Escher Fund for Autism
1590 Calaveras Avenue
San Jose, CA 95126
(408) 314-1655
jill.escher@gmail.com
website: germlineexposures.org

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

March 16, 2015

Re: Citizen Petition to Withdraw Approval for 17α-Hydroxyprogesterone Caproate ("17-OHPC," Including Brand "Makena") as a Drug Used in Pregnancy, Pending Fetal Germline Impact Assessment

To the Commissioner of the Food and Drug Administration:

The undersigned (or "Petitioner") respectfully submits this petition in accordance with 21 C.F.R. 10.30 to request that the Commissioner of Food and Drugs withdraw approval for the drug 17-alpha hydroxyprogesterone caproate ("17-OHPC," including brand "Makena") as a drug used in pregnancy, pending assessment of potential deleterious impacts to the fetal germline.

The undersigned was prenatally exposed to this drug in 1965, believes she has suffered injury as a result, and has located numerous similarly exposed individuals suffering similar unforeseen and grievous injury. The injuries are consistent with research demonstrating adverse epigenetic effects ("epimutation") of hormone signal-disrupting compounds on the delicate process of fetal germline synthesis, with temporal associations between the introduction of the drug and the unexpected deleterious effects, and with mounting evidence that autism and related neurodevelopmental abnormalities are at least in part caused by *de novo* perturbations of the germline.

The FDA may hesitate to re-evaluate a drug so long and so pervasively used. However, 17-OHPC was initially approved at a time before fetal germline vulnerability came to be broadly appreciated in biology and toxicology, and before generational effects of

synthetic hormone signal disruption[1] came to be appreciated. As when the thalidomide tragedy belatedly shattered the false belief in placental impermeability and shone a light on the particularly horrific nature of derangements occurring during critical developmental windows, and as when the diethylstilbestrol (DES) catastrophe upended conventional wisdom by revealing time-delayed or invisible effects of prenatal exposure, we now face a third wave of most unfortunate revelation: that pregnancy medications can, however inadvertently, "drug the DNA" of grandoffspring, a biological phenomenon that, once again, requires an urgent response by regulators.

A. Action requested

This petition requests that the Commissioner immediately withdraw approval of 17-OHPC (including Makena) as a drug for use during pregnancy pending evaluation of potential fetal germline impact.[2]

B. Statement of grounds

This petition is made pursuant to 21 U.S.C. Sec. 355-1(b)(3) to present to the FDA "new safety information" regarding a particular drug. Under that statute, new safety information may include "scientific data deemed appropriate by the Secretary about a serious risk or an unexpected serious risk associated with use of the drug that the Secretary has become aware of (that may be based on a new analysis of existing information) since the drug was approved."

The term "serious risk" means a risk of a serious adverse drug experience. 21 U.S.C. Sec. 355-1(b)(5). A "serious adverse drug experience" is defined an adverse drug experience that results in, among other things, "a congenital anomaly or birth defect." 21 U.S.C. Sec. 355-1(b)(4).

This petition involves the increased risk of subtle but serious birth defects in the form of 17-OHPC-induced epimutation of the fetal germline, the delicate molecular material of heritability within fetal germ cells (egg and sperm precursors) that gives rise to the

---

[1] Hormone signal disruption is often referred to as "endocrine disruption." For the purposes of this petition, these two terms are equivalent.

[2] As explained in this petition, Part B(5), evaluation should primarily focus on assessing the developmental health of the F2 offspring of F1 human cohorts prenatally exposed to 17-OHPC within the approximate 1956-1980 timeframe. Other safety evaluations may include molecular assays of sperm of adult males who were prenatally exposed to the drug, animal models, and/or biomarker studies of offspring (F2) of individuals (F1) prenatally exposed via F0 maternal administration. Further, the FDA, to overcome long-ignored realities of human developmental and reproductive biology, should convene an expert committee to add the dimension of fetal germline vulnerability to FDA drug-testing protocols. 17-OHPC is unlikely to be the only pregnancy drug with the potential to induce errors in fetal germline programming. Such pharmaceuticals may include, among others, anti-nausea drugs (e.g., Diclegis, the subject of Petitioner's first petition to the FDA, docket no. FDA-2013-P-0522, hereinafter "First Petition"), psychoactive drugs such as antidepressants, which are known to have endocrine-disrupting properties, pain medications, and other synthetic hormone drugs used in pregnancy. Cigarette smoke, a known mutagen and epimutagen, also represents an exposure likely to perturb fetal germline.

subsequent generation.

In support of its request, this petition presents the following explanatory sections:

(1) Pharmacology of 17-OHPC and its hormone signal-disrupting properties
(2) History of 17-OHPC and use in obstetric practice 1956–today
(3) Fetal germline vulnerability to epimutation caused by hormone signal disruptors
(4) Differential developmental harm of 17-OHPC in offspring and grandoffspring
(5) The public health imperative and the FDA's options
(6) Conclusion: the risks of 17-OHPC outweigh its potential modest benefits

(1) Pharmacology of 17-OHPC and its hormone signal-disrupting properties

17α-hydroxyprogesterone caproate is a synthetic steroid hormone, classified as a progestin, or synthetic progestogen. 17-OHPC is a laboratory-made chemical with a structure that does not correspond to any naturally occurring steroid. Its biological actions mimic but do not duplicate those of naturally occurring progesterone. The human body does not make the caproate molecule.[3]

17-OHPC was designed to act like a steroid hormone without the structure of action of the natural progesterone. Progesterone and 17-OHPC have different physiologic properties and pharmacologic profiles. A visual comparison of the chemical structures of progesterone and 17-OHPC is shown below, in figure 1:[4]

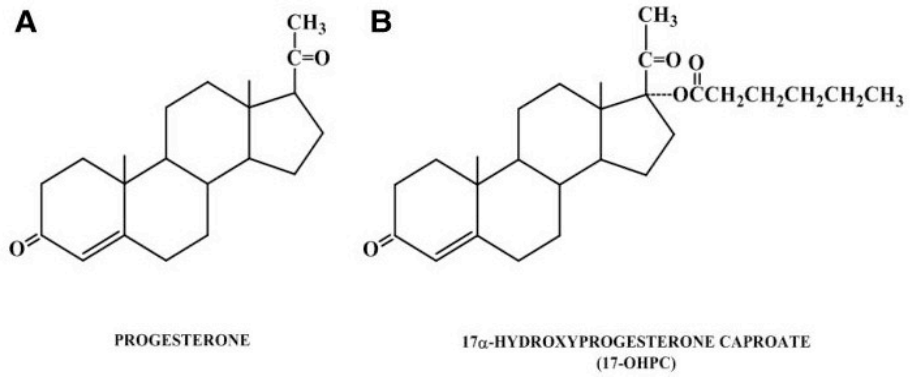

Fig. 1: A visual comparison of the chemical structures of progesterone and 17-OHPC.

[3] For a broader discussion, see, e.g., Romero. Progesterone is not the same as 17α-hydroxyprogesterone caproate: implications for obstetrical practice. Am J Obstet Gynecol. 2013;208(6): 421-6.

[4] From Romero 2013.

Table 1 compares characteristics of progesterone to 17-OHPC:[5]

Comparison between progesterone and 17α-hydroxyprogesterone caproate

Variable	Progesterone	17α-hydroxyprogesterone caproate
Type of progestogen	Natural	Synthetic
Myometrial activity (in vitro)	Decreases	No effect or increases
Cervical ripening	Prevents	Unknown effect
Clinical indication		
History of preterm birth	Only in patients who have a short cervix	Yes
Short cervical length	Yes	No
Safety	No safety signal	Potential safety signal
Increased risk of gestational diabetes mellitus	No	Maybe

Romero. Progestogen and progestins: what is the difference? Am J Obstet Gynecol 2013.

Table 1: Some of the different characteristics of progesterone and 17-OHPC.

