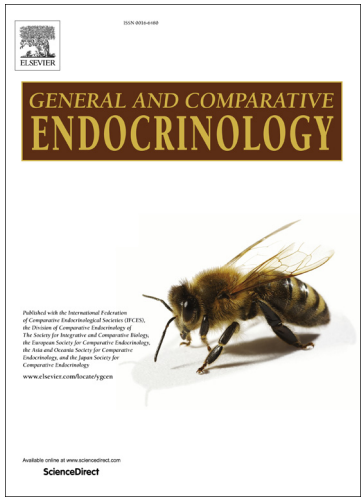

Effects of Environmental chemicals on Fish Thyroid Function: Implications for Fisheries and Aquaculture in Australia

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PII: S0016-6480(16)30037-5
DOI: http://dx.doi.org/10.1016/j.ygcen.2016.02.021
Reference: YGCEN 12319

To appear in: *General and Comparative Endocrinology*

Received Date: 5 May 2015
Revised Date: 22 February 2016
Accepted Date: 24 February 2016

Please cite this article as: Nugegoda, D., Kibria, G., Effects of Environmental chemicals on Fish Thyroid Function: Implications for Fisheries and Aquaculture in Australia, *General and Comparative Endocrinology* (2016), doi: http://dx.doi.org/10.1016/j.ygcen.2016.02.021

Effects of Environmental chemicals on Fish Thyroid Function: Implications for Fisheries and Aquaculture in Australia.

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ABSTRACT

Numerous environmental stressors exert acute or chronic effects on the fish thyroid cascade. Such effects could be mediated via thyroidal alterations, imbalance of plasma T4 and T3 levels or damage to the structure of the thyroidal tissues (thyroid hypertrophy, hyperplasia). The thyroidal system is intricately linked to other endocrine systems in vertebrates including the control of reproduction. Disruption of fish thyroid function by environmental stressors has the potential to result in deleterious effects including the inhibition of sperm production, reduction in egg production, gonad development, ovarian growth, swimming activity, fertilisation and increase in larval mortality. Thyroid hormones play a major role in the development and growth of fish, particularly during their early life stages, thus, thyroid disruption by environmental stressors could inhibit the growth of fish larvae and juveniles in wild fish and cultured species, limit fish seed production and result in a decline in wild fisheries. This review highlights the effects of several environmental toxicants including PBDE, PCBs, PCDD & PCDF, PAH/Oil, phthalates, metals, pesticides, mixed pollutants/chemicals, cyanide; and other stressors including acid (low pH) and ammonia, on fish thyroid function. Environmental sources of chemical stressors and appropriate water quality guidelines to protect the freshwater and marine species for the relevant pollutants are also discussed including (when available) the Australian guidelines (2000) and Canadian water quality guidelines (where Australian guidelines are not available). To date there has been no published research on the effects of anthropogenic environmental pollutants on the thyroid system of any native Australian fish species. However, the detection of high risk chemicals (notably PBDEs, PCBs, PAHs, metals and pesticides) in Australian waterways and Australian fish and shellfish implies that thyroid disruption of Australian wild fish and aquacultured species could occur. It is therefore imperative that the effects of such pollutants on the thyroid system of Australian native fish be investigated.

Keywords: Chemical stressors, Fish thyroid, T4, T3, Australian native fish; Fisheries, Aquaculture, PBDE, PCB, PAH, PCDD, Metals, Pesticides, Mixed pollutants

Abbreviation

AHR: Aryl hydrocarbon receptor
AMD: Acid mine drainage
ANZECC: Australian and New Zealand Environment and Conservation Council
ARMCANZ: Agriculture and Resource Management Council of Australia and New Zealand
DDT: Dichlorodiphenyltrichloroethane
DEHP: di(2-ethylhexyl) phthalate
EROD: Elevated ethoxyresorufin-O-deethylase
FT4: Free T4
FT3: Free T3
GH: Growth hormone
GSI: Gonadosomatic index
HPT: Hypothalamo-pituitary-thyroid axis
K_{ow}: octanol-water partition coefficient.

MEHP: Mono-(2-Ethylhexyl) Phthalate
mRNA: Messenger RNA
NO_X: Nitrogen oxide
PAH: Polycyclic aromatic hydrocarbons
PBDE: Polybrominated diphenyl ethers
PCB*:* polychlorinated biphenyls
PCDD: Polychlorinated dibenzo-p-dioxins
PCDF: Polychlorinated dibenzofurans
PVC: Polyvinyl chloride
SO_2: Sulphur dioxide
T3: Triiodothyronine
T4: Thyroxine
TH: Thyroid hormone
TSH: Thyroid-stimulating hormone
TT3: Total T3
TT4: Total T4
UDPGT: glucuronosyltransferase

1. Introduction

In fish, thyroid hormones (TH) are involved in the control of osmoregulation, metabolism, somatic growth, skin pigmentation, development, reproduction, post-hatching metamorphosis and behaviour (Brown et al., 2004a, 2004b; Scott and Sloman, 2004; Blanton and Specker, 2007; Brar et al., 2010; Schnitzler et al., 2011; Yu et al., 2015). TH is produced upon activation of the neuroendocrine hypothalamo-pituitary-thyroid (HPT) axis (Brown et al., 2004a; Brar et al., 2010). Under hypothalamic control, the pituitary secretes thyroid-stimulating hormone (TSH) which proceeds to the thyroid gland to activate synthesis of thyroxine (T4; 3,3',5,5'- tetraiodo-L-thyronine) and then to the biologically more active hormone 3,3',5-triiodo-L-thyronine (T3). T3 and T4 are partially composed of iodine. A deficiency of iodine leads to decreased production of T3 and T4 as TH synthesis is dependent on the availability of free iodide (Blanton and Specker, 2007). The conversion of T4 to T3 occurs in peripheral tissue including the liver. In general, T4 represents more than 95% of the thyroid hormone output and is typically present in higher quantities than T3 in the blood circulation in mammals (Hulbert, 2000). T4 and T3 promote growth, health and metamorphosis from larva to adult in fish (Lam, 1994 and literature reviewed therein, Brown et al,.2004a). The role of THs in the smoltification of salmon has also recently been elucidated (see Holzer and Laudet, 2015). T4 has been considered a prohormone, required for production of T3 (Blanton and Specker, 2007). Circulating plasma levels of T4 are similarly higher than T3 in freshwater fish (Nugegoda et al. 2000) while marine and estuarine species, including the adult Australian black bream *Acanthopagrus butcheri* have higher levels of T3 than T4 (Toogood and Nugegoda in prep.) Analysis of fish eggs and whole body tissue of fish larvae have demonstrated both T4 and T3; with freshwater species having higher quantities of T4, and conversely marine species higher quantities of T3 (Tagawa et al., 1990, Lam, 1994 and literature reviewed therein, Nugegoda et al., 1994, Nugegoda and Lam, 1995, Toogood and Nugegoda, in prep). The physiological reasons for this difference have not been investigated to date.

There is increasing evidence that endocrine disruption by exposure to chemicals is impacting adversely on wildlife, especially aquatic species adversely on a global scale (Sumpter 2003, Tyler and Goodhead,2010). Numerous environmental stressors such as chemical pollutants can exert acute or chronic effects on the fish thyroid cascade. The disruption of thyroidal status and functions by pollutants/chemical contaminants could occur at several steps in the synthesis, regulation, metabolism, and action of THs (Brown et al., 2004a; Wan and Zoeller, 2007,Brar et al., 2010). Some chemicals interfere directly with thyroid function (e.g., by inhibiting the uptake of iodine, thyroperoxidase, or thyroglobulin metabolism as reviewed by Brucker-Davis, 1998 and Decherf et al, 2010), or de-iodinase activity (Toogood and Nugegoda, in preparation). Others interfere with metabolism of the THs (e.g., by inducing glucuronidase enzymes) (Liu et al., 1995), or interact directly with TH receptors (Zoeller, 2005) and affect TH signalling (Demeneix, 2014).

