# Vulnerability of the Developing Brain to Thyroid Abnormalities: Environmental Insults to the Thyroid System

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Neurologic development follows orderly patterns that can be severely disturbed when thyroid hormones are deficient or excessive. Should this occur at appropriate development periods, irreversible neurologic damage can result. The nature of the deficits depends upon the specific development period and the severity of the thyroid disturbance. PCBs and dioxins are structurally similar to the thyroid hormones. Their binding characteristics are similar to those of thyroid hormones and all three groups bind to the cytosolic *Ah* receptor, the thyroid hormone receptor and the serum thyroid hormone binding protein transthyretin. Depending upon the dose of toxin and the congener used, the toxins either decrease or minic the biological action of the thyroid hormones. Either effect, if occurring during brain development, can have disastrous consequences. Children and animals exposed to PCBs or dioxins *in utero* and/or as infants can exhibit varying degrees of behavioral disorders. These disorders resemble those seen in children exposed to thyroid hormone deficiencies *in utero* and/or in infancy. The mechanism of developmental neurotoxicity of PCBs and dioxins is not known but data suggest it could be partially or entirely mediated by alterations in availability and action of thyroid hormones during neurological development. It is possible that transient exposure of the mother to doses of toxins presently considered nontoxic to the mother could have an impact upon fetal or perinatal neurological development. If the toxins act via their effect on thyroid hormone action, it is possible that doses of toxins that would normally not alter fetal development, could become deleterious if superimposed on a pre-existing maternal/or fetal thyroid disorder. —
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## Introduction

Thyroid hormones have profound effects on neurological function in people of all ages. However, while the neurological impairment associated with disturbances in thyroid function in adults is readily reversible with appropriate treatment of the thyroid disorder, disturbances during a critical period of fetal and perinatal development produce irreversible neurological damage. These effects can range from subtle effects such as behavioral problems and minimal brain dysfunction to gross mental retardation. The nature of the problems depends upon when in development the thyroid disorder occurs and the severity of the thyroid disturbance. While both excesses and deficiencies create problems, only hypothyroidism will be discussed in this article. The critical period begins *in utero* and extends until 2 years of age in humans. As thyroid hormones are essential for normal neurological development and many environmental toxins mimic or block the action of thyroid hormones, even in nontoxic doses, it is possible that low levels of certain toxins can alter neurological function by their effects on thyroid hormone action.

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## Thyroid Hormone Action on the Developing Nervous System

Thyroid hormones have been shown to act on neurological development in the following manner (Figure 1). a) They increase the rate of neuronal proliferation in the cerebellum (*1*,2). b) They act as the "time clock" to end neuronal proliferation and stimulate differentiation (*1–3*). c) Once neurons are formed, they follow an orderly pattern of migration to the appropriate areas in the brain. This is particularly apparent in the cerebral and cerebellar cortex. A deficiency of thyroid hormones in the neonatal rat has been shown to cause disorganization of the cerebellar cortex (*3–5*). Galaburda has shown disorganization of specific regions of the cerebral cortex in a patient with attention deficit disorder (*6*), a problem sometimes seen in children exposed to intrauterine hypothyroidism. d) They stimulate the formation and development of neuronal processes—both axons and dendrites (*4,7*). e) Development of neuronal processes leads to formation and development of synapses. Neuronal outgrowth requires an intact functional cytoskeleton; and thyroid hormones are important for normal formation, function, and stability of this cytoskeletal system (*4,8–10*). f) In the absence of thyroid hormones, myelinization is delayed, as is the normal biochemical maturation of neurons (*11–13*).

