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Windows of sensitivity to toxic chemicals in the development of the endocrine system: an analysis of ATSDR's toxicological profile database

MC Buser, **HR Pohl**, **HG Abadin**

US Department of Health and Human Services, Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA, USA

Abstract

This review utilizes the robust database of literature contained in toxicological profiles developed by the Agency for Toxic Substances and Disease Registry. The aim was to use this database to identify developmental toxicity studies reporting alterations in hormone levels in the developing fetus and offspring and identify windows of sensitivity. We identified 74 oral exposure studies in rats that provided relevant information on 30 chemicals from 21 profiles. Most studies located provided information on thyroid hormones, with fewer studies on anterior pituitary, adrenal medulla, ovaries, and testes. No studies pertaining to hormones of the posterior pituitary, pancreas, or adrenal cortex were located. The results demonstrate that development of the endocrine system may be affected by exposure to environmental contaminants at many different points, including gestational and/or lactational exposure. Moreover, this review demonstrates the need for more developmental toxicity studies focused on the endocrine system and specifically alterations in hormone levels.

Keywords

Hormones; development; in utero exposure; environmental exposure

Introduction

Chemicals that affect the normal function of the endocrine system are called endocrine-disrupting chemicals (EDCs). These are defined by the US Environmental Protection Agency (EPA) as 'exogenous agents that interfere with synthesis, secretion, transport, metabolism, binding action or elimination of natural blood-borne hormones that are present

CONTACT MC Buser, wyf9@cdc.gov, MPH, Centers for Disease Control and Prevention, Agency for Toxic Substances and Disease Registry, 4770 Buford Hwy, MS S102-1, Atlanta, GA, USA.

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Disclosure of interest

The authors report no conflict of interest.

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in the body and are responsible for homeostasis, reproduction, and developmental process' (US EPA 1997). Anin-depth review and scientific statement from the Endocrine Society focused on seven different topics, which strengthens the knowledgebase of EDCs' actions on endocrine health-related effects (Gore et al. 2015). Considering the impact on several different toxicokinetics/toxicodynamic processes listed above, it is not surprising that the mechanism of action of these chemicals is complex. It was established that there are at least five important mechanisms, four of which involve induction of receptors (the aryl hydrocarbon [Ah] receptor, the peroxisome proliferator activated receptor [PPAR], the constitutive androstane receptor [CAR, phenobarbital induction], the pregnane X receptor [PXR, rifampicin induction]) (Fuhr 2000). The end result is increased expression of various enzymes. Another type of induction (ethanol-like) is mediated by ligand stabilization of the CYP2E1 enzyme. A detailed discussion on the mechanism of action of EDCs is beyond the scope of this paper; interested readers should consult a literature review of the topic (Fuhr 2000; Gore et al. 2015).

Developmental stages of the embryo/fetus present unique opportunities for harmful action by xenobiotics. These stages may contain specific windows of sensitivity, to EDC during fetal development, for different outcomes of interest. Therefore, our first assumptions regarding the endocrine system can be based on embryogenesis.

- In humans, the endocrine glands have a highly increased sensitivity during weeks 4–9 of gestation when the organs first develop (O'Rahilly 1983)
- Later on, windows of sensitivity may occur with the differentiation of specific cells. (O'Rahilly 1983)

Frank pathological changes, such as hermaphroditism or cretin dwarfism, affecting the development of the endocrine system are easily recognized (Guyton and Hall 2000). Specifically, effects seen after exposures to known EDCs in medications, foods, and workplaces have been reported (Rogers and Kavlock 2010). However, more subtle changes in humans, such as alterations in hormone levels, are difficult to confirm and often don't manifest adverse effects until later in life (Rogers and Kavlock 2010). Epidemiological studies examining environmental exposures may indicate possible associations; however, a confirmed link (evidence of causality) is lacking due to missing exposure data to the chemical studied, possible cofounding factors, and co-exposure to multiple EDCs. Therefore, laboratory studies in animals are highly instrumental in identifying EDCs, their targets, and possible windows of sensitivity.

This review is part of a series (Buser and Pohl 2015; Ingber and Pohl 2016; Buser et al. 2018) aimed at understanding developmental windows of sensitivity utilizing the robust database of toxicological profiles published by the Agency for Toxic Substances and Disease Registry (ATSDR). ATSDR publishes toxicological profiles for hazardous substances that include only the highest quality, peer-reviewed toxicology studies (https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf). ATSDR extrapolates from these studies to determine levels of exposure for humans that may result in adverse health effects (https://www.atsdr.cdc.gov/toxprofiles/index.asp). The aim of this study was to review available data from ATSDR toxicological prohles and addenda

related to developmental effects of the endocrine system (specifically developmental alterations to hormone levels) and to use this data to evaluate possible windows of sensitivity.

Methods

The primary literature search, conducted on 2 July 2019, examined ATSDR Toxicological Prohles (n = 185) and Addenda (n = 33). The prohles and addenda were searched for data pertaining to chemically-induced developmental effects of the endocrine system; specifically, the review is focused on alterations to hormone levels (Supplemental Table 1). The review was limited to studies in rats because of the well-established developmental timeline in this species, the understanding of the relationship between developmental timing in humans and timing in rats, the abundance of toxicology studies in this species, and the documented utility of using the rat as a model for endocrine disruptor screening and testing (Gray et al. 2004).

Any prohles or addenda that documented studies with endocrine system developmental effects in rats – which included the thyroid, pituitary, adrenal, pancreas, ovaries and testicles – were moved into the data extraction phase (n = 21 substances). The following data were extracted from each animal study: chemical name and form; strain; exposure route and vehicle; exposure duration and frequency; no observed adverse effect level (NOAEL), where applicable; lowest observed adverse effect level (LOAEL); and adverse effect observed. Results were stratified according to endocrine system gland – thyroid, pituitary, adrenal, pancreas, ovaries and testicles – and further stratified according to affected hormone within each of those glands.