The chemical and biochemical properties of 17-OHPC and natural progesterone differ in important ways. 17-OHPC is esterified from hydroxylated progesterone formed from caproic acid (hexanoic acid). It is highly potent and displays prolonged gestational activity. The caproate ester, attached to the hydroxyprogesterone, makes 17-OHPC more biologically active than naturally occurring progestational hormones. The chemical formula of 17-OHPC is $C_{27}H_{40}O_4$, with a molecular mass of 428.6041; in contrast, the chemical formula for natural progesterone is $C_{21}H_{30}O_2$, with a molecular mass of 314.46.

17-OHPC does not inhibit contractions of human myometrial cells in vitro, whereas progesterone does, presumably acting through nongenomic receptors after preliminary metabolization. The synthetic derivative 17-OHPC is resistant to metabolism by traditional steroid-transforming enzymes and is thus unlikely to replicate all of the actions of natural progesterone. 17-OHPC is not a prodrug, and is not cleaved to 17 alpha-hydroxyprogesterone, a metabolite of progesterone already endogenously produced by the placenta in large amounts. The only metabolism observed with 17-OHPC is oxidation by cytochrome P450 3A in hepatocytes to monohydroxy, dihydroxy, and trihydroxy derivatives, with unknown resulting activity. Unlike progesterone, 17-OHPC is not converted to androgens, estrogens, or corticosteroids.

17-OHPC crosses the human placenta efficiently, and the drug is detectable in both maternal and fetal blood for at least 44 days after the last injection. Even when 17-OHPC doses are administered as much as a week apart, plasma concentrations of the drug continue to increase with repeat injections. The metabolism of 17-OHPC is inhibited significantly by endogenous steroids (in particular, progesterone), but with large individual variability. This relative metabolic stability of 17-OHPC ensures a long

[5] From Romero 2013.

half-life (7.8 days) and allows for less frequent dosing in clinical practice compared with natural progesterone.[6]

Both natural and synthetic sex steroids, including 17-OHPC, cross the placenta, enter fetal tissues, and diffuse freely in the cytoplasm. Once in the cells, steroid hormones regulate gene function via their highly specific molecular configuration, which has specific binding patterns with specific receptors. Receptor proteins contain several key structural elements that enable them to bind to their respective ligands with high affinity and specificity, recognize and bind to discrete response elements within the DNA sequence of target genes with high affinity and specificity, and regulate gene activity. As signaling molecules, steroids do their work by securing to receptors in the cell and altering function and expression of the genome within the cell. Steroids also activate key enzymes that control epigenetic shifts in the DNA.

In vitro receptor binding studies show 17-OHPC to be better than progesterone at inducing progesterone-responsive gene transcription.[7] 17-OHPC appears to be comparable to progesterone in binding affinity for the progesterone receptor[8] and displays greater selectivity for receptor isoform B (transcriptional activator) than isoform A (transcriptional repressor).

The Endocrine Society defines an endocrine disruptor (herein called a hormone signal disruptor) as "an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action." Steroid hormones with abnormal molecular structures such as 17-OHPC are broadly acknowledged as hormone signal disruptors that operate abnormally on receptors, binding to natural receptors either as agonists or antagonists. EDCs can also alter the synthesis and breakdown of natural hormones and modify the production and functioning of hormone receptors. 17-OHPC is not only a hormone signal disruptor, but unlike some of the other drugs featuring inadvertent hormone signal-disrupting effects, it is a hormone signal disruptor *by design*.

In summary, 17-OHPC has a different structure than progesterone, is metabolized differently, and has differential actions on tissue via differential receptor activity. It acts as a steroid hormone but with different outcomes than natural progesterone. There is no question that 17-OHPC is a hormone-disrupting chemical.

(2) History of 17-OHPC and use in obstetric practice 1956-today

17-OHPC was previously marketed by Squibb under the trade name Delalutin and was approved by the FDA in 1956 for the ostensible maintenance of pregnancy. For many

---

[6] For more on biologic actions of 17-OHPC, see, e.g., Vidaeff. Critical appraisal of the efficacy, safety, and patient acceptability of hydroxyprogesterone caproate injection to reduce the risk of preterm birth. Patient Prefer Adherence 2013;7:683–691.

[7] Zeleznik abstract 2006, cited in presentation by Adeza Biomedical to FDA Advisory Committee Meeting, Reproductive Health Drugs, August 29, 2006.

[8] Attardi abstract 2006, cited in presentation by Adeza Biomedical to FDA Advisory Committee Meeting, Reproductive Health Drugs, August 29, 2006.

decades thereafter, 17-OHPC was marketed as effective in preventing miscarriage, and was administered to millions of women deemed to be “at-risk” for miscarriage for any number of reasons, including those who were termed “habitual aborters,” defined very liberally in the 1950s through 70s as women who had suffered two or three previous miscarriages. The medical establishment of the time also administered synthetic hormones to gravidas considered “at risk” for any number of other reasons, including advanced maternal age, underlying health conditions such as Type 1 diabetes, carrying twins, spotting or cramps during pregnancy, and small stature. Later trials of the drug demonstrated that 17-OHPC was not in fact effective in preventing miscarriage.

The common deployment of 17-OHPC in the days of anti-miscarriage practice is reflected in medical texts of the era. Dr. Edward Tyler, among the most exalted fertility practitioners of the time and founder of the Tyler Medical Clinic in Los Angeles, published his influential 1960 book, “Sterility: Office Management of the Infertile Couple,” (available online free at http://catalog.hathitrust.org/Record/001566807) which touted the use of the new synthetic hormones for a variety of fertility and other obstetric problems. Dr. Tyler suggested large doses of 17-OHPC (which he termed 17-AHPC) for miscarriage prevention:[9]

> A new injectable progestogen, 17a-hydroxyprogesterone caproate, differs from progesterone in two major respects: large doses, for example, 250 mg per injection, can be given with relative freedom from local reactions; and, the therapeutic effect of each injection is prolonged so that a single injection produces progestational activity for 8 to 10 days. These qualities of prolonged action and relative freedom from local reactions make 17-AHPC a generally more desirable therapeutic agent than progesterone for intramuscular use, but dosage must be controlled carefully. (Sterility, pp. 253–256)

---

[9] In a stroke of one-in-a-million good luck, one of Dr. Tyler’s West Los Angeles patients several years ago obtained records of her 1964-65 “anti-miscarriage” treatments through her obstetrician, whose office retained records on microfilm. Additional records detailing her treatments were later obtained, rather miraculously, by her daughter, the Petitioner, via records from a study on developmental effects of prenatal synthetic steroid hormone drugs, a study which, by astonishing coincidence, Petitioner had been enrolled as a child.

According to the records, Petitioner’s prenatal exposures included Deluteval (17-OHPC plus estradiol valerate), by injection 250 mg every week, for 19 weeks during the second and third trimesters, in addition to regular doses of Deladroxate (dihydroxyprogesterone acetophenide) and Prednisolone during earlier stages of the pregnancy.

Petitioner freely admits that the other synthetic hormone drugs may have also contributed, either cumulatively or synergistically or both, to germline epigenomic errors and her children’s grotesquely yet idiopathically abnormal neurodevelopment. Research is showing that a wide array of exogenous hormone signal-disrupting compounds can adversely affect germline during critical windows of germline synthesis. Petitioner submits it is probably unwise however for a regulatory agency charged with protection of public health to split hairs about which exact man-made pseudohormones may be more or less threatening to the germline epigenome. Clearly, given abnormal molecular signaling actions of synthetic steroids, the precautionary principle should prevail in lieu of requiring testing for every conceivable combination and dose of these potent development-skewing chemicals.

Consistent with the mainstream medical thinking of the time, Dr. Tyler did not express concern about any long-term fetal effects or about the fetal germline. The only adverse effect mentioned by Tyler in his book is the possibility of female virilism (growth of male genitalia on females), but he dismissed that as not in evidence with 17-OHPC, as it was with other synthetic progestins, and seemed to simply assume it had no other ill effects.