## Pathologies Resulting from Thyroid Disorders in Humans

### Endemic Cretinism

Endemic cretinism is the result of dietary iodine deficiency. Some of the most serious neurologic impairment occurs in people with neurologic endemic cretinism. This disorder is characterized by a relatively high incidence of severe mental retardation. Computed tomographic scans and pathologic observations suggest that there is a decreased number of cerebral cortical neurons in individuals with neurological cretinism (*14*). Deaf-mutism is also common in these individuals. Anatomical and physiological problems with ear development include abnormal ossification of the middle ear ossicles and abnormalities in the Organ of Corti (*15*). In addition, these individuals frequently have problems with perceptive hearing loss. Even where hearing is not impaired, there are problems with learning and understanding the spoken word and expressing ideas in speech. Their speech is

dysarthic. In spite of severe speech and hearing problems, the visual system is largely spared. These individuals tend to have problems with gross and fine motor coordination (*14–18*). They may exhibit squint, spasticity, gait disturbances, and complete or partial inability to stand. The motor problems suggest damage at the cortical level and damage involving the corticospinal and rubrospinal tracts (*14,15*).

The cerebrum begins development relatively early in gestation and neurogenesis in the basal ganglia and the cerebral cortex occur predominantly between 10 and 18 weeks. The deficits observed in these individuals most likely result from problems occurring in the first half of gestation. The Organ of Corti of the inner ear is formed between weeks 12 and 18 (*14*). As only maternal thyroid hormone is available to the developing fetus during most of the first half of gestation, these deficiencies are likely, at least in part, to be associated with deficiencies of maternal hormone. The severity of the symptoms in the child correlate inversely with maternal serum thyroxine (T4) deficiencies during pregnancy; however, little correlation is seen with maternal triiodothyronine (T3) levels, and maternal T3 levels are frequently within the normal range (*19*). In fact, in many cases the mother's thyroid has compensated for the iodine deficiency and, although her serum T4 levels are low, she is not functionally hypothyroid. In rats, maternal T4, but not T3, replacement will elevate fetal brain thyroid hormone levels (*20*) (Figure 2). In neurologic cretins, the infant's thyroid can often compensate for the iodine deficiency such that, while a hormone deficiency likely occurs *in utero*, it may not necessarily occur throughout the entire postnatal critical period (*14*).

## Congenital Hypothyroidism

Congenital hypothyroidism is relatively common. It is seen in approximately 1:5000 newborns in the United States (*21*). In this condition the hormonal deficiency begins late in fetal development and extends postnatally. In the absence of treatment, the following symptoms are commonly seen: There may be mental retardation of varying degrees that can be severe. Treatment initiated at birth can prevent the mental retardation; hence, neonatal thyroid screening programs have become routine. While these individuals do not usually show the deaf-mutism so frequently seen in neurologic cretinism, they do sometimes have problems with high frequency sounds and minor speech disorders are common. They show poor coordination and balance and they exhibit abnormal fine motor movements, spasticity and tremor. Some of the motor problems originate in the cerebral cortex (*22,23*).

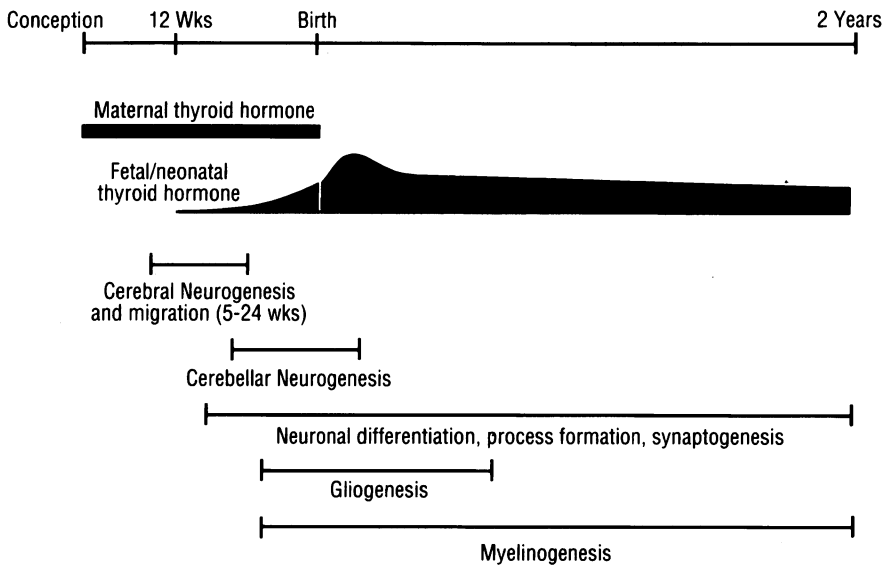


**Figure 1.** Potential availability of thyroid hormones during fetal/neonatal brain development relative to brain developmental stages.

