Street Drugs Overview and Effects on Pregnancy
Part 1

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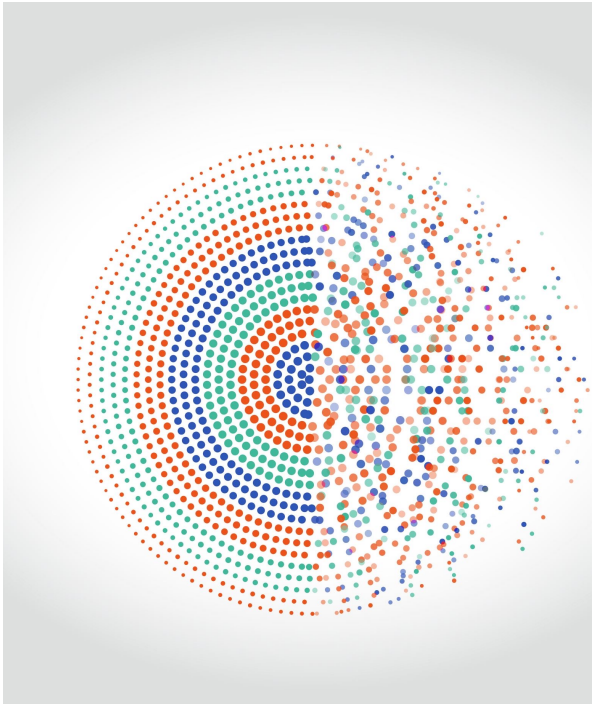


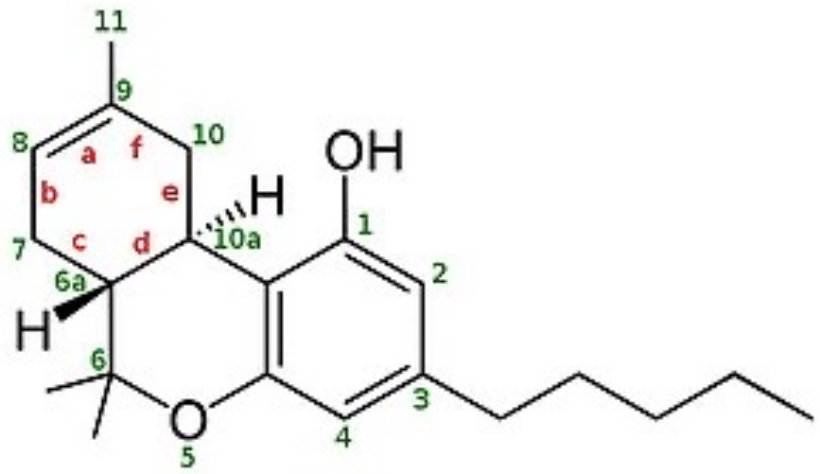
"Street Drugs"

- Delta 8 THC
- Alcohol
- Amphetamines
- Bath Salts
- Black Mamba
- Benzodiazepines
- Caffeine Pills and Drinks
- Cannabis Leaf, Oil, Dabs
- Cocaine
- Counterfeit Drugs
- Date Rape Drugs: GHB and Rohypnol
- DXM
- Fentanyl
- Flakka
- Gas Station Drugs
- Heroin
- Imodium
- Inhalants
- Khat
- Kratom

"Street Drugs"

- Ketamine
- Krokodil
- LSD
- MDMA
- Mescaline
- Methadone
- Methamphetamine
- Methylphenidate
- Magic Mushrooms
- Opioids
- Peyote
- Pink
- Poppers
- Pseudoephedrine
- Salvia
- Synthetic Marijuana
- Tianeptine
- Tobacco/Nicotine
- Vaping and the Brain


GRAND OPENING
TOBACCO HUT
VAPE - CIGARS - CBD - KRATOM
DELTA 8



The Pharmacology of Delta 8 THC

What Is Delta 8 THC?

Unlike CBD, delta-8-THC produces euphoric effects that are similar to but milder than those of delta-9-THC, the well-known psychoactive compound in cannabis.

Delta-8-THC is an isomer of delta-9-THC. The only difference between the two molecules is the location of a double bond between two carbons.

The delta-8-THC craze began when an oversupply of CBD extracted from US-grown hemp caused the price of CBD to plummet.

Producers began looking for ways to turn the glut of CBD into something profitable. Using simple chemistry reported in the 1960s, the industry got creative and started experimenting with ways to convert CBD into delta-8-THC.

