Evidence for Prenatal Exposure to Thyroid Disruptors and Adverse Effects on Brain Development

Barbara A. Demeneix

CNRS/UMR7221, Muséum National d'Histoire Naturelle/Université Paris-Sorbonne, Paris, France

Keywords

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Abstract

Thyroid hormone regulates vital processes in early brain development such as neuronal stem cell proliferation, migration, and myelination. The fetal thyroid is not fully functional until mid-pregnancy (18–20 weeks), so placental transfer of maternal thyroid hormones during early pregnancy is crucial, as is the maternal iodine status. The volume of chemical production has increased 300-fold since the 1970s. Thus, chemical exposure is ubiquitous; every child born today has dozens of man-made xenobiotic compounds in its blood. Increasing evidence from both epidemiological and animal or in vitro studies demonstrates that many of these chemicals have the potential to interfere with thyroid hormone availability and action at different physiological levels. These chemicals are found in numerous consumer products and include certain plastics, pesticides, perfluorinated compounds, and flame retardants. The last decades have seen

exponential increases in neurodevelopmental disease including autism spectrum disorder and attention deficit/hyperactivity disorder. We hypothesize that prenatal exposure to mixtures of thyroid hormone-disrupting chemicals, with iodine deficiency potentially exacerbating the situation, has a strong probability of contributing to this increased incidence of neurodevelopmental disease, but could also entail a surreptitious, but socio-economically consequential, loss of IQ. Thyroid hormone receptor actions can modulate gene transcription, most often through epigenetic mechanisms. Thus, interference with epigenetic regulations is increasingly thought to link neurodevelopmental disease and IQ loss to thyroid hormone disruption.

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Introduction

Gabriella Morreale de Escobar was one of the earliest researchers to formulate the concept that low levels of maternal thyroid hormone (TH) during early pregnancy could have adverse effects on the child's brain development [1]. Since her prescient observations many other

authors have provided solid epidemiological data to support the concept. Both low and high maternal TH levels during this period have been associated with autism spectrum disorder (ASD), attention deficit/hyperactivity disorder (ADHD), and lower IQ and grey matter volume [see 2 and references therein, as well as 3]. Similarly, experimental data from rodent and other vertebrate models have bolstered the notion that maternal TH is vital for early vertebrate brain development. In egg-laying vertebrates, maternal TH is provided in the egg yolk, as in teleosts, frogs, and birds. The idea that TH plays cell- and temporally specific roles during the precocious stages of neurogenesis is increasingly documented. Further, observational studies demonstrate that in humans even mild maternal iodine deficiency can be associated with impaired child brain development and IQ loss [4].

Iodine is a major component of THs and pivotal for TH synthesis. In line with this, iodine deficiency in pregnancy is associated with an increased ADHD risk and IQ loss in the offspring [5, 6]. In these studies, large cohorts were analysed. For ADHD risk the respective study examined over 77,164 mother-child pairs [5], whilst for the IQ loss study [6] 1,040 mothers were studied along with outcomes in their children at 8 years of age. For ASD the data are sparser, and no full studies have yet appeared, as large samples are required to take into account the lower incidence of the disorder. However, the risk of maternal hypothyroidism and ASD is well demonstrated in animal models [3, 7], or associations are suggested by epidemiology [see 3]. However, whether this could be linked to iodine deficiency has not been investigated yet in large cohorts.

Simultaneous with our awareness of the importance of maternal TH and iodine provision for brain development, there has been a continuous acceleration in chemical production. The increase began before the 1940s but has developed exponentially since the 1970s, with production in both developed and emerging countries growing over 300-fold [8]. The growth in production has been accompanied by intense diversification of manufactured and marketed compounds. Needless to say, this fact has led to continuous and ubiquitous environmental and human exposure. Many of these chemicals are thought, or have been demonstrated, to act as endocrine-disrupting chemicals (EDCs). EDCs have a number of features that make their regulation particularly difficult. First, they can often display non-monotonic dose-response curves, with low-dose responses making threshold determination exceedingly difficult. Second, their presence during vulnerable periods of development can induce effects that are

not seen immediately but are only evident at later life stages. This notion has been formalized as underlying the DOHaD (Developmental Origins of Health and Disease) hypothesis [9]. Third, multiple EDCs present in the environment negatively affect not only the biodiversity equilibrium but also human health. The thorny question of EDC mixture regulation is one that many global authorities are currently attempting to resolve [10]. What is more disquieting is that many chemicals, notably those that are halogenated, either resemble TH or have the capacity to interfere with TH production or action at different physiological levels [11, 12].

Given both the importance of maternal iodine and TH levels for early brain development and the documented expansion and diversification of chemical production, it is biologically plausible to connect these ideas with the massive increase in neurodevelopmental disease and the observed decreases in IQ in exposed populations [13, 14].

