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1 **Telomere dynamic in humans and animals: review and perspectives in**
2 **environmental toxicology**

3

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10 **Keywords**

11 telomeres, attrition, vertebrates, invertebrates, ageing, pollutants

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21 **Abstract**

22 Telomeres (TLs) play major roles in stabilizing the genome and are usually shortened
23 with ageing. The maintenance of TLs is ensured by two mechanisms involving telomerase
24 (TA) enzyme and alternative lengthening telomeres (ALT). TL shortening and/or TA
25 inhibition have been related to health effects on organisms (leading to reduced reproductive
26 lifespan and survival), suggesting that they could be key processes in toxicity mechanisms (at
27 molecular and cellular levels) and relevant as an early warning of exposure and effect of
28 chemicals on human health and animal population dynamics. Consequently, a critical analysis
29 of knowledge about relationships between TL dynamic and environmental pollution is
30 essential to highlight the relevance of TL measurement in environmental toxicology.

31 The first objective of this review is to provide a survey on the basic knowledge about
32 TL structure, roles, maintenance mechanisms and causes of shortening in both vertebrates
33 (including humans) and invertebrates. Overall, TL length decreases with ageing but some
34 unexpected exceptions are reported (*e.g.*, in species with different lifespans, such as the
35 nematode *Caenorhabditis elegans* or the crustacean *Homarus americanus*). Inconsistent
36 results reported in various biological groups or even between species of the same genus (*e.g.*,
37 the microcrustacean *Daphnia sp.*) indicate that the relation usually proposed between TL
38 shortening and a decrease in TA activity cannot be generalized and depends on the species,
39 stage of development or lifespan. Although the scientific literature provides evidence of the
40 effect of ageing on TL shortening, much less information on the relationships between
41 shortening, maintenance of TLs, influence of other endogenous and environmental drivers,
42 including exposure to chemical pollutants, is available, especially in invertebrates.

43 The second objective of this review is to connect knowledge on TL dynamic and
44 exposure to contaminants. Most of the studies published on humans rely on correlative

45 epidemiological approaches and few *in vitro* experiments. They have shown TL attrition
46 when exposed to contaminants, such as polycyclic aromatic hydrocarbons (PAH),
47 polychlorinated biphenyls (PCB), pesticides and metallic elements (ME). In other vertebrates,
48 the studies we found deals mainly with birds and, overall, report a disturbance of TL dynamic
49 consecutively to exposure to chemicals, including metals and organic compounds. In
50 invertebrates, no data are available and the potential of TL dynamic in environmental risk
51 assessment remains to be explored.

52 On the basis of the main gaps identified some research perspectives (*e.g.*, impact of
53 endogenous and environmental drivers, dose response effects, link between TL length, TA
54 activity, longevity and ageing) are proposed to better understand the potential of TL and TA
55 measurements in humans and animals in environmental toxicology.

56

57 **1. Introduction**

58 Telomeres (TLs) are repetitive, non-coding DNA sequences located at the ends of
59 chromosomes. TLs were identified in the 1930s by McClintock (1941) and Müller (1938),
60 who described their potential functions in maintaining chromosome stability by observing the
61 chromosomes of corn and drosophila. It was postulated that cells were not able to divide
62 themselves into “infinity” (Weismann, 1889). This theory was confirmed in the 1960s
63 (Hayflick and Moorhead, 1961; Hayflick, 1965) on a human foetal cell culture (division
64 ability between 40 and 60 times before entrance in a senescence phase). Olovnikov theorized
65 the *Hayflick limit*, which postulates that somatic cells have a limited number of divisions in
66 connection with the loss of DNA sequences at the extremities of chromosomes, *i.e.*, TLs.
67 When this limit is exceeded, cells enter senescence (Olovnikov, 1971). The popularity of TLs
68 grown over the last four decades since the discovery of a repeated sequence of six telomeric

69 nucleotides of a ciliated protozoan, *Tetrahymena thermophila* (CCCCAA), and of the
70 protective role of this sequence against chromosome degradation (Yao et al., 1981; Szostak
71 and Blackburn, 1982; Shampay et al., 1984). TLs are mainly known to protect and stabilize
72 DNA by protecting chromosomes from degradation (end-to-end fusion and erosion),
73 stabilizing broken chromosome ends, modulating the DNA repair machinery of double strand
74 break (DSB) damage with non-homologous end-joining (NHEJ), counting the number of cell
75 divisions (replicative potential of cells), participating in mitotic and meiotic chromosome
76 segregation and the attachment of chromosomes to the nuclear envelope (Haber, 1999; de
77 Lange, 2005; Oeseburg et al., 2010; Grach, 2013). For humans, TL length decreases with
78 ageing (Aubert and Lansdorp, 2008) and TL attrition is recognized as a biomarker of the nine
79 hallmarks of ageing (Lopez-Otin et al., 2013). Mechanisms of TL maintenance limit fast TL
80 attrition and are closely associated with the activities of some enzymes, the most well known
81 being telomerase, or TA (Greider and Blackburn, 1985; Greider and Blackburn, 1989).

82 If TL attrition occurs naturally, some studies report that it can be accelerated by various
83 biological (*e.g.*, infections) and environmental (*e.g.*, chemical substances) stressors known for
84 their toxicological effects. However, there is a lack of knowledge of various stressors (*e.g.*,
85 contaminants, biotic and abiotic factors) and species, including invertebrates. Furthermore,
86 data regarding the actions of these stressors on TL maintenance pathways that are key to
87 protecting and stabilizing the genome against various stressors, including pollutants, are
88 lacking. Based on data showing that chemicals are able to induce human premature ageing
89 and decrease lifespan (Chen et al., 2013; Puri et al., 2017), it appears relevant to investigate
90 on TL dynamic to search for bridges between molecular and cellular effects (impact on TL
91 length and/or TL maintenance), health effects (*e.g.*, survival, reproductive lifespan) and
92 consequences on populations (*e.g.*, density, growth).

93

94 The aim of this review is to identify research questions on TL dynamic in vertebrates and
95 invertebrates in relation to ageing, lifespan and environmental toxicology. The main question
96 concerns the potential use of TL measurement as a relevant biomarker, especially in the
97 framework of the One Health concept, to assess the effects of multiple stressors at the human-
98 animal-ecosystem interface (Destoumieux-Garzón et al., 2018). Thus, the first objective of
99 this review is to report basic knowledge about the structure, roles and maintenance
100 mechanisms of TLs and causes of TL shortening in the animal kingdom. On the basis of this
101 premise, the second objective is to connect knowledge on TL dynamic and exposure to
102 contaminants. Finally, based on the lack of knowledge of TL dynamic in environmental
103 toxicology, some perspectives are proposed.

104 **2. Structure variability of telomeres in the animal kingdom**

105 In animals, TL sequences (TTAGGG)_n are highly conserved (Meyne et al., 1989; Traut et
106 al., 2007), with slight variations in phyla such as Arthropoda (Gomes et al., 2010). Sequence
107 conservation results, for example, in similar TL sequences for a heterothermic invertebrate
108 (the snail *Cantareus aspersus*) and a homeothermic vertebrate (*Homo sapiens*), while most
109 insects possess a pentameric motif (TTAGG), with the exception of Coleoptera (Frydřichovà
110 et al., 2004; Vitkovà et al., 2005; Gomes et al., 2011). TL sequences have been determined in
111 various species (**Table 1**), among which some are used as bioindicators in environmental
112 toxicology (e.g., *Daphnia pulex*, *Eisenia foetida*, *C. aspersus*). The repetition number of TL
113 sequences is variable according to species or age and can frequently reach several thousands
114 of nucleotides in Metazoa. For instance, in human lymphocytes, the size ranges between 2.5
115 to 15 kilo base pairs (kbp) depending on the patient (O'Callaghan and Fenech, 2011).