It was once thought that if replacement hormone therapy is initiated shortly after birth in these children, all neurologic damage could be prevented. However, long-term follow-up studies of treated congenitally hypothyroid children have shown that there are residual problems that would be characterized as minimal brain dysfunction. Rovet (*24*) has shown a higher-than-normal incidence of behavioral problems in these children. They may have difficulties with practical reasoning, perceptomotor and visuomotor discrimination, spatiomotor skills, memory skills, sensorineural hearing, language comprehension, fine motor skills, and extrinsic eye movement. While their IQs are usually within the normal range, there is a downward shift in the mean IQ. At 9 years of age, 16% of these children were found to be in full-time special education classes (vs 1% in Ontario). While these problems can suggest that the thyroid disorder is not adequately corrected in the neonatal period, the basis for the problem is more likely the decreased availability of fetal thyroid hormones for the developing brain. The severity of the neurological impairment correlates well with the severity of the hypothyroidism at the time of birth (*25,26*).

## Maternal Hypothyroidism during Pregnancy

Children of mothers who are hypothyroid during pregnancy show a higher-than-normal incidence of behavioral and neurologic

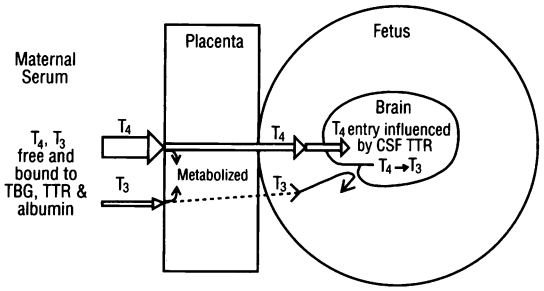


**Figure 2.** Potential sources of fetal brain thyroid hormones prior to the beginning of fetal thyroid function. The availability of maternal thyroid hormones (T4, T3) to the placenta depends upon both serum levels and the extent of serum binding of the hormones. Once crossing the placenta, thyroid hormones must reach the brain. The predominant source of fetal brain thyroid hormones has been shown to be fetal serum T4, not T3. Cerebrospinal fluid TTR binding of thyroid hormones may be important in providing thyroid hormones to the fetal brain. Once T4 enters the brain, it is deiodinated to T3. TBG, thyroid binding globulins; TTR, transthyretin; CSF, cerebrospinal fluid.

disorders (*27,28*). These disorders are those classified as minimal brain dysfunction. These results have been duplicated in rats (*29*). In rats, it can be shown that when maternal thyroid hormone levels are low, fetal brain hormone levels are likewise low (*30*). Such a maternal hormone deficiency in rats results in increased fetal and neonatal mortality, decreased pup size at birth, delayed brain biochemical maturation, delayed cell acquisition, and delayed neuronal maturation (*31*). While as adults the thyroid function of these progenies is relatively normal, they show learning and memory deficiencies and are hyperactive (*29*). These problems resemble those seen in the children of hypothyroid women (*27,28*) and in hormonally replaced congenitally hypothyroid children (*24*); in all of the aforementioned cases, the neurological problems probably result from brain thyroid hormone deficiencies *in utero*.

