Comparative Biochemistry and Physiology, Part C 238 (2020) 108853

Contents lists available at ScienceDirect

Comparative Biochemistry and Physiology, Part C

journal homepage: www.elsevier.com/locate/cbpc

Review

The effects of exposure to crude oil or PAHs on fish swim bladder development and function

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ARTICLE INFO

Keywords:
Petrochemicals
Gas bladder
Polycyclic aromatic hydrocarbons
Surface film
Swim-up behavior

ABSTRACT

The failure of the swim bladder to inflate during fish development is a common and sensitive response to exposure to petrochemicals. Here, we review potential mechanisms by which petrochemicals or their toxic components (polycyclic aromatic hydrocarbons; PAHs) may affect swim bladder inflation, particularly during early life stages. Surface films formed by oil can cause a physical barrier to primary inflation by air gulping, and are likely important during oil spills. The act of swimming to the surface for primary inflation can be arduous for some species, and may prevent inflation if this behavior is limited by toxic effects on vision or musculature. Some studies have noted altered gene expression in the swim bladder in response to PAHs, and Cytochrome P450 1A (CYP1A) can be induced in swim bladder or rete mirabile tissue, suggesting that PAHs can have direct effects on swim bladder development. Swim bladder inflation failure can also occur secondarily to the failure of other systems; cardiovascular impairment is the best elucidated of these mechanisms, but other mechanisms might include non-inflation as a sequela of disruption to thyroid signaling or cholesterol metabolism. Failed swim bladder inflation has the potential to lead to chronic sublethal effects that are as yet unstudied.

1. Introduction

The major components of petrochemicals that are putatively believed to cause toxicity in fish are polycyclic aromatic hydrocarbons (PAHs) (Incardona et al., 2013). Three- to five-ring members of this class of molecules, in particular, can cause embryotoxicity at concentrations observed during oil spills (Hodson, 2017). These toxic effects include acute mortality as well as sub-lethal effects that may reduce survival and fitness later in life (Heintz et al., 2000; Hicken et al., 2011; Incardona et al., 2015; Mager et al., 2014). One commonly observed phenotype in larval PAH exposure studies is failed or delayed inflation of the swim bladder (Alves et al., 2017; Incardona et al., 2004; Li et al., 2019; McIntyre et al., 2014; Vergauwen et al., 2015) (Table 1). Given the importance of this organ to maintaining proper buoyancy, it is likely that this phenotype has consequences for metabolic efficiency and swimming performance (Czesny et al., 2005; Gee, 1983; Marty et al., 1995), and ultimately, survival.

At a physiological level, impaired cardiac development and function are major toxic consequences of PAH exposure. Pericardial edema is frequently reported in response to PAH exposure (Incardona et al., 2013; Pasparakis et al., 2019; Philibert et al., 2016; Wincent et al., 2015), and is accompanied by reduced cardiac function (Edmunds et al., 2015; Incardona et al., 2013; Incardona et al., 2012; Khursigara et al., 2017; Li et al., 2019; Madison et al., 2015; McIntyre et al., 2014). Such effects on the heart may be mediated by cardiac aryl hydrocarbon receptor (AhR) signaling, although PAHs can also elicit effects via AhR-independent mechanisms (Incardona et al., 2011). Other oil-induced physiological phenotypes are therefore often thought to be secondary effects of reduced cardiac function (Incardona et al., 2004; Incardona et al., 2013; Li et al., 2019; Pasparakis et al., 2019). Failed swim bladder inflation is often considered to be one of these secondary effects (Li et al., 2019), although other mechanisms are also possible. Here, we review the various studies documenting failed swim bladder inflation as a result of oil or PAH exposure, and discuss the several potential mechanisms driving this abnormality.

2. Relevant biology of the swim bladder

The swim bladder is an air-filled organ that can have several functions, including involvement in hearing and sound production, but is notably important for maintaining neutral buoyancy (Tytler, 1978). Physostomes, including most soft-rayed fish, retain a connection – the pneumatic duct – between the gut and the swim bladder throughout life. Initial inflation occurs by gulping air at the surface and diverting it to the swim bladder (Goolish and Okutake, 1999; Lindsey et al., 2010; Tait, 1960). Regulation of swim bladder volume also generally occurs

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https://doi.org/10.1016/j.cbpc.2020.108853
Received 11 February 2020; Received in revised form 3 July 2020; Accepted 27 July 2020
Available online 08 August 2020

Table 1
Studies reporting swim bladder inflation outcomes after exposure to oil, water-accommodated fractions, PAHs, or derivatives in early life stage fish.

