

Effects in Humans and Animals from Exposure to Palytoxins

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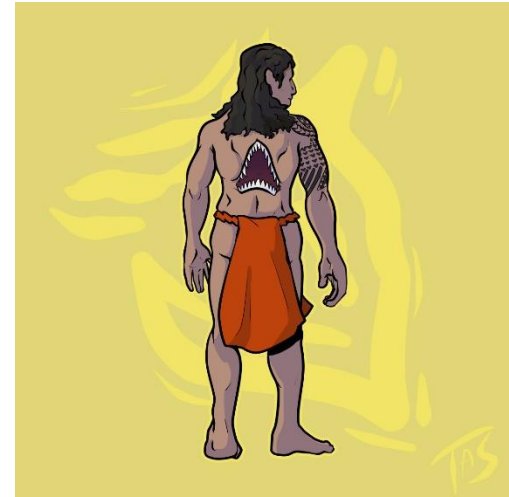
Palytoxin Discovery

1961: Palytoxin described from zoanthid *Palythoa toxica*

- Ancient Hawaiian legend: “Limu-make-o-Hana” Deadly Seaweed of Hana (Moore & Scheuer 1971)

1981: Structure elucidated (Moore & Bartolini 1981; Uemura et al. 1981)

1989: Synthesized (Armstrong et al. 1989)



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Palytoxin Discovery



KA LIMU MAKE O MUOLEA.

E KA LUNAHOOPOPOHO : Aloha oe :—

E 'ae oho'olu mai ia'u e hoike aku i kekahi mau mea e pili ana i ka Limu make o Muolea ma Hana, Maui Hikian.

I ka manawa kahiko, aole no i ulu loa elike me ko keia manawa ia manawa, aole no i maopopo i na kamaaina e no ho koke ana maia mau kabeka he mea make keia, aka eia ka mea i keia; I ka wa e h-le ai na kamalii maia mau kabeka i ka hohonu ina ohua (ia) a ai ae ina nui ka ai ana i na ohua, e ponioniu uanei a waiho a make ma na kabeka, a anai ia i ka laau, ulaila e pohola hou mai no.

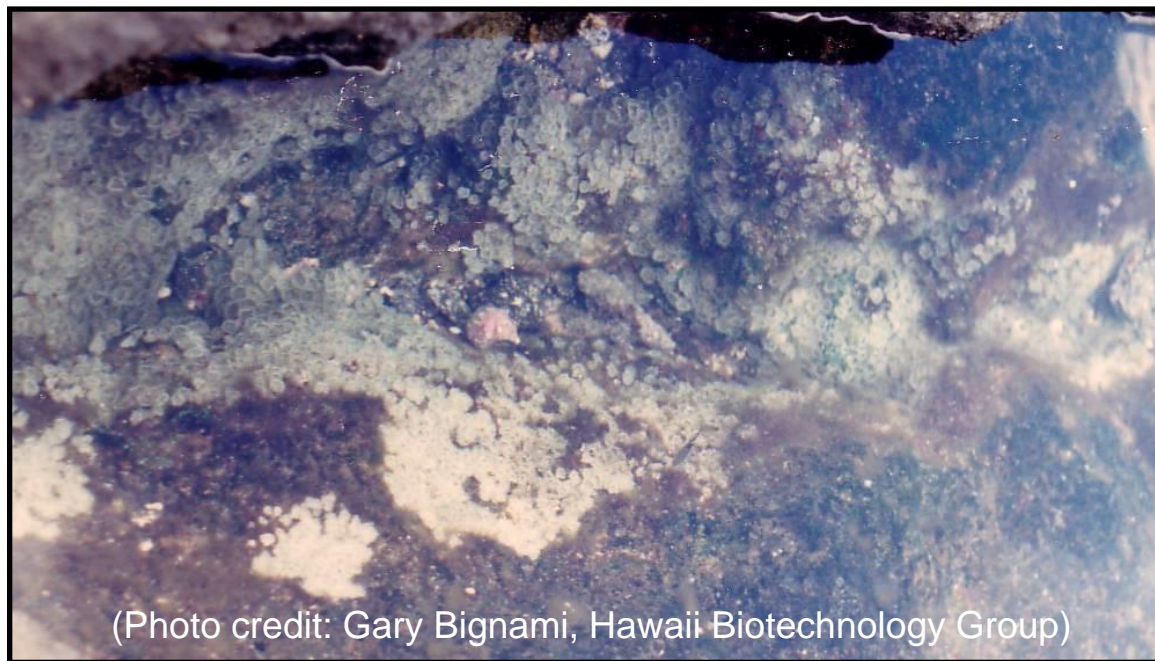
No keia mea ua 'hookapu loa ia na kamaaina oia mau wahi, aole e hele wale kekahi mea ma'aila me ke kuleana ole.