A number of authors [13, 15, 16] have suggested that the increases in neurocognitive and behavioural disabilities, including ASDs and ADHDs, could implicate environmental factors often acting through epigenetic mechanisms (see next section). Moreover, the link to TH-disrupting chemical exposure is best established for pre- and early postnatal exposure, when epigenetic effects on developmental processes are determinant. Similar arguments have been advanced for many non-communicable, or non-infectious, diseases such as obesity and metabolic disorders (including type 2 diabetes), precocious puberty, infertility, and reproductive cancers, amongst others. Most often, early-life exposure to xenobiotics is linked to the DOHaD hypothesis [9, 17], which, in turn, is often linked to endocrine disruption [9, 18, 19]. Another point is that those studies that investigated the effects of T₄ supplementation in women with subclinical hypothyroidism or hypothyroxinaemia on the offspring's IQ [see, for instance, 20] did not take into account prenatal EDC exposure and its potential effect on children's cognition.

Epigenetic Regulation as a Potential Mechanism Underlying TH Disruption by EDCs

TH receptors (TRs), by definition, act through epigenetic mechanisms. Epigenetics is most often defined as modification of gene activity subsequent to changes in chromatin structure or DNA methylation. Other definitions consider epigenetic changes as dependent on inheritance, through cellular division, but both definitions group the concept of alternative states of chromatin with-

Fig. 1. Numerous chemicals are documented to affect thyroid hormone production, distribution, and tissue availability. Schematic representation of the different levels through which endocrine-disrupting chemicals have been shown to interfere with thyroid hormone availability. The multiplicity of potential actions means that a series of different in vitro assays and screening methods will be required for each level. This problem is even more acute in the context of the effects of thyroid hormone on different mechanisms

and specific processes and areas during brain development. Note that each structure (cell and brain) is not drawn to scale. NIS, sodium-iodide symporter; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; T₃, triiodothyronine (the most active form of thyroid hormone); T₄, thyroxine (a less active form of thyroid hormone); TH, thyroid hormone; TBT, tributyltin; TPO, thyroid peroxidase; TR, thyroid hormone receptor; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

out any underlying change in the actual DNA sequence [21]. The effects of TH disruptors on brain development are increasingly thought to be related to their capacity to interfere at different levels with intracellular TH availability and, hence, to deregulate transcription and TH-induced epigenetic effects on target genes [9]. Interference with TH production and availability can occur at multiple levels (Fig. 1): blocking iodine uptake; inhibition of TH production; displacing T₄ and T₃ from TH-distributing proteins; activating hepatic metabolism and reducing circulating levels of TH; interference with transmembrane cellular transporters (MCT8 and OATP1C1); modification of deiodinase enzyme activities; and, less commonly, directly acting at the level of the TR ligand-binding pocket or domain (LBD) [12].

The volume of the hydrophobic ligand-binding pocket (LBD) of the TR is around 600 Å³, which is essentially

the same as the volume of the ligand (T₃), i.e., 530 Å³. This feature can partially explain the difficulty encountered (and most often the failure) to synthesize selective agonists and antagonists that can interact with the TR LBD. This characteristic also explains why there are no widely used cell-based TR screening methods for TH disruption, whereas a plethora of cellular methods exist for the androgen receptor, oestrogen receptors, peroxisome proliferator-activated receptors, and other nuclear receptors. The lack of plasticity of the TR LBD contrasts with that of the pregnane X receptor (PXR), where at least two EDCs (*trans*-nonachlor and 17α-ethinylestradiol) cannot only bind, but synergistically activate, PXR [22].

At whatever level the disruption occurs, it can result in modification of the amount of T₃ available to interact with intracellular TRs, and thereby to modulate transcriptional activity and induction of epigenetic regula-

tions. Epigenetic regulation is the basis of a continual interplay between cellular plasticity at the gene regulation level and transgenerational, epigenetic heredity. Although many cellular factors are implicated (including polycomb proteins, non-coding RNAs, microRNAs, and the 3D chromatin architecture itself), succinctly, the two major mechanisms underlying epigenetic regulations are heterochromatin (histone) modifications and DNA methylation. Chromatin, of which the main component is histone proteins, can be modulated according to the methylation, acetylation, and phosphorylation status of the individual histone molecules [23]. The second epigenetic component is DNA methylation (most often involving cytosine methylation, i.e., the presence of 5-methylcytosine), which can affect gene function by suppressing or activating transcription [24].

