



**SITOX**

# 20° Congresso Nazionale

Società Italiana di Tossicologia

**Sostanze  
di origine naturale:  
farmaci, veleni o entrambi**

**BOLOGNA** 25-26-27 Ottobre 2021

[www.sitox.org](http://www.sitox.org)

# Un noto veleno con potenzialità terapeutiche: la tetrodotossina

Dr. Marco Pelin

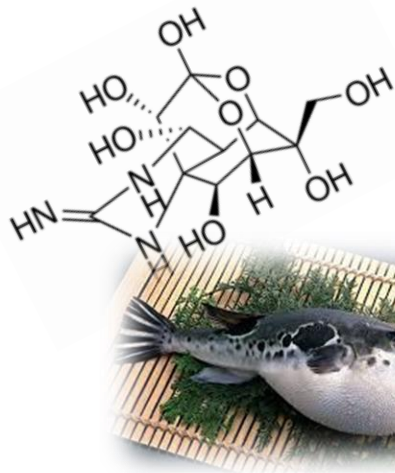
Università di Trieste – Dipartimento di Scienze della Vita



UNIVERSITÀ  
DEGLI STUDI  
DI TRIESTE

Dipartimento di  
Scienze della Vita



July  
2016Horizon Scanning Research  
& Intelligence Centre

## Tetrodotoxin for moderate to severe, inadequately controlled cancer-related pain

### LAY SUMMARY

Cancer-related pain can arise from both ongoing tissue damage and treatments such as surgery or radiotherapy. Many patients use opioid-based pain killers to manage cancer-related pain but often they do not have complete pain relief.

Tetrodotoxin is a new drug that blocks pain transmission. It is reported to be a well-tolerated, more potent analgesic than aspirin and morphine, and a non-addictive alternative to opioids.

If licensed, tetrodotoxin will offer an additional treatment option for patients with cancer-related pain who may have few, well-tolerated and effective therapies.

NIHR HSRIC ID: 5173

*This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.*

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

NIHR Horizon Scanning Research & Intelligence Centre,  
University of Birmingham, Email: [horizonscanning@bham.ac.uk](mailto:horizonscanning@bham.ac.uk)  
Web: [www.hsrhc.nihr.ac.uk](http://www.hsrhc.nihr.ac.uk)

**NIHS**  
National Institute for  
Health Research

# La tetrodotossina

**Tetrodotossina (TTX):** termine derivante dal nome **Tetraodontidae** della famiglia di appartenenza del pesce palla (*Takifugu rubripes*), in cui è stata inizialmente identificata la tossina

## Ordine Tetraodoniformes:

Include 2 sotto-ordini, 10 famiglie, 93 generi and 430 specie

**Ampia distribuzione:** da zone tropicali a temperate

## Organismi produttori:

batteri endosimbionti  
(*Vibrio* sp., *Pseudomonas* sp., *Photobacterium* sp., *Aeromonas* sp.,  
*Alteromonas* sp., *Bacillus* sp., *Micrococcus* sp., *Acinetobacter* sp.)



# La tetrodotossina

Intossicazioni da ingestione di pesce palla contaminato: *fugu*

## SINTOMI INIZIALI:

intorpidimento delle labbra e della lingua (10-45 min)

## SINTOMI SECONDARI:

parestesia al viso ed alle estremità, cefalea,  
dolore gastrico, nausea e vomito

## SINTOMI TERZIARI:

paralisi e morte per insufficienza respiratoria (4-6 ore)



# La tetrodotossina

## Intossicazioni da ingestione di pesce palla contaminato: *fugu*

Table B.1: Case reports of TTX poisoning

Location (year)	Implicated food	No of cases	Fatalities	TTX concentration	Reference
Taiwan (1988-1995)	Pufferfish, gastropods, goby fish	20 incidents involving 52 cases (27 M, 21 F, 4 not specified)	7	NR	Yang et al. (1996)
China 1977-1988 and 1998-2001	Gastropods: <i>Zeuxis sampllicutus</i>	42 incidents involving 309 cases	16	50-300 (in snails inducing death; calculated in the paper using 1 MU = 0.18 µg TTX)	Shui et al. (2003)
Cox's Bazar district, Bangladesh (1998)	Pufferfish roe	8	5	11.8-21.3 MU/g in the skin, 2.8-4.9 MU/g in the muscle, < 2-5.9 MU/g in the liver, < 2-3.6 MU/g in the testis, 24.5-323.8 MU/g in the ovary and 12.8-46.3 MU/g in the viscera (except liver) 2	Mahmud et al. (1999)
Bangladesh (1988-1996)	Pufferfish	10 outbreaks involving 55 cases	17	< 4 MU/g assumed from data reported earlier by Zaman et al. (1997)	Mahmud et al. (2000)
New South Wales, Australia (2001-2002)	Pufferfish	11	-	NR	Isbister et al. (2002)
Taiwan (2001)	Gastropods: <i>Zeuxis sufflatus</i> and <i>Niotha clatharata</i>	4	-	<i>Z. sufflatus</i> : 586 MU (~ 104 µg) <i>N. clatharata</i> : 254 MU (~ 58 µg) (mean per specimen)	Hwang et al. (2002)
South Zhejiang, China	Gastropod: <i>Zeuxis sampllicutus</i>	31 (18 M, 13 F)	-	111 ± 45 MU (mean ± SD) 1	Sui et al. (2002)
Taiwan (2001)	Pufferfish	6	1	NR	How et al. (2003)
Kaohsiung City, Taiwan (2002)	<i>Nassarius papillosus</i> and <i>N gruneri</i> gastropods	2 (1 M, 1 F)	-	<i>N papillosus</i> - 320 MU/g <i>N gruneri</i> - 386 MU/g	Liu et al. (2004)
Australia (2004)	Toadfish	7 (5 M, 2 F)	-	NR	O'Leary et al. (2004)
Tungsa Island, Taiwan (2004)	Gastropod: <i>Nassarius glans</i>	6 (22-48 y)	2	5,188 ± 1,959 MU/specimen [1 MU = 0.178 µg]	Hwang et al. (2005)
Taiwan (2001)	Unknown fish	6	1	NR	Tsai et al. (2006)
Haifa, Israel (NR)	Puffer fish	2 (1 M, 1 F)	-	NR	Bentur et al. (2007) (abstract only)
Khulna, Bangladesh (2005)	Pufferfish liver	6 (3 M, 3 F, aged 4-35 years)	0	NR	Chowdhury et al. (2007a)
Bangladesh (2001-2006)	Pufferfish	53	8	NR	Chowdhury et al. (2007b)
Taiwan (2005)	Gastropod	1	0	42-60 mg/kg; STX: 3-6 mg/kg	Jen et al. (2007)