Me ka mahalo i na keiki nelele hua kerua o ka piri pi me ka Luna Hooponopone ko'u aloha.

ABR. KAHI.

Muolea Hana, Aug. 11, 1877.

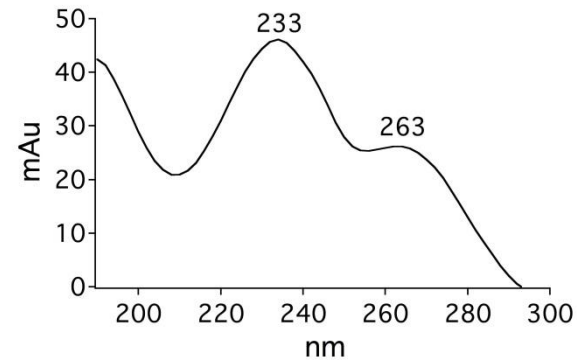
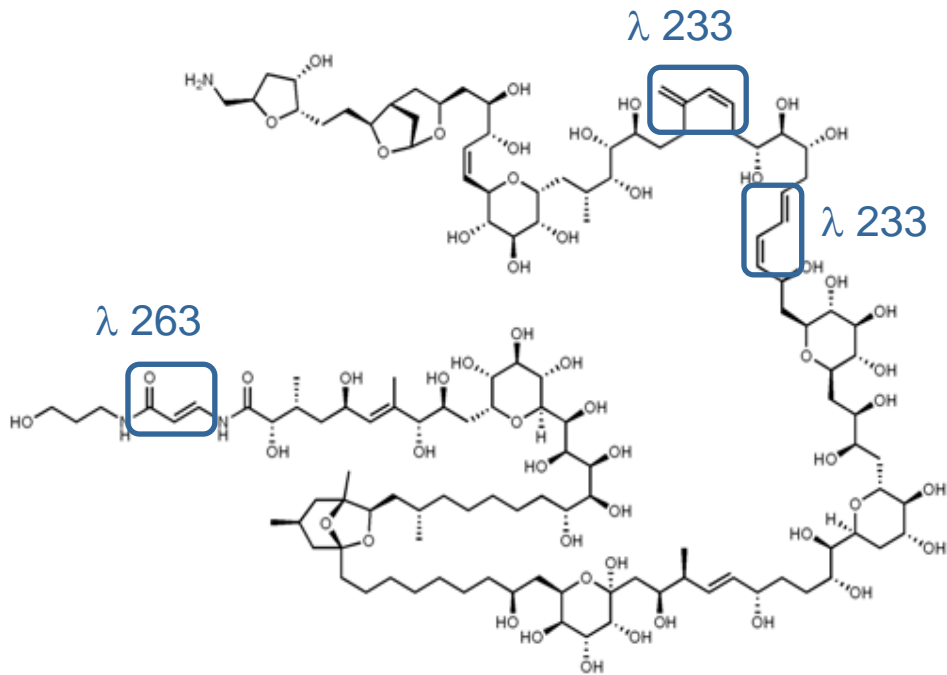
Letter to the editor:
Newspaper *Ka Lahui Hawaii*
August 23, 1877



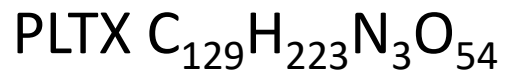
(Photo credit: Gary Bignami, Hawaii Biotechnology Group)

