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Review

Methylmercury and Polycyclic Aromatic Hydrocarbons in Mediterranean Seafood: A Molecular Anthropological Perspective

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Abstract: Eating seafood has numerous health benefits; however, it constitutes one of the main sources of exposure to several harmful environmental pollutants, both of anthropogenic and natural origin. Among these, methylmercury and polycyclic aromatic hydrocarbons give rise to concerns related to their possible effects on human biology. In the present review, we summarize the results of epidemiological investigations on the genetic component of individual susceptibility to methylmercury and polycyclic aromatic hydrocarbons exposure in humans, and on the effects that these two pollutants have on human epigenetic profiles (DNA methylation). Then, we provide evidence that Mediterranean coastal communities represent an informative case study to investigate the potential impact of methylmercury and polycyclic aromatic hydrocarbons on the human genome and epigenome, since they are characterized by a traditionally high local seafood consumption, and given the characteristics that render the Mediterranean Sea particularly polluted. Finally, we discuss the challenges of a molecular anthropological approach to this topic.

Keywords: review; DNA methylation; genetic polymorphisms; ecogenetics; anthropology; environmental pollutants; methylmercury; polycyclic aromatic hydrocarbons; seafood

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1. Introduction

Despite being usually considered a healthy food [1], seafood carries several contaminants that can negatively affect human health [2]. It is recognized that the benefits of fish intake exceed the potential risks, but here we address how contaminants levels in seafood are significantly affected by biological and ecological factors [3–8]. Moreover, seafood habitual intake is a crucial factor in determining contaminants exposure [9,10].

In the present study, we first give a glimpse into the latest findings on the genetic diversity underlying differences in human response to mercury (Hg) and polycyclic aromatic hydrocarbons (PAHs) exposure, and on the impact of these pollutants on human DNA methylation patterns. We decided to include only epidemiological investigations assessing environmental chemical exposures using biomarkers (such as hair and blood mercury, and PAHs urine metabolites). We excluded studies addressing occupational exposure because we were interested in the potential effects on human molecular variability of Hg and PAHs from seafood. As detailed before, Hg in aquatic organisms is mostly found in the form of methylmercury (MeHg), while in occupational exposure, elemental Hg vapor is the major contributor of Hg load in the human body [11,12]. Concerning PAHs, occupational

settings are associated with exposure levels much higher than those resulting from diet [13]. Then, we address the ecological evidence that makes Mediterranean coastal communities a potential informative case study to explore this topic.

We decided to focus on MeHg and PAHs because they are two of the most concerning and widespread seafood contaminants, and because of their high levels in Mediterranean seafood.

2. Seafood Contaminants

2.1. MeHg

Hg is a heavy metal found naturally in the Earth's crust. From here, mercury is released into the atmosphere via natural phenomena such as volcanic activity and forest fires, and human activities, such as the burning of coal, oil and wood, and mining. In particular, artisanal and small-scale gold mining in developing countries has recently replaced coal combustion as the largest anthropogenic mercury emission source globally [14]. Once released into the environment, it starts to circulate following what is known as the global mercury cycle, which can last up to 3000 years [15]. When mercury passes into water, it is readily transformed by bacteria in its organic form, methylmercury, which can interact with biological components and eventually biomagnify along aquatic food chains [16]. Many studies have suggested that climate change will increase mercury inputs and methylmercury production and bioaccumulation in aquatic ecosystems [14]. Seafood is recognized as the main source of mercury in the general population, and MeHg accounts for the majority (70–100%) of Hg found in muscle tissue of fishes, molluscs and crustaceans [17].

MeHg is a well-established neurotoxicant, and exposure to MeHg has been associated with nervous system damage in adults and impaired neurological development in infants and children [18]. Decrements in memory, attention, language, and visual–motor skills in childhood have been associated with MeHg biomarkers at birth in populations with moderate MeHg exposure from regular seafood consumption [19]. Even low mercury levels (i.e., levels lower than 4 μg/g in hair; 20 μg/L in cord blood, or approximately 12 μg/L in adult blood) can negatively affect fetal and infant growth and cause neurologic outcomes [20]. Urinary levels of Hg are frequently used to estimate the level of exposure to Hg vapours or inorganic Hg (IHg), whereas blood, hair and toenail [11] Hg predicts MeHg exposure.

Because of the threat that mercury poses to human health, the EU set a maximum level of mercury in seafood of 1 or 0.5 mg/kg, depending on the species, after which seafood shall not be placed on the market [21], while the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established a tolerable intake of 1.6 μg/kg bodyweight per week for methylmercury in order to protect the developing fetus from neurotoxic effects [22]. On the basis of multiple epidemiological studies [23,24] that observed adverse effects in children as consequences of maternal exposures, the European Food Safety Authority (EFSA) eventually decreased this limit to 1.3 μg/kg bodyweight per week [25], corresponding to a Hg level of ~11.5 mg/kg and ~46 μg/L in hair and blood, respectively. This threshold value has been adopted for all classes of consumers, even though adults may be less sensitive to the adverse effects of MeHg [26]. Furthermore, the US-EPA established an oral reference dose (RfD) for MeHg—that is, the maximum acceptable oral dose for this contaminant—of 1×10^{-4} mg/kg day^{-1} (US-EPA, 2010).

2.2. PAHs

PAHs are a class of organic compounds consisting of two or more fused benzene rings, deriving from the incomplete combustion or pyrolysis of organic materials. Natural sources of PAHs include volcanoes, forest fires and petroleum seeps, while the combustion of fossil fuels, oil and wood are among the main anthropogenic sources [27,28]. Due to their physicochemical properties, PAHs are persistent pollutants, in that they can stay in the environment for long periods [29]. They represent the largest share among the main organic contaminants present in the marine environment, due to marine traffic and possible accidents involving oil tankers [30]. Although most PAHs are metabolized a

short time after uptake, thanks to their lipophilic nature, a fraction accumulates in lipid-containing tissues such as liver, eggs and muscle [8]. The most important non-occupational source of human exposure to PAHs is the consumption of contaminated food, including seafood [31], especially mollusks and crustaceans [32]. Sixteen PAHs are categorized as priority environmental pollutants, and some of them are deemed to be probable human carcinogens by the US Environmental Protection Agency (US-EPA), with benzo(a)pyrene (B(a)P) arousing more concern because of being the most carcinogenic, teratogenic and toxic compound [33]. The most used biomarkers of PAH exposure are metabolites of PAHs, particularly 1-hydroxypyrene (1-OHP), and PAH–DNA or protein adducts. 1-OHP is the principal product of pyrene metabolism [34], and its urinary excretion has been attributed mainly to the ingestion of PAHs through the diet [35]. Rather, PAH–DNA adducts, which are the products of the Phase I metabolism of PAHs, are deemed a biomarker that integrates multiple BB(a)P exposure routes (including inhalation, dermal absorption, and ingestion) and reflects a biologically effective dose [36]. PAH–DNA adduct formation is significantly influenced by individual susceptibility, which is linked to specific genetic polymorphisms [36,37]. Urine PAHs metabolites and, to a less extent, PAH–DNA adducts are also related to parent air PAH exposures, both at elevated exposures in occupational cohorts, and at low levels of air pollution [34,38].

The EU set a maximum level of B(a)P in seafood to be sold ranging from 2 μg/kg wet weight, for muscle meat of fish (other than smoked fish), to 10 μg/kg for bivalve mollusks [21]. Concerning human exposure, the US-EPA set an RfD for several PAH compounds, including anthracene (0.3 mg/kg day^{-1}), acenaphthene (0.06 mg/kg day^{-1}), fluorene (0.04 mg/kg day^{-1}), fluoranthene (0.04 mg/kg day^{-1}), pyrene (0.03 mg/kg day^{-1}), naphthalene (0.02 mg/kg day^{-1}) and B(a)P (0.0003 mg/kg day^{-1}).

Several findings point to an important role of genetic diversity in shaping individual susceptibility to Hg [39] and PAHs [40] exposure, and consequently some authors claim the urgent need to include this factor in risk assessment and decision making [41]. Moreover, Hg and PAHs, similar to several other environmental toxicants [42], can impact the human epigenome through different mechanisms, and some of the epigenetic alterations driven by these two substances were shown to be associated with adverse health effects [43,44].

Being a semi-enclosed sea, delimited by highly industrialized countries and characterized by large deposits of cinnabar (HgS), the Mediterranean Sea is at a high-risk for contamination by toxic compounds [45], and evidence exists that significant anthropogenic chemical inputs into the Mediterranean began in prehistoric times [46]. In line with this, several studies have shown higher levels of contaminants in marine organisms from the Mediterranean Sea compared to those from other geographic areas [47]. At the same time, the European countries bordering the Mediterranean are among the world's highest seafood consumers, with Spain, Italy and France accounting for more than half of the European expenditure on fish and fishery products, despite having only around a third of the EU's population (EUROSTAT, 2014). Accordingly, high Hg concentrations in the blood and hair of several Mediterranean communities [6] have been found. Given such a traditionally high consumption of contaminated seafood, in our view, it is important to gain insights into the molecular diversity underpinning potential differences in susceptibility to MeHg and PAHs exposure in these communities. Moreover, Mediterranean populations might represent an interesting case study to investigate the potential impact of Hg and PAHs on the human genome and epigenome.

Modern technologies allow us to explore human genomic and epigenomic variability in a cost- and time-efficient way, enabling us, for example, to portray molecular diversity at the populational level [48], and to detect natural selection footprints in genomic regions [49].

3. Human Genetic Diversity

Epidemiological investigations are showing the role of genetics in shaping individual susceptibility to MeHg and PAHs. Through a literature search, we identified 18 (Tables 1 and S1 for further details) and 3 (Tables 2 and S2 for further details) epidemiologi-

cal studies addressing the role of genetic polymorphisms in MeHg and PAHs toxicokinetics, respectively. Below, we describe some of the main findings of the above studies. Please refer to the tables for the full list of retrieved publications.

Table 1. List of epidemiological studies investigating the influence of genetic polymorphisms on MeHg toxicokinetic. Genes in which the above polymorphisms were identified, biomarkers affected, and samples studied are shown for each study.

Study	Genes	Biomarker	Sample
[50]	GCLC; GSTP1	Erythrocyte Hg	Swedish cases of acute myocardial infarction/stroke and controls
[51]	GSTM1; GSTT1	Hair Hg	Students in Austria
[52]	GCLM; GSTP1	Erythrocyte Hg	Fish-eating Swedish individuals
[53]	GSTP1; MT4; GSTM1; GCLC; GSTT1	Blood and hair Hg	Students in Austria
[54]	GSTM1; GSTT1	Maternal and cord blood Hg	Korean mothers and their infants
[55]	GSTT1; GSS; GSTP1; SEPP1	Hair and urinary Hg	Michigan dental professionals
[56]	MT1M; MT2A; MT1A	Hair and urinary Hg	Michigan dental professionals
[57]	APOE	Cord blood Hg	Children in Taiwan
[58]	GCLM; GSTM1	Blood and hair Hg	Amazonian population in Brazil cronically exposed to MeHg from fish
[59]	TF	Umbilical cord Hg	Children from Bristol
[60]	GCLC; GCLM; GSTM1	Plasmatic Hg and MeHg; whole blood Hg	Fish-eating communities of Brazilian Amazon
[61]	ABCB1; ABCC1; ABCC2	Cord blood Hg	Pregnant women from Greece, Italy and Spain
[62]	APOE	Cord blood Hg	Children in Taiwan
[63]	ABCB1; ABCC1; ABCC2	Hair Hg	Seychellois mother–child pairs with a diet rich in fish of mixed African, European and East Asian origin
[64]	GLRX2; GSTA4; GSTM3; GSTO1; SELS; MT1M; (see Table S1 for the whole list)	Blood and urinary Hg	American dental professionals
[65]	CBS; TXNRD2; SEPHS2; CYP1A2; CBS; MTRR; (see Table S1 for the whole list)	Blood Hg	Inuit from Canada
[66]	GCLC; GCLM; GSTP1	Maternal blood and hair Hg and cord blood Hg	Seychellois mother–child pairs with a diet rich in fish of mixed African, European and East Asian origin
[67]	BDNF; GSTP1	Hair Hg	Children in Valentia

3.1. MeHg Exposure and Human Genetic Diversity

The majority of ingested MeHg passes into the bloodstream, by which route it reaches all tissues. Here, MeHg enters cells thanks to its ability to form water-soluble complexes with the amino acid cysteine. After forming a complex with reduced glutathione (GSH) (Figure 1), MeHg is excreted by the liver cells into the bile. At this point, the glutathione is hydrolyzed, leading to the release of the methylmercury–cysteine complex. The latter is mostly secreted into the intestine tract, where MeHg is demethylated by intestine microflora. The resulting inorganic Hg is then eliminated via the feces [70].

Table 2. List of epidemiological studies investigating the influence of genetic polymorphisms on PAHs toxicokinetics. Genes in which the above polymorphisms were identified, biomarkers affected, and samples studied are shown for each study.

Study	Genes	Biomarker	Sample
[68]	XRCC1	Sperm PAH–DNA adducts	Infertile adult men from Nanjing, China
[69]	MPO; NAT2; ERCC5	Blood PAH–DNA adducts	Non-smoking healthy women from eastern Golestan Province, Iran
[36]	CYP1A1; GSTT2; CYP1B	Cord blood B(a)P–DNA adducts	Mother–infant pairs from Krakow, Poland

B(a)P, Benzo(a)pyrene.

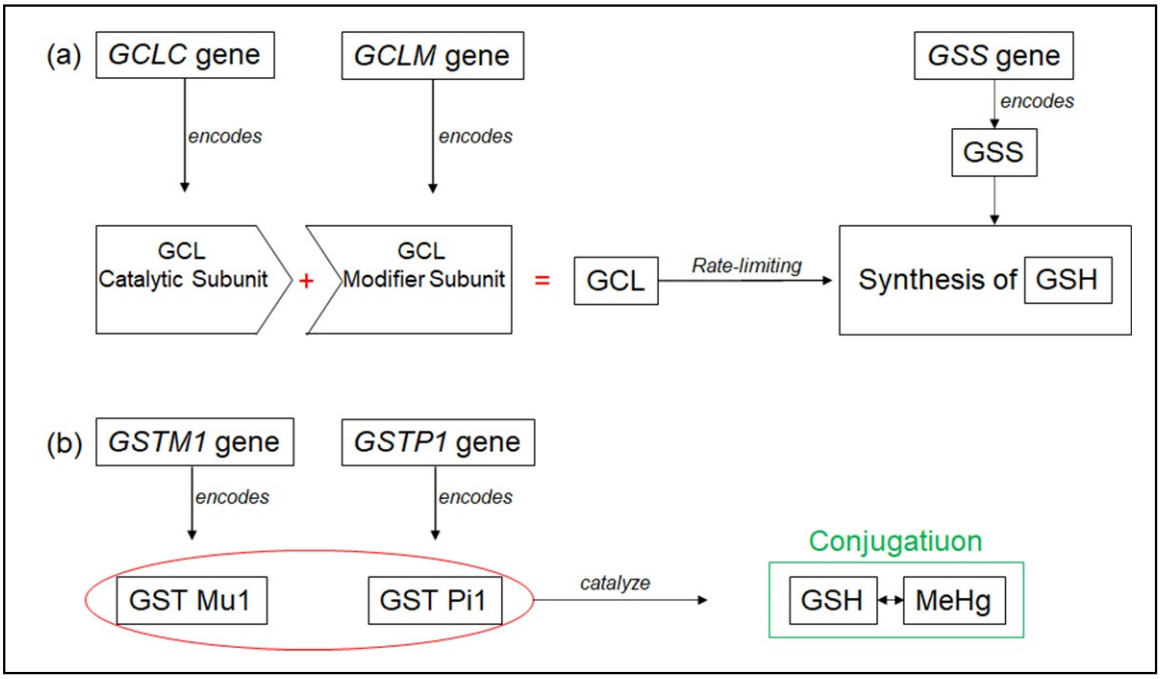

Figure 1. Schematic representation of the role played by several genes in MeHg elimination from the body. (**a**) The GCLC and GCLM genes encode the catalytic and modifier subunits of the glutamate–cysteine ligase (GCL) enzyme, respectively. The GCL is the first rate-limiting enzyme of glutathione (GSH) synthesis. The GSS gene encodes the glutathione synthetase (GSS), another enzyme involved in GSH synthesis. (**b**) The GSTM1 and GSTP1 genes encode the glutathione S-transferases (GST) Mu1 and Pi1, respectively, which catalyze the conjugation of GSH to MeHg.

