

# Mercury in cetaceans: exposure, bioaccumulation and toxicity

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1 **Abstract**

2 The fate and transportation of mercury in the marine environment are driven by combinations  
3 of anthropogenic atmospheric and aquatic sources, as well as natural geological inputs.  
4 Mercury bioaccumulates and biomagnifies up the food chain and can result in the accumulation  
5 of toxic concentrations in organisms even when the concentrations in the marine environment  
6 remain below the threshold level for direct toxicity. As a result, mercury exposure has been  
7 recognised as a health concern for both humans and top marine predators, including cetaceans.  
8 There appears to be no overall trend in the global measured concentrations reported in  
9 cetaceans between 1975 - 2010, although differences between areas show that the highest  
10 concentrations in recent decades have been measured in the tissues of Mediterranean  
11 odontocetes. There is increasing concern for the impacts of mercury in the Arctic marine  
12 ecosystem with changes in water temperatures, ocean currents and prey availability all  
13 predicted to impact the exposure of Arctic species to mercury. The accumulation of mercury  
14 in various tissues has been linked to kidney and liver damage as well as other neurotoxic,  
15 genotoxic and immunotoxic effects. These effects have been documented through studies on  
16 stranded and by-caught individuals as well as *in vitro* cell culture experiments. Demethylation  
17 of methylmercury and protection by selenium have been suggested as possible mercury  
18 detoxification mechanisms in cetaceans that can help to explain the very high concentrations  
19 measured in tissues of some species with no apparent acute toxicity. Thus, the ratio of selenium  
20 to mercury is of importance when aiming to determine the potential toxicity of the contaminant  
21 load at an individual level. The long-term population level effects of mercury exposure are  
22 unknown, and continued monitoring of odontocete populations in particular is advised in order  
23 to predict the uptake and impact of mercury on marine food chains in the future.

24

25 **Key Words**

26 detoxification, health, marine mammals, methylmercury, toxicity

27 **1. Introduction**

28 Mercury (Hg) in the marine environment originates from both natural and anthropogenic inputs  
29 (Gworek, et al. 2016). Natural inputs include volcanic activity, and the weathering of rocks  
30 and soils enriched with mercuric minerals (Gworek, et al. 2016), while anthropogenic inputs  
31 historically included a range of industrial processes including the manufacture of paints,  
32 pesticides and catalysts (Horowitz, et al. 2014). Currently, approximately a quarter of the  
33 environmental mercury inputs are through mercury vapour as a by-product of coal-fired power  
34 stations (Chen and Driscoll 2018; Obrist, et al. 2018), and small-scale gold-mining operations  
35 which still use mercury to separate the pure metal from silt (Chen and Driscoll 2018; Obrist, et  
36 al. 2018). Since the 1950s, mercury has been recognised as a health concern for exposed  
37 humans (Ha, et al. 2017) and marine biota (Dietz, et al. 2013), and a recent review concluded  
38 that radical emission reductions need to be put in place on a global scale in order to significantly  
39 reduce exposure in both humans and wildlife (Sonke, et al. 2013). In August 2017, the  
40 “Minamata Convention on Mercury” was ratified by 91 countries with the aim of reducing  
41 global emissions and thus protecting human health and the environment. Continued monitoring  
42 of mercury in the marine environment is therefore required to determine whether new measures  
43 agreed by this treaty do, in fact, reduce the uptake and impact of mercury on marine food chains  
44 in the future.

45 In this review, the transport and fate of mercury in the marine environment is discussed, with  
46 emphasis on its bio-magnification, the process by which mercury is transferred and  
47 accumulated up the food chain at higher concentrations, in cetaceans as marine top predators.  
48 Cetaceans have a limited ability to eliminate mercury, and therefore sequester it in their tissues

49 (Nigro and Leonzio 1996; Waggerman et al. 1998; Das et al. 2003; Monk et al. 2014). As a  
50 result, mercury concentrations in cetaceans may be between 10 and 100 times higher than those  
51 measured in other predators at the same trophic level that have a similar average life span and  
52 dietary intake, like tuna species for example (Nigro and Leonzio 1993). Cetaceans are therefore  
53 considered as sensitive and reliable tracers of environmental mercury contamination (Capelli  
54 et al. 2000). Here, the current understanding of the exposure to, and impacts of high mercury  
55 concentrations on cetacean health in terms of the effects on kidney and liver function,  
56 immunocompetence, and the nervous system in particular is reported. Key priorities for further  
57 research are identified, particularly within the framework of understanding how mercury  
58 exposure may play a role in contributing to the other cumulative anthropogenic stressors that  
59 can have population level impacts for cetaceans.

60

## 61 **2. The Mercury Cycle: Transportation and Fate**

62 Mercury exists in three forms: elemental (metallic), inorganic (e.g. mercury salts like mercuric  
63 sulphate ( $\text{HgSO}_4$ ) and mercuric chloride ( $\text{HgCl}_2$ )), and organic (e.g. methylmercury ( $\text{MeHg} /$   
64  $\text{CH}_3\text{Hg}^+$ )) (Bjørklund, et al. 2017). Most of the mercury that enters the ocean directly from  
65 either land-based sources or the atmosphere (Fig. 1), is mercury in its elemental form.  
66 Elemental mercury can then be adsorbed onto sediment particles where, both as a result of  
67 chemical reactions and biological factors (such as the activity of sediment-bound, sulphate-  
68 reducing bacteria), the organic forms of mercury, namely methylmercury and dimethylmercury  
69 are produced (King, et al. 2001; Mazrui, et al. 2016; Chouvelon, et al. 2018) (Fig. 1). Organic  
70 mercury is also produced from inorganic mercury within the water column itself (Cossa, et al.  
71 2009; Sunderland, et al. 2009) (Fig. 1). The methylation of mercury resulting from these abiotic  
72 and biotic processes is affected by a range of factors including pH, temperature, solar radiation,

73 organic matter remineralisation, and the availability of sulphates and organic carbon (Lee and  
74 Fisher 2017). Overall, through a combination of these processes, methylmercury is the most  
75 common form of organic mercury in the marine environment and bio-magnifies most readily  
76 up the food chain (see below). The transportation and fate of marine mercury is therefore  
77 complex because of the size and open nature of the ecosystem, the multiple import and export  
78 pathways, the transformations between its elemental, inorganic and organic forms, and the  
79 diversity of marine habitats (Braune, et al. 2015).

80

### 81 **3. Bio-magnification: Mercury in Marine Food Webs**

82 Marine wildlife species are exposed to mercury largely through their diet because low  
83 concentrations in air and water lead to minimal transfer through dermal exposure and inhalation  
84 (Rodgers 1994; Hall, et al. 1997; Duffy, et al. 2001). Bacteria and phytoplankton are the main  
85 entry points for the uptake of mercury into marine food webs (Atwell, et al. 1998; Campbell,  
86 et al. 2005). Mercury is then bio-magnified up the higher trophic levels to marine top predators  
87 including marine mammals and seabirds (Fig. 2). The rate of bio-magnification of mercury  
88 through the food chain has been estimated to be about  $6.0 \pm 3.7$  times for each trophic level in  
89 polar marine food webs (Lavoie, et al. 2013), and 5.4 for each trophic level in tropical marine  
90 food webs (Kehrig, et al. 2013). In top predators, mercury concentrations are often higher in  
91 older and larger individuals because they consume larger prey that are, themselves, at a higher  
92 trophic position (Kehrig, et al. 2017).

