

# Effects of Common Teratogens on Prenatal Development: Alcohol, Smoking, and Drugs

Ameya Gourisetty

Gifted Gabber

## ABSTRACT

Teratogens are responsible for a large number of congenital abnormalities. The repercussions of ignorance to the agents a pregnant person could possibly be exposed to can result in irreversible malformation in a fetus. This paper uses studies done by the National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC) to explore three major teratogenic agents--alcohol, smoking, and drugs--and the effects they can have on a fetus on the molecular level, with a focus on the specific components that cause the defects and the possible abnormalities that the fetus is at risk of.

## **Introduction**

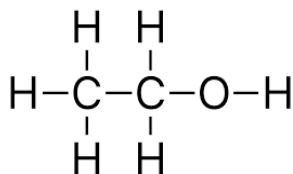
Teratogens are defined as any agent that causes the malformation of an embryo [1] (Genetic Alliance; District of Columbia Department of Health., 2010). These agents--such as infections, hereditary health factors, maternal health, environmental chemicals, and toxins like alcohol and drugs--can cause congenital anomalies and neurodevelopmental disabilities. The severity of the abnormalities is determined by the genetic susceptibilities of the mother and fetus, what agents the fetus was exposed to, and the duration of that exposure. As the embryonic period, which takes place 14 to 60 days post-conception, is the most sensitive phase at which the fetus has the greatest chance of being affected, the first trimester has the highest risk [2] (Alwan, S., & Chambers, C. D., 2015). Teratogens can cause physical malformations, but they also can affect cognitive and behavioral/emotional development. Additionally, they also can cause complications during later stages of pregnancy such as preterm labor, spontaneous abortions, and miscarriages. All of which have the potential to harm the pregnant person as well.

Teratogens are known to be harmful, but how do they actually affect a fetus? What precautions can pregnant people take to avoid teratogenic agents? How do the most common and addictive teratogens-- alcohol, smoking, and drugs-- affect fetuses on a molecular level and what abnormalities do they cause?

### Alcohol--Ethanol

The most common and well-known example of teratogens affecting prenatal development is fetal alcohol syndrome, which is the leading cause of birth defects and neurodevelopmental disabilities. It has been estimated that at least 1% of live births are affected by FAS or FASDs. According to the CDC 1 in 7 pregnant people reported that they had drunk alcohol in the past 30 days at the time of the survey. [3] (*Data & Statistics*, n.d.)

Alcohol can be passed from the bloodstream through the placenta to the fetus. As the fetus cannot break down alcohol as quickly as an adult can, the alcohol levels remain higher and in the body for longer.



#### Molecular structure of Ethanol<sup>1</sup>

Ethanol, which is the fundamental base of all alcohol, is the cause of the abnormalities produced by fetal alcohol spectrum disorders. Specifically, prenatal ethanol exposure can affect a fetus's developing brain and can cause neural impairment, and cognitive and behavioral effects.

Ethanol has a negative impact on nearly all tissues, but stem cells are especially vulnerable to its toxicity. [4] (Armant, n.d.) During pregnancy, amniotic fluid plays the role of a messenger of sorts between the fetus and the mother, delivering essential nutrients and exosomes that contain extracellular RNA to the fetus. The RNA is easily absorbed before 9 weeks of gestation as the skin has not yet been keratinized, and after entering the body it travels to the GI tract where it reaches the 'niche' in the gastric glands where stem cells are located. Stem cells play an essential role in embryonic and fetal development. Stem cells are pluripotent which means they can become any type of cell in the body, this versatility is why the cells are used to regenerate parts of injured vital organs. Because of their adaptable nature, stem cells give rise to other cell and tissue types and perform necessary repairs. However, ethanol slows the multiplication of stem cells which affects the functionality of the cells and ultimately puts the fetus at risk. [5] (Di Rocco, G., Baldari, S., Pani, G., & Toietta, G., 2019)

Prevention is as easy as abstaining from alcoholic substances, however since according to the NIH, approximately half of all pregnancies in the United States are unplanned it is suggested that women who are pregnant, might be pregnant, or are considering becoming pregnant should avoid alcohol.