In recent years, epidemiological studies on populations exposed to MeHg have been showing that several genes mediating the toxicokinetics of Hg are polymorphic in humans, and may influence inter-individual variability in Hg exposure biomarker values and health outcomes (Tables 1 and S1 for further details). In line with this, as demonstrated by kinetic studies, MeHg half-life, which is a direct determinant of the Hg body burden [71], can vary widely in humans, which may be due also to a naturally occurring biological basis for the variation in MeHg toxicokinetics.

Goodrich and colleagues [55] analyzed Single-Nucleotide Polymorphisms (SNPs; genetic variants due to a base substitution or the insertion or deletion of a single base) variability in a cohort of dental professionals exposed to inorganic Hg via dental amalgams and to MeHg via seafood consumption, in order to investigate potential associations with Hg levels in hair and urine. In this study, fish consumption as estimated by a self-administered survey was the best predictor of measured hair Hg level, and two SNPs were associated with this biomarker. In particular, SEPP1 3′UTR (rs7579) T allele was associated with lower hair Hg per unit of intake from fish consumption, while the GSS 5′ (rs3761144) minor allele (i.e., the less common allele of a SNP) (G) was associated with increasing

hair Hg concentration per unit of fish Hg. SEPP1 encodes a selenoprotein, which combats the oxidative stress created by Hg by binding the toxicant directly via a selenocysteine residue. The latter is an amino acid unique to selenoproteins that can bind Hg–selenium conjugates or MeHg. Interestingly, as demonstrated by previous studies, the 3′UTR T allele is linked to greater SEPP1 expression and Hg-binding capacity. The GSS gene encodes for an enzyme, glutathione synthetase (Figure 1a), that is involved in the synthesis of GSH, to which Hg is conjugated before being eliminated (Figure 1b). The association of the minor allele with increasing hair Hg concentration may be ascribable to a decreased expression of GSS and, thus, to decreased GSH synthesis, which in turn could impact the body's ability to eliminate MeHg as a GSH conjugate, with the higher body burden reflected in hair Hg levels.

The study of de Oliveira and colleagues [60] was the first to investigate the genetic predisposition to mercury accumulation in the plasma, where this pollutant is more bioavailable and therefore potentially harmful to human health. In this study, authors focused on riverside communities of the Brazilian Amazon, for which the only source of Hg exposure was the intake of contaminated fish. They genotyped two glutathione-related genes, GSTM1 and GCLC. The first encodes a glutathione S-transferase, an enzyme that catalyzes the conjugation of GSH to MeHg (Figure 1b), while the second encodes the catalytic subunit of the glutamate-cysteine ligase (GCL), the first rate-limiting enzyme of glutathione synthesis (Figure 1a). What the study found is that null homozygotes for GSTM1, that is, individuals that possess two copies of a non-functional allele for this gene, showed higher plasmatic MeHg levels (MeHgP) compared to subjects with functional GSTM1, which may be related to their lower MeHg-conjugating activity, lower MeHg excretion, and a higher MeHg retention. Moreover, individuals carrying at least one T allele for GCLC (rs17883901) also had significantly higher MeHgP.

As recent findings suggest, apart from being associated with hair mercury level, the SNPs in glutathione-related genes can influence the impact of methylmercury exposure on early child neurodevelopment. Wahlberg and colleagues [66] analyzed GSH-related gene variability in mothers with a diet rich in fish coming from the population of Seychellois. Genotypes of these mothers were analyzed in association with maternal hair and blood Hg, cord blood Hg, and children's mental and motor development, as expressed by the Mental Developmental Index (MDI) and the Psychomotor Developmental Index (PDI), respectively. The authors genotyped SNPs within three genes: GCLC, whose function have been described above; GCLM, encoding the modifier subunit of the GCL (Figure 1a), and GSTP1, which encodes a glutathione S-transferase (Figure 1b). What they found is that individuals with GCLC rs761142 TT genotype showed higher mean maternal hair Hg than AG and GG. Moreover, individuals carrying the combination of GCLC rs761142-TT and GCLM rs41303970-CC genotypes showed higher hair Hg than G plus T carriers. Finally, increasing Hg in maternal and cord blood was associated with lower PDI among GCLC rs761142 TT carriers, while increasing Hg in hair was associated with lower MDI among GSTP1 rs1695 GG carriers.

Another recent study carried out on children from Valentia [67] showed that hair Hg levels were associated with worse neurobehavioral development, and that several SNPs located in the GSTP1 (rs1695) and BDNF (rs1519480, rs7934165, rs7103411) genes modified the association between Hg levels in children's hair samples and two indexes of neurobehavioral function. The brain-derived neurotrophic factor (BDNF), in particular, is a protein that promotes neural survival in adult brains, and is poorly expressed in several diseases, such as Alzheimer's and Parkinson's.

Two recent reviews [39,72] focusing on this topic collectively listed thirty-two genes whose variation is related to Hg body burden and susceptibility to Hg toxicity, and, in particular, twelve of these genes are related to hair Hg level and/or to MeHg exposure outcomes.

3.2. PAHs Exposure and Human Genetic Diversity

PAHs metabolism is a complex process consisting of two major phases (Figure 2): In the first phase, following ingestion or inhalation, the xenobiotic compound is epoxidated by enzymes belonging to the cytochromes P450 family, with the formation of diols and dihydrodiols [31]. Dihydrodiols can thus bind to the DNA, to give rise to DNA adducts, starting the mutagenic processes and eventually leading to cancer [73]. Then, in the second phase, the intermediate diols conjugate with glutathione, thanks to glutathione s-transferase enzymes. This leads to the formation of polar compounds, which can be easily excreted by renal or biliary routes [74]. The liver is the major site of the metabolism of PAHs. However, in the case of ingestion, gut micro flora and intestinal cytochrome P450 enzymes can also contribute to the process [31].

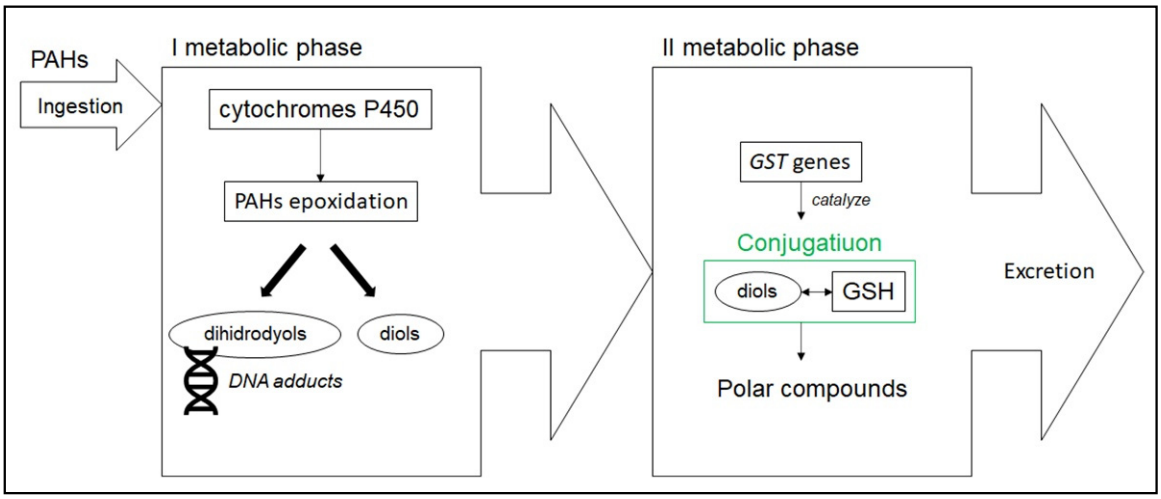

Figure 2. Schematic representation of the metabolic phases following PAHs ingestion. In the first phase, following ingestion or inhalation, PAHs are epoxidated by enzymes belonging to the cytochromes P450 family, with the formation of diols and dihydrodiols. Dihydrodiols can thus bind to the DNA, to give rise to DNA adducts. Then, in the second phase, the intermediate diols conjugate with glutathione, thanks to glutathione s-transferase enzymes. This leads to the formation of polar compounds, which can be easily excreted.

Epidemiological studies showed that polymorphisms at several genes influence levels of biomarkers of exposure to PAHs in several human populations (Tables 2 and S2 for further details).

As suggested by much evidence, PAH–DNA adducts may be a potential source of heritable prezygotic DNA damage in spermatozoa. Ji and colleagues [68] detected PAH–DNA adducts in ejaculated sperm of infertile adults environmentally exposed to low levels of PAHs, showing that the consumption of PAH-rich meals at least three times a week contributed significantly to an increase in DNA adduct formation. Moreover, the authors demonstrated an association between specific XRCC1 polymorphisms and an increase in sperm adduct levels. XRCC1 encodes a protein that is essential to providing an efficient repair of the DNA, and thus polymorphisms at this gene may be useful to identify individuals susceptible to DNA damage resulting from PAHs exposure.

Myeloperoxidase (MPO), an enzyme central to the microbicidal activity of neutrophils, and *N*-acetyltransferase 2 (NAT2), which functions to both activate and deactivate drugs and carcinogens, are involved in Phase I and Phase II of PAH metabolism, respectively, while ERCC5 is a single-strand-specific DNA endonuclease that participates in DNA excision repair. The SNPs in these genes have been shown to affect the PAH-driven formation of the DNA adduct. In a study [69] of more than one hundred healthy female non-smokers from Golestan Province, a region in north-eastern Iran, characterized by very high levels of exposure to PAH probably due to diet and methods of food preparation, the DNA adduct level in blood was significantly lower in homozygotes for NAT2 slow alleles,

which are responsible for a less efficient detoxification of carcinogen-reactive metabolites, and the ERCC5 (rs1047768) non-risk-allele genotype. In contrast, DNA adduct level was higher in the MPO (rs2333227) homozygote risk-allele genotype.

In a cohort of non-smoking Polish mothers and newborns, Iyer and colleagues [36] observed a significant interaction between maternal exposure to airborne PAHs, measured by personal air monitoring, and SNPs in selected B(a)P metabolism genes on cord blood B(a)P–DNA adducts. These genes included: maternal CYP1A1 and GSTT2, and newborn CYP1A1 and CYP1B1. CYP1A1 and CYP1B1 are involved in metabolizing the parent B(a)P compound to the reactive B(a)P 7,8-diol-9,10-epoxide (BPDE) metabolite, which is involved in the formation of B(a)P–DNA adducts. In contrast, GSTT2 is involved in shifting B(a)P metabolism so as to prevent the formation of the reactive BPDE. In particular, the authors concluded that the T allele at the GSTT2 SNP position in mothers is protective with regard to cord B(a)P–DNA adduct formation, while the maternal and newborn G allele at the CYP1A1 SNP position, and the newborn G allele at the CYP1B1 SNP position, are not.

4. The Epigenetic Impact of Seafood Contaminants

Several studies have demonstrated the role of the environment in shaping human molecular variability at the epigenetic level in different populations [48,75–77]. Epigenetic changes are defined as any stable changes in the chromatin structure that are heritable from cell to cell, and can result in alteration of gene expression without altering DNA sequences [75]. The epigenome functions as an interface between the inherited genome and the dynamism imposed by the environment [78], and, as such, can be affected by the latter.

DNA methylation is among the most frequently studied epigenetic modifications. It consists in the covalent addition of a methyl group from a methyl group donor, the coenzyme S-adenosylmethionine (SAM), to the fifth carbon atom of a cytosine ring, and it is catalyzed by the DNA methyltransferase (DNMT) enzyme family. In mammals and insects, cytosine methylation is found almost exclusively in the context of CpG dinucleotides [75].

Changes in DNA methylation status influence genes' accessibility, thus altering gene expression, and aberrant DNA methylation has been discovered in a wide range of pathophysiological conditions [79].

Environmental chemicals, such as Hg and PAHs, can interfere with the one-carbon and citric acid metabolism pathways, resulting in anomalous DNA methylation status all over the genome [42]. Hg and PAHs can alter DNA methylation profiles in specific genes [80].

Three reviews address this topic [42,80,81]. Briefly, Ruiz-Hernandez and colleagues retrieve and discuss two and three epidemiologic studies investigating the association between DNA methylation and Hg [82,83] and PAHs [84–86], respectively, in adults. Considering all the strengths and weaknesses of the various studies, e.g., the lack of adjustments for potential confounding, such as sex, age, smoking status and tissue cell heterogeneity, the authors' conclusion is that the evidence they accrued supports the importance of environmental exposures in modulating the epigenome, but is insufficient to support causality because of the heterogeneity among epidemiologic studies in addressing the residual confounding of the associations, differences in DNA methylation assessment methods, and random error. The review of Culbreth and Aschner concludes that, despite some inconsistencies across different studies, dependent on the tissue or species examined, MeHg undoubtedly induces epigenetic modifications, and these modifications can potentially mediate its toxicity. In particular, regarding DNA methylation changes, controlled exposure studies on human and animal in vitro and animal in vivo models reveal that MeHg can lead to hypomethylation of the DNA in brain-derived tissue, but not in the liver, while selected individual genes show exposure-driven DNA hypermethylation.

Through a literature search, we identified seven (Tables 3 and S3 for further details) and eight (Tables 4 and S4 for further details) epidemiological studies assessing the impact

of MeHg and PAHs on DNA methylation. Below, we describe some of the main findings of the above studies. Please refer to the tables for the full list of retrieved publications.

Table 3. List of epidemiological studies investigating the impact of MeHg exposure on DNA methylation. Genes in which the differentially methylated CpG dinucleotides were identified, biomarkers measured, tissues from which DNA was extracted, and samples studied are shown for each study.

Study	Genes	Biomarker	Tissue (DNA)	Sample
[82]	GSTM1	Whole blood Hg	Whole blood	Women from San Francisco
[83]	SEPP1	Hair Hg	Buccal mucosa	Michigan dental professionals
[87]	TCEANC2; ANGTP2; PRPF18; FOXD2	Cord whole blood Hg and MeHg	Cord blood	Newborns from Baltimore, USA
[88]	PARM1; PFKFB3; LGMN; CCDC68; LRBA; FBXO31; (see Table S2 for the whole list)	Maternal toenail Hg	Cord blood	Mother–infant pairs from USA
[89]	EMID2	Infant toenail Hg	Placenta	Rhode Island infants
[90]	PON1	Maternal red blood cell Hg	Cord blood and children buffy coat	Mother–children pairs from Massachusetts, USA
[91]	GRIN2B; NR3C1	Maternal hair Hg	Children saliva	Children from Europe and US populations

Table 4. List of epidemiological studies investigating the impact of PAHs exposure on DNA methylation. Genes in which the differentially methylated CpG dinucleotides were identified, biomarkers measured, tissues from which DNA was extracted, and samples studied are shown for each study.

Study	Genes	Biomarker	Tissue (DNA)	Sample
[92]	ACSL3	PAM	Umbilical cord white blood cell	Nonsmoking Dominican and African American mother-infants pairs
[93]	Global DNA methylation	Pyr and B(a)P in PAM	Umbilical cord blood leukocytes	Nonsmoking women from NYC
[94]	IRS2	Nap, Ace, Fl, Phe and Ant in VAT	VAT	Nonsmoking women from Korea with myoma
[95]	LINE1	B(a)P-DNA adducts	Buffy coat	Nonsmoking pregnant women from Tongliang County, China
[96]	239 quality-controlled autosome CpGs	Urinary ΣOH-PAHs, 9-OH-Phe and 1-OH-Pyr	Whole blood	Nonsmoking healthy Chinese individuals
[97]	PAX3	ΣH_PAHs in maternal serum	Fetal neural tissue	Mother–fetus pairs
[44]	ZIC4	ΣH_PAHs in fetal liver tissue	Fetal neural tissue	NTD fetuses
[98]	PLEC1	Urinary ΣOH-PAHs		Nonsmoking healthy Chinese individuals

1-OH-Pyr, 1-hydroxypyrene urinary metabolite; 2-OH-Nap, 9-hydroxynaphthalene urinary metabolite; 9-OH-Phe, 9-hydroxyphenanthrene urinary metabolite; Ace, acenaphthene; Ant, anthracene; B(a)P, benzo(a)pyrene; Fl, fluorine; Nap, naphthalene; NTD, neural tube defects; PAM, personal air monitor; Phe, phenanthrene; PMA, phenylmercuric acetate; Pyr, pyrene; VAT, visceral adipose tissue; ΣH_PAHs, sum of high-molecular weight PAHs including pyrene, benz[a]anthracene, chrysene, benzo[b]fluoranthene; ΣOH-PAHs, total urinary monohydroxy-PAH metabolites.

