Escher Fund for Autism
Humans start as molecules
GermlineExposures.org
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Via Email and U.S. Mail

June 21, 2019

Re: NIH research program on heritable (germline) impacts of general anesthesia, a response to Dr. Bianchi's November 27, 2018 letter

Dear Dr. Collins and Institute Directors:

On November 4, 2018 I took the liberty of writing to you suggesting a research program on the adverse heritable impacts of general anesthesia (GA) (Escher 2018b). On November 27, 2018 Dr. Bianchi kindly responded, expressing skepticism about the hypothesis and rejecting the idea that the question warranted any particular action by the NIH (Bianchi 2018). She did allow, however, that the NIH would consider investigator-initiated grant applications proposing studies on this topic (but, alas, I have it on good information that when such an application was recently made it was met with rejection).[1]

I am now asking you to reconsider the NIH's response to my earnest suggestion. This is not me saying, "Please spend a zillion dollars studying mating habits of fruit bats," but instead, "Rates of autism —a highly heritable but not classically genetic disorder — have hit a **catastrophic 1 in 59 U.S. children**, please, at the very least, consider a modest sum to investigate the heritable

[1] Imagine that in 1971 proposals to investigate diethylstilbestrol carcinogenicity in humans were rejected owing to lack of human studies demonstrating carcinogenicity. This is the absurd Catch-22 we face today with respect to germline GA exposure studies, even though progeny neurodevelopmental impairment was witnessed in animal models more than 30 years ago.

impacts of **the most toxic exposure our germ cells commonly encounter,** one with proven adverse heritable neurodevelopmental impacts."

I strenuously disagree with Dr. Bianchi's assertion that "At present, there are limited scientific data to support your hypothesis," as even a casual glance at the research literature reflects not just the unmistakable plausibility for this idea, but also the tremendous urgency of the issue. GA is genotoxic and a powerful modifier of chromatin. It is a germ cell toxicant that is known to dysregulate the expression of brain development genes. And moreover, when volatile inhalation anesthetic gases are actually tested for heritable impacts via germ cell exposure, neurobehavioral abnormality is **the result seen in animal models***,* and with a male-affected bias (as Dr. Bianchi noted in her letter). But molecular plausibility is just the beginning, as the hypothesis **also features strong congruence with abundant findings in autism research**, including temporal and prevalence trends, heritability patterns, neurobiology and epidemiology.

I will not repeat any of the **red-flag family stories** as I did to an extent in my November 4 letter. But I can assure you that <u>just one single individual</u> seemingly impaired by germ cell anesthesia toxicity can easily cost the family and public $10 million over a lifetime. In light of the astronomical costs that may be resulting in part from GA-damaged germline, is it too much to ask the NIH to sponsor, say, $1 million in pilot research? What are these germline toxicants doing to our germ cells now, and how much heritable damage have they done since their introduction in the late 1950s?[2] [3] [4]

There is only one way to find out. And that is a robust research program.[5] With that goal in mind I will explain what the studies are already telling us, and why they compel us to do much more.

1. GA gases can penetrate germ cells and enter the nucleus, where they can damage DNA and chromatin

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[2] Because most of the GA toxicity research involves the synthetic volatile inhalation gases halothane (introduced to clinical practice in the late 1950s), enflurane (late 1960s), isoflurane (1981), desflurane (1992), and sevoflurane (1992), I will limit my discussion to these. This is not to say that other forms of anesthesia are unimportant, but the volatile inhalation gases are better understood and are alone sufficient to raise concern.

[3] I fully appreciate that GA, and in particular the advent of the synthetic volatile inhalation gases, represents one of the greatest medical achievements in history. These substances, though technically destructive and poisonous, have made possible the practice of modern surgery that has saved countless millions of lives. As someone who benefitted from GA for delicate spinal surgery several years ago, my personal gratitude to modern anesthesiology knows no bounds. But our enthusiasm for the technological triumph of GA should not divert us from ascertaining molecular risks which could promote outsize, if unanticipated, developmental havoc.

[4] In no way do I suggest that other hypotheses are not worth exploring. For example, adverse neurodevelopmental impacts of early germ cell exposure to smoking (Golding et al. 2017) and drugs such as synthetic steroid hormones (Kioumourtzoglou et al. 2018) stand out as particularly important. Other emerging hypotheses include immune activation and adverse perinatal events, for example. At best, the germline toxicity of some GA exposures would explain a portion of the autism increase.