116 The end of the TL is commonly called a loop because it looks like a hairpin structure
117 (Griffith et al., 1999). Loops are formed by double-stranded TL repeats, the T-loop and the D-
118 loop (Greider, 1999). The terminal region of the TL is a single-stranded overhang that is 3' G-

119 rich and is known as the G-tail (guanine-rich hairpin tail). This region forms G-quadruplexes,
120 where each guanine base participates in hydrogen bond formation (Lipps and Rhodes, 2009)
121 in a square planar arrangement that is stabilized by central cations (Williamson et al., 1989;
122 Moyer et al., 2015). TL functions are dependent on G-quadruplexes that are associated with
123 proteins (Paeschke et al., 2005). In humans, TLs bear a protein complex, the shelterin
124 complex, which is mainly composed of six different proteins: TRF1, TRF2, RAP1, TIN2,
125 TPP1 and POT1 (Palm and de Lange, 2008; Oeseburg et al., 2010) (**Figure 1**). This DNA-
126 protein complex is essential to protect TLs by the implication of TL maintenance machinery,
127 as it avoids the inhibition of various DNA damage response (DDR) and DNA repair
128 machinery (de Lange, 2009; Lu et al., 2013). Some proteins in humans associated with the
129 shelterin complex have also been found in several animal species, such as POT1 in
130 *Caenorhabditis elegans* (Ferreira et al., 2013) or in *Daphnia sp* (Schumpert et al., 2015). All
131 these proteins play various roles in TL maintenance (Martinez and Blasco, 2010) and are
132 summarized in **Table 2**.

133 Although the structure presented in **Figure 1** is accepted as the most commonly found in
134 animal kingdom, some studies have shown that it is not ubiquitous, notably for insects, such
135 as, *Chironomus sp.*, *Drosophila melanogaster* and *Bombyx mori* (Louis, 2002; Fujiwara et al.,
136 2005; George et al., 2006; Mason et al., 2008; Pardue and DeBaryshe, 2008). For *D.*
137 *melanogaster*, the shelterin complex is replaced by a same architecture, the terminin complex
138 (Raffa et al., 2013), composed by five proteins (HOAP, HIPHOP, MOI, VER and TEA) and
139 the function of terminin for diptera is mainly to protect telomere from fusion events or DNA
140 damage response (Raffa et al., 2013; Zhang et al., 2016; Cicconi et al., 2017).

141 **3. Maintenance of telomeres (TLs)**

142 Various mechanisms operate to limit TL attrition (*i.e.*, TA, ALT) and/or to repair TLs
143 when they are damaged.

144

145 **3.1. Roles of telomerase (TA)**

146 Telomerases are a group of enzymes coupled to RNA that synthesize *de novo* the
147 extremities of the TL to limit its fast attrition in proliferative cell types (Greider and
148 Blackburn, 1985; Greider and Blackburn, 1989). For example, a single TA enzyme able to
149 synthesize 74 telomeric nucleotides per minute *in vitro* has been described in the ciliated
150 protozoan *Tetrahymena thermophila* (Greider, 1991). To synthesize TLs, TA uses a catalytic
151 component, TERT (telomerase reverse transcriptase; Nakamura et al., 1997), that has been
152 characterized in many animals (*e.g.*, *Xenopus laevis* and *Bombyx mori*) (Kuramoto et al.,
153 2001; Osanai et al., 2006). The activation of TERT requires its binding with two proteins of
154 the shelterin complex, TPP1 and POT1 (Sandin and Rhodes, 2014). Then, TERT fosters the
155 *de novo* synthesis of TLs by using the second subunit of TA, an RNA template (TERC or
156 telomerase RNA component). In addition, TA can interact with G-quadruplexes to allow TL
157 extension (Moye et al., 2015).

158 TA stability and activity can be reduced by the actions of hormone (*e.g.*, corticosterone;
159 Gopalakrishnan et al., 2013; Angelier et al., 2018) and/or altered genes (*e.g.*, DKC1, dyskerin
160 pseudouridine synthase 1; Bertuch, 2016). The instability and inactivity of TA are a cause of
161 diseases such as dyskeratosis congenita (Zinsser-Cole-Engman syndrome), a telomeropathy
162 leading to premature ageing (Drachtman and Alter, 1992; Vulliamy et al., 2001; Armanios
163 and Blackburn, 2012; Armanios et al., 2013). If TA limits the shortening of TLs by adding
164 small repeated segments of DNA at the ends of chromosomes at each cell division, their
165 overexpression can be detrimental to individuals by causing diseases, such as cancer. In 80%
166 to 90% of all cancers, cancer cells often have high TA activity (Jafri et al., 2016) due to
167 mutations in the core promoter region of TERT (Horn et al., 2013; Grüner et al., 2018; Liu et
168 al., 2018) which is considered a key factor for tumour development.

170 **3.2. Roles of alternative lengthening telomeres (ALT)**

171 The ALT pathway, an alternative pathway used to synthesize TLs, has been reported in
172 immortal human cell lines (Bryan et al., 1995; Bryan et al., 1997). The ALT pathway can be
173 activated after epigenetic aberrations and mutations in genes encoding proteins involved in
174 chromatin remodelling at TLs and other genomic sites or tumour suppressors, such as p53
175 (Chung et al., 2012; Cesare and Reddel, 2013; Conomos et al., 2013; Naderlinger and
176 Holzmann, 2017). There are various mechanisms involved in the ALT pathway (*e.g.*, TL
177 elongation performed by homologous recombination) (Natarajan and McEachern, 2002;
178 Natarajan et al., 2003; Topcu et al., 2005; Cesare and Reddel, 2010; Cesare and Reddel, 2013;
179 Conomos et al., 2013). Some proteins are associated with the ALT pathway and are involved
180 in the restart of telomeric DNA replication, such as HR protein complexes (MRN, MRE11,
181 RAD50, NSB1, NBN), proteins located on chromosome 5 for the structural maintenance of
182 TLs (SMC5, SMC6), Fanconi anaemia proteins (FANCD2, FANCA) and endonucleases
183 (FEN1) (Cesare and Reddel, 2010). The ALT pathway was evidenced in human somatic cells
184 (especially those that lose tumour protein 53 (TP53), which are genetically unstable) and
185 promotes proliferative cancer cells in humans (15% of cancers) (Henson et al., 2002; Cesare
186 et al., 2009; Lovejoy et al., 2012; Conomos et al., 2013; Neumann et al., 2013; Roake and
187 Artendi, 2016; Chen et al., 2017; Min et al., 2017).

188 **3.3. DNA repair of telomeres**

189 The maintenance of functional TLs is critical for genome stability. When damages affect
190 TL extremities, TA or the ALT pathway is recruited for maintenance. However, damage (*e.g.*,
191 breaks, oxidation of nucleotides, alkylations) can also take place at various locations in the TL
192 sequence. In this case, other mechanisms, *i.e.*, DNA repair pathways are mobilized. These

193 pathways are the same as those that watch over the rest of the genome, such as base excision
194 repair (BER), nucleotide excision repair (NER), homologous recombination (HR), non-
195 homologous end-joining (NHEJ) and mismatch repair (MMR) (Webb et al., 2013; Jia et al.,
196 2015). The DNA BER pathway involves endonucleases (such as APE1) and is a major way to
197 protect genomes from oxidative stress in association with the shelterin complex through, for
198 instance, interaction with TRF2 to stabilize telomeric DNA (Madlner et al., 2013). Moreover,
199 DNA repair mechanisms are also essential when damage occurs in genes encoding proteins
200 involved in TL dynamic (e.g., TERT, POT1, MRN).

201

202 **4. Causes and consequences of telomere attrition**

203 **4.1. Ageing**

204 Several causes of TL shortening have been identified (*Figure 2*). The main one, ageing is
205 natural and is due to cell division (Blackburn, 2005), because at each division, chromosomes
206 lose telomeric patterns. TLs have a critical minimal size that, when reached, induces an
207 inhibition of cell division cycles and cellular senescence processes (Harley et al., 1990;
208 Blackburn, 1991; Amanions and Blackburn, 2012; Reichert et al., 2017). In various animal
209 groups, it has been reported that TLs shorten with ageing (*Table 3*). The relation between
210 ageing and shortened TLs has been evidenced mainly for vertebrates (*i.e.*, mammals, fish and
211 birds), for example in cats (McKevitt et al., 2003) and rodents (Coviello-McLaughlin et al.,
212 1997). However, for some vertebrates (e.g., long-lived species like the bird, *Oceanodroma*
213 *leucorhoa*, or the water python, *Liasis fuscus*), no relationship between the age of individuals
214 and TL length has been highlighted, probably due to reduced oxidative damage (Hausman et
215 al., 2003) or high TA activity stimulated by hormones notably estrogens (Ujvari and Masden,
216 2009). *Table 3* shows a lack of knowledge on TL dynamic as a function of age in

