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Windows of Sensitivity to Toxic Chemicals in the Development of Cleft Palates

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Abstract

Cleft lip and cleft palate are among the most common birth defects worldwide. There is a genetic component to the development of these malformations, as well as evidence that environmental exposures and prescription drug use may exacerbate or even produce these manifestations. Thus, it is important to understand the underlying mechanisms and when these exposures affect development of the growing fetus. The purpose of this investigation was to critically review the available literature related to orofacial cleft formation following chemical exposure and identify specific time frames for windows of sensitivity. Further, an aim was to evaluate the potential for predicting effects in humans based on animal studies. Evidence indicates that chemical causes of cleft palate development are due to dose and timing of exposure, susceptibility of the species (i.e., the genetic makeup), and mechanism of action. Several studies demonstrated that dose is a crucial factor; however, some investigators argued that even more important than dose was timing of exposure. Data show that the window of sensitivity to environmental teratogens in the development of cleft palates is quite narrow and follows closely the window of palatogenesis in the fetus of any given species.

Cleft lip and cleft palate are birth defects termed orofacial clefts, which are some of the most common birth defects. Studies in genetics and embryology suggested that clefts of the primary (hard) palate that involve the lip and/or palate have a different mechanism of origin than those clefts affecting only the secondary palate (Parker et al. 2010). Therefore, these malformations are treated separately in most investigations. The Centers for Disease Control and Prevention (CDC) reported that in the United States, the estimated number of annual cases of babies born with a cleft palate was 2651 (1 in 1574 births) and of babies born with a cleft lip with or without a cleft palate was 4437 (1 in 940 births) for the time period of 2004–2006 (Parker et al. 2010). These clefts were probably caused by a combination of genetic predisposition and environmental exposures (Watkins et al. 2014). Increased risk of cleft palate occurrence is also associated with smoking during pregnancy (Little et al. 2004; Honein et al. 2007; 2014) and with diabetes diagnosed in mothers before pregnancy (Correa et al. 2008).

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In humans, the facial region develops between wk 4 and 8 of gestation, and palatal development specifically takes place between wk 7 and 12 of gestation (Sucheston and Cannon 1973). The development can be divided into formation of the primary palate comprised of the prolabium, premaxilla, and cartilaginous septum and formation of the secondary palate consisting of the hard and soft palates (Sucheston and Cannon 1973). By wk 4 of gestation, five processes (two maxillary, two mandibular, and a single frontal) are observed surrounding the stomodeum. During wk 5, olfactory placodes occur that develop into pits surrounded by the medial and lateral nasal processes. During wk 6, the maxillary and lateral nasal processes merge, and the two mandibular processes unite. Between wk 7 and 8, the upper lip is completed by maxillary mesoderm that joins at the midline. The maxillary and mandibular processes form the cheeks. In addition, in wk 7, two vertical palatal processes extend from the primary palate to the tonsillar pillars. Between wk 8 and 9, these processes migrate to a horizontal position but remain separated by the tongue. The secondary palate is fully formed by fusion of the processes during wk 10 to 12 when the tongue descends to the bottom of oral cavity and the teeth and neck are formed.

The mouse was suggested as a reliable model to research genetic and environmental causes affecting normal development of the lip and palate (Gritli-Linde 2012). During early craniofacial development, the embryos of mice and humans look similar, and their developmental stages resemble each other. In addition, both species share genes that are involved in orofacial clefting. The major difference pertains to the time scale when each developmental event occurs. Mouse palatogenesis starts at embryonic day 11.5 and manifests with the formation of palatal shelves extending from the maxillae (Chai and Maxson 2006). Between day 12.5 and 13.5, the palatal shelves protrude downwards laterally on both sides of the tongue. Meanwhile, the maxillary and mandibular processes unite, the tongue descends, and the palatal shelves position horizontally above the tongue. Fusion of the palatal shelves occurs on day 14.5. The timetable of events in humans and mice in formation of the palate is presented in Figure 1.

Similar developmental events also occur in rats. However, in this species, the palatal shelf elevation occurs at day 16.4 (Ferguson 1978). The palatal shelf elevation and shelf fusion start in the anterior part; the extreme posterior part of each shelf is horizontal from the beginning of rat palatogenesis and develops into soft palate (Ferguson 1978; 1981). Studies in other animals may add valuable information, because not all species are affected by the same chemical to the same extent; for example, in the case of dioxins, there are differences in Ah receptor levels and in affinities for the ligand (Agency for Toxic Substances and Disease Registry [ATSDR] 1998).

As previously indicated, environmental exposures to toxic chemicals are one of the possible causes of orofacial congenital malformations. The Agency for Toxic Substances and Disease Registry (ATSDR) publishes toxicological profiles for hazardous chemicals, and one of the specific end-points detailed in the profiles is developmental toxicity. The profiles were used as a major source of information for this review. The purposes of this review are as follows:

- Review available animal data related to cleft palate formation following chemical exposure and make comparisons.

- Evaluate how narrow the windows of sensitivity are.

Methods

Literature Search

The primary search examined ATSDR Toxicological Profiles (n = 173) and Addenda (n=41) in search of evidence of cleft palate development in association with chemical exposure. All profiles and addenda that described studies with the outcome of cleft palate were moved into the data extraction phase (n = 28 profiles and 1 addenda).