Palythoa toxica in the “shark” tidepool at Mū’olea,
Hāna, east Maui 1987-1990

Palytoxin

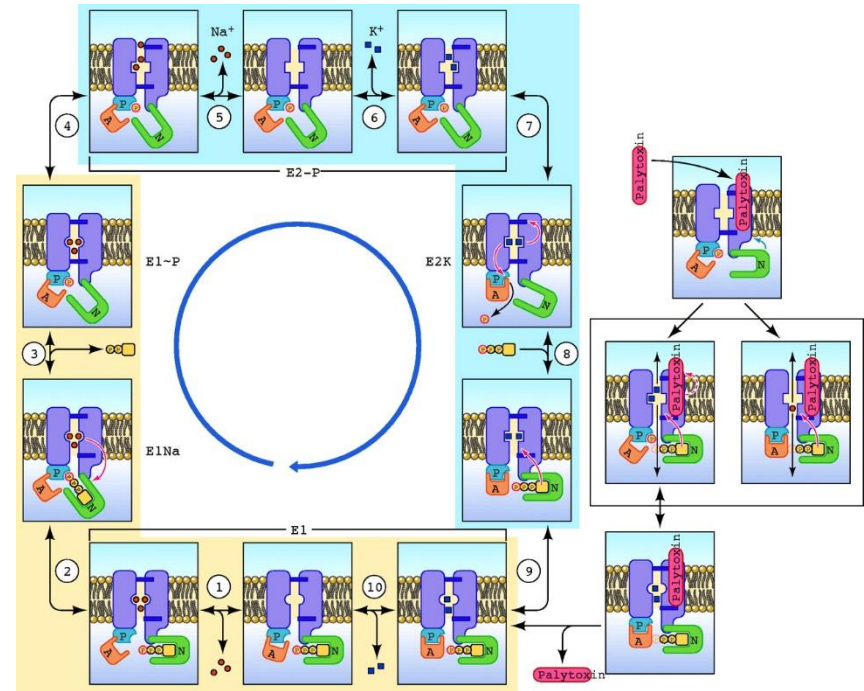


UV Spectra



Toxic Properties

- i.p. LD₅₀ 100-400 ng/kg
- >100-fold less toxic by intragastric administration
- 10-fold less toxic by intratracheal administration
- Potent tumor promoter (non TPA-type)
- Delayed hemolysis with large pre-lytic K⁺ release
- Blockable by ouabain
- Cytotoxic to all cell types



(Horisberger 2004)

Mechanism of PLTX Lethality *In Vivo* (Munday 2011)

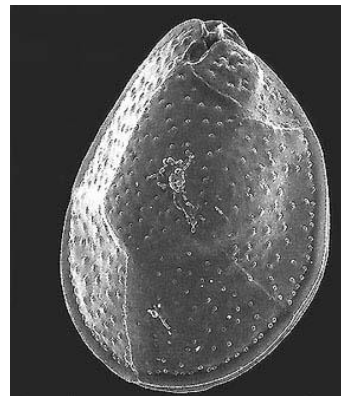
- Acute mortality (minutes)
 - Severe coronary vasoconstriction with subsequent cardiac failure
 - Myocardial ischemia
 - Dilation of the right ventricle from pulmonary hypertension
 - Protection from injection of vasodilators
 - No protection from ventilatory support
- Delayed mortality (hours)
 - Progressive ascending paralysis and decreased respiratory rate
 - Increases in CPK, LDH, ALT, and AST
 - Inflammation
 - Internal bleeding, oedema, erosion, and necrosis in multiple organs

Palytoxin-like Toxins in Dinoflagellates

***Ostreopsis* spp.**

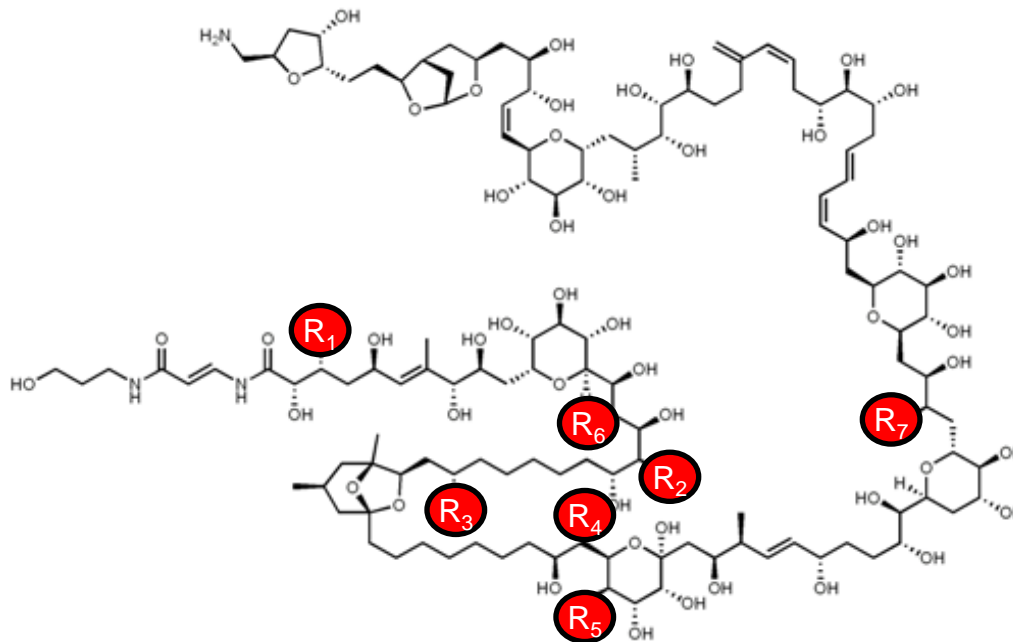
- o Tropical
- o Benthic/epiphytic
- o Occasionally tycooplanktonic
- o 50-175 μm diameter