217 invertebrates and the mechanism of ageing. Based on the few data available with a sufficient
218 number of individuals by age group, three patterns can be identified regarding relationships
219 between TLs, TA and ageing: increase, decrease and no variation. In the Baikal gastropod
220 *Kobeltocochlea martensiana*, an enlargement of TLs with ageing has been demonstrated
221 (Maximova et al., 2017). Studies on the planaria *Schmidtea mediterranea*, which has an
222 apparently limitless regenerative capacity, showed that TLs decrease with age in sexual
223 animals, while asexual planaria can maintain TL length during fission or regeneration (Tan et
224 al., 2012). In the aquatic arthropod *Daphnia sp.*, no relationship between age and TL length
225 was found in *D. pulex* while *D. pulicaria*, whose life cycle is twice as long as that of *D. pulex*,
226 showed TL attrition with ageing (Schumpert et al., 2015). In both species, TL dynamic
227 appears to be correlated with TA activity. These different patterns underline that phylogenetic
228 proximity does not mean similar patterns between TLs or TA responses and ageing. For the
229 nematode *Caenorhabditis elegans* (which can be described as a short-lived species with a
230 temperature-dependent lifespan between 5 and 100 days), no correlation between ageing and
231 TL length was detected (Raices et al., 2005). The same observation was made for the long-
232 lived arthropod, *Homarus americanus* (lifespan from 50 and 100 years), which was
233 unexpected regarding its special longevity in an optimal environment. Ageing phenomena are
234 absent in this species, and mortality is often caused by the increased weight of individuals that
235 preclude moult (Klapper et al., 1998; Krupp et al., 2000).

236 In humans (Aubert and Lansdorp, 2008) and mice (Rudolph et al., 1999; Tomas-Loba et
237 al., 2008), TL attrition is considered one of the nine hallmarks of ageing (Lopez-Otin et al.,
238 2013) and is a marker of cellular senescence (Bernadotte et al., 2016). A relationship between
239 the shortening of TLs in human leukocytes and all causes of death has been demonstrated
240 (Boonekamp et al., 2013; Opresko et al., 2017). However, according to Farzaneh-Far et al.
241 (2008), death cannot be predicted with a simple measure of TL length, and depends also on

242 disease advancements or genotype. For example, it has been found that in humans, the
243 heterozygous genotype for some genes, including SERPINE, is associated with a longer TL
244 length, a longer lifespan (7 or more years on average), better cardiovascular capabilities,
245 lower fasting insulin levels, and a lower incidence of diabetes mellitus (Khan et al., 2017).

246 Hence, although a correlation between TL attrition, decrease in TA activity and ageing has
247 been often reported, it does not seem to be generalizable throughout the animal kingdom.

248 **4.2. Other causes**

249 Various mechanisms (*e.g.*, genotoxicity, oxidative stress) can impact TL length (**Figure**
250 **2**). DNA damage such as a single strand break (SSB) or a double strand break (DSB) can be a
251 source of TL attrition (Pottier et al., 2013; Grach, 2013), notably when the DNA repair
252 machinery is inefficient (Webb et al., 2013; Jia et al., 2015). Deficiencies in enzymes
253 supported by the BER pathway (*e.g.*, OGG1 and UNG) can contribute to TL shortening by
254 altered TL sister chromatid exchanges, an increased number of SSBs and DSBs, preferential
255 TL G-strand losses, accumulation of uracil on TLs, increased TL fragility and aberrant TL
256 recombination (Oikawa and Kawanishi, 1999; Wang et al., 2010; Vallabhaneni et al., 2013;
257 Webb et al., 2013; An et al., 2015; Jia et al., 2015; Vallabhaneni et al., 2015). Telomeric DNA
258 is highly susceptible to oxidative-induced DNA damage because of its high guanine content
259 (Kawanishi and Oikawa, 2004). Among oxidative lesion bases at TLs, 8-oxo-dG is the most
260 frequent (Zhou et al., 2017). Therefore, TLs can also be indirectly altered by mutagenicity
261 when reactive oxygen species (ROS) induce mutations (*e.g.*, 8-oxo-dG induces a transversion
262 G:C to A:T) in genes coding for TL structure and maintenance or the DNA repair of TLs
263 (Wood et al., 1990; Henle et al., 1999; von Zglinicki, 2002; Chang et al., 2003; Vasseur and
264 Cossu-Leguille, 2003; Houben et al., 2008; Coluzzi et al., 2017; Stauffer et al., 2018). A
265 disorder in protein recruitment in the TL complex shelterin can also be the cause of TL

266 attrition because the T-loop cannot be easily formed, making the end of the chromosome
267 unprotected. This phenomenon can also be at the origin of apoptosis or senescence via
268 activation of the p53 or p16link4a pathways (Oeseburg et al., 2010). In addition, the absence
269 or deficiency of TA may also be a cause of premature TL shortening (Ziegler et al., 2017).

270 TL shortening in human populations is related to psychological stress, diseases, infections,
271 diets and lifestyles including smoking, as reported for example by Valdes et al. (2005),
272 Lansdorp (2009), Mirabello et al. (2009), and Gomes et al. (2012). Similar studies have been
273 performed on mammals (Illmonen et al., 2008), showing that repeated infection by
274 *Salmonella enterica* can cause TL attrition in house mice (*Mus musculus*). Many biotic and
275 abiotic factors, such as nutrient (e.g., folate and selenium) deprivation, can accelerate TL
276 attrition. Indeed, the antioxidant activity of these nutrients has a protective effect against
277 oxidative DNA telomeric damage (Liu et al., 2004; Boccardi et al., 2013). Among other
278 factors that can influence TL dynamic, food availability, number of breeding events and
279 antioxidant capabilities have been described in birds (Hall et al., 2004; Foote et al., 2011;
280 Heidinger et al., 2012; Bebbington et al., 2016; Sletten et al., 2016; Angelier et al., 2018).

281 **4.3. Consequences of TL attrition on organism and population**

282 Telomere shortening and short TL length is associated with various diseases including
283 diabetes (Sampson et al., 2006; Uziel et al., 2007), cardiovascular diseases (Fitzpatrick et al.,
284 2007), obesity (Valdes et al., 2005), cancers (Srinivas et al., 2019) and pathologies of the
285 female reproductive tract (Kalmbach et al., 2013). These studies focusing on humans support
286 that TL length alteration can affect individual fitness in relation to a reduced lifespan reduced
287 for various animal species (Monaghan and Hausman, 2006). Interspecies comparisons
288 provide additional information to understand relations between TL dynamic and lifespan.
289 Higher rates of TL loss are associated with a shorter lifespan when comparing different bird

290 (Tricola et al., 2018) or mammal species. For instance, in humans, the rate of TL loss is 20-40
291 bp/year for a lifespan of 75 years while, it is 360 bp/year in dogs with a lifespan of 12 years
292 (Unryn et al., 2015). Generally, in vertebrates, TL length is inversely correlated with the
293 lifespan of a species (Gomes et al., 2011).

294 If TLs length is predictive of the longevity of individuals of species as demonstrated for
295 *Acrocephalus arundinaceus* or *Daphnia pulicaria* (Asghar et al., 2015; Schumpert et al.,
296 2015), an accelerated attrition of TLs within a population may cause a decrease of the mean
297 reproductive lifespan and of individual fitness, so reduce fertility rate, which should lead to
298 changes in population dynamics (Reichert, 2013). However, if theoretical links between TL
299 dynamic, individual life-history traits and population dynamic seems obvious, the published
300 literature dealing with the ecological repercussion of accelerated TL shortening remains very
301 limited.

302 **5. Contaminants and effects on telomere dynamic**

303 Besides ageing and the other factors influencing TL dynamic we listed above, effects of
304 toxic contaminants released by anthropogenic activities on individual health, life-history traits
305 and population dynamic have been widely reported in the scientific literature. The interactions
306 between a toxic compound and a biological system occurred first at the molecular and cellular
307 levels. Then, ecological processes may also act, for instance when a predator suffers a
308 decrease in prey availability because of poisoning. According to the mechanism(s) of action
309 and depending on the sensitivity of the exposed species, this usually involves that the
310 compound reaches one (or several) molecular target(s) and/or induces oxidative stress to
311 express its toxicity at higher levels of biological organization. As reported above, TL dynamic
312 is related to life-history traits and potentially to population dynamic. Thus, it can be assume
313 that changes in TL dynamic is among the key processes linking toxic compounds,

314 molecular/cellular disturbances and consequences on individual health, fitness and
315 population.