Study	Species	Chemical	Notes
Li et al. (2019)	Zebrafish (*Danio rerio*)	Oman and Merey crude oils	Non-inflation observed.
Alves et al. (2017)	Zebrafish (*Danio rerio*)	Gas station effluents containing PAHs	Complete inhibition of swim bladder inflation at high concentrations
Wincent et al. (2015)	Zebrafish (*Danio rerio*)	Soil Extracts containing PAHs and Oxygenated PAHs	Non-inflation observed
Chibwe et al. (2015)	Zebrafish (*Danio rerio*)	PAH-contaminated Soil Extracts	Non-inflation; reduced after bioremediation
McIntyre et al. (2014)	Zebrafish (*Danio rerio*)	Highway runoff	Non-inflation observed
Geier et al. (2018)	Zebrafish (*Danio rerio*)	Mixture of 10 PAHs prevalent in a contaminated site, and individual PAHs	Non-inflation in high concentration mixtures of PAHs
Legler et al. (2011)	Zebrafish (*Danio rerio*)	Extracts from landfill soil	Non-inflation when exposed to extracts containing nitrogenated PAHs
Incardona et al. (2004)	Zebrafish (*Danio rerio*)	7 PAHs	Non-inflation after exposure to several PAHs
Alharthy et al. (2017)	Zebrafish (*Danio rerio*)	Benzo[*a*]pyrene	Complete inhibition of swim bladder inflation
Corrales et al. (2014)	Zebrafish (*Danio rerio*)	Benzo[*a*]pyrene	Multigeneration study following parental exposure. F1 fish had reduced inflation, but F2 fish had higher inflation rate than controls
Vergauwen et al. (2015)	Zebrafish (*Danio rerio*)	Phenanthrene	Non-inflation observed
Knecht et al. (2013)	Zebrafish (*Danio rerio*)	38 specific oxygenated PAHs	Several OPAHs caused swim bladder non-inflation (see also Table 3)
González-Doucel et al. (2008)	Medaka (*Oryzias latipes*)	Fresh and weathered *Prestige* oil	Oils caused non-inflation following embryonic exposure
Madison et al. (2015)	Medaka (*Oryzias latipes*)	Dilbit, retene, and dispersant	Inflation failure associated with dilbit, retene, and dispersant
Madison et al. (2017)	Medaka (*Oryzias latipes*)	Dilbit and dispersant	Inflation failure associated with dilbit and dispersant.
Koehler and Hardy (1999)	Medaka (*Oryzias latipes*)	Outboard motor emissions	Swim bladder absence at high concentrations
Mu et al. (2017)	Medaka (*Oryzias latipes*)	PAH mixtures from contaminated sediment	Hypoxia caused inflation failure, which was exacerbated by co-exposure to PAHs.
Le Bihanic et al. (2014a)	Medaka (*Oryzias latipes*)	PAH mixtures from contaminated sediment and Arabian Light and Erika crude oils	No significant effect; variation might be caused by measurement at various times between 0 and 24 hph
Lin et al. (2015)	Medaka (*Oryzias latipes*)	Several PAHs and alkyl PAHs	Non-inflation observed with all chemicals
Le Bihanic et al. (2014b)	Medaka (*Oryzias latipes*)	Fluoranthene	Non-significant trend toward non-inflation; small sample size may limit power
Ortiz-Delgado and Sarasquete (2004)	Gilt-head Bream (*Sparus aurata*)	Benzo[*a*]pyrene	No effect on swim bladder inflation up to 1 μg per liter

by gulping air at the surface and releasing air by diffusion to the blood or via the pneumatic duct and anus. Some physostomes also have some degree of volume regulation via a gas gland, although gas secretion rates are not as high as those of physoclists (Blaxter and Batty, 1990; Tytler, 1978; Smith and Croll, 2011). Other physostomes lack a gas gland completely, although some gas secretion may occur by cells in the swim bladder wall (Finney et al., 2006; Smith and Croll, 2011). The commonly studied zebrafish is apparently unable to secrete gas into the swim bladder and requires access to the surface for regulation of its volume (Smith and Croll, 2011). This trait may make the zebrafish a simplified model for studying toxicological effects on swim bladder inflation, although it may also limit applicability to other taxa.