Tyler's colleague, Dr. M. Edward Davis, contributed a chapter concerning endocrine therapy for threatened miscarriage, explaining the theoretical basis for such intervention. His writing reflects how the medical practice that spawned 17-OHPC was based on theory without proof of safety or efficacy. He wrote:

> Progesterone is the pregnancy hormone and the logical substance to use in threatened abortion. If it can be demonstrated that the pregnancy is still viable, this hormone can be administered in moderately large doses. This key steroid may compensate for inadequate production of hormones by the corpus luteum or early chorion. Temporary supplementation of this vital steroid may bridge the gap during the transition from corpus luteum to chorionic hormonal support of the pregnancy.
>
> It has been argued by some authors that no therapy is indicated in patients who threaten to abort, for in more than one-half of these women threatening symptoms will subside and the pregnancies will culminate successfully. Furthermore, the high incidence of ovular defects decreases tremendously the number of pregnancies that are worth salvaging. However, such an attitude of defeat and resignation does not conform to modern dynamic medicine. If only 5 or 10 per cent of patients in whom the threatened abortion would have become inevitable can be helped to carry their pregnancies by intelligent therapy it is worthwhile. (Sterility, pp. 326-27)

Dr. Davis continues his enthusiastic endorsement of the "overabundant" clinical use of 17-OHPC in “modern dynamic medicine,” lamenting the prior difficulties with natural progesterones, as follows:

> Until the last two years, 100 mg of progesterone in oil was administered intramuscularly to the patient four or five times each week. This was continued until she felt life at about 16 to 18 weeks if on previous occasions she belonged to the group who aborted early in pregnancy. If the pattern for previous abortions indicated that the terminations occurred most often at midpregnancy, however, the medication was continued until the baby reached a safe period of viability, about 6 weeks from term. No other steroids were administered.
>
> The frequency of the intramuscular administration and the occasional discomfort they induced interfered to some extent in the above regimen. Unfortunately, progesterone is metabolized rapidly, for the administration of 50 mg per day to the patient who is not pregnant produces no holdover effects for longer than 48 hours. The introduction of 17a-hydroxyprogesterone caproate (Delalutin) provided a long-acting progestational agent. Although its

> metabolism differs from crystalline progesterone, its biologic action is similar. The length of its action is dependent on an adequate supply of estrogens. It is possible that additional estrogens may be indicated in some cases. The habitual aborter can now receive 250 mg of 17a-hydroxyprogesterone caproate intramuscularly twice a week, or even 500 mg once a week. There have been no undesirable sequelae following the administration of this new progestational agent. The administration of crystalline progesterone and 17a-hydroxyprogesterone caproate during pregnancy has not resulted in virilism in the newborns in our experience.
>
> [...]
>
> [A]n overabundance of [progesterone] may improve the uterine environment of the conceptus and result in a more adequate circulation, a more substantial implantation, and a quiescent abode for the embryo.(Sterility, pp. 332-333)

A 1964 medical text by Walter Williams, MD, also advised use of Delalutin (250 mg) with estradiol valerate (Deluteval) or Depo-Provera in the use of miscarriage prevention. See Walter Williams, MD. Sterility. 1964;346.

A 1969 medical text, “The Use of Progestins in Obstetrics and Gynecology,” by RW Kistner explained to physicians the then standard-of-care treatment for “habitual aborters” as follows:

> **Provera**: ... 10 mg daily, orally, during the first trimester of pregnancy; then 20 mg daily, orally, during the second trimester and 30 mg, daily, orally, during the third trimester.
>
> **Delalutin**: (hydroxyprogesterone caproate) 375-500 mg (3-4 cc., intramuscularly) every week, starting as soon as pregnancy is confirmed and continuing to fetal viability.
>
> **Deluteval** (hydroxyprogesterone caproate plus estradiol valerate): 500 mg Delalutin plus 10 mg Delestrogen, intramuscularly, every week from the time of confirmation of pregnancy until fetal viability.”
>
> If progesterone is administered, it is best started before conception and continued during pregnancy.... Progesterone, hydroxyprogesterone caproate and oral medroxyprogesterone acetate may be used in the prophylactic management of the habitual aborter. (RW Kistner. The Use of Progestins in Obstetrics and Gynecology. 1969;112-13.)

In sum, the literature of the era reflects a once-widespread medical practice of prophylactically drugging pregnant women who had suffered more than one previous miscarriage or were otherwise deemed “at risk” with heavy doses of synthetic

hormones, particularly progestins, and more particularly 17-OHPC,[10] and to a lesser extent estrogens and corticosteroids, sometimes in combination. This practice was particularly prevalent among somewhat upper income women who could afford the expensive therapies.

17-OHPC, marketed as Delalutin or Deluteval, was the preeminent clinical choice in the postwar era, as clinicians enthusiastically embraced the ineffective anti-miscarriage synthetic hormone concoctions. It gained a foothold in medicine at a time when safety and efficacy were untested and of little concern, when endocrine disruption (herein called hormone signal disruption) was barely a scientific concept, and when the fetal germline was presumed somehow miraculously imperturbable.

Over time, it became clear that the drug was not effective in preventing miscarriage[11] and it was voluntarily withdrawn in 1999 by Bristol Myers Squib. The compound was resurrected via FDA approval in 2011 as a drug to prevent preterm birth and is currently sold under the trade name Makena and also through compounding pharmacies. The 17-OHPC formulation currently approved by the FDA for ostensible preterm birth prevention is identical to that of Delalutin as approved in 1956 for the maintenance of pregnancy. It is composed of 17-OHPC (250 mg) in castor oil (1 mL) with 46% benzyl benzoate and 2% benzyl alcohol. The benzyl alcohol is added as a preservative, while the benzyl benzoate enhances the dissolution of 17-OHPC in the castor oil.

Although the evidence of clinical benefit is questionable,[12]17-OHPC is now heavily marketed and widely used for the prevention of preterm birth. Treatment involves weekly intramuscular injections of 250 mg given from week 16–20 up to week 36 of gestation. This means a fetus — and its germ cells — exposed to the full dosing schedule will be treated with approximately 5,000 mg of 17-OHPC over the course of early development, a period of very dynamic and steroid-vulnerable epigenomic

---

[10] 17-OHPC was available under several brand names, including Delalutin, Deluteval (combined with low dose estradiol valerate), and Deluteval 2x. Other common progestin drugs of the time included Colprosterone, Norlutin, Provera and Provest, among others. See, e.g., Reinisch and Karow. Prenatal Exposure to Synthetic Progestins and Estrogens: Effects on Human Development. Arch. Sex. Behav. 1977;6:4. Estrogens (such as diethylstilbestrol) and corticosteroids were also widely used.

[11] See, e.g., Keirse. Br J Obstet Gynaecol. 1990 Feb;97(2):149-54. “This analysis provides no support for the view that 17 alpha-hydroxyprogesterone caproate protects against miscarriage.” Progestogen administration in pregnancy may prevent preterm delivery. Confirming the growing medical consensus, a Cochrane Review concluded, “There is no evidence to support the routine use of progestogen to prevent miscarriage in early to mid-pregnancy.” Haas. Progestogen for Preventing Miscarriage. Cochrane Review. 2008;10.