#### Effects of alcohol on stem cells<sup>2</sup>

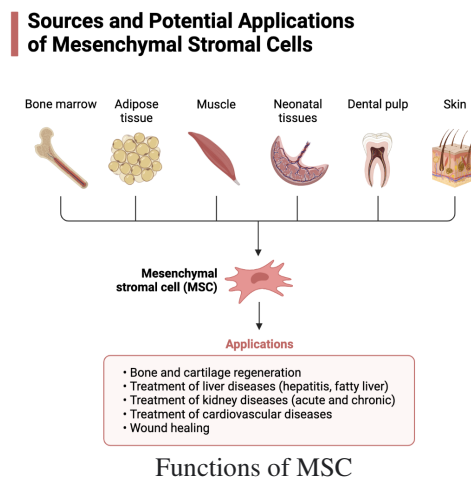
Cell type	Observed changes	Main references
Neural progenitor cells	Reduced proliferation; effects on cell fate determination	[10, 16, 17, 20]
Hepatic stem cells	Reduced proliferation; promotion of mesenchymal transition	[43]
Intestinal stem cells	Decreased the expression of stem cell markers,	[46]
BM-derived MSC	Reduced osteogenic differentiation; adipogenic effect; induction of senescence	[34, 52, 57, 59]

<sup>1</sup> Mižoch, L. (n.d.). *File:Ethanol-structure.svg*. Wikimedia Commons. Retrieved August 4, 2022, from <https://commons.wikimedia.org/wiki/File:Ethanol-structure.svg>

<sup>2</sup> Di Rocco, G., Baldari, S., Pani, G., & Toietta, G. (2019). Stem cells under the influence of alcohol: effects of ethanol consumption on stem/progenitor cells. *Cellular and molecular life sciences : CMLS*, 76(2), 231–244. <https://doi.org/10.1007/s00018-018-2931-8>

Cell type	Observed changes	Main references
Dental pulp stem cells	Dysregulation of odontogenic/osteogenic differentiation.	[58, 63, 64]
Adventitial progenitor cells	Decreased proliferation; reduced myogenic differentiation	[69]
Embryonic stem cells	Inhibition of differentiation; apoptosis induction	[78, 86]
Hematopoietic progenitors	Effects on cell fate determination; DNA damage	[91,92,93, 97]
Cancer stem cells	Phenotypic changes; microenvironmental alterations.	[105, 108]

BM bone marrow, MSC mesenchymal stromal cells

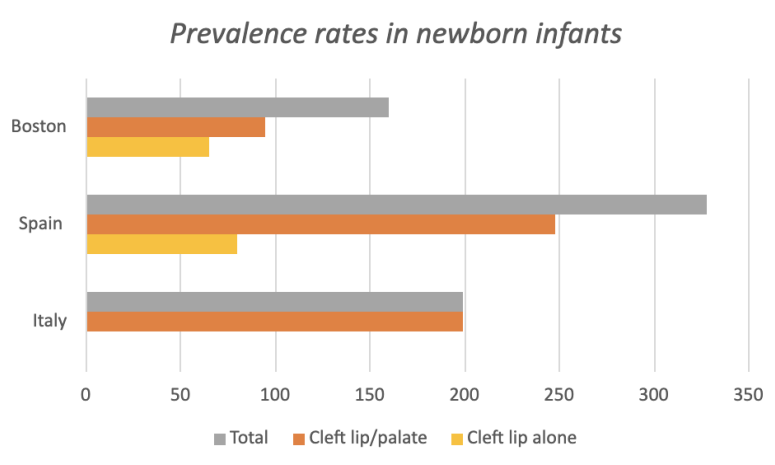


Functions of MSC

## Smoking--N-acetyltransferase 1 and 2

Smoking is a very well-known cause of birth defects. One of every five babies born to people who smoke has a low birth weight. Additionally, babies that were born to people who smoke or have been exposed to secondhand smoke after birth are three times more likely to die of SIDS and have reportedly weaker lungs than other babies[6](CDC., n.d.). This also makes them susceptible to many other health problems as a result.

	Italy (1981-1986) n= 220,927	Spain (1980-1985) n= 382,340	Boston (1972-74, 1979-2000) n= 206,244
Cleft lip alone	not provided	0.21/1,000 (n= 80)	0.29/1,000 (n=65)
Clift lip/palate	0.9/1,000 (n=199)	0.65/1,000 (n= 248)	0.43/1,000 (n= 50)
Combined	0.9/1,000 (n=199)	0.86/1,000 (n= 328)	0.72/1,000 (n= 160)