As for many other nuclear receptors, where transcriptional states are modulated according to binding of their cognate ligands, epigenetic mechanisms will be central to their actions. Transcriptional controls and DNA methylation are highly dynamic and integrate signals from the environment, thereby affecting multiple gene clusters. These processes thus represent a central mechanism for coordinating environmental effects on transcription and, more importantly, developmental transitions such as amphibian metamorphosis and its equivalent in mammals: birth. In the case of TH, a number of genes that control histone modifications and DNA methylation and/or demethylation are regulated by the presence or absence of liganded TRs. It is interesting to note that for TRs it is not simply a case of an unliganded TR inducing transcriptional repression and a liganded TR activation, but that many physiological situations have been described where the liganded TR induces repression. This is the case with liganded TR β 2 acting on both of the hypothalamic *Trh* and the *Mc4r* mouse genes [25], as well as with liganded TR α 1 acting on the pluripotency gene, *Sox2*, in the subventricular zone of the adult mouse brain [26]. These examples underline the complexity of TH-disrupting chemicals' potential for interference with TR-dependent signalling.

Of the numerous TH-related genes implicated in epigenetic modifications, two are of particular interest: (1) deiodinase 3 (*DIO3* encoding D3) [27] and (2) the de novo DNA methyltransferase *DNMT3A* (encoding DNMT3A) [28]. In placental mammals, D3 is an imprinted gene. It inactivates T₄ and T₃, respectively, producing rT₃ and metabolites such as 3,3'-T₂. In the mouse and other mammals, *Dnmt3a* is a TH-induced gene, implicated not only in brain development but also in that of

other tissues, including those involved in metabolic control, such as the hypothalamus and the liver. Gene targets that are subject to the TH-induced DNA methylation status include *Bdnf*, *Reln* (encoding Reelin), and the TRs themselves. Correct expression of *Bdnf* and *Reln* is crucial to neuronal migration and brain development. Hypothyroxinaemia leads to hypermethylation of hippocampal *Bdnf* exon IV and impaired learning [29]. *Bdnf* expression has been demonstrated to be affected by multiple EDCs, i.e., those affecting TH signalling, such as flame retardants [see for instance 30].

Therefore, changes in TH availability – and hence DNA methylation rates – during organogenesis and developmental transitions can increase the risks not only of a decreased IQ and neurodevelopmental disease, but also of cardiovascular and metabolic diseases or cancer. Each of these diseases involves different TH-dependent gene sets.

Evidence for the Main Chemical Classes That Interfere with TH Production, Availability, and Action Present in Pregnant Women

Multiple data sets from both epidemiological and experimental settings have demonstrated that early pregnancy is the most vulnerable period for exposure either to xenobiotic chemicals or to iodine lack [13]. One of our main current hypotheses is that iodine lack can exacerbate the effects of TH disruption. This concept is being investigated in collaboration with the groups working on the Generation R and the SELMA cohorts (see, for instance, Levie et al. [31] and Derakhshan et al. [32]).

We have recently reviewed the main classes of TH-disrupting chemicals, which include perchlorate, plastics, pesticides, perfluorinated compounds, and flame retardants [see 12 and references therein]; hence, only the main classes of chemicals known to be present in most pregnant women will be described briefly here. It is important to note that few chemicals in each class have been fully tested for their endocrine-disrupting activity. However, as certain chemicals are researched at greater depth and shown to act as EDCs, they may be replaced with chemicals having similar structures and often similar, adverse effects. Replacing EDCs with other chemicals that can exert equally harmful effects is known as “regrettable substitution.” For instance, bisphenol A (BPA; see below) has in many products been replaced by bisphenol S or F, which can have similar or worse endocrine-disrupting properties, including on TH levels [32]. Another consid-

eration is that although many substances were banned decades ago, they remain environmentally relevant due to their previously high production volumes and exceptionally long half-lives, which means that they can still be present as mixture components, including in physiologically relevant fluids such as human amniotic fluid [33].

The need for iodine to make TH has been known for over 100 years. It was by exploiting the iodine content of thyroxine that Kendall first isolated the substance on Christmas Day, 1915. Unsurprisingly, exposure to different voluminous anions that inhibit the sodium-iodide symporter at the level of the thyroid gland can result in reduced TH production. Perchlorate, nitrate, and thiocyanate anions inhibit sodium-iodide symporter transport, with perchlorate being 20 times more potent than thiocyanate and over 500-fold more potent than nitrate. Perchlorate is found in amniotic fluid at 10^{-8} M [33]. Both perchlorate and thiocyanate are of particular concern, as they are found in drinking water and in cigarette smoke, respectively. Prenatal exposure to smoking, whether active or passive, has been shown to alter maternal TH levels and thyroid gland development [34].

The second well-known category of TH disruptors includes many current – as well as legacy – pesticides and biocides. Legacy pesticides are those that were banned years ago, such as DDT (dichlorodiphenyltrichloroethane), but because of their long half-lives (for DDT, over 150 years in water and 15 years in soil) are still present in human fluids, including amniotic fluid [33]. In 2013 (though regularly updated and opened for comments in early 2019), the European Food Safety Authority (EFSA) examined 287 pesticides, most of which are still currently on the market [35]. They reported that 101 of them had features that indicated that they could negatively affect TH signalling, and 68 others displayed neurotoxic effects. Thus, 60% of the pesticides examined could interfere with brain development, most often by interfering with TH production or hepatic metabolism. Certain pesticides and fungicides are known to inhibit thyroid peroxidase (TPO) activity and, hence, TH levels. Certain of the TPO-inhibiting pesticides have recently been banned (e.g., maneb), whilst others are still on the market (mancozeb and metiram). The latter group includes carbamate fungicides, for which the common metabolite is methylthiouracil, a TPO inhibitor. Epidemiological data regarding exposure and potential effects on TH metabolism are largely lacking for these fungicides.