93 Methylmercury, and other organic mercury compounds, are highly lipophilic and are therefore  
94 transferred up the food chain into fish and other vertebrates more readily than other forms of  
95 mercury because they are more efficiently assimilated into tissues following absorption.  
96 Methylmercury is also relatively slowly eliminated from the body with a half-life of between  
97 10 and 15 days from different organs (Evans, et al. 2016). Once methylmercury is absorbed, it

98 enters the blood stream and is distributed quickly to various tissues and organs as it binds to  
99 cysteine in fluids mimicking methionine, which makes it easily transported across cell  
100 membranes by amino acid transporters (Clarkson, 1993). First, it is distributed to the liver,  
101 kidney and spleen, and is then later to muscle and the brain (Oliveira Ribeiro, et al. 1999). In  
102 contrast, inorganic mercury (e.g. mercuric chloride) is poorly absorbed in the vertebrate  
103 gastrointestinal tract and is mostly excreted fairly rapidly in urine and faeces following  
104 ingestion (Clarkson 1997). In addition, inorganic mercury does not bind as efficiently with  
105 cysteine and therefore does not travel around the body as efficiently as organic forms of  
106 mercury (Clarkson, 1993). However, methylmercury is slowly metabolised to inorganic  
107 mercury, and has also been shown to accumulate in various tissues and organs (Bridges and  
108 Zalups, 2010).

109

#### 110 **4. Exposure in Cetaceans: Measured Concentrations and Temporal Trends**

##### 111 **4.1 Target Organs and Tissues**

112 The main target organ for mercury in cetaceans is the liver. Other tissues such as brain, kidney,  
113 blubber, muscle, blood, skin, teeth and even cetacean earplugs also contain measurable  
114 concentrations (Stavros, et al. 2007; Stavros, et al. 2008; Outridge, et al. 2009; Savery, et al.  
115 2013; Trumble, et al. 2013). Mercury concentrations in striped dolphins (*Stenella*  
116 *coeruleoalba*) and bottlenose dolphins (*Tursiops truncatus*) that stranded along the Italian coast  
117 were highest in the liver compared to the heart, kidney, muscle and lung of both species (8 -  
118 1,752 µg/g dry weight for striped and 10 - 1,404 µg/g dry weight for bottlenose dolphins)  
119 (Bellante, et al. 2012). A similar result was reported in the tissues of bottlenose, striped and  
120 Risso's (*Grampus griseus*) dolphins from the Croatian waters of the Adriatic Sea where mean  
121 concentrations in the liver were 11 - 34 times higher than in the other tissues (Bilandžić, et al.  
122 2012). Highest total mercury concentrations were also measured in the liver of a range of

123 cetacean species sampled from Japanese meat markets compared to raw blubber, muscle,  
124 intestine and tongue (Simmonds, et al. 2002).  
125 Monitoring mercury exposure in these target organs obviously requires lethal sampling, so  
126 there are increasing efforts to determine how these concentrations are related to concentrations  
127 in tissues accessible for sampling from live animals; skin and blubber (Reif, et al. 2017).  
128 Mercury concentrations were measured in the skin, blubber, liver and kidneys of four species  
129 of stranded and/or bycaught small cetaceans (common dolphin (*Delphinus delphis*), harbour  
130 porpoise (*Phocoena phocoena*), bottlenose dolphin and striped dolphin), and significant  
131 correlations were shown between all tissue types (Aubail, et al. 2013). In 2014, Monk and  
132 colleagues reported concentrations of mercury in the blubber of both live and dead-stranded  
133 individuals of a newly identified species of bottlenose dolphin (*Tursiops australis*), and the  
134 relatively high levels were attributed to chronic low dose exposure. These studies therefore  
135 demonstrate the potential use of blubber and skin from biopsy samples to make inferences  
136 about mercury exposure in live cetaceans.

137

#### 138 **4.2 Highest Measured Concentrations**

139 A number of studies have reported the concentrations of total mercury (organic and inorganic)  
140 in the tissues of a wide variety of stranded cetacean species since the 1990s (for review see  
141 Marsili, et al. 2017). In terms of regional exposure, the highest concentrations in recent decades  
142 have been reported in the liver of striped dolphins from the Mediterranean Sea with a maximum  
143 of 5,374 µg/g dry weight in one individual (mean 514 µg/g d.w., n = 50, (Wafo, et al. 2014)).  
144 Individuals that stranded on the French coasts showed significantly higher levels compared to  
145 those from the other Mediterranean areas, and overall, individuals from the eastern  
146 Mediterranean basin showed the lowest concentrations. It has been hypothesised that the high  
147 mercury levels measured in Mediterranean dolphins originate from natural sources because of

148 the weathering of cinnabar ores throughout the Mediterranean Basin (André, et al. 1991), but  
149 other studies have suggested that the high concentration are as a result of industrial pollution  
150 (Bellante, et al. 2012). Liver and kidney concentrations of mercury were higher in 1990 - 1993  
151 than in 2007 - 2009 in Mediterranean striped dolphins, which suggests that measures to reduce  
152 emissions specifically in western European countries have been somewhat effective in reducing  
153 mercury pollution in open waters (Borrell, et al. 2014).

154 Two short-finned pilot whales (*Globicephala macrorhynchus*) stranded on the coast of New  
155 Caledonia in the South Pacific also showed extremely high concentrations of total mercury up  
156 to 1,452 µg/g dry weight in the liver (Bustamante, et al. 2003). Concentrations were up to  
157 1,980 µg/g wet weight in the livers of small odontocetes sold for human consumption in Japan  
158 (Endo, et al. 2002), and high concentrations (max. 1,571 µg/g wet weight) were also found in  
159 the liver of an adult female false killer whale (*Pseudorca crassidens*) from the Hawaiian Islands  
160 region (Hansen, et al. 2016). High concentrations were measured in the livers of a small number  
161 of bottlenose dolphins stranded in the Canary Islands between 1997 and 2013 (max. 700  
162 µg/g dry weight), and unlike in the western Mediterranean, displayed an increasing temporal  
163 trend over the sampling period (García-Alvarez, et al. 2015).

164 A review of published concentration data from the literature was conducted by searching  
165 ScienceDirect, Google Scholar, and additional references from relevant articles. The mean  
166 total mercury concentrations measured in cetacean livers reported in 101 technical reports and  
167 peer-reviewed articles published between 1972 and 2016 were collated (for the full list of  
168 references see the Supplementary Material Reference List). This produced a total of 284 liver  
169 total mercury measurements in 43 different cetacean species. Values are reported here as µg/g  
170 dry weight either as reported in the original study, or converted to dry weight  
171 using the correction factor (w.w. / d.w.) of 0.25 (Becker, et al. 1995). Across these studies, the  
172 means were calculated based on varying sample sizes ranging from multiple samples from just



173 one individual, up 129 individuals sampled in a single study. A number of studies separated  
174 samples based on age and sex class, while others also separated samples into discrete time  
175 periods. The separation of samples, and thus the reporting of mean total mercury concentrations  
176 was not consistent over the 101 studies. For this reason, these data were grouped here broadly  
177 by region and species group, and the mid-point of the data collection period used as a “time-  
178 stamp”.

179 Where there were more than 10 mean concentration measurements reported for a particular  
180 region (eg. of the 284 reported concentrations use here, there were 35 from the North Sea, while  
181 there were only 7 from the Baltic Sea), these were plotted by species group and over time (Fig.  
182 3). Overall, between 1975 and 2010, the highest concentrations have been measured in the  
183 Mediterranean, and the lowest in the Arctic (Fig. 3). The delphinids dominated the datasets  
184 from the majority of these eight regions, and there is no apparent change in reported  
185 concentrations over time across these regions (Fig. 3). Overall, the highest mercury  
186 concentrations have been reported particularly in odontocetes, and these may result in adverse  
187 health effects (see below).

