衞生防護中心
Centre for Health Protection

Scientific Committee on Enteric Infections and Foodborne Diseases

Tetrodotoxin poisoning in Hong Kong

Purpose

This paper reviews the epidemiology of tetrodotoxin poisoning and examines the public health measures for prevention and control of the disease in Hong Kong.

Background

2. Tetrodotoxin poisoning results from the ingestion of the flesh or viscera of certain species of fish belonging to the family Tetraodontidae (puffer fish) which possess the extremely potent neurotoxin, tetrodotoxin (TTX). TTX is one of the common causes of biotoxin food poisoning that has been responsible for human intoxications and fatalities.

Tetrodotoxin (TTX)(1-3)

3. It is suggested that TTX is produced primarily by marine bacteria. Puffer fish accumulates the toxin via the food chain that begins with the bacteria (4). TTX is used as a defensive biotoxin by TTX-bearing organisms to stave off predation or as predatory venom. It is water soluble, heat resistant and can be absorbed through human mucous membranes and small intestines. TTX acts as a sodium channel blocker that binds to and blocks sodium channel in excitable tissues such as nerve and muscle. The inhibition of sodium entry through ion channels leads to failure of depolarization and propagation of action potentials in these tissues. TTX can act on both central and peripheral nervous systems and hence, motor, sensory and autonomic systems can all be affected. Its direct central effect on the chemoreceptor trigger zone can cause

衞生防護中心乃衞生署
轄下執行疾病預防
及控制的專業架構
The Centre for Health Protection is a professional arm of the Department of Health for disease prevention and control

nausea, vomiting as well as depression of respiratory and vasomotor systems. TTX is one of the most toxic substances known. It is about 10,000 times more lethal than cyanide by weight (2) and 50 times more potent than strychnine or curare (3). The minimum lethal dose of TTX to human is estimated to be 2 to 3 mg and the minimum dose that necessary to cause symptoms is about 0.2 mg (5), but this may vary depending on age, health and sensitivity of the patients. The level of tissue toxicity in puffer fishes varies across season. In females, ovary toxicity markedly increases during maturation from December to March while liver toxicity is high during ordinary period. In males, little maturation-associated change in the toxin distribution could be observed (6).

Distribution of TTX (2, 4, 7)

4. Puffer fish of the family Tetraodontidae generally contains a large amount of TTX (Annex 1). Puffer fish is distributed worldwide and there are approximately 187 species of puffer fish identified in both freshwater and marine environments. Among them, some species are popular for human consumption and are considered as delicacy. The level of toxicity among puffer fish varies across regions, species and organs (1, 8), with the highest concentrations of TTX found in the liver, gonads such as the ovary, intestines and skin. Besides puffer fishes, other animals including gastropods, newts, goby fish, frogs, horseshoe crab and starfish flatworms have also been reported to be TTX-bearing (9) (Annex 2).

Clinical Presentation (1, 8, 10-12)

5. The usual route of human intoxication is via the ingestion of TTX-bearing puffer fish or other animals' organs. Patients with TTX poisoning usually develop symptoms within 30 minutes to 6 hours of ingestion. Both central and peripheral nervous systems are affected after ingesting TTX. Depending on the amount of TTX ingested, the time after ingestion of TTX, hydration state of the body and the general health status of the patient, there may be a spectrum of symptoms including (i) gastrointestinal symptoms such as nausea, diarrhea, and vomiting, abdominal discomfort, (ii) neurological symptoms such as paresthesia in the face, motor in-coordination, muscle weakness and slurred

speech and, (iii) other symptoms including hypotension, hypoxia and tachycardia. According to Fukuda and Tani (13), the clinical toxicity of TTX poisoning can be graded into 4 stages according to the neurological and cardiovascular features (Table 1).

Table 1. Clinical grading system for TTX poisoning based on signs and symptoms (13)

Grade	Clinical features
1	Perioral numbness with or without gastrointestinal symptoms
2	Numbness involving tongue, face and distal areas; early motor paralysis and incoordination; slurring of speech; normal reflexes
3	Generalised flaccid paralysis; dyspnoea or respiratory failure; aphonia
4	Hypoxia and severe respiratory failure; cardiovascular effects including hypotension, bradycardia and arrhythmia

6. The first symptom of intoxication is slight oral numbness of the lips and tongue, typically appearing 20 minutes to 3 hours after ingestion of the toxin but the onset can be earlier with higher dose of toxin. The next symptom is increasing paraesthesia in the face and extremities, which may be followed by sensations of lightness or floating. Headache, epigastric pain, nausea, diarrhea, vomiting and occasionally, reeling or difficulty in walking may occur as well. The next stage of intoxication is progressive paralysis including inability to move, difficulty in sitting, increasing respiratory distress, speech problem, dyspnea, cyanosis and hypotension. In serious cases, paralysis may increase and convulsions, mental impairment and cardiac arrhythmia may occur. Respiratory failure and cardiovascular collapse can occur usually within 4 to 6 hours (with a known range of about 20 minutes to 8 hours) and may result in death (1). If the victim survives in the first 24 hours, they are expected to have full recovery as the toxin can be removed from human body through urination.

Diagnosis and Laboratory Investigation

7. Diagnosis is usually established based on the patient's signs and symptoms, supported by a positive food consumption history and detection of TTX in

patients' samples or food remnant such as the tissue of puffer fish.

Food analysis

8. Mouse bioassay is widely used internationally for testing of food remnant that has been contaminated by TTX. Food specimens are collected and dissected into different anatomical tissues, and then each tissue is bioassayed according to the official guidelines of the Japan Food Hygiene Association. Lethal potency is expressed in mouse units (MU) in which one MU indicate the amount of toxin required to kill a 20g male mouse of ddY strain in 30 minutes after intraperitoneal injection (14).