# La tetrodotossina

## Intossicazioni da ingestione di pesce palla contaminato: *fugu*

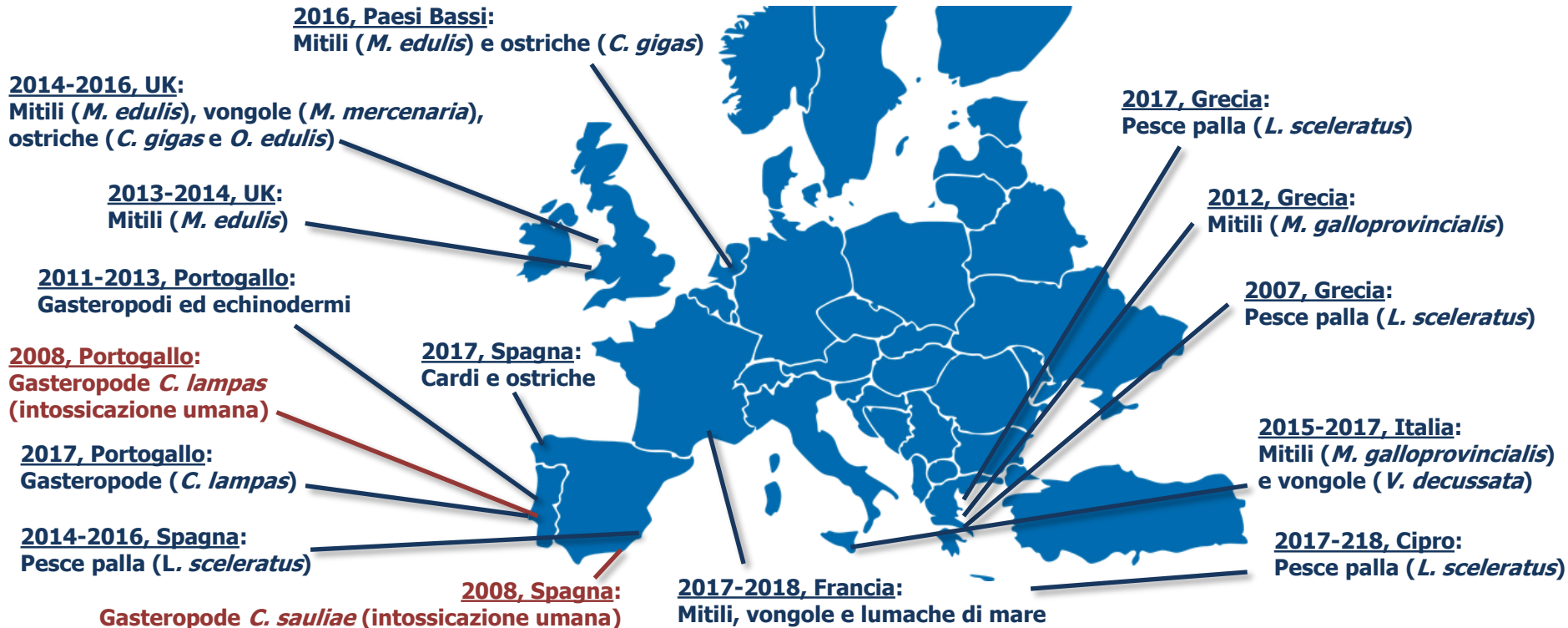
Location (year)	Implicated food	No of cases	Fatalities	TTX concentration	Reference
Burla, India (2007)	Pufferfish	8	2	NR	Behera et al. (2008)
Kaohsiung, Taiwan (2006)	Gastropod: <i>Niotha clathrata</i>	3	–	0.009-0.088 mg/specimen	Jen et al. (2008)
Chicago, USA (NR)	Pufferfish	2 (1 M, 1 F)	–	NR	Thompson et al. (2008)
Malaga, Spain (NR)	Trumpet shellfish ( <i>Charonia lampas sauliae</i> )	1 (M, aged 49 years)	–	249 mg/kg	Fernandez-Ortega et al. (2010)
Narshingdi, Dhaka and Naore districts, Bangladesh (2008)	'Large marine pufferfish'	63 (32 M, 31 F, median age 25 years)	14	NR	Homaira et al. (2010)
French Guyana (NR)	Unknown fish	3 (2 M adults + 1 child age 2 years)	1 (adult)	NR	Villa et al. (2010) (abstract only)
Maiskhal, Bangladesh (2008)	Pufferfish eggs	6	2 (4-50 years)	NR	Islam et al. (2011)
Japan (1957-2008)	Gastropods	6 outbreaks involving 11 cases	3	4,290 MU/g reported for one of the incidents	Noguchi et al. (2011b)
Japan (1995-2010)	Pufferfish	477 outbreaks involving 698 cases	40	NR	Noguchi et al. (2011a)
Taiwan (2004)	Gastropod: <i>Nassarius glans</i>	5	2	NR	Noguchi et al. (2011a)
Korea (2010)	Unknown fish	3	1	NR	Cho et al. (2012)
Taiwan (1988-2011)	Pufferfish > gastropod > goby	192	22	Data reported for 3 outbreaks: 525 MU/g in fish; 1,100 MU/g in unidentified fish roe; 3,450 MU/g in adulterated mullet roe <sup>(a)</sup>	Lin and Hwang (2012)
Singapore (NR)	Dried pufferfish	1 M	–	NR	Phua (2013)
Duque de Caxias City, Brazil (NR)	Spotted pufferfish	11	–	NR	Simões et al. (2014)
Taipei, Taiwan (2010)	Octopus <i>Haplochaena fasciata</i>	2 M	–	118 ± 7.5 µg (mean ± SD) per specimen	Wu et al. (2014)
Minneapolis, USA (2014)	Dried pufferfish	4 (1 M, 2 F, 2 not specified)	–	Mean 19.8 µg/g (range 5.7-72.3 µg/g)	Cole et al. (2015)