Another major class of pesticides with TH-disrupting capacities is the organophosphate group, with its most notorious member, chlorpyrifos (CPF), and the related

CPF-methyl. These widely used insecticides target acetylcholinesterase. Multiple epidemiological studies have demonstrated that high levels of prenatal CPF exposure reduce brain cortical thickness and lead to deficits in working memory and IQ loss. A recent analysis of the data submitted for evaluation to regulatory authorities showed misleading representations of the statistical analysis of rat brain data [36]. Although to the author's knowledge the presence of CPF metabolites has not yet been demonstrated in human amniotic fluid (though its presence in other human fluids, including that of pregnant women, is well documented), much experimental work on fish and rodents has underlined the TH-disrupting capacity of CPF, providing a highly plausible link to the observations of IQ loss in children.

For the more recently introduced pesticides such as pyrethroids, phenylpyrazoles, or neonicotinoids, a number of experimental studies, both in vivo and in vitro, have shown all groups to affect TH signalling. However, epidemiological studies have as yet failed to show any effects on TH function in humans. This could be due to their shorter half-lives and weaker tendencies for bioaccumulation, which in turn could make biomonitoring of their metabolites difficult. These features do not mean that the parent compounds or their metabolites would not be found in maternal fluids, nor that they are without effect on TH metabolism or action. This point is especially valid in light of potential mixture effects (see below).

Turning to a biocide, triclosan (2,4,4'-trichloro-2'-hydroxydiphenyl ether [TCS]) is a well-documented TH disruptor, which is found in amniotic fluid at concentrations in the order of 10^{-7} M, depending on the population studied [33]. TCS is a widely used chlorinated phenol antimicrobial and antifungal, first introduced in the 1970s. TCS can be found in close to 98% of pregnant women's urine samples in Europe [14]. Its usage in soaps and shampoos was banned in the USA in 2016 (primarily for lack of any demonstrated antimicrobial effect), as well as in the EU for use in any material that might involve contact with food. For cosmetic preparations in the EU, there are concentration limits applied according to the product.

TCS has a short half-life, 11 h following oral ingestion. As it is rapidly metabolized and excreted in urine, exposure must be constant for it to be found so regularly at such high levels in biomonitoring surveys. Both epidemiological and animal experimentation studies have demonstrated the TH-disrupting properties of TCS. In rodent studies, TCS exposure decreases body weight as well as circulating levels of T_3 and T_4 . In the SELMA study

we have found TCS levels in urine samples taken during early pregnancy to be associated – together with eight other chemicals – with reduced birth weight [37]. Other endocrine pathways affected by TCS exposure include effects through receptors of the principal reproductive hormones, oestrogen and androgen (oestrogen receptors and androgen receptors). Activation of liver metabolism has been reported for TCS. Increased hepatic metabolism has been demonstrated to decrease circulating TH in many models. As TCS is very persistent in the environment, it has a tendency to accumulate in sludge and sediments.

Many phenol derivatives besides TCS, notably BPA (4,4'-isopropylidenediphenol), exert multiple effects on TH signalling. Exposure to BPA is widespread [14]; hence, it can be found in amniotic fluid [33]. Its most-documented effects are through the oestrogen receptor, but TH disruption is increasingly documented. Many epidemiological studies have found significant associations, both positive and negative, with BPA levels and TH levels in different populations. One explanation for the differing results might be that some variation might have occurred due to sampling times and exposure to other compounds. If we examine the TH-dependent brain and neurodevelopmental effects of BPA, the data are somewhat more consistent. For instance, prenatal exposure to BPA is significantly related to internalizing behaviour and to ADHD risk [for references, see 12, 14]. Furthermore, the SELMA data revealed that BPA levels in early pregnancy were associated with language delay [37].

Other plasticizers include the vast number of phthalates on the market. Phthalates are used as softeners and plasticizers in a spectrum of commercial products from building materials and furniture to medical equipment, cosmetics, and food packaging. Besides disrupting TH at different levels, phthalates as a group are known for their antiandrogenic properties. One of the most-studied phthalate is DEHP (di[2-ethylhexyl] phthalate). Again, depending on the cohort, DEHP is found at concentrations between 10^{-7} and 10^{-6} M in amniotic fluid, along with another common phthalate: DBP (dibutyl phthalate) [14, 33; see also references in 14 for details on currently banned phthalates in Europe].