- *O. lenticularis* - Pacific, Gambier Islands
- *O. heptagona* - Caribbean, Florida Keys
- *O. mascarenensis* - Indian Ocean, Caribbean Sea
- *O. ovata* - Pacific Ocean, Mediterranean Sea
- *O. siamensis* - Pacific Ocean, Indian Ocean, Caribbean Ocean, Florida Keys



(Faust & Morton, 1995)

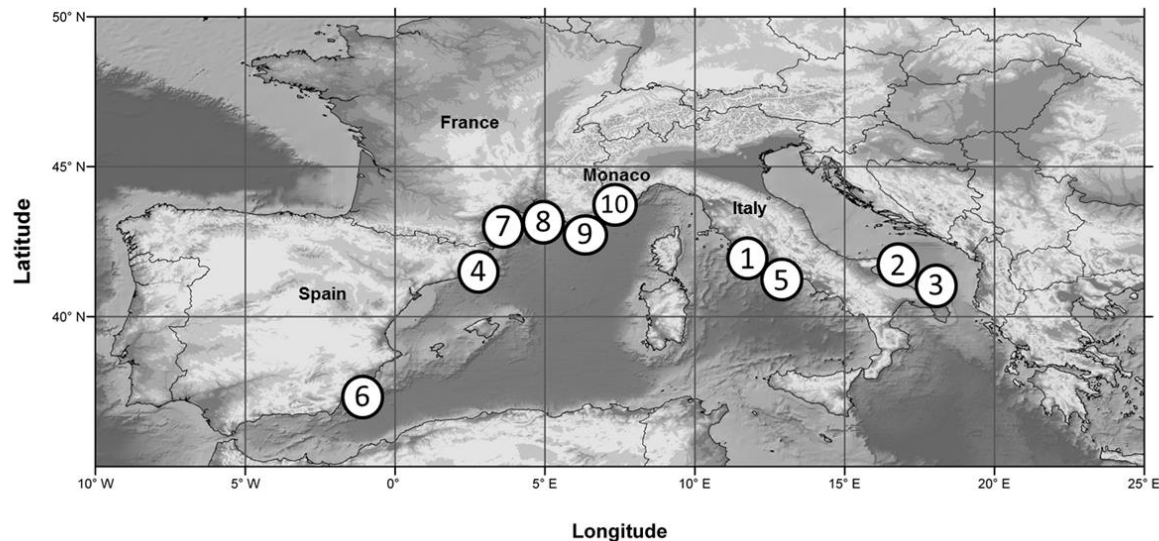
Major Palytoxin Derivatives



	R1	R2	R3	R4	R5	R6	R7
Palytoxin	Me	OH	Me	H	OH	OH	OH
42-OH-Palytoxin	Me	OH	Me	OH	OH	OH	OH
Ostreocin-D	H	H	H	OH	H	OH	OH
Ovatoxin-a	Me	OH	Me	OH	H	H	H

(Adapted from Pelin et al. 2016)

Algal Syndrome Reports (1998-2010)



	Location / Year(s)	Reference		Location / Year(s)	Reference
1	Italy / 1998, 2000, 2001	Sansoni et al. 2003	6	Spain / 2006	Barroso García et al. 2008
2	Italy / 2001	Di Turi et al. 2003	7	France / 2006	Kermarec et al. 2008
3	Italy / 2003, 2004	Gallitelli et al. 2005	8	France / 2008	Tichadou et al. 2010
4	Spain / 2004	Kermarec et al. 2008	9	France / 2008	Tichadou et al. 2010
5	Italy / 2005, 2006	Durando et al. 2007	10	Monaco / 2008	Tichadou et al. 2010

Algal Syndrome Definition (Durando et al. 2007)

- Proximity to the sea during an *Ostreopsis* spp. algal bloom
- Seeking medical care
- ≥ 2 of the following signs/symptoms



www.lamonde.fr

1. Local dermatitis
2. Systemic cutaneous rash
3. Numbness or weakness of the extremities
4. Dizziness
5. Myalgia
6. Chest pain
7. Difficulty breathing
8. Fever
9. Neurological disorders