9. The Government Laboratory in Hong Kong employs chemical testing methods such as Liquid chromatography-mass spectrometry (LC-MS) for identification of TTX in food and DNA technique for identification of species of fish. Morphological identification of unprocessed local fish species that potentially harbours TTX is also possible by Agriculture, Fisheries and Conservation Department.

Detection of TTX in urine and blood samples

10. TTX can be found in blood up to 24 hours after ingestion while it can also be detected in urine up to 4 days from the time of ingestion. It is therefore important to collect urine and blood samples from affected patients as early as possible for clinical diagnosis. There are several analytical methods for detecting TTX in urine and blood samples including chromatography based methods and enzyme-linked immunosorbent assay (ELISA). Testing of TTX in urine is available in the Division of Clinical Biochemistry of Queen Mary Hospital in Hong Kong for patients admitted to public hospitals.

Patient Management

11. There is no antidote for TTX poisoning at present and the mainstay of treatment is primarily supportive. For victim who presents to hospital shortly after ingestion of TTX, generally within 1 hour, gastric lavage or activated charcoal can be considered to remove the unabsorbed toxin but medical

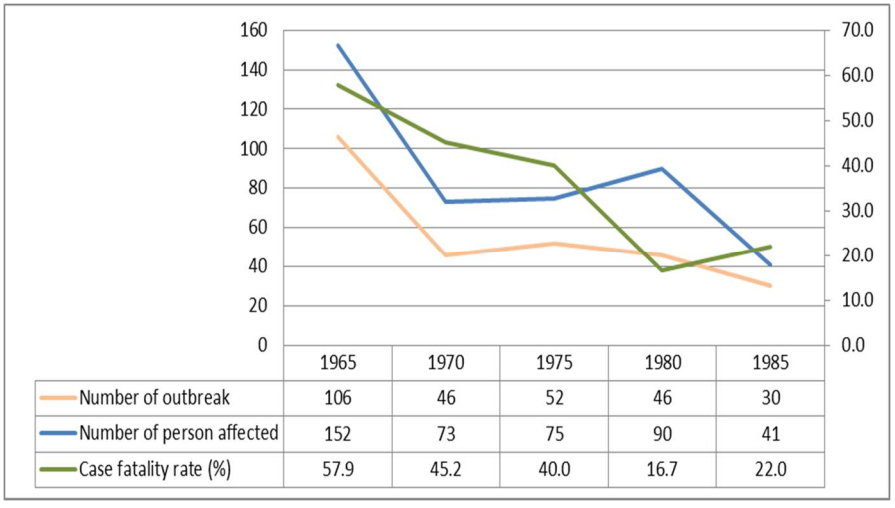
parameters such as blood pressure, heart rhythms, respiratory function and electrolyte balance must be carefully monitored (1, 15).

Global Epidemiology

12. TTX poisoning is frequently reported in Japan, mainland China, Taiwan, Bangladesh and Southeast Asia (7) and, is also occasionally reported in other places, such as the US, Europe and Australia.

Situation in Asia

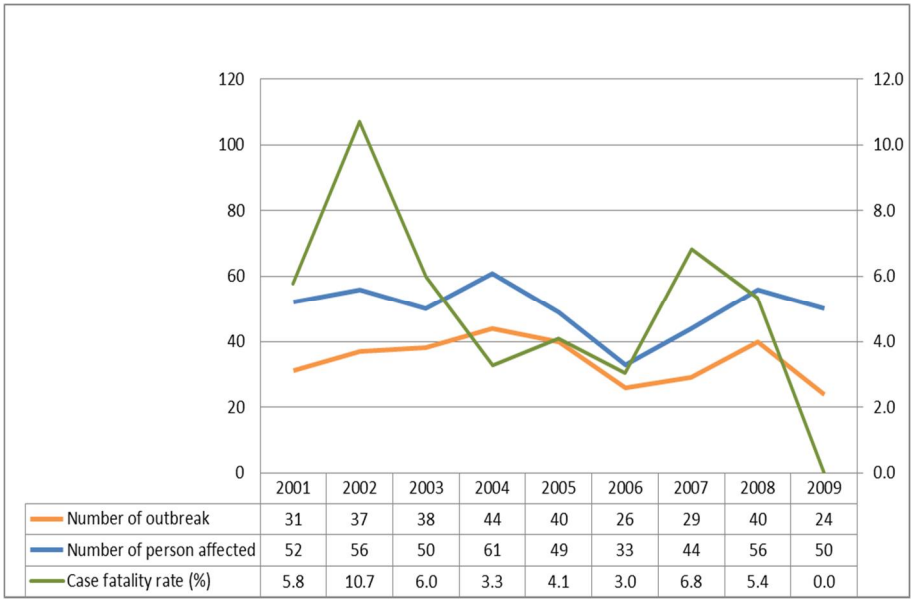
13. In Japan, puffer fish poisoning is the most common natural marine toxin causing food poisoning. Puffer fish, also called "fugu" in Japan, is a popular traditional dish serving as sashimi or chiri nabe (a hot pot dish). Some Japanese enjoy eating liver of puffer fish, fugu kimo, as it is considered as delicacy although its toxicity is high. Most of the cases reported in Japan were related to self-preparation and amateur anglers. From 1965 to 1985, the number of incidents and fatal cases had been decreasing with time. The number of incidents were decreased from 106 (affecting 152 persons) to 30 (affecting 41 persons) while the number of deaths were decreased from 88 in 1965 to 9 cases in 1985. During the same period, the case fatality rate also decreased from 57.9% to 22.0% (Figure 1a) (4).