Results

Of the 185 toxicological profiles and 33 addenda that were published between 1989 and 2019, 74 oral exposure studies provided relevant information on 30 chemicals from 21 toxicological profiles (Table 1). The majority of studies located provided information on thyroid hormones, with fewer studies focusing on anterior pituitary, adrenal medulla, ovaries, and testes. No studies pertaining to hormones of the posterior pituitary, pancreas, or adrenal cortex were located. A majority of the studies utilized full-gestational or gestational plus lactational exposures. However, there were a few studies within each endocrine system that utilized shorter exposures, including several looking at single-day exposures. Most studies evaluated the hormone levels immediately following cessation of exposure; additionally, some studies evaluated levels later in life as a follow-up.

Thyroid hormones

The thyroid was the most studied endocrine gland, with thirty-nine studies investigating the effects of twelve different chemicals on the circulating levels of the major thyroid hormones triiodothyronine (T3) and thyroxine (T4) (Figure 1).

Exposure and adverse effects on triiodothyronine (T3) were found in thirteen studies assessing exposure to nine different chemicals (doses ranging from 0.0002 mg/kg/day to

1300 mg/kg/day). The majority of the studies reported decreases in T3 levels following *in utero* or lactational exposure. Most of the studies focused on full-gestational or gestational plus lactational exposures, thus the ability to determine a narrow window of susceptibility is more difficult. However, one study evaluated a narrower window of GD10-16. This study involved exposure to PCBs at a relatively high dose of 16 mg/kg/day and reported decreases in plasma concentrations of T3 (Kobayashi et al. 2008). Another study reported decreases in serum T3 levels following a single day exposure on GD15 to 0.2 mg/kg/day of 2,3,7,8-TCDD (Nishimura et al. 2003).

Changes to thyroxine (T4) levels was the most studied effect, with thirty-seven different studies involving eleven different chemicals investigating this endpoint. All studies reported decreases in T4 levels following developmental exposure to doses ranging from 0.0001 mg/kg/day to 1300 mg/kg/day (most doses were below 30 mg/kg/day). As with T3, the majority of studies reporting effects on T4 levels assessed full-gestational exposure or gestational plus lactational exposure. However, a few studies did attempt to narrow this window further by looking at exposures to 16 mg/kg/day PCBs or 0.0001 mg/kg/day 2,3,7,8-TCDD on GD10-16 (Seo et al. 1995; Morse et al. 1996; Kobayashi et al. 2008) or single exposure to 0.001 mg/kg/day or 0.0002 mg/kg/day 2,3,7,8-TCDD on GD15 (Fenton et al. 2002; Nishimura et al. 2003). The overlap in alterations of T3 and T4 following exposure on GD10-16, and specifically on GD15, suggests that this may represent a window of sensitivity to induce thyroid changes in the developing fetus.

Additionally, several studies on thyroid-hormone alterations utilized lactational only exposure to BDEs, PCBs, perchlorate, atrazine, chlorine dioxide, and PFOS (Toth et al. 1990; Goldey et al. 1995; Stoker et al. 2000, 2004; Mahle et al. 2003; Kuriyama et al. 2007; Yu et al. 2009; Lee et al. 2010). Taken together, these studies may indicate that the development of the endocrine system extends after birth, and post-natal exposure may adversely affect the normal levels of circulating hormones.

Anterior pituitary hormones

Alterations to pituitary hormones – growth hormone (GH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin – were reported in many of the studies identified by this review, second only to the number of studies on thyroid hormones (Figure 2). Of these, GH and prolactin were the least studied, with only a single study reporting alterations to these hormones following full gestational and lactational exposure to 6.12 mg/kg/day endosulfan (Caride et al. 2010). The directionality of the results for this gland was varied; the results for TSH were the most consistent with seven of the eight studies reporting increased TSH levels in pups. Results for LH and for FSH were less consistent.

The body of evidence pertaining to the development of the pituitary gland generally utilized longer exposure durations; however, several studies did employ acute exposures. For the longer duration studies, some focused on gestational only exposure with a few including exposure prior to mating, others were limited to lactational only exposure, and several spanned periods of gestation and lactation. On the other hand, alterations to TSH, LH, and FSH levels were all reported in studies utilizing single-day exposures spanning from GD

11 through LD 10. There were additional acute duration studies that reported alterations in hormones following *in utero* exposure to 100 mg/kg/day atrazine on GD1-8 (Cummings et al. 2000) or exposure to 75 mg/kg/day or 100 mg/kg/day bromodichloromethane on GD6-10 (Bielmeier et al. 2004, 2007). These results suggest that development of the endocrine system occurs over a lengthy period and both *in utero* and post-natal exposure on any given day may adversely affect the normal functioning of this system.

Adrenal medulla hormones

Alterations in levels of hormones produced in the adrenal medulla – noradrenaline, norepinephrine, and dopamine – were noted in seven studies following exposure to seven different chemicals (Figure 3). Dopamine was the most commonly investigated with six studies reporting developmental changes to this hormone following doses ranging from 0.61 mg/kg/day to 50 mg/kg/day; noradrenaline and norepinephrine were each investigated in two studies. The directionality of the results varied, with some studies reporting increases, some reporting decreases, and others simply reporting alterations in the levels of the hormones. Furthermore, the exposure durations do not suggest a clear narrow window; one, four, and three studies investigated gestational only, lactational only, and gestational plus lactational exposures, respectively. This body of evidence precludes the identification of a window of susceptibility although it does show that chemical exposure during any of those exposure periods results in alterations to adrenal gland hormones.