Palytoxin Poisoning from Seafood

**Federated States of
Micronesia (1985)**



Triggerfish (*Melichtys vidua*)
(Fukui et al. 1987)

Japan (1986)



Parrotfish (*Scarus ovifrons*)
(Noguchi et al. 1987)

Japan (2000)



Grouper (*Epinephelus* sp.)
(Taniyama et al. 2002)

Hawaii (1986)



Scad (*Decapterus macrosoma*)
(Kodama et al. 1989)

Madagascar (1994)



Herring (*Herklotsichtys quadrimaculatus*)
(Onuma et al. 1999)

Symptoms of Palytoxin Exposure

Cutaneous	Inhalational	Oral
Rash	Cough/sore throat	Malaise
Numbness or weakness of the extremities	Nausea or vomiting	Nausea, vomiting, and/or diarrhea
Dyspnea	Dyspnea	Dyspnea
Myalgia	Rhinorrhea	Myalgia
Fever	Fever	Elevated CPK
Chest pain	Headache	Cardiac dysfunction
Dizziness	Lacrimation	
Neurological dysfunction	Rash	

(Tubaro et al. 2011)

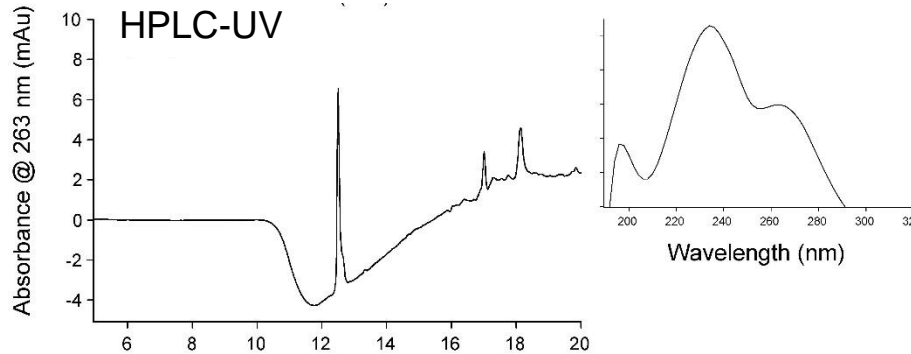
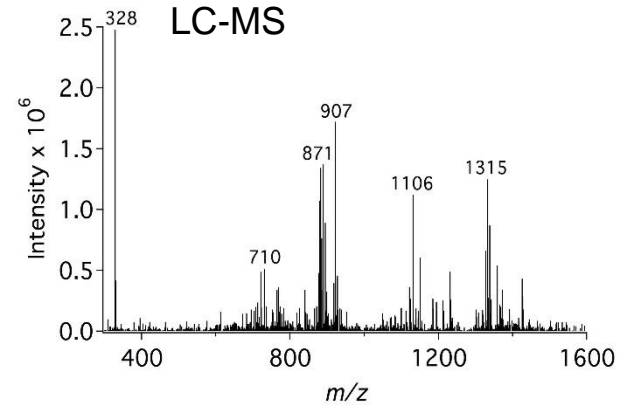
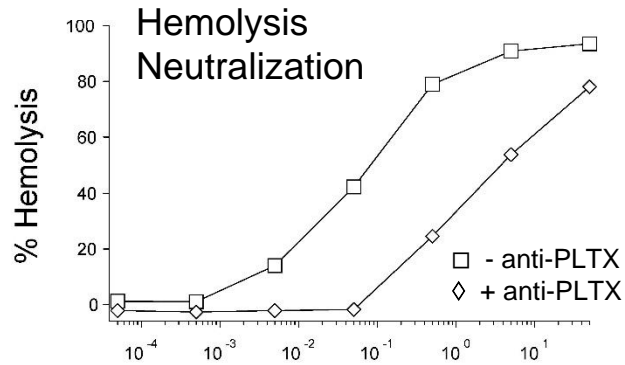
U.S. Aquarium Poisonings (2006-2007)

- **2006: Cutaneous exposure**
 - Chest pain, weakness, elevated heart rate and blood pressure
 - Elevated CPK, hospitalized
 - PLTX not confirmed
- **2007: Inhalational exposure**
 - 20 min: rhinorrhea, coughing
 - 4 hrs: difficulty breathing, chest pain, severe fits of coughing, hospitalized
 - PLTX confirmed by multiple methods



(Deeds & Schwartz 2010)