Physoclists, including most of the spiny-rayed fishes, lack a connection between the gut and the swim bladder as adults. Many of these species have a pneumatic duct at early life stages but lose the connection between the gut and the swim bladder during development. That is, many physoclists are transient physostomes. For these species, initial inflation occurs by gulping air at the surface as in physostomes (Al-Abdul-Elah, 1990; Chatain and Ounais-Guschemann, 1990; Kitajima et al., 1981; Rieger and Summerfelt, 1998; Tsuji et al., 2016). After the pneumatic duct atrophies however, swim bladder volume can only be regulated via the gas gland/ovale system, which tends to have much greater capacity in physoclists than physostomes (Blaxter and Batty, 1990). Gas secretion to the swim bladder is achieved under high pressure by a counter-current multiplier system (rete mirabile) in the blood vessels that lead to the gas gland. Gas resorption in physoclists occurs in many cases via the ovale, a specialized region of the swim bladder that is controlled by a sphincter muscle (Lagler et al., 1962).

2.1. Primary (initial) inflation

Primary inflation of the swim bladder by surface air gulping is a critical developmental event in many fish, including both physostomes and physoclists (Chatain and Ounais-Guschemann, 1990; Kitajima et al., 1981; Lindsey et al., 2010; Rieger and Summerfelt, 1998). Failed primary inflation is a major source of mortality in aquaculture, and has been observed in natural populations as well (Egloff, 1996). Some physostomes are known to be able to achieve 'late' inflation if denied air access at early life stages (Tait, 1960), although fish may incur stress and reduced survival rates until inflation is achieved (Goolish and Okutake, 1999). Physoclists that fail to inflate the swim bladder can survive to adulthood in the wild (Egloff, 1996), but survival rates are greatly diminished, as failed inflation is associated with difficulties with feeding (Czesny et al., 2005), slower growth (Czesny et al., 2005; Marty et al., 1990), and greater susceptibility to stress (Chatain, 1989). These effects are thought be the direct result of non-inflation of the swim bladder, primarily owing to higher energy expenditures associated with swimming to maintain position in the water column (Czesny et al., 2005; Marty et al., 1995; Palińska-Żarska et al., 2013). Additionally, non-inflation often causes lordosis (excessive spinal curvature) (Al-Abdul-Elah, 1990; Goolish and Okutake, 1999; Iwasaki et al., 2017; but see Kurata et al., 2015; Kitajima et al., 1981; Paperna, 1978) which occurs due to swimming at an angle (Chatain, 1994), and can sometimes be rescued by late-inflation of the swim bladder (Chatain, 1994).

Although some physoclists achieve initial inflation via gas secretion by the gas gland or other mechanisms (Doroshev et al., 1981; Johnston, 1953; McEwan, 1940; Perlberg et al., 2008; Schwartz, 1971), many physoclists (those that are transient physostomes) have a critical window of time during which primary inflation must occur by gulping surface air (Bailey and Doroshov, 1995; Trotter et al., 2005). This is likely due to the extremely high partial pressures required to maintain a small gas bubble (Al-Abdul-Elah, 1990; Tytler, 1978).

In physoclists, the pneumatic duct generally regresses by the end of the larval period (Czesny et al., 2005), but it often stays patent for longer in individuals that fail to inflate the swim bladder; inflation itself appears to be the stimulus for duct atrophy (Bulak and Heidinger, 1980;

Goodsell et al., 1996; Trotter et al., 2005). Other mechanisms may also prevent inflation by gulping surface air after this critical window, such as collapse and adhesion of the swim bladder (Trotter et al., 2005) and hypertrophy and epithelial proliferation of the swim bladder and gas gland (Bennett et al., 1987; Goodsell et al., 1996; Paperna, 1978). Thus for some species, swim bladder inflation does not seem to occur following this developmental window (Bennett et al., 1987; Egloff, 1996; Trotter et al., 2005). In other species, a 'late' inflation may occur in a high percentage of fish that originally failed to inflate during the critical window (Chatain, 1994; Jacquemond, 2004; Kurata et al., 2015). The mechanism by which this late inflation occurs is unknown, but is thought to be via gas gland secretion (Chatain, 1994; Jacquemond, 2004). Nonetheless, these late-inflating individuals are often poorer quality compared to 'normal'-inflating individuals, having small swim bladders (Chatain, 1994; Jacquemond, 2004), a higher incidence of lordosis that may not be rescued by late inflation (Chatain, 1994), and slow juvenile growth (Kurata et al., 2015).

