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

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Abstract

Development of the fetus is a complex process influenced by many factors including genetics, maternal health, and environmental exposures to toxic chemicals. Adverse developmental effects on the reproductive system have the potential to harm generations beyond those directly exposed. Here, we review the available literature in Agency for Toxic Substances and Disease Registry toxicological profiles related to reproductive-developmental effects in animals following *in utero* exposure to chemicals. We attempt to identify windows of sensitivity. In the discussion, we correlate the findings with human development. The endpoints noted are fertility, estrus, anogenital distance, sex ratio, spermatogenesis, and mammary gland development. We identified some windows of sensitivity; however, the results were hampered by chronic-exposure studies designed to detect effects occurring throughout developmental, including multi-generational studies. This paper demonstrates the need for more acute studies in animals aimed at understanding time periods of development that are more susceptible to chemically induced adverse effects.

Keywords

Reproductive system development; *in utero* exposure; environmental exposure

Introduction

There is general agreement that developing mammals are especially vulnerable to harmful effects of toxic chemicals. It is a long-standing quest to recognize the periods of increased susceptibility during development. For the reproductive system, this includes periods of key developmental events during which chemical exposure may have the greatest potential to influence future reproductive capability. Development of the reproductive system begins at fertilization with chromosomal sex determination and extends from the fetal period through infancy, prepubescence, adolescence, and adulthood (Carlson 2014). The development

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process can be broken down into seven major stages that span *in utero* and postnatal growth. Table 1 presents an overview of these different time periods and the major events in reproductive system development that occur within each stage. The timing of these different stages in both humans and rats is illustrated in Figure 1. The reproductive system starts as a group of cells that has the potential to develop into either male or female gonads. Thus, the same group of cells and tissues differentiates into the embryonic genital structures in both males and females. Differentiation from a bipotential gonad into testes or ovaries begins around gestational day (GD)12 in mice and GD13.5 in rats. In humans, this typically begins in the fifth week of gestation. This sequence of events is described in several embryology books (Carlson 2014). For a quick reference, it is useful to illustrate the differentiation of human genital structures in a tabular form (Table 2). There are differences between exposure scenarios for laboratory animals during testing and environmental exposure of humans to chemicals, the latter of which is generally considered to be chronic.

Previously, we have investigated the windows of sensitivity in the development of cleft palates (Buser and Pohl 2015) and of motor function (Ingber and Pohl 2016) using the Agency for Toxic Substances and Disease Registry's (ATSDR's) toxicological profiles. ATSDR publishes toxicological profiles for hazardous substances that examine, summarize, and interpret available toxicological studies in order to ascertain levels of exposure for humans that may be associated with health effects (https://www.atsdr.cdc.gov/toxprofiles/index.asp). These profiles include only the highest quality, peer-reviewed toxicology studies, and the goal is to provide the necessary and sufficient evidence to support a conclusion on a health effect. Profiles are reviewed on a regular basis to make sure that the conclusions drawn remain current and relevant. One specific health effect category that is evaluated in the profiles is developmental toxicity, which focuses on developmental health effects on the offspring following exposures to parental germ cells, the conceptus through the pre-implantation blastocyst stage, and all subsequent developmental stages up through sexual maturity in animals.

In this paper, we examine animal data from ATSDR toxicological profiles and addenda in an effort to identify developmental windows of sensitivity to chemical exposures for adverse effects on the reproductive system. There is difficulty in defining specific windows of exposure in human populations. Therefore, based on the authors' analyses of the ATSDR animal data, relevance to humans will be discussed.

Methods

Literature search

The literature search examined ATSDR toxicological profiles (n = 181) and addenda (n = 46). The profiles and addenda were searched for data pertaining to chemically induced developmental effects on the reproductive system. Any profiles or addenda that documented studies with reproductive system developmental effects in laboratory mammals (specifically rats and mice) were moved to the data extraction phase (n = 45 chemicals). The review is focused on studies in rats and mice because these provide the majority of studies in the toxicological profile database, which provides a robust amount of data to potentially identify windows. Moreover, the developmental timeline in these animals has been very well defined,

thus allowing for more certainty in extrapolation to humans than other laboratory species. These studies looked at exposure to the developing fetus *in utero* and/or during lactation, and assessed outcomes on the reproductive system of these developing organisms and their future generations.

Data extraction

The following data were extracted from each animal study: chemical name and form; animal species and strain; exposure route and vehicle; exposure duration and frequency; no observed adverse effect level (NOAEL), where applicable; and lowest observed adverse effect level (LOAEL). Exposure duration was plotted in figures showing the days during pre-fertilization, gestation, and/or lactation when animals were exposed. Results were stratified according to specific endpoints related to reproductive system development. The following endpoints were identified as being susceptible to chemically induced effects: fertility, anogenital distance (AGD), spermatogenesis, estrus, sex ratio, and mammary effects. Differences among species, strain, and sex were evaluated in order to determine if these would play a significant role in defining windows of sensitivity. Visual inspection of the figures determined if there were any specific days during gestation or lactation that were possibly deemed especially susceptible to chemically induced alterations in the normal development of the reproductive system. This was based mostly on acute duration studies with heavy focus on single-dose studies to determine if any single days were sufficient to induce alterations. Confirmation for these days came from intermediate and chronic duration studies.

Results

We identified 121 studies in toxicological profiles that evaluated developmental effects of the reproductive system in experimental animal models following exposure to 45 different chemicals. The chemicals broadly fell into eight different categories, with inorganic substances (25%) and pesticides (23%) representing nearly half of the chemicals followed by volatile organic compounds (15%) and dioxins/furans/polychlorinated biphenyls (PCBs) (10%). A vast majority of the studies ($n = 97$) investigating these effects used rats as the model organism; furthermore, most of the included studies utilized full-gestational or gestational plus lactational exposures ($n = 75$). However, there were a few studies within each reproductive endpoint that utilized shorter exposures, including several single-day exposure studies ($n = 30$). Most of the studies found effects at the lowest doses tested; therefore, only LOAELs are presented for most studies. However, a few studies ($n = 32$) demonstrated that dose is a critical factor, and reported NOAELs and LOAELs. The studies with NOAELs and LOAELs spanned across all exposure durations. The overall results observed do not allow for extensive dose response because so few studies reported both NOAELs and LOAELs. Furthermore, the studies that do report NOAELs and LOAELs span many different chemicals, different exposure periods, and different outcomes, which preclude synopsis of dose analysis. Differences among strain, species, and sex were evaluated. There were no noteworthy patterns for strain or sex; however, there were some differences in effects noted for species, so results were stratified by species.

Results of the specific endpoints that were evaluated are presented below. A majority of the individual endpoints support GD 15 in rats as a particularly sensitive day for chemically induced developmental effects on the reproductive system. Furthermore, it seems that regardless of species, sex, or chemical used in the studies, this day represents a consistent window of sensitivity. Based on Carnegie staging in mammals, this day in rats equates to stages 18–19; Carnegie stages 18–19 in humans correspond to week 7 of gestation. Development in the reproductive system during these stages includes opening of the paramesonephric duct, rete ovarii cord development, growth of the uterus mullerian duct in females, and rete testes development from seminiferous cords in males. Thus, it makes sense that perturbations in development during these stages could affect various aspects of normal reproductive system development in both males and females. However, our analyses also indicate that this is not the only day when exposure may adversely affect the development of the reproductive system. Single-day exposure studies on other days and longer duration studies that do not include GD15 suggest that exposure on GD15 may not be necessary for all reproductive developmental effects. Taken together, our analyses as a whole support the knowledge that development of the reproductive system is a process that starts early in fetal development and extends into maturity, and that chemical exposure at different points during this developmental process may affect reproductive health in the generation exposed and future generations.

Fertility

Effects on fertility in offspring following *in utero* exposure was one of the most investigated endpoints in the included studies, with 25 total studies investigating 19 different chemicals (Figure 2). All of the studies resulted in decreased or impaired fertility, with some resulting in complete infertility or sterility. Nineteen of the studies were conducted in rats, and six were conducted in mice. The majority of the exposure durations of these studies does not allow for a window of sensitivity to be established; 15 of the studies exposed animals from prefertilization through full gestation and lactation, with nine of those studies continuing exposure into adulthood. Two studies utilized single-day exposures during gestation; these studies found that exposure on GD 15 to ≥ 0.01 mg/kg/day 2,3,7,8-tetrachlorodibenzodioxin (2,3,7,8-TCDD) resulted in a decreased pregnancy rate and decreased fertility in offspring (Gray and Ostby 1995; Bruner-Tran and Osteen 2011). A series of studies evaluating lactational exposure to PCBs in rats found decreased fertility in male (Sager 1983; Sager et al. 1987, 1991) and female (Sager and Girard 1994) offspring following exposure on lactational day (LD) 1 through 9 (LD1–LD9). The rest of the studies evaluating fertility focused on much longer exposure durations; thus, this information precludes the identification of a window of sensitivity. However, it does show evidence that exposure to these chemicals during any of these exposure periods – gestational only, lactational only, or gestational plus lactational – can result in adverse effects on fertility.