4.1. The Impact of the Exposure to MeHg on DNA Methylation

Epidemiological investigations on different populations have demonstrated the ability of Hg to impact the DNA methylation pattern in several genes (Tables 3 and S3 for further details).

A study [82] showed increased DNA methylation of the GSTM5 promoter in women with higher Hg levels in whole blood. This gene is a member of th eGSTM gene family, which encodes for enzymes that are involved in the metabolism of several environmental agents.

Hg can also influence the DNA methylation status of genes that are involved in the protection against chemical toxicity. As previously mentioned, the SEPP1 gene encodes a protein known to bind Hg that has antioxidant properties. Its promoter shows a trend of DNA hypomethylation with increasing hair Hg levels, which was predicted by estimated Hg from fish consumption [83].

Some of the neurologic outcomes of the exposure to Hg were associated with DNA methylation changes [43]. The suppressive effect that MeHg exposure has on the expression of the BDNF gene, which is poorly expressed in depressed patients, seem to be mediated also by the hypermethylation of the DNA [99]. As demonstrated by Maccani and colleagues [89], after crossing the placenta, MeHg can disrupt placental DNA methylation patterns, leading to the DNA hypomethylation of the EMID2 gene, and likely to adverse neurobehavioral outcome in infants. Cardenas and collaborators [90] found that, in male children, maternal prenatal blood mercury levels were associated with DNA hypomethylation of the Paraoxonase 1 gene (PON1), a gene involved in drug and fatty acids metabolism, and the DNA methylation pattern of this gene predicted lower cognitive test scores during early childhood. It is important to note that cord blood Hg level has previously been demonstrated to be a more accurate measure of prenatal MeHg exposure than maternal hair Hg level, and so DNA methylation changes associated with this biomarker potentially reflect MeHg effects more accurately [81]. In another very recent study [91], carried out on 406 mother–child pairs from a population who consume large amounts of fish and who are characterized by hair Hg levels that are higher than those in European and US populations, the authors found a positive association between prenatal MeHg exposure and DNA methylation in two nervous system-related genes, GRIN2B and NR3C1, measured in children's saliva. GRIN2B encodes a subunit of receptors that are important for the regulation of neural morphology, learning and memory, while NR3C1 is a receptor that is crucial to the stress responses in the brain. As stated by the authors, the observed DNA methylation changes associated with MeHg prenatal exposure at these two genes are predicted to lead to lower gene expression, and are likely to influence neurodevelopment and mental health.

4.2. The Impact of the Exposure to PAHs on DNA Methylation

Both in vitro and in vivo analyses have revealed the ability of these substances to disrupt human DNA methylation patterns [42] (Tables 4 and S4 for further details).

The developing fetus is particularly susceptible to PAH-induced DNA damage, and studies support the hypothesis that this may be due also to epigenetic dysregulations caused by these chemicals. In a study of non-smoking African-American and Dominican women from New York City [93], the authors found that prenatal exposure to PAHs measured using a personal air monitor was associated with lower global DNA methylation levels measured in umbilical cord blood DNA.

Kim and colleagues [94] analyzed samples of visceral adipose tissue of non-smoking female patients with myoma. They showed that the DNA methylation level of IRS2 gene increased as the concentrations of PAHs in adipose tissue increased. Interestingly, the IRS2 gene mediates the effects of insulin on various cellular processes, and it has been associated with several diseases, such as type 2 diabetes. Furthermore, promoter methylation of the IRS2 gene turned out to mediate the transcriptional silencing of this gene in the same study, and this led the authors to suggest that exposure to PAHs might contribute to the pathogenesis of insulin resistance through the methylation-mediated suppression of IRS2.

PAHs can accelerate human aging through epigenetic modifications. In their study of Chinese and Caucasian populations, Li and collaborators [96] first developed a DNA methylation age predictor based on the methylation status of many CpG sites across the genome, and then defined two aging indicators: Δage, defined as methylation age minus chronological age; and aging rate, defined as the ratio between methylation age and chronological age. Evaluating the association of PAHs exposure biomarkers with the above-defined aging indicators, the authors found that the increase in several urine PAHs metabolites was associated with an increase in both Δage and aging rate.

Possible hints of PAHs-mediated DNA methylation changes that may affect neurodevelopment emerged also from a study of pregnant women living close to a coal-fired power plant in China [95]. In that study, the authors analyzed cord blood samples for PAH–DNA adducts and assessed global DNA methylation by measuring genomic long interspersed nuclear elements (LINE1) methylation. LINE1 is one of the transposable repetitive elements, repetitive DNA sequences scattered across the genome and found in most eukaryotic organisms, which can change their position. Changes in LINE1 methylation can disrupt gene expression, and have been associated with birth defects, such as NTDs. In Lee and collaborators' study, a significant inverse relationship was observed between PAH–DNA adducts and LINE1 DNA methylation. Interestingly, the latter was a positive predictor of IQ (Intelligence Quotient) scores at 5 years of age in women enrolled before the closure of the power plant.

Neural tube defects (NTDs) are common and severe congenital malformations that arise from a failed or disordered closure of the neural tube during embryogenesis. Studies have linked NTDs to abnormal genome-wide DNA methylation. Authors found that PAX3, a gene encoding a transcription factor involved in development, is hypermethylated in NTD cases, and that the mean DNA methylation level of this gene in fetal neural tissue is positively correlated with median concentrations of PAHs in maternal serum [97]. Moreover, mean DNA methylation levels in the promoter region and 5′ UTR of ZIC4 gene tended to be inversely associated with levels of HMW-PAHs in the livers of NTD fetuses in a recent survey [44]. ZIC4 encodes a zinc finger protein whose absence can hamper cerebellum development in both humans and mice.

Concerning potential mechanisms underlying DNA methylation changes driven by Hg and PAHs, several findings support different hypotheses. Evidence exists that MeHg exposure is associated with the reduced expression or biochemical activity of DNMT, but Hg may also affect the methionine cycle, thus influencing the availability of SAM for DNA methylation [41]. Moreover, various studies support the hypothesis that oxidative stress mediates the effects of PAHs exposure on DNA methylation, via both the suppression of DNMT and excessive SAM consumption [44].

Even if not exhaustive, given that they report all the evidence on the subject beyond the scope of this paper, the above-described results demonstrate the ability of these important seafood pollutants to impact the human epigenome and, in particular, the DNA methylation profiles.

5. An Anthropological Perspective

Human populations that traditionally consume seafood are at an increased risk of MeHg exposure and bioaccumulation. This is supported by recent data that demonstrate that populations consuming more fish or marine mammals have greater blood MeHg values than those consuming marine foods less than once a week [17]. Moreover, evidence exists that fish-eating populations tend to show the typical symptoms associated with Hg exposure at a high rate [19]. One of the first studies addressing this topic was carried out on a cohort of 1022 consecutive singleton births from the Faroe Islands [100], where maternal exposure to MeHg is derived from the consumption of pilot whale meat. This study found a statistically significant relationship between higher prenatal Hg exposure and poorer scores on tests of neurologic function [101]. In a cross-sectional study conducted on the adults of six fishing villages of the Pantanal region of Brazil, Hg exposures associated with

fish consumption, as measured by hair mercury levels, were associated with detectable alterations in performance in tests of fine motor speed, dexterity, and concentration, and the magnitude of the effects increased with hair mercury concentration, consistent with a dose-dependent effect [102].

At present, unlike the case of MeHg, there is no direct evidence that populations that consume high amounts of seafood are more exposed to PAHs. Nonetheless, evidence exists that traditional fish smoking methods can introduce potentially harmful combustion by-products into the smoked fillets, leading to concentrations of PAHs that pose a threat to human health [103,104]. Moreover, human exposure to PAHs in seafood may date back to ancient times: with fish, shellfish and sea mammals being rich in fats, and considering the high lipophilicity of PAHs, these foods may have had absorbed substantial amount of PAHs from the bitumen used for prehistoric container production [105]. Finally, as detailed below, several investigations revealed high levels of PAHs in several commercially relevant marine species, with concentrations sometimes exceeding legal limits.

Modern technologies allow us to explore human molecular variation, both at a locus-specific and at a genome-wide level, enabling us to answer several questions about population evolutionary history and the relationship between environment and human biodiversity.

The first evidence of human adaptation to a toxic chemical was reported in arsenic-exposed women from the northern Argentinean Andes [106]. The inhabitants of this region, which is characterized by elevated arsenic concentrations in available drinking water, show a uniquely efficient arsenic metabolism. Accordingly, the authors found that the AS3MT gene, which encodes the arsenite methyltransferase and functions as the major gene for arsenic metabolism in humans, strongly differentiates the Argentinean Andes population from a highly related Peruvian population much less exposed to this environmental toxicant. Then, they confirmed that SNPs mapping in that gene was positively selected.

Similar results were obtained from investigations on another Andean community. Through analyses of ancient human remains from the Camarones Valley, it has been shown that the inhabitants of the area have been exposed to arsenic-contaminated drinking water for the last 7000 years [107]. Interestingly, a decreasing trend has been detected in the average hair and bone arsenic levels, starting from Archaic hunter–gatherers and leading to the current populations, and this evidence has been interpreted as the potential result of an adaptive increasingly efficient metabolic detoxification [108]. In support of the above scenario, analyses carried out through polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), targeting SNPs strongly associated with arsenic metabolization, showed that, contrary to alleles associated with increased toxicity risk, protective variants are much more frequent in exposed populations compared to a southern Chilean community [109].

Potential hints of human adaptation to PAHs exposure come from the comparison between the exome sequence (i.e., the sequence of nucleotides that make up the protein-coding portion of the genome) of the aryl hydrocarbon receptor (AHR) gene in Neanderthal, Denisovan and modern human individuals [110]. Once activated by endogenous or exogenous ligands, such as diet-derived metabolites and PAHs, respectively, the complex made up of AHR and other proteins passes from the cytoplasm to the nucleus. Here, following further biochemical mechanisms, the AHR regulates the CYP1A1/1A2/1B1 genes expression, thus initiating PAHs metabolism, with the resultant production of PAHs' reactive metabolites and DNA adducts. Hubbard and colleagues found that modern humans carry the same allele at a codon of the AHR gene that is unique to our species, and which is associated with a reduced AHR activation by PAHs, specifically 2,3,7,8-tetrachlorodibenzofuran (TCDF), B(a)P and benz(a)anthracene, compared to Neanderthal and other primates receptors. On the other hand, modern humans and Neanderthal AHR showed similar levels of activation by endogenous ligands. Based on the above results, the authors postulate that exposure to potentially toxic environmental AHR ligands, such as PAHs derived from controlled fires in caves, may have driven the selection of genetic variants conferring a reduced sensitivity to AHR exogenous ligands, and thus a lower DNA adduct synthesis [110].

As demonstrated also by the above-mentioned studies, molecular anthropologists are only starting to depict the role that environmental toxicants could have had in human evolution, and this is thanks to modern genomic technologies. Moreover, environmental toxicants can impact human biological variability at multiple levels, as shown by above-mentioned studies on the DNA methylation.

Environmental pressures can shape DNA methylation variability across human groups, and methods have been developed to explore the epigenetic side of human diversity at different levels. In a study analyzing the DNA methylation profiles of three human populations at 450,000 CpG sites, the authors found that DNA methylation differences contribute to the phenotypic variability of these populations, and that 68% of differentially methylated CpG sites were significantly related to underlying genetic variation, while the remaining 32% was probably related to external stimuli able to induce epigenetic changes with an impact on subsequent generations (e.g., toxic xenobiotics, differences in dietary or hormone exposure, or stress response) [111].

Many toxicants are sources of differences within human populations [80]. In Giuliani and colleagues' [112] investigation, for example, the authors compared the DNA methylation of individuals living in areas that were heavily sprayed with Agent Orange during the Vietnam War with that of individuals from non-contaminated areas. What they found is that past exposure to dioxin, the main ingredient of Agent Orange, led to DNA methylation changes among Vietnamese individuals from areas heavily sprayed, and in those whose parents participated in the war in sprayed zones.

6. Mediterranean Coastal Communities as an Informative Case Study

Certain Mediterranean communities may be more exposed to the negative effects of seafood contaminants, for both environmental and cultural reasons.

The Mediterranean Sea is a semi-enclosed basin, surrounded by countries highly industrialized and with high agricultural development, and, as such, is of particular concern with respect to contamination by toxic compounds. The Mediterranean Sea is generally considered a geological hot spot for mercury [26], as it is characterized by large deposits of HgS that account for about 65% of the global mercury reserves [113]. Moreover, it should not be surprising that several studies have shown higher levels of contaminants in marine organisms from the Mediterranean Sea compared to those from other geographic areas [6,47,114–116], with levels of PAHs and especially Hg often exceeding recommended limits for human consumption [6,30,117,118]

Concerning Hg, in particular, the highest concentrations in Europe tend to be found in fish caught in the Mediterranean Sea [16]. Data showed a more marked Hg bioavailability in the Tyrrhenian and the Adriatic coastal waters compared to the rest of the Mediterranean [119], and MeHg levels higher than the legal limit have been discovered in seafood caught in both areas [117,118,120–124], as well as in the Ionian Sea (Sidimar 2018), and in different classes of marine organisms, including fishes, crustaceans, and mollusks. MeHg contamination hotspots are represented by the Trieste gulf [125], the coastal waters between Cattolica and Rimini, in the Central Adriatic Sea [124], and those between Anzio and Civitavecchia, in the Central Tyrrhenian Sea [126]. Turning to PAHs, potential contamination hotspots are generally deemed to be located near Taranto, Trieste [125], Naples [127,128], Genoa and Palermo [127]. It is also worth reporting that some studies revealed possible risks to human health arising from the consumption of PAHs-contaminated seafood from the Mediterranean. The above conclusions were drawn from the calculation of risk indexes, such as the Excess Lifetime Cancer Risk (ELCR) and the Target Hazard Quotient (THQ) [30,73,129] The authors calculated the ELCR according to the following equation:

$$\text{ELCR} = \text{EF (day/y)} \times \text{ED (y)} \times \text{IR (Kg/day)} \times \text{CSF (mg Kg}^{-1}\text{ day)} \div \text{BW(Kg)} \times \text{AT}$$

where EF is the exposure frequency (365 days/year), ED is the exposure duration (y), IR is the ingestion rate, which is equal to PAH concentration times the mean ingestion rate of the species, CSF is the Cancer Slope Factor for each of the analyzed PAHs (OEHHA, 2009), BW is the body weight, and AT is the averaging time, which is equal to EF × ED.

A CR above the acceptable lifetime risk (ALR) of 10^{-5} [130] indicates a probability greater than 1 in 100,000 of developing cancer [30].

THQ indicates the ratio between exposure and the reference dose, and is calculated through the formula:

$$\text{THQ} = \text{EF (day/y)} \times \text{ED (y)} \times \text{IR (Kg/day)} \times \text{C (mg Kg}^{-1}\text{)} \div \text{RfD (mg kg}^{-1}\text{ day)} \times \text{BW(Kg)} \times \text{AT}$$

In Europe, coastal populations consume greater amounts of seafood compared to inland populations [11]. Moreover, Mediterranean coastal populations are characterized by food habits based on local seafood consumption [26], and European countries bordering the Mediterranean are among the world's highest seafood consumers, with Spain, Italy and France accounting for more than half of the European expenditure on fish and fishery products, despite having only around a third of the EU's population (EUROSTAT, 2014). In Italy, apparent consumption of fish and seafood products amounted to 28.4 kg per capita, a share significantly higher than the EU average (EUROFISH, 2015). The traditionally high consumption of local seafood can lead to high MeHg and PAHs exposure levels among Mediterranean communities.