[12] Dubious data, lack of evidence of improved fetal outcomes, and minute improvements onnational preterm birth rates are among the reasons cited. See, eg, Silver RM, Cunningham FG, Deux ex Makena? Obst Gynecol 2011;117:1263-5; and Petrini JR, Estimated effect of 17 alpha-hydroxyprogesterone caproate on preterm birth in the United States. Obstet Gynecol. 2005 Feb; 105(2):267-72.

programming.[13]

In sum, 17-OHPC is a potent hormone signal-disrupting synthetic chemical compound that took root in pharmacology in an unfortunate era when physicians and drug marketers promoted the idea that overabundance of super-potent fake hormones could address "accidents of pregnancy."[14] It was used for decades after 1956 for maintenance of pregnancy. After recognition that 17-OHPC had adverse effects on the fetus (see part 5(a), below), and was ineffective, it was withdrawn. Today, the chemical continues to be used for ostensible preterm birth prevention, despite lack of robust data demonstrating safety and efficacy. Women administered the weekly intramuscular injections of the drug receive no information about potential impacts to the F2 generation and are only informed that the F1 fetus suffers no demonstrable ill effects, though no long-term studies on the F1 generation have been performed.

(3) Fetal germline vulnerability to epimutations caused by hormone signal disruptors

Pregnancy drugs affect three generations at once: the mother (F0), her fetus (F1 offspring), and the fetal germ cells (F2 grandoffspring). Fetal germ cells are the precursors to the baby's eggs or sperm, containing both genetic and epigenetic material that together provide the overwhelmingly complicated instruction book for the development of the next generation.

Fetal germline synthesis is recognized as perhaps the most epigenetically dynamic and vulnerable phase of the human lifecycle. During fetal development, the germline contained within the primordial germ cells undergoes a rapidly changing, precise, and hormonally informed molecular dance to prepare this elaborate instruction manual for the future F2 offspring: the result is the restoration of totipotency but in an epigenomic, sex-specific manner. To enable this remodeling, primordial germ cells are first specified within the early, mostly undifferentiated, embryo and segregated from the somatic cells that will form the embryo body and placenta. They then migrate and proliferate on a march to reach the developing fetal gonads. Old epigenetic marks are erased and new marks are laid depending on whether the fetus is male or female (i.e., whether the germ cells are proto-egg or proto-sperm), a delicate process known as genomic imprinting. Remethylation continues in a sex-specific manner through fetal development.

---

[13] While this petition concerns the particular synthetic hormone drug 17-OHPC, all synthetic hormones must be scrutinized for potential fetal germline disruption. Apart from progestogens used in preterm birth prevention, a large number of related synthetic steroid hormonal pharmaceuticals are given to women undergoing assisted reproductive technologies. In addition, of the tens of millions of women who use oral contraceptives, which contain synthetic progestins, close to half a million have unintended pregnancies. Some of these women, unaware that they are pregnant, continue oral contraceptive use well into the first trimester. Hormone signal-disrupting synthetic hormone drugs, including progestins, now enter the womb, the fetus, and the human germline by many means.

[14] DES, or diethylstilbestrol, was of course the most notorious of this class of super-potent synthetic hormones popular in obstetrics and "miscarriage prevention" during the post-war decades.

The timing of this process also depends on the sex of the fetus.[15] In females, establishment of the epigenetic female imprint occurs post-embryonically and after the first stage of meiosis is complete. However, in male fetuses, establishment of the imprint begins shortly after sex determination but before meiosis. Because germline genes are imprinted differently depending on whether they are of maternal or paternal origin, erasure is essential to ensure that the epigenetic marks in the primordial germ cells are reset and appropriately reflect the sex of the developing embryo.

Steroid hormones play a leading role in the epigenomic switching on and off of genes, as these molecules serve to activate DNA, a process accomplished through highly conserved enzymatic processes. Because major changes in DNA methylation and other types of chromatin marking occur during germ cell development, exposures during this period can have long-term repercussions resulting from abnormal DNA methylation (adding or removing methyl groups to specific sites along the DNA sequence to silence or activate gene expression) and architectural changes in chromatin such as histone modification (altering the structure/accessibility of the protein scaffolding around which the helix is wrapped to form chromatin). Steroids also affect miRNAs, which play an important regulatory role in gene expression. These aberrations in DNA marking and architecture, and thus changes in ensuing gene expression without changes to the underlying nucelotide sequence, are terms epimutations.

Epimutation comes down to abnormal choreography of the enzymatic processes, which are influenced by receptor activity mediated by endogenous and exogenous signals, including steroid hormones or their imposters. Estrogen, progesterone, and androgens directly regulate epigenome-modifying enzymes and directly alter gene expression.

For the purpose of risk assessment, it is critical for the FDA to understand that germline reprogramming occurs in a fashion that differs completely from that of somatic cells.[16] These processes are biologically divergent and require independent analyses. Lack of obvious perturbation of somatic DNA does not imply lack of germline effects: the two are essentially separate and distinct biological processes within the envelope of the same fetal body.

Based on ever-accumulating evidence, there is now no question that hormone signal-disrupting substances can cause F1 germline epimutation via F0 gestational exposure. For examples, see the following: Rissman et al. Gestational Exposure to Bisphenol A Produces Transgenerational Changes in Behaviors and Gene Expression. Endocrinology. 2012;1195; Hunt et al. Bisphenol A alters early oogenesis and follicle formation in the fetal ovary of the rhesus monkey. PNAS 2012; Susiarjo et al. Bisphenol A Exposure Disrupts Genomic Imprinting in the Mouse. 2013; PLoS Genet 9(4); De

---

[15] For a discussion, see Dunn et al. Sex-specificity in transgenerational epigenetic programming. Hormone Behav. 2011; 59: 290–295.

[16] For a detailed explanation of differential methylation process in the germline, see, eg, Messerschmidt et al. DNA methylation dynamics during epigenetic reprogramming in the germline and preimplantation embryo. Genes & Dev. 2014;28:812-828.

Assis et al. High-fat or ethinyl-oestradiol intake during pregnancy increases mammary cancer risk in several generations of offspring, Nat Commun. 2012; 3:1053; Gillette et al. Sexually Dimorphic Effects of Ancestral Exposure to Vinclozolin on Stress Reactivity in Rats. Endocrinology. 2014;155:10, 3853-3866; Guerrero-Bosagna et al. Epigenetic transgenerational actions of vinclozolin on promoter regions of the sperm epigenome. 2010 PLoS ONE 5:e13100; Anway et al., Endocrine disruptor vinclozolin induced epigenetic transgenerational adult-onset disease. Endocrinology. 2006;147:5515–5523; Chamorro-Garcia et al. Transgenerational inheritance of increased fat depot size, stem cell reprogramming, and hepatic steatosis elicited by prenatal obesogen tributyltin in mice, Environ Health Perspect. 2013 Mar;121(3):359-66; Skinner et al. Transgenerational epigenetic programming of the brain transcriptome and anxiety behavior. 2008; PLoS ONE 3(11): e3745; Anway et al. Transgenerational effect of the endocrine disruptor vinclozolin on male spermatogenesis. J Androl. 2006; 27:868–879; Manikkam et al, Plastics Derived Endocrine Disruptors (BPA, DEHP and DBP) Induce Epigenetic Transgenerational Inheritance of Obesity, Reproductive Disease and Sperm Epimutations, PLOS One. 2013; 8(1); Crews et al., Epigenetic transgenerational inheritance of altered stress responses, PNAS. 2012; 109:23; Doyle et al. Transgenerational Effects of Di-(2-ethylhexyl) Phthalate on Testicular Germ Cell Associations and Spermatogonial Stem Cells in Mice. Biology of Reproduction. 2013;88:5-112; Manikkam et al, Dioxin (TCDD) induces epigenetic transgenerational inheritance of adult onset disease and sperm epimutations, PLoS ONE. 2012; 7(9); Bruner-Tran et al. Developmental exposure to TCDD reduces fertility and negatively affects pregnancy outcomes across multiple generations. Reprod Toxicol. 2011; 31: 344–350; Manikkam et al. Pesticide and insect repellent mixture (permethrin and DEET) induces epigenetic transgenerational inheritance of disease and sperm epimutations. Reprod Toxicol. 2012; 34: 708–719; Nilsson et al. Environmentally induced epigenetic transgenerational inheritance of ovarian disease. PLoS One. 2012; 7: e36129; Del Mazo et al, The effects of different endocrine disruptors defining compound specific alterations of gene expression profiles in the developing testis. Reproductive Toxicol. 2012; 33:1, 106–115; Manikkam et al. Pesticide Methoxychlor Promotes the Epigenetic Transgenerational Inheritance of Adult-Onset Disease through the Female Germline. PLoS ONE. 2014; 9(7); Anway et al. Transgenerational effects of the endocrine disruptor vinclozolin on the prostate transcriptome and adult onset disease. Prostate. 2008;68:517–529; Drake et al. Intergenerational consequences of fetal programming by *in utero* exposure to glucocorticoids in rats. Am J Physiol Regul Integr Comp Physiol. 2005; 288: R34–R38;