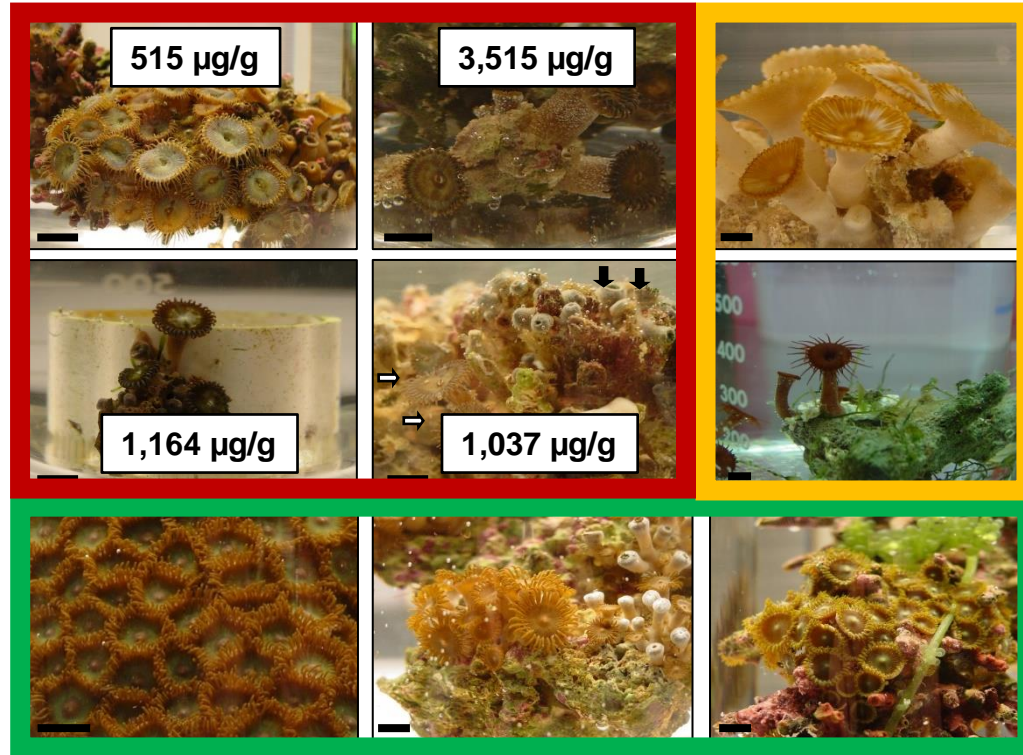
2007 Inhalational Exposure



613 µg PLTX/g ww

(Deeds & Schwartz 2010)

Aquarium Store Survey (2011)



None detected



Detected by hemolysis assay



Detected by hemolysis assay, HPLC-UV, HRMS

(Deeds et al. 2011)

Home Aquarium Exposure (2012)

- Scrubbing rocks under hot running water to remove zoanthids
- Admitted to hospital with uncontrolled coughing, bloody sputum, chills, and vomiting
 - Six days in intensive care unit
 - Prolonged symptoms
 - Additional family also effected
- 3,000-5,000 μg PLTX/g in samples sent by owner



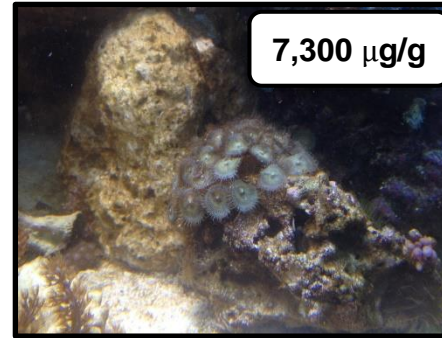
Occupational Exposure (2012)

Patient	Acute Symptoms	Laboratory Findings	Chronic Symptoms
¹ Aquarium technician	Nausea, cough, bitter taste, choking sensation	Fever, tachypnea, tachycardia, leukocytosis	Dyspnea, impaired cognition and memory, dizziness, poor balance
² Homeowners	Nausea, vomiting	NA	NA
² Child #1 (3 years old)	Nausea, vomiting, cough, sleepiness	Fever, leukocytosis, elevated LDH, hyperphosphatemia, proteinuria	NA
² Child #2 (2 months old)	Vomiting, sleepiness	Fever, leukocytosis, elevated LDH/AST/ALT, hyperkalemia, hyperphosphatemia, proteinuria,	NA

(¹ Chang et al. 2020; ² Rumore & Houst 2014)

Case Series Alaska 2012-2014 (Hamade et al. 2015)