For both physostomes and those physoclists that are transiently physostomous, surface air gulping is accomplished by a stereotyped swimming toward the surface termed 'swim-up behavior' (Lindsey et al., 2010; Palińska-Żarska et al., 2013; Rieger and Summerfelt, 1998). This can involve multiple upward movements toward the surface, separated by resting while attached to a substrate (Lindsey et al., 2010), whereas some deep-water species are capable of swimming long distances upward to the surface without resting (Tait, 1960).

In this review, we bring together information on the biology of various species in an attempt to understand the effects oil and PAHs can have on the swim bladder in general. However, most studies of petrochemicals and the swim bladder have been conducted on only two species, zebrafish (*Danio rerio*) and medaka (*Oryzias latipes*) (Table 1). We have summarized the basic swim bladder biology for these two species in Table 2. Although it is useful to conduct research with model species, this also means that there may be much more variation in swim bladder responses to PAHs than is currently known (cf. Pasparakis et al., 2019).

3. Potential causes of swim bladder defect

The effect of oil exposure on swim bladder inflation could occur by various mechanisms (Fig. 1). Here we divide these into two broad categories: failed primary inflation, and diminished swim bladder function.

3.1. Failed primary inflation

3.1.1. Presence of a surface film

Because physostomes and most physoclists achieve primary inflation by gulping air, an oily film at the surface can prevent larvae of these species from breaking the water-air boundary and inflating the swim bladder. Oily surface films caused by food have long been known to cause swim bladder non-inflation in aquaculture, and are remedied by surface skimming (Chatain and Ounais-Guschemann, 1990; Kurata et al., 2012; Trotter et al., 2005; Tsuji et al., 2016).

Although we know of no documented failure of fish inflating their swim bladders due to oily films associated with crude oil spills, this seems like a likely consequence given the extent and thickness of oil slicks in large oil spills (MacDonald et al., 2015). Many laboratory studies of the toxic consequences of oil exposure use water-accommodated fractions (WAF), which remove the floating slick layer. Thus, failed swim bladder inflation with such preparations (e.g., Li et al., 2019) suggest that other mechanisms are mediating effects on swim bladder inflation. Madison et al. (2015) noted that any component of oil that affects surface tension of water might increase rates of failed inflation, and they attributed the high rates of inflation failure in Japanese medaka exposed to diluted bitumen and/or dispersants to an altered air-water interface. Nonetheless, small concentrations of PAHs are capable of inhibiting swim bladder inflation presumably without altering surface tension, suggesting other mechanisms can be responsible for failed inflation.

3.1.2. Inability to complete swim-up

The swim-up procedure is a complex behavior integrating the function of multiple physiological systems. Therefore, fish can be prevented from gulping air by failure of any of the physiological systems involved in swimming behavior, including abnormal muscle development, neurological or visual impairment (Magnuson et al., 2018), and cardiovascular performance. The common laboratory model zebrafish, for example, has an arduous swim-up procedure, requiring several movements toward the surface separated by resting on substrates (Lindsey et al., 2010). Thus for this species, failure to inflate the swim bladder could occur as a secondary effect resulting from failed swim-up behavior, the latter occurring due to the failure of some other system. In studies where inflation versus noninflation is merely an endpoint and fish behavior is not recorded, it can be difficult to distinguish this mechanism from other, more direct mechanisms.

3.1.3. Failed inflation due to developmental abnormality of the swim bladder

Developmental abnormality can prevent inflation, as evidenced by complete inhibition of inflation by estradiol-treated zebrafish (Alharthy et al., 2017). The cause of such developmental abnormalities could potentially include downstream effects of cardiotoxicity, as well as direct toxic effects on swim bladder tissues. Notably, CYP1A activity can be induced in the swim bladder rete mirabile by Benzo[*a*]pyrene (Schlezinger and Stegeman, 2000), demonstrating a potential for direct effects of PAH on swim bladder or rete tissue.

As part of a syndrome of toxicity, abnormal or failed swim bladder inflation often occurs alongside reduced cardiovascular function upon exposure to crude oils or PAHs (Alves et al., 2017; Incardona et al., 2004; Li et al., 2019; McIntyre et al., 2014) (Fig. 2). This has led to the hypothesis that failed inflation is a secondary consequence of cardiac impairment (Incardona et al., 2004).