Spermatogenesis

Chemically induced effects on spermatogenesis were studied in 23 studies, of which 17 were conducted in rats and six in mice (Figure 3). The outcomes reported included decreased sperm count and motility as well as increased percentages of abnormal sperm. These studies included all exposure periods: prefertilization only, gestational only, lactational only, or

gestational plus lactational. The most common exposure period was gestational only, with twelve studies reporting altered spermatogenesis, including eight studies that looked at single-day exposures. Exposure to 2,3,7,8-TCDD on GD15 resulted in an increased percentage of abnormal sperm, decreased daily sperm production, reductions in ejaculated sperm count, and decreased cauda sperm reserve (Gray et al. 1997; Ohsako et al. 2002; Simanainen et al. 2004; Bell et al. 2007a). Single exposures on any of GD5 (Kuriyama and Chahoud 2004), GD6 (Kuriyama et al. 2005), GD14 (Hsu et al. 2007), GD18 (Ohsako et al. 2002), or GD20 (Suzuki et al. 1990) also resulted in disruptions in spermatogenesis. One study looked at single exposures during lactation and reported reduced spermatid and sperm counts at maturity following exposure to lindane on LD8 or LD13 (Dalsenter et al. 1997). Another study reported increased proportion of abnormal sperm in offspring following exposure to 2,3,7,8-TCDD during prefertilization only (Bell et al. 2007b). Taken together, the studies investigating alterations to spermatogenesis demonstrate that exposure during any of the periods investigated – prefertilization only, gestational only, lactational only, or gestational plus lactational periods – resulted in these adverse effects to spermatogenesis. Furthermore, GD14–15 seems to represent a particularly sensitive window, with five single-day exposure studies during this period and ten longer duration studies that include one or both of these days. Other single-day exposure studies outside of this window suggest that this period may not be necessary to induce alterations in spermatogenesis, but exposure on these days does seem to be sufficient for spermatogenic effects.

General reproductive system effects in males

Chemically induced effects on the development of the male reproductive system were studied in 34 total studies following exposure to 13 different chemicals (Figure 4). The majority of the studies utilized the rat as the model organism ($n = 28$). The main effect noted in these studies related to alterations in testicular development, as well as hypospadias and cryptorchidism. Sixteen studies exposed animals during gestation only, and half of these studies utilized single-day exposures; 11 studies observed effects in animals exposed during gestation through lactation, with a few extending into adulthood. Single-day exposures on any of GD6 (Kuriyama et al. 2005), GD8 (Gray and Ostby 1995), GD15 (Mably et al. 1992; Bjerke and Peterson 1994; Bjerke et al. 1994; Ohsako et al. 2002), or GD18 (Ohsako et al. 2002) impaired proper development of the male reproductive system. The most common single-day exposure was on GD15 with four studies exposing animals on this day, suggesting that this represents a sensitive window for chemical exposure. Furthermore, all but seven of the other studies had exposure periods that included GD15, thus providing additional support that GD15 may represent a sensitive window for developmental effects in the reproductive system following chemical exposure.

General reproductive system effects in females

Thirty-four studies focused on developmental outcomes specific to female offspring following exposure to 15 different chemicals (Figure 5). The majority of the studies ($n = 31$) used rats as the model organism. These studies included all exposure periods of interest – with some starting during prefertilization ($n = 8$) and extending through birth. The majority of studies included some exposure during gestation ($n = 30$), with 12 focusing solely on gestational exposure, 9 of which were single-day exposures. The most common adverse

effect observed was a change in the timing of the vaginal opening of the exposed fetuses and offspring, with fifteen studies reporting a delay in opening and five others reporting precocious vaginal opening. Other noted effects included alterations in vaginal morphology and delay in pubertal onset. Seven of the single-day exposure studies exposed fetuses on GD15, reporting altered vaginal morphology (Gray and Ostby 1995; Dienhart et al. 2000; Hurst et al. 2002) or alterations in timing of vaginal opening (Brown et al. 1998; Fenton et al. 2002; Kakeyama et al. 2008). All but six of the studies reporting female reproductive system effects – two with single-day exposures on GD6 (Talsness et al. 2005, 2008)) and four with lactational exposure only (Stoker et al. 2004; Banu et al. 2008; He et al. 2011; Samuel et al. 2011) – had exposure periods that included GD15.

Estrus

Alterations to the normal estrus cycle were observed in 21 studies following exposure to 12 different chemicals (Figure 6). The main outcomes reported were those related to disruption of estrus cycles – including acyclicity and lengthened cycles – or alterations in folliculogenesis. These studies looked at all different exposure periods in both rats and mice. The most common exposure periods were gestational only and gestational plus lactational exposure ($n = 19$). Five studies utilized a single-day exposure and reported alterations to normal estrus cyclicity. Four of the studies exposed animals to 2,3,7,8-TCDD on GD15 and reported disruption to the estrus cycle, decreased numbers of ovarian follicles, and earlier first estrus (Brown et al. 1998; Heimler et al. 1998; Salisbury and Marcinkiewicz 2002; Kakeyama et al. 2008). Thus, it seems that this specific day during gestation may represent a window of sensitivity to chemically induced effects on the normality of the estrus cycle. This window was supported by the studies that utilized longer duration exposures throughout prefertilization, gestation, and/or lactation. While the majority of the single-day exposures looked at effects following exposure to 2,3,7,8-TCDD, the studies utilizing other chemicals noted similar effects; therefore, it is possible that the defined window could potentially be applicable to other chemicals that disrupt the estrus cycle.

Anogenital distance (AGD)

Seventeen studies looked at chemically induced changes to AGD by seven different chemicals (Figure 7). Eleven of the studies focused on just three chemicals – 2,3,7,8-TCDD, DDT/DDE/DDD, and DBP – all of which reported decreased AGD. Overall, six studies looked at gestational plus lactational exposure, and eleven looked at gestational only exposure. All but one study utilized exposure periods that included any or all of GD14–16. Since all of these studies reported changes in AGD in the developing animals, GD14–16 was determined to be a window of sensitivity for AGD effects. Furthermore, three studies found decreased AGD following exposure to 2,3,7,8-TCDD on GD15 only (Ohsako et al. 2001, 2002; Simanainen et al. 2004), suggesting that exposure on GD15 may be sufficient to induce alterations to AGD.

Sex ratio

The effects of chemical exposure *in utero* on the sex ratio of fetuses were evaluated in ten studies assessing six chemicals (Figure 8). Seven of the studies were conducted in rats and three were conducted in mice. All of the studies in mice found decreases in the male/female

ratio, while five of the seven studies in rats found decreases in the male/female ratio, and two found increases. Full gestational and lactational exposure to sulfur mustard resulted in an increased male/female ratio (Sasser et al. 1996), as did exposure to pentachlorophenol from GD6–15 (Schwetz et al. 1974). Conversely, exposure to DBP, 2,3,7,8-TCDD, or tetraBDE at different points during gestation and lactation resulted in decreased male/female ratios in rats (Saillenfait et al. 1998; Ema et al. 2000a; Ikeda et al. 2005a, 2005b; Talsness et al. 2008) and mice (Ishihara et al. 2007, 2010). These results suggest that exposure period or species do not appear to be the sole reason behind the difference in the directionality of effect.

The studies looked at all different exposure periods. One study exposed animals during prefertilization only, five looked at exposure during gestation only, including three single-day exposures, and four looked at gestational plus lactational exposure. The three studies that utilized single-day exposures showed that exposure on any of GD6, GD14, or GD15 was sufficient to induce changes in the male/female ratio of the fetuses and offspring (Saillenfaiet et al. 1998; Ikeda et al. 2005a; Talsness et al. 2008).

Mammary gland

Alterations in the development of the mammary gland in fetuses/offspring were the least studied reproductive outcome (Figure 9). Only four studies reported this outcome. One study looked at exposure to PFOA in mice and reported altered mammary gland development in female pups following exposure on either GD8–17 or GD12–17 (White et al. 2007). Three studies reported impaired structural differentiation in the mammary gland in rat fetuses following gestational exposure. These studies all reported impaired mammary gland development following gestational (Loeffler and Peterson 1999; Lewis et al. 2001) or gestational plus lactational (Kodavanti et al. 2010) exposure. The gestational exposure periods of all of the studies overlapped for GD13–GD17, and one study utilized a single-day exposure on GD15 (Lewis et al. 2001). These findings suggest that the critical window for chemically induced alterations to mammary gland development may include GD15 as well.