Thyroid disruption could severely compromise fitness and survival in fish (Leatherland and Sonstegard., 1978; Brown et al., 2004a). Research has demonstrated that exposure to numerous pollutants have altered both T4 and T3 levels in plasma of several fish species after both acute (Sinha et al., 1991a) and chronic exposure (Hontela et al., 1995; Zhou et al., 1999, 2000; Scott and Solman, 2004). This review highlights the effects of various chemical and physical stressors on fish thyroid function/disruption and its potential implications for wild fisheries and aquaculture in Australia, since to date there is no published research on the effects of environmental stressors on the thyroid function of Australian native fish species while potential thyroid disrupting chemicals have been detected in aquatic ecosystems in Australia (as reviewed below). We have investigated, in our laboratory, the effects of an organochlorine pesticide congener and the toxic metal mercury, on THs and associated deleterious effects on larval quality and physiological endpoints in the Australian black bream (Toogood and Nugegoda, in preparation) and are currently investigating the effect of brominated flame retardants on THs in the Murray river rainbowfish *Melanotaenia fluviatilis* (Miranda and Nugegoda, unpublished). This review highlights the need for further research of this nature together with sampling of fish from contaminated sites in Australia to investigate for evidence of disruption of their thyroidal status. Environmental sources of chemical and physical stressors and appropriate water quality guidelines used to protect freshwater and marine fish species are also referred to in the relevant context.

2. Effects of environmental chemicals on thyroid function in fish, and levels of environmental chemicals in Australia

2.1. PBDEs (Polybrominated diphenyl ethers)

2.1.1 Environmental sources: PBDEs have been extensively used as flame retardants in a variety of consumer products such as plastics, textile, carpets, polyurethane foams, television sets, electronic devices, computers and building materials. They are hydrophobic, lipophilic and undergo bioaccumulation and biomagnification in the food chain (Boas et al., 2012) and persist in the environment (https://www.environment.gov.au/system/files/resources/8e81d7e1-a379-4590-b296-19e14a72d909/files/factsheet.pdf). PBDEs can be transported by air and water to locations far from their source and as a consequence PBDE contamination can be found worldwide (Lema et al, 2008). Of the various PBDEs, the penta-, octa- and

deca-brominated mixtures are the most commercially used (Muirhead et al., 2006). BDE-47 has been detected in electrical and electronic equipment waste (e-waste) recycling sites (Zheng et al. 2012).

2.1.2 Effects on fish thyroid function: Table 1, section 1.1 summarises some effects of PBDEs on fish thyroid function with reference to congeners used, targeted fish species, exposure route, exposure period, exposure concentrations and the main results of each study. PBDEs altered TH levels (TT4, FT4, TT3 and FT3; note: TT4= total T4; FT4= free T4, TT3 = total T3; FT3=Free T3) (Feng et al., 2012) in exposed fish including reducing T4 concentration: PBDEs lowered T4 levels in juvenile lake trout (*Salvelinus namaycush*) when exposed to13 BDE congeners (Tomy et al., 2004); depressed plasma T4 in fathead minnow (*Pimephales promelas*) exposed to BDE-47 (Lema et al., 2008); significantly reduced TT4 level and growth rate in zebra fish embryos (*Danio rerio*) exposed to BDE-71 from fertilization to 14 days (Yu et al., 2010) and caused decline in circulating TT4 and TT3 in fathead minnows exposed to BDE-209 (Noys et al. 2013). Other impacts of PBDE on fish include declines in the GSI and increased mortality in fathead minnows (Noys et al., 2013), reduced cumulative egg production, egg protein content and mature sperm of fathead minnows exposed to BDE-47 (Muirhead et al., 2006), affected gonad development, delayed hatching, altered swimming behaviour, and affected male gamete quantity and quality in F0 parental fish of zebra fish exposed to BDE- 209 (He et al., 2011) and delayed hatching upto 4.5 days of killifish (*Fundulus heteroclitus)* exposed to BDE-71 (Timme-Laragy et al.,2006).

2.1.3 Guidelines: There are no Australian guidelines for PBDEs. In cases where there are no Australian guidelines, the Canadian guidelines will be cited, as they are readily accessible to the public, free of charge. The Canadian Federal Environmental Quality Guidelines for Polybrominated Diphenyl Ethers are as follows: penta BDE (BDE 99, BDE100) for environmental water, fin fish tissue and sediment: 02-4 ng/L, 1 ng/g ww and 0.4 ng/g dw respectively; octaBDE (total) for environmental water and sediment 17 ng/L; 5600 ng/g dw; and decaBDE (total) for sediments 19 ng/g dw (https://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=05DF7A37-1).

2.1.4 PBDEs in Australian aquatic environments and fish tissue: In 2004, the Australian Government Department of the Environment and Water Resources commissioned a study to determine levels of PBDEs in agricultural, urban and industrial locations from all states and territories and found that PBDE levels were highest in sediments from urban and industrial areas, in particular downstream from sewage treatment plants (range: non-detected to 60,900 pg/g dry weight (dw). The sites with the highest concentrations (> 10,000 pg/g dw) were Port Phillip Bay (Victoria), Port Jackson West and the Parramatta River (New South Wales) (Toms et al. 2006; http://www.environment.gov.au/system/files/resources/6aab3116-5a64-498b-a408-a338c944379e/files/bfr-aquatic.pdf.; Toms et al. 2008) In another study, Roach et al., 2008 reported accumulation of PBDE in Australian bream (*Acanthopagrus australis*) and flounder (*Pseudorhombus jenynsi*) collected from the Sydney harbour (range 26 - 36.3 ng/g lipid). The dominant congeners detected were BDE 47 (69 %) and BDE 100 (15 %) in bream and BDE 47 (57 %), BDE 99 (15 %) and BDE 100 (8 %) in flounder. The detection of PBDEs, which are lipophilic and hence readily bioaccumulated (Toms et al. 2006) in Australian environments and fish implies that PBDEs, could result in significant detrimental effects on Australian wild fish and species culture in open systems (e.g. cages or pens) in areas where elevated PBDEs have been detected. In order to establish risks and to take appropriate actions and measures to reduce risks of PBDEs, sediment and aquatic life protection guideline values should be established for PBDEs in Australia.

2.2 PCB (polychlorinated biphenyls)

2.2.1 Environmental sources: Although the use of PCBs have been banned by the Stockholm Convention on Persistent Organic Pollutants in 2001, they are still formed as by-products during the manufacture of various types of polymeric products such as adhesives, plastic, polyethylene, pesticides and rubber. There are a total of 209 PCB compounds (congeners) possible, based on the number of chlorine atoms able to substitute for hydrogen atoms. Various commercial mixtures of PCB congeners are sold under trade names such as Aroclor, Clophen, or Kanechlor. PCBs were used in the past, mainly as dielectric fluids in electrical products such as transformers, and in hydraulic fluids, printing inks, adhesives and paints. PCBs are also formed during incomplete incineration as well as burning of waste materials in dust bins (Brown et al., 2004a). PCBs are highly stable and tend to bioccumulate (log K_{ow} 3.76 for biphenyl to 8.26 for decachlorobiphenyl) (CCME 1992) with a bio-concentration factor of 60,000-270,000. PCBs persist in the environment by having a long half-life (2-8 years) (Srogi, 2008; Kibria et al., 2010a) and are transferred up food chains with the highest levels accumulating in top predators including humans. PCBs fall into two distinct categories based on toxicity: coplanar or non-ortho-substituted congeners (similar in nature to dioxin or PCDDs/PCDF which bind to aryl hydrocarbon receptors (AhR)) in living organisms) and non-coplanar or ortho-substituted congeners (do not activate the AhR and are not part of dioxin group).

2.2.2 Effects on fish thyroid function: Table 1, section 1.2 summarises some effects of PCBs on the fish thyroid system with reference to congeners used, targeted fish species, exposure route, exposure period, exposure concentrations and main findings. Exposure of PCB congeners (Aroclor 1254, Clophen A50, PCB 77, PCB 126) caused increases in TH in fish, for example, Aroclor 1254 increased plasma T3 levels in coho salmon (*Oncorhynchus kisutch*) (Folmar et al., 1982) and Clophen A50 in flounder (*Platichthys flesus*) respectively (Besselink et al., 1996). The PCB congeners that increased T4 levels in fish were PCB 126 in lake trout (*Salvelinus namaycush*) (Brown et al., 2004b) and Clophen A50 in flounder (*Platichthys flesus*) (Besselink et al., 1996). Brar et al., (2010) reported significantly reduced T4 levels in surfperch (*Cymatogaster aggregate*) sampled from aquatic systems that were contaminated by various PCB congeners, both co-planar (dioxin-like) and non-co-planar PCBs (Brar et al., 2010). Brown et al. (2002) reported lowering of both serum T4 and T3 levels in fish exposed to PCBs; decline in muscle concentrations of T3 and T4 and growth rate in rainbow trout (*Oncorhynchus mykiss*) exposed to PCB 126. Dong et al. (2014) reported similar results in flounder (*Platichthys flesus*). PCB 77 increased hepatic T4ORD (T4 outer ring deiodination) activity and decreased plasma T3 levels in American plaice (*Hippoglossoides platessoides*) whereas PCB 126 enhanced hepatic IRD (inner-ring deiodination) activity (Adams et al., 2000).