316

317 **5.1. In humans**

318 Currently, most of the studies questioning the impact of contaminants on TL length and
319 TA activity concern humans, especially leukocytes. The general trend is that TL length and
320 TA activity decrease concomitantly when cells or humans are exposed to contaminants (*Table*
321 *4*). This premise fits well with the commonly proposed hypothesis that exposure to pollutants
322 causes cell damage together with a decrease in TL length and TA activity.

323 Exposure to metallic elements (ME) has been related to TL length changes, two patterns
324 can be distinguished: decrease or increase (*Table 4*). For example, cadmium (Cd) can cause
325 TL attrition, as shown in placenta from newborns (Lin et al., 2013), in saliva from adolescents
326 (Fillman et al., 2016) and in leukocytes from adults (Zota et al., 2015; Patel et al., 2017).
327 Similar trends were reported for lead (Pb) (Pottier et al., 2013; Pawlas et al., 2015; Pawlas et
328 al., 2016), arsenic (As) (Ferrario et al., 2009; Srinivas et al., 2019) and the combination of As,
329 Cd and/or tungsten (W) (Wai et al., 2018; Grau-Perez et al., 2019). Organic chemicals, such
330 as polycyclic aromatic hydrocarbons (PAH), polychlorinated biphenyls (PCB),
331 polybrominated diphenyl ethers (PBDE) and air pollutants (*e.g.*, benzene, toluene and fuel
332 smoke) can lead to TL attrition (*Table 4*). Some PCBs and PBDEs induced a decrease in TL
333 length, TA activity and the expression of fundamental genes implicated in TL maintenance
334 and stability (Xin et al., 2016; Ziegler et al., 2017; Yuan et al., 2018).

335 Toxicologists have also paid special attention to carcinogenic compounds such as ME
336 (*e.g.*, As), some persistent organic pollutant (POP) or air contaminants (NO_x, NO₂, PM_{2.5} and

337 PM₁₀) (Dioni et al., 2011; Gao et al., 2015; Hou et al., 2015; Joyce and Hou, 2015; Mitro et
338 al., 2016; Jimenez Villarreal et al., 2018; Zhao et al., 2018). A study conducted by Gao et al.
339 (2015) on leukocytes from 167 participants demonstrated that a higher As urinary
340 concentration was associated with increased TL length, overexpression of WRN (a gene
341 involved in the ALT pathway), and decreased expression of TERF2, TERF2IP (shelterin
342 complex), DKC1 (upregulation of TA), and OBFC1 (upregulation of TA). A similar trend
343 was reported on leukocytes that presented an elongation of TL and an increase of the level of
344 two proteins of the shelterin complex (TRF1 and TRF2) following As exposure (Chatterjee et
345 al. 2015). As previously stated, abnormal TL elongation should not necessarily be considered
346 as positive, since strong activities of TA or ALT can be related to tumour development. In the
347 study of Gao et al. (2015), the WRN gene, implicated in ALT pathway, was up-regulated in
348 leukocytes and TL were lengthened after exposure to As. Moreover, it was demonstrated that
349 methylation of CHK1 or PML genes may activate ALT pathway in human or mouse
350 (Naderlinger and Holzmann, 2017), especially after exposure by PCBs and PCDEs (Yuan et
351 al., 2018). Therefore, for carcinogenic contaminants, a possible mechanism of action could be
352 an increase in TL length caused by TA and/or ALT upregulation rather than TL attrition
353 (Finnon et al., 2000; Jafri et al., 2016; Dagg et al., 2017). A pathway explaining an
354 overactivation of the ALT pathway could be epigenetic alterations, such as methylations,
355 induced by some contaminants (Reichard and Puga, 2010; Nica et al., 2017).

356 **5.2. In animals**

357 There is a growing interest in ecology to measure TLs in various organisms, including
358 vertebrates and invertebrates, with approximately five publications in 1995 vs one hundred in
359 2015 (Angelier et al., 2018). However, in ecotoxicology, studies are limited to vertebrates and
360 mainly birds (*Table 5*), but no studies on invertebrates has been published. In some of the few

361 studies that assessed with the impact of contaminants on TLs or TA in animals, TL attrition
362 was related to high exposure. [Stauffer et al. \(2017\)](#) showed inconsistent trends when
363 investigating the interaction between exposure to ME, oxidative stress and TL length in wild
364 populations of two birds (*Parus major* and *Ficedula hypoleuca*). They demonstrated that great
365 tit nestlings exposed to ME had shorter TLs than those living in unpolluted areas. However,
366 this correlation was not found when investigating pied flycatcher nestlings or adult females of
367 two species. The authors investigated whether the redox status that varied among species and
368 age groups may explain these differences but no link with TL length was found. For *Rissa*
369 *tridactyla*, an arctic seabird species, [Blévin et al. \(2016\)](#) showed that TL attrition was higher
370 in wild adult females exposed to the major metabolite of chlordane mixture (oxychlordane)
371 than in males. More expectedly, oxidative stress could accelerate TL attrition, as shown
372 experimentally in wild-caught house mice (*Mus musculus musculus*), for which an inhibition
373 of superoxide dismutase (SOD) activity was related to TL attrition ([Stauffer et al., 2018](#)). A
374 study on the fish *Epinephelus coiodes* showed a concomitant decrease in TA activity with
375 high exposure to benzo(a)pyrene (a PAH) ([Peterson et al., 2015](#)). **As reported in *Figure 2*,**
376 **potential relationships between TL attrition and increases of DNA damages has been shown**
377 **on *Ctenomys torquatus* exposed to PAH and ME from coal ([Matzenbacher et al., 2019](#)).** All
378 these studies show that TL length and TA activity can be altered by contaminants in various
379 vertebrate species, including birds, fishes and mammals.

380 However, other studies have not revealed that TL attrition is associated with chemical
381 exposure. White-tailed eagle (*Haliaeetus albicilla*) nestlings sampled from a site
382 contaminated by organohalogenated compounds did not exhibit TL shortening or reduced
383 SOD activity ([Sletten et al., 2015](#)). [Blévin et al. \(2017\)](#) measured an increase in TL length in
384 both sexes of *Rissa tridactyla* (Black-legged kittiwake) exposed to perfluoroalkyl substances
385 (PFAs).

386 The impact of pollutants on TLs and TA is still a new field of research in environmental
387 toxicology; on the basis of the recent data published, it remains difficult to identify general
388 trends. This could be partly due to a lack of knowledge about the influence of various
389 individual (*e.g.*, gender, age, species) and/or environmental (*e.g.*, weather conditions, food
390 availability, pathogens, pollutions) factors on TL dynamic. In the following section, we
391 propose several lines of research to improve knowledge on the impact of pollutants on TLs
392 and TA in environmental toxicology for humans and animals (mainly those used as
393 bioindicators for ecotoxicological purposes).

394 **6. Perspectives for the assessment of telomere dynamic in environmental toxicology**

395 Environmental toxicology concerns the toxic effects of environmental contaminants on
396 living organisms in their environments. Gaining more knowledge on the impact of
397 contaminants on TL dynamic could be relevant to understand these effects and possibly to
398 propose adverse outcome pathways (AOP), which would impact life traits and population, as
399 recommended by the [OECD \(2018\)](#). This review showed that the level of knowledge on TLs,
400 in general and particularly in environmental toxicology, is quite different for humans,
401 vertebrates and invertebrates. Thus, perspectives for the possible use of TL length and TA
402 activity as biomarkers in environmental toxicology depend on the considered group; they will
403 be briefly developed for each of these groups of organisms, before moving to more specific
404 consideration (either technical or biological).

405 For humans, although TLs are already used as biomarkers (*Table 4*), further studies are
406 necessary to better fulfil some specifications (*e.g.*, the link between TL variation and
407 biological consequence or between TL lengthening and exposure to compounds with
408 carcinogenic properties). For other vertebrates (*Table 5*), with the possible exception of birds,
409 the use of TL length and TA activity as biomarkers appears far from ready in routine use for

410 ecotoxicological purposes. This review highlights a lack of knowledge on TL dynamic in
411 almost all bioindicator species: for the majority, the relation between ageing and TL length
412 remains to be characterized, as well as the influence of many endogenous and environmental
413 factors (acting possibly in interactions) on TL dynamic. This is also true for invertebrates, for
414 which this area of research is virtually untouched.