The above scenario is supported by several lines of evidence. Assuming an exposure frequency of 365 days a year, an exposure duration of 80 years (equivalent to the average lifetime in Italy in 2011), an ingestion rate of 18 g per day, and a body weight of 70 kg, after measuring Hg levels in various species of demersal fish commonly consumed in Italy, Storelli and Barone calculated a high target hazard quotient (THQ) and estimated weekly intake (EWI) for larger fish specimens caught in the Adriatic Sea [123]. In a study taking into account various commercially relevant marine species from the Ionian Sea, assuming a consumption rate greater than once per week, the authors found a possible risk for chronic systemic effects derived from Hg content [131]. Similar findings were derived from several other studies on seafood from various parts of the Mediterranean Sea, focusing on levels of Hg [124,132] and PAHs [129].

Given all the above, and considering the high average seafood consumption in the Mediterranean regions, we highlight the need for policymakers to take into account evidence of potentially high exposure to seafood contaminants among Mediterranean communities, especially as regards MeHg, and to consider if it is reasonable to revise law limits and/or recommendations.

In line with the above-mentioned evidence, studies on newborns and preschool children from Mediterranean populations have shown high Hg concentrations in blood and hair [6]. Analyzing data collected from over 200 cross-sectional studies measuring Hg biomarkers in human populations, Basu and collaborators [12] found geographic differences in Hg exposure, with pooled central median blood mercury concentrations being higher in general background populations (i.e., those with no particular or significant exposure to mercury) living in certain geographic areas, including the Eastern Mediterranean. They also found that subpopulations that consume high amounts of seafood are approximately four times more exposed than the general background population. In particular, exposures were higher in Indigenous people in many regions of the world, in populations living in proximity to water bodies or associated with marine ecosystems, among which were populations living along the Mediterranean Sea.

Višnjevec and colleagues [11] compared the results of several investigations on Hg exposure in Europe countries, and found that the highest hair Hg levels were found in Madeira fishermen, habitual tuna consumers in Sardinia, and Greenlandic children and mothers.

A study on the adult population of Naples, Italy, found a strong correlation between total mercury concentrations (THg) in hair and fish consumption, while almost no association was found between THg and number, surface and area of dental amalgam fillings, another possible source of MeHg in the general population, thus confirming previous findings of the major role of seafood consumption in human exposure to this pollutant [133]. Moreover, the same study found THg levels higher than the reference dose adopted by the U.S. Environmental Protection Agency (0.1 μg per kg body weight) in 5.9% of the samples.

Finally, it is interesting to note that two of the three Mediterranean countries taken into consideration in the EU-funded human biomonitoring study named DEMOCOPHES [134], i.e., Spain and Cyprus, with the fourth being Slovenia, are respectively the first and the third countries as regards mercury levels in the hair of mothers compared to all the others, with Spain being also the second European country for per capita seafood consumption in 2016 [135], as well as the Mediterranean country with the second highest share of domestic wild capture consumption compared to imported seafood (FAOSTAT, 2018), after Croatia, which was not included in the DEMOCOPHES study.

Some subgroups of the Mediterranean coastal population may be more exposed than others to the harmful action of seafood pollutants. As shown by the above-described review from Basu and colleagues [12], coastal communities are more exposed to MeHg. A study [136] of mother–infant pairs from Croatia found higher levels of Hg and selenium (Se) in hair, blood, placenta and cord blood of mothers from the coast compared to those living in continental areas, due to higher fish consumption. Interestingly, in this study, the authors also evaluated the relationship between Hg and Se levels and a polymorphism (rs28366003) in the MT2A-5 gene, which encodes a protein that plays a role in the detoxification of heavy metals, but they did not find any association.

Fishermen, in particular, have shown a tendency for a greater accumulation of Hg derived from fish, and this is related to their higher mean consumption of this food compared to the general population. Evidence in this sense comes from a fishing community on the Mediterranean coast of Morocco. In this community, researchers measured hair Hg levels, and found that these were closely related to fish intake, and that fishermen and their families were the most exposed population subgroup [137]. Additionally, in Sicily, greater Hg accumulation has been proven in fishermen, as they showed significantly higher mean hair Hg levels (6.45 ± 7.03 μg g^{-1} vs. 0.23 ± 0.4 μg g^{-1} in the control group) [138]. Similar results have been derived from investigations carried out on Italian coastal communities from the northern Adriatic Sea [139].

What may emerge from all the above is that Mediterranean fishing communities could represent an informative case study to gain insight into the potential impact of Hg and PAHs on the human genome and epigenome.

Additionally, to fulfil the need for an "ecogenetic approach" to the study of the health effects of environmental chemicals stressed by Basu and colleagues [41], what we suggest is to extend the research on Mediterranean seafood contamination by Hg and PAHs by including information about the genomic and epigenomic backgrounds of the exposed communities. Such an approach would involve the following main steps: identification of communities that are particularly exposed to seafood contaminants, in terms of both cultural (i.e., traditional high consumption of local seafood) and environmental factors (i.e., subsisting on resources caught from pollution hotspots), and the selection of communities that would represent the control group, for example inland communities, characterized by a very low fish intake; simultaneous collection of biological samples (e.g., buccal mucosa cells) and information on the family history, diet and lifestyle of participants (e.g., through a Food Frequency Questionnaire); analysis of the genetic variability and DNA methylation profiles of those genes implicated, for example, in fatty acids metabolism and in susceptibility to environmental chemicals. Such an approach would enable us to answer different questions, such as, are there any biological differences between fishing and non-fishing communities that could have been caused by different seafood intakes? Are there any differences in the biological predisposition of Mediterranean communities to the health effects of seafood intake?

7. Challenges

The main challenges in such a study refer to the epigenetic investigation, and this is for several reasons. First of all, DNA methylation may be influenced by several factors [80], including many dietary components (e.g., folate, vitamin B6, vitamin B12, betaine, methionine and choline) [75], other environmental chemicals [42], pathogens load, various

environmental and climatic conditions [140], sex and age [42], socioeconomic status [141], and genetic background [48,78]. Consequently, it is difficult to tell which is the actual correlative factor underlying the observed patterns, even when an association between a given factor or biomarker has been detected.

The simultaneous analysis of genetic and epigenetic data, coupled with information on eating habits and lifestyle and personal details of participants, would allow us to account for several potential confounders, possibly distorting the association between estimated exposure and epigenetic changes. To this end, it is important to gather information that is crucial to depict the whole set of environmental stimuli affecting the individual's methylome (e.g., smoking status, diet, occupation), as well as to identify, sample and to compare populations that differ markedly when it comes to seafood consumption rate and/or levels of Hg and PAHs in fish consumed.

However, it is worth noting that the potential simultaneous exposure of individuals to a plethora of chemicals constitutes one of the main challenges in the field.

Seafood, along with other food items, contains several nutrients and contaminants, which can impact human biology at a molecular level, and this may confound the association between MeHg and/or PAHs exposure and DNA methylation.

Among seafood contaminants, the heavy metals arsenic (As), cadmium (Cd) and lead (Pb) also constitute an emerging issue due to their concentrations often exceeding regulatory limits [123,142,143] and studies have demonstrated their ability to elicit DNA methylation changes [80]. This is quite expected, as comparisons of the mechanisms of action reported similar biological pathways of these metals inducing toxicity, such as ROS generation, weakening of the antioxidant defense, enzyme inactivation, and oxidative stress (for a detailed review see [144]).

Moreover, epidemiological studies showed a general hypomethylation of LINE-1 elements after PAHs, As, Cd and Pb exposure [145–149].

In vitro and animal studies performed under rigorous experimental conditions constitute a powerful method to identify the impact of single chemicals on DNA methylation. In this respect, molecular anthropological investigations could help to make a list of candidate genes to be tested through functional studies, or vice versa, could constitute a method to evaluate the real effect.

Another crucial aspect to consider is the tissue-specificity of DNA methylation [42]. Most of the retrieved epidemiological studies on MeHg and PAHs epigenetic effects measured DNA methylation in blood, with only one study using buccal mucosa [83], another study sampling saliva [91], one study measuring adipose tissue DNA methylation [94], and two studies using neural tissue [44,97]. Molecular anthropologists, on the other hand, often collect saliva or buccal mucosa cells as an alternative DNA source, because whole blood is difficult to collect during fieldwork [150,151]. It is also important to note that, despite the risk of discordant results due to potential tissue-specific DNA methylation changes (and especially to heterogeneity in cell composition), several studies demonstrated high correlations between the DNA methylation profiles of blood and saliva [152–154], pointing to the suitability of saliva as a source for genomic DNA in cohort studies. In the same way, recent investigations have shown that DNA methylation also correlates well between saliva and the brain [155]. Additionally, buccal cells also offer potential advantages to human epigenetic studies, as they represent a better surrogate tissue for brain tissues, with both being ectodermal tissues, and because they can be collected via a non-invasive method (buccal swabs) [156]. Finally, it should be noted that statistical methods to account for cell composition in DNA methylation assays are implemented and available [157].

Seafood is not the only source of exposure to Hg and PAHs. Working with dental amalgam fillings and working or residing among artisanal and small-scale gold mining sites result in elevated exposures to elemental and inorganic Hg [12], which may lead to DNA methylation changes [83,158]. In the same way, several occupations, such as coke oven manufacturing, chimney sweeping, paving and roofing, entail relevant exposure to PAH mixtures [159,160], with consequent impacts on the DNA methylation status [86,161].

Asking participants about their occupation is therefore of fundamental importance in order to address potential confounders of the association between exposure level to MeHg or PAHs via seafood consumption and DNA methylation changes.

As regards the influence of genetics on the individual's biological response to MeHg and PAHs exposure, it should be considered that, sometimes, the same genes are involved in the toxicokinetic of and/or susceptibility to different substances. This, obviously, complicates the detection of genes that may be subject to natural selection driven by a specific chemical. This is the case of GSTP1, MT4 and ALAD genes, whose variation can influence the toxicokinetic of Hg (Tables 1 and S1), but also of Cd [162] and Pb [163–165]. The same is true for NAT2 gene polymorphisms, which influence the toxicokinetics of both Hg [65] and PAHs [69] (Tables 3 and 4).

A further level of complexity is related to the fact that concentrations of these chemicals in edible tissues of aquatic organisms are influenced by several factors.

Several studies have highlighted the role of trophic level, habitat and size of the organism in determining the level of MeHg in sea animals. In particular, despite discordant evidence [121,166], MeHg concentration in fishes often increases with trophic level [126,167], size and age [47], with MeHg uptake being a process of bioaccumulation during the whole life [118], and other studies show that MeHg concentrations are affected also by changes in feeding habits during fish lifespan [132]. The relationship between size and MeHg concentration in marine invertebrates is rather less clear: while some results point to a positive correlation between these two variables in bivalves and crustaceans [124,168], others show a negative [120,169] or no significant correlation [124] in the same taxonomic classes, or even in the same species. As regards PAHs, only few studies have tried to assess the influence of biological factors on their accumulation in aquatic organisms [8], and these led to discordant results. Several studies found no significant correlation between PAHs concentrations and fish size or age [170–173], while Frapiccini and colleagues [28] found a negative correlation between body size and PAH concentrations in the liver and gills of common soles caught in the Po Delta and off Chioggia. Additionally, the sex [170,173,174] and the reproductive stage [8] of the organism seem to affect PAHs accumulation and metabolism in fish.

MeHg and PAHs concentration in fish also vary with seasons [8,171,175–178] and with the geographic origin of the fished specimen, with some areas of the Mediterranean being more polluted than others.

Addressing the above factors through a questionnaire is not easy, if not impossible, which means that a proper estimate of the habitual seafood intake or, more generally, of the eating habits of the sampled individuals, does not always correspond to a precise estimate of their habitual MeHg and/or PAHs intake [179].

To overcome these limitations, the most effective solution is the use of biomarkers of exposition. In particular, as already mentioned, hair mercury level has proven to predict exposition to MeHg [136,180], whose primary route in the general population is seafood consumption [181], while urinary excretion of the metabolite 1-OHP has been attributed mainly to the ingestion of PAHs through the diet [35,182].

However, it is important to note that, unlike MeHg, seafood is not always the main dietary contributor to PAHs intake, and that the concentrations of PAHs in food are also influenced by cooking procedures [183]; as a consequence, it would be difficult to tell whether eventual epigenetic modifications correlated with 1-OHP urinary level are actually driven by PAHs in seafood, unless a very detailed questionnaire on eating habits is collected.

As regards the uncertainties on the geographic origin of seafood consumed, sampling fishermen could help trace the origin of the fish they eat, as fishermen tend to consume their own catch (unpublished data). Moreover, as already mentioned, fishermen represent an interesting case study, given their exposure to high levels of MeHg and, potentially, PAHs, due to their traditionally high seafood consumption. Studying fishermen, however, implies the inclusion of a potential further modifier of the effect of MeHg and PAHs on

DNA methylation, that is, the typical lifestyle of fishermen. Fishing is strongly demanding, both physically and psychologically, implying, among the several challenges, working long hours, frequent night shifts, the unpredictability of the sea, and prolonged separation from the family [184]. Moreover, several investigations have linked the above factors to health conditions and harmful habits that are common among fishermen from different parts of the world, including the Mediterranean Sea [185], which comprise tobacco smoking, alcohol abuse, sleep deprivation, chronic stress, and so on [186,187]. Such habits are known to impact human DNA methylation [188–191], and hence must be taken into consideration when asking sampled individuals about their daily life.

8. Conclusions

The Mediterranean Sea is considered a pollution hotspot for both natural and anthropogenic factors. As a consequence, Mediterranean communities may be particularly exposed to MeHg and PAHs through ingestion, due to their traditional high consumption rate of local seafood, and much evidence supports the above scenario. MeHg and PAHs can impact DNA methylation patterns in humans, even at low doses. Moreover, some of the epigenetic changes associated with MeHg and PAHs exposure are in turn associated with their known health outcomes. Finally, increasing evidence points to a significant contribution of human genetic variability in determining individual susceptibility to the chronic exposure to these chemicals, which, in certain cases, may be the results of population adaptation to certain ecological settings. In this framework, and also considering the growing concern about MeHg pollution due to climate change, we highlighted the benefit of an integrated approach, including molecular anthropologists and environmental and marine chemists, to the investigation of the relationship between the molecular diversity of Mediterranean communities and the exposure to MeHg and PAHs through seafood intake. Such an approach will help us to cope with uncertainties when it comes to risk assessment and decision-making about contaminant limits in seafood.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/app112311179/s1, Table S1: List of epidemiological studies investigating the influence of genetic polymorphisms on MeHg toxicokinetic. Genes in which above polymorphisms were identified, polymorphisms, alleles/genotypes effect on biomarkers, and samples studied are shown for each study. Table S2: List of epidemiological studies investigating the impact of MeHg exposure on DNA methylation. Genes in which differentially methylated CpG dinucleotides were identified, technology used for methylation assay, biomarkers measured, tissues in which biomarkers were measured, tissues from which DNA was extracted, and samples (with sample sizes) studied are shown for each study. Table S3: List of epidemiological studies investigating the influence of genetic polymorphisms on PAHs toxicokinetic. Genes in which above polymorphisms were identified, polymorphisms, alleles/genotypes effect on biomarkers, and samples studied are shown for each study. Table S4: List of epidemiological studies investigating the impact of PAHs exposure on DNA methylation. Genes in which differentially methylated CpG dinucleotides were identified, technology used for methylation assay, biomarkers measured, tissues in which biomarkers were measured, tissues from which DNA was extracted, and samples (with sample sizes) studied are shown for each study.