2.2.3 Guidelines: There are no Australian guidelines for PCBs in aquatic sediments. Guidelines for the protection of aquatic life (sediments): Canadian interim sediment quality guidelines for the protection of freshwater and marine/estuarine life are 34.1 µg/kg dw and 21.5 µg/kg dw respectively and for Aroclor 1254 are 60 µg/kg dw (freshwater) and 63.3 µg/kg dw (marine/estuarine) (http://ceqg-rcqe.ccme.ca/download/en/244). Trigger values for the protection of aquatic life: Aroclor 1242 (the most toxic form and thus most heavily researched), 0.43 µg/L (99 % protection of freshwater species) and Aroclor 1245, 0.01 µg/L (99 % protection of freshwater species) (ANZECC & ARMCANZ, 2000).

2.2.4 PCBs in Australian aquatic systems and fish tissue

PCBs were detected in fish from Perth, Hobart, Sydney, Brisbane, Townsville and Atherton (concentration range 0.22 to 720 ng/g wet weight), of which fish sampled from Sydney, Brisbane and Hobart contained relatively higher concentrations than those from other areas

such as Townsville and Atherton. In particular, fish sampled from Sydney contained high concentrations of PCBs. These include the snapper *Pagrus auratus*(22-34 ng/g wet wt), morwong *Nemadactlys douglasii* (99-100 ng/g), blue groper *Acheorodus viridis* (720 ng/g) and shovelnose ray *Aptychotrema rostrata* (5.6-160ng/g) (Kannan et al. 1995; https://www.environment.gov.au/system/files/resources/d1dc8aaa-7c4c-4641-ad08-f8cc8a1c613b/files/pcbmonitoring.pdf). The detection of PCBs in Australian environments and fish implies that PCBs could result in significant effects on Australian wild fish and species culture in open systems (cages and pens) in areas where elevated PCBs have been detected. In order to establish risks and to take appropriate actions and measures to reduce risks of PCBs, sediment and aquatic life protection guideline values should be established for PCBs in Australia.

2.3. PCDDs (polychlorinated dibenzo-p-dioxins) & PCDFs (polychlorinated dibenzofurans)

2.3.1 Environmental sources: Dioxins are ubiquitous all over the world including the Arctic and Antarctic due to long range aerial transport. They are released into the environment as a result of combustion activities including power generation, waste incineration (e.g. municipal, medical waste), metal smelting, chlorine bleaching of pulp and paper mill and manufacture of some chemicals (e.g. pesticides and herbicides). They are also produced from natural processes such as bushfires and forest fires, compost burning, wood stoves and volcanoes. Dioxins are extremely persistent and can bio-accumulate in the body fat of fish, wildlife, other animals (e.g. domestic and farm animals) and humans. Dioxins tend to remain unchanged for long periods and are carcinogenic (IARC class 1). Aquatic organisms may take up PCDD/Fs from water or sediment, or through the consumption of contaminated food (Kibria et al., 2010a).

2.3.2 Effects on fish thyroid function: Table 1, section 1.3 summarises some effects of PCDDs and PCDFs on fish thyroid with reference to congeners used, targeted fish species, exposure route, exposure period, exposure concentrations and the main results of each study. TCDD depressed plasma total T4 levels in European flounder (*Platichthys flesus)* but did not result in changes to total T3 or free T4 in plasma (Besselink et al., 1997). Exposure to P_5CDF did not modify the seasonal plasma T4 and T3 patterns, but caused transient reductions in circulating lymphocytes and elevated ethoxyresorufin-O-deethylase (EROD), increased liver size and depleted retinoid stores in male rainbow trout fish (*Oncorhynchus mykiss*) (Brown et al., 1998).

2.3.3 Guidelines: There are no Australian guidelines for PCDDs and PCDFs. Guidelines for the protection of aquatic life: Canadian interim sediment quality guidelines for the protection of freshwater and marine/estuarine life are 0.85 ng/kg dw (freshwater) and 0.85 ng/kg dw (marine/estuarine) (http://ceqg-rcqe.ccme.ca/download/en/245).

2.3.4 PCDDs in Australian aquatic systems and fish tissue

Müeller et al., 2004 carried out a reconnaissance survey to determine PCDD and PCDF levels in Australian aquatic environments. The authors reported elevated PCDD and PCDF at estuarine sediment samples compared to the samples from freshwater and marine locations (*freshwater:* not detectable to 3,500 pg/g dry matter (mean 490 pg/g dry matter); *estuarine:* 7.6-110,000 (mean 14,000 pg/g dry matter); *marine*: not detectable to 2,500 pg/g dry matter (mean 460 pg/g dry matter (Müeller et al., 2004)). PCDD and PCDF were also detected in bivalves (0.43-230 pg/g fresh mass) and fish (0.17-4.4 pg/g fresh mass).

2.4. PAHs (polycyclic aromatic hydrocarbons)/Oil

2.4.1 Environmental sources: PAHs include acenaphthene, naphthalene, anthracene, phenanthrene, benzo[a]pyrene and are often a result of environmental pollution by oil and oil spills. Other environmental sources of PAHs include refinery effluents, aluminium smelting, domestic sewage, storm water runoff and the wood preservative industry (Kibria *et al.* 2010).
2.4.2 Effects on fish thyroid function: Table 1, section 1.4 summarises some effects of PCDDs and PCDFs on fish thyroid with reference to congeners used, targeted fish species, exposure route, exposure period, exposure concentrations and the main results of each study. Benzo[a]pyrene elevated testosterone, and caused significant increase in plasma free T3 concentration in Areolated grouper (*Epinephelus areolatus*) (Wu et al., 2003) and impaired ovarian growth and decreased circulating sex steroids in Atlantic croaker (*Micropogonias undulatus)* (Thomas, 1990). Water soluble crude oil increased whole body concentrations of T4, increased larval mortalities and affected swimming activity of larvae of Turbot (*Scophthalmus maximus*) (Stephens et al., 1997).
2.4.3 Guidelines: There are no Australian guidelines for PAHs except for naphthalene: Naphthalene 16 µg/L (95 % protection of freshwater species) and 50 µg/L (99 % protection of marine species) (ANZECC & ARMCANZ, 2000). Guidelines for the protection of aquatic life: Canadian Water Quality Guidelines for the Protection of Aquatic Life for PAHs are as follows: Freshwater life protection: Acenaphthene (5.8 µg/L), Acridine (4.4 µg/L), Anthracene (0.012 µg/L), benz(a)anthracene (0.018 µg/L), benzo(a)pyrene (0.015 µg/L), fluoranthene (0.04 µg/L), fluorene (3.0 µg/L), naphthalene (1.1 µg/L), phenanthrene (0.4 µg/L), pyrene (0.025) µg/L, quinoline (3.4 µg/L); Marine: Naphthalene 1.4 µg/L (http://ceqg-rcqe.ccme.ca/download/en/201).
2.4.4 PAHs in Australian aquatic systems and fish tissue: PAHs were detected in Australian fish including sea mullet *(Mugil cephalus*; 54-195 ng/g), bony bream (*Nematolosa come;* 64-77 ng/g), blue cat fish (*Arius graeffei;* 43-56 ng/g) and mud crab *(Scylla serrata*; 56-156 ng/g) (wet weight basis) (Kayal and Connell, 1995).