NR: not reported; M: male; F: female; MU: mouse unit; SD: standard deviation.

(a): Toxins identified by chemical assays, but quantified data were not provided.





# Rilevamento della tetrodotossina in EU





# La tetrodotossina in EU

La distribuzione geografica di TTX e degli organismi produttori sembra associata ai **cambiamenti climatici**

	climate change	confidence level	
Impact	Climate change may moderately aggravate the impact of the considered hazard with respect to the reference condition (Delta value: 0.228)	Medium (Variance: 0.905)	
Likelihood	Climate change may mildly increase the likelihood of emergence of the issue with respect to the reference condition (Delta value: 0.248)	Low (Variance: 0.895)	

*The explanation and full scale of the symbols can be found in section 3.3.4 of the report.*

## Outcome

Climate change may moderately aggravate the impact and mildly increase the likelihood of emergence. In the near future scenario, the impact is expected to be moderate (59% probability for moderate or lower impact) and the issue will be likely to emerge (47% probability of a likelihood of emergence > 66%).

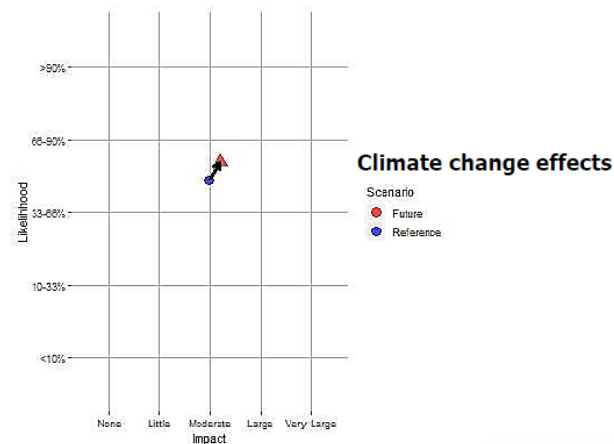
## Climate change and food safety

APPROVED: 11 June 2020

doi:10.2903/sp.efsa.2020.EN-1881



## Climate change as a driver of emerging risks for food and feed safety, plant, animal health and nutritional quality

European Food Safety Authority (EFSA),  
Angelo Maggiore, Ana Afonso, Federica Barrucci, Giacomo De Sanctis



# La tetrodotossina in EU

Possibile causa: diffusione di *Vibrio parahaemolyticus*  
(crescita influenzata dalla temperatura del mare)

	climate change	confidence level	
Impact	Climate change may seriously aggravate the impact of the considered hazard with respect to the reference condition (Delta value: 0.361)	High (Variance: 0.62)	
Likelihood	Climate change may moderately increase the likelihood of emergence of the issue with respect to the reference condition (Delta value: 0.606)	High (Variance: 0.327)	

*The explanation and full scale of the symbols can be found in section 3.3.4 of the report.*

## Outcome

Climate change may seriously aggravate the impact and may moderately increase the likelihood of emergence. In the near future scenario, the impact is expected to be moderate (59% probability for moderate or lower impact) and the issue will be likely to emerge (96% probability of a likelihood of emergence > 66 %).