188

### 189 **4.3 Arctic Species**

190 There is increasing concern for the impact of mercury in the Arctic marine ecosystem (Braune,  
191 et al. 2015) and its top predators, including cetaceans (Dietz, et al. 2013). Specifically, mercury  
192 concentrations have been measured in the livers of belugas (*Delphinapterus leucas*) (5 - 53  
193 µg/g wet weight) (Lockhart, et al. 2005), narwhals (*Monodon monocerus*) (7 to 17 µg/g wet  
194 weight) (Braune, et al. 2015)), walrus (*Odobenus rosmarus*) (<3 µg/g wet weight) (Braune,  
195 et al. 2015)) and polar bears (*Ursus maritimus*) (~ 5 – 60 µg/g wet weight) (Routti, et al. 2011)).  
196 Liver concentrations have also been reported in Arctic phocids: ringed (*Phoca hispida*),  
197 bearded (*Erignathus barbatus*) and harbour (*Phoca vitulina*) seals (mean wet weight

198 concentrations of 0.2 µg/g, 0.1 µg/g and 2.2 µg/g for each species respectively) (Young, et al.  
199 2010). A significantly higher mean concentration of total mercury in western, compared to  
200 eastern Arctic marine mammals was first reported in 1995 by Wagemann and colleagues, and  
201 was attributed, partly, to geological differences in the sediments between the two regions  
202 (Westgate and Johnson 1995). Of particular concern is that even though direct anthropogenic  
203 inputs into the ecosystem are thought to be minimal, longitudinal studies monitoring mercury  
204 in the Arctic have shown that there has been an increase in some marine biota (Braune, et al.  
205 2015).

206 The most extensively studied Arctic cetacean is the beluga. Teeth were collected from various  
207 regions of the Canadian Arctic to investigate temporal trends from the pre-industrial period in  
208 the 15<sup>th</sup> and 17<sup>th</sup> century up until 1993, and showed that much of the anthropogenic increase of  
209 mercury in Beaufort Sea belugas had already taken place by 1960 (Outridge, et al. 2009). In  
210 the central Canadian Arctic, between the late 1800s and the 1990s specifically, there was a 1.2  
211 to 5.5 fold increase in total mercury measured in teeth, but teeth from the 1920s - 40s contained  
212 similar mercury concentrations to those from the 1890s, suggesting that modern increases  
213 occurred after the early decades of the 20th Century (Outridge, et al. 2005). Later, in the 1990s,  
214 liver mercury levels in Beaufort Sea belugas tripled in comparison with levels measured in the  
215 1980s, and were the highest relative to other Canadian Arctic beluga populations (Lockhart, et  
216 al. 2005). By the early 2000s, although concentrations were still higher than in the 1980s,  
217 mercury levels dropped and were comparable to other Arctic populations (Lockhart, et al.  
218 2005). Most recently, no changes in liver mercury concentrations were observed between 2002  
219 and 2012 for young belugas in the Beaufort Sea, but a significant decrease was seen in adults  
220 (Loseto, et al. 2015). It was concluded that these most recent declines do not follow trends in  
221 mercury emissions, and are not easily explained by diet markers, thus highlighting the

222 complexity of the relationships between foraging, food web dynamics and mercury uptake in  
223 this species (Loseto, et al. 2015).

224 A number of studies have also investigated mercury concentrations in narwhals (Wagemann,  
225 et al. 1998; Wagemann and Kozłowska 2005; Braune, et al. 2015). The average concentration  
226 of methylmercury in narwhal skin is nearly identical to that measured in the skin of eastern  
227 Arctic belugas (~0.5 µg/g wet weight) (Wagemann, et al. 1998), and between 1978 and 2004,  
228 narwhal liver mercury concentrations appear to have remained stable off Baffin Island (Braune,  
229 et al. 2015). There are few data regarding the mercury concentrations in Arctic baleen whales,  
230 but muscle samples from minke whales (*Balaenoptera acutorostrata*) taken as part of whaling  
231 operations in the Barents Sea in 2011, showed that total mercury concentrations varied from  
232 0.05 to 0.5 µg/g wet weight, all of which was methylmercury. Interestingly, mean  
233 concentrations were slightly lower than measured in animals sampled from the same area nine  
234 years earlier, in 2002 (Kleivane and Børsum 2003).

235 While, overall, mercury exposure in Arctic cetaceans is lower than in other areas, how exposure  
236 will be affected by climate change is uncertain. Unprecedented changes have taken place in the  
237 Arctic over the last few decades in terms ocean warming and the resulting loss of sea ice. These  
238 environmental changes modify the planktonic ecosystem which has knock-on effects from the  
239 lowest to highest trophic levels. Large-scale environmental change could therefore trigger  
240 ecological responses including shifts in the availability, abundance and types of prey species,  
241 which in turn, can influence mercury exposure in Arctic cetaceans. The combination of  
242 environmental changes and shifts in diet could therefore make Arctic species especially  
243 susceptible to the cumulative effects of mercury exposure together with the other increasing  
244 anthropogenic pressures in these particularly vulnerable environments including increased  
245 shipping traffic, increased industrial fishing activities and anthropogenic noise for example.

246

## 247        5. Toxicity in Cetaceans

### 248        5.1 Mercury Detoxification: Methylmercury Demethylation and Selenium Binding

249 Marine mammals are capable of detoxifying methylmercury through the demethylation of  
250 methylmercury in the liver (Caurant, et al. 1996; Wagemann, et al. 1998) and its subsequent  
251 binding to selenium to form insoluble and toxicologically inert mercuric selenide (HgSe)  
252 crystals. The toxicologically inert HgSe crystals then accumulate in the tissue. These crystals  
253 were first detected using a combination of electron microscopy and histology in cetacean liver  
254 samples (Martoja and Viale 1977; Martoja and Berry 1980; Nigro and Leonzio 1996). Later,  
255 Nakazawa and colleagues (2011) investigated the formation of HgSe in various other cetacean  
256 tissues and organs (kidney, lung, spleen, pancreas, muscle and brain) using micro-X-ray  
257 fluorescence imaging and micro-X-ray diffraction. The authors confirmed the presence of  
258 HgSe in all the tissues examined suggesting that selenium could be involved in the  
259 detoxification process of mercury in tissues other than just the liver. It is hypothesised that this  
260 capacity to demethylate and sequester mercury with selenium in a non-toxic form may give  
261 cetaceans a greater tolerance to dietary mercury exposure than terrestrial animals, and therefore  
262 reduces some of the *direct* toxic effects of mercury in different organs and on various  
263 physiological processes described in detail below (Fig. 4).

264 As individuals reach their adult size, they demethylate methylmercury from their diet more  
265 efficiently, and in the case of high mercury exposure, a close to 1:1 molar ratio of Hg:Se is  
266 maintained in adulthood (Sakamoto, et al. 2015; Hansen, et al. 2016). In fact, many studies  
267 have reported a significant correlation between selenium and mercury concentrations in both  
268 cetacean liver and kidney samples, with molar ratios of close to 1 (Bustamante, et al. 2003;  
269 Yang, et al. 2007; Capelli, et al. 2008; Cáceres-Saez, et al. 2013; Hansen, et al. 2016) or below  
270 1 (Krone, et al. 1999). It is thought that an animal with a liver molar excess of selenium (Hg:Se

271 < 1) is likely to be at lower risk of direct mercury toxicity, whereas an animal with a molar  
272 excess of mercury (Hg:Se > 1) is at greater risk (Hansen, et al. 2016). The toxicological  
273 significance for individuals and populations from studies reporting levels of mercury without  
274 associated selenium levels are therefore hard to interpret. Future monitoring efforts should  
275 always report mercury and selenium ratios to better understand which populations, or specific  
276 groups within populations are potentially most at risk of direct mercury toxicity.