The number of perfluorinated compounds manufactured today has reached over 4,000 chemicals [14]. Needless to say, certain of these chemicals – perfluorooctanoic acid (PFOA, or C8 as it is commonly referred to) and perfluorooctanesulphonic acid (PFOS) – are each found in amniotic fluid at concentrations of 10^{-8} M, where they exert demonstrable anti-TH effects [33]. To this one can add the numerous brominated, as well as the more re-

cently introduced organophosphate, flame retardants. Many of them have been identified as TH disruptors. This is notably the case for the different polybrominated diphenyl ethers (PBDEs) and the halogenated BPAs, such as tetrabromobisphenol A (TBBPA). Concentrations of different PBDEs in amniotic fluid were reported to be in the order of 10^{-9} M [33].

The many other molecules found in human amniotic fluid include the legacy compounds polychlorinated biphenyl (PCB), with its notorious TH-disrupting effects, especially marked during early pregnancy; 2-naphthol; the UV filter benzophenone-3; and the heavy metals lead and mercury. Mercury, besides being a well-known neurotoxicant, is of course a TH disruptor, interfering with selenium metabolism [13, 14]. The above list of compounds documented as TH disruptors that were found in amniotic fluid is by no means exhaustive. However, more studies are needed to fully monitor the situation, taking into account that amniotic fluid samples are difficult to obtain and measurements are costly.

Other common groups of molecules with the capacity to interfere with TH availability include the parabens and phenol-based flavonoid TH disruptors. The latter category includes the naturally occurring flavonoids found in food, such as those present in soy product: genistein and daidzein. Genistein inhibits both iodine uptake and TPO activity. Two other naturally occurring phenols are silychristin and silybinin, which inhibit T_3 and T_4 entry into cells through the mct8 transporter [12, and references therein]. Another common pollutant to which many populations, especially city dwellers, are exposed is atmospheric particulate matter (PM), especially particles <2.5 and <10 μm in diameter (PM_{2.5} and PM₁₀, respectively). Positive associations have been found between 3rd-trimester PM levels, decreased fetal TH levels, and reduced birth weight [38]. It was postulated that such effects could affect fetal brain development.

The Reality of Exposure to Complex Mixtures

As mentioned in the Introduction, the problem of multiple exposure to EDCs is a major preoccupation [10, 14], not only in terms of regulatory decision-making, but also in terms of scientific understanding of the mechanisms implicated. Exposure to numerous chemicals by different routes is a reality; it can include air-borne exposure, dietary sources including water, and skin contact. Thus, combined exposure or an “exposure cocktail” refers to exposure to multiple chemicals by multiple routes,

Fig. 2. Addition or synergy arising from mixture of endocrine-disrupting chemicals (adapted from Demeneix and Slama [14]). **a** Schematic representation of an additive versus a synergistic response. Note that besides addition or synergy, antagonism can also be found, but this is not included in the figure. **b** Representation of an additive mixture effect where each single molecule present in a mixture has no effect by itself, but in the presence of other molecules acting on the same pathways, the mixture can induce significant effects.

or from one primary source and/or use(s). Usually, mixtures of commercial products are classed as “intentional mixtures.” These formulations will include a list of not only the active substances but also the different factors that enhance the penetration or efficiency of the active substance: adjuvants, stabilizers, and excipients. Examples include pesticide or biocide formulations, or personal products (cosmetics).

Different physiological situations can underlie disease mechanisms following exposure to mixtures. Firstly, exposure to mixtures can act additively or synergistically at the time of exposure. Alternatively, there can be an “exposure memory” that is registered by the body, even if the exposure is transient (e.g., if the compound has a short half-life) and the substances are excreted. Clearly, such actions may implicate epigenetic regulations. Such mechanisms could account for the delayed incidence of disease following early exposures (as opposed to occurring simultaneously). An example of this situation is girls exposed in utero to DDT having a higher risk of breast cancer 50 years later [39]. Another possibility is that diseases such as cancer could arise from a multi-hit or multi-step process involving genetic and epigenetic insults, whatever the source of the initiating event.

As represented in Figure 2, if an organism is exposed to a mixture, a number of possibilities exist. In the case of an additive effect, each chemical is present at a dose that would not have a detectable effect if applied alone, but the mixture exerts an effect equivalent to the sum of the responses induced by each chemical by itself at the dose at which it is present in the mixture. This situation has been reported for TH disruption [33], as well as for antiandro-

genic and oestrogenic effects. An example of certain EDCs interfering with different axes is that of the PBDEs [30], which not only impact the thyroid axis but also affect oestrogen receptor signalling and other hormonal endpoints. Synergistic effects have not yet been reported at the actual level of TRs, but they are not impossible for effects on TH availability. In contrast, such situations have been well documented for PXR [22].