Ovaries and testes hormones

Alterations in levels of hormones produced in the ovaries (Figure 4) and testes (Figure 5) were noted in fifteen and twelve laboratory rat studies, respectively. Hormones produced in the ovaries – estradiol, estrogen, and progesterone – were affected by exposure to seven different chemicals, following exposure to doses ranging from 7×10^{-6} mg/kg/day to 200 mg/kg/day. The majority of the noted effects were decreased levels of the circulating hormones, although there was less consistency with the three studies reporting changes in estrogen levels following exposure to 200 mg/kg/day atrazine, 0.001 mg/kg/day 2,3,7,8-TCDD, or 150 mg/kg/day methoxychlor. The majority of the studies employed longer exposure durations, precluding the identification of a narrow window (Figure 4). However, a series of studies on the effects of *in utero* bromodichloromethane exposure (75–100 mg/kg/day) on progesterone levels did utilize shorter durations of exposure (Bielmeier et al. 2001, 2004, 2007). These studies exposed rats between GD 6–10 and noted reduced serum progesterone in the offspring. Moreover, Bielmeier et al. (2001) employed single day exposures to 75 mg/kg/day bromodichloromethane on GD 8 or GD 9 and noted similar decreases in serum progesterone following exposure to the same dose used in the longer duration studies. Interestingly, several studies focused on exposure later in gestation (starting around GD 14) and on lactational exposure. An additional study by Stoker et al. (2000) dosed the developing rats with 200 mg/kg/day atrazine from post-natal day 23–53 and reported dose-related increases in serum estradiol and estrone. These studies together may indicate that the development of the endocrine system extends after birth, and post-natal exposure may adversely affect the normal levels of circulating hormones.

While a few studies investigating effects on hormones of the testes did note increases following exposure to 0.0005 mg/kg/day 2,3,7,8-TCDD or 10 mg/kg/day tributyltin chloride during gestation or during lactation (Haavisto et al. 2001; Omura et al. 2001), the majority of the studies consistently reported decreases in testosterone levels following exposure to any of eight different chemicals (Figure 5). About half of the studies exposed rats during gestation while the other half focused on lactational exposure. Moreover, there were single-day exposures utilized for both of these time periods. Exposures to 2,3,7,8-TCDD (doses ranging from 6.4×10^{-5} mg/kg/day to 0.001 mg/kg/day) or 6 mg/kg/day lindane on any of GD 11, 13, or 15 or PND 9, 10, 11, 12, 13, or 14 resulted in alterations to the normal circulating levels of testosterone in rat offspring (Mably et al. 1992a; Bjerke and Peterson 1994; Dalsenter et al. 1997; Haavisto et al. 2001; Adamsson et al. 2008). Similar to that noted for the effects on ovary hormones, these results suggest that development of the endocrine system occurs over a lengthy period and both *in utero* and post-natal exposure on any given day may adversely affect the normal functioning of this system.

Discussion

This review utilized the robust database of literature contained in ATSDR's toxicological profiles. The benefit of using this database is that the profiles provide a summary of the highest quality studies on which to base health effects conclusions. Of interest in this review, with profiles on 185 substances, information on developmental alterations of hormones was only found in 21 profiles. This suggests a possible gap for developmental data on a range of substances.

Epidemiological studies that have investigated developmental effects on the endocrine system reported hormonal changes in association with exposure to environmental toxicants. Available studies mostly concentrated on thyroid hormone levels and reproductive hormone levels. The following discussion is not intended as an all-inclusive list of EDCs, but rather an illustrative selection based on ATSDR's toxicological profiles and some of the chemicals discussed above under animal studies.

TSH and thyroid hormones

TSH and thyroid hormones were the most often studied endpoints following exposure to EDCs in humans. Halogenated aromatic hydrocarbons were the focus of many of the studies evaluated. For example, increased levels of TSH in newborns exposed to TCDD *in utero* in the Seveso cohort indicated possible related to regulation of thyroid hormone metabolism (Baccarelli et al. 2008). The authors reported that the mean TCDD levels correlated with TSH levels above 5 μU/mL serum. The 5 μU/mL standard is significant as it was established by the World Health Organization (WHO) as an indicator of potential thyroid problems in neonates. The authors noted that higher TCDD exposures across all three different exposure zones showed increased TSH concentrations. The group mean of 39 ppt TCDD was associated with TSH levels above the standard. When PCBs (polychlorinated biphenyls) were measured in maternal milk, it was reported that high levels of PCBs were associated with reduced total T3 and total T4 in mothers and increased levels of TSH in newborns (Koopmanesseboom et al. 1994). A cohort of mother-infant pairs (n = 232) was

studied in Germany to assess the potential impact of environmental exposure to CDDs, dioxin-like PCBs and six indicator PCBs (mono- and di-ortho PCBs) on TSH and thyroid hormone status in newborns and neurodevelopment (Wilhelm et al. 2008). In contrast to the above studies, multiple regression analysis showed no decrease of thyroid hormones related to total toxic equivalents (TEQ; a value providing toxicity information for mixtures of structurally-related chemicals) in blood and milk of mothers and their newborns.

A number of studies evaluated effects on thyroid hormones in neonatal serum or cord blood associated with *in utero* exposure to polybrominated diphenyl ethers (PBDEs). Abdelouahab et al. (2013) evaluated the potential associations between thyroid hormone levels in the umbilical cord blood and maternal serum concentrations of PBDEs collected at <20 weeks of pregnancy (n = 380). Significant negative associations were observed between maternal PBDE levels and both free and total T4 in cord blood, but not free or total T3 or TSH in cord blood. Similarly, neonatal TSH assessed in blood samples collected 24 hours after birth (on average) was not related to PBDE concentrations in maternal serum collected at the start of the third trimester or at delivery from 289 expectant mothers living in the Salinas Valley of California (Chevrier et al. 2011).