277 However, while selenium binding appears to act as a defensive mechanism against the direct  
278 toxic effects of mercury exposure, this binding process itself may cause other *indirect*  
279 physiological problems. As methylmercury has such a strong binding affinity for selenium,  
280 Spiller (2018) suggests that the previously suggested “protective effect” of selenium against  
281 mercury toxicity may in fact be backwards in that the effect of mercury is to produce a selenium  
282 deficient state. For example, as methylmercury sequesters selenium, it directly affects both the  
283 synthesis and activity of important selenium-dependent enzymes (selenoenzymes) (Ralston, et  
284 al. 2012). As a result, methylmercury is now recognised as a highly specific, irreversible  
285 inhibitor of selenoenzymes (Ralston, et al. 2012). Oxidative damage, particularly in the brain  
286 and neuroendocrine tissues, are prevented due to the activity of these selenoenzymes which  
287 inhibit many inflammatory mechanisms (Forceville 2006). Inhibition of their synthesis and  
288 their protective activities when selenium levels are depleted therefore appears to contribute to  
289 the neuro-toxic effects of methylmercury (Ralston and Raymond 2010).

290 A recent study investigating the formation of HgSe clusters in the brain and the liver of long-  
291 finned pilot whales supports this theory as it provided evidence of the depletion of bioavailable  
292 selenium (Gajdosechova, et al. 2016). So, while cetaceans, and perhaps other top marine  
293 predators, have the capacity to demethylate mercury and then form toxicologically inert HgSe  
294 crystals, this protective effect is only maintained if equally high levels of selenium can also be  
295 maintained from the diet. It is therefore critical that an adequate selenium status can be

296 maintained in mammals exposed to high levels of mercury in order to mitigate its toxicity. This  
297 is a problem for cetaceans as top predators, as it has been shown that mercury bio-accumulates  
298 up the food chain at a higher rate than selenium (2.4 times for selenium and 5.4 times for  
299 mercury) (Kehrig, et al. 2013). A key research priority moving forward is thus a better  
300 understanding of these *indirect* effects of mercury toxicity caused by the generation of a  
301 potentially selenium-deficient state, and how they interact with the *direct* effects of mercury  
302 exposure itself. A better understanding of these two toxicity pathways is imperative for future  
303 risk assessments of mercury exposure.

304

## 305 **5.2 Health Effects**

306 An understanding of the links between contaminant concentrations, including mercury, and  
307 health effects largely comes from studies on laboratory animals where the underlying cellular  
308 mechanisms that cause harm can be assessed in experimental set-ups in which mercury  
309 exposure to individuals or cell lines can be controlled. The current understanding of these  
310 processes from various laboratory studies on model species and in humans is summarised  
311 below for context. To date, the only experimental studies on marine mammals, with regards to  
312 the effects of ingesting trace metal contaminated food items, were conducted on harp seals  
313 (*Phoca groenlandica*) in the 1970s (Freeman, et al. 1975; Ronald, et al. 1977). In these studies,  
314 seals were given a dietary intake of mercury of between 0.25 and 25.0 mg/kg body weight per  
315 day for 60 and 90 days. They showed a reduction in appetite and mass loss (Ronald, et al.  
316 1977), auditory damage and altered steroid metabolism (Ramprashad and Ronald 1977).

317 In cetaceans, most work to date has focused on reporting measured concentrations of mercury  
318 in different tissues, rather than cause and effect relationships associated with different health  
319 effects. However, there is evidence from stranded and harvested animals that link tissue and  
320 organ mercury concentrations to specific pathologies (Fig. 4). The direct effects of mercury

321 toxicity on key organs and processes are discussed below, and while few data are available to  
322 assess toxicity thresholds for environmentally-exposed wildlife, published effect thresholds for  
323 a small number of cetacean studies are summarized in Table 1. Future risk assessments for the  
324 effects of mercury exposure on cetaceans need to consider both these direct effect thresholds  
325 and the indirect effects associated with the generation of a selenium deficient state discussed  
326 above.

327

### 328 **5.2.1 Central Nervous System**

329 In mammals generally, methylmercury toxicity is manifested primarily as central nervous  
330 system damage (Das, et al. 2003). Transport of methylmercury around the body is facilitated  
331 by complexes formed with cysteine groups which are able to cross the blood–brain barrier and  
332 may accumulate in brain tissue (Roos, et al. 2010). Thus, mercury in the brain is often  
333 predominantly (Basu, et al. 2009), but not exclusively methylmercury (Squadrone, et al. 2015).  
334 Typically, damage results in sensory and motor deficits and behavioural impairment as animals  
335 become anorexic and lethargic (Das, et al. 2003; Oken, et al. 2005). These deficits are caused  
336 as methylmercury has the potential to block neurotransmitter release, interfere with the  
337 transport of amino acids and ions, bind to sulfhydryl groups and inhibit protein synthesis.  
338 Together, these effects result in the neuropathological damage including focal necrosis of  
339 neurons in regions of the cerebral cortex, which, overall, results in cerebral oedema  
340 (Nagashima 1997; Castoldi, et al. 2001). In fact, methylmercury exposure has been shown to  
341 result in the widespread loss of neurons and gliosis, with the hypertrophy of a number of  
342 different glial cells including astrocytes, microglia, and oligodendrocytes in the human and  
343 rodent cerebellum and midbrain, as well as the cerebral cortex (Mottet, et al. 1997). Of  
344 particular concern is that methylmercury is transferred across the placenta (Wagemann, et al.

345 1988) and concentrates in the fetal brain (Wolfe, et al. 1998) resulting in developmental  
346 alterations in the fetus and/or fetal death.

347 New evidence suggests that despite previous assumptions regarding its poor ability to cross  
348 biological barriers, inorganic mercury, as well as methylmercury, can cross the blood-brain  
349 barrier (Evans, et al. 2016) and result in neurotoxic effects in mammals. In rats, it was observed  
350 that chronic, low-dose exposure to inorganic mercury resulted in a reduction in both balance  
351 and fine motor coordination (Teixeira, et al. 2018). In the same study, at the cellular level, it  
352 also resulted in the formation of mercury deposits and oxidative stress through a decrease in  
353 the total antioxidant capacity. It was concluded that exposure to continued, low-doses of  
354 inorganic mercury caused cell death through a combination of cytotoxicity and induction of  
355 apoptosis which resulted in a decreased number of neurons and astrocytes in the motor cortex  
356 (Teixeira, et al. 2018). This has potential implications for other mammals too, although the  
357 extent to which inorganic mercury can cause brain damage in other species requires further  
358 investigation.