Significantly, other toxicants not generally considered as hormone disruptors also have germline reprogramming effects. For examples, see the following studies: Rehan et al, Perinatal nicotine exposure induces asthma in second generation offspring, BMC Medicine. 2012, 10:129. Jia et al. HDAC inhibition imparts beneficial transgenerational effects in Huntington's disease mice via altered DNA and histone methylation. Proc Nat Acad Sci 2015; 112:1; Zhu et al. Transgenerational Transmission of Hyperactivity in a Mouse Model of ADHD. J Neurosci. 2014, 34(8): 2768-2773; Lambrot et al. Low paternal dietary folate alters the mouse sperm epigenome and is associated with negative pregnancy outcomes. Nat Commun. 2013; 4: 2889; Tracey et al. Hydrocarbons (jet fuel JP-8) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. Reprod Toxicol. 2013; 36: 104–116.

Perhaps most importantly, synthetic steroid hormone pharmaceutical drugs have already been demonstrated to disrupt the fetal germline.[17] Steroid hormone disruption caused by the "anti-miscarriage" synthetic hormone drug diethylstilbestrol (DES) has already been shown to cause F2 pathologies in human and animal studies, including increased risks for cancer and abnormal urogenital development mediated by epigenetic changes. For examples, see the following studies: Newbold et al. Adverse effects of the model environmental estrogen diethylstilbestrol are transmitted to subsequent generations. Endocrinology. 2006; 147: S11–S17; Ruden et al. Hsp90 and environmental impacts on epigenetic states: a model for the trans-generational effects of diethylstilbestrol on uterine development and cancer. Hum Mol Genet. 2005; 14: R149–R155; Li et al. Diethylstilbestrol (DES)-stimulated hormonal toxicity is mediated by ERalpha alteration of target gene methylation patterns and epigenetic modifiers (DNMT3A, MBD2, and HDAC2) in the mouse seminal vesicle. Environ Health Perspect. 2014; 1228: 262–268; Harris et al. Diethylstilboestrol: a long-term legacy. Maturitas. 2012; 72: 108–112; Bromer et al. Hypermethylation of homeobox A10 by in utero diethylstilbestrol exposure: an epigenetic mechanism for altered developmental programming. Endocrinology. 2009; 150: 3376–3382; Newbold. Lessons learned from perinatal exposure to diethylstilbestrol. Toxicol Appl Pharmacol. 2004; 199: 142–150.

In sum, fetal germline synthesis is an epigenetically dynamic and vulnerable phase of the human lifecycle, and research has repeatedly demonstrated that fetal germline programming is vulnerable to epimutations caused by steroid hormone signal disruptors. Not only is 17-OHPC a hormone signal disruptor, it is one introduced into the uterine environment in intentionally heavy, consistent doses during a dynamic phase of germline synthesis.

(4) Differential developmental harm of 17-OHPC in offspring and grandoffspring

This section is broken down as follows:

a. Proximal fetal effects (F1)

b. Grandoffspring effects (F2)

- i. Case reports
- ii. Temporal associations with autism explosion
- iii. Consistency with autism etiology
- iv. Germline effects of other synthetic hormone drugs, DES, and DEX

a. Proximal fetal effects (F1 effects)

---

[17] As emphasized in Petitioner's First Petition (docket no. FDA-2013-P-0522), pharmaceutical exposure is merely one variety of chemical exposure, albeit with typically more intensive, acute and consistent doses than those imposed by ambient environmental chemical exposures. That most studies in the literature investigate "chemicals" rather than "pharmaceuticals" is of little or no biological relevance. If anything the synthetic chemical literature should clang louder alarm bells regarding synthetic drugs, since drug exposures are typically more acute and chronic, not to mention intentionally biologically active.

Adverse fetal somatic (F1) effects of 17-OHPC and similar progesterone-like compounds have been known since the 1970s. The groundbreaking study, "Prenatal Exposure to Synthetic Progestins and Estrogens: Effects on Human Development," by Reinisch and Karow, Arch Sex Behav. 1977; 6:4, detailed for the first time personality differences in synthetic-hormone–exposed children.[18] These effects are unsurprising given that steroid hormones, including progesterone, are well known to affect brain organization and development, beginning early in embryonic life with the appearance of hormone receptor sites in discrete populations of neurons.

Since that time, 17-OHPC has been repeatedly shown to have adverse fetal effects beyond behavioral development.[19] 17-OHPC was classified as a category D drug due to evidence of fetal harm. Embryo–fetal toxicity signals have been observed in the two largest clinical trials of 17-OHPC conducted to date. Embryo–fetal toxicity signs are also reported for 17-OHPC in rhesus monkeys and possibly in one rodent species. See, eg, Christian et al, Embryo–fetal toxicity signals for 17α- hydroxyprogesterone caproate in high-risk pregnancies: A review of the non-clinical literature for embryo–fetal toxicity with progestins. 2007;20:2, 89-112.

b. Grandoffspring effects (F2 effects)

i. Case reports

In support of the argument that gametes exposed to 17-OHPC during the period of early germline programming are at increased risk of producing neurodevelopmental abnormalities in resulting offspring, Petitioner hereby submits examples of disabled F2 human children borne of 17-OHPC-treated germ cells. These examples are just a few of those collected by Petitioner through personal contact and interviews with the

---

[18] The undersigned Petitioner was, by astonishing coincidence, among the 71 synthetic hormone-exposed subjects included in that study. Based on the original study records obtained by Petitioner, she was considered by the researchers to have been "heavily exposed" to progestins, including 17-OHPC. As for sequelae caused by the exposures, the study abstract stated: "Progestin regime exposed subjects were characterized as more independent, sensitive, self- assured, individualistic, and self-sufficient," but without suffering impaired intelligence.

[19] While 17-OHPC is now used (as Makena or compounded drugs) in the second and third trimesters and not the first, where its more obvious impairments manifest, this is of little relevance to the question of germline vulnerability, since the germline epigenome is constructed in a manner and time wholly different than that of the somatic cells. Subtlety of somatic effects does not imply subtlety of germline effects.

exposed F1 parents and/or their spouses.[20]

Jonathan Escher, b 1999, autism
Sophie Escher, b. 2006, autism
Mandy, b. 2003, learning disabilities, idiopathic NF-like neurological condition
Natalie Young, b. 2004, anxiety disorder
Sean Young, b. 2000, ADD
Baby X Young, b. 1992, d. 1992, Turner's syndrome
Patrick, b. 1984, ADD
Thomas B, b. 1993, autism
Michael W, b. 2005. autism, psychosis
Gustavo H, b. 1989, autism
Julio H b. 1997, autism
Kathie H b. 2005, autism
Marco R, b 2006, autism
Joe G, b. 2002, autism
John G, b. 2004, autism (Asperger's)

These developmentally impaired offspring (F2) come from families with no history of autism or developmental abnormality. Clinical assessments failed to discern any known etiology for the often profound and "genetic-like" disabilities. Yet all these F2 have one thing in common: they sprang from gametes treated with 17-OHPC or similar compounds during the early phase of fetal germline synthesis. That is, one of their parents (female or male F1s known to Petitioner) had been exposed *in utero* in the 1960s or 70s as part of anti-miscarriage or fertility treatments. Importantly, as a case control, where the parents (F1) have unexposed siblings (F1 sibs), the F1 sibs' offspring (F2) are developmentally normal.