2.5. Phthalates

2.5.1 Environmental sources: Phthalate esters such as di(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DBP) and di-n-octyl phthalate (DOP) are a group of industrial chemicals extensively used as plasticizers in a variety of commercial products, such as polyvinyl chloride (PVC) floors, food packaging, clothing, toys, films, paints, adhesives, lubricants, cosmetics, electronics, ink printers and biomedical devices (e.g., blood transfusion bags) (Kibria et al. 2010). Of the various phthalates, DEHP is one of the most frequently used phthalates which accounts for approximately 50 % of total plasticizer production (Zhai et al., 2014).
2.5.2: Effects on fish thyroid function: Table 1, section 1.5 summarises some effects of phthalates on fish thyroid with reference to congeners used, targeted fish species, exposure route, exposure period, exposure concentrations and main results of each study. Exposure of DEHP (5000 mg DEHP kg/body weight) caused significant increase in the hepatic somatic index of male fish, a reduction in fertilisation success of spawned oocytes, and a reduction in the proportion of spermatozoa in zebra fish (*Danio rerio*) (Uren-Webster et al., 2010). Zhai et al., 2014 found significantly decreased whole-body T4 contents and increased whole-body T3 contents in zebra fish embryos/larvae after exposure to Mono-(2-Ethylhexyl) Phthalate or MEHP) (a metabolite of DEHP) inferring that the upregulation of genes related to thyroid hormone metabolism (*Dio2* and *UGT1ab*) may be responsible for decreased T4 content. Exposure to MEHP also significantly induced transcription of genes involved in thyroid

development (*Nkx2.1* and *Pax8*) and TH synthesis (*TSHβ*, *NIS* and *TG*). However, genes encoding proteins involved in TH transport (transthyretin, *TTR*) were down-regulated after exposure to MEHP indicating toxicity (Zhai et al., 2014).

2.5.3 Guidelines: There are no Australian guidelines for Phthalates (DEHP). Guidelines for the protection of aquatic life: Canadian Water Quality Guidelines for the Protection of Aquatic Life for Phthalates are as follows: Freshwater life protection: 16 µg/L for DEHP and 19 µg/L for DBP (http://ceqg-rcqe.ccme.ca/download/en/206). Trigger values for the protection of aquatic life: dibutyl-phthalate 9.9 µg/L (99 % protection of freshwater species), Diethyl-phthalate 1,000 µg/L (95 % protection of freshwater species) (ANZECC & ARMCANZ, 2000).

2.5.4 Phthalates in Australian aquatic systems and fish tissue There is no information available on the levels of phthalates in Australian environments or biota. However phthalates (DEHP, DBP) have been detected in sediments and surface waters China, Denmark, Germany, Italy, Malaysia and the Netherlands (Kibria et al., 2010a). Huang et al., 2008 reported accumulation of phthalates to various levels in a number fish in Taiwan including the Nile tilapia *Oreochromis miloticus niloticus*, greenback mullet *Liza subviridis*, blackhead seabream *Acanthopagrus schlegeli,* pale chub *Zacco platypus* and Taiwan torrent carp *Acrossocheilus paradoxus* with the highest concentration of DEHP in *Liza subviridis* (1.7–253.9 mg/ kg dw) and *Oreochromis miloticus niloticus* (1.4-129.5 mg/kg dw) (Huang et al., 2008).

2.6. Trace metals/metalloids

2.6.1 Environmental sources: Human activities such as mining, industry and sewage treatment discharges as well as electronic wastes (computers, printers, photocopy machines, TV sets, mobile phones and toys) and agriculture (agriculture fertilizers) are some of examples of anthropogenic sources contributing to the elevated levels of trace metals in aquatic environments (Kibria et al. 2010a; Hossain et al. 2015).

2.6.2 Effects on fish thyroid function: Table 1, section 1.6 summarises some effects of trace metals on fish thyroid with reference to compounds used, targeted fish species, exposure route, exposure period, exposure concentrations and main findings. Plasma T4 and T3 levels were found significantly elevated in brown trout (*Salmo trutta*) from a habitat (forest stream) polluted with aluminium and with a low pH (acidic) environment (Whitehead and Brown, 1989). Arsenic decreased or delayed the increase in plasma T4 level in coho salmon (*Oncorhynchus kisutch*) (Nicholos et al., 1984). Short term acute (2-4 h) exposure increased both plasma cortisol and T4 levels in juvenile rainbow trout (*Oncorhynchus mykiss*) (Hontela et al., 1996) but had no effect on plasma T3; however, following a subacute exposure (0.4 and 0.8 mg Cd/L for one week), plasma cortisol levels of the exposed fish increased, plasma T4 levels decreased and plasma T3 levels remained stable. Juvenile and adult rainbow trout that had been exposed for a longer period (30 days) had decreased plasma T4 and T3 levels. This appeared to be directly correlated with the lower cadmium exposure concentrations of 10 and 25 µg Cd/L for adults, and 1 and 5 µg Cd/L for juveniles Ricard et al., (1998). The liver size, glycogen content and body mass gain were also significantly reduced in the exposed juvenile and adult rainbow trout (Ricard et al., 1998) indicating an overall deterioration in the physiological health of the fish possibly mediated through endocrine function. Exposure of the walking catfish (*Clarias batrachus*) to cadmium reduced thyroid epithelial cell height, lowered plasma TH concentrations and resulted in a significant reduction in gonosomatic index (ratio of gonad weight to whole body weight) (Jadhao et al., 1994). Cadmium exposure in rainbow trout resulted in delayed growth hormone mRNA

expression (Jones et al., 2001). Lead (5 mg/L) impaired thyroid function and lead (25 mg/L) caused thyroid epithelial cell hypertrophy, reduced thyroid colloid content, inhibited thyroid iodine uptake (^{131}iodine; radioiodine) in the walking catfish *Clarias batrachus* (Katti and Sathyanesan, 1987) and lowered plasma TH concentrations in *C. batrachus (*Gupta et al., 1997). Exposure to compounds of mercury increased both plasma T3 and T4 in rainbow trout (*O. mykiss*) (Bleau et al., 1996) while exposure to inorganic mercury depressed TT3 and increased TT4 in the plasma of juvenile Australian black bream *Acanthopagrus butcheri* (Toogood and Nugegoda, in preparation).

2.6.3 Guidelines: Guidelines for the protection of aquatic life: Trigger values for the protection of aquatic life: aluminium at pH > 6.5 55 µg/L (95 % protection of freshwater species); arsenic III 13 µg/L (95 % protection of freshwater species); cadmium 0.2 µg/L and 0.7 µg/L (for 99 % and 95 % protection of freshwater and marine species respectively); lead 3.4 µg/L and 0.4 µg/L (95 % protection of freshwater and marine species, respectively); mercury (inorganic) 0.06 µg/L and 0.1 µg/L (99 % protection of freshwater and marine species, respectively) (ANZECC & ARMCANZ, 2000).

2.6.4 Trace metals in Australian aquatic systems and fish tissue: Metals (chromium, cadmium, copper, mercury, lead, zinc) were detected in various catchments in Australia including North and Central Victorian Waterways (Kibria et al. 2010b). Cadmium, copper, lead, mercury and zinc had also been detected in muscle tissue in a number of Australian commercial fish harvested from New South Wales waters including yellowfin bream *(Acanthopagrus australis)*, dusky flathead *(Platycephalus fuscus),* sea mullet *(Mugil cephalaus)*, snapper (*Chrysophris auratu)*, tailor (*Pomatomus saltatrix*) mulloway (*Sciaena Antarctica)*, yellow tail kingfish *(Seriola grandis)*, Australian salmon (*Arripis trutta)* and yellowfin tuna (*Thunnus albacares)* (Bebbington et al., 1977). Brown et al. (2004c) reported contamination of fish: dusky flathead (*Platycephalalus fuscus*) and luderick (*Girella tricuspidata*) and shellfish (Sydney cockle *Anadara trapezia* and Sydney rock oyster *Saccostrea commercialis*) with metals (arsenic, cadmium, lead, mercury, zinc) harvested from lake Illawarra, New South Wales.

2.7. Pesticides

2.7.1 Environmental sources: Pesticide residues may enter into the environment as a result of spray drift, vaporisation, surface run-off, unlawful acts, spills and drainage discharges, and through leaching or soil dusts (Kibria et al., 2010a).

2.7.2 Effects on fish thyroid function: Table 1, section 1.7 summarise some effects of pesticides on fish thyroid with reference to targeted fish species, exposure route, exposure period, exposure concentrations and main findings. Pesticides such as carbaryl (Sinha et al., 1991b) and endrin (Bhattacharya et al., 1978) decreased plasma T4 levels in walking catfish (*Clarias batrachus*) and climbing perch (*Anabas testudineus*), respectively. Exposure to DDT resulted in a decrease in thyroid epithelial cell height, degeneration in epithelial cells and depleted cell colloid in mullet (*Liza parsia*) (Pandey et al., 1995). Exposure to endosulfan for 96 hours significantly increased serum T4 and pharyngeal thyroid follicles concurrent with induction of peroxidase activity in the walking catfish (*Clarias batrachus*). However, the T3 level and T3/T4 ratio decreased in serum. No change was noticed in any of these parameters in the anterior kidney but in the posterior kidney endosulfan reduced T3 and the T3/T4 raio without affecting T4 levels and peroxidase activity. Sixteen days of endosulfan treatment also had a similar impact, except that it did not influence the studied parameters in pharyngeal thyroid (Sinha et al.,1991a). Malathion decreased thyroid radioiodide uptake and

caused thyroid hyperplasia and hypertrophy in spotted snakehead (*Channa punctatus*) (Ram et al., 1989). Endrin reduced radioiodide uptake into thyroid follicles and reduced pituitary and serum TSH content in stinging catfish (*Heteropneustes fossilis*) (Singh and Singh, 1980). Ghosh et al., (1989) found that exposure to Metacid-50 (an organophosphate pesticide) and Carbaryl (a carbamate pesticide) caused a significant inhibition of brain acetylcholinesterase activity together with a lowering of serum T4 levels with a concurrent increase in acetylcholine and serum T3 in spotted snakehead (*Channa punctatus*), and concluded that both neural and hormonal functions in fish were affected by these pesticides.