359 In cetaceans, odontocetes appear to be one of the most vulnerable groups, with high  
360 concentrations of mercury recorded in brain tissue with associated signs of neurochemical  
361 effects (Dietz, et al. 2013). In fact, belugas exhibit brain concentrations of total mercury that  
362 are an order of magnitude higher than those measured in polar bears and Arctic seals (Lemes  
363 et al. 2011). Threshold concentrations for total mercury for neurotoxic endpoints detected in  
364 laboratory animals and field observations established from the literature were collated by Krey  
365 and colleagues (2015) (Table 1), and were compared to measured concentrations in the brains  
366 of belugas. It was seen that they exceeded all four of these neurotoxicity thresholds (Krey, et  
367 al. 2015). Another study on belugas explored the relationships between mercury and selenium  
368 concentrations and neurochemical biomarkers in different brain regions (Ostertag, et al. 2014).  
369 It was found that methylmercury exposure is associated with neurochemical variation in the



370 cerebellum of belugas and that selenium may partially protect it from methylmercury  
371 associated neurotoxicity (Ostertag, et al. 2014). Interestingly, while high concentrations of  
372 total mercury were measured in both the liver and the lymph nodes of 50 Atlantic bottlenose  
373 dolphins, no significant neuropathology was documented in these cases (Turnbull, et al. 1998).  
374 The authors therefore hypothesised that the dolphins have unique mechanisms for tolerating  
375 persistently high mercury concentrations that are neurotoxic in other mammals (Turnbull, et  
376 al. 1998). This, together with other evidence suggests that the high Se:Hg molar ratio in the  
377 brain of these species could, at least to some extent, protect the animals from mercury-  
378 associated neurotoxicity (Krey, et al. 2015).

379

### 380 **5.2.2 Liver**

381 Unlike terrestrial animals, in marine mammals and seabirds, the main organ where mercury  
382 accumulates at the highest concentrations, as well as being demethylated, is the liver. Studies  
383 on humans have shown that at the cellular level, methylmercury-related toxic effects are  
384 thought to be caused by binding of methylmercury to the cysteinyl groups of proteins, which  
385 can have severe implications for the synthesis of cellular glutathione, and lead to oxidative  
386 damage (Choi, et al. 2017). Oxidative stress has thus been identified as an important reason for  
387 hepatotoxicity. The mechanisms of its toxicity have been suggested to also involve  
388 degeneration, and changes in the energy metabolism of renal cells, but these mechanisms are  
389 not fully understood (Choi, et al. 2017). Overall, hepatotoxicity occurs through cell death,  
390 mitochondrial dysfunction, endocrine disruption, and metabolic disorders through combinations  
391 of the deregulation of oxidative stress, intrinsic apoptotic pathways, and nuclear receptor and  
392 kinase activity (Choi, et al. 2017).

393 Few studies have determined threshold concentrations for health effects in marine mammals,  
394 although it was first reported that concentrations around 60 µg/g total mercury (wet weight) in

395 the liver of marine mammals were damaging to hepatic processes (Law, et al. 1991). In another  
396 study using HgSe concentration data collected from the livers and respiratory systems of 25  
397 stranded bottlenose dolphins, it was calculated that the minimum body burden to produce mild  
398 lesions, specifically mild fatty liver, was 600mg for a 300kg dolphin (Rawson, et al. 1995).  
399 This is approximately 7 times the threshold required to cause mild lesions in humans. Chronic  
400 mercury accumulation has been associated with liver abnormalities in bottlenose dolphins  
401 (Rawson, et al. 1993; Rawson, et al. 1995). For example, a fourfold increase in active liver  
402 disease in the dolphins suggested a significant health effect associated with liver mercury  
403 concentrations above 61µg/g wet weight of tissue (Rawson, et al. 1993). In this study, deposits  
404 of a brown pigment, identified as lipofuscin, were observed in the livers of nine animals with  
405 high hepatic mercury levels (>60 µg/g wet weight).

406 Lipofuscin is derived from damaged subcellular membranes, and these deposits were strongly  
407 correlated with mercury concentrations. As mercury inhibits the activity of lysosomal digestive  
408 enzymes, this reduces the degradation of proteins, which in turn, leads to excessive  
409 accumulation of lipofuscin within cells and results in cell death (Rawson, et al. 1995).  
410 Interestingly, while liver and kidney damage have been documented in bottlenose dolphins,  
411 lesions characteristic of acute or chronic mercury exposure were not found in harbour porpoises  
412 from the North and Baltic Seas with high mercury concentrations in the liver and kidney (upper  
413 range 449 µg/g and 160 µg/g wet weight, respectively) (Siebert, et al. 1999). The threshold for,  
414 and effects of hepatotoxicity may therefore be somewhat species specific, and/or a function of  
415 mercury-selenium interactions which have not been reported in these studies.

416

### 417 **5.2.3 Kidneys**

418 In humans and other terrestrial mammals, the kidneys are the primary organs where mercuric  
419 ions accumulate after exposure to elemental, organic and inorganic forms of mercury (for

420 review see Zalups, 2000). While all forms of mercury are nephrotoxic, the inorganic forms of  
421 mercury are most acutely nephrotoxic (Zalups 2000). Specifically, mercuric chloride leads to  
422 acute tubular necrosis where the tubular epithelial cells that form the renal tubules of the  
423 kidneys die (Zawada, et al. 1998). As a result of the high bonding affinity between mercury  
424 and sulphur, interactions between mercuric ions and the thiol group(s) of proteins, peptides and  
425 amino acids including albumin, metallothionein, glutathione, and cysteine have been  
426 implicated in the mechanisms involved in the proximal tubular uptake, accumulation, transport,  
427 and toxicity of mercuric ions in the kidneys of mammals (Zalups 2000).

428 In cetaceans, an increase in blood urea nitrogen was observed in bottlenose dolphins with  
429 increased mercury concentrations in both the skin and the blood suggesting a decrease in  
430 kidney function in these animals (Schaefer, et al. 2011). Varying doses of mercuric chloride  
431 were shown to induce apoptosis *in vitro* in cultured Atlantic Spotted Dolphin (*Stenella*  
432 *plagiodon*) renal cells (Wang, et al. 2001) (Table 1). In the same study, the protective effects  
433 of sodium selenite against the toxic effects of mercuric chloride were documented, and it was  
434 concluded that inhibition of mercury-induced apoptosis in renal cells, provided by selenium,  
435 may contribute to the *in vivo* protection in this organ.

436

#### 437 **5.2.4 Immune System Function**

438 A large body of literature regarding *in vitro* experimental investigations has clearly shown that  
439 mercury compounds can have immunomodulatory effects (Moszczyński 1997). Specifically,  
440 both mercuric chloride and methylmercury have been shown to inhibit most lymphocyte  
441 functions including proliferation, expression of cell activation markers on the cell surface and  
442 cytokine production (Moszczyński 1997). *In vivo* studies on rats injected with mercuric  
443 chloride exhibit immunosuppression, and showed increased susceptibility to challenge with  
444 infectious agents or tumour cells (Moszczyński 1997). In marine mammals specifically,

445 methylmercury was shown to alter the *in vitro* synthesis of steroid hormones which play an  
446 important role in modulating both inflammatory and immune responses (Freeman and  
447 Sangalang 1977). These kinds of *in vivo* and *in vitro* studies have not been carried out to the  
448 same extent in cetaceans, but potentially similar immunosuppressive effects have been  
449 documented in various species using strandings data in case-controlled approaches to  
450 investigate the prevalence of infectious diseases in mercury-contaminated animals.

451 Siebert and colleagues (1999) examined the possible relationship between mercury tissue  
452 concentrations and disease in harbour porpoises from the North and Baltic seas. Higher  
453 mercury concentrations were found in porpoises from the North Sea compared to the Baltic  
454 Sea and were associated with an increased prevalence of parasitic infection and pneumonia.