- 10 cases identified
 - 5 recreational/5 occupational
 - 3 reported multiple exposures
- 3 hospitalizations
 - 2 requiring intensive care



Most Commonly Reported Symptoms			
Tremors	100%	Dyspnea	70%
Fever	90%	Joint/Muscle Pain	70%
Weakness	80%	Paresthesia	50%
Bitter Metallic Taste	80%	Nausea	50%

Toxicity of palytoxin congeners after aerosol administration in rats (Poli et al. 2018)

24 hr LD₅₀ – Aerosol Administration

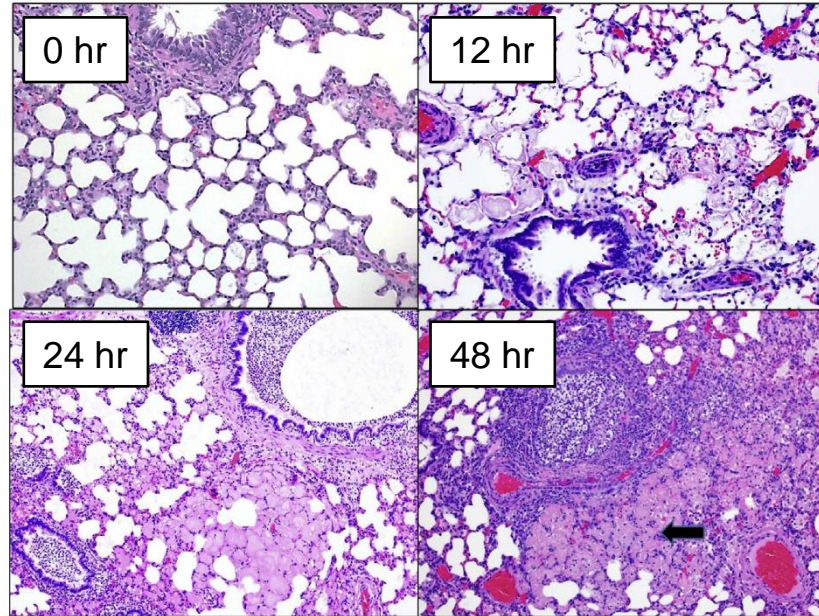
Toxin	Source	LD ₅₀ (µg/kg)
PLTX	<i>P. tuberculosa</i> (Wako, Japan)	0.041 (0.032-0.052)
42-OH-PLTX	<i>P. toxica</i> (Hawaii)	0.045 (0.037-0.055)
50:50 mix	<i>P. tuberculosa</i> (Hawaii)	0.063 (0.053-0.078)
Ovatoxin-a	<i>O. ovata</i> (Japan)	0.031 (0.025-0.039)

24 hr LD₅₀ – Comparative Routes

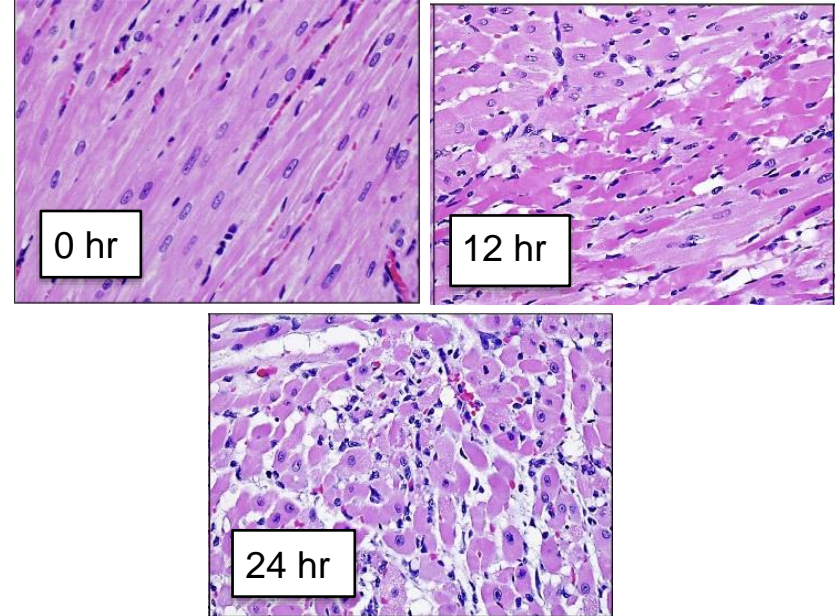
Route	LD ₅₀ (µg/kg)	Reference
Intravenous	0.089 (0.080-0.098)	Wiles et al. 1974
Intraperitoneal	0.63 (0.44-0.91)	Wiles et al. 1974
Oral (mice)	510 (311-809)	Munday 2006
Intratracheal	5-7.5	Ito et al. 2009