The resulting products target consumers who are looking to relieve stress and anxiety, especially those who don't want to use traditional cannabis products or those who live in places where cannabis products are not legally available.

What Is Delta 8 THC?

But with no regulatory oversight and limited laboratory testing, most products sold as delta-8-THC are not actually pure delta-8-THC.

Such products typically contain a high percentage of delta-8-THC and small amounts of other cannabinoids, including delta-9-THC, and reaction by-products.

Some of the cannabinoids are not naturally found in cannabis. In most cases, nothing is known about the health effects of these impurities.

Several states are starting to crack down on sales of delta-8-THC products.

But as long as they are derived from hemp and contain no more than 0.3% of delta-9-THC on a dry-weight basis—the limit under federal law—many lawyers and hemp industry officials consider them legal.

Regardless of whether delta-8-THC is legal, chemists are sounding the alarm after finding several unidentified compounds in products labeled as delta-8-THC.

The Unregulated Distribution And Sale Of Consumer Products Marketed As "Marijuana Light" or Delta-8 THC

- **Delta-8 differs in structure from Delta-9 THC in the placement of a double bond between carbon atoms 8 and 9 rather than carbon atoms 9 and 10.**
- **Due to its altered structure, Delta-8 THC has a lower affinity for the CB1 receptor, and therefore has a lower psychotropic potency than Delta-9 THC.**
- **Relative to the psychotropic potency of Delta-9 THC, Delta-8 THC has been estimated to be about 75% or perhaps two-thirds as potent.**
- **Delta-8 THC has been described as "marijuana light" or "pain relief with less psychoactivity."**
- **Although Delta-8 THC does exist naturally in the cannabis plant, it is only present at very low levels.**
- **The cost-effective manufacturing process of Delta-8 THC involves the isomerization of CBD via exposure to an acidic environment. Delta-8 THC can also be manufactured from Delta-9 THC.**


3CHI
ENHANCED OIL
Δ8THC
300MG
10 MG/ML
1 OZ (30 ML)


vitality
DELTA-8
THC OIL
500 MG
Δ8 THC
A DIETARY SUPPLEMENT
1 FL. OZ. (30 ML)
vitality
DELTA-8
THC OIL
Δ8 THC
500 MG
30 ML
A DIETARY SUPPLEMENT


DELTA8PRO
4200MG
INFUSED OIL
120 SERVINGS
PER BOTTLE
3000mg Delta 8 THC
600mg CBN
600mg CBG
DELTA8PRO
D8 HEMP INFUSED
PYRAMID
GUMMIES
MANGO
VEGAN
NO ARTIFICIAL COLORS
ORGANIC INGREDIENTS
MADE IN USA
DELTA8PRO
DELTA 8
MOON ROCKS