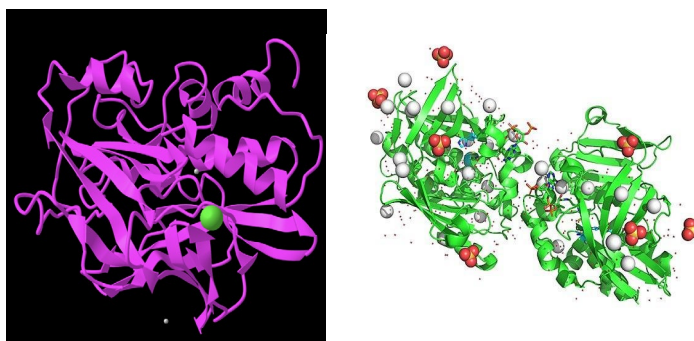


Data depicting prevalence rates of orofacial clefts in newborns {3}

Smoking is also related to genetic variation in a gene that is associated with birth defects. The N-acetyltransferase genes help metabolize drugs and other xenobiotics, but their main job is to detoxify tobacco smoke constituents such as aromatic amines. The N-acetyltransferase enzymes produced by the genes can render drugs inactive.

N-acetyltransferases 1 and 2 are both enzymes that have been linked to orofacial clefts in newborns. Specifically, polymorphisms -- two or more variations in a specific DNA sequence -- in the sites of 1088 and 1096 in the NAT1 enzyme significantly increase the risk of both cleft lip and cleft palate. Additionally, aromatic amines have been proven to cause polymorphisms in the NAT genes which prevent bladder and breast cancer and therefore puts anyone with these genetic variations at risk.

Another congenital abnormality that children of smoking mothers are at risk of is clubfoot, as the deformity is associated with the presence of the NAT-2 acetylator which is responsible for activating and deactivating drugs and carcinogens [7] (Holmes, L. B., 2011). To avoid genetic variation in these genes expecting mothers should avoid smoking cigarettes, taking certain anticonvulsant drugs, and drinking an excessive amount of alcohol. Alternatively taking folic acid supplements can be used as a protective measure and reduce the risk of oral clefts.



Ribbon model of NAT-1(left<sup>3</sup>) and NAT-2(right<sup>4</sup>)

<sup>3</sup> Wu, H., Dombrovsky, L., Tempel, W., Martin, F., Loppnau, P., Goodfellow, G. H., Grant, D. M., & Plotnikov, A. N. (2007). *Structural basis of substrate-binding specificity of human arylamine N-acetyltransferases*. National Center for Biotechnology Information. Retrieved August 4, 2022, from <https://www.ncbi.nlm.nih.gov/Structure/pdb/2PQT>

<sup>4</sup> *N-acetyltransferase*. (n.d.). Wikipedia. Retrieved August 4, 2022, from <https://en.wikipedia.org/wiki/N-acetyltransferase>

## Drugs--Benzene

Some of the more complex agents that can negatively impact prenatal development are drugs. The use of illicit drugs can cause miscarriage, preterm labor, birth defects, stillbirth, withdrawal symptoms in the baby after birth, a higher risk of sudden infant death syndrome (SIDS), poor fetal growth rate, and cognitive and behavioral problems [8] (*Effects of Drug Use During Pregnancy*, 2021). It is important to realize that drugs consist of more than just illicit drugs such as methamphetamine or cocaine, it also includes naturally occurring molecules like insulin or hormones. Drugs are divided into many categories by their effects specifically stimulants, antidepressants, opioids, and cannabinoids, each have different symptoms and side effects.

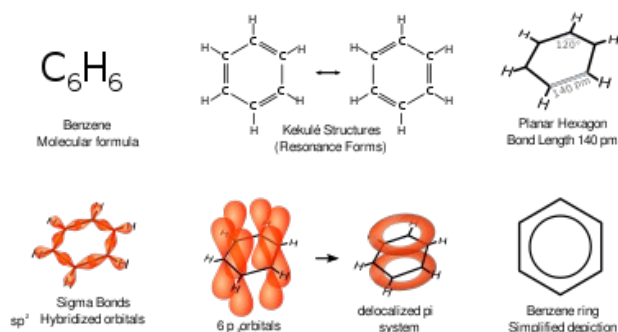
Prescribed stimulant medication slightly increases the chances of pre-eclampsia--a pregnancy complication characterized by high blood pressure-- and preterm birth. Antidepressants also slightly increase the chances of development defects, miscarriages, and premature birth. Opioid use disorders have been linked to maternal death and for the fetus, poor fetal growth, preterm birth, stillbirth, and specific birth defects. It also causes neonatal abstinence syndrome (NAS) which is a group of symptoms that result from withdrawal. NAS causes dangerous symptoms which can result in irreversible damage and a range of long term of long-term effects. Cannabinoids also result in lower birth weight and abnormal cognitive development.