Several studies have demonstrated experimentally that proper swim bladder development is dependent on cardiac function. Working with a circulation knockdown morphant zebrafish, Winata et al. (2010) demonstrated that blood circulation was necessary for growth of the anterior chamber primordium of the swim bladder, while other aspects of the swim bladder appeared normal. Circulation knockdown morphants also failed to inflate the swim bladder (Winata et al., 2010). Such an effect might be mediated directly by lack of circulation to the swim bladder.

In another zebrafish study, a circulation knockdown morphant had

Table 2
Common fish models in petrochemical toxicology, their normal inflation period, and critical windows of toxicant exposure leading to failed swim bladder inflation.

Species	Anatomy	Normal Period of Swim Bladder inflation	Critical Window of Exposure
Zebrafish (*Danio rerio*)	Physotome	72–120 hpf. Only 15% inflated by 96 h (Lindsey et al., 2010).	PAHs: Unknown. TCDD: 72–96 hpf (Yue et al., 2015) TBC: 72–96 hpf (Li et al., 2011)
Medaka (*Oryzias latipes*)	Physoclist (transient physostome)	0–24 h post-hatch (González-Doucel et al., 2008; Marty et al., 1995)	PAHs: Unknown.

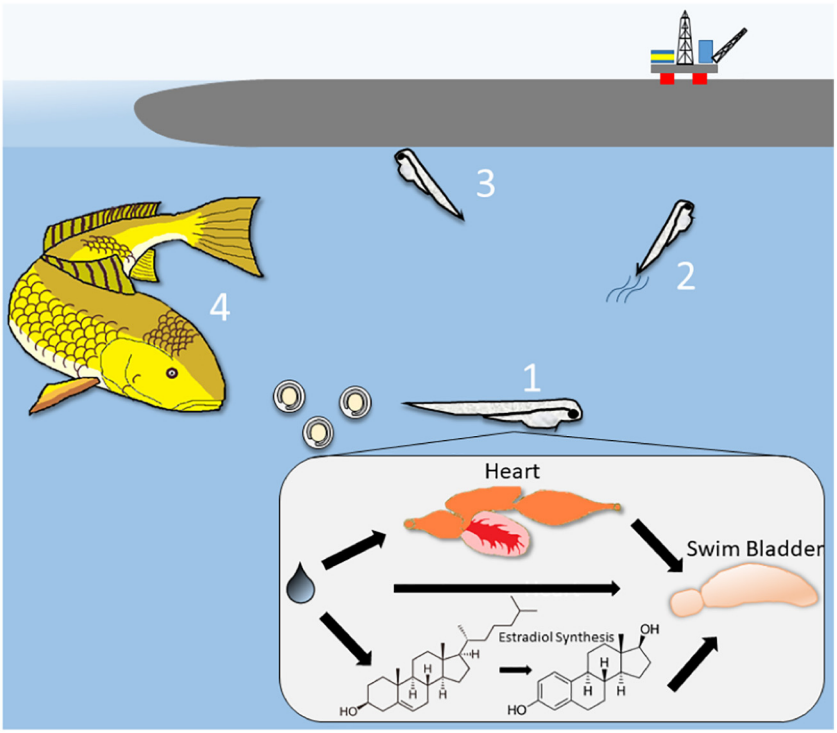

Fig. 1. Potential mechanisms by which petrochemicals can impair swim bladder function. Exposure at early life stages can lead to failed swim bladder development by direct effects of PAHs on the swim bladder or indirect actions via cardiovascular impairment, hormone imbalance, or other routes (1). Swim bladder inflation may be prevented if swim-up behavior is diminished (2) by these or other toxic effects, such as underdeveloped musculature or impaired vision. Initial inflation can also be prevented if larvae cannot gulp air at the surface due to the physical barrier of oil or other surface films (3). Adults may suffer diminished gas gland function following exposure to PAHs (4).