415 The basic question here is whether early TL shortening could be a biomarker to reveal the
416 impact of stress (physical, chemical and biological) on premature ageing and thus organism
417 health and longevity. For this purpose, TL length and TA activity must satisfy some
418 specifications: good sensitivity, knowledge about biological consequences for interpreting the
419 responses of the biomarker, feasibility, field application, knowledge about variations in the
420 amplitudes of responses, and the identification of confounding factors (*i.e.*, capacities to
421 discriminate variations that could be caused by pollutants or environmental factors) ([Garric et al., 2010](#)). According to these specifications, many technical and biological issues must be
422 better considered for reliable TL length and TA activity assessments in environmental
423 toxicology:
424

- 425 • The choice of analytical technique to assess TL length and TA activity. Currently,
426 many methods exist to measure TLs (qPCR, flow-fluorescence *in situ*
427 hybridization (FISH), qFISH, single TL length analysis (STELA), terminal
428 restriction fragment by southern blot or in-gel hybridization, dot blot) and detect
429 TA activity (ddPCR). The choice of methods depends on scientific questions and
430 technical considerations (see, for example, the reviews of [Montpetit et al., 2014](#)
431 and [Nussey et al., 2014](#)). For example, for the same sample, qPCR provides an
432 estimate of the average TL length in a DNA extract but the diversity of the TL size
433 for each cells cannot be determined. Molecular biology kits exist and have often

434 used (*e.g.*, by [Schumpert et al. \(2015\)](#) to measure TA activity on two *Daphnia sp.*)
435 For reasons related to quickness, simplicity, robustness and cost, the qPCR TL
436 measurement technique seems well appropriate and is widely used ([Cawthon et al.,](#)
437 [2002](#); [Shay and Wright, 2019](#)), even if the results are semiquantitative (but
438 sufficient to identify variations between various exposures to contaminants).

- 439 • Influence of the quality of DNA extraction. In terms of measurement techniques
440 and TL size, different kits can be preferred. It is important to use the same
441 extraction method during all the studies ([Nussey et al., 2014](#); [Raschenberger et al.,](#)
442 [2016](#)).
- 443 • Influence of storage conditions of the sample that can impact measurements. For
444 example, FTA cards (*Flinders Technology Associates cards*) are not recommended
445 for long-term storage ([Reichert et al., 2017](#)) and repeated cycles of
446 freezing/thawing can cause DNA alterations.
- 447 • Influence of the choice of biological tissue or cell type ([Gardner et al., 2007](#);
448 [Kesäniemi et al., 2019](#)) according to physiological characteristics (*i.e.*: TA
449 activity, ALT, cell division properties) and toxicological characteristics (*i.e.*:
450 target, storage or metabolism of xenobiotics) is important to be considered. For
451 example, [Yip et al. \(2017\)](#) chose to measure TLs on Medaka fish liver cells
452 because of the regulatory functions of metabolism and homeostasis. For small
453 organisms (*e.g.*, arthropods) the recourse of pools and whole body may be
454 relevant.
- 455 • Experiments must use of a sufficient number of individuals by age and/or
456 environmental condition class to make reliable statistical comparisons to account
457 for interindividual variations.

458 • The link between TL length, TA activity, longevity and ageing needs to be
459 investigated in a wide range of animals, including invertebrates (notably those
460 commonly used in ecotoxicological risk assessment, *e.g.*, **crustacean, earthworms**
461 **and mollusks**, for which no data are available). Indeed, interspecific comparison to
462 estimate variation of TL length or TA activity with ageing for species for which
463 the dynamic of TLs is unknown is difficult because various patterns have been
464 demonstrated for phylogenetically close species (*e.g.*, between various bird
465 species). For example, a relation between TL length and ageing for *Daphnia*
466 *pulicaria* has been evidenced (Schumpert et al., 2015) and suggests that it could be
467 interesting to assess the sublethal effects of contaminants or other stressors on this
468 taxon with TL length measurements. However, this relation is not the same for
469 *Daphnia pulex* where TL length does not evolve with ageing. Understanding the
470 reason for the differences observed in phylogenetically close species, offers an
471 exciting challenge.

472 • **Many studies concerning the impact of contaminants on TL dynamic are**
473 **correlative. To better evaluate the relevance of TL dynamic studies in**
474 **environmental toxicology and to highlight by which mechanisms TL changes are**
475 **related to exposure to chemicals, it is essential to develop more laboratory**
476 **approaches. Some experiments conducted under controlled conditions should**
477 **address the following questions:**

478 ○ **What is the influence of environmental and individual factors on TL**
479 **dynamic such as, gender, hormones, food source, crowding, disturbance,**
480 **noise, infection, pathogens, parasites, and climatic factors, as described by**
481 **Angelier et al. (2018)? For example, in female Medaka fish, oestradiol may**
482 **be involved in TL maintenance by i) increasing TA activity (TERT mRNA**

483 upregulation, TERT phosphorylation) and ii) limiting oxidative DNA
484 damage at the level of TLs (antioxidant gene upregulation) (Yip et al.,
485 2017).

- 486 ○ What are the consequences of TL attrition on survival or reproductive
487 abilities and consequently on population dynamic?
- 488 ○ What is the pattern(s) of the relationship between TL length and
489 contaminant exposure? This question is supported by the fact that some
490 carcinogenic compounds could lead to an elongation of TLs and because
491 dose-reponse relationships have not been established even for the most
492 prevalent pollutants either single or in mixture. This should be done
493 considering acute but also subchronic and chronic exposure scenario.
- 494 ○ What are the main mechanisms, including direct (DNA damages) and
495 indirect ones (modulation of maintenance processes, oxidative stress...),
496 linking chemical exposure and the alteration of the natural TL dynamic?

497

498 **7. Conclusion**

499 TLs are highly conserved in the animal kingdom, ubiquitous and appear “universal” in
500 living organisms. However, many studies are still needed, as noted in the present review,
501 before TLs can be used as a relevant biomarker (in species belonging to many biological
502 groups) to predict the effects of various stressors (*e.g.*, chemical contaminants) on health for
503 humans and animal populations in the wild. More data on TL dynamic could help build new
504 AOP for chemical risk assessment based on mechanistic reasoning. TL dynamic studies could
505 improve environmental monitoring and our understanding of the impact of disrupted
506 anthropic ecosystems (on the health status, lifespans and dynamic of populations) and could
507 reduce disciplinary borders in the One Health concept, because epidemiologists,

508 ecotoxicologists, veterinarians and economists look for universal information concerning an
509 organism's health.

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515 The authors declare no disclosures of interest.

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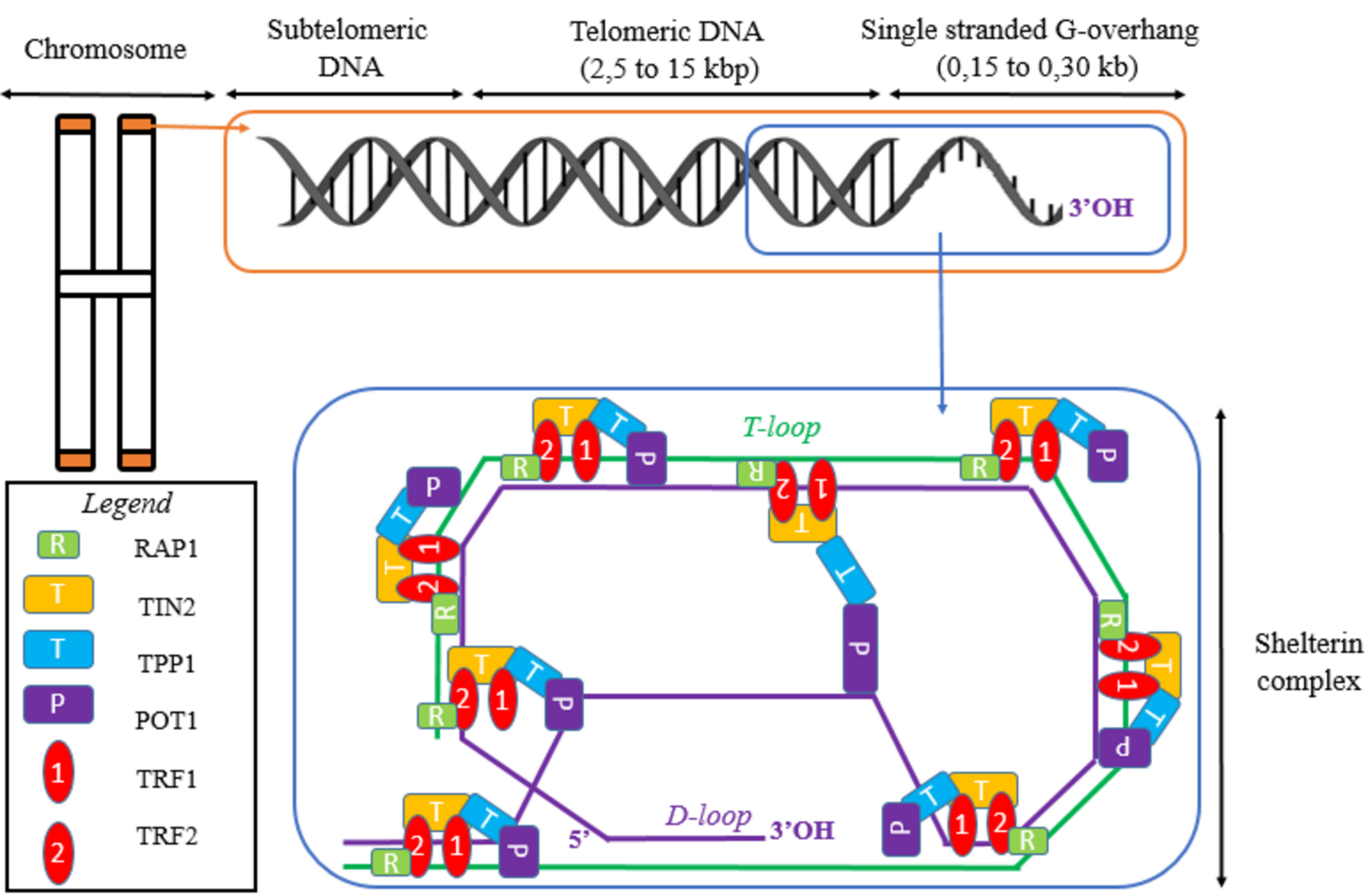
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1192