Data Extraction

For animal studies, the following data from each study were extracted: chemical name and form; species and strain; exposure route and vehicle; exposure time, duration, and frequency; no-observed-adverse-effect level (NOAEL), where applicable; and lowest-observed-adverse-effect level (LOAEL).

Results

Mouse

The mouse was the most utilized model for examining cleft palate development, which was not unexpected, as mouse models are versatile, easily manipulated genetically, and have palatal development similar to humans (Gritli-Linde 2012). Figure 2 contains data extracted from these studies. Taken together, these studies suggest a short duration of sensitivity that is a narrow window of susceptibility for cleft palate development.

CD-1—CD-1 mice were the most commonly used strain in these identified studies. Many of the studies examined durations of exposure that encompassed the periods of mouse development specific to palatogenesis, with the most typical being for gestational days (GD) 6–15 or GD 7–16 (Courtney 1976; Courtney et al. 1976; Marks et al. 1982; National Toxicology Program [NTP] 1983; Rogers et al. 1981; Tyl and Neeper-Bradley 1989). All investigations that perused this range of gestational days found significant increases in the incidence of cleft palate (Figure 2). A few studies examined even narrower exposure windows of one to three days. Bolon et al. (1993) investigated the effects of methanol and noted that exposure during GD 7–9 or GD 9–11 significantly elevated the incidence of cleft palate. In addition, two other studies evaluated single day exposures. A single exposure to endrin on GD 9 (Ottolenghi et al. 1974) or a single exposure to gamma radiation on GD 12 (Saad et al. 1991) each significantly induced development of cleft palate (Figure 2).

C57BL/6J—C57BL/6J was another mouse strain widely used in these developmental studies. Chlorinated dibenzo-*p*-dioxins (CDD) and chlorodibenzofurans (CDF) were extensively studied within this specific mouse strain, and both chemicals were investigated within narrow exposure windows. Four studies examined CDD, and all focused on single day exposures (Abbott and Birnbaum 1989a; 1989b; Dasenbrock et al. 1992; Weber et al. 1985; Yuan et al. 2012). Data shown in Figure 2 indicate that a single-day exposure to CDDs during GD 9–12 was sufficient to significantly increase the incidence of cleft palate within

this mouse strain. Similarly, studies examining CDF also suggest a narrow window of exposure for induction of cleft palate development. Two studies demonstrated significant elevation in cleft palate after exposure to CDF on GD 10–13 (Birnbaum et al. 1987a; 1987b; Weber et al. 1984), and two additional studies found that a single-day exposure to CDF on GD 12 was sufficient to induce significant cleft palate development within C57BL/6J mice (Hassoun et al. 1984; Yamada et al. 2006) (Figure 2). While these investigations were typically designed to determine dose level rather than day of exposure, these results, taken together, suggest that cleft palate development as a consequence of chemical exposure may be induced during a very narrow window of exposure.

Rat

The rat is another highly utilized model in studies on cleft palate development (Figure 2). Similar to the mouse, most investigations employing the rat as a model also provide an opportunity to more accurately identify the specific time and duration of potential windows of sensitivity to chemical exposures.

Wistar—Wistar rats were the most commonly used strain in these studies. Many of the investigations focused on exposure durations between 8 and 11 d; these exposures were typically within the period of GD 6–17. However, several studies also noted significantly increased incidence of cleft palate after 3-d exposure durations during GD 7–9 (Ema et al. 1994; 1995a), GD 11–13 (Uriu-Adams et al. 2001), or GD 13–15 (Ema et al. 1994; 1995a; 1995b). Further, one study investigated the effects of single-day exposure to polybrominated biphenyls (PBB) and found that exposure to a high dose of 800 mg/kg on any single day between GD 6 and GD 14 was sufficient to significantly increase the incidence of cleft palate development (Beaudoin 1977) (Figure 2).

Sprague-Dawley—Five studies were identified that used Sprague-Dawley (SD) rats to investigate cleft palate development. Results of these studies are helpful in narrowing the window of sensitivity for rats. Two of these studies reported that exposures during GD 2–20 (Thibodeaux et al. 2003) or GD 6–15 (Schwetz et al. 1973) induced significant cleft palate development. Several other investigations observed similar effects with narrower windows of exposure such as GD 11–15 (Zangar et al. 1989) and GD 12–14 (Springer et al. 1986) (Figure 2). Further, Bruni et al. (1994) showed that exposure to gamma radiation on GD 9.5 was enough to induce cleft palate formation. Taken together, these studies help to define a small window of sensitivity to chemically induced cleft palate development in rats.