>.3 Δ THC
NESSY'S
CHERRY PIE
with
DELTA-8
700MG
DELTA-8


EXPERIENCE
DELTA 8
CANNABIS CARTRIDGES
Wedding Cake
100% HEMP
DERIVED
LAB
TESTED
ZERO
CUTTING
AGENTS
DELTA-8 THC
920MG
TERPENES INFUSED
NOT TO BE SOLD TO MINORS
1 ML
Compatible with any 510 thread e-cig battery. Inside this cartridge is a rich, sweet taste of vanilla and other tangy flavors. Wedding Cake is an uplifting indica dominant hybrid strain that is known for its relaxing and euphoric effects. Such a delicious treat, you may even want to double the dose!
INGREDIENTS: Hemp-Derived Delta-8 THC Extract & Natural Terpenes
WHAT'S YOUR MOOD?
UPLIFTING
HAPPY
RELAXED
SUGGESTED USE: Remove silicone covers and screw into battery. DO NOT overtighten. One single serving is one 3-second draw. Up to 300 Servings/package. (Servings may vary.)
Produced in accordance with Section 7606 of the 2014 U.S. Farm Bill and 2018 Farm Bill. Contains undetectable levels of delta-9 tetrahydrocannabinol concentration (<0.3% THC). May show up on drug test analysis. This product has not been evaluated by the Food and Drug Administration.
WARNING: DO NOT TAKE if you are pregnant, lactating, or operating any machinery. Always consult with a doctor before modifying your diet or using any new products. This product is not intended to diagnose, treat, cure or prevent any diseases.
DISTRIBUTED BY: Sixth Gear Distribution, Myrtle Beach, SC, USA
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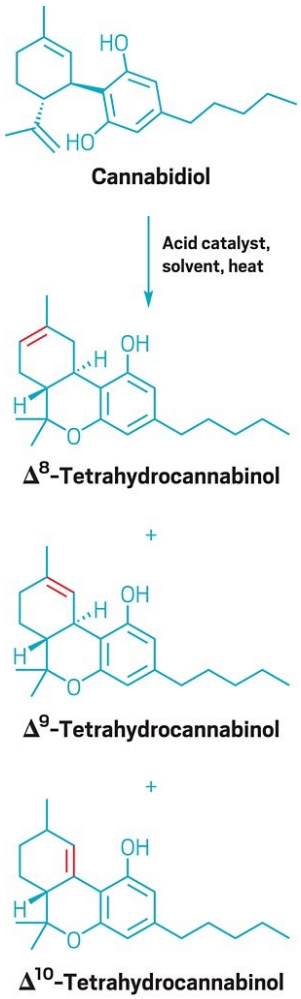
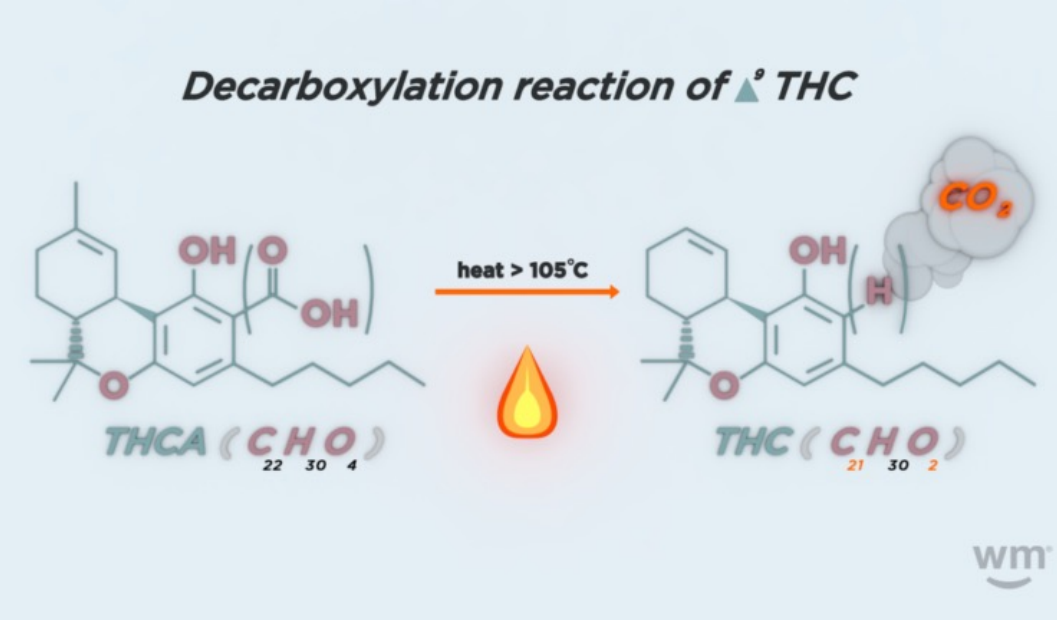
SCAN FOR
LAB
ACCURACY
@EXPERIENCE_CBD