Inconsistent findings were also observed when thyroid hormones and PBDEs levels were evaluated in infant serum and/or cord blood. For example, Mazdai et al. (2003) found no correlations between PBDE concentrations and thyroid hormone levels (free and total T4 and free and total T3) in umbilical cord blood (n = 12). Similarly, there was no correlation between PBDEs and thyroid hormone levels in umbilical cord blood in another study of 21 South Korean mothers undergoing Cesarean section (Kim et al. 2012a). Both T3 and free T3 in cord blood were significantly inversely related to PBDE in a study of 54 Taiwanese births (Lin et al. 2011); however, T4, free T4, and TSH were unaffected in this study. Kim et al. (2012b) analyzed blood samples collected from infants in neonatal screening tests. They found a positive relationship between PBDEs and TSH (BDE 197 and BDE 196 only) and a negative association with T3 (BDE 154 only) for babies without congenital hypothyroidism (n = 12), and no significant relationships between PBDEs and thyroid hormones in babies with congenital hypothyroidism (n = 26).

Another group of chemicals of concern are pesticides. An association between prenatal exposure to 17 organochlorine pesticides (OCPs) and concentrations of free T3, free T4, and TSH in the cord blood of newborns (n = 115) was studied in China (Luo et al. 2017). The authors reported marginally significant inverse associations of cord plasma measurements of total hexachlorcyclohexanes, ρ,ρ'-DDE and methoxychlor with free T4 levels, but not with free T3 and TSH levels. In addition, higher cord plasma levels of aldrin, dieldrin, total DDTs, and all OCPs were found to be related to the increase in cord plasma TSH levels after the adjustment for confounders. In Tokyo, 147 mother-neonate pairs were investigated for the influence of prenatal pyrethroid exposure and hormone levels in neonates (Zhang et al. 2014). The results showed that maternal pyrethroid exposure had no apparent effect on the neonatal thyroid hormone status. When exposure to 17 OCPs was measured in 220 placentas from a male birth cohort in Southern Spain, newborns with higher levels of endrin in placenta had higher odds of TSH cord blood levels ≥ 5 mU/L (80th percentile); whereas,

higher prenatal exposure to endosulfan-sulfate was associated with lower odds of TSH ≥ 5 mU/L (Freire et al. 2011).

Of course, many authors realized that humans are exposed to mixtures of chemicals and tried to encompass in their studies several chemical groups. PCBs, organochlorine pesticides and poly- and perfluoroalkyl substances (PFAS) were measured in 221 cord blood samples collected in Belgium between 2013 and 2016 (Dufour et al. 2018). Multivariate statistical analyses indicated a decrease of TSH level in male newborns with detectable levels of 4,4′-DDE in comparison with those with no detectable level. The authors also found a negative association between perfluorononanoic acid (PFNA) concentration and TSH in male newborns.

In a Norwegian study, 19 POPs (persistent organic pollutants) and 10 thyroid parameters were analyzed in serum from 391 pregnant women in their second trimester (Berg et al. 2017). TSH concentrations were also obtained from heel-prick blood of the infants. Several POPs were significantly associated with changes in TSH and thyroid hormone levels. Perfluorooctane sulfonic acid was positively associated with TSH. PCBs, HCB, and non-chlorinated chemicals were inversely associated with T3, T4, and FT4. Additionally, perfluorodecanoic acid and perfluoroundecanoic acid were inversely associated with T3 and free T3.

In a study from Korea, PCBs, PBDEs, and organo chlorine pesticides were compared with five thyroid hormones in cord serum of newborn infants as well as TSH in bloodspot collected at 2 days after birth (n = 104) (Kim et al. 2015). In cord serum, BDE-47, −99, and Σchlordane (CHD) showed significant positive associations with cord or bloodspot TSH. At the same time, p,p’-DDE and HCB revealed negative associations with total T3 and total T4 in cord serum, respectively. Maternal exposure to β-HCH, ΣCHD, ΣDDT, or p,p’-DDE were also associated with neonatal thyroid hormones changes.

Reproductive hormones

Changes in reproductive hormone levels were also studied in association with exposure to EDCs. For example, a follow-up to the previously cited German study (Wilhelm et al. 2008) related environmental exposure to CDDs, dioxin-like PCBs, and six indicator PCBs to the potential impact on gonadal hormones in newborns (Cao et al. 2008). Testosterone and estradiol levels were measured in maternal and cord serum of 104 mother-infant pairs, representing a subsample of the total sample of 232 participants. Testosterone reduction was more prominent in cord serum of females, and estradiol reduction was more prominent in that of male infants. In general, decreased hormone levels were more pronounced for dioxins than for indicator PCBs.

Adolescent boys (n = 438) were included in a study of the general population of the Faroe Islands (Grandjean et al. 2012). PCBs and p,p’-DDE were measured in cord blood at birth and in serum from clinical examination at age 14. Higher prenatal PCB exposure was associated with lower serum concentrations of both LH and testosterone in 14-year-old boys. In addition, sex hormone binding globulin was positively associated with both prenatal and concurrent PCB exposures.

Prenatal exposure to OCPs and their influence on steroids and reproductive hormones in cord blood was analyzed in a Hokkaido study (Araki et al. 2018). Samples (n = 232) with both OCP and hormone data were obtained, and the results indicated that chlordanes, cis-hexachlorobenzene, heptachlor epoxide, mirex, and toxaphenes in maternal blood were inversely associated with testosterone, cortisol, cortisone, sex hormone-binding globin, prolactin, and androstenedione-dehydroepiandrosterone (DHEA) and testosterone-androstenediones ratios among boys.