Rabbit

Boron (in the form of boric acid), CDDs (specifically 2,3,7,8-tetrachlorodibenzo-*p*- dioxin [TCDD]), and cobalt (from a radiocobalt source) were found to induce cleft palates in the developing rabbit model. Price et al. (1996) demonstrated that boron exposure during GD 6–19 significantly enhanced the occurrence of cleft palates (Figure 2). Exposure to 2,3,7,8-TCDD on GD 6–15 also resulted in a significant rise in the incidence of cleft palates (Giavini et al. 1982). In addition, a single-day exposure to a radiocobalt source on either GD 10, 11, or 12 was found to significantly increase development of cleft palates in rabbits (Chang et al. 1963) (Figure 2). It is difficult to determine a specific window of susceptibility

for cleft palate formation when the results are also dependent on the exposure dose rather than simply the timing, such as day(s) of exposure. However, it is interesting to note that each of these three studies helped to narrow down a window of sensitivity in rabbits. Price et al. (1996) had the largest window of exposure, but it included the exposure time frames of Giavini et al. (1982), which further included the windows from Chang et al. (1963). It should be noted that exposure at a high enough dose on any single day between GD 10 and 12 was sufficient to induce cleft palate development in rabbits (Figure 2).

Hamster

Studies investigating cleft palate development in hamsters used a very narrow window of exposure days. Exposure to aldrin/dieldrin on any of GD 7, 8, or 9 induced significant development of cleft palate (Ottolenghi et al. 1974). In addition, exposures to endrin (Ottolenghi et al. 1974) or 2,3,7,8-TCDD (Kransler et al. 2007) on GD 9 or mercuric acid on GD 8 (Gale and Ferm 1971) each resulted in a significant elevation in cleft palate development (Figure 2). While the hamster model has the same limitations as those previously discussed for mouse and rat, namely, that differences in susceptibility are also dependent on dose level rather than simply the time such as day(s) of exposure; these findings, as shown in Figure 2, suggest that a single-day exposure on any of GD 7, 8, or 9 is sufficient to induce significant cleft palate development.

Discussion

From a review of the literature cited in the preceding, it was confirmed that the main elements that determine whether a chemical exposure causes development of cleft palate are the specific chemical, dose, timing of exposure, and susceptibility of the species. In addition, inherent in this is the mechanism of action (MOA) of the chemical, as described in the following.

Dose and Timing

As demonstrated in our results, the window of sensitivity to environmental teratogens in the development of cleft palate is quite narrow and follows closely the window of palatogenesis in the fetus of any given species. It is in sharp contrast to neurological development, since the neurological system develops not only in utero, but also for some period after birth (Makri et al. 2004; Cooke 2014; S. Ingber and H. R. Pohl personal communication 2015). Therefore, the window of sensitivity is broader for neurodevelopmental effects. Obviously, no palatal clefts are expected following exposures during the period after development of the orofacial area. However, a single-day exposure to BP-6 before the palatogenesis window (Beaudoin 1977) and even exposure to TCDD 2 wk prior to conception (Giavini et al. 1983) resulted in adverse effects in rats. This may be attributed to the longer half-lives of these chemicals and their persistence in the body (ATSDR 1998; 2004). Several studies demonstrated that dose is a critical factor, showing the NOAEL following administration of lower doses and LOAEL following higher doses (Domingo et al. 1989; Ema et al. 1991; Faqi et al. 1997; Hackett et al. 1984; Huuskonen et al. 1994; Kransler et al. 2007; Noda et al. 1991; NTP 1983; Schwetz et al. 1973).

However, some investigators argued that even more important than dose was the timing of exposure. When retinoic acid (RA) was administered to rats on different treatment days within the GD 8–12 period, exposure on days GD 10 and GD 10.5 produced the most severe effects (Gunston et al. 2005). Interestingly, a dose of 30 mg/kg RA on GD 8–11 produced more severe consequences than a higher dose of 100 mg/kg administered on GD 8–9, indicating an even narrower window for severe effects on GD10 and 11. Retinoic acid is a known mor-phogen and was studied extensively (Schilling et al. 2012). Shenefelt (1972) treated pregnant hamsters with single doses of RA sodium salt at different stages of pregnancy. Shenefelt (1972) determined that a single oral dose of RA on any day during GD 7–11 produced significant increases in cleft palate development in fetuses, with peaks on GD 8 and 9.

Another study investigating timing of exposure rather than dose investigated the fetal effects of methanol inhalation exposure on pregnant CD-1 mice (Rogers and Mole 1997). Researchers assessed critical periods for methanol developmental toxicity by exposing pregnant mice to 10,000 ppm methanol or to filtered air on 2 consecutive days from GD 6-13 or on a single day during GD 5–9. Cleft palate was induced in fetuses with 2-day exposures on any of GD 6–7 through GD 11–12, with peak induction on GD 7–8. Further, single-day exposures from GD 5 through GD 9 resulted in significant increases in cleft palate in the fetuses with peak on GD 7. Tiboni et al. (2006) attempted to define critical periods for cleft palate development in mice after exposure to itraconazole. Cleft palate defects developed in fetuses after single-day exposures during GD 9–11, with the most significant effects being observed after a single exposure on GD 10.

Interestingly, an earlier study determined two critical periods for cleft palate development. Peterka and Jelinek (1978), in a study in ICR-Velaz mouse embryos, not only determined two critical periods of development but also defined the independent causes of cleft palate development within these two critical periods. Treatment with a teratogen on GD 12 resulted in development of cleft palate in 80% of embryos, while treatment with a different teratogen on GD 14 resulted in 90% treated embryos developing cleft palate. A similar study found that the critical period for induction of cleft palate might depend on the nature of the teratogen. Gebhardt and Schade (1969) treated pregnant Swiss albino mice with four different teratogens to investigate whether the critical periods differed. Data showed that treatment with x-rays or cyclophosphamide initiated the most significant induction of cleft palate on GD 11 or 12, whereas the optimal induction period for induction of cleft palate by dexamethasone or 6-aminonicotinamide was GD 13 or 14.