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References

1. Weichselbaum, E.; Coe, S.; Buttriss, J.; Stanner, S. Fish in the Diet: A Review: Fish in the Diet. *Nutr. Bull.* **2013**, *38*, 128–177. [CrossRef]
2. Thompson, L.A.; Darwish, W.S. Environmental Chemical Contaminants in Food: Review of a Global Problem. *J. Toxicol.* **2019**, *2019*, 1–14. [CrossRef]
3. Marini, M.; Frapiccini, E. Persistence of Polycyclic Aromatic Hydrocarbons in Sediments in the Deeper Area of the Northern Adriatic Sea (Mediterranean Sea). *Chemosphere* **2013**, *90*, 1839–1846. [CrossRef]
4. Marini, M.; Frapiccini, E. Do Lagoon Area Sediments Act as Traps for Polycyclic Aromatic Hydrocarbons? *Chemosphere* **2014**, *111*, 80–88. [CrossRef]
5. Ferrante, M.; Copat, C.; Mauceri, C.; Grasso, A.; Schilirò, T.; Gilli, G. The Importance of Indicators in Monitoring Water Quality According to European Directives. *Epidemiol. Prev.* **2015**, *5*, 71–75.
6. Junqué, E.; Garí, M.; Llull, R.M.; Grimalt, J.O. Drivers of the Accumulation of Mercury and Organochlorine Pollutants in Mediterranean Lean Fish and Dietary Significance. *Sci. Total Environ.* **2018**, *634*, 170–180. [CrossRef]
7. Schartup, A.T.; Thackray, C.P.; Qureshi, A.; Dassuncao, C.; Gillespie, K.; Hanke, A.; Sunderland, E.M. Climate Change and Overfishing Increase Neurotoxicant in Marine Predators. *Nature* **2019**, *572*, 648–650. [CrossRef]
8. Frapiccini, E.; Panfili, M.; Guicciardi, S.; Santojanni, A.; Marini, M.; Truzzi, C.; Annibaldi, A. Effects of Biological Factors and Seasonality on the Level of Polycyclic Aromatic Hydrocarbons in Red Mullet (Mullus Barbatus). *Environ. Pollut.* **2020**, *258*, 113742. [CrossRef] [PubMed]
9. Castaño, A.; Cutanda, F.; Esteban, M.; Pärt, P.; Navarro, C.; Gómez, S.; Rosado, M.; López, A.; López, E.; Exley, K.; et al. Fish Consumption Patterns and Hair Mercury Levels in Children and Their Mothers in 17 EU Countries. *Environ. Res.* **2015**, *141*, 58–68. [CrossRef] [PubMed]
10. Domingo, J.L. Nutrients and Chemical Pollutants in Fish and Shellfish. Balancing Health Benefits and Risks of Regular Fish Consumption. *Crit. Rev. Food Sci. Nutr.* **2016**, *56*, 979–988. [CrossRef]
11. Višnjevec, A.M.; Kocman, D.; Horvat, M. Human Mercury Exposure and Effects in Europe: Human Mercury Exposure and Effects in Europe. *Environ. Toxicol. Chem.* **2014**, *33*, 1259–1270. [CrossRef] [PubMed]
12. Basu, N.; Horvat, M.; Evers, D.C.; Zastenskaya, I.; Weihe, P.; Tempowski, J. A State-of-the-Science Review of Mercury Biomarkers in Human Populations Worldwide between 2000 and 2018. *Environ. Health Perspect.* **2018**, *126*, 106001. [CrossRef] [PubMed]
13. Jacob, J.; Seidel, A. Biomonitoring of Polycyclic Aromatic Hydrocarbons in Human Urine. *J. Chromatogr. B* **2002**, *778*, 31–47. [CrossRef]
14. Krabbenhoft, D.P.; Sunderland, E.M. Global Change and Mercury. *Science* **2013**, *341*, 1457–1458. [CrossRef]
15. Selin, N.E. Global Biogeochemical Cycling of Mercury: A Review. *Annu. Rev. Environ. Resour.* **2009**, *28*, 43–63. [CrossRef]
16. EEA EEA Report No 11/2018. *Mercury in Europe's Environment. A Priority for European and Global Action*; Publications Office of the European Union: Luxembourg, 2018; Available online: https://www.eea.europa.eu/publications/mercury-in-europe-s-environment (accessed on 13 October 2021). [CrossRef]
17. Szefer, P. Safety Assessment of Seafood with Respect to Chemical Pollutants in European Seas. *Oceanol. Hydrobiol. Stud.* **2013**, *42*, 110–118. [CrossRef]
18. Rice, K.M.; Walker, E.M.; Wu, M.; Gillette, C.; Blough, E.R. Environmental Mercury and Its Toxic Effects. *J. Prev. Med. Pub. Health* **2014**, *47*, 74–83. [CrossRef]
19. Zahir, F.; Rizwi, S.J.; Haq, S.K.; Khan, R.H. Low Dose Mercury Toxicity and Human Health. *Environ. Toxicol. Pharmacol.* **2005**, *20*, 351–360. [CrossRef]
20. Karagas, M.R.; Choi, A.L.; Oken, E.; Horvat, M.; Schoeny, R.; Kamai, E.; Cowell, W.; Grandjean, P.; Korrick, S. Evidence on the Human Health Effects of Low-Level Methylmercury Exposure. *Environ. Health Perspect.* **2012**, *120*, 799–806. [CrossRef]
21. EEA Commission Regulation (EC) No 1881/2006 of 19 December 2006 Setting Maximum Levels for Certain Contaminants in Foodstuffs (1). *Off. J. Eur. Union* **2006**, *49*, 5–24.
22. WHO Evaluation of Certain Food Additives and Contaminants. *Sixty-First Report of the Joint FAO/WHO Expert Committee on Food Additives*; WHO: Geneva, Switzerland, 2004.
23. Davidson, P.W.; van Wijngaarden, E.; Shamlaye, C.; Strain, J.J.; Myers, G.J. Putting Findings from the Seychelles Child Development Study into Perspective: The Importance of a Historical Special Issue of the Seychelles Medical and Dental Journal. *NeuroToxicology* **2020**, *76*, 111–113. [CrossRef] [PubMed]
24. Weihe, P.; Grandjean, P. Cohort Studies of Faroese Children Concerning Potential Adverse Health Effects after the Mothers' Exposure to Marine Contaminants during Pregnancy. *Acta Vet. Scand.* **2012**, *54*, S7, 1751-0147-54-S1–S7. [CrossRef]

25. EFSA Panel on Contaminants in the Food Chain (CONTAM). Scientific Opinion on the Risk for Public Health Related to the Presence of Mercury and Methylmercury in Food. *EFSA J.* **2012**, *10*, 2985. [CrossRef]
26. Brambilla, G. Mercury Occurrence in Italian Seafood from the Mediterranean Sea and Possible Intake Scenarios of the Italian Coastal Population. *Regul. Toxicol. Pharmacol.* **2013**, *9*, 269–277. [CrossRef]
27. Cocci, P.; Mosconi, G.; Bracchetti, L.; Nalocca, J.M.; Frapiccini, E.; Marini, M.; Caprioli, G.; Sagratini, G.; Palermo, F.A. Investigating the Potential Impact of Polycyclic Aromatic Hydrocarbons (PAHs) and Polychlorinated Biphenyls (PCBs) on Gene Biomarker Expression and Global DNA Methylation in Loggerhead Sea Turtles (Caretta Caretta) from the Adriatic Sea. *Sci. Total Environ.* **2018**, *619–620*, 49–57. [CrossRef]
28. Frapiccini, E.; Annibaldi, A.; Betti, M.; Polidori, P.; Truzzi, C.; Marini, M. Polycyclic Aromatic Hydrocarbon (PAH) Accumulation in Different Common Sole (Solea Solea) Tissues from the North Adriatic Sea Peculiar Impacted Area. *Mar. Pollut. Bull.* **2018**, *137*, 61–68. [CrossRef]
29. US-EPA Polycyclic Aromatic Hydrocarbons (PAHs) Fact Sheet. US EPA ARCHIVE DOCUMENT 2008. Available online: https://archive.epa.gov/epawaste/hazard/wastemin/web/pdf/pahs.pdf (accessed on 12 October 2021).
30. Ferrante, M.; Zanghì, G.; Cristaldi, A.; Copat, C.; Grasso, A.; Fiore, M.; Signorelli, S.S.; Zuccarello, P.; Oliveri Conti, G. PAHs in Seafood from the Mediterranean Sea: An Exposure Risk Assessment. *Food Chem. Toxicol.* **2018**, *115*, 385–390. [CrossRef]
31. Ramesh, A.; Walker, S.A.; Hood, D.B.; Guillén, M.D.; Schneider, K.; Weyand, E.H. Bioavailability and Risk Assessment of Orally Ingested Polycyclic Aromatic Hydrocarbons. *Int. J. Toxicol.* **2004**, *23*, 301–333. [CrossRef]
32. Balcıoğlu, E.B. Potential Effects of Polycyclic Aromatic Hydrocarbons (PAHs) in Marine Foods on Human Health: A Critical Review. *Toxin Rev.* **2016**, *35*, 98–105. [CrossRef]
33. Haritash, A.K. A Comprehensive Review of Metabolic and Genomic Aspects of PAH-Degradation. *Arch. Microbiol.* **2020**, *26*, 2033–2058.
34. Castano-Vinyals, G. Biomarkers of Exposure to Polycyclic Aromatic Hydrocarbons from Environmental Air Pollution. *Occup. Environ. Med.* **2004**, *61*, e12. [CrossRef] [PubMed]
35. Pruneda-Álvarez, L.G.; Pérez-Vázquez, F.J.; Ruíz-Vera, T.; Ochoa-Martínez, Á.C.; Orta-García, S.T.; Jiménez-Avalos, J.A.; Pérez-Maldonado, I.N. Urinary 1-Hydroxypyrene Concentration as an Exposure Biomarker to Polycyclic Aromatic Hydrocarbons (PAHs) in Mexican Women from Different Hot Spot Scenarios and Health Risk Assessment. *Environ. Sci. Pollut. Res.* **2016**, *23*, 6816–6825. [CrossRef]
36. Iyer, S.; Wang, Y.; Xiong, W.; Tang, D.; Jedrychowski, W.; Chanock, S.; Wang, S.; Stigter, L.; Mróz, E.; Perera, F. Significant Interactions between Maternal PAH Exposure and Single Nucleotide Polymorphisms in Candidate Genes on B[*a*]P–DNA Adducts in a Cohort of Non-Smoking Polish Mothers and Newborns. *Carcinogenesis* **2016**, *37*, 1110–1115. [CrossRef]
37. Gu, A.; Ji, G.; Jiang, T.; Lu, A.; You, Y.; Liu, N.; Luo, C.; Yan, W.; Zhao, P. Contributions of Aryl Hydrocarbon Receptor Genetic Variants to the Risk of Glioma and PAH-DNA Adducts. *Toxicol. Sci.* **2012**, *128*, 357–364. [CrossRef]
38. Nethery, E.; Wheeler, A.J.; Fisher, M.; Sjödin, A.; Li, Z.; Romanoff, L.C.; Foster, W.; Arbuckle, T.E. Urinary Polycyclic Aromatic Hydrocarbons as a Biomarker of Exposure to PAHs in Air: A Pilot Study among Pregnant Women. *J. Expo. Sci. Environ. Epidemiol.* **2012**, *22*, 70–81. [CrossRef]
39. Joneidi, Z.; Mortazavi, Y.; Memari, F.; Roointan, A.; Chahardouli, B.; Rostami, S. The Impact of Genetic Variation on Metabolism of Heavy Metals: Genetic Predisposition? *Biomed. Pharmacother.* **2019**, *113*, 108642. [CrossRef]
40. Shen, H.; Tao, S.; Liu, J.; Huang, Y.; Chen, H.; Li, W.; Zhang, Y.; Chen, Y.; Su, S.; Lin, N.; et al. Global Lung Cancer Risk from PAH Exposure Highly Depends on Emission Sources and Individual Susceptibility. *Sci. Rep.* **2015**, *4*, 6561. [CrossRef] [PubMed]
41. Basu, N.; Goodrich, J.M.; Head, J. Ecogenetics of Mercury: From Genetic Polymorphisms and Epigenetics to Risk Assessment and Decision-Making: Ecogenetics of Mercury. *Environ. Toxicol. Chem.* **2014**, *33*, 1248–1258. [CrossRef]
42. Ruiz-Hernandez, A.; Kuo, C.-C.; Rentero-Garrido, P.; Tang, W.-Y.; Redon, J.; Ordovas, J.M.; Navas-Acien, A.; Tellez-Plaza, M. Environmental Chemicals and DNA Methylation in Adults: A Systematic Review of the Epidemiologic Evidence. *Clin. Epigenetics* **2015**, *7*, 55. [CrossRef]
43. Ijomone, O.M.; Ijomone, O.K.; Iroegbu, J.D.; Ifenatuoha, C.W.; Olung, N.F.; Aschner, M. Epigenetic Influence of Environmentally Neurotoxic Metals. *NeuroToxicology* **2020**, *81*, 51–65. [CrossRef]
44. Huang, Y.; Lin, S.; Wang, C.; Pi, X.; Jin, L.; Li, Z.; Wang, L.; Ren, A. Neural Tube Defects and ZIC4 Hypomethylation in Relation to Polycyclic Aromatic Hydrocarbon Exposure. *Front. Cell Dev. Biol.* **2020**, *8*, 582661. [CrossRef]
45. Esposito, M.; De Roma, A.; Sansone, D.; Capozzo, D.; Iaccarino, D.; di Nocera, F.; Gallo, P. Non-Essential Toxic Element (Cd, As, Hg and Pb) Levels in Muscle, Liver and Kidney of Loggerhead Sea Turtles (Caretta Caretta) Stranded along the Southwestern Coasts of Tyrrhenian Sea. *Comp. Biochem. Physiol. Part C Toxicol. Pharmacol.* **2020**, *231*, 108725. [CrossRef]
46. Serrano, O.; Martínez-Cortizas, A.; Mateo, M.A.; Biester, H.; Bindler, R. Millennial Scale Impact on the Marine Biogeochemical Cycle of Mercury from Early Mining on the Iberian Peninsula: Early Hg Pollution in the Iberian Region. *Glob. Biogeochem. Cycles* **2013**, *27*, 21–30. [CrossRef]
47. Ancora, S.; Mariotti, G.; Ponchia, R.; Fossi, M.C.; Leonzio, C.; Bianchi, N. Trace Elements Levels in Muscle and Liver of a Rarely Investigated Large Pelagic Fish: The Mediterranean Spearfish Tetrapturus Belone (Rafinesque, 1810). *Mar. Pollut. Bull.* **2020**, *151*, 110878. [CrossRef]