	1965	1970	1975	1980	1985
Number of outbreak	106	46	52	46	30
Number of person affected	152	73	75	90	41
Case fatality rate (%)	57.9	45.2	40.0	16.7	22.0

Figure 1a. Puffer fish poisoning in Japan from 1965 to 1985

14. From 2001 to 2009, the case fatality rate in Japan was further decreased to zero percent to 10.7 % (median = 5.4%). Meanwhile, the trend of puffer fish poisoning outbreak was relatively stable (Figure 1b) (16).



	2001	2002	2003	2004	2005	2006	2007	2008	2009
Number of outbreak	31	37	38	44	40	26	29	40	24
Number of person affected	52	56	50	61	49	33	44	56	50
Case fatality rate (%)	5.8	10.7	6.0	3.3	4.1	3.0	6.8	5.4	0.0

Figure 1b. Puffer fish poisoning in Japan from 2001 to 2009

15. In Taiwan, although puffer fish is not as popular as in Japan, puffer fish poisoning is not uncommon. Of them, most cases were caused by consumption of wild puffer fish. From 1992 to 2012, a total of 28 clusters were reported that affected a total of 128 persons, with two to 27 persons (median = 3 persons) in each cluster, and 11 fatal cases (case fatality rate = 8.6 %) (17). The cases were usually associated with insufficient knowledge on identifying edible species of puffer fish, and the patients mistakenly ingested muscles of species that carry TTX. In some cases, patients ingested puffer roe that had been sold as a fake of dried mullet roe called “karasumi” and some cases consumed dried dressed fish fillet produced from toxic puffer fish by food processing company (18, 19).

16. In mainland China, puffer fish is also a popular cultural dish. Thirty two clusters of puffer fish poisoning affecting 131 persons were reported from 2004 to 2007. Although the number of puffer fish poisoning accounted for a small portion (1.4%) of the total number of food poisoning, 35 fatal cases were reported in this four- year period with case fatality rate of 26.7% (20).

17. In Bangladesh, puffer fish is called as "potka fish". It is very popular in poor rural communities due to its availability and low price. Severe puffer fish poisoning were reported from time to time, although formal statistics were not available. In 1998, eight persons were affected in a food poisoning outbreak associated with ingestion of puffer roe. The patients developed dyspnea, numbness of the lips, paralysis and stomachache followed by vomiting two hours after consumption. Two of them became unconscious and died within five hours after exposure, another three patients died after admission to a hospital and the remaining three patients had recovered (21). There was another severe outbreak of puffer fish poisoning happened in 2008 among the naïve inland populations. A total of 141 persons from three clusters were hospitalised. They consumed puffer fish that sold in markets and developed symptoms including perioral paraesthesia, tingling over the entire body, nausea and vomiting, dizziness, headache, abdominal pain and muscular paralysis of the limbs. Seventeen patients (12%) passed away due to acute respiratory failure, with the remaining patients recovered upon supportive treatment (22).

18. TTX poisoning is common in Thailand. A literature reported a TTX poisoning associated with ingestion of toxic eggs of the horseshoe crab between 1994 and 2006 in Chon Buri. A total of 280 patients were affected with 239 of them (97.5%) recovered uneventfully but five patients died (2%) and one patient (0.4%) suffered from anoxic brain damage (23). TTX poisoning due to ingestion of brackish water and marine puffers had also been reported in the past years that caused significant numbers of deaths (24, 25). Thus, selling puffers in Thailand has been forbidden since 2002. Nevertheless, the puffer fishes are still sold illegally in fresh markets that being mixed with other fish flesh for making fish balls (25).

19. In Singapore, puffer fish is getting more popular as it can be found in quite a few restaurants. TTX poisoning is a food poisoning which is a notifiable disease captured by the Ministry of Health of Singapore for surveillance (26, 27) but puffer fish poisoning is rarely reported. There was a case report of TTX poisoning in 2013. A 35-year-old lady developed numbness and tingling sensation around the mouth areas after an hour of ingesting fugu sashimi at a

Japanese restaurant. Her symptoms resolved the following day and she was recovered (10).

Situation in the United States (US)

20. Puffer fish poisoning is not common in the US and only a few outbreaks have been reported. One outbreak involved three chefs in California in 1996. They shared contaminated puffer fish that was bought by a co-worker from Japan as a pre-packaged and ready-to-eat food. The onset of symptoms began from 3 to 20 minutes after ingestion of the puffer fish. The quantity of puffer fish taken by them was minimal that ranging from approximately 0.25 to 1.5 oz. They were all transported to emergency department for management (28). There was another cluster reported in 2007 that affected two individuals in Chicago. They developed symptoms that were consistent with TTX poisoning after consuming a home-prepared puffer fish. The fish was bought in Chicago that was labeled as monkfish according to the retailer and supplier. TTX was detected at high levels in both food remnants of the meal and the fish retrieved from the implicated lot. This incident led to a voluntary recall of monkfish distributed by the supplier in three states and placement of the supplier on the U.S. Food and Drug Administration (FDA)'s Import Alert for species misbranding (29). Another case of TTX poisoning related to ingestion of puffer fish was reported in Virginia in January 2014. This case affected one person and the puffer fish was claimed to be imported from South Korea and received by the patient's relatives (30).

Situation in Europe

21. In Europe, ten deaths were reported from 1974 to 1979 as a result of eating wrongly labelled toxic puffer fish. TTX poisoning has been rarely reported in Europe since the sale has been prohibited (31).