Sublethal Effects of Aerosol Exposure

Effect on Lung Tissue



Effect on Myocardium



(Poli et al. 2018)

Ornamental Aquatic Trade Association Guidance - 2018

Recommendations to reef aquarists on how to prevent palytoxin poisoning

- **DO NOT** pour boiling/hot water over live rock/zoantharian colonies;
- **DO NOT** microwave live rock/coral frag plugs;
- **DO NOT** pressure (steam) clean aquarium ornaments or rock which may have been colonised by zoantharians;
- **DO NOT** wash live rock under running water/using a water sprayer (especially if using a brush as well).



It should also be borne in mind that live rock containing palytoxin producing zoantharians which is left outside to dry and not treated with household bleach has the potential to remain highly toxic for years.

suspect palytoxin poisoning
 signs of palytoxin poisoning following exposure either via the skin, eyes or
 38°C), cough, headache, difficulty breathing, sore throat, runny nose,
 heart rate, skin redness/itch, swelling, numbness/tingling, muscle pain,
 eye sensitivity to light and conjunctivitis. Additional indicators may
 include a foul smell or a bitter/metallic taste in the mouth.
 Note that currently there have been NO fatal cases involving marine
 palytoxin poisoning recorded. However, the symptoms of palytoxin
 poisoning develop quickly following exposure. If you suspect palytoxin poisoning
 you should seek urgent medical attention and advise medical staff that you
 suspect palytoxin poisoning is suspected.
 Palytoxin is inactivated by household bleach (sodium hypochlorite). Regular
 household bleach is typically sold at a concentration of 5% sodium
 hypochlorite. A suitable solution for cleaning aquarium equipment is
 one part household bleach to nine parts water. Surfaces/equipment
 which have had contact with palytoxin can be cleaned using the 1:9 bleach to water
 solution. Be aware that household bleach can give off chlorine gas and should therefore
 never be used in addition with other household cleaners and should be used in a well
 ventilated area.
 Thank Julian Sprung of Two Little Fishies, USA for providing detailed
 advice in relation to zoantharians and palytoxin. OATA also wishes to
 thank the Marine Centre, UK for providing advice.
 OATA is also grateful to Health Protection Scotland, NHS Lothian, City of Edinburgh
 Council and the Scottish Government for providing public health and toxicological advice.
 Palytoxin is a common Palythoa species. Image courtesy of Julian Sprung.

Handling of marine animals
 The greatest risk of palytoxin poisoning comes from exposing the slime coating

the water. First, suitable personal protective equipment must be worn i.e. safety glasses/
 goggles, gloves and a respirator face mask which covers the nose and mouth. If you
 wish to keep the zoantharian colony alive, it should be transferred to another aquarium.

which have had contact with palytoxin can be cleaned using the 1:9 bleach to water
 solution. Be aware that household bleach can give off chlorine gas and should therefore
 never be used in addition with other household cleaners and should be used in a well

Aquarists may undertake activities in an effort to sterilise live rock/coral frags or to
 clean live rock/aquarium ornaments or to shrink/kill coral colonies which inadvertently
 increase the risk of palytoxin poisoning by increasing the likelihood for the toxin to
 become aerosolised. We therefore recommend that the following activities should be
AVOIDED:

Under 'normal' circumstances, activated carbon will help to maintain the aquarium
 water free of palytoxin. However, bear in mind that activated carbon cannot remove
 large pulses of palytoxin entering the water and that some Palythoa species can grow
 into large colonies very quickly. It should also be borne in mind that activated carbon
 needs to be changed frequently.

Summary

- Palytoxins cause illness from cutaneous, inhalational, and oral exposure
 - Multiple sources
 - Symptoms differ by route of exposure
 - Lethal dose differs by route of exposure
- Home and commercial aquaria are a significant source of exposure
- Oral exposures rare and least potent route but mortalities have occurred



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Acknowledgements

- **Mark Poli, Keersten Ricks, Scott Olschner**
 - USAMRIID, USA
- **Gary Bignami**
 - Hawaii Biotechnology Group, USA
- **John Roberts**
 - University of Florida, USA
- **Ali Hamade**
 - Alaska Division of Public Health, USA
- **Kenneth Spaeth, Emily Chang**
 - Hofstra Northwell School of Medicine, USA



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