48. Giuliani, C.; Sazzini, M.; Bacalini, M.G.; Pirazzini, C.; Marasco, E.; Fontanesi, E.; Franceschi, C.; Luiselli, D.; Garagnani, P. Epigenetic Variability across Human Populations: A Focus on DNA Methylation Profiles of the *KRTCAP3*, *MAD1L1* and *BRSK2* Genes. *Genome Biol. Evol.* **2016**, *8*, 2760–2773. [CrossRef] [PubMed]
49. Sazzini, M.; Abondio, P.; Sarno, S.; Gnecchi-Ruscone, G.A.; Ragno, M.; Giuliani, C.; De Fanti, S.; Ojeda-Granados, C.; Boattini, A.; Marquis, J.; et al. Genomic History of the Italian Population Recapitulates Key Evolutionary Dynamics of Both Continental and Southern Europeans. *BMC Biol.* **2020**, *18*, 51. [CrossRef]
50. Custodio, H.M.; Broberg, K.; Wennberg, M.; Jansson, J.-H.; Vessby, B.; Hallmans, G.; Stegmayr, B.; Skerfving, S. Polymorphisms in Glutathione-Related Genes Affect Methylmercury Retention. *Arch. Environ. Health Int. J.* **2004**, *59*, 588–595. [CrossRef]
51. Gundacker, C.; Komarnicki, G.; Jagiello, P.; Gencikova, A.; Dahmen, N.; Wittmann, K.; Gencik, M. Glutathione-S-Transferase Polymorphism, Metallothionein Expression, and Mercury Levels among Students in Austria. *Sci. Total Environ.* **2007**, *385*, 37–47. [CrossRef]
52. Engström, K.S.; Strömberg, U.; Lundh, T.; Johansson, I.; Vessby, B.; Hallmans, G.; Skerfving, S.; Broberg, K. Genetic Variation in Glutathione-Related Genes and Body Burden of Methylmercury. *Environ. Health Perspect.* **2008**, *116*, 734–739. [CrossRef]
53. Gundacker, C.; Wittmann, K.J.; Kukuckova, M.; Komarnicki, G.; Hikkel, I.; Gencik, M. Genetic Background of Lead and Mercury Metabolism in a Group of Medical Students in Austria. *Environ. Res.* **2009**, *109*, 786–796. [CrossRef] [PubMed]
54. Lee, B.-E.; Hong, Y.-C.; Park, H.; Ha, M.; Koo, B.S.; Chang, N.; Roh, Y.-M.; Kim, B.-N.; Kim, Y.-J.; Kim, B.-M.; et al. Interaction between *GSTM1* / *GSTT1* Polymorphism and Blood Mercury on Birth Weight. *Environ. Health Perspect.* **2010**, *118*, 437–443. [CrossRef]
55. Goodrich, J.M.; Wang, Y.; Gillespie, B.; Werner, R.; Franzblau, A.; Basu, N. Glutathione Enzyme and Selenoprotein Polymorphisms Associate with Mercury Biomarker Levels in Michigan Dental Professionals. *Toxicol. Appl. Pharmacol.* **2011**, *257*, 301–308. [CrossRef]
56. Wang, Y.; Goodrich, J.M.; Gillespie, B.; Werner, R.; Basu, N.; Franzblau, A. An Investigation of Modifying Effects of Metallothionein Single-Nucleotide Polymorphisms on the Association between Mercury Exposure and Biomarker Levels. *Environ. Health Perspect.* **2012**, *120*, 530–534. [CrossRef]
57. Ng, S.; Lin, C.-C.; Hwang, Y.-H.; Hsieh, W.-S.; Liao, H.-F.; Chen, P.-C. Mercury, APOE, and Children's Neurodevelopment. *NeuroToxicology* **2013**, *37*, 85–92. [CrossRef]
58. Barcelos, G.R.M.; Grotto, D.; de Marco, K.C.; Valentini, J.; van Helvoort Lengert, A.; de Oliveira, A.Á.S.; Garcia, S.C.; Braga, G.Ú.L.; Schläwicke Engström, K.; de Syllos Cólus, I.M.; et al. Polymorphisms in Glutathione-Related Genes Modify Mercury Concentrations and Antioxidant Status in Subjects Environmentally Exposed to Methylmercury. *Sci. Total Environ.* **2013**, *463–464*, 319–325. [CrossRef]
59. Julvez, J.; Smith, G.D.; Golding, J.; Ring, S.; Pourcain, B.S.; Gonzalez, J.R.; Grandjean, P. Prenatal Methylmercury Exposure and Genetic Predisposition to Cognitive Deficit at Age 8 Years. *Epidemiology* **2013**, *24*, 643–650. [CrossRef]
60. De Oliveira, A.Á.S.; de Souza, M.F.; van Lengert, A.H.; de Oliveira, M.T.; de Camargo, R.B.O.G.; Braga, G.Ú.L.; de Cólus, I.M.S.; Barbosa, F.; Barcelos, G.R.M. Genetic Polymorphisms in Glutathione (GSH-) Related Genes Affect the Plasmatic Hg/Whole Blood Hg Partitioning and the Distribution between Inorganic and Methylmercury Levels in Plasma Collected from a Fish-Eating Population. *BioMed Res. Int.* **2014**, *2014*, 1–8. [CrossRef]
61. Llop, S.; Pisa, F.; Tratnik, J.S.; Mazej, D.; Murcia, M.; Rebagliato, M.; Bustamante, M.; Sunyer, J.; Antonopoulou, E.; Antoniadou, I.; et al. Polymorphisms in ABC Transporter Genes and Concentrations of Mercury in Newborns – Evidence from Two Mediterranean Birth Cohorts. *PLoS ONE* **2014**, *9*, 9. [CrossRef]
62. Ng, S.; Lin, C.-C.; Jeng, S.-F.; Hwang, Y.-H.; Hsieh, W.-S.; Chen, P.-C. Mercury, APOE, and Child Behavior. *Chemosphere* **2015**, *120*, 123–130. [CrossRef]
63. Engström, K.; Love, T.M.; Watson, G.E.; Zareba, G.; Yeates, A.; Wahlberg, K.; Alhamdow, A.; Thurston, S.W.; Mulhern, M.; McSorley, E.M.; et al. Polymorphisms in ATP-Binding Cassette Transporters Associated with Maternal Methylmercury Disposition and Infant Neurodevelopment in Mother-Infant Pairs in the Seychelles Child Development Study. *Environ. Int.* **2016**, *94*, 224–229. [CrossRef]
64. Parajuli, R.P.; Goodrich, J.M.; Chou, H.-N.; Gruninger, S.E.; Dolinoy, D.C.; Franzblau, A.; Basu, N. Genetic Polymorphisms Are Associated with Hair, Blood, and Urine Mercury Levels in the American Dental Association (ADA) Study Participants. *Environ. Res.* **2016**, *149*, 247–258. [CrossRef]
65. Parajuli, R.P. Genetic Polymorphisms Are Associated with Exposure Biomarkers for Metals and Persistent Organic Pollutants among Inuit from the Inuvialuit Settlement Region, Canada. *Sci. Total Environ.* **2018**, *10*, 569–578. [CrossRef]
66. Wahlberg, K.; Love, T.M.; Pineda, D.; Engström, K.; Watson, G.E.; Thurston, S.W.; Yeates, A.J.; Mulhern, M.S.; McSorley, E.M.; Strain, J.J.; et al. Maternal Polymorphisms in Glutathione-Related Genes Are Associated with Maternal Mercury Concentrations and Early Child Neurodevelopment in a Population with a Fish-Rich Diet. *Environ. Int.* **2018**, *115*, 142–149. [CrossRef]
67. Lozano, M.; Murcia, M.; Soler-Blasco, R.; González, L.; Iriarte, G.; Rebagliato, M.; Lopez-Espinosa, M.-J.; Esplugues, A.; Ballester, F.; Llop, S. Exposure to Mercury among 9-Year-Old Children and Neurobehavioural Function. *Environ. Int.* **2021**, *146*, 106173. [CrossRef]
68. Ji, G.; Gu, A.; Zhou, Y.; Shi, X.; Xia, Y.; Long, Y.; Song, L.; Wang, S.; Wang, X. Interactions between Exposure to Environmental Polycyclic Aromatic Hydrocarbons and DNA Repair Gene Polymorphisms on Bulky DNA Adducts in Human Sperm. *PLoS ONE* **2010**, *5*, e13145. [CrossRef]

69. Etemadi, A.; Islami, F.; Phillips, D.H.; Godschalk, R.; Golozar, A.; Kamangar, F.; Malekshah, A.F.-T.; Pourshams, A.; Elahi, S.; Ghojaghi, F.; et al. Variation in PAH-Related DNA Adduct Levels among Non-Smokers: The Role of Multiple Genetic Polymorphisms and Nucleotide Excision Repair Phenotype. *Int. J. Cancer* **2013**, *132*, 2738–2747. [CrossRef]
70. Clarkson, T.W.; Magos, L. The Toxicology of Mercury and Its Chemical Compounds. *Crit. Rev. Toxicol.* **2006**, *36*, 609–662. [CrossRef]
71. Caito, S.W.; Jackson, B.P.; Punshon, T.; Scrimale, T.; Grier, A.; Gill, S.R.; Love, T.M.; Watson, G.E.; van Wijngaarden, E.; Rand, M.D. Editor's Highlight: Variation in Methylmercury Metabolism and Elimination Status in Humans Following Fish Consumption. *Toxicol. Sci.* **2018**, *161*, 443–453. [CrossRef]
72. Andreoli, V.; Sprovieri, F. Genetic Aspects of Susceptibility to Mercury Toxicity: An Overview. *Int. J. Environ. Res. Public. Health* **2017**, *14*, 93. [CrossRef]
73. Conte, F.; Copat, C.; Longo, S.; Conti, G.O.; Grasso, A.; Arena, G.; Dimartino, A.; Brundo, M.V.; Ferrante, M. Polycyclic Aromatic Hydrocarbons in Haliotis Tuberculata (Linnaeus, 1758) (Mollusca, Gastropoda): Considerations on Food Safety and Source Investigation. *Food Chem. Toxicol.* **2016**, *94*, 57–63. [CrossRef]
74. Rehman, M.Y.A.; Taqi, M.M.; Hussain, I.; Nasir, J.; Rizvi, S.H.H.; Syed, J.H. Elevated Exposure to Polycyclic Aromatic Hydrocarbons (PAHs) May Trigger Cancers in Pakistan: An Environmental, Occupational, and Genetic Perspective. *Environ. Sci. Pollut. Res.* **2020**, *27*, 42405–42423. [CrossRef]
75. Feil, R.; Fraga, M.F. Epigenetics and the Environment: Emerging Patterns and Implications. *Nat. Rev. Genet.* **2012**, *13*, 97–109. [CrossRef]
76. Fagny, M.; Patin, E.; MacIsaac, J.L.; Rotival, M.; Flutre, T.; Jones, M.J.; Siddle, K.J.; Quach, H.; Harmant, C.; McEwen, L.M.; et al. The Epigenomic Landscape of African Rainforest Hunter-Gatherers and Farmers. *Nat. Commun.* **2015**, *6*, 10047. [CrossRef]
77. Natri, H.M.; Bobowik, K.S.; Kusuma, P.; Crenna Darusallam, C.; Jacobs, G.S.; Hudjashov, G.; Lansing, J.S.; Sudoyo, H.; Banovich, N.E.; Cox, M.P.; et al. Genome-Wide DNA Methylation and Gene Expression Patterns Reflect Genetic Ancestry and Environmental Differences across the Indonesian Archipelago. *PLoS Genet.* **2020**, *16*, e1008749. [CrossRef]
78. Carja, O.; MacIsaac, J.L.; Mah, S.M.; Henn, B.M.; Kobor, M.S.; Feldman, M.W.; Fraser, H.B. Worldwide Patterns of Human Epigenetic Variation. *Nat. Ecol. Evol.* **2017**, *1*, 1577–1583. [CrossRef]
79. Hodjat, M.; Rahmani, S.; Khan, F.; Niaz, K.; Navaei–Nigjeh, M.; Mohammadi Nejad, S.; Abdollahi, M. Environmental Toxicants, Incidence of Degenerative Diseases, and Therapies from the Epigenetic Point of View. *Arch. Toxicol.* **2017**, *91*, 2577–2597. [CrossRef]
80. Martin, E.M.; Fry, R.C. Environmental Influences on the Epigenome: Exposure- Associated DNA Methylation in Human Populations. *Annu. Rev. Public Health* **2018**, *39*, 309–333. [CrossRef]
81. Culbreth, M.; Aschner, M. Methylmercury Epigenetics. *Toxics* **2019**, *7*, 56. [CrossRef]
82. Hanna, C.W.; Bloom, M.S.; Robinson, W.P.; Kim, D.; Parsons, P.J.; vom Saal, F.S.; Taylor, J.A.; Steuerwald, A.J.; Fujimoto, V.Y. DNA Methylation Changes in Whole Blood Is Associated with Exposure to the Environmental Contaminants, Mercury, Lead, Cadmium and Bisphenol A, in Women Undergoing Ovarian Stimulation for IVF. *Hum. Reprod.* **2012**, *27*, 1401–1410. [CrossRef]
83. Goodrich, J.M.; Basu, N.; Franzblau, A.; Dolinoy, D.C. Mercury Biomarkers and DNA Methylation among Michigan Dental Professionals: Mercury and DNA Methylation. *Environ. Mol. Mutagen.* **2013**, *54*, 195–203. [CrossRef]
84. Pavanello, S.; Bollati, V.; Pesatori, A.C.; Kapka, L.; Bolognesi, C.; Bertazzi, P.A.; Baccarelli, A. Global and Gene-Specific Promoter Methylation Changes Are Related to *Anti* -B[*a*]PDE-DNA Adduct Levels and Influence Micronuclei Levels in Polycyclic Aromatic Hydrocarbon-Exposed Individuals. *Int. J. Cancer* **2009**, *125*, 1692–1697. [CrossRef]
85. Yang, P.; Ma, J.; Zhang, B.; Duan, H.; He, Z.; Zeng, J.; Zeng, X.; Li, D.; Wang, Q.; Xiao, Y.; et al. CpG Site–Specific Hypermethylation of *P16* $^{INK4\alpha}$ in Peripheral Blood Lymphocytes of PAH-Exposed Workers. *Cancer Epidemiol. Biomark. Prev.* **2012**, *21*, 182–190. [CrossRef]
86. Alegría-Torres, J.A.; Barretta, F.; Batres-Esquivel, L.E.; Carrizales-Yáñez, L.; Pérez-Maldonado, I.N.; Baccarelli, A.; Bertazzi, P.A. Epigenetic Markers of Exposure to Polycyclic Aromatic Hydrocarbons in Mexican Brickmakers: A Pilot Study. *Chemosphere* **2013**, *91*, 475–480. [CrossRef]
87. Bakulski, K.M.; Lee, H.; Feinberg, J.I.; Wells, E.M.; Brown, S.; Herbstman, J.B.; Witter, F.R.; Halden, R.U.; Caldwell, K.; Mortensen, M.E.; et al. Prenatal Mercury Concentration Is Associated with Changes in DNA Methylation at *TCEANC2* in Newborns. *Int. J. Epidemiol.* **2015**, *44*, 1249–1262. [CrossRef]
88. Cardenas, A.; Koestler, D.C.; Houseman, E.A.; Jackson, B.P.; Kile, M.L.; Karagas, M.R.; Marsit, C.J. Differential DNA Methylation in Umbilical Cord Blood of Infants Exposed to Mercury and Arsenic *in Utero*. *Epigenetics* **2015**, *10*, 508–515. [CrossRef]
89. Maccani, J.Z.J.; Koestler, D.C.; Lester, B.; Houseman, E.A.; Armstrong, D.A.; Kelsey, K.T.; Marsit, C.J. Placental DNA Methylation Related to Both Infant Toenail Mercury and Adverse Neurobehavioral Outcomes. *Environ. Health Perspect.* **2015**, *123*, 723–729. [CrossRef]
90. Cardenas, A.; Rifas-Shiman, S.L.; Agha, G.; Hivert, M.-F.; Litonjua, A.A.; DeMeo, D.L.; Lin, X.; Amarasiriwardena, C.J.; Oken, E.; Gillman, M.W.; et al. Persistent DNA Methylation Changes Associated with Prenatal Mercury Exposure and Cognitive Performance during Childhood. *Sci. Rep.* **2017**, *7*, 288. [CrossRef]
91. Cediel Ulloa, A.; Gliga, A.; Love, T.M.; Pineda, D.; Mruzek, D.W.; Watson, G.E.; Davidson, P.W.; Shamlaye, C.F.; Strain, J.J.; Myers, G.J.; et al. Prenatal Methylmercury Exposure and DNA Methylation in Seven-Year-Old Children in the Seychelles Child Development Study. *Environ. Int.* **2021**, *147*, 106321. [CrossRef]