Discussion

Development of the reproductive system is a complex process that can be influenced by many factors including exposure to environmental chemicals. Biomarkers of effect, such as morphological or physiological changes, can indicate the impact of chemical exposures during development. In humans, examples of biomarkers used to evaluate male reproductive system development include testicular histopathology (from biopsy), seminal sperm quality (number, structure, motility, viability, etc.), other seminal parameters (immature germ cells, Sertoli cells, Leydig cells, etc.), reproductive hormone levels (in blood), fertility status, and anatomical differences in reproductive organs. Biomarkers used to evaluate reproductive development in females include onset of puberty (age at first menstrual cycle, breast development, etc.), reproductive hormone levels, ovarian-oocyte stock, menstrual function (cycle frequency and length, cervical mucus, vaginal cytology, endometrial histology, etc.), fertility status, and anatomical differences in reproductive organs. In this review, we do not

report on the reproductive hormone levels, because this information will be part of the next paper in this series dealing with the endocrine system.

A number of chemicals with potentially different mechanisms of action may cause developmental changes in the reproductive system. Although this is not a mechanisms paper, a brief description of the principles of endocrine disruption is warranted. A generalized mechanism of action sequence for steroidal hormones after entry into the cell includes binding to specific receptor proteins in the cytoplasm or in the nucleus. Once a receptor–ligand complex has been formed, it translocates to the nucleus of the cell. There, the complex interacts with the genome. The subsequent series of events may result in the upregulation or downregulation of specific genes, corresponding to altered patterns of transcription and subsequent translation into patterns of protein synthesis (Alberts et al. 1989). Other potential mechanisms by which endocrine function can be disrupted include a change in the number of receptors that are elaborated in different germ tissues during development. Other means of disrupting endocrine function include interference with protein synthesis and direct interaction of the toxicants with the hormone, thereby altering its activity (DeRosa et al. 1998). For further in depth information, we would like to suggest for interested readers reviews of endocrine disruptors and their adverse action in living organisms (Diamanti-Kandarakis et al. 2009; Kabir et al. 2015).

Principal rules of toxicology discussed in our previous papers include: (1) the dose of the chemical,(2) time of exposure (sensitive window), and (3) species differences (Buser and Pohl 2015; Ingber and Pohl 2016). These variables are also critical for determining effects that tested chemicals may have on the development of the reproductive system. In regard to dose, it should be noted that chemicals that exhibit non-monotonic dose response curves (e.g. bisphenol A) could theoretically produce different windows of sensitivity in response to high and very low doses. These responses can result from several molecular mechanisms such as opposing effects induced by multiple receptors differing by their affinity, receptor desensitization, negative feedback with increasing dose, or dose-dependent metabolism modulation (Lagarde et al. 2015). However, such responses were not detected in this review. The understanding of non-monotonic dose responses stems from observing changing direction of effect over the range of doses examined within a study (Vandenberg et al. 2012). While it is possible that non-monotonic responses could potentially result in different effects following exposure at different time periods, this is not something that has been extensively studied and it is beyond the scope of the present review.

Development of a fully functioning reproductive system spans through several life stages of the individual. Critical windows of sensitivity may include periods of preconception through pregnancy, early childhood, and puberty. They reflect differentiation, development, and/or adult functioning of the reproductive system. Major limitations of this review include the fact that most studies did not try to establish windows of sensitivity, but rather tested for any induction of developmental reproductive effects by chemical exposures. Therefore, the exposures were not focused on smaller time intervals, but spanned through the whole gestation and/or lactation periods. To better understand windows of sensitivity to chemical exposure, additional studies should be conducted that expand on findings from previous studies. Examples of such studies follow. Gray et al. (1995) found a significantly decreased

number of implants when male rats exposed to 1 μg/kg 2,3,7,8-TCDD on GD15 were mated with unexposed females. Altered fertility was not observed in the male offspring of rats exposed to 2,3,7,8-TCDD on GD8 (Gray et al. 1995). It should be noted that in male rats, GD8 exposure was less toxic than GD15 exposure with regard to spermatogenesis and reduced sex gland sizes (Gray and Ostby 1995). Malformations of external genitalia (clefting, hypospadias, and vaginal thread), delayed vaginal opening (only significant in rats exposed on GD15 and not on GD8)(Gray and Ostby 1995), decreased number of ovarian follicles (only tested in GD15-exposed rats), and decreased fertility have been observed in female offspring of Holtzman and Long Evans rats exposed to a single dose of 1 μg/kg 2,3,7,8-TCDD on GD8 or GD15 (Gray and Ostby 1995; Heimler et al. 1998). GD8 exposure also resulted in accelerated onset of constant estrus, shortened reproductive lifespan, and increased incidences of cystic hyperplasia of the endometrium. Impaired development of the reproductive system including decreased epididymal sperm reserves, decreased testes and cauda epididymides weight, and delayed puberty has also been observed in male Syrian hamsters exposed to 2 μg/kg 2,3,7,8-TCDD on GD11 (equivalent to GD15 in rats) (Gray and Ostby 1995). An important observation here is that hamsters, who are relatively resistant to other effects of 2,3,7,8-TCDD such as lethality, can be impacted. In summary, the results indicate that although we have found a narrow window of sensitivity for induction of developmental reproductive effects at GD15, other days may be sensitive, as well. The Gray and Ostby (1995) experiments also show that the effects can be found across species. Previously, we have noted differences among strains of species (Buser and Pohl 2015). Differences among strains were evaluated for this review; however, there were no noteworthy patterns to report. This finding is in agreement with a comparative study among three strains of rats (DA/Han, Sprague-Dawley, and Wistar) that investigated responses to treatments with environmental estrogens using uterotrophic assay (Diel et al. 2004). The authors showed that sensitivity of various biological endpoints can vary slightly; however, the choice of rat strain does not result in marked differences in the evaluation of estrogenic chemicals. This review is limited by the focus on only the mouse and rat species. While ATSDR includes studies in other laboratory mammal species, the vast majority of the toxicological database is focused on these two species. Studies utilizing sheep have shown that exposure to environmental chemicals prior to conception only, during pregnancy only, or throughout life can affect the developing fetus differently (Bellingham et al. 2009, 2016; Lea et al. 2016). These results support findings in rodents. Although it is important to understand species differences, consistency across species provides additional support for understanding potential effects in humans following exposure during critical windows of development.

Another important limitation in this review is the focus on individual chemicals and not on mixtures. Human environmental chemical exposures are primarily to mixtures of chemicals. It is in contrast to most laboratory studies in animals, where single chemicals and their effects on development are tested. ATSDR (2018) developed a program for chemical mixtures, of which an integral part is a mixture health risk assessment. The updated framework document can be found at www.atsdr.cdc. gov/interactionprofiles/index.asp. Issues associated specifically with children development and exposure to mixtures were discussed by us previously (Pohl and Abadin 2008). According to ATSDR (2018), if there is

no information on a mixture of concern, hazard index (i.e. additivity approach) is used to evaluate the toxicity of the whole mixture. Individual binary combinations of chemicals in the mixture can be further qualitatively evaluated for specific endpoints (e.g. reproductive development) as to the possible direction of interactions. The results may influence the final assessment of the mixture. However, a large study of reproductive toxicants administered in utero in binary combinations or in mixtures of < 10 chemicals indicated that 'compounds that act by disparate mechanisms of toxicity to disrupt the dynamic interactions among the interconnected signaling pathways in differentiating tissues produce cumulative dose-additive effects, regardless of the mechanism or mode of action of the individual mixture component' (Rider et al. 2010).

In the late 1990s, the US Environmental Protection Agency (EPA) hosted the Workshop to Identify Critical Windows of Exposure for Children's Health, with the aim of compiling information correlating the timing of exposure (preconception, prenatal, and postnatal) with subsequent outcomes. One workgroup presented on critical windows related to reproductive health in children and adolescents (Lemasters et al. 2000). Our study expands on this workshop report by providing information on selected endpoints from a database of chemical exposure studies in animals found in the ATSDR's toxicological profiles. This earlier workshop noted that there was a deficit of information pertaining to reproductive effects in females. One way to address this deficit is by summarizing a larger body of information on female-specific endpoints, thereby adding to the overall body of evidence on developmental reproductive effects. In the following discussion, we relate the findings from experimental animal studies to potential human exposures and effects.