Mixtures

It is noted that not all available epidemiological studies found an association between exposure to endocrine disruptors and changes in hormone levels in newborns. Some of the reasons include different exposure levels to specific chemicals of interest, different congener make-up, population background, exposure to mixtures, etc.

Indeed, co-exposures to other chemicals that interact together may result in greater-than-additivity or less than-additivity, and thus may alter our assumptions about toxicity of the whole mixture. For example, PCB mixtures antagonized TCDD-induced immunosuppression (Bannister et al. 1987; Davis and Safe 1989) and developmental toxicity (cleft palate) in mice (Haake et al. 1987). Intermediate-duration dietary exposure of rats to binary mixtures of TCDD plus 2,2′,4,4′,5,5′-hexachlorobiphenyl showed evidence for synergistic action in decreasing thyroid hormone levels (serum T4) (van Birgelen et al. 1992) and increasing hepatic porphyrin levels (van Birgelen et al. 1996). However, no evidence was found for synergistic interactions between 2,3,7,8-TCDD and two other congeners 3,3′,4,4′,5-pentachlorobiphenyl or 2,3,3′,4,4′,5-hexachlorobiphenyl. Oral exposures to PCBs or CDDs such as 2,3,7,8-TCDD are associated with a wide selection of health effects that show considerable overlap. Although some PCB congeners have been demonstrated to produce effects via a common initial mechanistic step with 2,3,7,8-TCDD and other CDDs (binding to the Ah receptor), mechanistic understanding of subsequent processes is too incomplete to provide reliable predictions of the final outcome.

Another example is co-exposure of TCDD and p,p’-DDE and their effect on male reproductive organ development and function. Data is restricted to a single study that found that combined exposure to TCDD and p,p’-DDE led to decreased prostate weight in male rat offspring to a greater degree than either compound alone (Loeffler and Peterson 1999). However, the study design precluded the definitive conclusion regarding the direction of the interaction. Mechanistic information suggests that the chemicals may act on a molecular scale by independent anti-androgenic mechanisms. Anti-androgenic effects from p,p’-DDE are proposed to involve inhibition of androgen-binding to androgen receptors (Kelce et al. 1995, 1997); whereas, TCDD is not expected to interfere with androgen receptor-ligand binding and may indirectly affect androgen signaling by altering growth factor pathways (Roman et al. 1998). However, the mechanism must be further elucidated.

Strengths and limitations of the database

There are several strengths to this review, which includes the robust database included in ATSDR’s toxicological profiles. These profiles include only highest quality, peer-reviewed

toxicology studies, thus this review benefits from relying on previously vetted high-quality studies. There are differences in developmental stages across species that needs to be taken into account when extrapolating to human exposure periods. While this is an inherent limitation in toxicological studies, rats are recommended as a reliable experimental model for humans, including during prenatal and postnatal development. Because rats have a well-established developmental timeline that has been associated to developmental timing in humans, this review was limited to rats. While this is a limitation of the review, many toxicological studies are conducted in rats, thus limiting the review to rats only still provided a large number of studies across a range of substances. Moreover, there is documented utility of using the rat as a model for endocrine disruptor screening and testing, which further strengthens the rationale for limiting the review to this species.

Conclusion

This review attempted to identify specific windows when the developing animal may be more susceptible to chemically-induced alterations to hormone levels produced by the endocrine system. Laboratory animal studies are essential for investigating these windows of sensitivity, as it is often difficult to pinpoint these windows based on epidemiological studies. Our results suggest that development of the endocrine system occurs over a lengthy period and both *in utero* and post-natal exposure on any given day may adversely affect the normal functioning of this system. This suggests that we cannot only specify the windows that correlate with the basic development of the endocrine glands but must also find secondary windows that correlate with their further maturation. There is difficulty when dealing with hormones because of the multitude of ways that hormones can be affected (e.g. enzymes affecting levels of hormones in various tissues). In order for this review to be feasible, we focused on the actual hormone levels themselves and not on upstream enzymes. Because of the inconsistency of findings in both human and animal studies across the range of chemicals, it is impossible to draw specific conclusions regarding changes in hormone response. A major limitation we encountered in this review is the paucity of information on developmental alterations of hormones for the majority of substances. This suggests a possible gap for developmental data on a range of substances. Future research should focus on exposing animals to a broad range of substances, especially emerging chemicals of concern, throughout different stages of development in order to better identify windows of sensitivity. This information along with epidemiological studies on this subject may be useful for developing preventative measures to improve the health of exposed populations.