92. Perera, F.; Tang, W.; Herbstman, J.; Tang, D.; Levin, L.; Miller, R.; Ho, S. Relation of DNA Methylation of 5′-CpG Island of ACSL3 to Transplacental Exposure to Airborne Polycyclic Aromatic Hydrocarbons and Childhood Asthma. *PLoS ONE* **2009**, *4*, e4488. [CrossRef]
93. Herbstman, J.B.; Tang, D.; Zhu, D.; Qu, L.; Sjödin, A.; Li, Z.; Camann, D.; Perera, F.P. Prenatal Exposure to Polycyclic Aromatic Hydrocarbons, Benzo[*a*]Pyrene–DNA Adducts, and Genomic DNA Methylation in Cord Blood. *Environ. Health Perspect.* **2012**, *120*, 733–738. [CrossRef]
94. Kim, Y.H.; Lee, Y.S.; Lee, D.H.; Kim, D.S. Polycyclic Aromatic Hydrocarbons Are Associated with Insulin Receptor Substrate 2 Methylation in Adipose Tissues of Korean Women. *Environ. Res.* **2016**, *150*, 47–51. [CrossRef]
95. Lee, J.; Kalia, V.; Perera, F.; Herbstman, J.; Li, T.; Nie, J.; Qu, L.R.; Yu, J.; Tang, D. Prenatal Airborne Polycyclic Aromatic Hydrocarbon Exposure, LINE1 Methylation and Child Development in a Chinese Cohort. *Environ. Int.* **2017**, *99*, 315–320. [CrossRef]
96. Li, J.; Zhu, X.; Yu, K.; Jiang, H.; Zhang, Y.; Wang, B.; Liu, X.; Deng, S.; Hu, J.; Deng, Q.; et al. Exposure to Polycyclic Aromatic Hydrocarbons and Accelerated DNA Methylation Aging. *Environ. Health Perspect.* **2018**, *126*, 067005. [CrossRef]
97. Lin, S.; Ren, A.; Wang, L.; Santos, C.; Huang, Y.; Jin, L.; Li, Z.; Greene, N.D.E. Aberrant Methylation of Pax3 Gene and Neural Tube Defects in Association with Exposure to Polycyclic Aromatic Hydrocarbons. *Clin. Epigenetics* **2019**, *11*, 13. [CrossRef]
98. Liu, K.; Jiang, J.; Lin, Y.; Liu, W.; Zhu, X.; Zhang, Y.; Jiang, H.; Yu, K.; Liu, X.; Zhou, M.; et al. Exposure to Polycyclic Aromatic Hydrocarbons, DNA Methylation and Heart Rate Variability among Non-Current Smokers. *Environ. Pollut.* **2021**, *288*, 117777. [CrossRef]
99. Onishchenko, N.; Karpova, N.; Sabri, F.; Castrn, E.; Ceccatelli, S. Long-Lasting Depression-like Behavior and Epigenetic Changes of BDNF Gene Expression Induced by Perinatal Exposure to Methylmercury. *J. Neurochem.* **2008**, *106*, 1378–1387. [CrossRef]
100. Grandjean, P.; Weihe, P.; White, R.F.; Debes, F.; Araki, S.; Yokoyama, K.; Murata, K.; Sørensen, N.; Dahl, R.; Jørgensen, P.J. Cognitive Deficit in 7-Year-Old Children with Prenatal Exposure to Methylmercury. *Neurotoxicol. Teratol.* **1997**, *19*, 417–428. [CrossRef]
101. Axelrad, D.A.; Bellinger, D.C.; Ryan, L.M.; Woodruff, T.J. Dose–Response Relationship of Prenatal Mercury Exposure and IQ: An Integrative Analysis of Epidemiologic Data. *Environ. Health Perspect.* **2007**, *115*, 609–615. [CrossRef]
102. Yokoo, E.M.; Valente, J.G.; Grattan, L.; Schmidt, S.L.; Platt, I.; Silbergeld, E.K. Low Level Methylmercury Exposure Affects Neuropsychological Function in Adults. *Environ. Health* **2003**, *2*, 8. [CrossRef]
103. Akpambang, V.; Purcaro, G.; Lajide, L.; Amoo, I.; Conte, L.; Moret, S. Determination of Polycyclic Aromatic Hydrocarbons (PAHs) in Commonly Consumed Nigerian Smoked/Grilled Fish and Meat. *Food Addit. Contam.* **2009**, *22*, 1096–1103. [CrossRef]
104. Forsberg, N.D.; Stone, D.; Harding, A.; Harper, B.; Harris, S.; Matzke, M.M.; Cardenas, A.; Waters, K.M.; Anderson, K.A. Effect of Native American Fish Smoking Methods on Dietary Exposure to Polycyclic Aromatic Hydrocarbons and Possible Risks to Human Health. *J. Agric. Food Chem.* **2012**, *60*, 6899–6906. [CrossRef]
105. Sholts, S.B.; Smith, K.; Wallin, C.; Ahmed, T.M.; Wärmländer, S.K.T.S. Ancient Water Bottle Use and Polycyclic Aromatic Hydrocarbon (PAH) Exposure among California Indians: A Prehistoric Health Risk Assessment. *Environ. Health* **2017**, *16*, 61. [CrossRef]
106. Schlebusch, C.M.; Gattepaille, L.M.; Engström, K.; Vahter, M.; Jakobsson, M.; Broberg, K. Human Adaptation to Arsenic-Rich Environments. *Mol. Biol. Evol.* **2015**, *32*, 1544–1555. [CrossRef]
107. Arriaza, B.; Amarasiriwardena, D.; Cornejo, L.; Standen, V.; Byrne, S.; Bartkus, L.; Bandak, B. Exploring Chronic Arsenic Poisoning in Pre-Columbian Chilean Mummies. *J. Archaeol. Sci.* **2010**, *37*, 1274–1278. [CrossRef]
108. Apata, M.; Pfeifer, S.P. Recent Population Genomic Insights into the Genetic Basis of Arsenic Tolerance in Humans: The Difficulties of Identifying Positively Selected Loci in Strongly Bottlenecked Populations. *Heredity* **2020**, *124*, 253–262. [CrossRef]
109. Apata, M.; Arriaza, B.; Llop, E.; Moraga, M. Human Adaptation to Arsenic in Andean Populations of the Atacama Desert. *Am. J. Phys. Anthropol.* **2017**, *163*, 192–199. [CrossRef]
110. Hubbard, T.D.; Murray, I.A.; Bisson, W.H.; Sullivan, A.P.; Sebastian, A.; Perry, G.H.; Jablonski, N.G.; Perdew, G.H. Divergent Ah Receptor Ligand Selectivity during Hominin Evolution. *Mol. Biol. Evol.* **2016**, *33*, 2648–2658. [CrossRef]
111. Heyn, H.; Moran, S.; Hernando-Herraez, I.; Sayols, S.; Gomez, A.; Sandoval, J.; Monk, D.; Hata, K.; Marques-Bonet, T.; Wang, L.; et al. DNA Methylation Contributes to Natural Human Variation. *Genome Res.* **2013**, *23*, 1363–1372. [CrossRef]
112. Giuliani, C.; Biggs, D.; Nguyen, T.T.; Marasco, E.; De Fanti, S.; Garagnani, P.; Le Phan, M.T.; Nguyen, V.N.; Luiselli, D.; Romeo, G. First Evidence of Association between Past Environmental Exposure to Dioxin and DNA Methylation of CYP1A1 and IGF2 Genes in Present Day Vietnamese Population. *Environ. Pollut.* **2018**, *242*, 976–985. [CrossRef]
113. Droghini, E.; Annibaldi, A.; Prezioso, E.; Tramontana, M.; Frapiccini, E.; De Marco, R.; Illuminati, S.; Truzzi, C.; Spagnoli, F. Mercury Content in Central and Southern Adriatic Sea Sediments in Relation to Seafloor Geochemistry and Sedimentology. *Molecules* **2019**, *24*, 4467. [CrossRef]
114. Koenig, S.; Solé, M.; Fernández-Gómez, C.; Díez, S. New Insights into Mercury Bioaccumulation in Deep-Sea Organisms from the NW Mediterranean and Their Human Health Implications. *Sci. Total Environ.* **2013**, *442*, 329–335. [CrossRef]
115. Cammilleri, G.; Vazzana, M.; Arizza, V.; Giunta, F.; Vella, A.; Lo Dico, G.; Giaccone, V.; Giofrè, S.V.; Giangrosso, G.; Cicero, N.; et al. Mercury in Fish Products: What's the Best for Consumers between Bluefin Tuna and Yellowfin Tuna? *Nat. Prod. Res.* **2018**, *32*, 457–462. [CrossRef]

116. Cinnirella, S.; Bruno, D.E.; Pirrone, N.; Horvat, M.; Živković, I.; Evers, D.C.; Johnson, S.; Sunderland, E.M. Mercury Concentrations in Biota in the Mediterranean Sea, a Compilation of 40 Years of Surveys. *Sci. Data* **2019**, *6*, 205. [CrossRef]
117. Gallo, P.; De Carlo, E.; Marigliano, L.; Maglio, P.; Amato, A.; Improta, A.; Caruso, C.; De Roma, A. Food Safety Assessment of Heavy Metals in Uncommon and Abyssal Fish and Cephalopod from the Tyrrhenian Sea. *J. Consum. Prot. Food Saf.* **2018**, *13*, 399–402. [CrossRef]
118. Annibaldi, A.; Truzzi, C.; Carnevali, O.; Pignalosa, P.; Api, M.; Scarponi, G.; Illuminati, S. Determination of Hg in Farmed and Wild Atlantic Bluefin Tuna (*Thunnus Thynnus* L.) Muscle. *Molecules* **2019**, *24*, 1273. [CrossRef]
119. Copat, C.; Conti, G.O.; Fallico, R.; Sciacca, S.; Ferrante, M. Heavy Metals in Fish from the Mediterranean Sea. In *The Mediterranean Diet*; Elsevier: Amsterdam, The Netherlands, 2015; pp. 547–562. ISBN 978-0-12-407849-9.
120. Perugini, M.; Visciano, P.; Manera, M.; Abete, M.C.; Gavinelli, S.; Amorena, M. Contamination of Different Portions of Raw and Boiled Specimens of Norway Lobster by Mercury and Selenium. *Environ. Sci. Pollut. Res.* **2013**, *20*, 8255–8262. [CrossRef]
121. Perugini, M.; Visciano, P.; Manera, M.; Zaccaroni, A.; Olivieri, V.; Amorena, M. Heavy Metal (As, Cd, Hg, Pb, Cu, Zn, Se) Concentrations in Muscle and Bone of Four Commercial Fish Caught in the Central Adriatic Sea, Italy. *Environ. Monit. Assess.* **2014**, *186*, 2205–2213. [CrossRef]
122. Perugini, M.; Zezza, D.; Tulini, S.M.R.; Abete, M.C.; Monaco, G.; Conte, A.; Olivieri, V.; Amorena, M. Effect of Cooking on Total Mercury Content in Norway Lobster and European Hake and Public Health Impact. *Mar. Pollut. Bull.* **2016**, *109*, 521–525. [CrossRef]
123. Storelli, M.M.; Barone, G. Toxic Metals (Hg, Pb, and Cd) in Commercially Important Demersal Fish from Mediterranean Sea: Contamination Levels and Dietary Exposure Assessment: Toxic Metals in Fish. *J. Food Sci.* **2013**, *78*, T362–T366. [CrossRef]
124. Di Lena, G.; Casini, I.; Caproni, R.; Orban, E. Total Mercury Levels in Crustacean Species from Italian Fishery. *Food Addit. Contam. Part B* **2018**, *11*, 175–182. [CrossRef]
125. Bajt, O.; Ramšak, A.; Milun, V.; Andral, B.; Romanelli, G.; Scarpato, A.; Mitrić, M.; Kupusović, T.; Kljajić, Z.; Angelidis, M.; et al. Assessing Chemical Contamination in the Coastal Waters of the Adriatic Sea Using Active Mussel Biomonitoring with Mytilus Galloprovincialis. *Mar. Pollut. Bull.* **2019**, *141*, 283–298. [CrossRef]
126. Di Lena, G.; Casini, I.; Caproni, R.; Fusari, A.; Orban, E. Total Mercury Levels in Commercial Fish Species from Italian Fishery and Aquaculture. *Food Addit. Contam. Part B* **2017**, *10*, 118–127. [CrossRef]
127. Galgani, F.; Martínez-Gómez, C.; Giovanardi, F.; Romanelli, G.; Caixach, J.; Cento, A.; Scarpato, A.; BenBrahim, S.; Messaoudi, S.; Deudero, S.; et al. Assessment of Polycyclic Aromatic Hydrocarbon Concentrations in Mussels (Mytilus Galloprovincialis) from the Western Basin of the Mediterranean Sea. *Environ. Monit. Assess.* **2011**, *172*, 301–317. [CrossRef]
128. Arienzo, M.; Toscanesi, M.; Trifuoggi, M.; Ferrara, L.; Stanislao, C.; Donadio, C.; Grazia, V.; Gionata, D.V.; Carella, F. Contaminants Bioaccumulation and Pathological Assessment in Mytilus Galloprovincialis in Coastal Waters Facing the Brownfield Site of Bagnoli, Italy. *Mar. Pollut. Bull.* **2019**, *140*, 341–352. [CrossRef]
129. Conti, G.O.; Copat, C.; Ledda, C.; Fiore, M.; Fallico, R.; Sciacca, S.; Ferrante, M. Evaluation of Heavy Metals and Polycyclic Aromatic Hydrocarbons (PAHs) in Mullus Barbatus from Sicily Channel and Risk-Based Consumption Limits. *Bull. Environ. Contam. Toxicol.* **2012**, *88*, 946–950. [CrossRef]
130. US-EPA Guidance for Assessing Chemical Contamination Data for Use in Fish Advisories, Vol. II. Risk Assessment and Fish Consumption Limits EPA/823-B94-004 2000. Available online: https://www.epa.gov/sites/default/files/2015-06/documents/volume2.pdf (accessed on 12 October 2021).
131. Copat, C.; Vinceti, M.; D'Agati, M.G.; Arena, G.; Mauceri, V.; Grasso, A.; Fallico, R.; Sciacca, S.; Ferrante, M. Mercury and Selenium Intake by Seafood from the Ionian Sea: A Risk Evaluation. *Ecotoxicol. Environ. Saf.* **2014**, *100*, 87–92. [CrossRef]
132. Barone, G.; Storelli, A.; Garofalo, R.; Busco, V.P.; Quaglia, N.C.; Centrone, G.; Storelli, M.M. Assessment of Mercury and Cadmium via Seafood Consumption in Italy: Estimated Dietary Intake (EWI) and Target Hazard Quotient (THQ). *Food Addit. Contam. Part A* **2015**, *32*, 1277–1286. [CrossRef]
133. Díez, S.; Montuori, P.; Pagano, A.; Sarnacchiaro, P.; Bayona, J.M.; Triassi, M. Hair Mercury Levels in an Urban Population from Southern Italy: Fish Consumption as a Determinant of Exposure. *Environ. Int.* **2008**, *6*, 162–167. [CrossRef]
134. Den Hond, E.; Govarts, E.; Willems, H.; Smolders, R.; Casteleyn, L.; Kolossa-Gehring, M.; Schwedler, G.; Seiwert, M.; Fiddicke, U.; Castaño, A.; et al. First Steps toward Harmonized Human Biomonitoring in Europe: Demonstration Project to Perform Human Biomonitoring on a European Scale. *Environ. Health Perspect.* **2015**, *123*, 255–263. [CrossRef]
135. EUMOFA The EU Fish Market. European Market Observatory for Fisheries and Aquaculture Products. European Commission, Directorate-General for Maritime Affairs and Fisheries, Director-General, 2018. Available online: http://agricultura.gencat.cat/web/.content/de_departament/de02_estadistiques_observatoris/27_butlletins/02_butlletins_nd/documents_nd/fitxers_estatics_nd/2018/0218_2018_Pesca_Productes-pesquers-mercats-UE-2018-exportacions.pdf (accessed on 13 October 2021). [CrossRef]
136. Sekovanic, A.; Piasek, M.; Orct, T.; Grgec, A.S.; Saric, M.M.; Stasenko, S.; Jurasovic, J. Mercury Exposure Assessment in Mother–Infant Pairs from Continental and Coastal Croatia. *Biomolecules* **2020**, *27*, 821. [CrossRef]
137. Elhamri, H.; Idrissi, L.; Coquery, M.; Azemard, S.; Abidi, A.E.; Benlemlih, M.; Saghi, M.; Cubadda, F. Hair Mercury Levels in Relation to Fish Consumption in a Community of the Moroccan Mediterranean Coast. *Food Addit. Contam.* **2007**, *24*, 1236–1246. [CrossRef]