Due to the fact that the category 'Drugs' consists of a wide range of substances with many subcategories, it is difficult to narrow down a specific molecular cause of the congenital abnormalities that result from their usage. [13](Ross, E. J., 2015) However, a study published by the NIH analyzes the chemical formulas of many drugs to find a common molecular structure [9] (Mao et al., 2016).

The researchers analyzing the molecular skeletons chose to differentiate the 5120 drugs that they selected to study using two analytical methods: with and without regard to atom type, hybridization, and bond order.

Without regard to atom type, hybridization, and bond order: 1179 different frameworks among the 5120 compounds and half of the drugs containing the top 32 frequently occurring frameworks.

With regard to atom type, hybridization, and bond order: 2560 different frameworks and the drugs with the top 42 frequently occurring frameworks accounting for only a quarter. The article concluded that the most common framework was the benzene ring [9] (Mao et al., 2016).



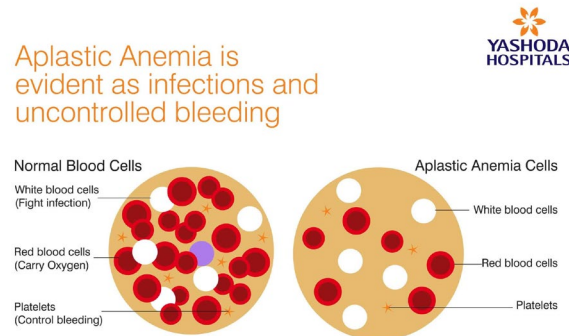
### Different models of Benzene<sup>5</sup>

However, benzene is not only found in drugs. It can be found in high concentrations in oil, gasoline, exhaust, and forest fires. Caron-Beaudoin, the Assistant Professor in environmental health in the Department of Health and Society at the University of Toronto, states that "High exposure to benzene during pregnancy is associated with low

<sup>5</sup> *Benzene*. (n.d.). Wikipedia. Retrieved August 4, 2022, from <https://en.wikipedia.org/wiki/Benzene>

birth weight, an increased risk of childhood leukemia and a greater incidence of birth defects such as spina bifida," [10] (University of Montreal, 2017)

Benzene in high concentrations damages bone marrow which decreases the number of red blood cells, white blood cells, and platelets in the body. The decrease in these cells ultimately causes a rare blood condition called aplastic anemia. Aplastic anemia prevents your body from creating the necessary amount of blood to function, the condition is very serious and the survival rate is only about 30 % within one year [11] (Snyder R., 2012). The chromosome changes that benzene causes in bone marrow can result in leukemia. Similar to the effects of ethanol, the treatment of aplastic anemia and leukemia caused by benzene is also a stem cell transplant.



Normal blood cells in comparison to aplastic anemia cells<sup>6</sup>

Studies also show that benzene exposure is linked to spina bifida and other neural tube defects. Neural tube defects are defined as “a category of neurological disorders related to malformations of the spinal cord” [12] (*Neural Tube Defects*, n.d.). Spina bifida is when the spine or spinal cord doesn't develop properly. While some cases of neural tube defects can be managed with treatment, which usually involves surgery, some cases that affect the brain are fatal. To avoid benzene exposure pregnant people should keep away from forest fires and high levels of exhaust. Folic acid supplements can be taken to reduce the chances of developing a fetal defect because of exposure.

## Conclusion

Teratogens include a wide variety of substances that all act differently on a molecular level. Some like ethanol can influence growth through the placenta and amniotic fluid, while others can harm a fetus genetically like the absence of the NAT-1 and NAT-2 genes and their enzymes. Although research is being done on how to identify congenital anomalies before birth through technology and techniques such as ultrasounds, biomarkers, and gene therapy--some methods to treat these malformations after birth are also becoming more widespread--the best way to face teratogenic agents, and the defects they cause, is by prevention. Learning about common risk factors and limiting exposure or avoiding them altogether is the best way to ensure the safety of both the mother and fetus. Additional measures can be taken to discover the probability of a fetus developing a congenital abnormality such as genetic counseling. All of the teratogenic agents covered in this paper are highly addictive, which not only makes them relatively much more common but also increases the risk of longer exposure as people are more likely to abuse the substance repeatedly. Unfortunately, this also increases the chances of fetus susceptibility. By educating the public on common harmful

<sup>6</sup> *Aplastic Anemia is evident as infections and uncontrolled bleeding.* (2016, March 28). Yashoda Hospital. Retrieved August 5, 2022, from <https://www.yashodahospitals.com/blog/aplastic-anemia-is-evident-as-infections-and-uncontrolled-bleeding/>

teratogenic agents and their devastating effects, preventative measures can be taken to reduce the risk of disrupting prenatal development.

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