Species Susceptibility and Mechanism of Action (MOA)

Although the emphasis of this review deals with environmental chemicals and their role in inducing cleft palates, this information would not be complete without acknowledging that genetics also play a major role in development of this malformation. In humans, there are significant differences in occurrence of this birth defect depending upon populations, ethnicity, and gender (Christensen 1999; Cooper et al. 2006; Mossey 2007). Asians and Native Americans have the highest rate of cleft lip with or without cleft palate (about 2 per 1,000 live births). Caucasians have a rate of about 1 per 1,000, and Africans have the lowest

rate of approximately 1 per 2,500 births. Gender differences noted in cleft lip with cleft palate gave a male to female ratio of 2:1. However, for cleft palate only, the ratio is 1:1. In Colorado, during the years 1982–1988, odds ratios (OR) of male gender (OR = 1.62), white race (OR = 2.87), and nonmetropolitan residence (OR = 1.59) were linked with elevated risk of displaying a cleft malformation of any type at birth (Amidei et al. 1994). In California, prevalence ratios (PR) were established for cleft lip with or without cleft palate and cleft palate alone in a cohort of more than 2 million births during the years 1983–1992 (Croen et al. 1998). Racial variations were as follows: Asians had the highest PR and African-Americans the lowest PR, with Caucasians intermediate. One interesting finding pointed to possible environmental factors affecting the risk of developing the clefts. There was a numerically lower PR among offspring of foreign-born Chinese mothers compared with United States-born Chinese mothers, and a quantitatively higher PR among offspring of foreign-born Filipino mothers versus the United States-born (Croen et al. 1998). However, the subcohorts were small and confidence intervals (CI) around these risks were wide. When a segregation analysis of cleft lip with or without cleft palate was conducted using Danish and Japanese cohorts, Chung et al. (1986) proposed that the Danish inheritance pattern is a combination of a major (recessive) gene action and of multifactorial inheritance. In contrast, Japanese data indicated multifactorial inheritance with markedly lower recurrence risks among relatives, although the overall incidence of malformation in the cohort was higher. There are many studies identifying genomic regions linked to development of cleft lip with or without cleft palate. It is beyond the scope of this review to list them all; interested readers can access the reviews on this topic (Marazita 2012; Prescott et al. 2001).

The mouse served as a model to study the genetics of cleft palate development (Gritli-Linde 2008; 2012; Juriloff and Harris 2008). Evidence indicates that mouse models demonstrate diversity of causative genes and mutations, and the effects such as clefting are likely genetically and developmentally heterogeneous (Juriloff and Harris 2008). This also applies to humans. Possible interaction of genetic and environmental factors has always been acknowledged in the literature. Prenatal secondhand smoke (SHS) exposure is one such example. Prenatal SHS exposure has been commonly associated with cleft palate development. Six studies examining prenatal SHS exposure via either direct maternal smoking or passive maternal smoking (defined as maternal exposure to smoke in the home or other public places during early pregnancy) found that SHS exposure was significantly positively associated with cleft palate development (Goncalves Leite and Koifman 2009; Honein et al. 2007; Jia et al. 2011; Li et al. 2010; Shaw et al. 2009; Zhang et al. 2011). Further, a meta-analysis by Little et al. (2001) analyzed 24 case-control and cohort studies and reported that consistent significant associations were found between maternal smoking and cleft palate development. Another meta-analysis by Molina-Solana and colleagues (2012) noted an overall significant rise in cleft palate incidence based on six studies. Recently, genetic research demonstrated evidence of gene–environment interaction for two genes on chromosome 4p16.1 and environmental tobacco smoke in 259 Asian case–parents trios (Wu et al. 2014).

The mechanism underlying cleft induction is not fully understood for all chemicals. However, the MOA of dioxin (2,3,7,8-tetrachlorodibenzo-*p*-dioxin or TCDD) and dioxin-like chemicals was studied extensively. TCDD and dioxin-like compounds act via a specific

receptor present in all cells: the aryl hydrocarbon (Ah) receptor (Poland and Glover 1973). This action is further mediated by the Ah receptor nuclear translocator (ARNT). ARNT interacts with the liganded Ah receptor to form a heterodimeric DNA-binding protein complex that binds DNA and activates gene transcription (Whitlock 1993).

As illustrated in Figure 2, exposure to TCDD during gestation produced an increased incidence of cleft palate in offspring of mice (Abbott and Birnbaum 1989a; Courtney 1976; Dasenbrock et al. 1992; Neubert and Dillman 1972; Smith et al. 1976; Weber et al. 1985), rats (Giaviani et al. 1983; Huuskonen et al. 1994), and rabbits (Giavini et al. 1983). Some clefts were induced without a notable maternal toxicity, and the most sensitive species was the mouse (Couture et al. 1990). An in vitro study with human embryonic palatal shelves indicated that human palates are less sensitive than C57BL/6N mouse palates to TCDD exposure (Abbott and Birnbaum 1991). Abbott et al. (1994a; 1994b) proposed that the TCDD-induced effects on palatal development may be mediated by the Ah receptor. Exposure to TCDD resulted in a dose-dependent down-regulation of the Ah receptor throughout the palate, which may have occurred at the transcriptional level as decreases in mRNA were also observed (Abbott et al. 1994a). A proof of the Ah receptor involvement originated from a study in Ahr-null mutant mice that were lacking the Ah receptor (Mimura et al. 1997). TCDD induced no cleft palates in the Ahr-null fetuses, but in heterozygotes with Ahr+/- genotypes, a haplo-insufficiency was found in the incidence of the malformation.