2.7.3 Guidelines: *Guidelines* for the protection of aquatic life: Trigger values for the protection of aquatic life: endrin 0.01 µg/L; parathion 0.004 µg/L; malathion 0.05 µg/L; DDT 0.006 µg/L and endosulfan 0.03 µg/L (99 % or 95 % protection of freshwater species), cadmium 0.2 µg/L and lead 3.4 µg/L (99 % and 95 % protection of freshwater species) (ANZECC & ARMCANZ, 2000).

2.7.4 Pesticides in Australian aquatic systems and fish tissue: Pesticides such as carbaryl (Schafer et al., 2011), DDT (Wightwick and Allinson, 2007), endosulfan (Rose and Kibria, 2007), endrin (Wightwick and Allinson 2007) and methyl parathion (Rose and Kibria, 2007) that pose a high risk to the health of non-target aquatic biota were detected in Australian surface waters.

2.8. Cyanide (SCN-)

2.8.1 Environmental sources: Main sources are from gold and silver mining used to dissolve these metals and their ores. It is a normal metabolite in fungi, bacteria, and blue–green algae and is formed by the release of cyanogenic glycosides during decomposition of higher plants (Brown et al. 2004a).

2.8.2 Effects on fish thyroid function: Table 1, section 1.8 summarises some effects of cyanides on fish thyroid with reference to targeted fish species, exposure route, exposure period, exposure concentrations and the main results of the study. Cyanide decreased plasma T4 and T3 levels in rainbow trout (*Oncorhynchus mykiss*) (Ruby et al., 1993) and caused thyroid hyperplasia and reduced colloid content in both juvenile rainbow trout (*Oncorhynchus mykiss*), and in fathead minnows (*Pimephales promelas*) (Lanno and Dixon, 1994; Lanno and Dixon 1996a; Lanno and Dixon 1996b).

2.8.3 Guidelines: *Guidelines* for the protection of aquatic life: Trigger values for the protection of aquatic life: 7 µg/L (95 % freshwater species protection); 4 µg/L (95 % marine species protection) (ANZECC & ARMCANZ, 2000).

2.9. Acidification of water (low pH)

2.9.1 Environmental sources: Acid precipitation caused by sulphur dioxide (SO_2), nitrogen oxide (NOx) emissions from industries, acid mine drainage (AMD) and climate change (rise of atmospheric CO_2) can depress surface water pH.

2.9.2 Effects on fish thyroid function: Table 1, section 1.9 summarises some effects of cyanides on fish thyroid with reference to targeted fish species, exposure route, exposure period, exposure concentrations and the main results of the study. Rainbow trout (*Oncorhynchus mykiss*) and brown trout (*Salmo trutta*) exposed to acidic water (pH 4) had elevated plasma T4 and decreased or unaltered T3 levels (Brown et al., 1984; Brown et al., 1989). Ocean acidification (due to increased CO_2) caused reduced survival and reduced growth rates of the estuarine fish silverside *Menidia beryllina* (Baumann et al., 2012) and

lethal tissue damage resulted in many internal organs (liver, pancreas, kidney, eye and the gut) of larvae of Atlantic cod (*Gadus morhua*) with the degree of damage increasing with CO_2 concentration (Frommel et al., 2012).

2.9.3 Guidelines: Guidelines for the protection of aquatic life: Trigger values for the protection of aquatic life: pH 6.5-8.0 (freshwater lakes & reservoirs); pH 7.0-8.5 (estuaries); and pH 8.0-8.4 (marine) (ANZECC & ARMCANZ, 2000).

2.10. Ammonia (NH_3)

2.10.1 Environmental sources: The major environmental sources of ammonia are municipal wastewater treatment plants, agricultural wastes from animal-rearing facilities, fertilizers and pulp mills, mines and food processing plants.

2.10.2 Effects on fish thyroid function: Table 1, section 1.10 depicts some details about the effects of ammonia on fish thyroid with reference to concentrations, targeted fish species, exposure route, exposure period, exposure concentrations and main findings. Exposure of ammonia to fish (snake head, *Channa punctatus* and climbing perch, *Anabas testudineus*) decreased plasma T4 levels and enzyme thyroidal glutathione peroxidase activity (Nathde and Bhattacharya, 1976; Bhattacharya et al., 1989). Ammonia exposure lowered kidney iodide peroxidase activity in spotted snakehead (*Channa punctatus*) (Nathde and Bhattacharya 1976; Murkerjee and Bhattacharya 1975). In teleost fish, since they lack a definite thyroid gland the kidney plays a very important role in biosynthesis of the thyroidal hormone, in which peroxidase has an indirect action. Any chemical that fish kidney peroxidase activity will interfere with their thyroid physiology (Murkerjee and Bhattacharya, 1975). Exposure to high levels of ammonia also resulted in thyroid gland hypertrophy (increase in cell size), hyperplasia (increased cell number), hyperemia (increase of blood flow) and reduction in colloid content in spotted snakehead (Ram and Sathyanesan, 1987).

2.10.3 Guidelines for the protection of aquatic life: Trigger values for the protection of aquatic life: 10 µg N/L (nitrogen per litre) (freshwater lakes & reservoirs); 15 µg N/L (estuaries); 15 µg N/L (marine) (ANZECC & ARMCANZ, 2000).

2.11. Mixed pollutants

2.11.1 Environmental sources: Direct or indirect discharge of effluents from agriculture, aquaculture, domestic, industries, mining, paper and pulp mills, waste water treatment plants and sewage sludge etc.

2.11.2 Effects on fish thyroid function: Some researchers found that fish from highly polluted habitats or that had been exposed to a mixture of chemicals had higher plasma T4 levels (De and Bhattacharya et al., 1976; Singh, 1989; Munkittrick et al., 1991; Zhou et al., 2000; Carletta et al., 2002) while others reported that they had lower plasma T4 levels (Leatherland and Sonstegard, 1978; Hontela et al., 1995; Levesque et al. 2003; Brar et al., 2010; Schnitzler et al., 2011). Others found evidence for larger thyroid follicles and taller thyroid epithelial cell heights in fish that had been exposed to pollutants (Zhou et al., 2000; Carletta et al., 2002) while some report that fish from polluted sites had smaller gonads (Munkittrick et al., 1991; Hontela et al., 1995) or lower epithelial cell height of thyroid follicles (Levesque et al., 2003; Schnitzler et al., 2011). Xu et al., (2002) found that free T3 in serum was significantly increased in fish that had been exposed to mixed pollutants and these fish also had elevated ethoxyresorufin-O-deethylase (EROD) and UDP glucuronosyltransferase (UDPGT) activities. Additional effects reported included significantly reduced gonadosomatic index (GSI) (Singh, 1989), lower muscular TH

concentrations, smaller thyroid follicles surrounded by epithelial cells with a less pronounced cell height, and a higher hepatic EROD activity (Schnitzler et al., 2011). Effects of industrial pollutants and factory effluents on fish kidney peroxidase activity were observed in the freshwater murrell (*Ophicephalus punctatus)* and the catfish (*Clarias batrachus)* (Murkerjee and Bhattacharya, 1975). Silver carp (*Hypophthalamichthys molitrix)* from a highly contaminated pond system with mixed pollutants in the Yangtze River region, China, had lowered T4 levels and showed visible deformities (Nugegoda et al., 2000, 2001).

2.11.3 Guidelines for the protection of aquatic life: see 2.1 to 2.10 for trigger values for various individual chemical and physical stressors (no guidelines exist for mixtures, as every combination is different).