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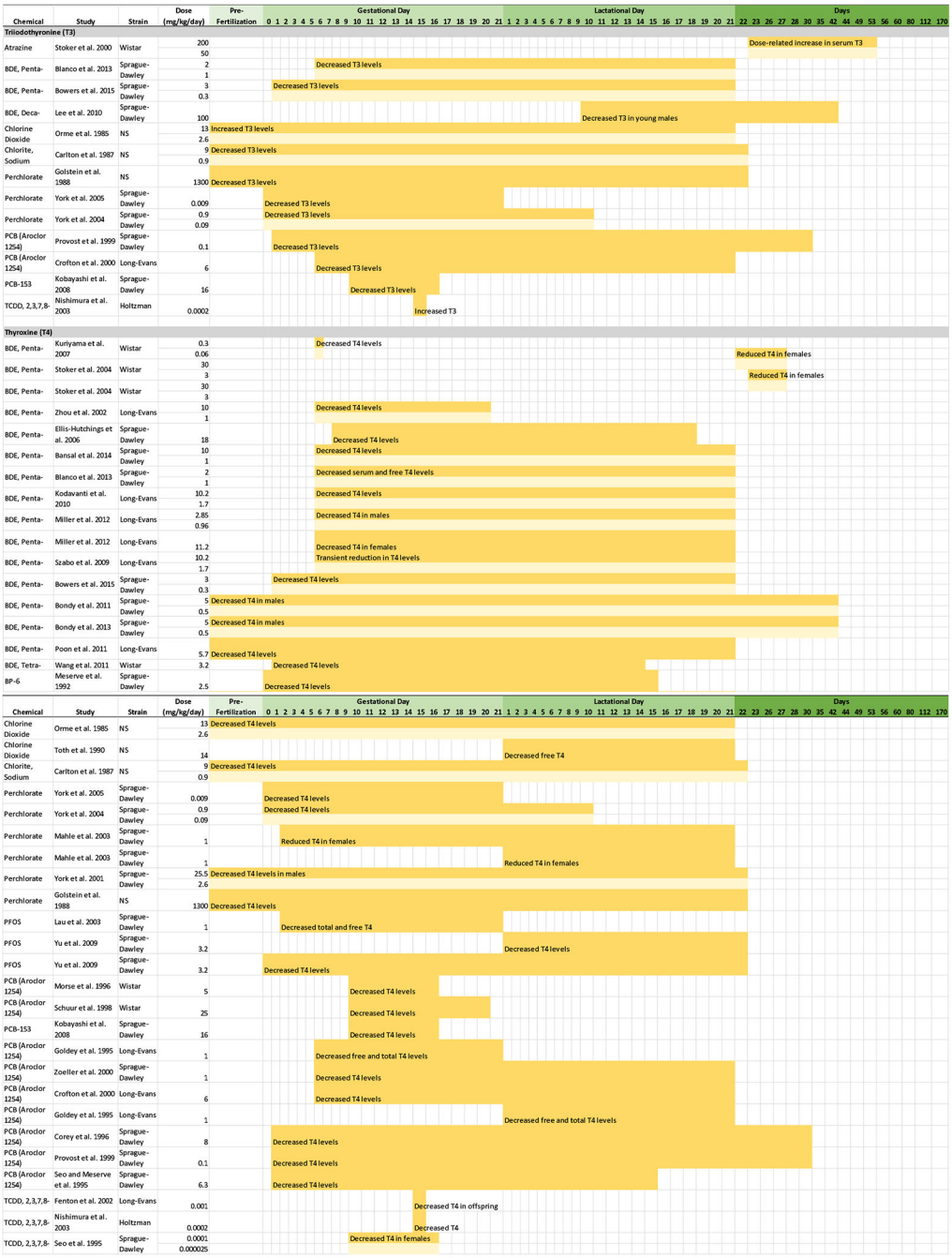

Figure 1.

Windows of exposure for laboratory rat studies noting alterations in hormones produced by the thyroid. Legend: BP-6: hexabromobiphenyl; decaBDE: decabromodiphyenyl ether; NS: not specified; pentaBDE: pentabromodiphenyl ether; PFOS: perfluorooctane sulfonic acid; PCB: polychlorinated biphenyl; 2,3,7,8-TCDD: 2,3,7,8-tetrachlorodibenzodioxin; tetraBDE: tetrabromobiphenyl ether; T4: thyroxine; T3: triiodothyronine. Dark yellow bars indicate significant exposure effect (LOAELs); pale yellow bars indicate no exposure effect (NOAELs); the width of the bars indicates the exposure period that the studies spanned

(i.e. squares filled in from GD7-18 indicate that animals in this study were exposed from GD7 through GD18).