TCDD-induced cleft palate is produced by failure of opposing palatal shelves to fuse (Pratt et al. 1984). Under normal development, there is a cessation of medial cell proliferation, a degeneration of peridermal medial cells, and a transformation of basal cells to mesenchymal cells as the opposing palatal shelves come into contact and fuse (Abbott and Birnbaum 1989b). TCDD exposure alters medial cell proliferation and differentiation, resulting in the formation of stratified squamous epithelium. Abbott and Birnbaum (1990) postulated that the altered proliferation and differentiation of the medial cells may be attributed to TCDD-induced reductions of several growth factors, including epidermal growth factor (EGF), transforming growth factor (TGF)-α, and TGF-β1, and increases in EGF receptor expression. EGF and TGF-α which both bind to the EGF receptor stimulate epithelial proliferation and differentiation and TGF-β1 inhibits epithelial proliferation. The elevated levels of EGF receptor appear to compensate for reduced EGF and TGFα levels resulting in continued proliferation. Teratogenicity of TCDD was studied in wild-type and knockout (−/−) mice that did not express EGF, TGF-α, or both EGF and TGF-α (Bryant et al. 2001). Cleft palates did not develop in EGF (−/−) and in EGF (−/−) + TGF-α (−/−) fetuses treated with TCDD, confirming the fact that EGF affects induction of cleft palate by TCDD. In addition, insulin-like growth factor 2 (Igf2) may also play a role in TCDD-induced teratogenicity (Wang et al. 2011).

The studies just cited demonstrate the impact of toxicodynamic differences among species on susceptibility to environmentally induced cleft palate. Toxicokinetic differences are also important. Dioxins are metabolized by CYP1A2 enzymes. The CYP1A1, CYP1A2, and CYP1B1 genes are upregulated by the Ah receptor. Dragin et al. (2006) demonstrated that mouse fetuses were protected against cleft palates by maternal hepatic CYP1A2

sequestering TCDD. Substitution of the human CYP1A2 transgene provided the same protection. In contrast, offspring of CYP1A2 (−/−) dams showed about sixfold higher sensitivity to cleft palate, hydronephrosis, and lethality after exposure to TCDD. CYP1A1 and CYP1B1 did not display any marked influence on development of birth defects.

Chlorinated dibenzofurans (CDF) and polybrominated dibenzofurans (PBDF) exert the same MOA as TCDD. However, when C57BL/6N mice were exposed on GD 10 to TCDD or three different PBDF, potency of the PBDF was lower than that of TCDD (Birnbaum et al. 1991). Pretreatment of C57BL/6N mice with hexachlorobiphenyl produced a limited antagonism of TCDD teratogenicity, as evidenced by cleft palate and/or hydronephrosis (Morrissey et al. 1992).

Altered expression of growth factors might be responsible for induction of cleft palates in mice exposed on GD 10 or 12 to TCDD alone or TCDD and RA (Abbott and Birnbaum 1990). The reduction was greater with exposures on GD 10. Abbott and Pratt (1991) also reported that retinoids altered the expression of EGF receptors in vitro. Subsequently, Jacobs et al. (2011) noted that secondary palate development was dependent on all-*trans*-retinoic acid (atRA) signaling, which is a hormone-like signal originated from retinoic acid that controls Ah receptor expression. An intact atRA signal was needed to enable TCDD to trigger cleft palate development. In conclusion, cleft palates are birth defects of multifactorial origins involving both genetic and environmental components. However, there is still much to be learned regarding the MOA by which these defects are being induced by environmental chemicals.

Summary

Windows of sensitivity to chemicals in development of cleft palate correlate with palatogenesis in the species examined. The effects are related to dose and timing of exposure. Although the MOA underlying induction of cleft palate by different chemicals is not fully understood, current research is focused on the importance of interactions between environmental factors and genetics. Genetic variability in sensitivity to the development of cleft palate does exist, as intraspecies and interspecies differences have been reported. Some animal models such as mouse are viewed as helpful in determining the development of cleft palate with results potentially applicable to humans. Genome-wide regions have also been identified that play a role in cleft palate development. Together, these findings indicate that cleft palate resulting from chemical exposure is highly dependent on specific and generally narrow windows of sensitivity—windows modulated by a complex interaction of specific chemical, MOA, species, dose, timing, and genotype.