455 Bennett and colleagues (2001) also used this indirect approach to investigate the hypothesis  
456 that increased exposure to toxic metals results in a lower resistance to infectious disease in  
457 harbour porpoises from the coasts of England and Wales. Mean liver concentrations of  
458 mercury, selenium, zinc and the Hg:Se ratio were significantly higher in the porpoises that died  
459 of infectious diseases compared to porpoises that died from physical trauma. As previously  
460 discussed, the authors concluded that the Hg:Se balance is a complex phenomenon that might  
461 be more important for the general health status of porpoises than absolute concentrations of  
462 mercury alone. Similarly, Mahfouz and colleagues (2014) also found that harbour porpoises  
463 stranded along the French coast between 2006 and 2013 that died from infectious disease had  
464 significantly higher hepatic concentrations of cadmium, mercury, selenium and zinc compared  
465 to healthy porpoises that died from physical trauma.

466 In order to better understand the mechanisms of immunosuppression associated with high  
467 mercury concentrations, Pellissó and colleagues (2008) studied the effects of varying mercury  
468 exposure on bottlenose dolphin lymphocyte and phagocyte function *in vitro*. A significant  
469 reduction in the lymphoproliferative response was found following exposure to just 1 mg/L of

470 mercury and decreased phagocytosis was observed at 5 mg/L (Table 1). The authors concluded  
471 that their results support the hypothesis that exposure to mercury could lead to a reduction in  
472 host disease resistance. Desforges and colleagues (2016) used a combination of field and  
473 laboratory data to determine effect threshold levels for suppression of lymphocyte  
474 proliferation. These were between 0.002 - 1.3 ppm for mercury and 0.009 - 0.06 ppm for  
475 methylmercury in polar bears and several pinniped and cetacean species combined.  
476 Finally, in another study on bottlenose dolphins, after controlling for age, a significant inverse  
477 relationship was observed between mercury concentrations measured in the blood, and several  
478 markers of endocrine function and hematologic parameters (Schaefer, et al. 2011). Specifically,  
479 an inverse relationship was observed between blood and skin mercury concentrations and  
480 thyroid hormone concentrations (total thyroxine and triiodothyronine), as well as absolute  
481 numbers of lymphocytes, eosinophils, and platelets (Schaefer, et al. 2011). Mercury is not  
482 specifically recognized as an endocrine-disrupting chemical, but it has been suggested that  
483 continuous exposure of the brain to mercury could affect the hypothalamic–pituitary axis which  
484 regulates thyroid activity, and thus the circulating concentrations of total thyroxine and  
485 triiodothyronine (Sin, et al. 1990). Further investigation of the roles of both mercury and  
486 selenium in the mechanisms that lead to reduced thyroid hormone production in marine  
487 mammals is necessary to confirm these results, and better interpret the implications for the  
488 reduced immunocompetence of individuals.

489

#### 490 **5.2.5 Genetic Effects**

491 Mercury exposure has been recognised to have both mutagenic and teratogenic effects  
492 (Aggarwal, et al. 2014). Once inside the cell, damage is thought to be caused by methylmercury  
493 compounds that bind to sulfhydryl groups of glutathione, leading to the formation of free  
494 radicals that cause DNA damage. When these compounds bind to sulfhydryl groups in the

495 microtubules responsible for providing structure and shape to the cytoplasm, it leads to  
496 impairment of spindle formation which then causes chromosomal aberrations  
497 (structural abnormality in one or more chromosomes) and aneuploidy (an abnormal number of  
498 chromosomes) (for review see Aggarwal et al. 2014). In humans, the genotoxic effects of  
499 methylmercury compounds have been assessed by quantifying chromosome aberrations and  
500 polyploidy cells in cultures of whole blood exposed to varying mercury concentrations. The  
501 number of polyploidy cells increased with the increasing mercury concentration while the  
502 mitotic index, and thus the cells' ability to divide normally, decreased at just 100 µg/L (Silva-  
503 Pereira, et al. 2005). Mercury therefore has strong genotoxic and cytotoxic effects at low  
504 concentrations in humans.

505 There is currently very little data on the extent to which mercury or methylmercury is genotoxic  
506 in cetaceans. Betti and Nigro (1996) evaluated the genetic effects of methylmercury in  
507 bottlenose dolphin lymphocytes *in vitro* using single cell microgel electrophoresis (the Comet  
508 assay). Lymphocytes were isolated from the blood of a single dolphin, and were exposed to  
509 methylmercury concentrations naturally occurring in the blood of wild dolphins in the  
510 Mediterranean (Betti and Nigro 1996). This induced DNA single-strand breaks and  
511 cytotoxicity in a dose-dependent manner. However, dolphin lymphocytes were more resistant  
512 to the genotoxic and cytotoxic effects of methylmercury than either human or rat cells (Betti  
513 and Nigro 1996). This resistance was interpreted as an adaption to limit the damage caused by  
514 methylmercury exposure. Further *in vitro* testing is therefore required to fully assess the  
515 potential genotoxicity of methylmercury in cetaceans.

516

517

518

519

## 520        **6. Conclusions and Future Directions**

521 Both natural and anthropogenic sources of mercury contribute to its accumulation in the tissues  
522 and organs of cetacean species around the world. This accumulation, together with the potential  
523 for toxic effects highlight how further monitoring of mercury in the environment, and in these  
524 top marine predators, is required to better understand its potential health effects and how these  
525 could ultimately lead to population-level impacts. Recent evidence demonstrating the potential  
526 use of blubber and skin samples from biopsies of live animals to quantify tissue mercury  
527 concentrations has important implications for large-scale population monitoring.

528 Given the reported ‘protective’ effects of selenium binding, of particular importance in future  
529 monitoring efforts is the need to measure both selenium and mercury concentrations in tandem  
530 in order to obtain a more accurate indicator of what measured concentrations mean in terms of  
531 compromising cetacean health. There is still limited data regarding the mechanisms of toxicity  
532 specific to cetaceans, and while comparing mercury concentrations in cetaceans with  
533 concentrations in appropriate laboratory studies can be used as a tool for risk characterization,  
534 using published thresholds and established cellular mechanisms of mercury toxicity in other  
535 animals adds uncertainty regarding the assessment of risk to cetaceans. Future investigations  
536 should prioritise a better understanding of both the direct effects of mercury toxicity and the  
537 indirect effects associated with the development of selenium deficiency. An improved  
538 understanding is imperative in order to better evaluate risk to individual and population-level  
539 health. In addition, efforts have been focused on understanding mercury toxicity in isolation,  
540 whereas there are likely important health effects associated with exposure to several, possibly  
541 interacting contaminants (Filipak Neto, et al. 2008). More research is therefore needed before  
542 the effects of both mercury alone, and its cumulative health effects in combination with other

543 heavy metals and persistent organic pollutants for example, can be addressed adequately in top  
544 marine predators.

545 A recent, highly comprehensive study investigated how the effects of climate change and other  
546 potential anthropogenic stressors are likely to modulate the bioaccumulation and bio-  
547 magnification of mercury in marine ecosystems in the future (Eagles-Smith, et al. 2018). In  
548 terms of potentially the most vulnerable environments, further research is especially required  
549 to identify the changing underlying processes linking the biogeochemical cycle responsible for  
550 methylation rates in Arctic seawater and bioaccumulation through the Arctic food web which  
551 will ultimately affect top marine predators (Braune, et al. 2015).