## Environmental Contaminants and the Thyroid

Many environmental contaminants alter thyroid function, either inhibiting the thyroidal system or mimicking it. A discussion of all of the toxins that alter thyroid function would be prohibitive in this manuscript. Consequently, only two groups of structurally similar compounds will be considered. These are the polyhalogenated biphenyls that include the (PCBs) and the family of chlorinated dibenzo-*p*-dioxins loosely referred to as dioxins. Both groups of compounds are present in the environment and some PCB contamination is seen virtually everywhere in the United States. There are multiple forms of these compounds and their actions on the thyroid depend both on the specific form studied and the dosage of toxin used. For expediency, they will be grouped and the predominant effect will be given. Some forms of these toxins are quite stable and, as they are fat soluble, they are accumulated in adipose tissue. They can be bioconcentrated in the environment, and fish from contaminated waters can contain relatively high levels of the toxins. They cross the placenta and are also concentrated in milk so that the fetus and newborn can be exposed by a contaminated mother both through the placenta and through her milk (*32,33*).

The proposal presented in this paper is that very low levels of these compounds—levels below those generally recognized as toxic—could influence both maternal and fetal thyroid function such that the fetal and neonatal child or animal has inappropriate levels of thyroid hormones at some time during the "critical period" of brain development. A second possibility is the untested proposal that the combined insult of exposure to the toxin in the presence of a pre-existing thyroid disorder could exacerbate the effect of the toxin.

### Structures of PCBs and Dioxin

PCBs, dioxins, and the active thyroid hormones T4 and T3 show similar structural properties that appear to be important in molecular recognition in biochemical systems (*34*) (Figure 3). They are all halogenated and have two phenol rings. PCBs, dioxin, and thyroid hormones all have similar protein binding characteristics and bind to the cytosolic dioxin-PCB Ah receptor and to thyroid hormone binding proteins such as transthyretin and the thyroid hormone receptor (*32,34*).

### Actions of PCBs and Dioxins on Thyroid Function

For expediency, the two groups of compounds will be treated collectively here. However, there are major differences among the various congeners. Furthermore, the logical differences in biological actions as a result of dosage differences will not be addressed. On the basis of the biological effects resulting from toxin exposure, it appears that these toxins are acting as a weak agonist and blocking the action of thyroid hormones. At higher doses, TCDD has been shown to potentiate or mimic thyroid hormone's actions (*35,37*). In fact, TCDD can stimulate expression of v-*erb*-A, the gene encoding the putative thyroid hormone receptor (*36*). In addition to binding to the receptors, these toxins compete for binding to the serum carrier proteins for the thyroid hormones. In fact, these compounds have a higher affinity than T4 for these carrier proteins (*38–40*). Humans have both the proteins thyroxine-binding-globulin (TBG) and transthyretin; however, lower species like rats lack TBG but have transthyretin. As most experimental research is with rats, the protein transthyretin will generally be the one discussed. Most of the circulating hormone is bound loosely with these proteins. The presence of the carrier protein allows larger quantities of these fat soluble hormones to be carried in blood and delays excretion and metabolism of the hormone. They might also play an important role in the availability of the hormones for placental transport. Because the toxins compete with thyroid hormones for binding to the carrier proteins, exposure to PCBs or dioxins typically decreases the serum total thyroid hormone levels (*32,34,41*). However, this alone does not indicate that the animal is hypothyroid. When thyroid hormone binding is decreased by other means, such as dilantin exposure, there is a decrease in total T4 without much change in total T3. This results, at least in part, from the much lower binding affinity of T3 for transthyretin. Furthermore, by decreasing T4 binding to transthyretin, the fractional turnover of the hormone is increased.