Decreased fertility

The estimate for prevalence of spontaneous abortions in humans varies. Many cases go unreported or are not even recognized by women in the very early stages of pregnancy. It has been estimated that 25% of childbearing women have had one or more spontaneous abortions (Price 2006). According to 2001 National Vital Statistics Data, fetal mortality over 20 weeks gestation is reported at a rate of about 6.5 deaths per 1000 live births in the US total population (Arias et al. 2003). However, racial, regional, and socioeconomic differences exist; for example, the ratio of infant mortality rate among black infants to that for white infants was reported to be 2.5 in this study. There are many causes for this adverse outcome: pathophysiological, genetic, infectious, etc. Exposure to environmental chemicals is just one of the possible causes, and its contribution to the total prevalence needs to be further elucidated.

In accordance with our animal data (Figure 2), several human studies have reported links between adverse outcomes of pregnancy following maternal exposure to endocrine disruptors such as phthalates and some metals. An association was reported for exposure to lead during pregnancy and increased risk for spontaneous abortions (Hertz-Picciotto 2000; Bellinger 2005), stillbirth, and pre-term delivery (Semczuk and Semczuk-Sikora 2001; McDiarmid et al. 2008; Caserta et al. 2013). A similar association was reported for exposure to mercury (Semczuk and Semczuk-Sikora 2001). Increased risk of spontaneous abortions (Bloom et al. 2010) and increased risk of fetal and infant mortality (Vahter 2008, 2009) were

also found with exposure to arsenic. Increased risks of clinical pregnancy loss were described in pregnant women with higher urinary levels of monoethyl phthalate, monoisobutyl phthalate, and mono-n-butyl phthalate (Mu et al. 2015). Increased urinary levels of mono-isobutyl phthalate and mono-2-ethylhexyl phthalate were also reported in women with unexplained recurrent spontaneous abortions (Peng et al. 2016).

Spermatogenesis

In approximately 40% of infertile couples, the male is the sole cause or at least a contributing factor to the problem (Chandra et al. 2013). In a number of studies, we found that chemical exposure resulted in decreases in sperm count and quality in animal studies (Figure 3). However, the applicability of these results to humans is not fully understood. In a review paper, an argument was raised for the biological credibility of the observation regarding disruption of spermatogenesis and sperm maturation by endocrine disrupters as reported by many laboratory and wildlife studies (Phillips and Tanphaichitr 2008). For interested readers, the pathophysiology is explained in detail. It should be noted that sperm count is used to evaluate male fertility, but it is not the ultimate marker for the effect. Overall, the scientific community is still divided as to whether there is a decline in sperm count in the general population. Some studies report a decline (Carlsen et al. 1992; Rolland et al. 2013), while others claim an increase in sperm count (Saidi et al. 1999; Jorgensen et al. 2012). A possible explanation is that regional variation of semen quality and quantity is likely due to differential exposures to environmental factors, including climate (temperature, sunlight), endocrine disrupters and other environmental chemicals, and regional differences in lifestyle (diet, exercise, alcohol/drug use) (Phillips and Tanphaichitr 2008).

Male reproductive development

If a substance affects Sertoli and Leydig cell differentiation at an early developmental stage, germ cell growth and testosterone production are impaired (Lemasters et al. 2000). As a consequence, genital abnormalities, such as cryptorchidism or hypospadias, may occur at birth, while fertility problems including poor semen quality and testicular germ cell cancer may occur later, with some effects not being seen until adulthood. Our review on alterations in normal development of the male reproductive system includes evidence of many of these effects (Figure 4). Testicular dysgenesis syndrome (TDS) is a condition characterized by the presence of such disorders in humans (Skakkebaek et al. 2001). It was postulated that the origin of TDS is due to both environmental and genomic factors affecting the development of the male reproductive system in fetuses (Toppari et al. 1996; Virtanen et al. 2005). From a genetic perspective, mutations in androgen receptor genes are associated with TDS with high probability, as these are involved in penile development, testes descent, and testes development (Skakkebaek et al. 2001). Similarly, testicular germ cell cancer shows a strong genetic disposition, with the most significant gene variants being those associated with gonad formation and germ cell function (Skakkebaek et al. 2016).

From an environmental perspective, *in utero* exposure of males to substances that disrupt hormone systems, particularly chemicals that inhibit the action of androgens, may result in TDS effects. Lemasters et al. (2000) already speculated that the severity and number of effects may reflect the timing of the environmental exposure (i.e. windows of sensitivity).

However, the window of sensitivity is difficult to pinpoint from epidemiologic studies because of the way the information about exposure is collected. For example, the impact of environmental estrogens measured as total effective xenoestrogen burden was investigated as a risk factor for male urogenital malformations in a nested case–control study (Fernandez et al. 2007). In this study, 50 newborns with diagnosis of cryptorchidism and/or hypospadias were compared with a matched control of 114 boys without malformations. Total effective xenoestrogen burden and levels of 16 organochlorine pesticides were measured in placental tissues. Total effective xenoestrogen burden from organohalogenated compounds was detectable in 72% and 54% of case and control placentas, respectively. Furthermore, the cases had an odds ratio (OR) for detectable versus non-detectable total effective xenoestrogen burden of 2.82 (95% CI: 1.10, 7.24). More pesticides were detected in cases than in controls; some of the ORs (95% CIs) were: 2.25 (1.03, 4.89) for o,p'-DDT, 2.63 (1.21, 5.72) for p,p'-DDT,3.38 (1.36, 8.38) for lindane, 2.85 (1.22, 6.66) for mirex, and 2.19 (0.99, 4.82) for endosulfan-α. Additionally, mothers' association with agriculture (OR = 3.47, 95% CI: 1.33, 9.03) and fathers' occupational exposure to xenoestrogens (OR = 2.98, 95% CI: 1.11, 8.01) were more common in cases than controls. Similarly, a nested case–control study (n = 29 cases and 60 health controls) on cryptorchidism and/or hypospadias following *in utero* exposure to anti-androgens yielded an OR (95% CI) of 2.33 (1.04, 5.23) (Arrebola et al. 2015). The authors concluded that the total effective xenobiotic burden of anti-androgens obtained from placenta after birth is suitable as a biomarker for risk of urogenital malformations in humans.

Altered menstruation

Following women's menstrual cycles is an obvious and nonintrusive way to obtain information about their reproductive health. It is estimated that irregular or abnormal ovulation explains about 25% of infertility problems in women (ASRM 2017). When comparing various mammalian species, it should be noted that there is a difference between species (e.g. rats and mice) who reabsorb the endometrium if conception does not occur during that estrus cycle and species (e.g. humans) who shed the endometrium through menstruation.

Information about changes in estrus cycle was gathered from our database and visualized in Figure 6. Even a narrow exposure window was capable of inducing effects. A review of the impact of developmental exposure to environmental endocrine disruptors on the female reproductive system – and specifically the ovaries – in animal *in vivo* and *in vitro* studies concluded that not only effects were seen in the generation exposed *in utero* but also transgenerational abnormalities were detected (Uzumcu and Zachow 2007).

Numerous human epidemiological studies examined the association between environmental exposure to chemicals and menstrual cycle characteristics of exposed women (Cho et al. 2001; Wennborg et al. 2001; Eskenazi et al. 2002; Buck Louis et al. 2011; Cragin et al. 2011; Lin et al. 2013a, b; Lyngsø et al. 2014). Several studies also attempted to link exposure of mothers during pregnancy to reproductive health of their daughters. For example, daughters (n = 436) of a Danish pregnancy cohort with known maternal serum levels of p,p'-DDE, HCB, and six PCB congeners were followed up at about 20 years of age

(Kristensen et al. 2016). Age of menarche, menstrual cycle length, and serum concentrations of reproductive hormones were obtained. Adverse long-term effects (lower follicle numbers) were noted in those daughters born to the mothers with the highest serum chemical levels. The authors noted that the use of oral contraceptives may have confounded these results, reporting that the free androgen index was inversely associated with high exposure to HCB only in those who did not use oral contraceptives. Another study investigated the fecundity of daughters (n = 289) of women who had measurable levels of DDE and DDT within 1–3 days of delivery (Cohn et al. 2003). The daughters' probability of pregnancy fell by 32% per 10 μg/L p,p'-DDT in maternal serum (95% CI 11–48). By contrast, the probability of pregnancy increased 16% per 10 μg/L p,p'-DDE. The authors did not attempt to explain the inconsistencies in results between the parent compound and metabolite exposures.

Anogenital distance (AGD)

AGD is the distance from the anus to the genitalia, i.e. the base of the penis or vagina. AGD is regulated by dihydrotestosterone and can be, therefore, affected by endocrine disruptors (Gray et al. 1999; Mylchreest et al. 2000). Measuring AGD in neonates has been used as a noninvasive method to determine male feminization (AGD is shorter in females); this has been well characterized in experimental animal studies (Figure 7) and has been used more recently to predict reproductive disorders in humans. In a study on boys who underwent operations for hypospadias repair, Cox et al. (2016) reported a positive correlation between the shortness of AGD and the severity of hypospadias.