Situation in Australia

22. In Australia, sporadic cases of puffer fish poisoning have been reported but outbreak was rarely documented. A 16-month study conducted by the New South Wales Poisons Information Centre received 5 reports of puffer fish

poisoning between 1 January 2001 and 13 April 2002. Two were mild cases that involved peoples who had been squirted with fluid from puffer fish. Three cases were reported from hospitals that involved a total of 11 persons. Two of them were sporadic cases affecting one person each while the remaining one was an outbreak that involved two children and seven adults who had ingested a soup that made from 30 puffer fishes. Among these patients, one child was asymptomatic, one female adult developed perioral paraesthesia, dysarthria, ataxia, limb weakness, hyporeflexia, ophthalmoplegia and respiratory failure, and most of the others exhibited typical neurological features such as perioral numbness and/or paraesthesia, distal limb numbness/ paraesthesia and ataxia. One patient had decreased sensation in the hands and feet, most of his symptoms resolved after 48 hours, but slight weakness and ataxia of the lower limbs remained. No fatal case was reported (32).

Local Epidemiology

23. TTX poisoning is not common in Hong Kong. From 2004 to 30 June 2014, the Centre for Health Protection (CHP) of the Department of Health (DH) recorded 21 cases of TTX poisoning affecting 38 persons in Hong Kong. More cases were reported in winter season (October to December) (Figure 2a). The annual number of cases ranged from one to four during this period (Figure 2b). More cases occurred in the year of 2007 (four cases), 2012 (four cases) and 2013 (four cases) but no epidemiological linkage was found among the outbreaks. The scale of the outbreaks ranged from one to four persons (median = 1 person). More males were affected with male-to-female ratio of 2.2:1. The age among the patients ranged from 22 to 68 years (median = 45.5 years).

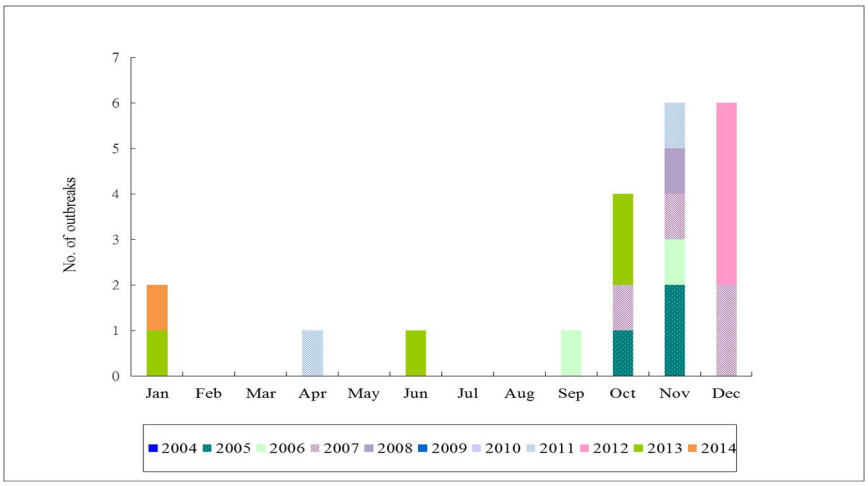


Figure 2a. Cumulative monthly number of puffer fish poisoning in Hong Kong, 2004-2014 (as of 30 June 2014)

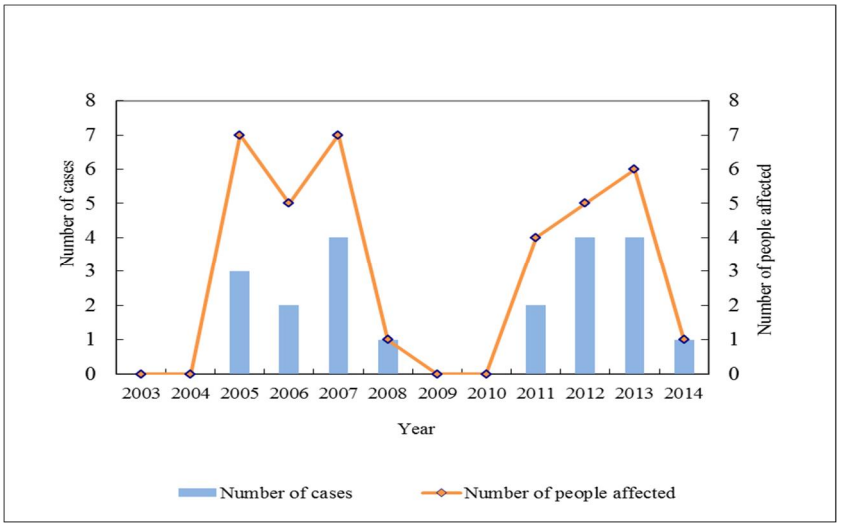


Figure 2b. Annual number of puffer fish poisoning and the number of persons affected, 2004-2014 (as of 30 June 2014)

24. The patients developed symptoms from 10 minutes to 24 hours (median= 3 hours) after consumption of the incriminated food. Besides, all of them recalled history of consuming puffer fishes before onset of symptoms. The most common symptom was limbs numbness (n= 30, 78.9%), followed by dizziness (n= 27, 71.1%), weakness (n= 19, 50.0 %), perioral numbness (n=16, 42.1%) and vomiting (n=9, 23.7%). Twenty six patients required hospitalization while six of them (23.1%) required intensive care. No fatal case was reported. Among those six patients that required intensive care, one had suffered from cardiac arrest and respiratory failure and required ventilation

support. The patient was subsequently transferred to a medical facility in mainland China after 25 days (including 11 days in ICU) of hospitalisation in Hong Kong. Another two required intubation and mechanical ventilation, while three others were admitted to the ICU for monitoring without intubation. Concerning the outcome, four of them had complete recovery on discharge. One patient required walking assistance and the outcome of the remaining patient could not be verified as he was transferred to mainland China. Another twenty patients (76.9%) were admitted to general ward of hospitals.

25. For cases with information available, the average length of stay was 2.8 days (range from 1 to 25 days, median = 1 day) and all showed complete recovery upon discharge.

Laboratory results

26. Among the 21 cases in Hong Kong, only one case had food remnant for laboratory investigation. TTX at a level of 55mg/kg was detected in the food remnant. No clinical sample was collected from the 38 patients.