[5] While our philanthropy can help support a few studies (small *in vivo*, *in vitro* and epidemiological pilots are now underway), these projects at best will only be able to produce small amounts of pilot data on extremely narrow subparts of this sprawling hypothesis.

The GA gases are potent, small lipophilic molecules that, on an organismal level, are lethal in their conventional doses: patients, whose brain and muscle function shut down, are kept alive only through a breathing apparatus and careful monitoring. The gases are basically powerfully poisonous organic solvents which diffuse through the body, particularly vessel-rich tissues such as the gonads, and every aspect of the cell, dramatically impacting receptors, signaling, chromatin, and even DNA. The gas gets free passage into the nucleus and all its structures including DNA, its support proteins, and epigenetic elements. When a body is anesthetized, so in effect are its germ cells and their heritable components.

Once the GA gases enter the germ cells, then what?[6] To a large extent this will depend not only on the pharmacokinetics of the particular substance but also on combination, dose, and **timing**. Timing is a critical variable for germ cells owing to enhanced vulnerabilities during early epigenetic reprogramming, chromatin remodeling, rapid mitotic proliferation, early stages of meiosis, genomic imprinting, and spermiogenesis in males and meiosis II in females.[7] It is beyond dispute that a transient exposure during a critical period of germline remodeling can cause changes that become fixed in the genetic apparatus, resulting in the dysregulation of gene expression and proper and timely neuronal development in progeny, a phenomenon already observed not only with respect to GA (Ju et al. 2018), but also overtly hormone-disrupting drugs such as diethylstilbestrol, synthetic corticosteroids, hormone-disrupting environmental chemicals, valproic acid, tobacco, nicotine and ethanol (reviewed in Escher and Robotti 2019). This phenomenon occurs because exogenous toxicants can act directly or indirectly to effectuate alterations in DNA methylation, histone modification and/or ncRNA expression in the germ cells (Marczylo et al. 2016; Gold et al. 2018; Western 2018), or, with respect to some exposures like tobacco, outright mutagenesis (DeMarini 2012).

Today, up to 75,000 pregnant women undergo inpatient surgical procedures each year, exposing the fetal germ cells. Additionally, 6 million children, 1.5 million of whom are infants, also undergo surgery (Gluncic et al. 2019), exposing their nascent germ cells.[8] Of additional concern is that GA gases are used in higher concentrations in infants under the age of one year, and in particularly high concentrations in maternal-fetal medicine for antenatal corrective surgeries (to relax the uterus, intensive concentrations of sevoflurane are used for many hours, exposing a very undeveloped fetus to unprecedented quantities of GA).

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[6] Another consideration is GA impact on the gonadal somatic support cells, Sertoli and Leydig cells in males, and granulosa and thecal cells in females. If those cells are damaged by gas, the germ cells they support would suffer indirectly.

[7] I am addressing what most describe as “intergenerational” effects—those resulting from a direct hit to the germ cell during gametogenesis— and not “transgenerational” effects, which by most definitions are limited to phenotypes that arise in subsequent generations absent any direct germ cell exposure (Miska and Ferguson-Smith 2016; Jarred et al. 2018), even though those effects may pose additional concerns for personal and public health.

[8] Prenatal, perinatal, neonatal and early childhood surgeries involving GA in the past or in current practice include maternal appendectomy, maternal injury, cerclage, cesarean section, correction of congenital malformations such as hernias, heart defects, fistulas, clefts or clubfoot, reconstruction after injuries, childhood appendectomies, tumor removal, and many others. As glorious and life-saving these procedures may be (and they are), one cannot deny that evolution did not prepare our delicate early germ cells for biologically unprecedented toxic insults like GA.

Beyond the question of timing is that of dose and recurrence. GA agents are used in varying combinations and concentrations, and for varying durations, depending on the judgment of the practitioner, the availability of the chemicals, and the demands of the surgical procedures. Often a condition requires several successive surgeries, resulting in a cumulative exposure that could exacerbate damage or derail the chromatin and DNA repair process in the GA-exposed nucleus.