Swan et al. (2005) demonstrated that mothers exposed to higher levels of phthalates had sons with shorter AGD, linking environmental exposure and human genital development. The study cohort consisted of 134 babies. Comparing boys with prenatal exposure to mono-n-butyl phthalate in the highest quartile with those in the lowest quartile of exposure, the OR (95% CI) for a shorter anogenital index was 10.2 (2.5, 42.2). AGD was also significantly correlated with penile volume (p = .001) and the fraction of boys with incomplete testicular descent (p = .02). Subsequently, in a larger study, AGD was measured in male infants (N = 366) and female infants (N = 373) (Swan et al. 2015). Concentrations of diethylhexyl phthalate (DEHP) metabolites in the first trimester maternal urine negatively correlated with AGD in boys, but not in girls. Babies with high total exposure to phthalates were ninety times more likely to have a short AGD, although not every type of the nine phthalates tested correlated with shorter AGD.

A lower than median AGD (52 mm in males) may also increase the likelihood of lowered sperm counts and testicular tumors in adulthood. When AGD was measured in infertile men (N = 117) and compared to fertile men (N = 56), infertile men had significantly shorter AGDs (p < .01) (Eisenberg et al. 2011). Shorter AGD was also positively correlated with decreased sperm density and total motile sperm count in a cohort of 69 men with obstructive azoospermia (OA) in Texas and 29 men with nonobstructive azoospermia (NOA) (Eisenberg et al. 2012). The NOA men had significantly shorter mean AGDs than the men with OA (p = .01). An AGD of less than 30 mm yielded a significantly increased odds of NOA compared to OA (OR 5.6, 95% CI: 1.10, 30.7). In another study, associations between AGD measures and semen quality were tested in 91 men in Spain (Mendiola et al. 2015).

Significantly positive associations between AGD measures and sperm concentration, total sperm count, and total sperm motile count were reported ($p < .05$). However, a recent study in 473 men concluded that although AGD is associated with sperm production on a population level, at the individual level, the AGD alone cannot accurately estimate the efficacy of spermatogenesis (Eisenberg and Lipshultz 2015).

Male/female sex ratio

In animals, perturbations of typical male/female sex ratio in litters is a common metric used to show disruptions in the overall reproductive health of the animals (Figure 8); these alterations may be due to any of several effects including selective loss of male embryos, changes to normal implantation/resorption frequency, etc. The laboratory observations regarding sex ratio changes were supported by studies in humans. In 1976, following an exposure at a chemical plant near Seveso, Italy, boys who were under 19 years of age and were exposed to the highest concentrations of 2,3,7,8-TCDD produced more girls than boys during procreation in adulthood (male/female sex ratio of 0.38 compared to 0.56 in unexposed males) (Mocarelli et al. 2000). The authors noted that the median exposure concentration of dioxin to the fathers in this study was similar to doses that have been shown to induce epididymal deficiencies in rats, and was about 20 times the estimated average exposure concentration of 2,3,7,8-TCDD reported for humans from industrialized countries. Another study found that Russian production workers exposed to 2,3,7,8-TCDD-contaminated 2,3,4-T had altered sex ratios in their children, with more females born than males (Basharova 1996). Similarly, male workers ($n = 9512$) exposed to chlorophenate wood preservatives contaminated with CDDs reported births of more females (51.4%) than males (48.6%) out of a total of 19675 births (Dimich-Ward et al. 1996).

Alterations to sex ratio have also been seen in the general public. A review on sex ratios reported in several industrial countries found that since 1950 the proportion of males born in Denmark and the Netherlands has significantly declined. In the United States and Canada, similar declines have been reported since 1970. Additionally, similar declines have been reported for Sweden, Germany, Norway, and Finland (Davis et al. 1998). The authors suggest that environmental and occupational exposures to chemicals may be contributing to the shifts being observed in human sex ratio. The above studies mostly look at paternal occupational exposure, so the window of exposure in these studies would typically coincide to prefertilization time periods.

Mammary gland development

Information regarding effects on the development of mammary glands following chemical exposures was limited in our database (Figure 9). A 2009 workshop – The Mammary Gland Evaluation and Risk Assessment Workshop – was convened to discuss the current state of evaluating mammary gland development, including effects of gestational or early life exposure on development and how these developmental perturbations may affect later in life lactation or cancer outcomes. The report from the workgroup concluded that ‘early life environmental exposures can alter mammary gland development, disrupt lactation, and increase susceptibility to breast cancer’ (Rudel 2011). However, inconsistent reporting methods make comparison across studies difficult, and relationships between altered

development and effects on lactation or carcinogenesis are still being investigated. A recent article by Osborne et al. (2015) provides an excellent review of the topic related to human experience. The authors note that mammary gland development is a complex process that encompasses several life stages, the most important being fetal/neonatal period, puberty, and pregnancy in females. Conversely, in males, mammary gland development stops before birth due to the action of androgens. During these windows, the mammary gland is sensitive to altered development and adverse effects including cancer and other diseases (e.g. problems with lactation in females or gynecomastia in males).

Conclusion

Windows of sensitivity to chemical exposures during development of the reproductive system in animals were examined. Overall, rodent models provide an appropriate exposure-response model for reproductive effects (Lemasters et al. 2000). However, it is important to note that there are numerous, important differences between animals (particularly rodents) and humans with regard to development of the reproductive system, including the timing of these events. Specifically, the duration of embryogenesis, infancy, and puberty in humans takes place over years compared to days and months in rodents. Therefore, identifying specific windows of sensitivity for the development of a complex system such as the reproductive system is difficult. A major limitation of this review is the availability of studies testing chemicals through small increments of time during gestation. Because most studies exposed animals throughout the entire pregnancy, specific windows of sensitivity were not obtainable. However, data from both experimental animal studies and epidemiological studies can together provide information that suggests time periods that are sensitive to perturbations in the development of the human reproductive system following chemical exposure. Future research should focus on exposing animals over several short time periods throughout different stages of development in order to better identify these specific windows of sensitivity.

Abbreviation

2,3,7,8-TCDD	2,3,7,8-tetrachlorodibenzodioxin
AGD	anogenital distanceATSDR: Agency for Toxic Substances and Disease Registry
CDD	chlorinated dibenzo-p-dioxin
CI	confidence interval
DBP	di-n-butyl phthalate
DDD	dichlorodiphenyldichloroethane
DDE	dichlorodiphenyldichloroethylene
DDT	dichlorodiphenyltrichloroethane
decaBDE	decabromodiphenyl ether

DEHP	di(2-ethylhexyl) phthalate
EPA	Environmental Protection Agency
GD	gestational day
HCB	hexachlorobenzene
IR	ionizing radiation
JP-5	jet propellant-5
JP-8	jet propellant-8
LD	lactational day
LOAEL	lowest observed adverse effect level
NOA	nonobstructive azoospermia
NOAEL	no observed adverse effect level
OR	Odds ratio
PAH	polycyclic aromatic hydrocarbon
PCB	polychlorinated biphenyl
PFOA	perfluorooctanoic acid
pentaBDE	pentabromodiphenyl
TCEP	tris(2-chloroethyl) phosphate
tetraBDE	tetrabromodiphenyl
TDS	testicular dysgenesis syndrome

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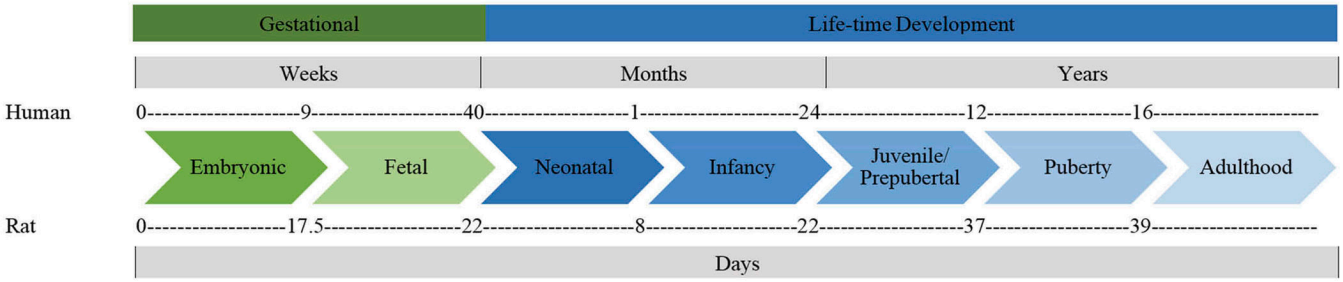

Figure 1.
Comparison of timing *in utero* and postnatal stage of development in humans versus rodents.