Some of the F1 parents have documentation of their 17-OHPC exposure; some have knowledge from their F0 mothers; others know generally of exposure to hormonal anti-miscarriage treatment, which, in all likelihood included 17-OHPC (see the History section above) or similar compounds. The medical records of the pregnant women (F0s) given progestin drugs in that era were for the most part destroyed long ago, and we must therefore rely on oral information about treatments from the F0 grandmothers in most cases.

The FDA may complain that Petitioner's list is unconvincing in light of the fact it has not

---

[20] Jonathan and Sophie are two of Petitioner's three offspring. Even if Petitioner's children were the only germline exposure cases known to Petitioner (and clearly, they are not), given the devastation of the autism epidemic and the consistency of the hypothesis with autism etiology and epidemiological research, her case *alone* should suffice to raise loud alarm bells within the halls of the FDA and NIH.

At the same time, Petitioner does not suggest that every germ cell treated with 17-OHPC during the phase of early germline synthesis will result in a developmental abnormality in offspring, just as not every thalidomide exposure resulted in limb defects, or every DES exposure resulted in adenocarcinoma of the vagina. Several F2s reported to Petitioner appeared to be developmentally normal in spite of springing from germ cells treated with synthetic steroid hormone drugs.

received previous reports of these “adverse events” related to germline effects of 17-OHPC or other synthetic progestogens. But under the circumstances, that absence is to be expected. Such reporting is nearly impossible owing to the near-complete unavailability of prenatal exposure records from the Delalutin era and the infrequency with which F1s know of their own prenatal exposures. With rare exception, such as those included above, the exposed F1 individuals do not have the slightest indication they had been exposed *in utero* to synthetic hormone drugs. Moreover, it is the rare parent who has the knowledge about germline epigenomics and intergenerational effects of hormone-disrupting exposures that would enable him or her to connect the dots between past *in utero* exposures and their children’s current developmental abnormalities.

To the extent the FDA questions Petitioner’s honesty about this list of F2s and its investigators and would like to interview any of the F1 parents of the F2 disabled offspring listed here, those investigators are welcome to contact the Petitioner to arrange contact. With the exception of two of the F1s whose F2 disabled offspring’s last names are listed (Escher and Young), the exposed parents have requested anonymity owing to the sensitive and personal nature of this information, and the extreme vulnerability of their children. However, Petitioner would in good faith attempt to put an FDA investigator in contact with F1s if requested.

ii. Temporal associations with autism explosion

The FDA is concerned with any temporal association between drug administration and the adverse event. 17-OHPC was introduced in 1956, with births of F1s beginning in approximately 1957. Procreation by the F1s would generally begin about 22 years later, with births 23 years later, approximately in 1980. Therefore, if 17-OHPC had adverse germline effects, one would expect to see developmental disturbances in the cohort born around 1980, with rates increasing from that point, as the use of the chemical expanded from the time of its introduction. This is exactly the pattern we see in the data.

The state of California maintains the most reliable autism data in the country, owing to its unique Lanterman Act which has long conferred upon developmentally disabled individuals an entitlement to services. Autism birth cohort data provided by the California Department of Developmental Services indicates a sharp uptick in autism births starting in about 1980, as shown in Figure 2 and Table 2:

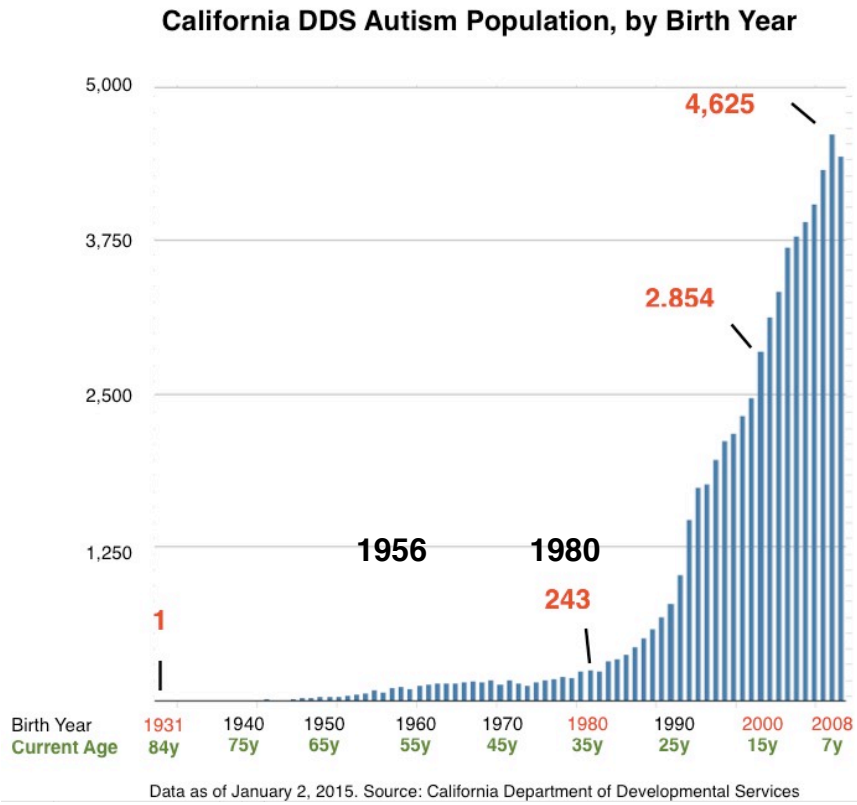

Figure 2: Temporal association between generations:

1956: 17-OHCP first introduced, gradually exposing increasing numbers of fetuses and their fetal germlines to high doses of hormone-disrupting molecules.

1980: Autism births begin to rise.

California Developmental Services Autism Cases, by Birth Year 1931-2010

1931	1	1951	33	1971	141	1991	1,476
1932	1	1952	48	1972	129	1992	1,741
1933	1	1953	55	1973	150	1993	1,768
1934	4	1954	64	1974	173	1994	1,967
1935	1	1955	87	1975	178	1995	2,122
1936	2	1956	70	1976	199	1996	2,187
1937	2	1957	109	1977	189	1997	2,326
1938	4	1958	116	1978	246	1998	2,474
1939	2	1959	102	1979	256	1999	2,525
1940	3	1960	124	1980	243	2000	2,854
1941	10	1961	133	1981	324	2001	3,128
1942	3	1962	143	1982	347	2002	3,338
1943	14	1963	147	1983	381	2003	3,699
1944	11	1964	143	1984	443	2004	3,789
1945	13	1965	152	1985	511	2005	3,904
1946	15	1966	164	1986	585	2006	4,051
1947	24	1967	149	1987	684	2007	4,335
1948	30	1968	172	1988	797	2008	4,625
1949	36	1969	139	1989	1,033	2009	4,444
1950	39	1970	172	1990	1,227	2010	4,395

Source: California Dept. of Developmental Services, data as of January 2015

Table 2: Autism cases skyrocket beginning in the early 1980s

The current DDS caseload (restricted to more severe forms of autism) has only about 200 autism births per year, compared to more than 4,000 per year today.

While some may assert that this dramatic increase is due to “better ascertainment” or “more awareness” of autism, or of diagnostic shifts from Mental Retardation/Intellectual Disability to Autism, with respect to the California data, studies have repeatedly been

shown this not to be the case.[21] Moreover, within the DDS system, there is no sign that the system has overlooked tens of thousands of incapacitated, developmentally disabled adults over the age of 35 with the striking autism symptomology. In fact, it is highly unlikely that the system, over its many decades of offering services and providing assessments, failed to detect more than a negligible number of Developmental Services-eligible autistic adults. The bar for eligibility is high, as clients must be considered substantially developmentally disabled and unable to care for themselves.