Incriminated food

27. Majority of cases (n=37) claimed that they had eaten puffer fishes before the onset of symptoms. There were also one and two cases with patients reported consumption of porcupine fish (刺猬神魚) and dried puffer fish products, respectively.

28. The sources of the incriminated puffer fish in 13 cases were reported to be caught from the sea by the victims. Seven cases with 12 affected persons involved crew members working on ships. They caught the puffer fishes from the sea in Hong Kong. There were seven cases (involved 13 persons) in which patients bought and/or consumed the incriminated food from local markets, illegal hawkers or food premises. For the remaining case, the puffer fish was purchased from Shenzhen and the patient refused to disclose the source. The incriminated food and the sources of each case are summarised in Table 2.

Table 2. Summary of 21 cases of TTX poisoning, 2004 – 2014 (as of 30 June, 2014)

Case No.	Person affected	Source of incriminated food	Food type	Incriminated food	ICU admission	Discharge outcome	Required ventilation support	Remark
Case 1	3	Caught from sea	Fresh	Puffer fish		Recovered		Crew members
Case 2	4	Caught from sea	Fresh	Puffer fish	Yes (2)	3 recovered, 1 required walking assistance	Yes (2)	Crew members
Case 3	1	Caught from sea	Fresh	Puffer fish	Yes	Recovered		Crew member
Case 4	4	Caught from sea	Fresh	Puffer fish		Recovered		Crew member
Case 5	1	Caught from sea	Fresh	Puffer fish	Yes	On oxygen supply and nasaogastric tube; transferred to a hospital in China	Yes	Crew members, (TTX detected in food remnant, 55mg/kg)
Case 6	1	Caught from sea	Fresh	Puffer fish		Recovered		Crew member
Case 7	1	Caught from sea	Fresh	Puffer fish		Recovered		Crew members
Case 8	1	Caught from sea	Fresh	Puffer fish	Yes	Recovered		
Case 9	2	Caught from sea	Fresh			Recovered		
Case 10	1	Caught from sea	Fresh	Puffer fish	Yes	Recovered		
Case 11	2	Caught from sea	Fresh	Puffer fish		Recovered		
Case 12	1	Caught from sea	Fresh	Puffer fish		Recovered		
Case 13	2	Caught from sea	Dried	Processed dried puffer fish		Recovered		The fish was freshly caught and processed by the patient's friend in China
Case 14	1	Local food premises	Dried	Dried puffer fish product (河豚燒)		Recovered		
Case 15	3	Illegal Hawker	Fresh	Puffer fish		Recovered		
Case 16	1	Local market	Fresh	Puffer fish		Recovered		
Case 17	3	Local market	Fresh	Puffer fish		Recovered		
Case 18	2	Local market	Fresh	Puffer fish		Recovered		
Case 19	1	Local market	Dried	Procupine fish (刺猬神魚)		Recovered		
Case 20	2	Local market	Fresh	Puffer fish		Recovered		
Case 21	1	A market in Shenzhen	Fresh	Puffer fish		Recovered		

Regulatory Control on Puffer Fish

29. Regulatory control on the availability of puffer fish is one of the important measures for the prevention of TTX poisoning. Many places have different statutory requirements or guidelines to regulate the import and sale of puffer fish. In Japan, as majority of the cases were associated with self-preparation of puffer fish that was caught recreationally, the Ministry of Health, Labour and Welfare (MHLW) published a list of edible puffer fishes in 1983. MHLW provides strict guidance and regulation for the harvesting and consumption of puffer fish. Under this guidance, the flesh for some species is considered safe to consume, if prepared properly by a trained expert. All viscera from all species of puffer fish, especially the liver and ovaries, are prohibited for use as food and serving in restaurants. Considering most of the incidents occurred at home, MHLW publish a list of edible puffer fishes in 1983 and this list was updated in 1993 and 1995 respectively to educate the general public (4, 18).

30. In the US, personal importation of puffer fish is prohibited but the Food and Drug Administration (FDA) permits muscle, skin, and testicles from a single species (*Takifugu rubripes*) to be imported and served in Japanese restaurants only by certified puffer fish chefs on special occasions. There is a cooperative agreement between FDA and the Japanese MHLW, ensuring that the imported puffer fish must be processed in certified facility by trained personnel and certified as safe for consumption before export by the Japanese government. Under the Inspection Orders based on Section 3, Article 26 of the Food Sanitation Law, any puffer fish products imported outside the guidelines of the agreement are subject to detention with physical examination (4).

31. In Canada, importation of puffer fish of the family Tetraodontidae is strictly prohibited (19).

32. In mainland China, China FDA prohibited the food trade from processing puffer fish, even though the puffer fish is being farmed for export (20).

33. In Taiwan, only certain species of puffer fish are considered to be safe for consumption and are used to produce dried fish fillets and fish balls (5). The

FDA of Taiwan, based on the food hygiene management regulations, stated that fishermen should not capture or farm puffer fish for supplying for food processing and the catering trade as ingredient. Besides, the FDA of Taiwan published a puffer fish manual listing out the edible puffer fish and its organ for the food trade and the public's references (12).

34. In Singapore, a new regulation has been put in place since 2011 for importation of puffer fish into Singapore. The imported puffer fish has to be accompanied by a health certificate from the relevant government authority of the exporting country certifying that the TTX-containing tissues/organs in the fish has been removed by a qualified chef and it is fit for human consumption (21).

Prevention and Control Measures in Hong Kong

Surveillance and food poisoning investigation

35. In Hong Kong, TTX poisoning as food poisoning, is a statutory notifiable disease since March 1974. Upon notification of food poisoning involving TTX, CHP will initiate prompt epidemiological investigation and control actions, particularly the source of incriminated food in order to stop its further distribution to and consumption by other persons. On risk communication, CHP will give health advice to the patients and food collaterals and, conduct public announcement to alert the general public of the food poisoning case and remind them on the measures for preventing the disease. So far, there was no further case arising from the same source after investigation and implementation of control measures among the sporadic cases reported to CHP.