## Climate change and food safety

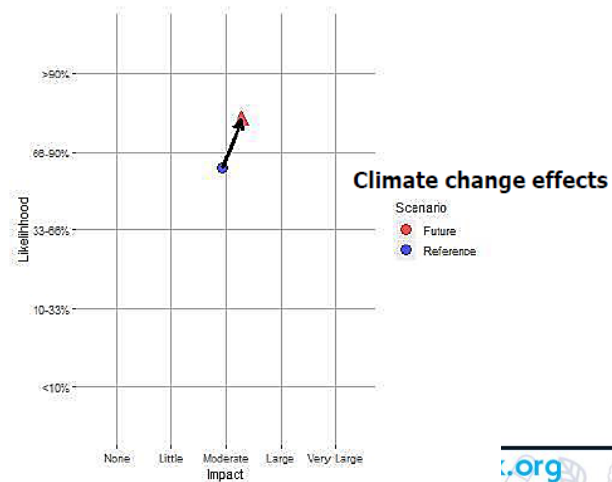
APPROVED: 11 June 2020

doi:10.2903/sp.efsa.2020.EN-1881

## Climate change as a driver of emerging risks for food and feed safety, plant, animal health and nutritional quality

European Food Safety Authority (EFSA),

Angelo Maggiore, Ana Afonso, Federica Barrucci, Giacomo De Sanctis



# La tetrodotossina: dati tossicologici

Dati epidemiologici nell'uomo suggeriscono che dosi di 4-42  $\mu\text{g}/\text{kg}$  possono indurre tossicità in seguito ad esposizione acuta

Uno studio di tossicità acuta *per os* nel topo ha individuato una **NOAEL** di **75  $\mu\text{g}/\text{kg}$**  (Abal et al., 2017)

Considerata la numerosità degli animali, la dose più bassa (25  $\mu\text{g}/\text{kg}$ ) è stata scelta come riferimento, derivando una **ARfD** di **0.25  $\mu\text{g}/\text{kg}$**

Considerando una porzione alimentare pari a 400 g e un peso medio di una persona pari a 70 kg, è stato calcolato un livello di sicurezza pari a **44  $\mu\text{g}$  di TTX-equivalenti/kg parti edibili**

## SCIENTIFIC OPINION



ADOPTED: 15 March 2017

doi: 10.2903/j.efsa.2017.4752

### Risks for public health related to the presence of tetrodotoxin (TTX) and TTX analogues in marine bivalves and gastropods

EFSA Panel on Contaminants in the Food Chain (CONTAM),  
Helle Katrine Knutsen, Jan Alexander, Lars Barregård, Margherita Bignami, Beat Brüscheweiler,  
Sandra Ceccatelli, Bruce Cottrill, Michael Dinovi, Lutz Edler, Bettina Gras-Kraupp,  
Christer Hogstrand, Laurentius (Ron) Hoogenboom, Carlo Stefano Nebbia, Isabelle P. Oswald,  
Martin Rose, Alain-Claude Roudot, Tanja Schwerdtle, Christiane Vleminckx, Günter Vollmer,  
Heather Wallace, Nathalie Arnich, Diane Benford, Luis Botana, Barbara Viviani, Davide Arcella,  
Marco Binaglia, Zsuzsanna Horvath, Hans Steinkellner, Mathijs van Manen and  
Annette Petersen

# La tetrodotossina: dati tossicologici (*updates*)

Studio di tossicità acuta nel topo, in seguito a somministrazione orale di TTX o SXT, singole o in miscela

Somministrazione orale via *gavage* o mediante *feeding*

**TTX**: considerando come dose di riferimento quella inferiore alla NOAEL (1010 nmoli/kg), una porzione alimentare di 400 g e un peso corporeo medio di 70 kg, è stato calcolato un livello di sicurezza pari a **560 µg di TTX-equivalenti/kg parti edibili**

**TTX e SXT singole**: LD<sub>50</sub> e NOAEL sovrapponibili

**TTX e SXT in miscela**: probabile **effetto additivo**



*toxins*



Article

## The Acute Toxicity of Tetrodotoxin and Tetrodotoxin–Saxitoxin Mixtures to Mice by Various Routes of Administration

Sarah C. Finch<sup>1,\*</sup>, Michael J. Boundy<sup>2</sup> and D. Tim Harwood<sup>2</sup>

<sup>1</sup> AgResearch Limited, Ruakura Research Centre, Private Bag 3123, Hamilton 3240, New Zealand

<sup>2</sup> Cawthron Institute, Private Bag 2, Nelson 7042, New Zealand; michael.boundy@cawthron.org.nz (M.J.B.); tim.harwood@cawthron.org.nz (D.T.H.)

\* Correspondence: sarah.finch@agresearch.co.nz

Received: 8 October 2018; Accepted: 19 October 2018; Published: 23 October 2018



Compound	LD <sub>50</sub> by Gavage (nmol/kg) <sup>1</sup>	Predicted LD <sub>50</sub> by Feeding	LD <sub>50</sub> by Feeding (nmol/kg) <sup>1</sup>	NOAEL by Feeding (nmol/kg) <sup>1</sup>
STX	1237 (1056–1630)		2850 (2468–3390)	1270 (1189–1470)
TTX	1890 (1669–2120)		2850 (2475–3410)	1294 (888–1480)
STX/TTX (1:2)	ND	2850	3532 (3016–7830)	ND
STX/TTX (1:1)	ND	2850	2850 (2382–3280)	ND
STX/TTX (2:1)	ND	2850	2850 (2475–3410)	ND

<sup>1</sup> Figures in brackets indicate 95% confidence limits; ND, Not determined.