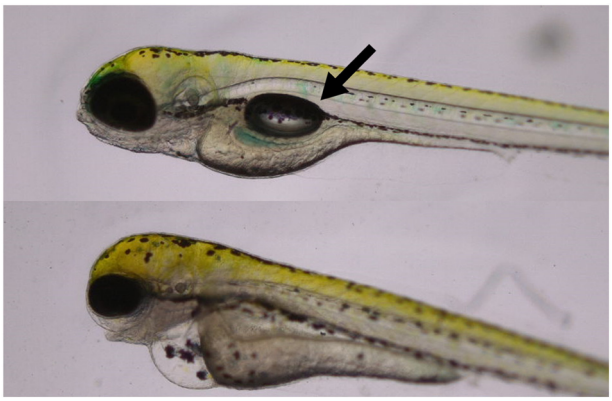

Fig. 2. Zebrafish larvae (96 hpf) showing inflated (top; arrow) and non-inflated (bottom) swim bladders. The bottom animal was exposed to a water-accommodated fraction of *Deepwater Horizon* crude oil starting a few hours post-fertilization; the top animal was unexposed. Note the pericardial edema present in the exposed fish. Photo credit: Fabrizio Bonatesta.

no swim bladder inflation, and normal swim bladder growth was stopped at a similar developmental timepoint as that caused by 2,3,7,8-tetrachlorodibenzodioxin (TCDD) exposure, a toxicant that is thought to affect the heart by an AhR-mediated mechanism (Yue et al., 2015). The same researchers also used a plasmid DNA construct to induce AhR signaling in a cardiomyocyte-specific manner. The resultant transiently transgenic fish had heart failure and malformation, and swim bladder growth and elongation failed at a similar developmental stage, strongly suggesting that swim bladder defect can occur as a secondary sequela of cardiac impairment (Yue et al., 2015; see similar findings by Lanham et al., 2014). Interestingly, TCDD exposure needed to occur prior to 96 h post-fertilization (hpf) to impair swim bladder inflation (Yue et al., 2015), a time course that aligns with that for zebrafish exposed to the brominated flame retardant tris(2,3-dibromopropyl) isocyanurate (TBC) (critical exposure window of 72–96 hpf), a toxicant that also causes cardiac impairment (Li et al., 2011). The existence of this critical window after which exposure does not prevent inflation further supports the interpretation that inflation failure is a secondary effect of cardiac impairment affecting swim bladder growth and elongation, as opposed to an effect mediated via surface films (inflation usually occurs at 96–120 hpf; Table 2). Oil and PAHs can cause a similar mechanism of swim bladder inflation failure as a downstream consequence of cardiac impairment: exposing zebrafish to several concentrations of crude oil WAFs, Li et al. (2019) found a strong negative correlation between cardiac output and the percentage of fish that failed to inflate the swim bladder.

Although these studies demonstrate that cardiac impairment alone can prevent proper swim bladder inflation, they do not preclude additional direct toxic effects on the swim bladder (Li et al., 2019; Yue et al., 2015). For example, Li et al. (2019) found changes in zebrafish swim bladder gene expression that were dependent on dosage of exposure to crude oil WAFs, and concluded that swim bladder non-inflation at high doses may result from direct (or synergistic) toxic effects on the swim bladder. Additionally, some studies have rescued the cardiotoxic effect of select PAHs or other toxicants – for example by inhibiting AhR2 signaling – but this failed to rescue swim bladder inflation (Alharthy et al., 2017; Jönsson et al., 2007; Prasch et al., 2003; Wincent et al., 2015) (but see Jönsson et al., 2012 for an alternative interpretation).

Notably, swim bladder non-inflation can be a more sensitive toxic endpoint (i.e., has a lower 50% or 20% effect concentration [EC_{50} or EC_{20}]) than measures of cardiac impairment like pericardial edema or heart rate (Table 3). This is also in accord with data showing that some PAHs (e.g., naphthalene, anthracene, and chrysene) caused swim bladder inflation failure at concentrations that had no effect on cardiac morphology, and little or no effect on cardiac function (Incardona et al., 2004). Similarly, other toxicants such as PCB126 demonstrate a lower EC_{50} for swim bladder non-inflation than for cardiac impairment (Jönsson et al., 2007; Jönsson et al., 2012). Together, these findings demonstrate that PAHs can cause swim bladder abnormalities that are independent of cardiotoxicity. The mechanisms driving failed inflation in these cases are not clear. For various toxicants including PAHs, proposed (non-exclusive) mechanisms include: changes in AhR2 signaling in the swim bladder that may be CYP1-independent (Jönsson et al., 2012; Prasch et al., 2003; Wincent et al., 2015); alteration of the

Table 3
EC_{50} or EC_{20} values for cardiac function and swim bladder inflation failure or malformation in zebrafish following exposure to petroleum products, PAHs or oxygenated PAHs.