3. Implications for Australian Wild Fisheries and Aquaculture

Wild fish populations and aquaculture fish species would be at risk from environmental stressors (chemical and physical stressors) since they cause significant impact on fish thyroid function via thyroidal alterations, imbalance of plasma T4 and T3 levels, damage to thyroid structure and systems (thyroid hypertrophy, hyperplasia) as evidenced by the literature cited in this review. Disruption of fish thyroid function by environmental toxicants like PBDEs, PCBs, PAHs, phthalates, metals, pesticides and mixed pollutants could result in a number of adverse effects on wild fisheries and aquaculture species including inhibition of sperm production, reduction in egg production, gonadal development, ovarian growth, swimming activity, fertilisation and increase in larval mortality. Thyroid hormones are important in the development and growth of fish, particularly during their early life stages, thus thyroid disruption by exposure to environmental toxicants could inhibit the growth of fish larvae and juveniles and reproduction in adults in wild and cultured fish. The result would be reduced fish production, and recruitment resulting in the decline of valuable wild fisheries. In particular, with an increase in environmental pollution and detectable levels of endocrine disrupting and other organic chemicals in Australian freshwaters (Scott et al., 2014a,b) and coastal marine waters (Toms et al., 2008). It is apparent from this review that there are no previous studies on the effects of environmental chemicals on fish thyroid disruption of Australian fish and aquacultured species. However, the detection of high risk chemicals (notably PBDEs, PCBs, PAHs, metals and pesticides) in Australian waterways and Australian fish and shellfish (as highlighted in sections 2.1.4, 2.2.4, 2.3.4, 2.4.4, 2.5.4, 2.6.4, 2.7.4) implies that thyroid disruption of Australian wild fish and aquacultured species, especially those in open culture (ponds and cages) could occur or may indeed be occurring.

The Australian continent has been geologically isolated for millennia and Australian aquatic ecosystems (especially freshwater) contain numerous and unique native and endemic species of fish (Allen et al. 2002), many of which are threatened and outcompeted by invasive species (Lloyd and Walker, 1986. Sunderam et al, 1992). There are few studies on the effects of toxicants on Australian fish (Kibria et al.,2010 and references therein); and most research on the effects of EDCs has been restricted to the reproductive system of one or two species held in the laboratory (Shanthanagouda et al., 2013, Batiya et al, 2015). The comparative sensitivity of different Australian fish to EDCs has not been investigated. However, in a study evaluating the effects of pesticides on the Murray cod (*Maccullochella peelii peelii*) and the Murray river rainbowfish (*Melanotaenia fluviatilis*), Raymond et al. (2006) found that early life stages of the Murray cod were resilient to the tested chemicals while those of the Murray river rainbowfish were far more sensitive. Published research on the effects of toxicants on the thyroid physiology of fish are restricted to Northern Hemisphere species (see table 1) and

most commonly, the laboratory bred zebrafish *Danio rerio* (Zhai et al, 2014). In this context, it is also worth noting that phylogenetic analyses of aromatase gene isoforms in the Australian *M. fluviatilis* clustered closely with that of the pejerrey (*Odontesthes bonariensis*), a closely related athernid found in South America, and not with those of Northern Hemisphere species (Shanthanagouda et al. 2011). These observations raise the question as to whether research on the effect of toxicants on Northern hemisphere laboratory fish species is adequate to predict the effects of toxicants on the physiology of Australian fish.

It is therefore imperative that the effects of chemical pollutants on the thyroid system of Australian native fish, especially endemic and threatened species, be investigated and wild populations in contaminated areas be monitored for evidence of thyroid disruption. In addition, several environmental toxicants (PBDE, PCBs, metals and pesticides) can bio-accumulate at high concentrations in fish muscle and other organs (Kibria et al., 2010a and references therein) posing a threat to seafood security and human health in Australia. Strict compliance with aquatic and sediment protection guideline values is essential in order to minimise risks of seafood contamination and impairment of fisheries in Australia.

Conflict of interest

There is no conflict of interest. Both authors (DN and GK) contributed equally to this paper.

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Table 1: Examples of previous research on environmental chemicals and their effects on thyroid function and impairment of health in fish.

[**BTEX** hydrocarbons=benzene, toluene, ethylbenzene, xylene; **BW**=body weight; **D**=days; **DBTC**= di-n-butyltindichloride; **DEHP**= (di(2-ethylhexyl) phthalate); **Deiodinase**= iodide peroxidase or "Monodeiodinase" is a peroxidase enzyme that is involved in the activation or deactivation of thyroid hormones; **FT3**=free T3; **FT4**= free T4; **GSI**= gonadal-somatic index (gonad mass as a proportion of the total body mass); **hpf:** hour post fertilization; **HPT**= hypothalamic-pituitary-thyroid axis; **MEHP**= (mono-(2-ethylhexyl) phthalate (MEHP), the active metabolite of DEHP; **mRNA**=messenger RNA (mRNA) that convey genetic information from DNA to the ribosome, where they specify the amino acid sequence of the protein products of gene expression; **NA**= not available; **PAH**=polycyclic aromatic hydrocarbons; **PBDE**=Polybrominated diphenyl ethers; **PCDD**= Polychlorinated dibenzodioxins or dioxins; **PCDF**= Polychlorinated dibenzofurans or furans; **TBTO**= bis(tri-n-butyltin)oxide; **TCDD**=2,3,7,8-Tetrachlorodibenzo-p-dioxin; **TH**= thyroid hormone; **TT3**= Total T3; **TT4**=; **T4**= thyroxine; **T3**= triiodothyronine; **TCDD**= 2,3,7,8-tetrachlorodibenzo-p-dioxin; **T4ORD**=outer ring deiodination].

Chemicals	**Chemical congener /class**	**Fish species**	**Exposure route**	**Fish age, exposure period**	**Exposure concentration**	**Main results**	References
1.1: PBDE	BDE-47	Fathead minnow, *Pimephales promelas*	Dietary	Adult fish; 21 days	2.4 and 12.3 µg/pair/day	Depressed plasma TT4 in 12.3 µg/pair/day group in both male and female fish; altered TH signalling at multiple levels of the hypothalamic-pituitary-thyroid (HPT) axis; Fewer mature spermatozoa in 12.3 µg/pair/day group	Lema et al., 2008
	BDE-47	Fathead minnow, *Pimephales promelas*	Dietary	25 days	28.7 µg/g	Reduced cumulative egg production and egg protein content; lost weight; erratic swimming behaviour; significant decreased in mature spermatozoa with male fish	Muirhead et al., 2006
	6-OH-BDE-47) 6-MeO-BDE-47	Zebrafish, *Danio rerio*	Waterborne	4-120 hpf, 116 h	8, 40 and 200 µg/L	Altered expression of genes involved in HPT axis	Zheng et al. 2012
	BDE-71	Zebra fish, *Danio rerio*	Waterborne	2 hpf; 14 days	1, 3 and 10 µg/L	Reduced TT4 levels in 10 µg/L group; altered expression of genes involved in HPT axis; significantly inhibited fish growth (grow inhibition could be due to disruption of TH production in zebrafish embryos and larvae by chemical)	Yu et al., 2010
	BDE-71	Killifish, *Fundulus heteroclitus*	Waterborne	0–7 days post fertilization	0.001-100 µg/L (0.001, 0.1, 0.5, 1, 10, 100 µg/L)	Delayed in hatching (upto 4.5 days); caused in tail curvature	Timme-Laragy et al.,2006
	BDE-71	Zebra fish, *Danio rerio*	Waterborne	2 hpf; 150 days	1, 3 and 10 µg/L	Higher TT4 levels in adult females and F1 larvae; altered expression of genes involved in HPT axis	Yu et al., 2011
	BDE-71	Zebra fish, *Danio rerio*	Waterborne	Adult fish, 30 days	16, 50, 160 and 500 µg/L	Decreased cumulative egg production	Kuiper et al., 2008
	BDE-71	Zebra fish, *Danio rerio*	Waterborne	Embryos; 120 days	0.005, 1 and 50 µg/L	Reduced spawning, fertilization, hatching success and larval survival	Han et al., 2013
	BDE-71	Zebra fish, *Danio rerio*	Waterborne	3 month old; 60 days	0.45 and 9.6 µg/L	Reduced egg production and egg protein content	Chen et al., 2012a
	BDE-209	Fathead minnow, *Pimephales promelas*	Dietary	28 days	3 ng/g and 300 ng/g bw-day	Decline in TT4 and TT3 in 3 and 300 ng/g groups; declines in the GSI and increased mortality of fathead	Noys et al., 2013
	BDE-209	Zebra fish, *Danio rerio*	Waterborne	8 hpf; 5 months	0.001–1 µM (0.001, 0.01, 0.1 and 1 µM)	Affected gonad development (decreased GSI, sperm quantity and quality); delayed hatching; altered swimming behaviour; reduced testis weight and sperm production	He et al., 2011
	BDE-209	Rare minnow, *(Gobiocypris rarus)*	Waterborne	Larvae; 21 days. Adult, 21 days	0.01, 0.1, 1 and 10 µg/L	Altered mRNA levels of TH related genes in the larvae and liver of adult fish; Lower GSI in females; altered expression of spermatogenesis genes	Li et al., 2014
	BDE-209	Zebra fish, *Danio rerio*	Waterborne co-exposed nano-TiO_2 and BDE-209	embryos	0.08 and 0.38 mg/L BDE-209 and 0.38 BDE-209 with TiO_2 NPs 0.1 mg/L	Bioaccumulation of BDE-209 Significantly increased whole-body thyroid hormone contents (T3 and T4); T4 content significantly increased in the larvae co-exposed with nano-TiO^2. Upregulation of several gene transcriptions (tshβ, tg, dio2) in the hypothalamic-pituitary-thyroid axis was also observed. Co-exposure of nano-TiO2 and BDE-209 caused a decrease in locomotion activity	