138. Giangrosso, G.; Cammilleri, G.; Macaluso, A.; Vella, A.; D'Orazio, N.; Graci, S.; Lo Dico, G.M.; Galvano, F.; Giangrosso, M.; Ferrantelli, V. Hair Mercury Levels Detection in Fishermen from Sicily (Italy) by ICP-MS Method after Microwave-Assisted Digestion. *Bioinorg. Chem. Appl.* **2016**, *2016*, 1–5. [CrossRef] [PubMed]
139. Barbone, F.; Valent, F.; Pisa, F.; Daris, F.; Fajon, V.; Logar, M.; Horvat, M. Prenatal low-level methyl mercury exposure and child development in an Italian coastal area. *Seychelles Med Dent. J.* **2004**, *7*, 149–154. [CrossRef]
140. Giuliani, C.; Bacalini, M.G.; Sazzini, M.; Pirazzini, C.; Franceschi, C.; Garagnani, P.; Luiselli, D. The Epigenetic Side of Human Adaptation: Hypotheses, Evidences and Theories. *Ann. Hum. Biol.* **2015**, *42*, 1–9. [CrossRef]
141. Lam, L.L.; Emberly, E.; Fraser, H.B.; Neumann, S.M.; Chen, E.; Miller, G.E.; Kobor, M.S. Factors Underlying Variable DNA Methylation in a Human Community Cohort. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 17253–17260. [CrossRef]
142. Bosch, A.C.; O'Neill, B.; Sigge, G.O.; Kerwath, S.E.; Hoffman, L.C. Heavy Metals in Marine Fish Meat and Consumer Health: A Review: Heavy Metals in Marine Fish Meat. *J. Sci. Food Agric.* **2016**, *96*, 32–48. [CrossRef]
143. Maggi, C.; Berducci, M.T.; Di Lorenzo, B.; Dattolo, M.; Cozzolino, A.; Mariotti, S.; Fabrizi, V.; Spaziani, R.; Virno Lamberti, C. Temporal Evolution of the Environmental Quality of the Vallona Lagoon (Northern Mediterranean, Adriatic Sea). *Mar. Pollut. Bull.* **2017**, *125*, 45–55. [CrossRef] [PubMed]
144. Balali-Mood, M.; Naseri, K.; Tahergorabi, Z.; Khazdair, M.R.; Sadeghi, M. Toxic Mechanisms of Five Heavy Metals: Mercury, Lead, Chromium, Cadmium, and Arsenic. *Front. Pharmacol.* **2021**, *12*, 643972. [CrossRef]
145. Alegría-Torres, J.A.; Carrizales-Yánez, L.; Díaz-Barriga, F.; Rosso-Camacho, F.; Motta, V.; Tarantini, L.; Bollati, V. DNA Methylation Changes in Mexican Children Exposed to Arsenic from Two Historic Mining Areas in San Luis Potosí: DNA Methylation Changes. *Environ. Mol. Mutagen.* **2016**, *57*, 717–723. [CrossRef]
146. Bandyopadhyay, A.K.; Paul, S.; Adak, S.; Giri, A.K. Reduced LINE-1 Methylation Is Associated with Arsenic-Induced Genotoxic Stress in Children. *BioMetals* **2016**, *29*, 731–741. [CrossRef]
147. Lambrou, A.; Baccarelli, A.; Wright, R.O.; Weisskopf, M.; Bollati, V.; Amarasiriwardena, C.; Vokonas, P.; Schwartz, J. Arsenic Exposure and DNA Methylation among Elderly Men. *Epidemiology* **2012**, *23*, 668–676. [CrossRef]
148. Hossain, M.B.; Vahter, M.; Concha, G.; Broberg, K. Low-Level Environmental Cadmium Exposure Is Associated with DNA Hypomethylation in Argentinean Women. *Environ. Health Perspect.* **2012**, *120*, 879–884. [CrossRef]
149. Li, C.; Yang, X.; Xu, M.; Zhang, J.; Sun, N. Epigenetic Marker (LINE-1 Promoter) Methylation Level Was Associated with Occupational Lead Exposure. *Clin. Toxicol.* **2013**, *51*, 225–229. [CrossRef]
150. Non, A.L.; Thayer, Z.M. Epigenetics for Anthropologists: An Introduction to Methods: Epigenetic Methods for Anthropologists. *Am. J. Hum. Biol.* **2015**, *27*, 295–303. [CrossRef]
151. Samson, C.A.; Whitford, W.; Snell, R.G.; Jacobsen, J.C.; Lehnert, K. Contaminating DNA in Human Saliva Alters the Detection of Variants from Whole Genome Sequencing. *Sci. Rep.* **2020**, *10*, 19255. [CrossRef] [PubMed]
152. Wu, H.-C.; Wang, Q.; Chung, W.K.; Andrulis, I.L.; Daly, M.B.; John, E.M.; Keegan, T.H.; Knight, J.; Bradbury, A.R.; Kappil, M.A.; et al. Correlation of DNA Methylation Levels in Blood and Saliva DNA in Young Girls of the LEGACY Girls Study. *Epigenetics* **2014**, *9*, 929–933. [CrossRef]
153. Langie, S.A.S.; Szarc vel Szic, K.; Declerck, K.; Traen, S.; Koppen, G.; Van Camp, G.; Schoeters, G.; Vanden Berghe, W.; De Boever, P. Whole-Genome Saliva and Blood DNA Methylation Profiling in Individuals with a Respiratory Allergy. *PLoS ONE* **2016**, *11*, e0151109. [CrossRef]
154. Murata, Y.; Fujii, A.; Kanata, S.; Fujikawa, S.; Ikegame, T.; Nakachi, Y.; Zhao, Z.; Jinde, S.; Kasai, K.; Bundo, M.; et al. Evaluation of the Usefulness of Saliva for DNA Methylation Analysis in Cohort Studies. *Neuropsychopharmacol. Rep.* **2019**, *39*, 301–305. [CrossRef] [PubMed]
155. Braun, P.R.; Han, S.; Hing, B.; Nagahama, Y.; Gaul, L.N.; Heinzman, J.T.; Grossbach, A.J.; Close, L.; Dlouhy, B.J.; Howard, M.A.; et al. Genome-Wide DNA Methylation Comparison between Live Human Brain and Peripheral Tissues within Individuals. *Transl. Psychiatry* **2019**, *9*, 47. [CrossRef]
156. Van Dongen, J.; Ehli, E.A.; Jansen, R.; van Beijsterveldt, C.E.M.; Willemsen, G.; Hottenga, J.J.; Kallsen, N.A.; Peyton, S.A.; Breeze, C.E.; Kluft, C.; et al. Genome-Wide Analysis of DNA Methylation in Buccal Cells: A Study of Monozygotic Twins and MQTLs. *Epigenetics Chromatin* **2018**, *11*, 54. [CrossRef] [PubMed]
157. McGregor, K.; Bernatsky, S.; Colmegna, I.; Hudson, M.; Pastinen, T.; Labbe, A.; Greenwood, C.M.T. An Evaluation of Methods Correcting for Cell-Type Heterogeneity in DNA Methylation Studies. *Genome Biol.* **2016**, *17*, 84. [CrossRef]
158. Narváez, D.M.; Groot, H.; Diaz, S.M.; Palma, R.M.; Muñoz, N.; Cros, M.-P.; Hernández-Vargas, H. Oxidative Stress and Repetitive Element Methylation Changes in Artisanal Gold Miners Occupationally Exposed to Mercury. *Heliyon* **2017**, *3*, e00400. [CrossRef] [PubMed]
159. Olsson, A.C.; Fevotte, J.; Fletcher, T.; Cassidy, A.; 't Mannetje, A.; Zaridze, D.; Szeszenia-Dabrowska, N.; Rudnai, P.; Lissowska, J.; Fabianova, E.; et al. Occupational Exposure to Polycyclic Aromatic Hydrocarbons and Lung Cancer Risk: A Multicenter Study in Europe. *Occup. Environ. Med.* **2010**, *67*, 98–103. [CrossRef]
160. Patel, A.B.; Shaikh, S.; Jain, K.R.; Desai, C.; Madamwar, D. Polycyclic Aromatic Hydrocarbons: Sources, Toxicity, and Remediation Approaches. *Front. Microbiol.* **2020**, *11*, 562813. [CrossRef]
161. Liu, Y.; Li, X.; Zhang, B.; Fu, Y.; Yang, A.; Zhang, H.; Zhang, H.; Niu, Y.; Nie, J.; Yang, J. CYP1A1 Methylation Mediates the Effect of Smoking and Occupational Polycyclic Aromatic Hydrocarbons Co-Exposure on Oxidative DNA Damage among Chinese Coke-Oven Workers. *Environ. Health* **2019**, *18*, 69. [CrossRef]

162. Khansakorn, N.; Wongwit, W.; Tharnpoophasiam, P.; Hengprasith, B.; Suwannathon, L.; Chanprasertyothin, S.; Sura, T.; Kaojarern, S.; Sritara, P.; Sirivarasai, J. Genetic Variations of Glutathione S-Transferase Influence on Blood Cadmium Concentration. *J. Toxicol.* **2012**, *2012*, 1–6. [CrossRef]
163. Chen, H.-I.; Chiu, Y.-W.; Hsu, Y.K.; Li, W.-F.; Chen, Y.-C.; Chuang, H.-Y. The Association of Metallothionein-4 Gene Polymorphism and Renal Function in Long-Term Lead-Exposed Workers. *Biol. Trace Elem. Res.* **2010**, *137*, 55–62. [CrossRef]
164. Nariya, A.; Pathan, A.; Shah, N.; Patel, A.; Chettiar, S.; Vyas, J.; Shaikh, I.; Jhala, D. Association of Delta-Aminolevulinic Acid Dehydratase Polymorphism with Blood Lead and Hemoglobin Level in Lead Exposed Workers. *Annu. Res. Rev. Biol.* **2017**, *17*, 1–7. [CrossRef]
165. Yang, Y.; Wu, J.; Sun, P. Effects of Delta-Aminolevulinic Acid Dehydratase Polymorphisms on Susceptibility to Lead in Han Subjects from Southwestern China. *Int. J. Environ. Res. Public. Health* **2012**, *9*, 2326–2338. [CrossRef] [PubMed]
166. Miniero, R.; Beccaloni, E.; Carere, M.; Ubaldi, A.; Mancini, L.; Marchegiani, S.; Cicero, M.R.; Scenati, R.; Lucchetti, D.; Ziemacki, G.; et al. Mercury (Hg) and Methyl Mercury (MeHg) Concentrations in Fish from the Coastal Lagoon of Orbetello, Central Italy. *Mar. Pollut. Bull.* **2013**, *76*, 365–369. [CrossRef]
167. Storelli, M.M.; Giacominelli-Stuffler, R.; Storelli, A.; D'Addabbo, R.; Palermo, C.; Marcotrigiano, G.O. Survey of Total Mercury and Methylmercury Levels in Edible Fish from the Adriatic Sea. *Food Addit. Contam.* **2003**, *20*, 1114–1119. [CrossRef]
168. Saavedra, Y.; González, A.; Fernández, P.; Blanco, J. The Effect of Size on Trace Metal Levels in Raft Cultivated Mussels (Mytilus Galloprovincialis). *Sci. Total Environ.* **2004**, *318*, 115–124. [CrossRef]
169. Puel, D.; Zsürger, N.; Breittmayer, J.P.H. Statistical Assessment of a Sampling Pattern for Evaluation of Changes in Mercury and Zinc Concentrations InPatella Coerulea. *Bull. Environ. Contam. Toxicol.* **1987**, *38*, 700–706. [CrossRef] [PubMed]
170. Vives, I.; Grimalt, J.; Fernandez, P.; Rosseland, B. Polycyclic Aromatic Hydrocarbons in Fish from Remote and High Mountain Lakes in Europe and Greenland. *Sci. Total Environ.* **2004**, *324*, 67–77. [CrossRef] [PubMed]
171. Perugini, M.; Visciano, P.; Giammarino, A.; Manera, M.; Di Nardo, W.; Amorena, M. Polycyclic Aromatic Hydrocarbons in Marine Organisms from the Adriatic Sea, Italy. *Chemosphere* **2007**, *66*, 1904–1910. [CrossRef] [PubMed]
172. Storelli, M.M.; Barone, G.; Perrone, V.G.; Storelli, A. Risk Characterization for Polycyclic Aromatic Hydrocarbons and Toxic Metals Associated with Fish Consumption. *J. Food Compos. Anal.* **2013**, *31*, 115–119. [CrossRef]
173. Rahmanpour, S.; Farzaneh Ghorghani, N.; Lotfi Ashtiyani, S.M. Polycyclic Aromatic Hydrocarbon (PAH) in Four Fish Species from Different Trophic Levels in the Persian Gulf. *Environ. Monit. Assess.* **2014**, *186*, 7047–7053. [CrossRef] [PubMed]
174. Vuorinen, P.J.; Keinänen, M.; Vuontisjärvi, H.; Baršienė, J.; Broeg, K.; Förlin, L.; Gercken, J.; Kopecka, J.; Köhler, A.; Parkkonen, J.; et al. Use of Biliary PAH Metabolites as a Biomarker of Pollution in Fish from the Baltic Sea. *Mar. Pollut. Bull.* **2006**, *53*, 479–487. [CrossRef] [PubMed]
175. Piccardo, M.T.; Coradeghini, R.; Valerio, F. Polycyclic Aromatic Hydrocarbon Pollution in Native and Caged Mussels. *Mar. Pollut. Bull.* **2001**, *42*, 951–956. [CrossRef]
176. Perugini, M.; Visciano, P.; Manera, M.; Turno, G.; Lucisano, A.; Amorena, M. Polycyclic Aromatic Hydrocarbons in Marine Organisms from the Gulf of Naples, Tyrrhenian Sea. *J. Agric. Food Chem.* **2007**, *55*, 2049–2054. [CrossRef]
177. Guerranti, C.; Grazioli, E.; Focardi, S.; Renzi, M.; Perra, G. Levels of Chemicals in Two Fish Species from Four Italian Fishing Areas. *Mar. Pollut. Bull.* **2016**, *111*, 449–452. [CrossRef] [PubMed]
178. Bajc, Z.; Kirbiš, A. Trace Element Concentrations in Mussels (Mytilus Galloprovincialis) from the Gulf of Trieste, Slovenia. *J. Food Prot.* **2019**, *82*, 429–434. [CrossRef] [PubMed]
179. Noisel, N.; Bouchard, M.; Carrier, G.; Plante, M. Comparison of a Toxicokinetic and a Questionnaire-Based Approach to Assess Methylmercury Intake in Exposed Individuals. *J. Expo. Sci. Environ. Epidemiol.* **2011**, *21*, 328–335. [CrossRef]
180. Branco, V.; Caito, S.; Farina, M.; Teixeira da Rocha, J.; Aschner, M.; Carvalho, C. Biomarkers of Mercury Toxicity: Past, Present, and Future Trends. *J. Toxicol. Environ. Health Part B* **2017**, *20*, 119–154. [CrossRef] [PubMed]
181. Kusanagi, E.; Takamura, H.; Chen, S.-J.; Adachi, M.; Hoshi, N. Children's Hair Mercury Concentrations and Seafood Consumption in Five Regions of Japan. *Arch. Environ. Contam. Toxicol.* **2018**, *74*, 259–272. [CrossRef]
182. Suzuki, K.; Yoshinaga, J. Inhalation and Dietary Exposure to Polycyclic Aromatic Hydrocarbons and Urinary 1-Hydroxypyrene in Non-Smoking University Students. *Int. Arch. Occup. Environ. Health* **2007**, *81*, 115–121. [CrossRef]
183. Domingo, J.L.; Nadal, M. Human Dietary Exposure to Polycyclic Aromatic Hydrocarbons: A Review of the Scientific Literature. *Food Chem. Toxicol.* **2015**, *86*, 144–153. [CrossRef]
184. Doddamani, A.; Ballala, A.B.K.; Madhyastha, S.P.; Kamath, A.; Kulkarni, M.M. A Cross-Sectional Study to Identify the Determinants of Non-Communicable Diseases among Fishermen in Southern India. *BMC Public Health* **2021**, *21*, 414. [CrossRef]
185. Zytoon, M.A. Occupational Injuries and Health Problems in the Egyptian Mediterranean Fisheries. *Saf. Sci.* **2012**, *50*, 113–122. [CrossRef]
186. Doza, S.; Bovbjerg, V.E.; Vaughan, A.; Nahorniak, J.S.; Case, S.; Kincl, L.D. Health-Related Exposures and Conditions among US Fishermen. *J. Agromedicine* **2021**, 1–8. [CrossRef]
187. Wu, Y.; Li, S.; Hu, K.; Yang, J. Evidence of the Moderating Role of Hair Cortisol and Hair Cortisone in the Relationship between Work Stress and Depression Symptoms among Chinese Fishermen. *J. Affect. Disord.* **2021**, *294*, 868–875. [CrossRef] [PubMed]
188. Skuladottir, G.V.; Nilsson, E.K.; Mwinyi, J.; Schiöth, H.B. One-Night Sleep Deprivation Induces Changes in the DNA Methylation and Serum Activity Indices of Stearoyl-CoA Desaturase in Young Healthy Men. *Lipids Health Dis.* **2016**, *15*, 137. [CrossRef]

189. Matosin, N.; Cruceanu, C.; Binder, E.B. Preclinical and Clinical Evidence of DNA Methylation Changes in Response to Trauma and Chronic Stress. *Chronic Stress* **2017**, *1*, 247054701771076. [CrossRef] [PubMed]
190. Mahna, D.; Puri, S.; Sharma, S. DNA Methylation Signatures: Biomarkers of Drug and Alcohol Abuse. *Mutat. Res. Mutat. Res.* **2018**, *777*, 19–28. [CrossRef] [PubMed]
191. Christiansen, C.; Castillo-Fernandez, J.E.; Domingo-Relloso, A.; Zhao, W.; El-Sayed Moustafa, J.S.; Tsai, P.-C.; Maddock, J.; Haack, K.; Cole, S.A.; Kardia, S.L.R.; et al. Novel DNA Methylation Signatures of Tobacco Smoking with Trans-Ethnic Effects. *Clin. Epigenetics* **2021**, *13*, 36. [CrossRef]