxins

In Moore and Scheuer's (1971) initial description of the marine toxin palytoxin, they recount the ancient Hawaiian legend of the "Limu Make o Hana" (deadly seaweed of Hana) in which a creature with a shark's mouth on its back is burned and its ashes cast into a tidal pool after it terrorizes a local village in Muolea, in the district of Hana on the island of Maui. As the legend goes, after this episode the Limu in the pool became toxic and the pool itself became kapu (taboo) to the Hawaiians who believed that an ill fate would befall anyone who attempted to gather the toxic limu. As part of ongoing research to determine the biological origins of ciguatoxin, researchers at the Hawaii Institute of Marine Biology set out to determine the location of this fabled pool where warriors were once said to smear the limu on spear points to make their wounds fatal. On December 31, 1961 the pool was finally visited and found to contain no limu (seaweed) but a previously undescribed species of coelenterate zoanthid eventually named *Palythoa toxica* (Walsh and Bowers, 1971). Coincidentally, a fire destroyed the main building of the Hawaii Marine Laboratory in Oahu that very afternoon. After two subsequent collection trips to the pool (one each in 1963 and 1964), purified ethanolic extracts of approximately 0.75 kg of *P. toxica* yielded a non-protein compound of ca. 3300 molecular weight with an i.v. $LD_{50}$ of 0.15 μg/kg in mice making it one of the most toxic substances known to this day.

Nearly a decade later, the structure of palytoxin (PTX) was reported independently by two groups (Moore and Bartolini, 1981; Uemura et al., 1981). Moore and Bartolini (1981) described a PTX of molecular formula $C_{129}H_{221}N_3O_{54}$ ($M_r$ 2659)[1] from a Tahitian *Palythoa* sp. and 2 isomeric hemiketals of the molecular formula $C_{129}H_{223}N_3O_{54}$ ($M_r$ 2677) from Hawaiian *P. toxica*. Uemura et al. (1981) described a PTX of molecular weight (2680 Da)[2] from Japanese *Palythoa tuberculosa* with the same chemical formula and structure as one of the isomeric hemiketals from Moore and Bartolini (1981). PTX from *P. toxica* (chemical formula $C_{129}H_{223}N_3O_{54}$) possesses 115 carbons in a continuous chain, making it the longest continuous chain of carbons known in a natural product. Subsequently, numerous PTX-like substances have been described from various marine organisms (for detailed review, see Mundy, 2008). Homo-PTX, bishomo-PTX, neo-PTX, and deoxy-PTX were isolated and characterized from *P. tuberculosa* (Uemura et al., 1985). A compound termed Caribbean palytoxin (C-PTX) (structure not described) was isolated from Puerto Rican *Palythoa caribaeorum* (Beress et al., 1983). A compound with the same molecular weight and HPLC retention time as PTX from *P. toxica* was described from Japanese *Palythoa* aff *margaritae* (Oku et al., 2004). In addition to large (>5000 Da) polypeptide toxins, a PTX-like toxin indistinguishable by U.V., I.R., and NMR spectroscopy from PTX from *P. toxica* was described from the sea anemone *Radianthus macrodactylus* from the Seychelle Islands (Mahnir et al., 1992). Two PTX analogs were isolated from the red alga, *Chondria armata*, which was also reported to produce domoic acid (Maeda et al., 1985, as reported in Yasumoto and Murata, 1990). A PTX analog named ostreosin-D (42-hydroxy-3,26-didemethyl-19,44-dideoxypalytoxin) from the dinoflagellate *Ostreopsis siamensis* has been described to have a molecular weight of 2636 Da and a chemical formula of $C_{127}H_{220}N_3O_{53}$ (Usami et al., 1995; Ukena et al., 2001). Additional putative palytoxin analogs were later identified from *Ostreopsis* spp.; mascarenotoxins A and B from Indian Ocean *O. mascarenensis* (Lenoir et al., 2004), molecular weights between 2500 and 2535 Da, and ovatoxin-a, from Mediterranean *Ostreopsis ovata* (Ciminiello et al., 2008), molecular weight 2647 Da and molecular formula of $C_{129}H_{223}N_3O_{52}$ (both inferred from mass spectral data only). Lastly, a compound with biological activity consistent with PTX was described from an *Ostreopsis* sp. from Japan (Taniyama et al., 2003) while two compounds, ostreotoxin-1 and 3, have been described from Caribbean *Ostreopsis lenticularis* (Mercado et al., 1994). Unlike PTX, ostreotoxin 3 was later shown to be active against voltage dependent sodium channels (Menuier et al., 1997). Structural similarity to PTX has not been determined for the ostreotoxins.

## 3. Toxicity

In 1964, long before the structure of palytoxin was elucidated, Dr. Friedrich Hoffman brought a sample of Moore and Scheuer's semi-purified material from Hawaiian *Palythoa vestitus* (although this appears to be the same material described to be from *Palythoa* sp. in Moore and Scheuer (1971) and *P. toxica* in Moore and Bartolini (1981)) to the US Army Toxicology Division located at the Edgewood Arsenal of the Aberdeen Proving Grounds, Maryland, USA for further toxicological evaluation (Wiles et al., 1974). During these studies, a combination of monkeys, dogs, rabbits, guinea pigs, rats, and mice was evaluated by various routes of exposure including intramuscular, subcutaneous, intraperitoneal, intratracheal, intragastric, intrarectal, percutaneous, and ocular. Although this work was done with semi-purified material, as evidenced by the fact that the authors admit that in earlier work different batches of toxic extracts gave different animal lethality scores, this work remains the most thorough evaluation to date of the potential risks of palytoxin exposure in mammals. The average 24-h $LD_{50}$ results for the various routes of exposure for the animal species tested in these studies are summarized in Table 1. A summary of toxic effects in these animal species are provided below.

[1] The chemical formula of $C_{129}H_{221}N_3O_{54}$ ($M_r$ 2659) given for palytoxin from Tahitian *Palythoa* sp. is most likely an error and should be $C_{129}H_{221}N_3O_{53}$ which would be consistent with both the given relative molecular weight and the figure of this compound on page 2494 of Moore and Bartolini (1981).

[2] Both Moore and Bartolini (1981) and Uemura et al. (1981) report a palytoxin of the chemical formula $C_{129}H_{223}N_3O_{54}$ from Hawaiian *P. toxica* and Japanese *P. tuberculosa*, respectively, but Moore and Bartolini (1981) report a relative molecular weight ($M_r$) of 2677 while Uemura et al. (1981) report a molecular mass (MW) of 2680.168 Da. The difference in the units used explains this apparent inconsistency.