Some of the actions that have been shown for PCBs and dioxins on thyroid function are listed below:

- Competition for binding to the thyroid hormone receptor
- Competition for binding to thyroid hormone transport proteins in blood (particularly transthyretin)
- Decreased serum total T4; no change in serum total T3
- Increased serum TSH

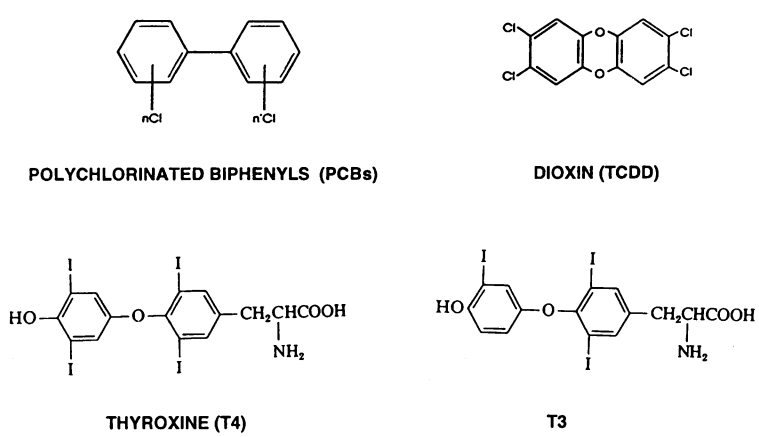


**Figure 3.** The thyroid hormones thyroxine (T4) and 3,3',5'-triiodothyronine (T3) show structural similarities to the polychlorinated biphenyls and dioxin.

- Increased thyroid weight
- Increased the biliary excretion of T4
- Increased the turnover of thyroid hormones
- Increased serum cholesterol (hypothyroidism can also cause this)

Serum total T4 is decreased, but unless free T4 is also decreased, this does not necessarily indicate hypothyroidism. Some reports show free T4 is also decreased (*41,42*). Frequently, no change in total serum T3 is shown (*42,43*). Most commonly, animals will have an elevated serum thyrotropin (TSH) (*42,43*) which would suggest that, at least at the pituitary level, the animal is not responding adequately to the action of thyroid hormones. Whether this is an effect on the biological action of the thyroid hormones in other tissues is not conclusively known. Thyroid weights frequently increase after exposure to PCBs or dioxins, and histological changes suggesting an increase in TSH stimulation have been noted (*43*). Exposed individuals can show lymphocytic autoimmune thyroiditis that can lead to primary hypothyroidism (*37,44,45*). There is an increased thyroid hormone turnover and increased biliary excretion of thyroxine (*41–43*). The preferential effect of the toxins on serum T4 levels could have neurological implications because 80% of the thyroid hormones in the brain come from serum T4 (*46*). Furthermore, in rats, maternal T4 administration in pregnancy can increase fetal brain thyroid hormone levels (both T4 and T3), but maternal T3 administration is without effect (*20*). In humans with an iodine deficiency, neonatal neurological impairment is more closely correlated with the low maternal T4 than T3 (*19*). In addition, transthyretin is present in cerebrospinal fluid and may be important in transportation of thyroid hormones to neurons (*47,48*). If toxins decrease thyroid hormone binding to cerebrospinal fluid transthyretin, they could significantly alter brain thyroid hormone availability. Furthermore, thyroid hormones enter cells by specific transport systems (*48*). If toxins competitively bind to these carriers, they could also alter intracellular availability of the hormones.

During 1972 to 1976, when Great Lakes PCB and TCDD contamination was increasing, there was an increase in the incidence of goiter in coho salmon (from 44–79.5%) (*49,50*). Feeding rats Great Lakes fish for 2 months resulted in a significant decrease in serum total T4 levels with no change in T3 levels (*51*). The *in vitro* liver activity of type I 5'-deiodinase, the enzyme converting T4 to T3 was not affected (*42*). Exposure to either of the two types of toxins increases the excretion of T4 in the bile and increases the fractional turnover of the hormone (*41,43*). An increase in serum cholesterol occurs following toxin exposure and an increase in serum cholesterol is seen in hypothyroidism (*42,52*).