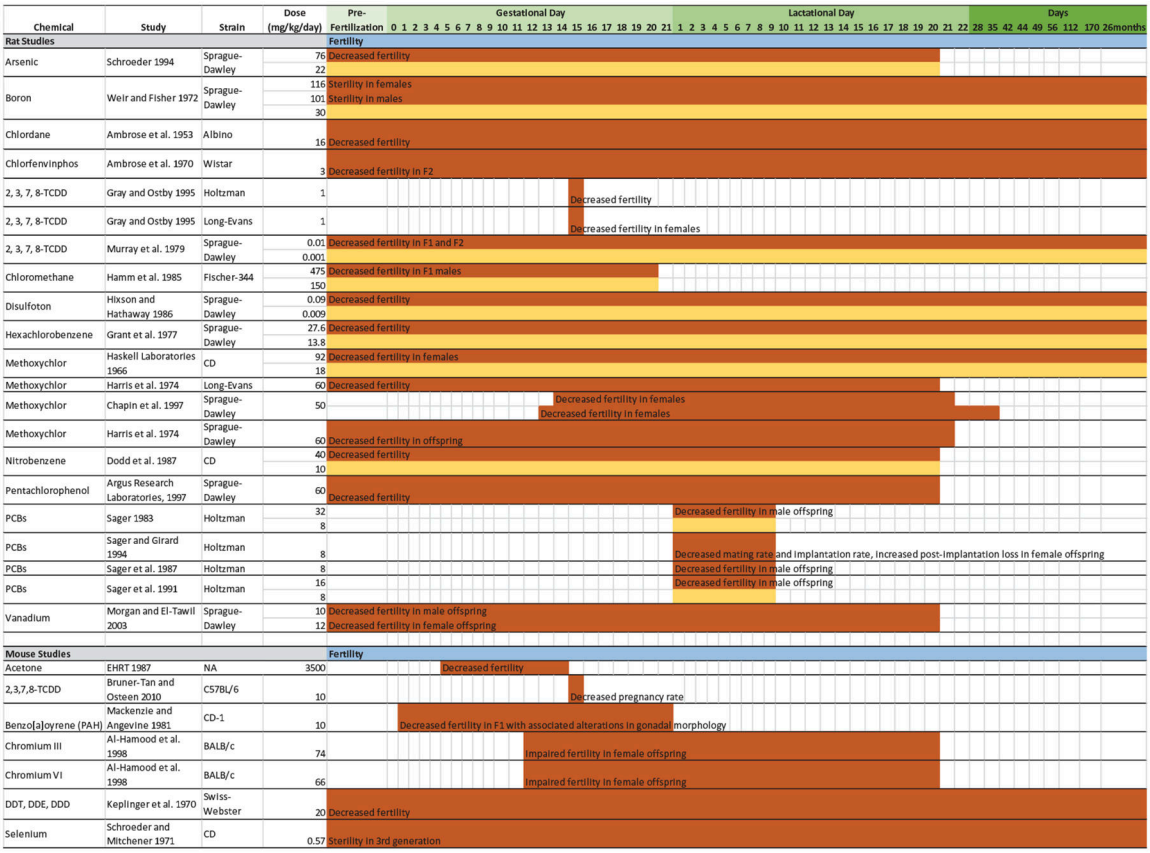

Figure 2. 2,3,7,8-TCDD: 2,3,7,8-tetrachlorodibenzodioxin; DDD: dichlorodiphenyldichloroethane; DDE: dichlorodiphenyldichloroethylene; DDT: dichlorodiphenyltrichloroethane; PAH: polycyclic aromatic hydrocarbon; PCBs: polychlorinated biphenyls.

Yellow bars indicate no exposure effect (NOAELs); orange bars indicate significant exposure effect (LOAELs); 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).

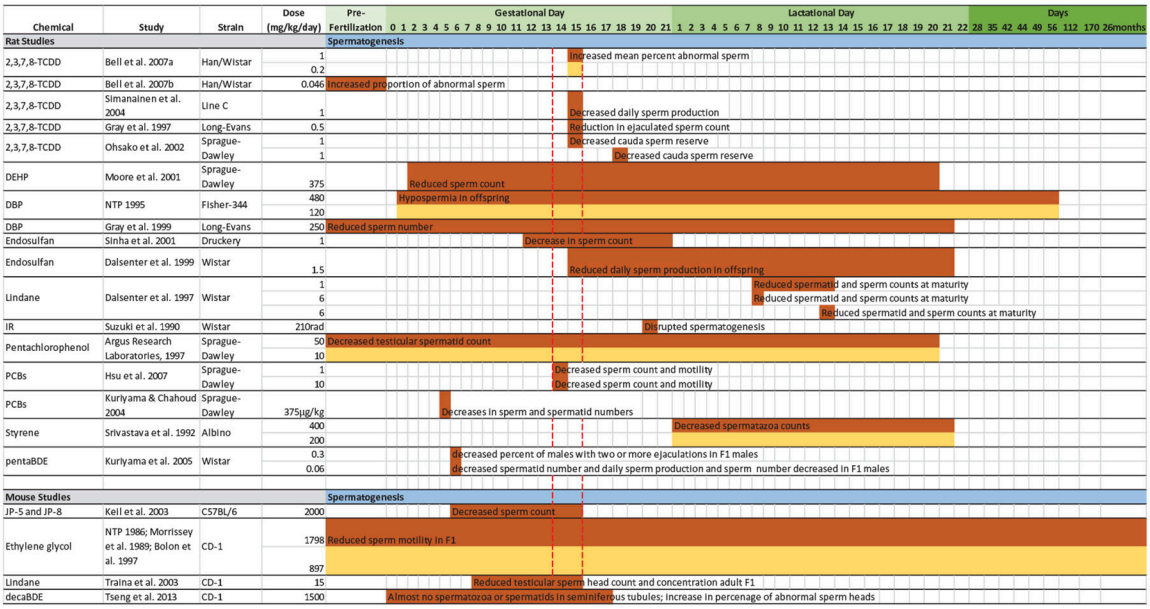

Figure 3. 2,3,7,8-TCDD: 2,3,7,8-tetrachlorodibenzodioxin; DBP: di-*n*-butyl phthalate; decaBDE: decabromodiphenyl ether; DEHP: di(2-ethylhexyl) phthalate; IR: ionizing radiation; JP-5: jet propellant-5; JP-8: jet-propellant-8; PCBs: polychlorinated biphenyls; pentaBDE: pentabromodiphenyl ether.

Red dashed lines indicate the narrowest critical exposure window identified based on overlap of exposure durations found to cause significant developmental effects on spermatogenesis combined with NOAEL data from short and single-dose duration studies. Yellow bars indicate no exposure effect (NOAELs); orange bars indicate significant exposure effect (LOAELs); 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).