Stress factors (lifestyles, environmental stress including pollutants, infections, noises, etc.)

Error of DNA replication on telomeres

Recruitment problem of proteins in shelterin complex

Hormones

DNA Mutations

Capacity of DNA repair at telomeres ↓

Genotoxic stress

Metabolic stress and Xenobiotics metabolism

Antioxidant capabilities ↓

Ageing

Instability of telomeres

Instability of shelterin complex

Telomerase activity ↓

Telomeropathy

DNA Damage ↑

Double or single strand breaks and alkylations ↑

Oxidative stress ↑

Oxidation of nucleotides ↑

Number of cell divisions ↑

Telomere attrition ↑

1 **Telomere dynamic in humans and animals: review and perspectives in**
2 **environmental toxicology**

3
4 **List of the figures**

5
6 File fig1.tif: **Figure 1:** Human TL structure and six TL binding proteins: TRF1, TRF2, RAP1,
7 TPP1, TIN2, POT1 (modified from [Blasco, 2005](#), [Martinez and Blasco, 2010](#), [Lu et al., 2013](#),
8 [Sandin and Rhodes, 2014](#)).

9 File fig2.tif: **Figure 2:** Some causes of TL attrition.

10
11 **List of the Tables**

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17 various biological groups of animals.

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19 contaminants in humans.

20 **Table 5:** Relationship between telomere dynamics and environmental contamination by
21 contaminants in animal.

28 **Table 1:** No-exhaustiv list of telomere sequences of bioindicator taxons in environmental
 29 toxicology

SEQUENCES	SPECIES	SOURCES
(TTAGGG) _N	Vertebrates (Fishes, Birds, Mammals, Amphibians), Invertebrates (Snails as <i>Cantareus aspersus</i> , Earthworms as <i>Eisenia foetida</i> , Planaria)	Meyne et al., 1989 , Vitturi et al., 2000 , Vitturi et al., 2005 , Koroleva et al., 2013 , Tasaka et al., 2013 .
(TTAGG) _N	Invertebrates (<i>Daphnia sp.</i> , <i>Chironomus sp.</i> , <i>Bombyx mori</i>)	Okazaki et al., 1993 , Rosen et Edstrom, 2000 , Schumpert et al., 2015
(TTAGGC) _N	Invertebrates (Nematod, <i>Caenorhabditis elegans</i>)	Wicky et al., 1996

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48 **Table 2:** Roles of the six telomere binding proteins: TRF1, TRF2, RAP1, TPP1, TIN2, POT1

49 (adapted from [Iwano et al., 2004](#), [Okamoto et al., 2008](#), [Martinez and Blasco, 2010](#))

PROTEINS ROLES	TIN2	RAP1	TPP1	TRF2	TRF1	POT1
BRIDGING SHELTERIN	X		X			
CAPPING SHELTERIN			X	X	X	
G-STRAND PROTECTION						X
INTERACTIONS WITH DNA DAMAGE RESPONSE (DDR)		X		X	X	X
INTERACTIONS WITH MITOSIS REGULATIONS					X	
PREVENTION OF TELOMERE FRAGILITY		X	X		X	
PREVENTION OF TELOMERE RECOMBINATION AND END-TO-END FUSION		X		X		X
STIMULATING SUBTELOMERIC SILENCING		X				
ALLOWS TA RECRUITMENT			X			
TL ACCESSIBILITY FOR TA INHIBITION						X
TELOMERIC LOCALIZATION OF OTHER SHELTERIN COMPONENTS REGULATION	X				X	

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Table 3: Links between telomere shortening and ageing with others biologicals markers in various biological groups of animals.

BIOLOGICAL SPECIES	STUDIED AGES	N	BIOLOGICAL TISSUES	EFFECTS OF AGEING ON TELOMERE DYNAMICS	EFFECTS OF AGEING ON OTHERS BIOLOGICALS MARKERS	SOURCES
INVERTEBRATES						
<i>Strongylocentrotus franciscanus</i> (Sea urchin)	4 to > 100 years	?	Some tissues (Aristotle's lantern muscle, ampullae, esophagus, intestine, gonad)	↓ telomere lengths, O telomerase activity	↑ body size	<i>Francis et al., 2006</i>
<i>Lytechnius variegatus</i> (Sea urchin)	> 3 years	?		↓ telomere lengths, O telomerase activity	↑ body size	<i>Francis et al., 2006</i>
<i>Schmidtea mediterranea</i> (Planaria)	7 days to 3 years	73 (min. 7 per ages)	Somatic cells	↓ telomere lengths	-	<i>Tan et al., 2012</i>
<i>Daphnia pulex</i> (Daphnia)	Embryos, 1, 2 and 3 weeks	25 to 30 individuals in pools/age	Body	O telomere lengths, ↑ telomerase activity	↑ mortality	<i>Schumpert et al., 2015</i>
<i>Daphnia pulicaria</i> (Daphnia)	Embryos, 1, 4 and 8 weeks	25 to 30 individuals in pools/age	Body	↓ telomere lengths, ↓ telomerase activity	↑ mortality	<i>Schumpert et al., 2015</i>
<i>Drosophila melanogaster</i> (Vinegar fly)	0 to 100 days	2000 (100 per 5 days)	Body	O telomere lengths	↓ fecundity, ↓ fertility	<i>Walter et al., 2007</i>
<i>Benedictia fragilis</i> (Baikal gastropods)	0 to 8 years	95	Foot	↓ telomere lengths	-	<i>Maximova et al., 2017</i>
<i>Benedictia baicalensis</i> (Baikal gastropods)	0 to 8 years	121	Foot	↑ telomere lengths	-	<i>Maximova et al., 2017</i>
<i>Kobeltocochlea martensiana</i> (Baikal gastropods)	0 to 8 years	111	Foot	↑ telomere lengths	-	<i>Maximova et al., 2017</i>
FISHS						
<i>Oryzias melastigma</i> (Medaka)	4, 8, 12 months	15 (5/age)	Liver	, ↓ telomere lengths, Δ telomerase activity, Δ TERT mRNA expression in liver,	In liver: ↑ 8-OH-dG level, ↑ protein carbonyl level, Δ omERα mRNA expression, in plasma: Δ testosterone (T) and Δ estrogen (E2) levels	<i>Yip et al., 2017</i>
<i>Danio rerio</i> (Zebrafish)	8 days to 24 months	140 (~5/age, ~100 at 8 days)	Some tissues (testis, gut, head kidney, muscle, skin)	↓ telomere lengths, ↑/↓ telomerase activity (Δ f(tissues))	-	<i>Henriques et al., 2013, Henriques et al., 2017</i>
REPTILES						
<i>Alligator sinensis</i> (Chinese alligator)	3 to 10 years	30	Erythrocytes	↓ telomere lengths	-	<i>Xu et al., 2009</i>
<i>Alligator mississippiensis</i> (American Alligator)	0 to 7 years	34	Erythrocytes	↓ telomere lengths	↑ body size	<i>Scott et al., 2006</i>
<i>Liasis fuscus</i> (Water python)	0 to 20 years	70	Erythrocytes	↑ telomere lengths	-	<i>Ujvari et Masden, 2009</i>
BIRDS						
<i>Taeniopygia guttata</i> (Zebra finch)	1 to 7 years	99	Erythrocytes	↓ telomere lengths	-	<i>Heidinger et al., 2012</i>
<i>Taeniopygia guttata</i>	0 to 8 years	25	Erythrocytes	↓ telomere lengths	-	<i>Hausman et al., 2003</i>
<i>Tachycineta bicolor</i> (Tree swallow)	0 to 7 years	42	Erythrocytes	↓ telomere lengths	-	<i>Hausman et al., 2003</i>