In sum, GA gas is potent and penetrant, even to the germ cell nucleus, but it is timing, dose, and repetition that may "make the poison" to the exposed germ cells.[9]

2. GA is a powerful modulator of epigenome and chromatin

GA gases have been shown to be powerful modulators of chromatin remodeling and epigenetic function that induce a wide variety of morpho-functional effects when administered during critical periods of brain development (Vutskits et al. 2018; Bang 2015). The injury often occurs via changes in key transcription factors leading to dysreguation of gene expression necessary for normal neurodevelopment (Vutskits et al. 2018; Csoka and Szyf 2009). From a neurological point of view, damage includes neuronal apoptosis, impairments in synaptogenesis and defects in neuronal migration, leading to ectopic neurons (Gluncic et al. 2019). Adverse outcomes observed have included learning impairments, brain abnormalities, behavioral abnormality (Id).

Research finding epigenetic and transcriptional impacts in brain cells date back to several studies published 2006. In cultured neurons, isoflurane altered several genes involved with neurotransmitter transport, signaling and cellular structure (Pan et al. 2006). Isoflurane was also seen to affect widespread changes in genetic control in the rat amygdala, and alter gene expression related to DNA transcription, protein synthesis, metabolism, signaling cascades, cytoskeletal structural proteins, and neural-specific proteins, among others (Rampil et al. 2006). Isoflurane with nitrous oxide caused persistent changes in hippocampal gene expression in rats. The majority of differentially expressed genes are implicated in cell stress and replication, signal transduction, transcription, protein biosynthesis, cell structure, and metabolism (Culley et al. 2006).

Later studies confirmed and expanded on these findings. In rats, isoflurane altered hippocampal protein expression, affecting processes including synaptic plasticity, stress response, detoxification, and cytoskeleton (Kalenka et al. 2010). In mice, even a brief exposure to isoflurane persistently upregulated expression in several genes in the hippocampus (Pekny et al. 2014). Neonatal sevoflurane anesthesia (in combination, mirroring clinical reality) in rats was found to produce long-lasting alterations in histone acetylation, resulting in impairments of hippocampal synaptic plasticity: reduced density of dendritic spines, reduced levels of the brain-derived neurotrophic factor, c-fos protein, microtubule-associated protein 2, synapsin1, postsynaptic density protein 95, pCREB/CREB, CREB binding protein, and acetylated histones H3 and H4, and increased levels of histone deacetylases 3 and 8 (Jia et al. 2016). A cascade of events was seen to be initiated by sevoflurane-induced epigenetic modulations. By promoting CBP degradation, the gas induced significant down-regulation of full-length CBP protein, which

[9] I have no reason to believe that GA gases are so germline-toxic that they always or even often disturb gametic contents. Based on the literature as a whole, adverse impacts are likely limited to vulnerable developmental periods and/or very heavy and repeated exposures. However, given the extensive and increasing use of synthetic volatile inhalation GA throughout the population over the past six decades, even a five percent increase in heritable risk for abnormal neurodevelopment could silently result in a calamitous, if unforeseen, population-wide impact.

resulted in a decrease in its HAT activity. This, in turn, caused H3 hypoacetylation, an epigenetic change that leads to more condensed chromatin structure less conducive to transcription of the target genes *BDNF* and *c-Fos*, which are critical for cognitive development. An impairment in proper dendritic arborization leads to impaired neuronal connectivity resulting in faulty formation of neuronal circuits and compromised synaptic neurotransmission (Jia et al. 2016).

The GA isoflurane, with associated sedatives, can modulate histone acetylation and as such may have deleterious effects on transcription of genes crucial for proper synapse formation and cognitive development. During synaptogenesis, epigenetic changes have been shown to involve key transcription factors (e.g. cAMP response element-binding [CREB] protein, CREB-binding protein) leading to downregulation of target genes (e.g. brain-derived neurotrophic factor, c-Fos) via histone modification (Dalla Massara et al. 2016).

Most recently, neonatal sevoflurane-induced alteration of brain gene expression, modulation of KCC2 gene expression via modification of DNA methylation, was noted in rats (Ju et al. 2018), along with adverse impacts on progeny gene expression and neural function (discussed later in this letter). A study looking at isoflurane effects on migration of cerebral cortical neurons revealed that significant number of neurons failed to acquire their correct cortical position and remained dispersed within inappropriate cortical layers and/or adjacent white matter, linked to diminished expression of proteins critical for neuronal migration. Behavioral abnormalities in exposed offspring were also noted (Gluncic et al. 2019).