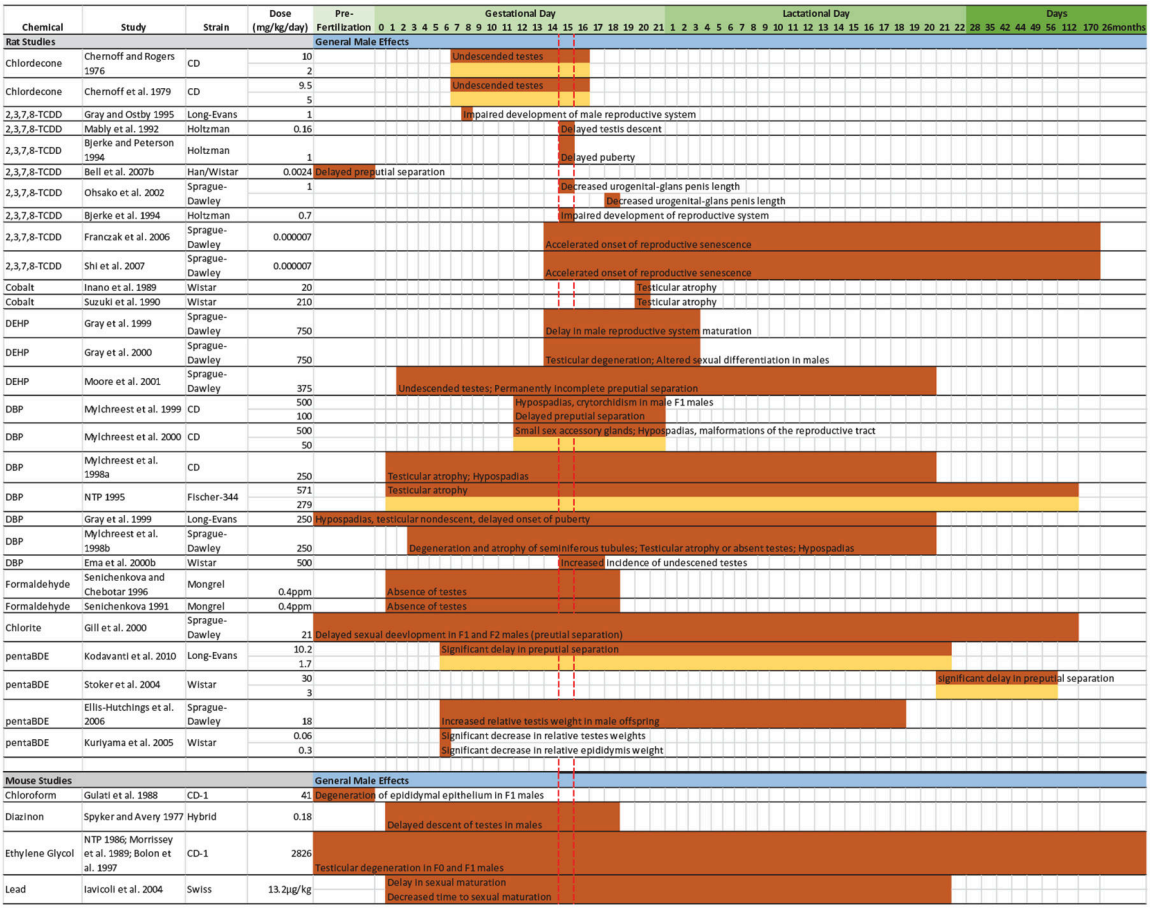

Figure 4. 2,3,7,8-TCDD: 2,3,7,8-tetrachlorodibenzodioxin; DBP: di-*n*-butyl phthalate; DEHP: di(2-ethylhexyl) phthalate; pentaBDE: pentabromodiphenyl ether.

Red dashed lines indicate the narrowest critical exposure window identified based on overlap of exposure durations found to cause significant developmental effects on general effects in the male reproductive system with NOAEL data from short and single-dose duration studies. Yellow bars indicate no exposure effect (NOAELs); orange bars indicate significant exposure effect (LOAELs); the width of the bars indicates the exposure period that the studies spanned (i.e. squares filled in from GD7 to GD18 indicate that animals in this study were exposed from GD7 through GD18).

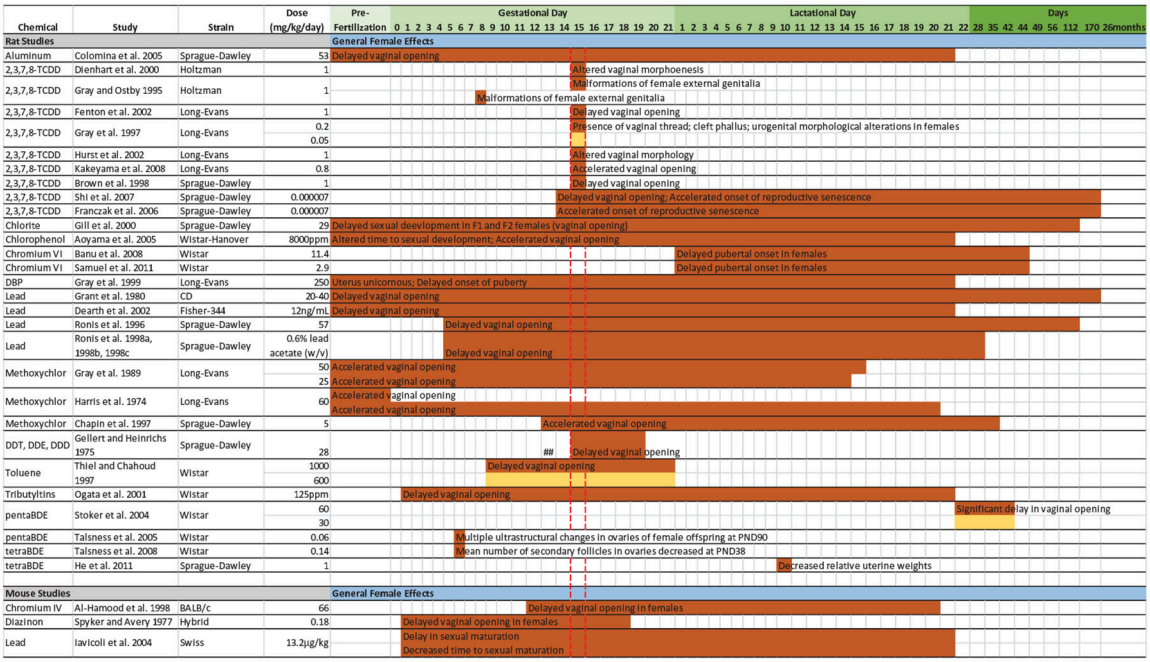

Figure 5. 2,3,7,8-TCDD: 2,3,7,8-tetrachlorodibenzodioxin; DBP: di-*n*-butyl phthalate; decaBDE: decabromodiphenyl ether; DDD: dichlorodiphenyldichloroethane; DDE: dichlorodiphenyldichloroethylene; DDT: dichlorodiphenyltrichloroethane; pentaBDE: pentabromodiphenyl ether.

Red dashed lines indicate the narrowest critical exposure window identified based on overlap of exposure durations found to cause significant developmental effects on general effects in the female reproductive system combined with NOAEL data from short and single-dose duration studies. Yellow bars indicate no exposure effect (NOAELs); orange bars indicate significant exposure effect (LOAELs); the width of the bars indicates the exposure period that the studies spanned (i.e. squares filled in from GD7 to GD18 indicate that animals in this study were exposed from GD7 through GD18)

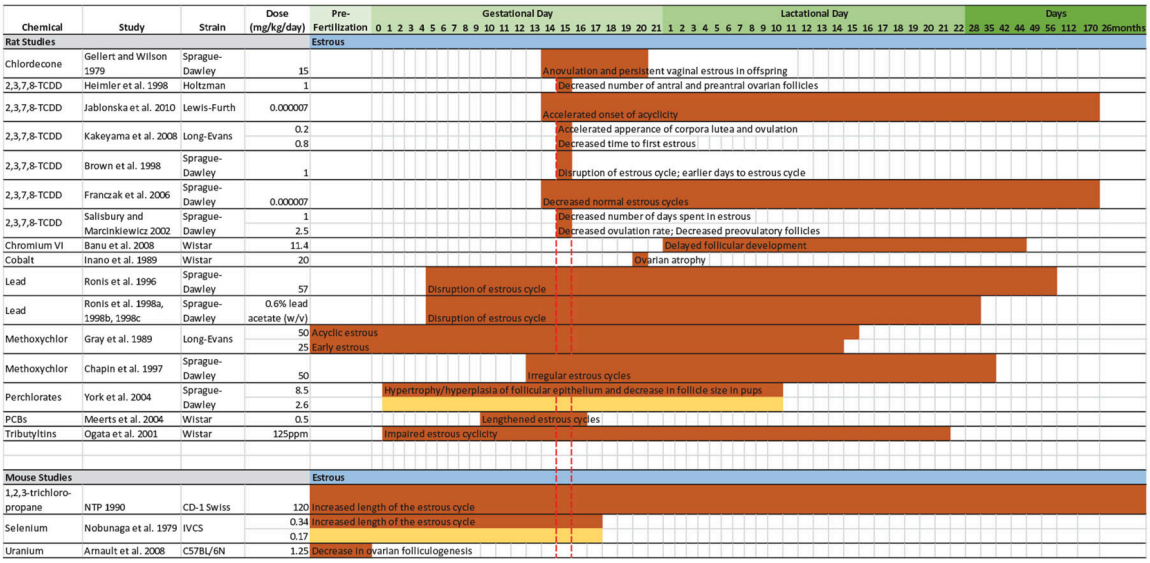

Figure 6. 2,3,7,8-TCDD: 2,3,7,8-tetrachlorodibenzodioxin; PCBs: polychlorinated biphenyls.

Red dashed lines indicate the narrowest critical exposure window identified based on overlap of exposure durations found to cause significant developmental effects on estrous cyclicity combined with NOAEL data from short and single-dose duration studies. Yellow bars indicate no exposure effect (NOAELs); orange bars indicate significant exposure effect (LOAELs); the width of the bars indicates the exposure period that the studies spanned (i.e. squares filled in from GD7 to GD18 indicate that animals in this study were exposed from GD7 through GD18).