Study	Chemical (unit)	EC_{50}			EC_{20}		
		Swim bladder	Pericardial edema	Circulation	Swim bladder	Heartbeat	Circulation
Alves et al. (2017)	Gas station effluent mixtures (phenanthrene equivalents)	**4.9 μg l^{-1}**	**> 24 μg l^{-1}**				
Alves et al. (2017)	Gas station effluent mixtures (naphthalene equivalents)	**21.8 μg l^{-1}**	**> 136 μg l^{-1}**				
Alves et al. (2017)	Gas station effluent mixtures (chrysene equivalents)	**34.1 μg l^{-1}**	**> 190 μg l^{-1}**				
Li et al. (2019)	Oman crude WAF (total petroleum hydrocarbons)				**0.5 mg l^{-1}**	**3.2 mg l^{-1}**	**2.8 mg l^{-1}**
Li et al. (2019)	Merey Crude WAF (total petroleum hydrocarbons)				**1.2 mg l^{-1}**	**3.6 mg l^{-1}**	**3.2 mg l^{-1}**
Knecht et al. (2013)	12-hydroxybenzo[*a*]pyrene	50 μM	40 μM	95 μM			
Knecht et al. (2013)	Xanthone	**50 μM**	**59 μM**	**n.c**			
Knecht et al. (2013)	Aceanthrenequinone	**45 μM**	**60 μM**	**400 μM**			
Knecht et al. (2013)	1–2-dihydroxyanthraquinone	90 μM	78 μM	n.c			
Knecht et al. (2013)	4H-cyclopenta[*def*]phenanthren-4-one	**90 μM**	**97 μM**	**n.c**			
Knecht et al. (2013)	1–3-dihydroxynaphthalene	n.c.	75 μM	n.c.			
Knecht et al. (2013)	9-fluorenone	350 μM	129 μM	n.c.			
Knecht et al. (2013)	Chromone	450 μM	350 μM	n.c.			
Knecht et al. (2013)	1–5-dihydroxynaphthalene	n.c.	35 μM	n.c.			
Knecht et al. (2013)	1–8-dihydroxyanthraquinone	180 μM	16 μM	180 μM			
Knecht et al. (2013)	Perinaphthenone	n.c.	10 μM	n.c.			
Knecht et al. (2013)	6H-benzo[c-d]pyren-6-one; naphthranthrone	65 μM	6 μM	65 μM			
Knecht et al. (2013)	Benzo[*a*]fluorenone	10 μM	10 μM	500 μM			
Knecht et al. (2013)	2-hydroxyanthraquinone	20 μM	8 μM	8 μM			
Knecht et al. (2013)	1–4-dihydroxyanthraquinone	5 μM	500 μM	1.2 μM			
Knecht et al. (2013)	9-hydroxybenzo[*a*]pyrene	n.c.	1.2 μM	n.c.			

n.c.: not calculable. Bold type highlights cases where EC_{50} or EC_{20} for swim bladder effects were lower than the corresponding value for cardiac dysfunction.

expression of key swim bladder development genes (Li et al., 2019); improper surfactant production and secretion (Li et al., 2011); and mitochondrial damage (Li et al., 2011).

Swim bladder non-inflation could also be caused by downstream effects of other (non-cardiac) toxic effects, such as thyroid disruption. Swim bladder development is under thyroid hormone regulation, and inflation failure (of the posterior or anterior swim bladder) can be induced by hyperthyroid, hypothyroid, and deiodinase knockdown manipulations (Bagci et al., 2015; Godfrey et al., 2017; Nelson et al., 2016; Stinckens et al., 2016), possibly acting via thyroid hormones' regulation of surfactant protein expression in the swim bladder (Godfrey et al., 2017). While swim bladder failure by this mechanism has not specifically been investigated in association with PAH exposure, crude oil and PAHs can cause thyroid hormone disruption in teleosts (Brown et al., 2004; Kim et al., 2016; Stephens et al., 1997), and this mechanism deserves further investigation. Another possible mechanism involves cholesterol synthesis, which appears to be increased in response to crude oil exposure based on transcriptomic studies in haddock and mahi-mahi (Sørhus et al., 2017; Xu et al., 2017), and which has the potential to affect the production of downstream metabolites including steroid hormones. Given the ability of estradiol disturbance to drastically affect swim bladder inflation (Alharthy et al., 2017), this mechanism also deserves further study.