The Cost of IQ Loss and Increases in Neurodevelopmental Disease

In 2015, a group of scientists and clinicians led by Leonard Trasande carried out a study on the socio-economic costs of EDCs. The methodology chosen was derived from that used by the Intergovernmental Panel on Climate Change (IPCC) [40]. It applied the classic “attributable fraction” approach, which utilizes measures of exposure for each compound studied, followed by an estimation of the dose-response function(s) for the disease or condition outcome affected. The biological plausibility of connections was then detailed, most often with evidence from experimental studies on rodents. As the dose-response functions from each epidemiological study were adjusted for confounders, this approach introduces less bias than other methods, notably integrating other disease causes and genetic factors. Overall, the average costs were EUR 163 billion (above EUR 22 billion with a 95% probability and above EUR 196 billion with a 25% probability). This represents approximately 1.25% of the annual gross domestic product of the EU. As cited, in the

Fig. 3. Effect of a theoretical 5-point decrease in IQ on the numbers of gifted or intellectually challenged persons in a given population. The graph shows the distribution of IQs within two populations of 100 million people, one with a mean IQ of 100 and another, equivalent population with a mean IQ of 95. As noted with the 5-point IQ loss, the number of gifted persons decreases, whilst the number of those with intellectual disability increases substantially.

paper, the estimates provided were only for those EDCs with the highest probability of causation. A wider analysis would have produced even higher cost estimates.

The greatest part of the costs was related to neurodevelopmental disease and IQ loss, reaching EUR 157 billion per annum. For the specific issue of IQ loss or neurodevelopmental disease, we examined longitudinal cohort data delineating prenatal exposure and incidence. Unfortunately, we had to limit our study to three EDCs as there were insufficient data sets for other common EDCs. The EDCs for which data sets on prenatal exposure levels and disease incidence or IQ were available were the organophosphate pesticide CPF, the brominated flame retardant PBDE, and phthalates [41]. With respect to all EDCs for which longitudinal data were available, exposure to just organophosphate pesticides and PBDE alone accounted for most of the enormous costs of IQ loss and increased risk of neurodevelopmental disease.

The finding that over 90% of the annual cost of EDC exposure in the EU is due to IQ loss and neurodevelopmental disease is largely explained by two facts. First, the symptoms of neurodevelopmental disease are detected earlier than those of other non-communicable diseases such as cancers of the reproductive system or infertility. For instance, language delay, which can often be associated with ASD, can be assessed at 18 or 24 months, and complete IQ tests can be run as early as 3 years of age [37]. In contrast, infertility monitoring will require longer-

term studies, as will the assessment of reproductive cancers. As mentioned earlier, intrauterine DDT exposure is associated with a 4-fold increase in breast cancer risk. However, the data were not available until 50 years after exposure [39]. Second, the cost of IQ loss or neurodevelopmental disease will have lifelong effects. For instance, treating severe ASD with intellectual deficiency can cost upwards of EUR 80,000 per year during the whole lifespan, whereas the cost of treating, say, reproductive cancer is far lower.

Adequate neurocognitive function in children is an important determinant of learning abilities, educational attainment, quality of life, and adult health. Not surprisingly, even though at the individual level the loss of a few IQ points may not be noticeable, across a population it is highly significant (Fig. 3), and this incurs enormous costs. In 2001, Muir and Zegarac [42] estimated that a 5-point IQ loss incurred an annual cost of USD 275–326 billion per year in the USA alone.

Conclusion

Neurocognitive and behavioural disabilities, including ASD, ADHD, and learning disabilities, are increasingly common. To this one can add documented decreases in IQ in certain populations as a function of chemical exposure or iodine deficiency. Early pregnancy is an acutely

sensitive period, in which organogenesis and key processes of brain development take place. Thus, even though 50 years of postnatal thyroxine therapy has eliminated the scourge of cretinism, we have to be concerned about pre- and postnatal exposure to TH-disrupting chemicals. A suboptimal fetal environment during this period can lead to irreversible damage and failure to reach one's full cognitive potential and brain functioning during childhood and adolescence. Multiple data sets show that prenatal exposure to the cocktail of TH disruptors found at significant concentrations in pregnant women can modify TH signalling. There are some possible caveats regarding the overall hypothesis presented herein – for instance, the fact that many epidemiological studies only examine one time point and that certain experimental studies do not consider all environmentally relevant doses. However, all the epidemiological studies presented *do* take into account the numerous confounding factors (maternal/paternal age, smoking, socio-economic status, etc.). Thus, taken together, the data presented here allow one to propose that TH disruption in utero may contribute to an increased risk of neurodevelopmental disease, learning difficulties, and IQ loss.