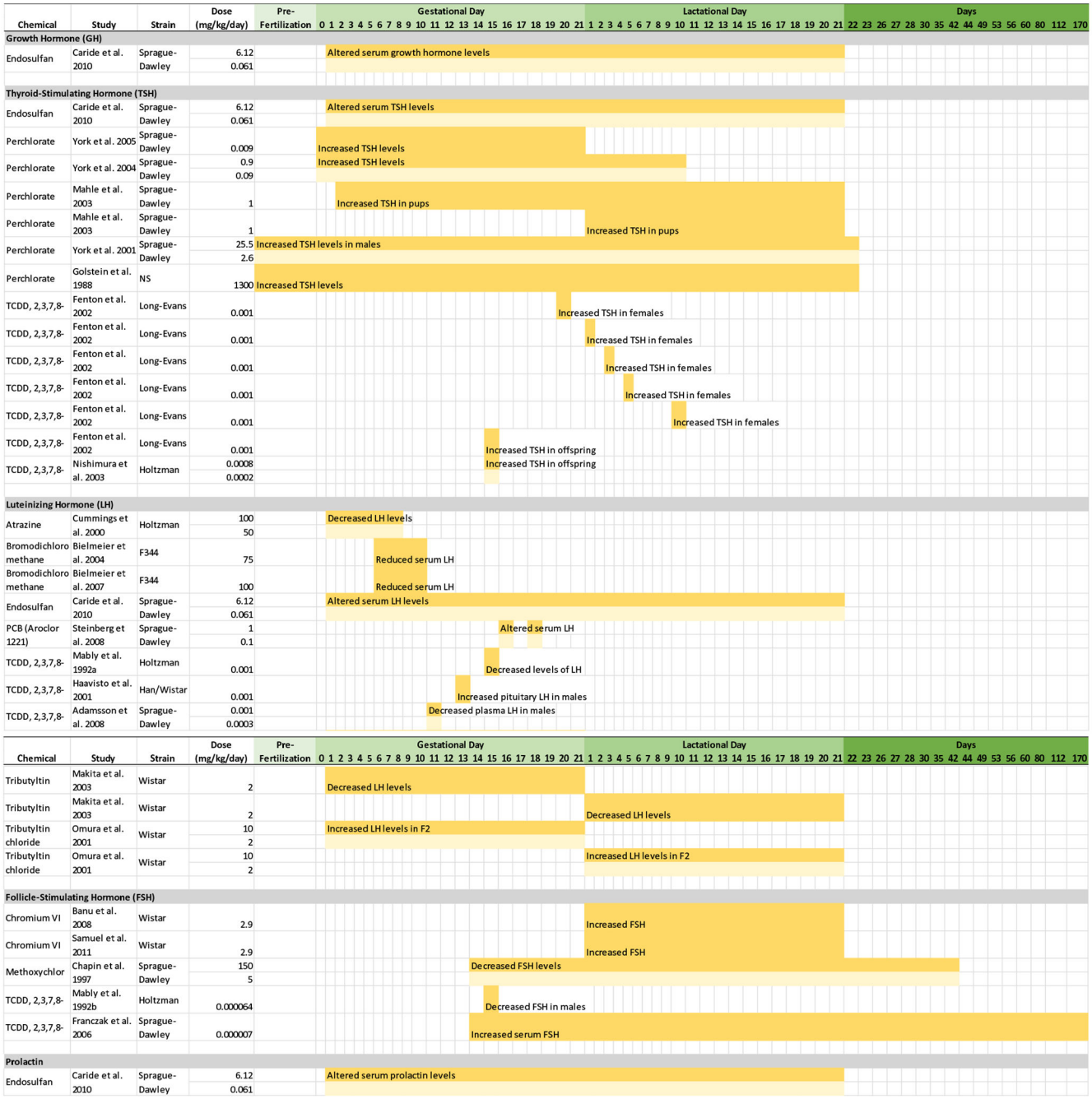

Figure 2.

Windows of exposure for laboratory rat studies noting alterations in hormones produced by the anterior pituitary. Legend: FSH: follicle-stimulating hormone; GH: growth hormone; LH: luteinizing hormone; NS: Not specified; 2,3,7,8-TCDD: 2,3,7,8-tetrachlorodibenzodioxin; TSH: thyroid-stimulating hormone. Dark yellow bars indicate significant exposure effect (LOAELs); pale yellow bars indicate no exposure effect (NOAELs); the width of the bars indicates the exposure period that the studies spanned

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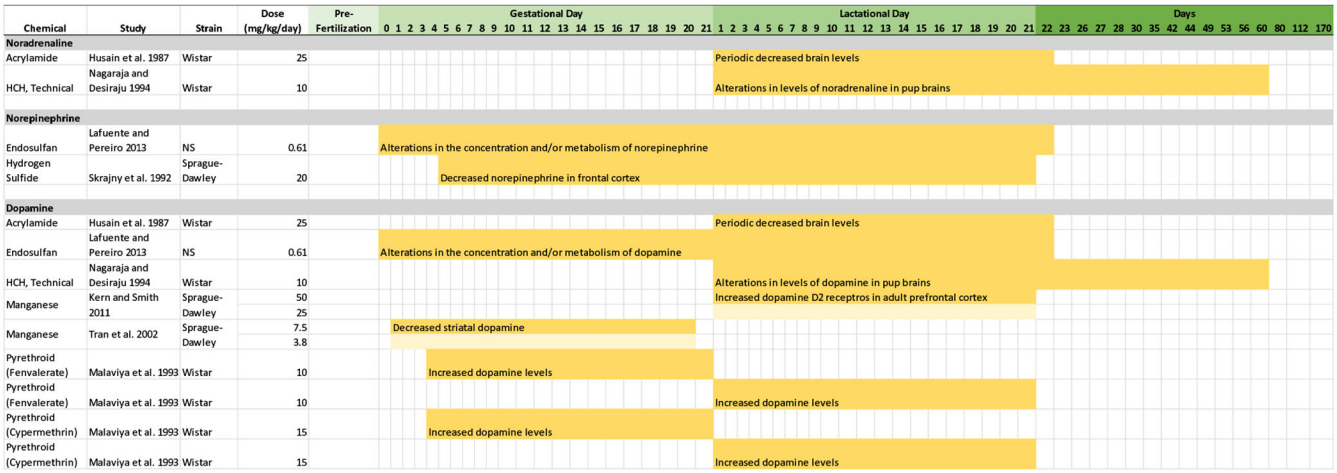

Figure 3.

Windows of exposure for laboratory rat studies noting alterations in hormones produced by the adrenal medulla. Legend: HCH: Hexachlorocyclohexane; NS: Not specified. Dark yellow bars indicate significant exposure effect (LOAELs); pale yellow bars indicate no exposure effect (NOAELs); the width of the bars indicates the exposure period that the studies spanned (i.e. squares filled in from GD7-18 indicate that animals in this study were exposed from GD7 through GD18).