3.1.4. Failed primary inflation in complete physoclists

Physoclists that do not have a transient physostomous phase at early life stages have not been studied extensively. We know of no study directly demonstrating effects of PAHs on swim bladder inflation in complete physoclists. At least some of these species seem to rely on the gas gland for primary inflation (Schwartz, 1971), and we therefore expect that a toxic effect on gas gland development could potentially reduce inflation success. Similarly, any cardiac impairment due to PAH exposure could affect the development and function of the rete mirabile. Cardiac impairment prevents proper development of the zebrafish kidney glomerulus and pronephros (Incardona et al., 2004; Serluca et al., 2002), an effect that has been attributed to a requirement for local circulation and stimulation of stretch receptors (Serluca et al., 2002). It seems reasonable to hypothesize that similar effects could occur during development of the rete mirabile, thereby affecting proper inflation in complete physoclists. Furthermore, AhR agonists can induce CYP1 signaling in the rete mirabile (Otte et al., 2010; Schlezinger and Stegeman, 2000), opening the possibility of direct toxicity of PAHs on the rete.

3.2. Diminished swim bladder function

3.2.1. Failed maintenance of swim bladder volume following primary inflation

If swim bladder function is compromised (e.g., gas secretion rate by the gas gland is reduced), swim bladder volume might not be maintained even if primary inflation occurs. This could occur as sequelae to cardiac impairment or as direct damage to the gas gland or rete mirabile, and might not be easily distinguishable from failed primary inflation. For example, Winata et al. (2010) noted that the non-inflated swim bladders observed in their circulation knockouts might represent failed maintenance of swim bladder volume rather than failed primary inflation itself. Given the role of the gas gland and associated rete to drive oxygen diffusion for swim bladder inflation by locally decreasing blood pH, impairment to whole animal acid-base balance might also contribute to failed maintenance of swim bladder volume. This could occur either directly or through impaired osmoregulation considering the linkage of these physiological functions through the exchange of ions for acid-base equivalents. While there have been limited reports of osmoregulatory disturbance as a result of crude oil exposure in fishes (see Grosell and Pasparakis, 2021 for review), we are aware of no reports that reveal an acid-base disturbance as a result of crude oil or PAH exposure. Nevertheless, this possibility cannot be ruled out. It is unclear how important these potential causes are for a physostome that relies less on the gas gland and more on surface gulping for maintenance of swim bladder volume. For a physoclist, failure to maintain swim bladder volume may for some species irreversibly prevent swim bladder inflation, given that inflation itself appears to promote regression of the pneumatic duct (Bulak and Heidinger, 1980; Trotter et al., 2005). On the other hand, the critical window in which some toxicants must act (Li et al., 2011; Yue et al., 2015) (Table 2) to cause swim bladder defects implies that exposure following this window does not affect volume maintenance.

3.2.2. Diminished swim bladder function as adults

Even if primary inflation is successful, adult fish could suffer from impaired functioning of the gas gland following exposure to PAHs, which in turn could cause limited growth and reproduction due to limited mobility in the water column. A toxic effect might be caused by acute adult exposure, or as a latent sublethal effect acquired during early life stages. Again, such impairment could be mediated by direct effects of PAHs on the gas gland or as a downstream effect of diminished cardiovascular function. There has been no study directly measuring adult swim bladder function after exposure to PAHs. However, latent sublethal effects on the cardiovascular system have been described (Hicken et al., 2011; Incardona et al., 2015; Mager et al., 2014), and presumably have the potential to affect gas gland function and swim bladder volume maintenance.

4. Conclusions

Impairment of swim bladder inflation is commonly reported with oil and PAH exposure. Swim bladder inflation is apparently a sensitive phenotype that can be affected by multiple physiological mechanisms. The cardiovascular dysfunction caused by PAH exposure is sufficient to cause failed inflation, but cannot explain all cases of swim bladder impairment; other putative mechanisms include direct effects of PAH on swim bladder and associated tissues, and secondary effects of altered hormone regulation. Moreover, in crude oil spills, the presence of an oil slick at the surface may be an important yet understudied barrier to inflation for larval and even adult fish. Swim bladder dysfunction has the potential to lead to chronic sublethal effects, but this has not yet been well studied.

Funding

The authors were supported by a grant from the Gulf of Mexico Research Initiative.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Fabrizio Bonatesta for graciously sharing his photos of zebrafish for inclusion in this review.

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