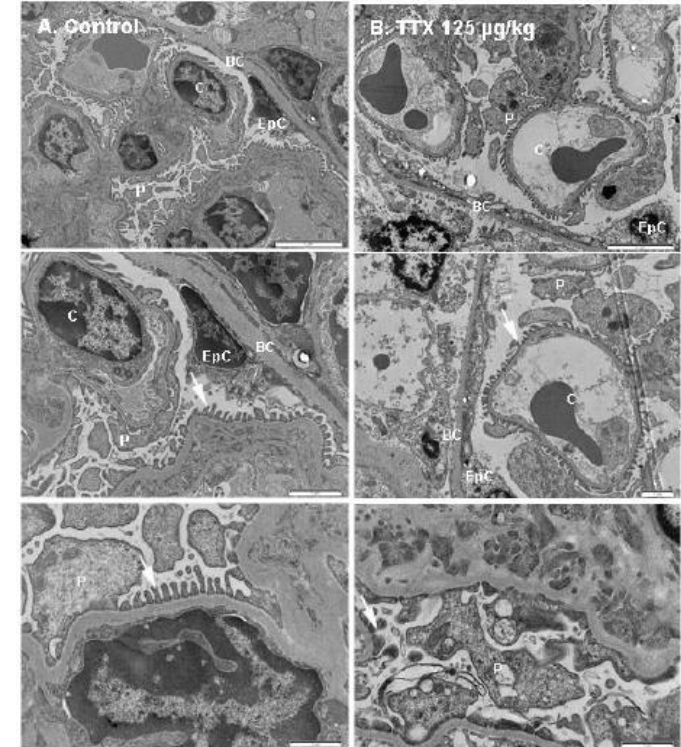
# La tetrodotossina: dati tossicologici (*updates*)

Tossicità nel topo in seguito a somministrazione orale di TTX ripetuta per 28 giorni

Dose ( $\mu\text{g}/\text{kg}$ )	Total Mice	Dead	Survival Time (Days)	Mortality %
Control	5	0	28	0
25	3	0	28	0
75	4	2	1, 5, 28, 28	50
125	5	2	3, 7, 28, 28, 28	40

Principali effetti:

- Riduzione della quantità di urina;
- Alterate caratteristiche dell'urina (torbidità, proteinuria);
- Degenerazioni ultrastrutturali a livello dei glomeruli renali;
- Alterazioni ultrastrutturali a livello cardiaco.



# La tetrodotossina: dati tossicologici (*updates*)

Tossicità nel topo dopo somministrazione orale ripetuta per 28 giorni di TTX (44 µg/kg) e SXT (5.3 – 54 µg/kg).

**TTX:** Non sono stati osservati mortalità, alterazioni del peso corporeo o segni di tossicità.

**TTX:** Non sono state osservate alterazioni nella quantità e qualità delle urine.

**TTX e STX in miscela:** mortalità dopo somministrazione di TTX e SXT (5.3 e 54 µg/kg, ma non 17 µg/kg).



Article

## Oral Chronic Toxicity of the Safe Tetrodotoxin Dose Proposed by the European Food Safety Authority and Its Additive Effect with Saxitoxin

Andrea Boente-Juncal <sup>1</sup>, Paz Otero <sup>1</sup>, Inés Rodríguez <sup>2</sup>, Mercedes Camiña <sup>3</sup>, Mercedes Rodríguez-Vieytes <sup>3</sup>, Carmen Vale <sup>1,\*</sup> and Luis M. Botana <sup>1,\*</sup>

<sup>1</sup> Laboratorio de Farmacología, Farmacia e Tecnoloxía Farmacéutica, Universidade de Santiago de Compostela, Facultad de Veterinaria, Campus Universitario s/n, 27002 Lugo, Spain; andrea.boente.juncal@usc.es (A.B.-J.); paz.otero@usc.es (P.O.)

<sup>2</sup> Laboratorios Cifga, Benigno Rivera, 56, 27003 Lugo, Spain; inesrguez@cifga.es

<sup>3</sup> Departamento de Fisiología, Facultad de Veterinaria, Universidad de Santiago de Compostela, 27002 Lugo, Spain; merchi.camina@usc.es (M.C.); mmercedes.rodriguez@usc.es (M.R.-V.)

\* Correspondence: mdlcarmen.vale@usc.es (C.V.); luis.botana@usc.es (L.M.B.); Tel.: +34-9828-22-223 (C.V.); +34-9828-22-233 (L.M.B.)

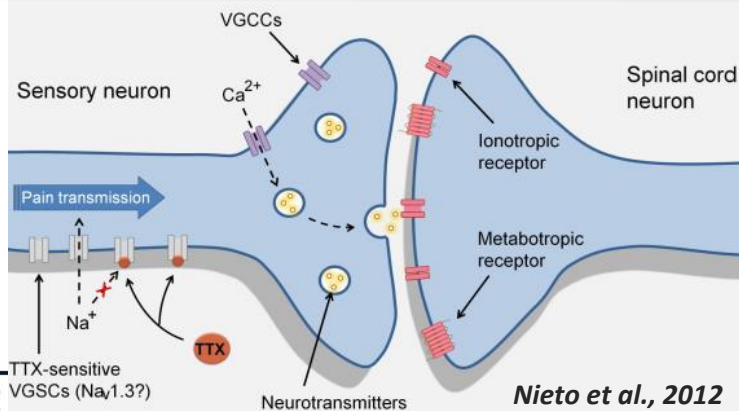
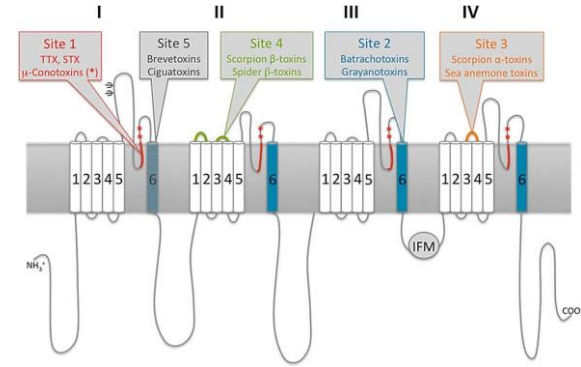
Received: 3 April 2020; Accepted: 7 May 2020; Published: 9 May 2020