The Different Delta CBD and THC

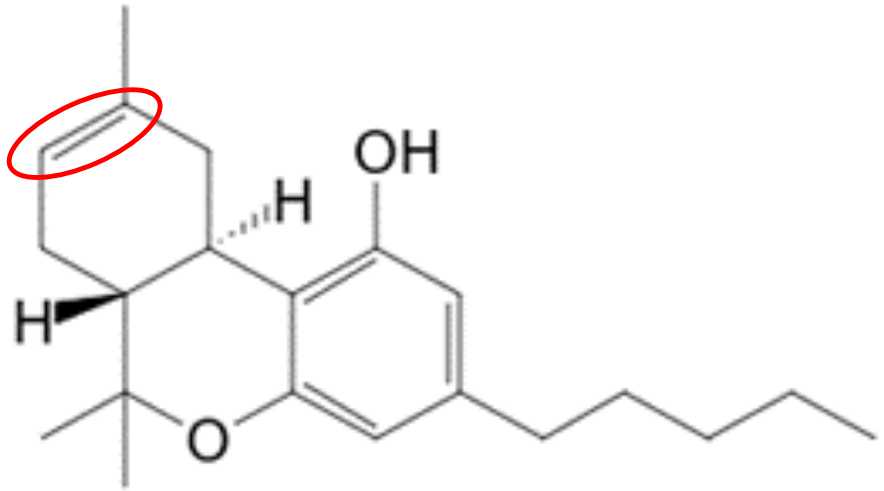


THC - Structure

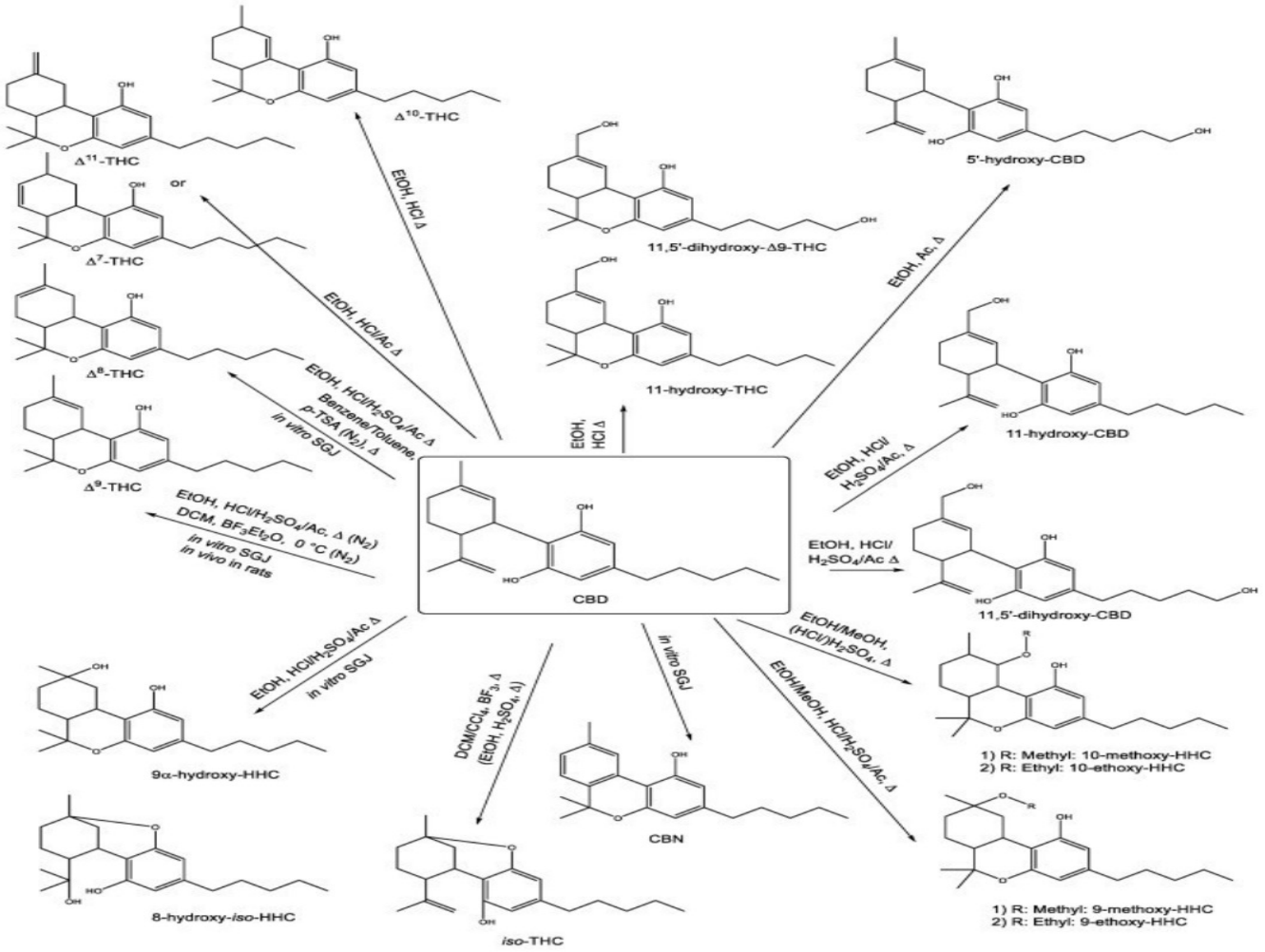


- **Converted from THCa by drying, heating.**

Delta 8 Cannabinoids



Overview of various chemical conversions of cannabidiol (CBD) to different conversion products and the respective conditions, which are reported in the literature.



Delta 8 THC Clinical Effects

Cases of delta-8-THC ingestions reported to poison control centers have been associated with a variety of clinical symptoms, including euphoria, relaxation, drowsiness, bradycardia, and hypotension sometimes requiring vasopressors.