						and downregulation of specific genes and proteins involved in the central nervous system of developing zebrafish larvae	
	BDE-28, - 47, - 66, -77, - 85, - 99, - 100, -138, - 153, - 154, - 183, -190, - 209	Lake trout, *Salvelinus namaycush*	Dietary	Juvenile, 56 days	2.5 and 25 ng/g	Lowered T4 levels in 2.5 and 25 ng/g groups	Tomy et al., 2004
1.2: PCBs	Aroclor 1254	Coho salmon, *Oncorhynchus kisutch*	Waterborne	6 weeks, yearling	50,100, 150 µg/kg	Alterations in the normal developmental patterns of T4, delayed plasma T4; significant mortalities	Folmar et al., 1982
	Aroclor 1254	Japanese flounder, *Paralichthys olivaceus*	Waterborne	Juvenile, 25 or 50 days	10, 100, and 1000 ng/L	Exposure for 50 days increased follicular cell height, colloid depletion, and hyperplasia (enlargement of an organ); significantly decreased of plasma TT4, TT3 and FT3 levels; environmentally relevant concentrations of Aroclor 1254 caused significant thyroid disruption	Dong et al., 2014
	Aroclor 1254, Aroclor 1260	Sea bass, *Dicentrarchus labrax*	Dietary	7 to 20 g; 120 days	0.3, 0.6, 1.0 and 10.0 µg/ g per g of food pellets	Exposure to environmentally relevant doses of PCB (0.3–1.0 µg) modified hepatic T4 outer ring deiodinase and induced the hormone synthesis and secretion .	Schnitzler et al. 2011
	Clophen A50	Flounder, *Platichthys flesus*	Waterborne	18.0 and 22.0 cm (2 years of age)	20, 100 and 500 mg/kg body weight (BW)	Did not result in a dose-related alteration of total T4 concentrations in plasma; total T3 concentrations in plasma were only significantly increased at day 2 after exposure; it is concluded that flounder is not a sensitive species to PCB exposure	Besselink et al., 1996
	PCB 77, PCB 126	American plaice, *Hippoglossoides platessoides*	Dietary	78 g, 121 g	5, 25, 50, 500 ng/g	PCB 77 increased hepatic T4ORD (outer ring deiodination) activity and decreased plasma T3 levels (5 and 25 ng/g); PCB 126 enhanced hepatic IRD (inner-ring deiodination) activity (50 and 500 ng/g).	Adam et al., 2000
	PCB126	Lake trout, *Salvelinus namaycush*	Dietary	3+ years, 336 ± 7 g,	0, 0.7, 1.2, 25, 40 µg/kg BW	Only highest doses of PCB 126 caused increased thyroid epithelial cell height and plasma T4 dynamics and there were no effects on fish growth or condition.	Brown et al., 2004b
	PCB 126	Rainbow trout, *Oncorhynchus mykiss*	Dietary	Juvenile; 2–5 g, 160 days	12.4, 126 ng/g wet weight	Muscle concentrations of T4 and T3 were declined as the fish grew	Brown et al., 2002
	PCBs	Surfperch, *Cymatogaster aggregate*	Wild fish	Sampled from the highly impacted sites	-	T4 significantly reduced; altered T4 deiodination	Brar et al., 2010
1.3: PCDD & PCDF	TCDD	Flounder, *Platichthys flesus*	Waterborne	10 days	0.01, 0.1, 1, 10, or 100 mg TCDD/kg BW	TCDD depressed plasma TT4 levels at 100 µg but no changes in TT3 or FT4 plasma levels	Besselink et al., 1997
	P_5CDF	Rainbow trout, *Oncorhynchus mykiss*	Waterborne	2–4 years old fish; 967 g; 10 months	1 ml/kg or 8.8 nmol/ml; 3 µg/ml	Exposure to P_5CDF did not modify the seasonal plasma T4 and T3 patterns; the P_5CDF exposure caused transient reductions circulating lymphocytes and elevated ethoxyresorufin-O-deethylase (EROD), increased liver size and depleted retinoid stores in male rainbow trout	Brown et al., 1998
1.4: PAH	Benzo[a]pyrene (B[a]	Areolated grouper, *Epinephelus areolatus*	Dietary	Juvenile (26.6 g), 4 weeks	0.25 µg, 12.5 µg B[a]P/g body wt/d	Growth and RNA:DNA ratio were unaltered; plasma FT3 concentrations were significantly increased in the fourth week; development and reproduction may potentially be at risk during chronic exposures	Wu et al., 2003
	Crude oil (BTEX hydrocarbons)	Turbot, *Scophthalmus maximus*	Waterborne	Larval and juveniles, 6 h, 25 h, 33 h	25, 33 and 50% WSF (water soluble fraction) of crude oil	Water soluble crude oil increased whole body concentrations of TT4 and affected the swimming activity; it caused increased in larval morality (yolk-sac larvae were found most sensitive compared to larvae and juvenile fish- the higher lipid content in yolk-sac could possibly have caused higher hydrocarbon uptake and thus more mortality); larval activity was found significantly reduced	Stephens et al., 1997
1.5: Phthalates	DEHP	Zebrafish, *Danio rerio*	Waterborne	Embryos (6, 8 and 24 hpf),	0.5, 50 and 5000 mg DEHP kg/BW	Caused significant increase in the hepatic somatic index of male fish, a reduction in fertilisation success of spawned oocytes, and a reduction in the proportion of	Uren-Webster et al., 2010