While Petitioner hardly contends the skyrocketing cases of autism and abnormal neurodevelopment arise solely from 17-OHPC-induced germline defects (clearly, there are likely multiple substances that have perturbed fetal germlines over the past decades, including other pregnancy drugs and maternal smoking), the timing of the autism explosion is at least consistent with F2 exposure since the introduction and ascendance of 17-OHPC use.

It is also noteworthy that autism epidemiological studies have detected an increase in autism prevalence in areas where these synthetic hormone drugs were more commonly used, including upper income SES and certain metropolitan areas, including the West Los Angeles autism supercluster identified in 2011. See King et al. Socioeconomic Status and the Increased Prevalence of Autism in California. Am Sociol Rev. 2011;76(2): 320–346. Intriguingly, the autism rate appears to be particularly high in New Jersey, home of Squibb, the maker of Delalutin and Deluteval. See Centers for Disease Control http:// www.cdc.gov/ncbddd/autism/addm.html (The number of children identified with ASD is 1 in 45 children in areas of New Jersey).

iii. Consistency with autism etiology

Epigenomic marks play a particularly important regulatory role in brain development. See, eg, LaSalle, A genomic point-of-view on environmental factors influencing the human brain methylome. Epigenetics. 2011;6:862-869. Human neurodevelopment appears to be particularly sensitive to alterations in epigenetic pathways; neuronal development and functioning may be particularly affected by even subtle alterations in DNA methylation. Normal brain development is dependent on the normal epigenomic marking of the germline. Dysregulation of genomic imprinting in the germ cells can have devastating results and has a particularly profound effect on neurodevelopment in the resulting offspring. See, e.g., Peters. The role of genomic imprinting in biology and disease: an expanding view. Nature Reviews Genetics. 2014;15;517–530; Meany et al. Epigenetic Regulation in the Nervous System: Basic Mechanisms and Clinical Impact. 2014. For a library of information on this subject, see the genomic imprinting website, geneimprint.com.

Autism research has shown the condition to be highly heritable (i.e., germline-

---

[21] See, for example, Cal. Dept. Developmental Services, "Autistic Spectrum Disorders, Changes in the California Caseload An Update: June 1987 – June 2007," finding that from June 1987 through June 2007, California experienced a 12-fold increase in individuals with autistic disorder being served by the department and that this number did *not* include those on the autism spectrum subject to a broadening definition.

mediated) but typically with vastly heterogenous *de* novo presentation. With rare exception, autism has never been shown to be "genetic" in the classic Mendelian sense. To underscore this point, a recent study of siblings with autism found the vast majority did not share the same germline disruptions. Yuen et al., Whole-genome sequencing of quartet families with autism spectrum disorder. Nature Medicine. 2015; 21:185–191.

Evidence is mounting that epigenetic dysregulation in the germline contributes to autism risk. See, eg, Wong et al. Methylomic analysis of monozygotic twins discordant for autism spectrum disorder and related behavioural traits. Molecular Psychiatry (2014) 19, 495–503 (methylation differences in twins discordant for autism); Ladd-Acosta et al. Common DNA methylation alterations in multiple brain regions in autism. Mol Psychiatry. 2014 Aug;19(8):862-71 (methylation differences in post-mortem autism brains); Ben-David et al. Allelic expression analysis in the brain suggests a role for heterogeneous insults affecting epigenetic processes in autism spectrum disorders. Hum Mol Genet. 2014 Aug 1;23(15) (ASD brains had more genes that were up- or down-regulated in an individual-specific manner); Berko et al. Mosaic epigenetic dysregulation of ectodermal cells in autism spectrum disorder. PLoS Genet. 2014 May 29;10(5) (methylation differences in ectodermal cells of ASD children born to older mothers).

In addition, many studies demonstrate that ASD risk increases with parental (F1) endocrine abnormalities. See, eg, Krakowiak et al. Maternal Metabolic Conditions and Risk for Autism and Other Neurodevelopmental Disorders. Pediatrics. 2012; 129:5 (maternal obesity/diabetes associated with increased risk of autism); Palomba et al. Pervasive developmental disorders in children of hyperandrogenic women with polycystic ovary syndrome: a longitudinal case-control study. Clin Endocrinol (Oxf). 2012 Dec;77(6): 898-904 (mothers with PCOS more likely to have daughters with pervasive developmental disorders); Suren et al. Parental Obesity and Risk of Autism Spectrum Disorder. Pediatrics. 2014;133 (paternal obesity associated with increased risk of autism in offspring).

Finally, grandparental (F0) associations to F2 ASD have been detected in several studies. See, eg, Golding et al. Parental and Grandparental Ages in the Autistic Spectrum Disorders: A Birth Cohort Study. 2010;DOI: 10.1371/journal.pone.0009939 (grandmaternal age); Frans et al. Autism Risk Across Generations: A Population-Based Study of Advancing Grandpaternal and Paternal Age. Jama Psychiatry. 2013;70:5 (fathers born to older fathers, grandfather of ASD child, associated with risk of autism). Also supportive of the idea that ancestral hormone disruption is related to autism risk, autism rates are strongly associated with urogenital abnormalities, a known sequela of early fetal hormone disruption, in population-based samples. Rzhetsky et al. Environmental and State-Level Regulatory Factors Affect the Incidence of Autism and Intellectual Disability. PLOS Computational Biology. 2014; DOI: 10.1371/journal.pcbi. 1003518.

iv. Germline effects of other synthetic hormone drugs (DES and DEX)

The FDA is concerned with adverse events known to be caused by related drugs. The best-known case of germline and generational effects of synthetic chemicals is another

synthetic hormone drug used in “anti-miscarriage” practice, diethylstilbestrol, or DES, as discussed earlier. While the studies, to Petitioner’s knowledge, have not investigated possible neurodevelopmental impacts, effects on gonadal development and carcinogenesis have been found, indicating clear germline susceptibility to the synthetic hormone drug.

The adverse effect of another synthetic steroid hormone on the germline has been documented. Dexamethasone, or DEX, is a synthetic corticosteroid that mimics the anti-inflammatory and immunosuppressant effects of endogenous cortisol. For almost 30 years, DEX has been given to pregnant women at risk of delivering a child with congenital adrenal hyperplasia (CAH). IVF clinics have also used DEX, without any scientific foundation, to prevent miscarriage. DEX has been shown to induce germ cell apoptosis in the human fetal ovary. Fetal exposure to DEX during germ cell division (weeks 6–20 of pregnancy) decreased germ cell viability. Researchers found that when the fetal ovaries were exposed to dexamethasone in culture for only two weeks, the rate of germ cell death increased, and the density or total number of germ cells decreased, as did the expression of one of the genes associated with germ cell survival.

While there are no clinical trials of germline effects of 17-OHPC known to Petitioner, or any third- generation phenotype studies to date, this is only a sign of the incomplete risk paradigm employed by the FDA and the broader medical/pharmaceutical community, and not suggestive of any inherent lack of germline risk posed by this endocrine-disrupting chemical. In sum, fetal exposure to hormone-signal disrupting compounds during the critical period of reproductive organ development and germ cell division has been shown to have deleterious effects.

(5) The public health imperative and the FDA’s options

The FDA’s antiquated, narrow approach to evaluating adverse consequences of pregnancy drug exposures, *which completely ignores the very existence and vulnerability of the fetal germline*, has misled the medical establishment and the American public and lulled pregnant women into a false sense of security regarding the potential dangers of pregnancy drugs. As stressed in Petitioner’s First Petition, docket no. FDA-2013-P-0522, pregnant women and their partners have the right to know <u>all</u>, not just some, of the risks involved in ingesting pharmaceutical drugs, particularly to the developmental integrity of their descendants.