Other patients report feeling confused and anxious, with tachycardia and generalized numbness.

The variation in clinical effects from delta-8-THC use is not unexpected, as people respond to other cannabinoids, i.e. delta-9-THC, in a variety of ways.

Drug Testing for Delta 8 THC

Urine drug screens may be helpful as delta-8-THC may be detected on screening tests for THC metabolites.

However, these commercial urine drug screens do not differentiate among the cannabinoids.

Studies demonstrating detection of delta-8-THC and its cross-reactivity with various urine drug screens have not been conducted.

Products Available

- **Products have started appearing on the market, including:**
  - **Vape cartridges**
  - **Tinctures**
  - **Joints**
  - **Blunts**
  - **Gummies**
  - **Syrups**
  - **Other edibles and beverages**

Summary

Delta-8 has similar clinical effects to delta-9 including euphoria, confusion, tachycardia, relaxation, tranquility, and mild hallucinogenic effects.

One study from 1973 compared the effects of 20 mg delta-8, 40 mg delta-8, and 20 mg delta-9 and found that delta-8 is about 2/3 as potent as delta-9.

Besides this study and some animal data, comparative data in humans are lacking and anecdotal reports are clearly inadequate to describe the differences between the two compounds.

Anecdotal reports often describe delta-8 as "*weed light*" and state that it produces more of a body high with less hallucinogenic effects than delta-9.

Summary

Delta-8 is available in many forms including edibles (gummies, baked goods), vapes, dabs, and infused plant material.

In a study commissioned by the US Cannabis Council, 16 samples purported to be delta-8 were sourced in April of 2021 from various states.

The samples were analyzed by ProVerde Laboratories. All but one of the samples contained delta-9-THC at concentrations above the legal limit of 0.3%.

Some samples contained lead and other metals.

Summary

The largest concern with delta-8 is the lack of oversight with manufacturing and application of current laws. Over 100 persons have been hospitalized after consuming Delta 8 THC in 2021.

It is available in convenience stores and online in formulations that may be enticing to children.

Management of a patient after ingesting or inhaling delta-8 is supportive care (e.g., benzodiazepines for agitation and observation with attention to airway for sedation).

Testing via urine drug screen may identify "cannabinoids" either because of lack of specificity in the test or because of contamination with delta-9-THC.

The American Association of Poison Control Centers is actively monitoring for cases of delta-8 -THC. Call your local poison center to report any cases at 800-222-1222.

Review of pregnancy labeling of prescription drugs: Is the current system adequate to inform of risks?

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Gainesville, Fla, Columbus, Ga, Bonn, Germany, and Memphis, Tenn

AJOG 2002; 187: 333

FDA pregnancy category system

Category A: Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.

Category B: No evidence of risk in humans. Either animal study shows risk, but human findings do not, or if no adequate human studies have been done, animal findings are negative.

Category C: Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking. However, potential benefits may justify potential risk.

Category D: Positive evidence of risk. Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.

Category X: Contraindicated in pregnancy. Studies in animals or humans or investigational or postmarketing reports have shown fetal risk, which clearly outweighs any possible benefit to the patient.

~40% in PDR have pregnancy "risk"

A	**0.7%**
B	**19%**
C	**66%**
D	**7%**
X	**7%**

Delta 8 THC and Pregnancy

- **How Cannabinoids Affect Obstetrical Outcomes:**
- Implantation, the attachment of the fertilized egg to the uterine wall, is dependent upon a number of tightly regulated processes. Evidence suggests that there are five ways in which cannabinoids can affect implantation:
- **Impairment of Fallopian Motility:** Cannabinoid signaling controls muscle contraction and relaxation in the fallopian tube responsible for the movement of a fertilized egg through the fallopian tube and into the uterus.
- **Ectopic Pregnancy**: Previous studies have shown that the blood collected from women who have had ectopic pregnancies contains significantly higher levels of the naturally occurring cannabinoid, anandamide, compared to normal pregnant controls. Consistency between human and animal data adds confidence that the observed findings in animal models of altered cannabinoid signaling may play a role in ectopic pregnancy.
- **Non-Hatched or Non-Viable Embryo:** In mice models known to have altered cannabinoid signaling, an increased mortality of offspring was observed in association with implantation of slowly developing embryos (6).
- **Decreased Uterine Receptivity:** It is theorized that the binding of exogenous cannabinoids to CB1 receptors in the uterus has embryotoxic effects on the uterine environment. Modeling of this scenario has halted the development of blastocysts *in vivo* and *in vitro* (7).
- **Miscarriage (Spontaneous Abortion):** Folic acid (Vitamin B9) is essential for embryo development and cannot be synthesized by the body which is why women are encouraged to take folic acid supplements during pregnancy. THC significantly decreases fetal folic acid uptake. Low levels of folic acid during pregnancy are associated with higher rates of miscarriages, as well as neural tube defects and low birth weight.