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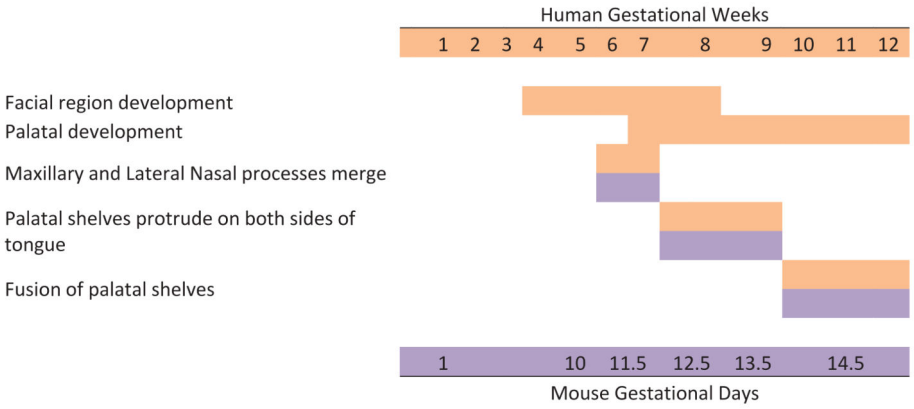
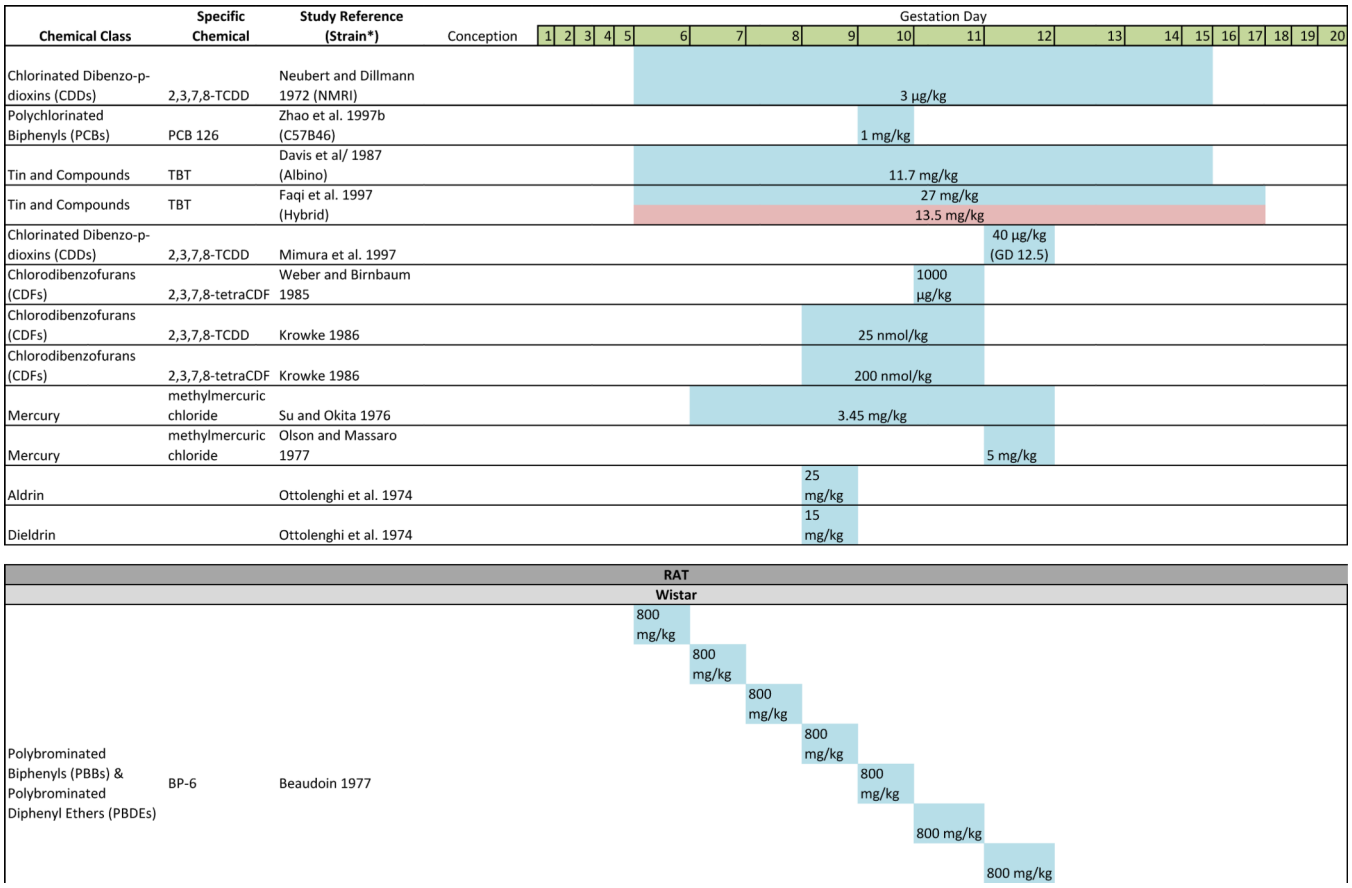


Figure 1.

Human and mouse developmental windows of orofacial development. Adapted from Sucheston and Cannon (1973) and from Chai and Maxson (2006).