# La tetrodotossina: meccanismo d'azione

Blocco selettivo dei **canali voltaggio dipendenti del Na<sup>+</sup>** (VGSC) su aa coinvolti nella formazione del poro

Blocco del potenziale d'azione in cellule neuronali e muscolari



Nella **trasmissione del dolore neuropatico**, il blocco di VGSC può essere sfruttato per bloccare il potenziale d'azione ectopico e la trasmissione dell'impulso nervoso

# Studi preclinici



Pain 72 (1997) 41–49

Tetrodotoxin inhibits neuropathic ectopic activity in ganglia and dorsal horn neurons



marine drugs

Imelda Osuna Zanata, Mohamed A. Elkhayat, John C. Hunter, David D. Neuroscience 311 (2015) 499–507

## ANTIHYPERALGESIC EFFECT OF TETRODOTOXIN ON THE DEVELOPMENT OF PERSISTENT MUSCLE PAIN

P. ALVAREZ<sup>a</sup> AND J. D. LEVINE<sup>a,b,\*</sup>

<sup>a</sup>Department of Oral and Maxillofacial Surgery, University of California San Francisco, San Francisco, CA, USA

<sup>b</sup>Department of Medicine, University of California San Francisco, San Francisco, CA, USA

Pain 137 (2006) 520–531

Tetrodotoxin inhibits the development and expression of neuropathic pain induced by paclitaxel in mice

Francisco Rafael Nieto<sup>a,1</sup>, José Manuel Entrena<sup>a,1</sup>, Cruz Miguel Cendán<sup>a</sup>, Esperanza Del Pozo<sup>a</sup>, José Miguel Vela<sup>b</sup>, José Manuel Baeyens<sup>a,\*</sup>

<sup>a</sup>Department of Pharmacology and Institute of Neuroscience, Faculty of Medicine, University of Granada, Avenida de Madrid 11, 18012 Granada, Spain

<sup>b</sup>Laboratorio Dr. Esteve S.A., Avenida Virgen de Monserrat 221, 08041 Barcelona, Spain

Received 17 January 2007; received in revised form 28 September 2007; accepted 8 October 2007



marine drugs

Article

## Effects of Tetrodotoxin in Mouse Model of Visceral Pain



Brain Research 871 (2000) 98–103

BRAIN RESEARCH

www.elsevier.com/locate/brain



Research report

## Low dose of tetrodotoxin reduces neuropathic pain behaviors in an animal model

Yeoung Su Lyu<sup>a</sup>, Soon Kwon Park<sup>a</sup>, Kyungsoon Chung<sup>a,b</sup>, Jin Mo Chung<sup>a,b,c,\*</sup>

<sup>a</sup>Marine Biomedical Institute, University of Texas Medical Branch, Galveston, TX 77555-1069, USA  
<sup>b</sup>Department of Anatomy and Neurosciences, University of Texas Medical Branch, Galveston, TX 77555-1069, USA  
<sup>c</sup>Physiology and Biophysics, University of Texas Medical Branch, Galveston, TX 77555-1069, USA

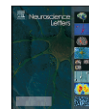
Accepted 25 April 2000

Neuroscience Letters 607 (2015) 108–113

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: [www.elsevier.com/locate/neulet](http://www.elsevier.com/locate/neulet)



research paper

## Tetrodotoxin suppresses thermal hyperalgesia and mechanical allodynia in a rat full thickness thermal injury pain model

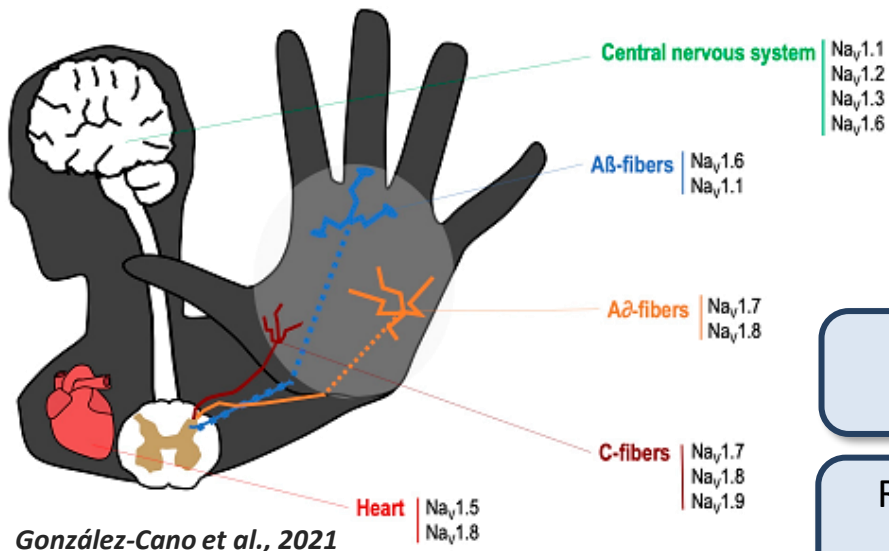
Margaux M. Salas<sup>a</sup>, Matthew K. McIntyre<sup>a</sup>, Lawrence N. Petz<sup>a</sup>, Walter Korz<sup>b</sup>, Donald Wong<sup>b</sup>, John L. Clifford<sup>a,\*</sup>