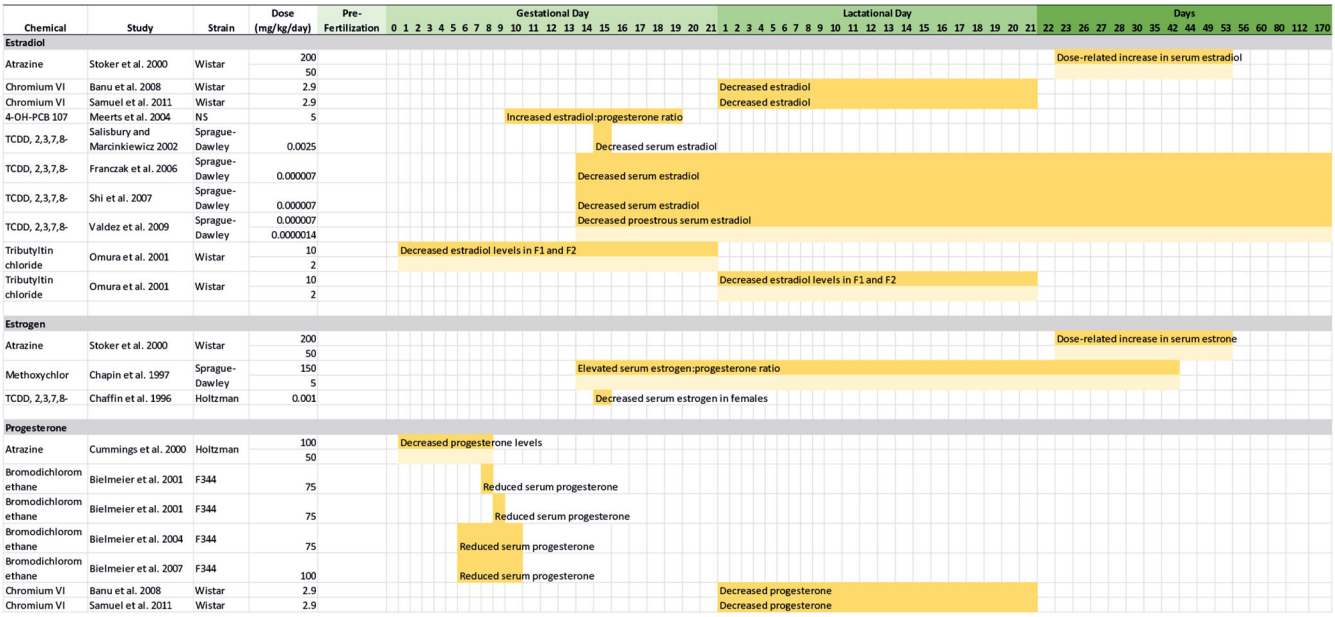

Figure 4.

Windows of exposure for laboratory rat studies noting alterations in hormones produced by the ovaries. Legend: NS: Not specified; OH-PCB: hydroxylated polychlorinated biphenyls; 2,3,7,8-TCDD: 2,3,7,8-tetrachlorodibenzodioxin. Dark yellow bars indicate significant exposure effect (LOAELs); pale yellow bars indicate no exposure effect (NOAELs); the width of the bars indicates the exposure period that the studies spanned (i.e. squares filled in from GD7-18 indicate that animals in this study were exposed from GD7 through GD18).

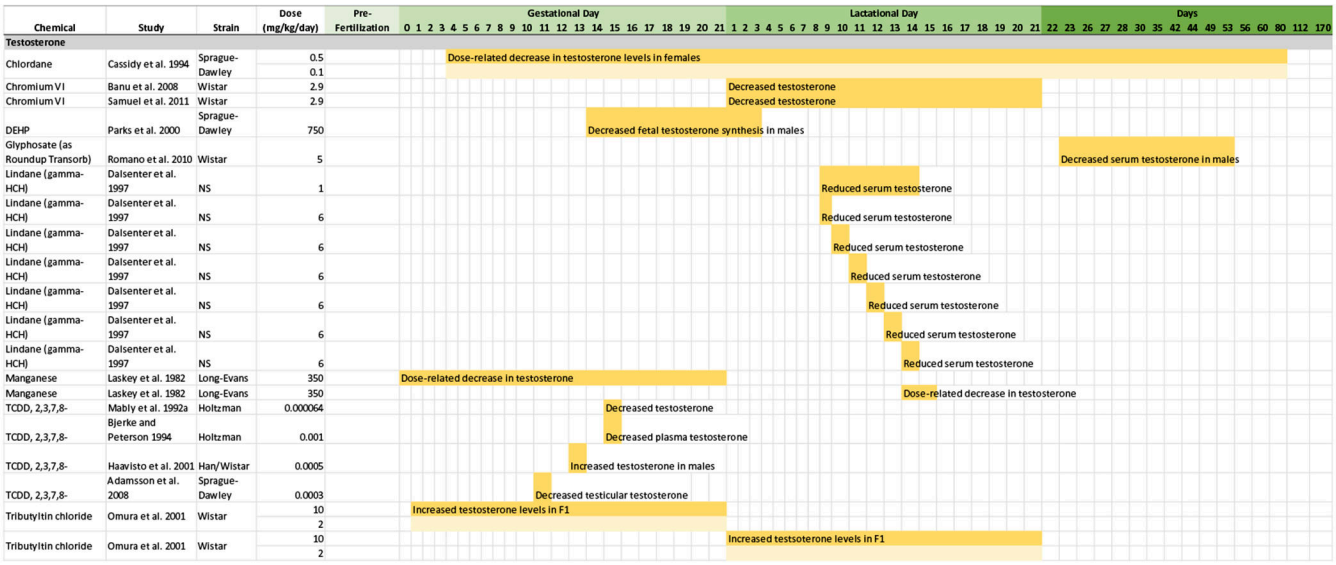

Figure 5.

Windows of exposure for laboratory rat studies noting alterations in hormones produced by the testes. Legend: DEHP: Di(2-ethylhexyl)phthalate; NS: Not specified; 2,3,7,8-TCDD: 2,3,7,8-tetrachlorodibenzodioxin; HCH: Hexachlorocyclohexane. Dark yellow bars indicate significant exposure effect (LOAELs); pale yellow bars indicate no exposure effect (NOAELs); the width of the bars indicates the exposure period that the studies spanned (i.e. squares filled in from GD7-18 indicate that animals in this study were exposed from GD7 through GD18).

Table 1.

General overview of the results of the review.

Hormone	Relevant chemicals (n)	Relevant studies (n)
Anterior Pituitary		
GH	2	1
TSH	3	8
LH	7	10
FSH	3	5
Prolactin	1	1
Thyroid		
T3	9	13
T4	11	37
Adrenal Medulla		
Noradrenaline	2	2
Norepinephrine	2	2
Dopamine	6	6
Ovaries		
Estradiol	5	9
Estrogen	3	3
Progesterone	3	6
Testes		
Testosterone	8	12