Chemical Class	Specific Chemical	Study Reference (Strain*)	Conception	Gestation Day 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Mouse				
CD-1				
Arsenic	DMA	Rogers et al. 1981		400 mg/kg 200 mg/kg
2-Butoxyethanol		Wier et al. 1987		1000 mg/kg 650 mg/kg
Chlorinated Dibenzo-p-dioxins (CDDs)	2,3,7,8-TCDD	Courtney 1976		25 µg/kg
Creosote	coal tar	Zangar et al. 1989		500 mg/kg
Endrin/Endrin aldehyde	Endrin	Ottolenghi et al. 1974		2.5 mg/kg
Hexachlorobenzene		Courtney et al. 1976		100 mg/kg
Ionizing Radiation	gamma radiation	Saad et al. 1991		400 rad
Methyl tert-Butyl Ether (MTBE)	MTBE	Tyl and Neeper-Bradley 1989		8000 ppm 1000 ppm
Perfluoroalkyls	PFOS	Thibodeaux et al. 2003		15 mg/kg
Phenol	Phenol	NTP 1983b		280 mg/kg 140 mg/kg
Xylenes	Mixed	Marks et al. 1982		2060 mg/kg 1030 mg/kg
methanol	methanol	Bolon et al. 1993		10000 ppm 10000 ppm 10000 ppm
C57/BL6J				
Chlorinated Dibenzo-p-dioxins (CDDs)	2,3,7,8-TCDD	Weber et al. 1985		12 µg/kg
Chlorinated Dibenzo-p-dioxins (CDDs)	2,3,7,8-TCDD	Abbott and Birnbaum 1989a		6 µg/kg 6 µg/kg
Chlorinated Dibenzo-p-dioxins (CDDs)	2,3,7,8-TCDD	Dasenbrock et al. 1992		15 µg/kg
Chlorinated Dibenzo-p-dioxins (CDDs)	2,3,7,8-TCDD	Yuan et al. 2012		64 g/kg
Chlorodibenzofurans (CDFs)	2,3,7,8-tetraCDF	Weber et al. 1984		50 µg/kg
Chlorodibenzofurans (CDFs)	2,3,4,7,8-pentaCDF	Birnbaum et al. 1987b		30 µg/kg
Chlorodibenzofurans (CDFs)	1,2,3,7,8-pentaCDF	Birnbaum et al. 1987a		100 µg/kg
Chlorodibenzofurans (CDFs)	1,2,3,4,7,8-hexaCDF	Birnbaum et al. 1987b		300 µg/kg

Chemical Class	Specific Chemical	Study Reference (Strain*)	Conception	Gestation Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Chlorodibenzofurans (CDFs)	2,3,7,8-tetraCDF	Hassoun et al. 1984													0.6 mg/lg								
Chlorinated Dibenzo-p-dioxins (CDDs)	2,3,7,8-TCDD	Yamada et al. 2006											40 µg/kg	40 µg/kg (GD 11.5)	40 µg/kg (GD 12.5)								
Other																							
Cesium	Cs gamma radiation	Kusama and Hasegawa 1993 (ICR)									150 rad (GD 8.75)		150 rad (GD 10.75)										
Ionizing Radiation	Cesium radiation	Kusama and Hasegawa 1993 (ICR)									150 rad (GD 8.25-12.75)												
Mercury	methylmercuric chloride	Yasuda et al. 1985 (ICR)											16 mg/kg 12 mg/kg		16 mg/kg 12 mg/kg								
Mercury	methylmercuric chloride	Fuyuta et al. 1979 (ICR)											12 mg/kg										
Methyl Parathion	methyl parathion	Tanimura et al. 1967 (ICR-JCL)											60 mg/kg										
Polybrominated Biphenyls (PBBs) &	BP-6	Corbette et al. 1975 (Swiss/ICR)								50 mg/kg 5 mg/kg													
Uranium	uranyl acetate	Domingo et al. 1989c (Swiss-Webster)						5.6 mg/kg															
Vanadium	Vanadyl sulfate	Paternain et al. 1990 (Swiss)						7.5 mgkg															
Chloroform	chloroform	Murray et al. 1979 (CF-1)									100 ppm												
Chlorinated Dibenzo-p-dioxins (CDDs)	2,3,7,8-TCDD	Smith et al. 1976 (CF-1)						1 µg/kg															
Chlorinated Dibenzo-p-dioxins (CDDs)	2,3,7,8-TCDD	Dasenbrock et al. 1992 (DBA2J)										150 µg/kg											