## Neurological Effects of the Toxins

Exposure of the developing brain to certain dioxins or PCBs has been shown to produce behavioral effects in humans and animals (*53–56*). Monkeys exposed to PCBs *in utero* or by nursing had impairments in associational and attentional processes (*56*), whereas TCDD exposure impaired components of discrimination-reversal learning (*55*). Taiwanese children of PCB-exposed mothers scored lower than children of nonexposed mothers on a test of cognitive function (*53*). Michigan children showed PCB-related problems with memory and cognitive function (*54*). A group of PCB-exposed North Carolina children showed delayed psychomotor development (*57*). Mice exposed to PCB mixtures during gestation showed hyperactivity as adults (*58,59*). This is also a common finding in monkeys (*60*). Schantz et al. (*61*) have shown learning deficits in monkeys that persist long after the perinatal exposure and have proposed that altered dopamine function may be involved. Perinatal exposure of rats to Aroclor 1254 resulted in delayed development of negative geotaxis and surface righting, cliff avoidance, and acquisition of active avoidance (*62*).

The effects of toxins on neurological function is obviously very complex and the consequences of exposure are dependent upon the developmental period of exposure, the specific congeners involved, the dosage of exposure and probably the species.

## Possible Problems from Thyroid Hormone-mediated Effects of Toxin Exposure during Development

If toxins change thyroid function, even transiently, in the fetal or neonatal period, they can cause permanent neurological problems. Furthermore, the normal patterns for the control of thyroid function are established in the perinatal period in rats. Exposure to abnormal levels of thyroid hormones during this period can lead to permanent disruption of the thyroid axis (*63,64*). Therefore, transient toxicity can lead to long-term thyroidal disturbances. Ness and Schantz (*65*), have shown that exposure in utero to PCB congeners can result in persistently low serum T4, no change in T3, and an increase in TSH. These results resemble those shown by Bakke et al. (*63*), following transient neonatal hypo- or hyperthyroidism. They are also similar to those shown by Porterfield and Hendrich to occur in the progenies of mothers that were hypothyroid or exposed to excess T4 during pregnancy (*64,66*).

## Similarities of the Effects of Hypothyroidism and PCB/Dioxin Exposure during the "Critical Period" of Brain Development

Exposure of the developing brain both to hypothyroidism and PCB-dioxin have been shown to impair memory and learning. Similarities of the effects of hypothyroidism and PCB-dioxin exposure during the "critical period" of brain development include

- Impaired learning and memory; lower scores on tests of cognitive function; poor short-term memory on verbal and quantitative tests
- Hyperactivity in mice, rats, and monkeys
- In mice and rats, delayed acquisition of auditory startle, cliff avoidance, negative geotaxis, and air-righting
- Decreased birth weight and litter size in rodents. A possible decrease in birth weight in humans

Such children have lower scores on tests of cognitive function and poorer short-term memory on verbal and quantitative tests (*24,53*). In mice, rats, and monkeys, exposed animals have been shown to be hyperactive (*29.55,58,59*). Furthermore, in mice and rats, both insults result in delayed acquisition of auditory startle, cliff avoidance, negative geotaxis, and air-righting (*62,67*). Rodents show a decreased birth weight and litter size after both exposures (*31–33*).

## Conclusions

PCBs and dioxins alter thyroid function. The preferential action on serum T4 levels can have neurological implications because most fetal brain thyroid hormones come from serum T4 rather than T3. If PCBs and dioxins functionally decrease thyroid function in the mother during pregnancy, or in the fetus or neonate during critical periods of neurological development, permanent brain damage is likely to result.

Competition of PCBs or dioxins with T4 for binding to transthyretin in cerebrospinal fluid can interfere with thyroid hormone transport into brain cells. Competition with thyroid hormones for membrane transport would also decrease brain cell hormone levels. Furthermore, the normal patterns for the control of thyroid function are established in the perinatal period. If transient alterations in thyroid hormone levels occur during this period, it is possible that permanent, subtle changes in thyroid function could result. Many of the neurological effects of prenatal or perinatal PCB or dioxin exposure resemble those associated with fetal or perinatal hypothyroidism. Consequently, the possibility exists that these toxins could, at low levels, be altering neurological development via their action on thyroid hormone availability during critical brain developmental periods. This hypothesis remains to be tested.

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