552 Marine mammal species, including cetaceans are thought to be good sentinels for human health  
553 for two main reasons; firstly, because they consume many of the same species of fish caught  
554 by commercial fisheries for human consumption, and secondly, they share similar life history  
555 traits including a high trophic level, low reproductive output and a long life-span. Together,  
556 these can make them particularly susceptible to the negative impacts of anthropogenic activities  
557 and environmental pollution and contamination. With the signing of the Minamata Convention  
558 on Mercury in 2017 there is a clearly an appetite for reducing the use and therefore the impact  
559 of mercury contamination at a global scale. But without continued, long-term monitoring of  
560 concentrations in species of concern, or those that are important ecosystem indicators (such as  
561 the odontocete cetaceans), it will be impossible to determine if any mercury exposure  
562 mitigation measures have been successful, and predict how mercury will affect the marine  
563 environment into the future.

564

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571

## 572 **Declarations of Interest**

573 None.

574

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932

933 **Table 1 – Reported thresholds for toxic effects of mercury exposure. N.B. Thresholds for**  
 934 **neurotoxic endpoints have not been published specifically for cetaceans.**

| Directly Toxic Effects                   | Species  | Study System    | End Point  | Reported Exposure Threshold for Effects  | Reference                    |
|--|--|-----------------|--|--|------------------------------|
| Neurotoxicity:<br>Central Nervous System | Mouse, rat, mink, river otter, cat, dog, horse, pig, macaque, squirrel monkey, harp seal, polar bear | <i>in vivo</i>  | clinical changes<br>neuropathological changes<br>neurochemical changes<br>neurobehavioural changes | Brain Concentration THg*:<br>> 6.75 mg/kg w.w.<br>> 4 mg/kg w.w.<br>> 0.4 mg/kg w.w.<br>> 0.1 mg/kg w.w. | Krey <i>et al.</i> 2015*     |
| Hepatotoxicity:<br>Liver                 | Bottlenose dolphin   | <i>in vivo</i>  | liver disease  | Liver Concentration THg: 61 µg/g wet weight  | Rawson <i>et al.</i> 1993    |
|  | Bottlenose dolphin   | <i>in vivo</i>  | liver disease  | Whole Body Burden THg: 2mg/kg  | Rawson <i>et al.</i> 1995    |
| Nephrotoxicity:<br>Kidneys               | Atlantic spotted dolphin   | <i>in vitro</i> | apoptosis of renal cells   | 20 µM HgCl <sub>2</sub>  | Wang <i>et al.</i> 2001      |
| Immune System Function                   | Bottlenose dolphin   | <i>in vitro</i> | suppression of lymphocyte proliferation<br><br>suppression of phagocytosis                         | 1mg/L Hg<br><br>5 mg/L Hg  | Pellissó <i>et al.</i> 2008  |
|  | Beluga   | <i>in vitro</i> | suppression of lymphocyte proliferation  | 0.067 ± 0.094 ppm Hg<br>0.016 ± 0.0049 ppm MeHg  | Desforges <i>et al.</i> 2016 |
| Genetic Effects                          | Bottlenose dolphin   | <i>in vitro</i> | DNA single-strand breaks and cytotoxicity  | 0-1 µg/ml MeHg   | Betti and Nigro, 1996        |

935

936 \* Authors conducted a literature review of threshold concentrations for toxic endpoints  
 937 detected in laboratory animals and field observations in order to establish potential thresholds  
 938 in marine mammals.

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942 **Fig. 1.** Mercury in the marine environment is cycled through biogeochemical processes with  
943 both anthropogenic and geological (natural) inputs from land-based sources, and deposition  
944 from the atmosphere. Mercury enters sediments through the actions of sediment-fixing  
945 bacteria. Methylmercury is produced through a combination of methylation of elemental  
946 mercury and inorganic mercury in sediments and in the water column itself through both abiotic  
947 and biotic processes. Methylmercury then enters, and bioaccumulates up the food chain from  
948 zooplankton up to top marine predators, including cetaceans.

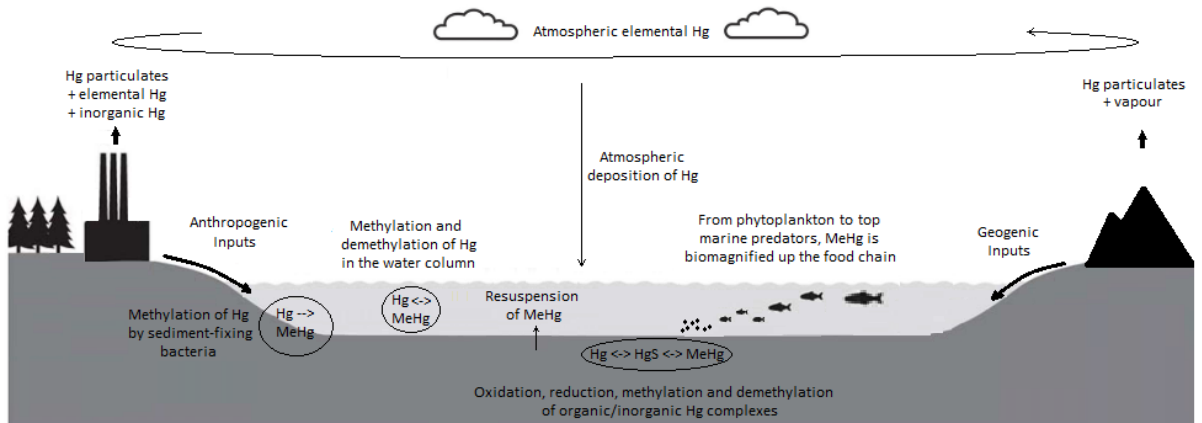
949 **Fig. 2.** Total mercury concentrations in example marine species in the Mediterranean show  
950 how bio-magnification occurs up the food chain. Total mercury values in  $\mu\text{g/g}$  dry weight are  
951 indicated based on published concentrations (Cresson, et al. 2014; Wafo, et al. 2014; Živkovic,  
952 et al. 2017). The total mercury concentrations here include both inorganic and organic mercury,  
953 and are shown as examples of the most widely available published data for comparison, rather  
954 than methylmercury alone.

955  
956 **Fig. 3.** Mean total mercury concentrations measured in the livers of cetaceans worldwide  
957 between 1975 and 2010 collated from 101 reports and published peer-reviewed articles. N.B.  
958 The total mercury concentrations on the y-axes are on different scales as minimum and  
959 maximum reported values vary between regions.

960  
961 **Fig. 4.** Mercury exposure in cetaceans has the potential to cause neurotoxicity, nephrotoxicity,  
962 hepatotoxicity, immunotoxicity and genotoxicity. The main toxicology findings from *in vivo*  
963 and *in vitro* investigations in cetaceans are summarised together with the proximate  
964 mechanisms described in model species where cetacean data are lacking.