References

- Morreale de Escobar G, Escobar del Rey F. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med*. 1999 Dec; 341(26):2015–6; author reply 2017.
- Korevaar TI, Muetzel R, Medici M, Chaker L, Jaddoe VW, de Rijke YB, et al. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. *Lancet Diabetes Endocrinol*. 2016 Jan;4(1):35–43.
- Levie D, Korevaar TI, Bath SC, Dalmau-Bueno A, Murcia M, Espada M, et al. Thyroid Function in Early Pregnancy, Child IQ, and Autistic Traits: A Meta-Analysis of Individual Participant Data. *J Clin Endocrinol Metab*. 2018 Aug;103(8):2967–79.
- Levie D, Korevaar TI, Bath SC, Murcia M, Dineva M, Llop S, et al. Association of Maternal Iodine Status with Child IQ: A Meta-Analysis of Individual Participant Data. *J Clin Endocrinol Metab*. 2019 Dec;104(12):5957–67.
- Abel MH, Ystrom E, Caspersen IH, Meltzer HM, Aase H, Torheim LE, et al. Maternal Iodine Intake and Offspring Attention-Deficit/Hyperactivity Disorder: Results from a Large Prospective Cohort Study. *Nutrients*. 2017 Nov;9(11):E1239.
- Bath SC, Steer CD, Golding J, Emmett P, Rayman MP. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Lancet*. 2013 Jul;382(9889):331–7.
- Román GC, Ghassabian A, Bongers-Schokking JJ, Jaddoe VW, Hofman A, de Rijke YB, et al. Association of gestational maternal hypothyroxinemia and increased autism risk. *Ann Neurol*. 2013 Nov;74(5):733–42.
- UNEP. Global Chemicals Outlook – Towards Sound Management of Chemicals: Trends and Changes. United Nations Environment Programme Publications; 2012. p. 44.
- Heindel JJ, Balbus J, Birnbaum L, Brune-Drisse MN, Grandjean P, Gray K, et al. Developmental Origins of Health and Disease: Integrating Environmental Influences. *Endocrinology*. 2015 Oct;156(10):3416–21.
- Kortenkamp A, Faust M. Regulate to reduce chemical mixture risk. *Science*. 2018 Jul; 361(6399):224–6.
- Duntas LH, Stathatos N. Toxic chemicals and thyroid function: hard facts and lateral thinking. *Rev Endocr Metab Disord*. 2015 Dec; 16(4):311–8.
- Mughal BB, Fini JB, Demeneix BA. Thyroid-disrupting chemicals and brain development: an update. *Endocr Connect*. 2018 Apr;7(4): R160–86.
- Demeneix B. Losing our minds: how environmental pollution impairs human intelligence and mental health. Oxford Series in Behavioral Neuroendocrinology. Oxford: Oxford University Press; 2014.
- Demeneix B, Slama R. Endocrine Disruptors: From Scientific Evidence to Human Health Protection. European Parliament Reports; 2019.
- Landrigan PJ, Lambertini L, Birnbaum LS. A research strategy to discover the environmental causes of autism and neurodevelopmental disabilities. *Environ Health Perspect*. 2012 Jul;120(7):a258–60.
- Tordjman S, Somogyi E, Coulon N, Kermarrec S, Cohen D, Bronsard G, et al. Gene × Environment interactions in autism spectrum disorders: role of epigenetic mechanisms. *Front Psychiatry*. 2014 Aug;5:53.
- Fukuoka H, Kubota T. One-Carbon Metabolism and Lipid Metabolism in DOHaD. *Adv Exp Med Biol*. 2018;1012:3–9.
- Montrose L, Padmanabhan V, Goodrich JM, Domino SE, Treadwell MC, Meeker JD, et al. Maternal levels of endocrine disrupting chemicals in the first trimester of pregnancy are associated with infant cord blood DNA methylation. *Epigenetics*. 2018;13(3):301–9.