Remarkably, the neuronal defects induced by developmental GA exposure, such a abnormal migration of cortical neurons and impaired synaptogenesis, mirror the impairments seen in post-mortem autism brains (Hutsler and Casanova 2015; Reiner et al. 2015), raising questions about dysregulation of the associated genes via the autistic subject's germline. It stands to reason that the neurodevelopment genes targeted by GA gases in brain cells would also be targeted in germ cells. But unlike differentiating neurons, a lesion at the blueprint germ cell level could potentially lead to more acute phenotypic consequences due to systemic interference with the precise tempo-spatial processes of brain development.

3. GA gases are also genotoxic, causing DNA damage

Data also indicate that GA is associated with genotoxic risks (reviewed in Yilmaz et al. 2016; Schifilliti et al. 2011; discussed in Çakmak et al. 2018), although those risks seem to be agent and dose dependent. Evidence shows that inhalation anesthetics cause DNA damage in a variety of cells: at site of contact (epithelial cells in the nose) and systemically (blood cells). At contact sites, short-term administration of sevoflurane was seen to induce micronucleus formation in nasal epithelial cells of patients (Kesimci et al. 2017). In blood, a comet assay detected DNA damage caused by halothane and isoflurane in human peripheral blood lymphocytes (PBLs) (Jaloszynski et al. 1999). In human patients, desflurane increased sister chromatid exchange in lymphocytes (Akin et al. 2005). The comet assay of halothane and desflurane were shown to be genotoxic in lymphocytes, increasing DNA migration in a dose-dependent manner (Karpinski et al. 2005). Dose-related genotoxicity of desflurane in lymphocytes was again observed as shown by comet assay (Aydinli et al. 2011). Consistent with a dose-dependent effect, in minimally invasive surgery, isoflurane and sevoflurane were not seen to induce DNA strand breaks or alkali-labile sites in PBLs (Braz et al. 2011). Halothane, isoflurane, sevoflurane and desflurane were investigated in human PBLs (and sperm cells also, discussed later) *in vitro* by alkaline comet assay. All drugs were capable of inducing DNA

damage on PBLs in a dose-dependent manner (Kaymak et al. 2012). In minor surgeries, desflurane caused statistically significant increases in DNA strand breaks/alkali-labile sites in lymphocytes the day after minimally invasive surgery in healthy patients (Nogueira et al. 2016).

4. GA gases are also cytotoxic to germ cells

In case there is any question that GA gases can reach and impair germ cells, it is widely observed that GA agents have generally deleterious impacts on morphology and integrity of mammalian and human germ cells.

Sperm/males

Morphologic changes in mouse sperm caused by various forms of anesthesia was first discussed in 1981 when significant increases in the percentages of abnormal spermatozoa were found for chloroform, trichloroethylene, and enflurane (Land et al. 1981). “These data suggest that direct examination of reproductive cells following exposure to general anesthetics *in vivo* may be useful in the investigation of the genetic toxicities of these compounds” (Id). Halothane produces an inhibition of rat masculine sexual behavior and reduced sperm motility (Oropeza-Hernández et al. 2002). Although not a halogenated volatile anesthetic, the inhalatory anesthetic ethyl ether during the neonatal period of brain sexual differentiation impaired later fertility and sexual behavior of male rats: a decrease in the number of spermatids and spermatozoa, an increase in the transit time of cauda epididymal spermatozoa and a decrease in daily sperm production. An alteration of sexual behavior was also observed. This may be because perinatal exposure to ethyl ether acting as a hormone disruptor during the critical period of male brain sexual differentiation (Arena et al. 2002). In rabbits, exposure to sevoflurane and isoflurane had negative effects on spermatogenesis and sperm morphology, concentration and motility (Ceyhan et al. 2005). An *in vitro* study of human sperm showed that isoflurane has a reversible increasing effect at the clinical concentration and a significant decreasing effect at the high concentration on the motility and vitality of sperm, while sevoflurane does not affect sperm motility and vitality at either concentration (Wang et al. 2008). Isofurane impaired rat seminiferous tubules and spermatogenesis, damage related to the alterations of sex hormones (Xu et al. 2012). In rats, sevoflurane damaged testicular and sperm morphology, and reproductive hormones were affected by chronic exposure (Kaya et al. 2013).[10]

Oocytes/females

As with most aspects of germ cell toxicology, information about the fate of oocytes is rare compared to the male gametes, but two studies suggest the germ cell toxicant impacts of the gases. In a study comparing rat euthanasia methods, euthanasia by isoflurane resulted in significantly fewer intact oocytes in females compared to those killed by cervical dislocation (Roustan et al. 2012). Sevoflurane in female rats results in significant histological ovarian injury and significant alterations in hormone levels (Dogru et al. 2017).[11]

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[10] The fact that GA acts as an endocrine disrupting chemical, administered in intensive doses, also presents a secondary level of toxic insult to developing germ cells (Marczyclo et al. 2016; De Felici and La Sala 2016; Krishnan et al. 2018).