<i>Pygoscelis adeliae</i> (Adélie penguin)	1 to 14 years	22	Erythrocytes	↓ telomere lengths	-	<i>Haussman et al., 2003</i>
<i>Sterna hirundo</i> (Common tern)	0 to 25 years	41	Erythrocytes	↓ telomere lengths	-	<i>Haussman et al., 2003</i>
<i>Oceanodroma leucorhoa</i> (Leach's petrel)	0 to 35 years	33	Erythrocytes	↑ telomere lengths	-	<i>Haussman et al., 2003</i>
<i>Phalacrocorax aristolelis</i> (European shag)	0 to 20 years	144	Whole blood (chicks), erythrocytes (adults)	↓ telomere lengths	-	<i>Hall et al., 2004</i>
<i>Diomedea exulans</i> (Wandering albatross)	0 to 42 years	92	Whole blood (chicks), erythrocytes (adults)	↓ telomere lengths	-	<i>Hall et al., 2004</i>
<i>Branta leucopsis</i> (Barnacle goose)	2 to 26 years	30	Whole blood	↓ telomere lengths	-	<i>Pauliny et al., 2012</i>
<i>Acrocephalus arundinaceus</i> (Great reed warbler)	0 to 6 years	174	Whole blood	↓ telomere lengths	-	<i>Asghar et al., 2015</i>
MAMMALS						
<i>Canis lupus familiaris</i> (Dogs)	0 to 15 years	175	Whole blood	↓ telomere lengths	↑ probability of death from cardiovascular disease	<i>Fick et al., 2012</i>
<i>Felis catus</i> (Cats)	cohort	32	Whole blood	↓ telomere lengths	-	<i>McKevitt et al., 2003</i>
<i>Mus spretus</i> (Western Mediterranean mouse)	0 to 2,5 years	20	Some tissues (testes, kidney, liver, spleen, brain)	↓ telomere lengths	-	<i>Coviello-McLaughlin et al., 1997</i>
<i>Homo sapiens</i> (Humans)	0 to 82 years	72	Leukocytes	↓ telomere lengths	-	<i>Frenck et al., 1998</i>
<i>Homo sapiens</i>	cohort	193	Leukocytes	↓ telomere lengths	↓ pulse wave velocity, pulse pression	<i>Benetos et al., 2001</i>

Legends: Δ = variations, ↑ = increasing, ↓ = decreasing, O = no effects

Table 4: Relationship between telomere dynamics and environmental contamination by contaminants in humans

BIOLOGICAL MATERIALS	EXPERIMENTALS CONDITIONS	CONTAMINANTS	EFFECTS ON TELOMERE DYNAMICS	OTHERS BIOLOGICALS EFFECTS AND ASSOCIATIONS WITH INTERNAL CONCENTRATIONS	SOURCES
<u>IN VITRO STUDIES</u>					
HL-60 cells	6 and 30 days <i>in vitro</i>	PCB126 and PCB153 (5 µM)	↓ Telomere length, ↓ Telomerase activity, ↓ hTERT, ↓ hTR, Δ POT1, Δ TRF1, Δ TRF2 expressions	↑ phases G0/G1 cells	Xin et al., 2016
Primary cultured lymphocytes	2, 7, 42 and 70 days <i>in vitro</i>	3-OH-CB28 (metabolite of PCB28) (1-50 µM)	↓ Telomere length, ↓ Telomerase activity, ↓ Telomerase genes expressions	O lymphocytes numbers, O TREC (T-cell receptor excision circle) levels	Ziegler et al., 2017
Cells of umbilical cord blood (huUCB)	30 minutes – 14 days	As inorganic (0,1 nM, 1 and 10 µM)	↓ Telomere length, ↓ hTERT expression	↑ ROS	Ferrario et al., 2009
Cells of carcinoma cell line (Clone B3, EJ30 bladder cell)	1 day	Pb(NO ₃) ₂ (0-1000 µM)	↓ Telomere length	↑ chromosomal abnormalities	Pottier et al., 2013
<u>STUDIES ON COHORTS OR ON PATIENTS</u>					
<u>METALLIC ELEMENTS</u>					
Placenta from 320 newborns	patients	Placental Cd and Pb concentration	↓ Telomere length	Association with [Cd] placental	Lin et al., 2013
Leukocytes from 6796 adults	cohort	Cd and Pb in blood and urines	↓ Telomere length	Association with [Cd] _{blood}	Zota et al., 2015 , Patel et al., 2017
Leukocytes from 334 smelters	cohort	Cd and Pb in blood (occupational exposure by air)	↓ Telomere length	Association with [Pb] _{blood}	Pawlas et al., 2016
Leukocytes from 365 children	cohort	Pb in blood	↓ Telomere length	Association with [Pb] _{blood}	Pawlas et al., 2015
Salivary cells from adolescents (12-16 years olds, n=351)	patients	As and Cd in urines	↓ Telomere length	Association with [Cd] _{urinary}	Fillman et al., 2016
Leukocytes from 73 female university students	cohort	Cd in urines	O Telomere length	-	Mizuno et al., 2019

Umbilical cord blood leukocytes from 410 mother-newborn pairs	cohort	Cd in urines	↓ Telomere length	Association with [Cd] _{urinary}	<i>Zhang et al., 2019</i>
Leukocytes from 167 participants	patients	As in urines	↑ Telomere length, ↑ Expression of WRN (ALT), ↓ Expressions of genes including TERF2 (shelterin complex), DKC1 (up-regulation of telomerase), TERF2IP (sheltering complex), OBFC1 (up-regulation of telomerase)	Association with [As] _{urinary}	<i>Gao et al., 2015</i>
Leukocytes from 188 male participants (76 exposed in drinking water > 10 µg.L⁻¹, 112 control group)	cohort	As in urines	↑ Telomere length	Association with [As] _{drinking water} and [As] _{urinary}	<i>Jimenez Villarreal et al., 2018</i>
Leukocytes from 1061 patients (528 with skin cancers, 533 hospital-based controls aged 30-79 years)	patients	As in urines	↓ Telomere length	Association with [As] _{urinary} and skin cancer	<i>Srinivas et al., 2019</i>
Leukocytes from 180 participants (60 unexposed, 120 exposed)	cohort	As in urines	↑ Telomere length, O telomerase activity, ↑ levels of TRF1 and TRF2 (shelterin complex)	Association with [As] _{urinary} , ↑ percentage of senescent cells, ↑ expression of cytokines (IL-6 and IL-8), ↑ expression of metalloproteases (MMP-1 and MMP-3), ↑ levels of p21 and p53, ↓ p16 level	<i>Chatterjee et al., 2015</i>
Leukocytes from 120 children (5 to 15 years) participants (68 exposed in drinking water > 10 µg.L⁻¹, 52 control group)	cohort	As in drinking water and in urines	O Telomere length	Association with [As] _{urinary} , ↑ micronucleus in buccal, urothelial cells and lymphocytes,	<i>Chatterjee et al., 2018</i>
Leukocytes from 1380 participants	cohort	As in urines	O/↓ Telomere length	Association with [As] _{urinary} /greater risk of subsequent skin lesion	<i>Zhang et al., 2018</i>
Leukocytes from 460 newborn	cohort	As, Cd and Pb in maternal urines	↓ Telomere length	Association with [As] or [Cd] _{urinary}	<i>Wai et al., 2018</i>
Leukocytes from 1702 participants	cohort	As, Cd and W in urines	↓ Telomere length	Association [As], [Cd] and [W] _{urinary}	<i>Grau-Perez et al., 2019</i>
ALCOHOL					
Leukocytes from 404	patients	Alcohol	↓ Telomere length	Association with alcohol abusers	<i>Pavanello et al., 2011</i>