				10 days		spermatozoa (rom exposure of 5000 mg); survival and development of the resulting embryos were unaffected by all treatments, and no evidence of DEHP-induced sperm DNA damage was observed	
	MEHP	Zebrafish, *Danio rerio*	Waterborne	Embryos 2 hpf-168 hpf	1.6, 8, 40, and 200 µg/L	Significantly decreased whole-body T4 contents and increased whole-body T3 from exposure of 200 µg/L; deiodinases (Dio1 and Dio2) were found significantly induced after MEHP exposure; induction in the transcription of Dio2 may be responsible for the reduction of T4 contents; increased transcription of Dio1 may have assisted to degrade the elevated T3 contents	Zhai et al., 2014
	DEHP, MEHP	Marine medaka, *Oryzias melastigma*	Waterborne	Larvae, 6 months	0.1 and 0.5 mg/L	Exposure to DEHP accelerated the start of spawning, decreased the egg production of exposed females; both DEHP and MEHP resulted in a reduction in the fertilization rate of oocytes; exposure to DEHP and MEHP caused endocrine disruption with males being more sensitive than females	Ye et al., 2014
1.6: Metals	Aluminium	Brown trout, *Salmo trutta*	Wild fish (forest stream)	10-15 cm, 4 days	pH 4.8, Al (600 mg/L)	Plasma T4 and T3 levels were found significantly elevated from a habitat polluted with aluminium and with a low pH acidic environment	Whitehead and Brown., 1989
	Arsenic	Coho salmon, *Oncorhynchus kisutch*	Waterborne	Parr-smolt; 6 months	300 µg As/L (as As_2O_3)	Decreased or delayed the increase in plasma T4 level; Coho salmon smolt were less successful in migrating to the sea from freshwater	Nicholos et al., 1984
	Cadmium	Rainbow trout, *Oncorhynchus mykiss*	Dietary	Immature male, female fish (80 g); 2, 4, 24, and 96 h, one week in hard water	0.4, 0.8 and 2.4 mg Cd/L; 0.4 and 0.8 mg Cd/L	Caused increased in both plasma cortisol and T4 levels but had no effect on plasma T3 (2-4 hours); Following a subacute exposure (1 week), plasma T4 levels decreased and plasma T3 levels remained stable	Hontela et al., 1996
	Cadmium	Rainbow trout, *Oncorhynchus mykiss*	Dietary	Adults (582 g) and juveniles (59 g); 30 days	10 and 25 µg Cd/L for adults, 1 and 5 µg Cd/L for juveniles (Cd as $CdCl_2$)	There was no significant variation in the plasma thyroid hormone levels, although a trend toward an exposure-related decrease in plasma T3 and T4 was revealed; fish exposed to Cd grew less and had lower energy reserves; the liver size, glycogen content and body mass gain were significantly reduced in the exposed juvenile and adult rainbow trout	Ricard et al., 1998
	Cadmium	Rainbow trout, *Oncorhynchus mykiss*	Waterborne	Embryos and larvae	103 µg/L	Delayed growth hormone (GH) mRNA expression	Jones et al., 2001
	Cadmium	Walking catfish, *Clarias batrachus*	-	7, 14 and 28 days	Cd Cl_2	Reduced thyroid epithelial cell height and lowered plasma TH concentrations; significant reduction in GSI	Jadhao et al., 1994
	Lead	Walking catfish, *Clarias batrachus*	-	150 days	5, 10, 25 mg/L	Lead (5 mg/L) impaired thyroid function; lead (25 mg/L) caused thyroid epithelial cell hypertrophy, reduced thyroid colloid content, inhibited thyroid iodine uptake (iodine 131 or radioiodine)	Katti and Sathyanesan, 1987
	Mercury	Rainbow trout, *Oncorhynchus mykiss*	Dietary	Juvenile; 4, 72 and 168 h	$HgCl_2$- 28, 112 µg/l Hg^2, CH_3HgCl- 12 and 24 µg/L Hg	Exposure to both mercury compounds increased plasma T4 and T3 levels	Bleau et al., 1996
	Mercury	Walking catfish, *Clarias batrachus*	Waterborne	70g	0.125 mg/L CH_3HgCl	Exposure to 0.125 mg/L decreased both plasma TT4 and TT3 levels	Kirubagaran and Joy., 1994
	Mercury	Black bream *Acanthopagrus butcher*	Waterborne	9g (6 month old) and 17g (18 month old) juveniles	1, 10 or 100 µg/L HgCl	Mercury depressed TT3 and increased TT4 in the plasma indicating downreguation of deiodinase activity	Toogood and Nugegoda in prep.)

	Tin-TBTO, DBTC	Japanese medaka, *Oryzias latipes*	Waterborne	Eggs, 1, 3 months (TBTO) and 1 month (DBTC)	TBTO: 0.1-32 µg/L and DBTC: 320-3200 µg/L	A series of histopathological effects on eyes, liver, kidney, and gas gland that included thyroid gland activation were observed at the highest concentrations.	Wester et al., 1990
1.7: Pesticides C=carbamate OC= organochlorine; OP=organophosphate	Carbaryl (C)	Snakehead, *Channa punctatus*	NA	NA	NA	Inhibited brain acetylcholinesterase activity and decreased in thyroxine level	Ghosh et al., 1989
	Carbaryl (C)	Walking catfish, *Clarias batrachus*	Waterborne	55-60 g; 96 h	12 mg/L	A decline in TT4 and an elevation in TT3 was observed	Sinha et al., 1991b
	DDT (OC)	Mullet, *Liza parsia*	Waterborne	15 days, 10.5 cm	0.02 mg/L	Resulted in a decrease in thyroid epithelial cell height, degeneration in epithelial cells, and depleted colloid	Pandey et al., 1995
	Endosulfan (OC)	Walking catfish, *Clarias batrachus*	Waterborne	55-60 g; 96 h	0.008 mg/L	Caused a significant increase in TT4 and a decrease in TT3 in plasma	Sinha et al., 1991b
	Endrin (OC)	Climbing perch, *Anabas testudineus*	Waterborne	48 h	0.005 mg/L	The thyroid formed less T4, monoiodotyrosyl (MIT), and diiodotyrosine (DIT)	Bhattacharya et al. 1978
	Malathion (OP)	Stinging catfish, *Heteropneustes fossilis*	Waterborne	96 h	10 mg/L	Malathion increased TT3 concentrations and reduced TT4 concentrations	Yadav and Singh, 1987
	Malathion (OP)	Walking catfish, *Clarias batrachus*	Waterborne	55-60 g; 96 h	0.007 ml/L	Decreased TT3 without altering the level of TT4	Sinha et al., 1991b
	Amitrole (H) 3-amino-1,2,4-triazole	Rare minnow, *Gobiocypris rarus*	Waterborne	0.39 g Three months old;	1, 10, 100, 1000, 10,000 ng/l	Plasma TTH levels did not change; livers were degenerated at 10,000 ng/; amitrole exposure could result in alternations of expression of TH-related genes transthyretin (ttr), deiodinases (d1, d2), and the thyroid hormone receptor (tra) gene expression; the expression of TH-related genes in males was more sensitive to amitrole than those of females	Li et al., 2009
1.8: Cyanide	HCN	Rainbow trout, *Oncorhynchus mykiss*	Waterborne	234-411 g (348 g), 12 days	0.01 mg/L HCN	Significant declines in plasma levels of both reproductive and metabolic hormones and T3; reproductive indicators including GSI and oocyte diameters also declined significantly, T4 showed lower values among HCN-exposed groups but the decline was not significant	Ruby et al., 1993
1.9: Acidification	Acidity	Air-breathing fish, *Anabas testudineus*	Waterborne	Freshwater (FW), salinity adapted (SA) water (20 ppt), 48 h, 96 h	pH 4.2, pH 5.2	A significant increase in plasma T4 was found after acidic exposure of both freshwater and salinity adapted air breathing fish	Peter and Rejitha, 2011
	Acidity	Brown trout, *Salmo trutta*	Waterborne	100-370 g fish	pH 4.0, pH 4.6	Increased plasma T4 in the brown trout after 3 h exposure to acid water having pH 4.0, most fish did not survive in acidic water	Brown et al., 1989
	Ocean acidification (CO_2)	Atlantic cod, *Gadus morhua*	Waterborne	Newly fertilized eggs to seven weeks post-hatch larvae	CO_2 concentrations: present day 380 µatm; medium (end of next century): 1,800 µatm and high (extreme): 4,200 µatm	Exposure to elevated CO_2 resulted in severe to lethal tissue damage in many internal organs, with the degree of damage increasing with CO_2 concentration; tissue damage was found in the liver, pancreas, kidney, eye and the gut of larvae of 32 days post hatch, thus may cause mass morality of fish (Cod) in the wild.	Frommel et al., 2012
	Ocean acidification (CO_2)	Estuarine fish, silverside *Menidia beryllina*	Waterborne	Fertilized eggs (<24 h old)	CO_2 concentrations: 390 to 1,100 ppm	Increased CO_2 caused severely reduced survival and growth rates; exposure of embryos to 1,000 ppm CO_2 reduced average survival and length by 74% and 18%, respectively, of which the egg stage was found more vulnerable to high CO_2-	Baumann et al., 2012

						induced mortality than the post-hatch larval stage	
1.10: Ammonia	Ammonia	Snake head, *Channa punctatus,* Climbing perch *Anabas testudineus*	Waterborne	30 days	NA	Caused an increase of iodide peroxidase (IPOD) activity and a decrease in plasma T4 levels	Bhattacharya et al., 1989
	Ammonium sulfate	Snake head, *Channa punctatus*	Waterborne	6 months	100 mg/L, 500 mg/L	Resulted in thyroid gland hypertrophy (increase in cell size), hyperplasia (increased cell number), hyperemia (increase of blood flow), and reduction in colloid content in spotted snakehead	Ram and Sathyanesan, 1987

- Environmental stressors exert acute or chronic effects on the fish thyroid cascade
- There has been no published research on the effects of anthropogenic environmental pollutants on any Australian native fish species
- This paper reviews effects of environmental toxicants and other stressors on fish thyroid function
- Highlights implications for wild Fisheries and cultured native fish in Australia