[11] It is worth noting that the gases can be so reproductively toxic to human females that even incidental exposure to waste anesthetic gases can raise the risk of miscarriage in operating room personnel (Yilmaz et al. 2016).

5. GA can exert adverse heritable impacts

Most importantly, research has directly demonstrated the adverse heritable impacts of GA. After Land et al. first noted the germ cell toxicity caused by enflurane in 1981, the lab of Herman Turndorf, MD at NYU questioned whether adulterations in the germline could cause heritable impairment. Turndorf's lab demonstrated that both halothane and enflurane exposed germ cells resulted in learning-impaired progeny (Chalon et al. 1981; Tang et al. 1985).

They observed that grandpups of female mice exposed to halothane as fetuses exhibited impaired learning due to what they perceived as a "genetic aberration" in the exposed mothers' fetal eggs (Chalon et al. 1981). Then again they found impaired learning function in the generation borne of enflurane-exposed mouse sires, prompting them to state that it "seems likely that spermatogenetic changes, caused by enflurane, are associated with genetic alterations" that affected the pups' brain development (Tang et al. 1985).

These crucial observations seemed to go into hibernation for more than three decades but were discussed again in Jia et al 2016 and then actually demonstrated again in Ju et al. 2018, which found that male, but not female, progeny showed signs of neurodevelopmental impairment induced by germline exposure to sevoflurane (Ju et al 2018).[12] In sum, the mammal studies so far published on this question all point in one direction — that germline exposure to GA can cause learning and behavioral impairment in progeny.

Relevance of the germline toxicity of GA to the autism increase in particular was first raised by Escher in 2018 and in Ju et al. 2018, a hypothesis repeated by Escher and Robotti in 2019, emphasizing the need for a rear-view-mirror approach to ascertaining heritable pathologies unwittingly induced by the historical growth in use of novel GA agents and other potent drugs developed in the post-war decades.

6. Consistency with findings from autism research

While studies indicate that GA can enter the nucleus, derange chromatin, epigenome and DNA, cause gametic abnormality, and induce adverse neurodevelopmental outcomes in progeny, what is equally striking that this historic-biologic phenomenon could explain many of the baffling patterns seen in the autism research literature. Here are some examples:

Temporal associations. The start of the autism increase, observed to have begun with births in the early 1980s (Nevison et al. 2018), comes roughly a generation after early germ cell

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[12] With the sole exception of the Ju paper, why did this urgent question fall into the scientific abyss for so many decades? After all, two papers had suggested the deeply troubling prospect of mental impairment in progeny via mysterious "genetic aberrations" or "genetic alterations" of female or male germ cells. Surely, if GA agents could damage our sperm and eggs' genetic material in a way that caused learning deficits in the next generation, that should have been a top priority for public health research. However, in appears the observations reported by Turndorf's lab fell victim to the weight of conventional dogma about inheritance. It was broadly accepted at that time that heritability of traits depended on genes from our parents, except in those rare cases where genes suffered a random mutation. The dogma left no room for other ideas about molecular sources of inheritance. Regrettably, even today, pathogenesis research seems paralyzed by old dogmas of the 20th century, with heritability typically equated to "genetic" (Escher and Robotti 2019).

exposures to synthetic volatile inhalation gases (starting with halothane in the late 1950s, which remained the most prevalent GA for decades).

Missing heritability of autism. The epigenetic / chromatin / genomic effects of GA could help explain the contrast between the strong heritability of autism and the surprisingly shallow findings from traditional DNA-sequence-focused genetics.

The 4:1 male:female sex ratio. The hypothesis is consistent with the sex-specific intergenerational responses to GA exposure as detected in Ju et al. 2018. Additionally, several studies in chemical disruption of germ cells have found male offspring more likely suffer adverse effects (e.g., Krishnan et al. 2018).