Chemical Class	Specific Chemical	Study Reference (Strain*)	Conception	Gestation Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
																800 mg/kg	800 mg/kg						
Tin and Compounds	TBT	Ema et al. 1995														25 mg/kg							
Tin and Compounds	TBT	Ema et al. 1997a										100 mg/kg											
Tin and Compounds	TBT	Noda et al. 1991a								16 mg/kg													
										8 mg/g													
Tin and Compounds	Dibutyltin dichloride	Ema et al. 1991b								5 mg/kg													
										2.5 mg/kg													
Polnoks R	Polnoks R	Sitarek and Sapota 2003						210 mg/kg															
								100 mg/kg															
Butyl Benzyl Phthalate	BBP	Uriu-Adams et al. 2001												1500 mg/kg									
														250 mg/kg									
Di-n-butyl Phthalate		Ema 1994, 1995a														750 mg/kg							
Di-n-butyl Phthalate		Ema 1994, 1995a								750 mg/kg													
Mirex	Mirex	Khera et al. 1976						12.5 mg/kg															
								6 mg/kg															
Mercury	methylmercuric chloride	Fuyuta et al. 1978								6 mg/kg													
Sprague-Dawley																							
Chlorinated Dibenzo-p-dioxins (CDDs)	HxCDD	Schwetz et al. 1973						100 µg/kg															
Cobalt	cGy gamma radiation	Bruni et al. 1994										50 rad (GD 9.5)											
Creosote	coal tar	Springer et al. 1986a													740 mg/kg								
Creosote	coal tar	Zangar et al. 1989												500 mg/kg									
Perfluoroalkyls	PFOS	Thibodeaux et al. 2003																					
														10 mg/kg									
Other																							
Cesium	Cs gamma radiation	Saad et al. 1991, 1994													400 rad								
Chlorinated Dibenzo-p-dioxins (CDDs)	2,3,7,8-TCDD	Giavini et al. 1983 (CRCD)	2 µg/kg (2 weeks prior to conception)																				
Chlorinated Dibenzo-p-dioxins (CDDs)	2,3,7,8-TCDD	Huuskonen et al. 1994 (Long-Evans)									5 µg/kg												
											1 µg/kg												

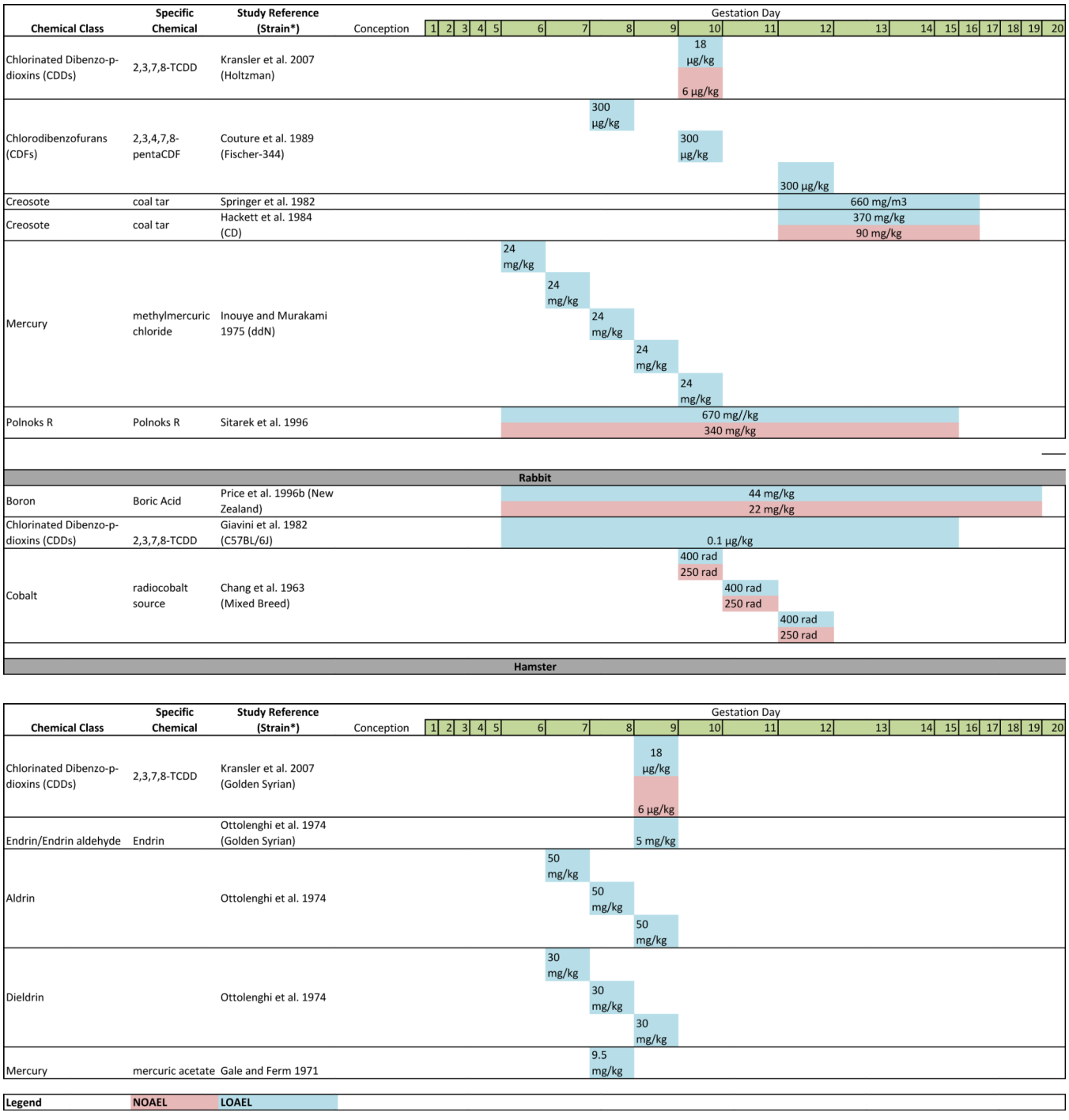


Figure 2.
Summary of windows of sensitivity for animals.