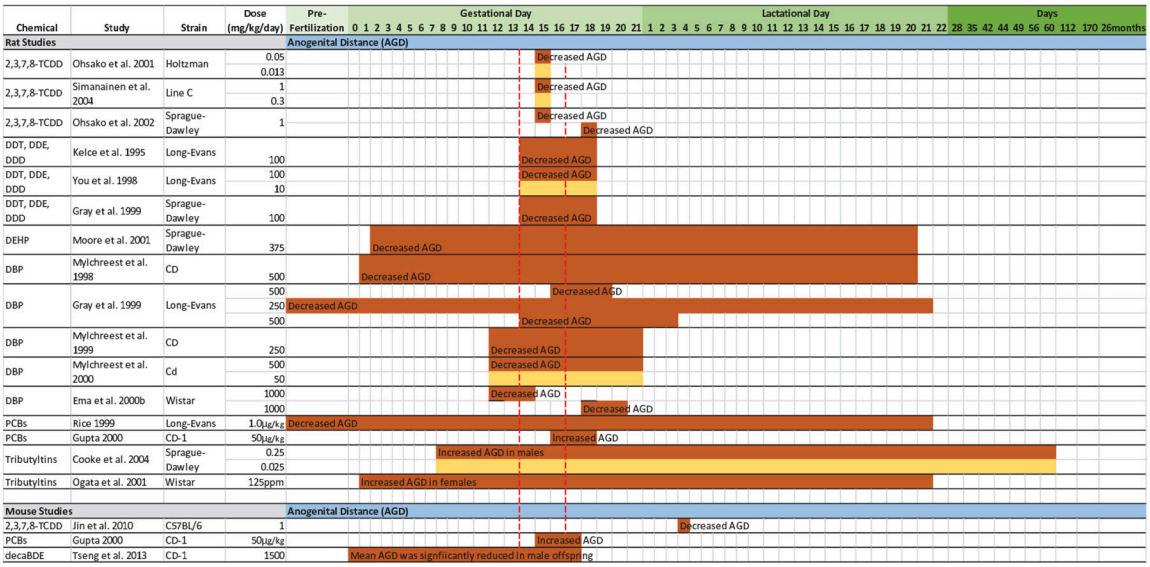

Figure 7. 2,3,7,8-TCDD: 2,3,7,8-tetrachlorodibenzodioxin; AGD: anogenital distance; DBP: di-*n*-butyl phthalate; decaBDE: decabromodiphenyl ether; DDD: dichlorodiphenyldichloroethane; DDE: dichlorodiphenyldichloroethylene; DDT: dichlorodiphenyltrichloroethane; DEHP: di(2-ethylhexyl) phthalate; PCBs: polychlorinated biphenyls.

Red dashed lines indicate the narrowest critical exposure window identified based on overlap of exposure durations found to cause significant developmental effects on AGD combined with NOAEL data from short and single-dose duration studies. Yellow bars indicate no exposure effect (NOAELs); orange bars indicate significant exposure effect (LOAELs); the width of the bars indicates the exposure period that the studies spanned(i.e. squares filled in from GD7 to GD18 indicate that animals in this study were exposed from GD7 through GD18).

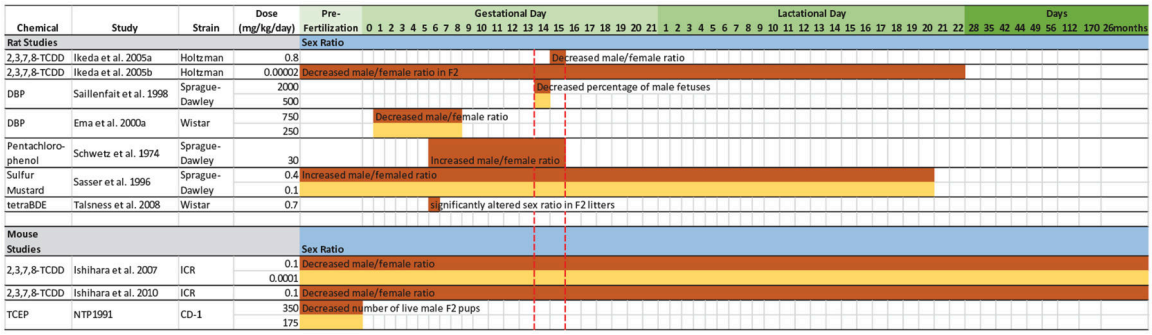

Figure 8. 2,3,7,8-TCDD: 2,3,7,8-tetrachlorodibenzodioxin; DBP: di-*n*-butyl phthalate; TCEP: tris(2-chloroethyl) phosphate.

Red dashed lines indicate the narrowest critical exposure window identified based on overlap of exposure durations found to cause significant developmental effects on sex ratio combined with NOAEL data from short and single-dose duration studies. Yellow bars indicate no exposure effect (NOAELs); orange bars indicate significant exposure effect (LOAELs); the width of the bars indicates the exposure period that the studies spanned (i.e. squares filled in from GD7 to GD18 indicate that animals in this study were exposed from GD7 through GD18).

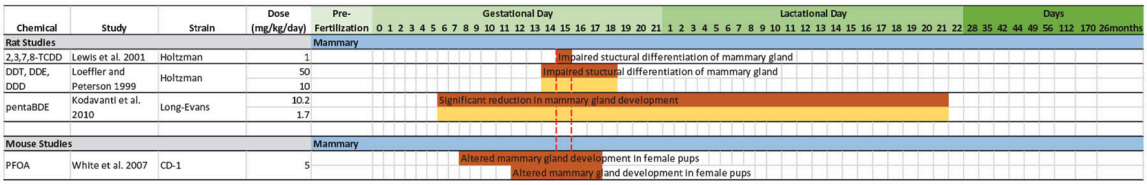

Figure 9. 2,3,7,8-TCDD: 2,3,7,8-tetrachlorodibenzodioxin; DDD: dichlorodiphenyldichloroethane; DDE: dichlorodiphenyldichloroethylene; DDT: dichlorodiphenyltrichloroethane; pentaBDE: pentabromodiphenyl ether; PFOA: perfluorooctanoic acid.

Red dashed lines indicate the narrowest critical exposure window identified based on overlap of exposure durations found to cause significant developmental effects on mammary gland development combined with NOAEL data from short and single-dose duration studies. Yellow bars indicate no exposure effect (NOAELs); orange bars indicate significant exposure effect (LOAELs); the width of the bars indicates the exposure period that the studies spanned (i.e. squares filled in from GD7 to GD18 indicate that animals in this study were exposed from GD7 through GD18).

Table 1.

Overview of major developmental time periods for the reproductive system shared across human and rat species.

Stage	Major events
Embryonic	• Chromosomal sex determined at fertilization
	• Major organogenesis
	• Establishment of primordial germ cell lineage and germ cell migration
	• Undifferentiated gonad → beginning of differentiation of gonad
	• Mammary bud formation begins
Fetal	• Ongoing organogenesis
	• Oogenesis
	• Differentiation of gonad completes
	• Development of internal and external genitalia
	• Sexual dimorphism of brain/endocrine system
	• Testicular descent begins
	• Mammary gland stimulation begins
Neonatal	• Formation of spermatogonial stem cells that will differentiate into spermatozoa at puberty
Infancy	• Secondary sexual characteristics begin (in rats)
Juvenile/prepubertal	• Secondary sexual characteristics begin (in humans)
	• Increase in number of spermatogonia continues
	• Spermatogenesis begins
	• Mammary gland in males and females essentially the same
Puberty	• Full function of reproductive organs attained
	• Spermatogenesis continues
	• Mammary gland maturation resumes
	• Menarche begins
Adulthood	• Spermatogenesis continues
	• Progression of arrested state oocytes in primordial follicles to primary and secondary follicular phases

*Adapted from (Carlson 2014).

Table 2.

Derivatives of embryonic genital structures.

Embryonic structure	Male	Female
Indifferent gonad	Testis	Ovary
Cortex		Ovarian follicles
Medulla	Seminiferous tubules	Medulla
	Rete testis	Rete ovarii
Urogenital mesentery	Mesorchium	Mesovarium
Gubernaculum	Gubernaculum testis	Ovarian ligament
		Round ligament of uterus
Mesonephric tubules	Ductuli effernetis	Epoophoron
	Paradidymis	Paroophoron
	Aberrant ductules	Duct of epoophoron
	Ductus epididymis	Duct of Gartner
	Ductus deferens	Ureter, pelvis, calyces, and collecting
	Ureter, pelvis, calyces, and collecting tubules	tubules
Mesonephric duct	Appendix of epididymis	
	Ejaculatory duct and seminal gland (vesicle)	
Paramesonephric duct	Appendix of testis	Hydatid (of Morgagni)
	Prostatic utricle	Oviduct or fallopian tubes
		Uterus
		Vagina (upper)
Genital tubercle	Penis	Vestibule
		Clitoris
Urogenital folds	Ventral (under) aspect of penis - penile urethra	Labia minora
Labioscrotal swellings	Scrotum	Labia majora

*Adapted from (Carlson 2014).