Food regulations

36. In Hong Kong, the public is generally protected by the Section 54 of the Public Health and Municipal Services Ordinance (Cap. 132) that any person selling food unfit for human consumption commits an offence to the Ordinance and can be prosecuted in cases of puffer fish food poisoning. Food and Environmental Hygiene Department (FEHD) is the statutory body to take enforcement actions against any sale of food that is not fit for human

consumption. In Hong Kong, there is no specific subsidiary legislation under the Public Health and Municipal Services Ordinance ("PHMSO", or Cap. 132) regulating the import or sale of puffer fish and related products at present because of a number of practical difficulties. Firstly, there is no standard on safe dose or limit of TTX in food. Secondly, sampling and testing cannot guarantee that the whole batch of puffer fish is safe for human consumption. Furthermore, identification of the TTX-bearing fishes is a very sophisticated process that the relevant authorities do not have much expertise in this highly specialized field.

37. Nevertheless, section 54 of, PHMSO enforced mainly by the FEHD, states that any person who sells, offers or exposes for sale, or has in his possession for the purpose of sale or preparation for sale any food that is unfit for human consumption commits an offence and is liable to a maximum fine of $50,000 and imprisonment for 6 months upon conviction. Therefore, general protection in connection with the sale of TTX-containing puffer fish, porcupine fish and their products is provided by section 54 of Cap.132. Under section 59 of Cap. 132, a FEHD officer is also empowered to examine, seize and remove any food, if it appears to him that such food is unfit for human consumption, such as when handling a complaint or food poisoning case involving puffer fish at a food premises or market stall. FEHD will also mark and seal all consignments of puffer fish found at the import level to prevent them from entering the market.

Food surveillance

38. In Hong Kong, Food Surveillance Programme operated by the Centre for Food Safety (CFS) of FEHD covers the surveillance of aquatic products like fish, shellfish, shrimp, prawn, crab, squid and their products. In 2011 to 2013, some 6 500 to 6 900 samples of aquatic products were collected each year for chemical and microbiological analysis and risk assessment would be conducted for unsatisfactory results. In June 2012, TTX at levels between 0.31 mg/kg and 1.7 mg/kg were detected in five food samples from a lot of prepackaged food products labelled as "grilled grouper" imported from Thailand. In response to the laboratory finding which indicating risk to public upon normal consumption, the trade concerned was informed and remaining stock of the

food item was surrendered to the CFS for disposal. Consumer level product recall was also initiated by the concerned trade immediately and corresponding authority of Thailand was informed. In addition, follow-up samples would be taken for chemical testing when it was available in markets again to ensure that the product was safe for human consumption.

Public education

39. As majority of the TTX poisoning cases in Hong Kong resulted from consumption of puffer fish caught by the victims, public education is very important in preventing the disease. FEHD have prepared a variety of health education materials to educate the food trade and the general public on puffer fish poisoning. These materials included a feature article on Food Safety Focus and a poster published in 2014 to educate the member of public to avoid eating puffer fish for preventing poisoning. Moreover, there is a TTX designated mini-web on CFS webpage, which contains information on puffer fish poisoning for the reference of food trade and general public.

Conclusion

40. TTX poisoning is not common but occasionally reported in Hong Kong. Though there is no recorded death due to TTX poisoning, the affected persons generally experienced serious or life threatening symptoms. Current surveillance, outbreak investigation and control are effective in containing propagation of the disease. Currently, there is no specific statutory requirement or trade guideline on the importation and sale of puffer fish due to a number of practical difficulties.

41. There has been ongoing public health education but still, sporadic cases of TTX due to consumption of puffer fish, particularly among crew members and fishermen, were reported.

Recommendations

42. It is recommended that targeted health education be given to fishermen and crew members advising them of the dangers of eating puffer fish. The most cost-effective channels to provide this information to this high-risk group should be identified.

The copyright of this paper belongs to the Centre for Health Protection, Department of Health, Hong Kong Special Administrative Region. Contents of the paper may be freely quoted for educational, training and non-commercial uses provided that acknowledgement be made to the Centre for Health Protection, Department of Health, Hong Kong Special Administrative Region. No part of this paper may be used, modified or reproduced for purposes other than those stated above without prior permission obtained from the Centre.

References:

1. The Center for Food Safety and Applied Nutrition of the Food and Drug Administration (FDA) US. Tetrodotoxin. Bad Bug Book: Foodborne Pathogenic Microorganisms and Natural Toxins
The Center for Food Safety and Applied Nutrition, of the Food and Drug Administration (FDA), U.S.; 2012.
2. Leung KS, Fong BM, Tsoi YK. Analytical challenges: determination of tetrodotoxin in human urine and plasma by LC-MS/MS. Marine drugs. 2011;9(11):2291-303.
3. Scholz H. The poisonous effect of tetrodotoxin and puffer Advisory Board for the German fisheries. 1986. p. 49-53.
4. Noguchi T, Arakawa O. Tetrodotoxin--distribution and accumulation in aquatic organisms, and cases of human intoxication. Marine drugs. 2008;6(2):220-42.
5. Centre for Food Safety FaEHD. The Tetrodotoxin Hong Kong SAR: Centre for Food Safety, Food and Environmental Hygiene Department,; 2007 [cited 2014 10 September 2014]. Available from: http://www.cfs.gov.hk/english/multimedia/multimedia_pub/files/FSF9%202007-4-18.pdf.
6. Ikeda K, Emoto Y, Tatsuno R, Wang JJ, Ngy L, Taniyama S, et al. Maturation-associated changes in toxicity of the pufferfish Takifugu poecilonotus. Toxicon : official journal of the International Society on Toxinology. 2010;55(2-3):289-97.
7. Bane V, Lehane M, Dikshit M, O'Riordan A, Furey A. Tetrodotoxin: chemistry, toxicity, source, distribution and detection. Toxins. 2014;6(2):693-755.
8. Nader MR IS, Boustany LE, . The Puffer Fish *Lagocephalus sceleratus* (Gmelin, 1789) in the Eastern Mediterranean. In: Food and Agriculture Organization of the United Nations, editor. Athens (Greece): FAO; 2012.
9. Miyazawa K and Noguchi T. Distribution and orgin of tetrodotoxin. Toxin Reviews. 2001;
Vol. 20, No. 1 , Pages 11-33(1):11 - 33.
10. Yong YS, Quek LS, Lim EK, Ngo A. A case report of puffer fish poisoning in singapore. Case reports in medicine. 2013;2013:206971.
11. Wan CK, Tsui SH, Tong HK. A case series of puffer fish poisoning. Hong Kong Journal of Emergency Medicine. 2007;Vol. 14(4):215-20.
12. Centers for Disease Control and Prevention. Guide to Confirming a Diagnosis in Foodborne Disease 2013 [27 June 2014]. Available from:

http://www.cdc.gov/foodsafety/outbreaks/investigating-outbreaks/confirming_diagnosis.html#parasitic.
13. Fukuda A, Tani, A.,. Report 3. Nippon Igaku Oyobi Kenko Hoken. 1941.
14. Saoudi M AA, and Feki AE,. Tetrodotoxin: a potent marine toxin. Toxin Reviews. 2010;29(2):60-70.
15. Centers for Disease Control and Prevention. Emergency Response Safety and Health Database U.S.: Centers for Disease Control and Prevention 2011 [updated 2013; cited 2014 3 July 2014]. Available from: http://www.cdc.gov/niosh/ershdb/EmergencyResponseCard_29750019.html.
16.Ministry of Health Labour and Welfare. 自然毒のリスクプロファイル:魚類:フグ毒 Japan: Ministry of Health Labour and Welfare. Available from: http://www.mhlw.go.jp/topics/syokuchu/poison/animal_det_01.html.
17. 行政院衛生署食品藥物管理局.「吃河豚、風險大- 臺灣常見有毒河豚(鮐)圖鑑手冊」 Taiwan: 行政院衛生署食品藥物管理局,; 2012. Available from: http://www.fda.gov.tw/upload/133/20121108184607602O4.pdf.
18. 衛生福利部食品藥物管理署. 河豚毒素(Tetrodotoxin). Available from: http://www.fda.gov.tw/tc/includes/GetFile.ashx?mID=133&id=10230&chk=0cd8bf55-138f-4ddf-9745-c1e6b5ab7921
19. Hwang DF, Hsieh YW, Shiu YC, Chen SK, Cheng CA. Identification of tetrodotoxin and fish species in a dried dressed fish fillet implicated in food poisoning. Journal of food protection. 2002;65(2):389-92.
20. 金连梅, 李群 2004-2007 年全国食物中毒事件分析. 疾病监测.24(6):459 - 61.
21. Noguchi T, Tanu MB, Mahmud YSU, Matsue (Japan),. First occurrence of a food poisoning incident due to ingestion of Takifugu oblongus, along with a toxicological report on three marine puffer species in Bangladesh J Food Hyg Soc Japan. 1999;40:473-80.
22. Islam QT, Razzak MA, Islam MA, Bari MI, Basher A, Chowdhury FR, et al. Puffer fish poisoning in Bangladesh: clinical and toxicological results from large outbreaks in 2008. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2011;105(2):74-80.
23. Kanchanapongkul J. Tetrodotoxin poisoning following ingestion of the toxic eggs of the horseshoe crab Carcinoscorpius rotundicauda, a case series from 1994 through 2006. The Southeast Asian journal of tropical medicine and public health. 2008;39(2):303-6.
24. Laobhripatr S, Limpakarnjanarat K, Sangwonloy O, Sudhasaneya S,

Anuchatvorakul B, Leelasitorn S, et al. Food poisoning due to consumption of the freshwater puffer Tetraodon fangi in Thailand. Toxicon : official journal of the International Society on Toxinology. 1990;28(11):1372-5.
25. Chulanetra M, Sookrung N, Srimanote P, Indrawattana N, Thanongsaksrikul J, Sakolvaree Y, et al. Toxic marine puffer fish in Thailand seas and tetrodotoxin they contained. Toxins. 2011;3(10):1249-62.
26. Health SMo. List of Infectious Diseases Legally Notifiable Under the Infectious Diseases Act Singapore Singapore Ministry of Health 2014 [cited 2014 25 Aug 2014]. Available from: http://www.moh.gov.sg/content/moh_web/moh_corp_mobile/home/diseases_conditions/List_of_Infectious_Diseases_Legally_Notifiable_under_the_Infectious_Diseases_Act.html.
27. Board HP. Preventing and Controlling Public Health Threats Singapore [26 August 2014]. Available from: http://www.hpb.gov.sg/HOPPortal/health-article/476.
28. Centers for Disease C, Prevention. Tetrodotoxin poisoning associated with eating puffer fish transported from Japan--California, 1996. MMWR Morbidity and mortality weekly report. 1996;45(19):389-91.
29. Cohen NJ, Deeds JR, Wong ES, Hanner RH, Yancy HF, White KD, et al. Public health response to puffer fish (Tetrodotoxin) poisoning from mislabeled product. Journal of food protection. 2009;72(4):810-7.
30. Food and Drug Administration. FDA Investigates Puffer Fish Poisoning Illness in Virginia U.S.2014 [cited 2014 3 July 2014]. Available from: http://www.fda.gov/food/recallsoutbreaksemergencies/outbreaks/ucm382240.htm.
31. Whittle K, Gallacher S. Marine toxins. British medical bulletin. 2000;56(1):236-53.
32. Isbister GK, Son J, Wang F, Maclean CJ, Lin CS, Ujma J, et al. Puffer fish poisoning: a potentially life-threatening condition. Med J Aust. 2002;177(11-12):650-3.