At this time, the agency and the drug makers are falsely informing millions of pregnant women of the risk-free status of Makena (and similar compounded substances containing 17-OHPC), and exposing millions of fetuses to potential germline epigenetic damage. The FDA has the discretion—and indeed, the Congressionally-mandated duty, should safety issues surface—to change its course today.

The present petition overcomes all of the alleged shortcomings identified by the FDA in

its denial of Petitioner's First Petition: 17-OHPC clearly crosses the placenta[22]; 17-OHPC clearly acts as a hormone signal disruptor (and was designed as such); 17-OHPC can affect somatic fetal tissues, particularly in the realm of neurodevelopment; synthetic steroid hormones or hormone signal-disrupting compounds, of which 17-OHPC is one, can induce germline defects; there are strong temporal associations between the introduction of 17-OHPC and the adverse outcomes; there are known cases of F2 abnormality where the precursor germline had been treated with 17-OHPC; and epigenomic dysregulation is generally associated with autism risk.

To protect the public health, the FDA has several options, including any of the following:

1. Do nothing, and continue to preside over a *de facto* prolonged, mass human experiment in synthetic steroid-mediated germline adulteration.

2. Issue a general warning concerning potential germline drug risks of 17-OHPC and other hormone signal-disrupting drugs via a warning statement issued to the public and clinicians licensed to prescribe pharmaceutical drugs.

3. Require that as a condition of prescribing 17-OHPC, clinicians must take steps to ensure exposed offsprings' medical records permanently contain detailed drug exposure information. Perpetuating the inexcusable status quo of near-complete ignorance of our prenatal drug exposures is an entirely avoidable tragedy.

4. Withdraw approval for 17-OHPC for use in prevention of preterm birth, advising other methods such as: natural progesterone supplementation where low progesterone levels are clinically determined; nutrient-dense, low-inflammation diets rich in healthy cholesterol (the substrate without which natural progesterone cannot be produced); and other methods such as cessation of smoking or antidepressant drugs, which are associated with increased risk of preterm birth.

5. Fund or mandate studies into F2 effects in cohorts prenatally exposed to 17-OHPC via F0 maternal administration. Such extant cohorts of F0s (with data on F1 as well) include, among others:

- Military medical records from the 1960s
- Child Health and Development Survey (CHDS) cohort (1959-1967 pregnancy records from California). See chdstudies.org.
- Collaborative Perinatal Project (1958-1965 pregnancy records from several east coast hospitals)
- Many cohorts in Scandinavian countries, including Denmark's Prenatal Development Project cohort, and Swedish and Finnish cohorts

---

[22] Petitioner notes she was rather taken aback when the FDA, in its Denial of the First Petition, complained that Petitioner had failed to demonstrate that the drugs in Diclegis crossed the placenta. Is not this fundamental, basic pharmacological fact something the FDA should know rather than a factual burden the FDA should impose on housewives like Petitioner? (And for the record, almost all drugs cross the placenta.)

• 17-OHPC exposed cohorts from the Reinisch Los Angeles or New Jersey studies (records on file at the Kinsey Institute in Indiana)

6. Conduct laboratory studies of sperm of adult males who were prenatally exposed to Delalutin, compared to controls.[23]

7. Conduct studies in animal models to ascertain germline differences in prenatally exposed animals.

8. Further, to overcome long-ignored realities of human developmental and reproductive biology, the FDA should promptly convene an expert committee to add the fetal germline to the scope of FDA testing protocols. 17-OHPC is unlikely to be the only pregnancy drug exposure that harms fetal germ cells. This committee should include experts on toxicology, developmental biology, germline development, epigenetics and imprinting, reproductive biology, and mutagenesis. Obviously, it should exclude any individual receiving any form of compensation from the chemical or pharmaceutical industries, as those individuals clearly would have a conflict of interest.

In sum, the FDA's safety assessment of 17-OHPC glaringly ignores an entire category of serious risk. However, the FDA has many options to protect public health including ascertainment of potential germline disruptive impacts of 17-OHPC, whether through epidemiology, case studies, animal studies, in vitro studies, or otherwise. It must, by now, be incumbent upon the FDA to require reasonable germline safety assessments before allowing continued use of this drug.

6. Conclusion

We know that 17-OHPC is a laboratory-made synthetic chemical with hormone signal disrupting properties. We know that an elaborate molecular process of germline

---

[23] In its denial of the First Petition, the FDA resisted any idea of laboratory ascertainment of epigenomic alterations, saying:

> "Because our current understanding of epigenetic processes in normal cellular function is incomplete, it is not possible to reliably distinguish whether epigenetic changes are caused by or associated with a specific toxicity, adverse event, or outcome. Additionally, no one assay or test can capture all epigenetic events. The tests that are currently available to assess epigenetic effects are unvalidated and insufficiently reliable to be used to form the basis of a regulatory decision."

FDA Denial letter dated August 4, 2014. This "we cannot test epigenomic effects perfectly therefore we won't look for adverse impacts" response ignores the reality that epigenetic differences in the germline, whether they can immediately be proven deleterious or not, must be seen as alarming and indicative of potential dysregulation in next-generation offspring. Moreover, for the purpose of addressing public health, it is of course unnecessary to know all details of events at the molecular level. The molecular mechanisms of thalidomide and DES were not known until decades after those drugs were found to be damaging. *Knowing molecular mechanisms or details is merely a luxurious addition to the arsenal of regulation, not a prerequisite.* If such detailed knowledge were deemed necessary, virtually all drug regulation would in effect cease to exist.

programming occurs in the fetal germline. We know that hormone signals play a role in germline reprogramming. We know that hormone signal disruptors can induce germline epigmutation. We know that epimutation can cause abnormal outcomes in offspring. We further know there are many cases of abnormal neurodevelopment in offspring of germ cells treated with 17-OHPC. We know similar drugs have adverse germline effects. We know that the epidemiology and timing of the autism epidemic is consistent with early germline effects of the 1956 introduction of Delalutin.

Treating fetuses and fetal germ cells with heavy and continual doses of synthetic steroid hormones is a perilous biochemical undertaking with likely profound and penetrant generational consequences. Such medical practices, which are essentially holdovers from the misguided and wanton prenatal drug boom of the 1950s and 60s, should not be undertaken in our contemporary medical culture without reliable evidence that the palpable benefits outweigh the multifold risks. But that is exactly what is happening.

After an approved drug enters the marketplace, the FDA may withdraw the drug if its risk-benefit profile is unfavorable. In light of the dimension of profound risk posed by potential germline perturbation, and when balanced against the questionable clinical benefits conferred by 17-OHPC, the risk-benefit profile of 17-OHPC does not meet the statutory standard of safety; thus, the FDA should promptly withdraw its approval of the drug.

C. Environmental impact

The requested action has no environmental impact, the petitioner claims categorical exclusion.

D. Economic impact

The requested action has no economic impact, excepting possible financial loss by manufacturers and marketers of 17-OHPC for use in pregnancy applications.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

//
//
//
//
//

The undersigned wishes to thank the FDA staff for its consideration of this petition.

Very truly yours,

Jill Gilbert Escher
Escher Fund for Autism
1590 Calaveras Avenue
San Jose, CA 95126

cc:
Food and Drug Administration
Center for Drug Evaluation and Research Division of Reproductive and Urologic Products 5901-B Ammendale Road
Beltsville, MD 20705-1266
Margaret Hamburg, Commissioner
Janet Woodcock, MD, Director, Center for Drug Evaluation and Research
Nancy Hayes, Acting Director, Office of Regulatory Policy, Center for Drug Evaluation and Research
Hylton V. Joffe, M.D., M.M.Sc., Director
Audrey Gassman, M.D., Deputy Director
Margaret Kober, Chief, Project Management Staff
Jennifer Mercier, Chief, Project Management Staff
Rachel Turow, counsel

American College of Obstetrics and Gynecology
American Society for Reproductive Medicine