Autism heterogeneity. Toxicant exposures to male or female germ cells over different times, in different doses, in different combinations, against a backdrop of varying genomic susceptibilities and different sexes, would likely exert widely variable effects. This roulette-wheel mix could help explain the heterogeneity of the autisms.

The "broader autism phenotype." The BAP has been observed among autism family members. In many cases, personalities and cognitive traits of parents themselves could have been influenced by their direct *in utero* or early life exposures to neurotoxic GA, and in addition, siblings who do not meet diagnostic criteria for autism could have sprung from germ cells that were more lightly damaged.

Parental age effects. It has often been noted that paternal and also maternal age is associated with offspring autism risk. One reason for this phenomenon, apart from rare random mutation of nucleotide sequence in the germline, could be the higher rates of toxicant exposure experienced by the parents over the pre-conception lives. Cumulative exposure may confer greater heritable risks (Gao et al. 2019).

Regional, socioeconomic, and ethnic disparities. Higher rates of autism in some countries, regions, ethnicities and socioeconomic strata may coincide with higher rates of GA exposures of the parents. Surgery is more prevalent in some countries and demographics than others.

Arising in early brain development. It has been frequently observed that autism arises from brain mis-wiring during early development in the womb. Increasingly it looks like chromatin and epigenomic factors may contribute, suggesting that "epigenetic dysfunction is a fundamental contributor to brain development and disease pathogenesis of neurodevelopmental disorders, including ASD" (Tremblay and Jiang, 2019). The dysregulation of brain development genes induced by GA germline exposure could help explain these phenomena.

A Priority for NIH Research

In sum, upon examination of the literature it is not difficult to connect the dots between germline exposure to agents of general anesthesia and heightened risk for progeny neurodevelopmental impairment. As we witness a baffling tsunami of young Americans with serious functional and behavior impairments — disorders shown to be highly heritable but not strongly genetic in any classic sense — the American public deserves a research program that considers that some of the causes of this catastrophe may lie in the disturbed molecular program of parental germ

cells. Several of the NIH Institutes could make this research a priority, both through intramural and extramural programs. For example:

NICHD: The NICHD supports both basic and applied research into germ cell health. Some of these funds could be directed to research on germline and heritable toxicity of GA, with emphasis on halothane (most prevalent in the autism parent generation) and sevoflurane (most prevalent today), and with reference to very early life exposures (prenatal and neonatal) and/or long-dose and successive surgeries.

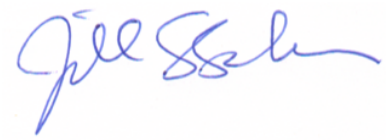
NIEHS: The NIEHS also supports both basic and applied research into adverse heritable impacts of exogenous toxicants. Some of these funds could be directed to research on germline and heritable toxicity of GA. For example, rodent models can provide a rough idea of impacts of GA on the next generation's gene expression, brain function, and behavior. As above, research should begin with the most vulnerable developmental periods (eg, fetal germ cells), the stronger concentrations and longer durations.[13]

NIMH: The NIMH is charged with sponsoring relevant research to uncover the causes of autism and other neurodevelopmental disorders. As such, it could direct a research program on a wide variety of retrospective studies across a multitude of human cohorts examining neurodevelopmental outomes in progeny of parents with very early and/or very intensive surgical exposure histories.

Of course the FDA should also play a role. However, based on many years of communication with staff at both the regulatory and research (NCTR) sides of the FDA, it is clear that the FDA presently has no program or interest in the adverse heritable consequence of this or any other pharmaceutical drug, with perhaps the exception of chemotherapy drugs, leaving a most vulnerable phase of the human lifecycle virtually orphaned, without any clear "home" among the many institutes mandated to advance research and safeguard public health.

For the reasons set forth above, I believe the time has come for the NIH to consider what the most common, intensive germline toxicant exposure has meant and continues to mean for America's children. Thank you for your consideration of this suggestion. Should you have any questions please contact me at jill.escher@gmail.com.

Very truly yours,



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NIEHS: Richard Woychik, Cindy Lawler (EEARN)

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[13] In 2018 The Escher Fund nominated the GA gases as a subject for intramural research at the NIEHS National Toxicology Project. The NIEHS response to the nomination is unknown at this time.

Louis Reichardt, Simon Foundation
Thomas Frazier, Autism Speaks

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