<sup>a</sup>US Army Institute of Surgical Research, 3698 Chambers Pass, Bldg 3611, JBSA Fort Sam Houston, TX 78234-6315, USA  
<sup>b</sup>WEX Pharmaceuticals Inc., Suite 420, 1090 West Pender Street, Vancouver, BC V6E 2N7, Canada





# Studi preclinici



La maggior parte degli studi sono focalizzati sul trattamento del **dolore neuropatico**

Ruolo cruciale di VGSC TTX-sensibili nel modulare la trasmissione del segnale nel dolore neuropatico

Danni ai neuroni periferici inducono *down-regulation* di **isoforme resistenti alla TTX** (Nav1.8, Nav1.9) e *up-regulation* di **isoforme TTX-sensibili** (Nav1.3)

## Original Article

## An Open-Label, Multi-Dose Efficacy and Safety Study of Intramuscular Tetrodotoxin in Patients with Severe Cancer-Related Pain

Neil A. Hagen, MD, FRCPC, Kim M. Fisher, PhD, Bernard Lapointe, MD, Patrick du Souich, MD, PhD, Srimi Chary, MD, Dwight Moulin, MD, FRCPC, Ed Sellers, MD, PhD, FRCPC, and Anh Ho Ngoc, PhD  
on Behalf of the Canadian Tetrodotoxin Study Group  
Tom Baker Cancer Centre (N.A.H.), Calgary, Alberta; Wex Pharmaceuticals International (K.M.F., A.H.N.), Vancouver, British Columbia; Jewish General Hospital (B.L.) and University of Montreal (P.d.S.), Montreal, Quebec; Royal University Hospital (S.C.), Saskatoon, Saskatchewan; University of Western Ontario and London Regional Cancer Centre, (D.M.), London Ontario; and Vantana Clinical Research (E.S.), Toronto, Ontario, Canada

## Studi clinici

## Original Article

## Tetrodotoxin for Moderate to Severe Cancer Pain: A Randomized, Double Blind, Parallel Design Multicenter Study

Neil A. Hagen, MD, FRCPC, Patrick du Souich, MD, PhD, Bernard Lapointe, MD, May Ong-Lam, MD, FRCPC, Benoit Dubuc, MD, David Walde, MD, FRCPC, Robin Love, MD, CCFP, and Anh Ho Ngoc, PhD  
on Behalf of the Canadian Tetrodotoxin Study Group  
Division of Palliative Medicine (N.A.H.), Department of Oncology, University of Calgary and Alberta Cancer Board, Calgary, Alberta; Department of Pharmacology (P.d.S.), Faculty of Medicine, University of Montreal, Montreal, Quebec; Palliative Care Program (B.L.), Sir Mortimer B. Davis – Jewish General Hospital, Montreal, Quebec; St. Paul's Hospital (M.O.-L.), Vancouver, British Columbia; Pain Clinic (B.D.), CHUM – Hotel Dieu, Montreal, Quebec; Algoma Regional Cancer Program/Sault Area Hospital (D.W.), Sault Ste. Marie, Ontario; Nanaimo Regional General Hospital (R.L.), Nanaimo, British Columbia; and Wex Pharmaceuticals (A.H.N.), Vancouver, British Columbia, Canada

## DRUG DEVELOPMENT IN CONTEMPORARY ONCOLOGY



## A multicentre open-label safety and efficacy study of tetrodotoxin for cancer pain

N.A. Hagen MD,\* B. Lapointe MD,† M. Ong-Lam MD,‡ B. Dubuc MD,§ D. Walde MD,|| B. Gagnon MD,¶ R. Love,\*\* R. Goel MD,†† P. Hawley MD,‡‡ A. Ho Ngoc PhD,§§ and P. du Souich MD PhD|||



toxins



## Article

## Tetrodotoxin for Chemotherapy-Induced Neuropathic Pain: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Dose Finding Trial

Samuel A. Goldlust<sup>1</sup>, Mojan Kavosi<sup>2\*</sup>, Jennifer Nezzar<sup>3</sup>, Mehran Kavosi<sup>2</sup>, Walter Koz<sup>2</sup> and Kenneth Deck<sup>4</sup>

- Hackensack University Medical Center, Hackensack, NJ 07601, USA; sgoldlust@hackensackUMC.org
  - WEX Pharmaceuticals Inc., Vancouver, BC V6E 4A6, Canada; mehrank@wexpharma.com (M.K.); walterk@wexpharma.com (W.K.)
  - Premier Research Group, Morrisville, NC 27560, USA; jnezzar@araonline.net
  - Alliance Research Centers, Laguna Hills, CA 92653, USA; kdeck@socsurgency.com
- \* Correspondence: mojan@wexpharma.com