Annex 1

Distribution of TTX in puffer fish species

Family	Habitat	Species	Maximal toxicity*						
			Ovary	Testis	Liver	Skin	Intestine	Muscle	Blood
Tetraod-ontidae	Marine	Japanese pufferfish *Takifugu niphobles*	●	○	●	◎	●	○	–
		T. poecilonotus	●	◎	●	◎	◎	○	–
		T. pardalis	●	○	●	◎	◎	×	×
		T. snyderi	●	×	●	◎	◎	○	–
		T. porphyreus	●	×	●	◎	◎	×	–
		T. chinensis	●	–	●	–	–	–	–
		T. obscurus	●	×	◎	◎	◎	×	–
		T. exascurus	●	×	◎	◎	–	×	–
		T. pseudommus	●	×	○	○	○	×	–
		T. chrysops	◎	×	◎	◎	○	×	×
		T. vermicularis	◎	×	◎	◎	○	×	–
		T. rubripes	◎	×	◎	×	○	×	×
		T. xanthopterus	◎	×	◎	×	○	×	–
		T. stictonotus	◎	×	◎	○	×	×	–
		Tetraodon alboreticulatus	●	–	○	○	◎	○	–
		Pleuranacanthus sceleratus	●	–	○	○	◎	○	–
		*Chelonodon patoca***	◎	◎	◎	●	–	◎	–
		Arothron firmamentum	◎	×	×	○	×	×	–
		Canthigaster rivulata	×	–	○	◎	○	×	–
		Lagocephalus lunaris	×	×	×	◎	×	●	–
		L. inermis	×	×	◎	×	×	×	–
		L. wheeleri	×	×	×	×	×	×	–
		L. gloveri	×	×	×	×	×	×	–
		Sphoeroides pachygaster	×	×	×	×	×	×	–
	Marine	Chinese pufferfish *Takifugu flavidus*	●	◎	●	◎	◎	○	–
	Brackish	Thai pufferfish *Tetraodon nigroviridis*	–	–	×	◎	○	○	–
		T. steindachneri	–	–	×	◎	×	×	–
Diodon-tidae	Marine	Japanese pufferfish *Diodon holocanthus*	×	–	×	×	×	×	–
		Chilomycterus affinis	×	–	×	×	×	×	–
Ostraci-idae	Marine	Japanese pufferfish *Ostracion immaculatum*	×	×	×	×	×	×	–
		Lactoria diaphana	×	×	×	×	×	×	–
		Aracana aculeata	×	×	×	×	×	×	–

* ×: <10 MU/g tissue; ○: 10-100 MU/g tissue (weakly toxic); ◎: 100-1000 MU/g tissue (moderately toxic); ●: >1000 MU/g tissue (strongly toxic), where 1 MU (mouse unit) is defined as the amount of toxin that kills a male mouse of ddY strain (20 g body weight) in 30 min after intraperitoneal administration. The amount is equivalent to about 0.2 μg of TTX. -: no data available. ** Marine to brackish water species

Source: Noguchi T, Arakawa O. Tetrodotoxin-distribution and accumulation in aquatic organisms, and cases of human intoxication. Marine drugs. 2008; 6(2): 220-42.

Annex 2 Distribution of TTX in animals other than puffer fish (4)

Animals		Toxic parts
Platyhelminthes		
Turbellaria		
Flatworms	*Planocera* spp.	Whole body
Nemertinea		
Ribbonworms	*Lineus fuscoviridis*	Whole body
	Tubulanus punctatus	Whole body
	Cephalothrix linearis	Whole body
Mollusca		
Gastropoda	*Charonia sauliae*	Digestive gland
	Babylonia japonica	Digestive gland
	Tutufa lissostoma	Digestive gland
	Zeuxis siquijorensis	Whole body
	Niotha clathrata	Whole body
	Niotha lineata	Whole body
	Cymatium echo	Digestive gland
	Pugilina ternotoma	Digestive gland
Cephalopoda	*Hapalochlaena maculosa*	Posterior salivary gland (adult)
		Whole body (semi-adult)
Annelida:		
Polychaeta	*Pseudopolamilla occelata*	Whole body
Arthropoda:		
Xanthidae crabs	*Atergatis floridus*	Whole body
	Zosimus aeneus	Whole body
Horseshoe crab	*Carcinoscorpius rotundicauda*	Egg
Chaetognatha:		
Arrowworms	*Parasagitta* spp.	Head
	Flaccisagitta spp.	Head
Echinodermata:		
Starfish	*Astropecten* spp.	Whole body
Vertebrata:		
Pisces		
Goby	*Yongeichthys criniger*	Skin, viscera, gonad
Amphibia		
Newts	*Taricha* spp.	Skin, egg, ovary, muscle, blood
	Notophthalmus spp.	Skin, egg ovary
	Cynopsis spp.	Skin, egg, ovary, muscle, blood
	Triturus spp.	Skin, egg, ovary, muscle, blood
Frogs	*Atelopus* spp.	Skin
	Colostethus sp.	Skin
	Polypedates sp.	Skin
	Brachycephalus spp.	Skin, liver

Source: Noguchi T, Arakawa O. Tetrodotoxin-distribution and accumulation in aquatic organisms, and cases of human intoxication. Marine drugs. 2008; 6(2):220-42.