participants

ATMOSPHERIC POLLUTION

Leukocytes from 333 schoolchildren	cohort	NO _x , NO ₂ , PM _{2.5} , PM ₁₀	↑ Telomere length	Association with annual air pollution exposure	<i>Walton et al., 2016</i>
Leukocytes from 120 truck drivers and 120 office workers	cohort	NO _x , NO ₂ , PM _{2.5} , PM ₁₀	↑ Telomere length	Association with PM _{2.5} , PM ₁₀	<i>Hou et al., 2012</i>
Leukocytes from 63 steel workers (3 days postexposure during 1 day)	cohort	PM ₁ , PM ₁₀	↑ Telomere length, ↓ hTERT mRNA	Association with PM ₁ and PM ₁₀	<i>Dioni et al., 2011</i>
Leukocytes from 264 patients	patients	Solid fuel combustion	↓ Telomere length	Association with solid fuel combustion for three decades	<i>Lin et al., 2017</i>
Leukocytes from 101 welders and 127 controls	patients	Respirable dust (between 1,2 mg/m ³ to 3,3 mg/m ³ , control: 0,1 mg/m ³)	O/↓ telomere length	O 8-oxodG levels, O/↓ DNA methylation	<i>Li et al., 2015</i>
Leukocytes from 50 pregnant women living in polluted area vs 50 in a non-polluted area	cohort	Atmospheric pollution and intense environmental pressure due to wastes	↓ Telomere length, ↓ hTERT mRNA	Association with polluted area	<i>De Felice et al., 2012</i>
Buccal cells and placenta cells from 233 patients	cohort	Residential traffic exposure	↓ Telomere length	Association with residential traffic exposure	<i>Bijnens et al., 2017</i>
Leukocytes from workers (77 street traffic officers and 57 office workers (referents))	cohort	Personal airborne benzene exposure (0 to 300 µg/m ³) and toluene exposure (12.5 to 1000 µg/m ³)	↓ Telomere length	Association with benzene and toluene exposure	<i>Hoxha et al., 2009</i>
Leukocytes from workers (43 and 43 in controls)	cohort	Workers exposed to benzene (31 ppm in 5 days)	↑ Telomere length	Association with benzene exposure (> 31 ppm in 5 days)	<i>Bassig et al., 2014</i>
Leukocytes from 157 rubber workers	cohort	Workers exposed to pyrene and nitrosamines	↓ Telomere length	Association with nitrosamines exposure	<i>Li et al., 2011</i>

PAH, PCB and PBDE

Cells of cord blood on 255 newborns	patients	PAH	↓ Telomere length	Association with PAH-DNA adducts	<i>Perera et al., 2018</i>
Leukocytes from 14 children	patients	PAH	↓ Telomere length	Association with PAH exposure	<i>Lee et al., 2017</i>
Leukocytes from 1330 adults	cohort	18 PCBs, 7 dioxins, 9 furans	↑ Telomere length	Association with TEQ (Toxic Equivalency)	<i>Mitro et al., 2015</i>
Leukocytes from 452 adults (136 in controls, 316 exposed)	cohort	25 PCBs and 11 PBDEs	↓ Telomere length, ↑ frequencies of telomere loss and multiple separate telomere at the ends of chromosomes, ↑ ALT activities,	↑ [PCBs] _{lipids} , ↑ [PBDEs] _{lipids} , ↑ abortion, stillborn, hypertension, diabetes and autoimmune diseases, ↑ relative expression of p53 and Rb in plasma, ↑ p16ink4a and p14-arf level in plasma, ↑ interleukines levels in plasma (IL-2, IL-6, IL-10),	<i>Yuan et al., 2018</i>
PESTICIDES					
Leukocytes from 30 farmers and 30 townfolk	patients	17 pesticides	O Telomere length	↑ micronuclei, ↑ nucleoplasmic bridges (correlation with [pesticides])	<i>Zeljezic et al., 2015</i>
Leukocytes from 568 cancer-free male farmers	cohort	57 pesticides	↓ Telomere length	Association with exposure of 2,4-D, diazinon, butylate, malathion (except for alachlor it's opposite)	<i>Andreotti et al., 2015</i>

Legends: Δ = variations, ↑ = increasing, ↓ = decreasing, O = no effects

Table 5: Relationship between telomere dynamics and environmental contamination by contaminants in animal

BIOLOGICAL MATERIALS	EXPERIMENTALS CONDITIONS	CONTAMINANTS	EFFECTS ON TELOMERE DYNAMICS	OTHERS BIOLOGICALS EFFECTS	SOURCES
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FISHS

<i>Epinephelus coioides</i> (Orange-spotted grouper) Muscle (n=5)	Bio-assays	B[a]P : 12 µg/g de poissons/j since 1, 2 and 4 weeks	↓ telomerase activity	Association with B[a]p exposure	<i>Peterson et al., 2015</i>
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BIRDS

<i>Haliaeetus albicilla</i> (White-tailed eagle) nestlings Red blood cells (n=35)	Biomonitoring <i>in situ</i> (Troms County, Northern Norway)	9 PCBs, p,p'DDE, HCB, oxy-chlordane, cis-chlordane, trans-nonachlor, cis-nonachlor	O Telomere length	↓ SOD activity, Δ IgY levels	<i>Stetten et al., 2016</i>
<i>Parus major</i> (Great tit) nestlings and adults females Livers cells (n=24 and n=21)	Biomonitoring <i>in situ</i> (Cu/Ni smelter in Harjavalta, Finland)	ME (Cu, Ni, As, Pb, Cd maj.)	↓ Telomere length (nestlings), O Telomere length (adults females)	↑ [As, Pb], ↓ SOD activity (nestlings), ↑ GPx activity, ↑ [Ca], ↓ lipoperoxidation	<i>Stauffer et al., 2017</i>
<i>Ficedula hypoleuca</i> (European pied flycatcher) nestlings and adults females Livers cells (n=22 and n=23)	Biomonitoring <i>in situ</i> (Cu/Ni smelter in Harjavalta, Finland)	ME (Cu, Ni, As, Pb, Cd maj.)	O Telomere length	↑ [As, Pb], ↓ Gr and GST activities, ↓ lipoperoxidation (nestlings),	<i>Stauffer et al., 2017</i>
<i>Rissa tridactyla</i> (Black-legged kittiwake) Red blood cells (n=38)	Biomonitoring <i>in situ</i> (Krvkkiefiellet colony of Kongsfjorden, Svalbard)	PCBs, p,p'DDE, HCB, cis-nonachlor, trans-nonachlor, [Oxychlordane] between 2000 to 7000 pg/g ww	↓ Telomere length (adults females), O Telomere length (adults males)	Association with [oxychlordane]	<i>Blévin et al., 2016</i>
<i>Rissa tridactyla</i> Red blood cells (n=55)	Biomonitoring <i>in situ</i> (Krvkkiefiellet colony of Kongsfjorden, Svalbard)	PFAs	↑ Telomere length (in both sexes)	Association with [PFAs]	<i>Blévin et al., 2017</i>

MAMMALS

<i>Rattus norvegicus</i> (Sprague-Dawley rats) Fibroblast-type cell line (ADIPO-P2)	18h to 15 days <i>in vitro</i>	Sodium citrate (20 mM) and Streptozotocin (2 mM)	↓ Telomere length, ↑ Telomere duplication, ↑ Translocation of telomeric sequences, ↑ Additional telomeric FISH signals, ↑ extra-chromosomal telomeric FISH signals	Association with chromosomal aberrations	<i>Paviolo et al., 2015</i>
<i>Ctenomys torquatus</i> (Collared tuco-tuco) kidney, muscle and skin tissues (n=30 control, n=36 exposed)	Biomonitoring <i>in situ</i> (Butia, Candiota and Pelotas in Brazil)	Coal (PAH, ME)	↓ Telomere length	↑ DNA damage, O global DNA methylation	<i>Matzenbacher et al., 2019</i>

Legends: Δ = variations, ↑ = increasing, ↓ = decreasing, O = no effects