Hindawi

Pain Research and Management

Volume 2017, Article ID 7121713, 7 pages

<https://doi.org/10.1155/2017/7121713>

## Clinical Study

## Tetrodotoxin for Moderate to Severe Cancer-Related Pain: A Multicentre, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Trial

Neil A. Hagen,<sup>1</sup> Lyne Cantin,<sup>2</sup> John Constant,<sup>3</sup> Tina Haller,<sup>4</sup> Gilbert Blaise,<sup>5</sup> May Ong-Lam,<sup>6</sup> Patrick du Souich,<sup>7</sup> Walter Koz,<sup>8</sup> and Bernard Lapointe<sup>9</sup>

<sup>1</sup>Tom Baker Cancer Centre and Division of Palliative Medicine, University of Calgary, 1331 29 Street NW, Calgary, AB, Canada T2N4N2

<sup>2</sup>ClinForce Services Inc., Vancouver, BC, Canada

<sup>3</sup>IPRA Health Sciences, Victoria, 655 Tyee Rd, Victoria, BC, Canada V8A 6X5

<sup>4</sup>Steele Consulting Services, 6 Mattson Drive, Caledon, ON, Canada L7E 0A3

<sup>5</sup>Département d'anesthésiologie, CHUM, 1560, rue Sherbrooke Est, Pavillon Deschamps, Local FS-1136,

Montréal, QC, Canada H2L 4M1

<sup>6</sup>St. Paul's Hospital, 1081 Burnard Street, Vancouver, BC, Canada V6Z 1Y6

<sup>7</sup>Département de Pharmacologie et Physiologie, Faculté de Médecine, Université de Montréal, CP 6128 Centre-Ville,

Montréal, QC, Canada H3C 3J7

<sup>8</sup>WEX Pharmaceuticals Inc., 420-1090 West Pender Street, Vancouver, BC, Canada V6E 2N7

<sup>9</sup>Clinical Research Unit, Jewish General Hospital, Room E-872 3755, Chemin de la Côte Sainte-Catherine,

Montréal, QC, Canada H3T 1E2

# Studi clinici

Efficacia nel trattamento del **dolore neuropatico oncologico severo** senza fenomeni di tolleranza

Dosaggio ottimale: 30 µg/die TTX s.c., 2 volte al giorno

Riduzione del dolore fino a 2 settimane se somministrato per almeno 4 giorni

**Effetti avversi:** blandi o moderati, generalmente ben tollerati e associati a parestesia (29.6%) e ipoestesia (24.8%) orali

Indice «*Numeric Pain Rating Scale*» non significativamente diverso tra gruppo di trattamento e placebo (numerosità dei campioni limitata), significatività che appare valutando la «*Quality of Life*»

**TECTIN<sup>®</sup>**  
**HALNEURON<sup>®</sup>**

TTX (15 µg/mL) in fiale da 2 ml per iniezione sottocutanea

*2 trial clinici (fase III)*

# Altri impieghi farmacologici



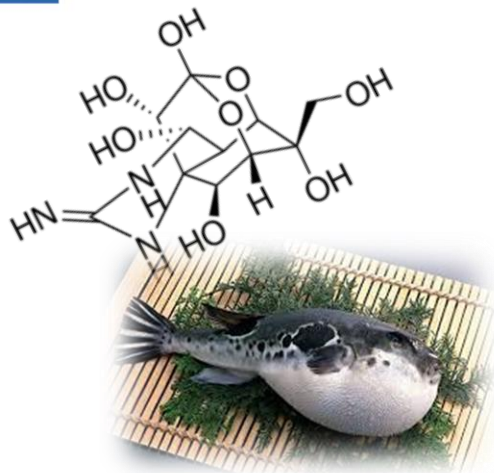
Sindrome da astinenza da eroina



Trattamento di disturbi neurologici  
(epilessia, emicrania, disturbi neurodegenerativi)

Dolori muscolari persistenti





- ✗ Composto estremamente tossico
- ✗ Limite proposto nei molluschi: 44 µg/kg
- ✗ Nuovi dati tossicologici da considerare (possibile effetto additivo con SXT)

- ✓ Meccanismo d'azione specifico
- ✓ Promettente utilizzo nella terapia del dolore neuropatico oncologico
- ✓ Ulteriori possibili applicazioni farmacologiche

July 2016

Horizon Scanning Research &amp; Intelligence Centre

### Tetrodotoxin for moderate to severe, inadequately controlled cancer-related pain

#### LAY SUMMARY

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

Cancer-related pain can arise from both ongoing tissue damage and treatments such as surgery or radiotherapy. Many patients use opioid-based pain killers to manage cancer-related pain but often they do not have complete pain relief.

Tetrodotoxin is a new drug that blocks pain transmission. It is reported to be a well-tolerated, more potent analgesic than aspirin and morphine, and a non-addictive alternative to opioids.

If licensed, tetrodotoxin will offer an additional treatment option for patients with cancer-related pain who may have few, well-tolerated and effective therapies.

NHRI HSRIC ID: 5173

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NIHR, the NIHR or the Department of Health.  
NIHR Horizon Scanning Research & Intelligence Centre,  
University of Birmingham, Email: [horizonscanning@bham.ac.uk](mailto:horizonscanning@bham.ac.uk)  
Web: [www.nihr.ac.uk](http://www.nihr.ac.uk)

**NHS**  
National Institute for Health Research

# Grazie per l'attenzione