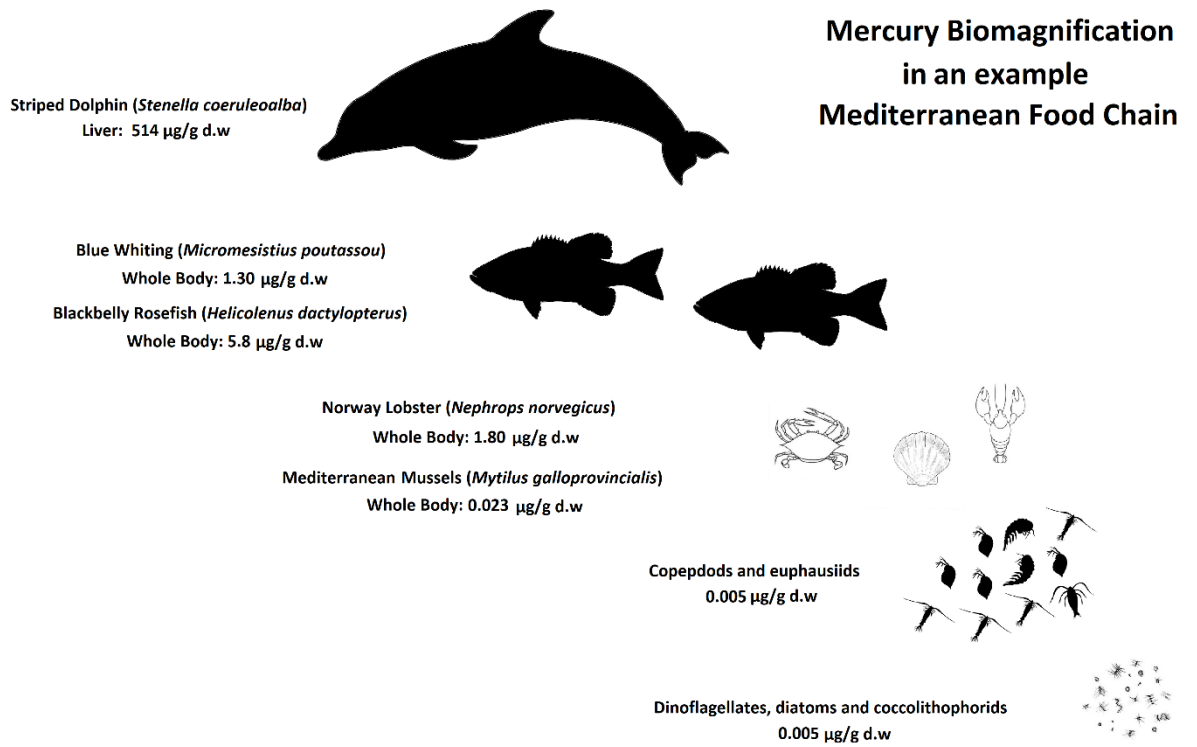
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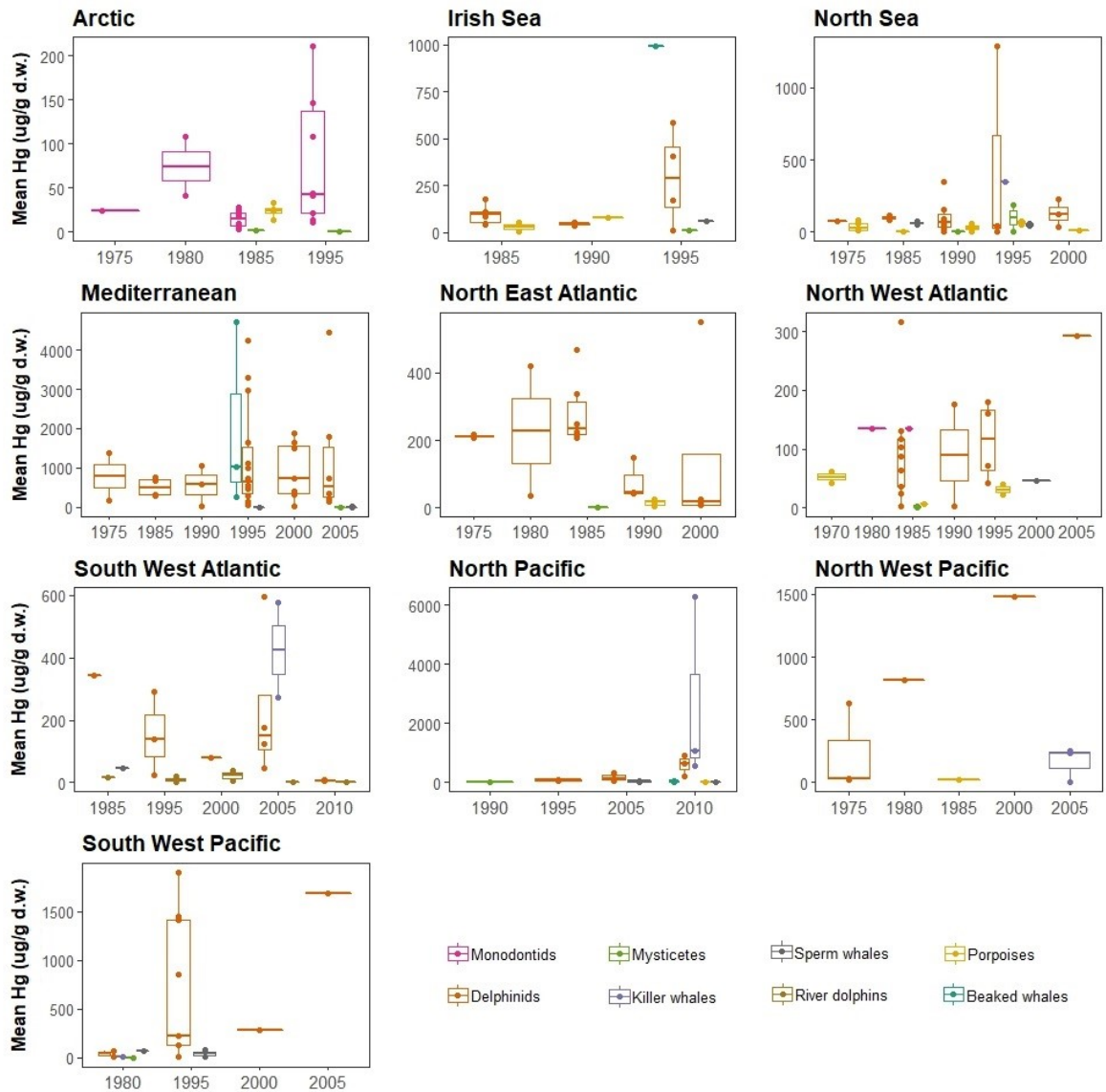
971 Figure 1.

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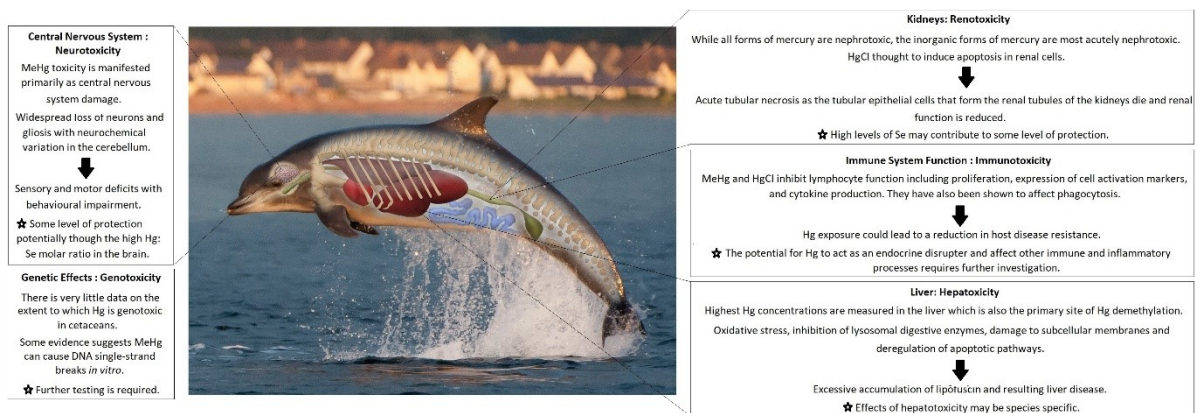
973 Figure 2.

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Figure 3.



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Figure 4.