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- 19 Barouki R, Melén E, Herceg Z, Beckers J, Chen J, Karagas M, et al. Epigenetics as a mechanism linking developmental exposures to long-term toxicity. *Environ Int*. 2018 May; 114:77–86.
- 20 Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, Hirtz DG, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network. Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. *N Engl J Med*. 2017 Mar;376(9):815–25.
- 21 Cavalli G, Heard E. Advances in epigenetics link genetics to the environment and disease. *Nature*. 2019 Jul;571(7766):489–99.
- 22 Delfosse V, Dendele B, Huet T, Grimaldi M, Boulahtouf A, Gerbal-Chaloin S, et al. Synergistic activation of human pregnane X receptor by binary cocktails of pharmaceutical and environmental compounds. *Nat Commun*. 2015 Sep;6(1):8089.
- 23 Kato S, Yokoyama A, Fujiki R. Nuclear receptor coregulators merge transcriptional coregulation with epigenetic regulation. *Trends Biochem Sci*. 2011 May;36(5):272–81.
- 24 Luo C, Hajkova P, Ecker JR. Dynamic DNA methylation: in the right place at the right time. *Science*. 2018 Sep;361(6409):1336–40.
- 25 Decherf S, Seugnet I, Koudhi S, Lopez-Juarez A, Clerget-Froidevaux MS, Demeneix BA. Thyroid hormone exerts negative feedback on hypothalamic type 4 melanocortin receptor expression. *Proc Natl Acad Sci USA*. 2010 Mar;107(9):4471–6.
- 26 López-Juárez A, Remaud S, Hassani Z, Jolivet P, Pierre Simons J, Sontag T, et al. Thyroid hormone signaling acts as a neurogenic switch by repressing Sox2 in the adult neural stem cell niche. *Cell Stem Cell*. 2012 May; 10(5):531–43.
- 27 Anselmo J, Scherberg NH, Dumitrescu AM, Refetoff S. Reduced Sensitivity to Thyroid Hormone as a Transgenerational Epigenetic Marker Transmitted along the Human Male Line. *Thyroid*. 2019 Jun;29(6):778–82.
- 28 Kyono Y, Subramani A, Ramadoss P, Hollenberg AN, Bonett RM, Denver RJ. Liganded Thyroid Hormone Receptors Transactivate the DNA Methyltransferase 3a Gene in Mouse Neuronal Cells. *Endocrinology*. 2016 Sep;157(9):3647–57.
- 29 Kawahori K, Hashimoto K, Yuan X, Tsujimoto K, Hanzawa N, Hamaguchi M, et al. Mild Maternal Hypothyroxinemia during Pregnancy Induces Persistent DNA Hypermethylation in the Hippocampal Brain-Derived Neurotrophic Factor Gene in Mouse Offspring. *Thyroid*. 2018 Mar;28(3):395–406.
- 30 Dingemans MM, van den Berg M, Westerink RH. Neurotoxicity of brominated flame retardants: (in)direct effects of parent and hydroxylated polybrominated diphenyl ethers on the (developing) nervous system. *Environ Health Perspect*. 2011 Jul;119(7):900–7.
- 31 Levie DA, Derakhshan A, Shu H, Broeren MAC, de Poortere RA, Peeters RP, et al. The association of maternal iodine status in early pregnancy with thyroid function in the Swedish Environmental Longitudinal, Mother and Child, Asthma and Allergy study. *Thyroid*. 2019 [Epub ahead of print].
- 32 Derakhshan A, Shu H, Peeters RP, Kortenkamp A, Lindh CH, Demeneix B, et al. Association of urinary bisphenols and triclosan with thyroid function during early pregnancy. *Environ Int*. 2019 Dec;133(Pt A):105123.
- 33 Fini JB, Mughal BB, Le Mével S, Leemans M, Lettmann M, Spirhanzlova P, et al. Human amniotic fluid contaminants alter thyroid hormone signalling and early brain development in *Xenopus* embryos. *Sci Rep*. 2017 Mar; 7(1):43786.
- 34 Filis P, Hombach-Klonisch S, Ayotte P, Nagrath N, Soffientini U, Klonisch T, et al. Maternal smoking and high BMI disrupt thyroid gland development. *BMC Med*. 2018 Oct; 16(1):194.
- 35 EFSA. Scientific Opinion on the identification of pesticides to be included in cumulative assessment groups on the basis of their toxicological profile. *EFSA J*. 2013;11(7):3293.
- 36 Mie A, Rudén C, Grandjean P. Safety of safety evaluation of pesticides: developmental neurotoxicity of chlorpyrifos and chlorpyrifos-methyl. *Environ Health*. 2018 Nov;17(1):77.
- 37 Birgersson L, Borbély G, Caporale N, Germain PL, Leemans M, Rendel F, et al. From cohorts to molecules: adverse impacts of endocrine disrupting mixtures. *bioRxiv*. 2018.
- 38 Janssen BG, Saenen ND, Roels HA, Madhloum N, Gyselaers W, Lefebvre W, et al. Fetal thyroid function, birth weight, and in utero exposure to fine particle air pollution: a birth cohort study. *Environ Health Perspect*. 2017 Apr;125(4):699–705.
- 39 Cohn BA, La Merrill M, Krigbaum NY, Yeh G, Park JS, Zimmermann L, et al. DDT exposure in utero and breast cancer. *J Clin Endocrinol Metab*. 2015 Aug;100(8):2865–72.
- 40 Trasande L, Zoeller RT, Hass U, Kortenkamp A, Grandjean P, Myers JP, et al. Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab*. 2015 Apr; 100(4):1245–55.
- 41 Bellanger M, Demeneix B, Grandjean P, Zoeller RT, Trasande L. Neurobehavioral deficits, diseases, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab*. 2015 Apr;100(4):1256–66.
- 42 Muir T, Zegarac M. Societal costs of exposure to toxic substances: economic and health costs of four case studies that are candidates for environmental causation. *Environ Health Perspect*. 2001 Dec;109 Suppl 6:885–903.