Delta 8 THC and Pregnancy

- **How Cannabinoids Affect Embryo Development:**
- THC crosses the placenta, enters fetal blood circulation, passes through the blood brain barrier, and is found at the highest levels in fetal fat tissue. The brain is 60% fat and therefore stores THC following maternal ingestion. The brain is also densely populated with CB1 receptors which mediate THC's psychoactive properties.
- **Folic Acid Uptake:** As stated above, THC interferes with fetal folic acid uptake. Low levels of folic acid during pregnancy are known to be associated with neural tube defects and low birth weight.
- **Cellular Growth:** Exogenous cannabinoids may interfere with critical pathways for cellular growth and angiogenesis (formation of new blood vessels).
- **Neural Development:** Cannabinoids acting upon the CB1 receptor have the ability to influence the differentiation of neural cells from stem cells in the brain. This has tremendous potential to negatively affect learning and memory as well as developmental processes such as limb development.

Delta 8 THC and Pregnancy

- **If cannabis is consumed, how long does it persist in the breast milk?**
- Cannabis concentrations in the breast milk are variable and are related to maternal dose and the frequency of dosing. However, there are some things that make cannabis a little different than alcohol or other recreational drugs. Cannabis and its byproducts are very fat-soluble or lipophilic. Because in women is the percentage of body fat is 25-30%, there is a large reservoir for the storage of cannabis. What this means is that it takes much longer for cannabis to leave one's system, compared to substances like alcohol. Furthermore, there is an especially long washout period in those who have been daily users. Long after the psychoactive effects have faded, THC and its metabolites can be detected in blood, urine, and breast milk.
- Studies focusing on the detection of THC in milk have yielded variable results, with duration of detection ranging from 6 days to greater than 6 weeks in various studies. The longevity of THC in the breast milk may be related, in part, to the extremely high fat content of breast milk and the lipophilic nature of THC, so that the breast milk "traps" the THC, in a sense acting like a reservoir for THC storage.
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Delta 8 THC and Pregnancy

- **What are the effects of exposure to cannabis in the nursing infant?**
- The bioavailability of cannabis and its metabolites ingested by neonates in the breast milk has not been well-characterized. There are conflicting data regarding the outcomes of infants exposed to cannabis during breastfeeding and very few studies assessing outcomes in this population. These studies are not easy to conduct. First of all, recreational use of cannabis continues to be illegal in many states. Furthermore, it is difficult to disentangle the direct effects of cannabis delivered in the breast milk from the indirect effects of cannabis on the quality of childcare and parenting, especially in heavy, chronic users or when cannabis is combined with other substances.
- In one study, 136 breastfeeding infants were assessed at one year of age. In the 68 infants exposed to cannabis during the first month of life, there was evidence of decreased motor development at one year, when compared with matched infants who were not exposed to cannabis. Specifically, there was a 1465-point decrease in the Bayley index of infant motor development. However, the authors of this study cannot conclude that these findings were entirely due to exposure via breastfeeding, as many of the women also used marijuana during pregnancy.
- In another study, 27 breastfed infants exposed to cannabis were compared to 35 unexposed breastfed infants. At one year, no differences were noted for motor and mental development using the Bayley Scales of Infant Development. However, the small size of this study limited statistical analysis.
- So the jury is still out regarding the effects of cannabis on the nursing infant.
- Both the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics recommend that women refrain from using cannabis during pregnancy and while breastfeeding. Because of the persistence of cannabis and its byproducts in the breast milk for days to weeks, using cannabis and waiting for it to clear out of the breast milk is not a viable option. For women who use cannabis for medical indications, alternative therapies with more safety data during breastfeeding should be considered.

How to report complaints and cases of accidental exposure or adverse events:

- **If you think you are having a serious side effect that is an immediate danger to your health, call 9-1-1 or go to your local emergency room. Health care professionals and patients are encouraged to report complaints and cases of accidental exposure and adverse events to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:**
- **Call an FDA Consumer Complaint Coordinator if you wish to speak directly to a person about your problem.**
- **Complete an electronic Voluntary MedWatch form online or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the form, or submit by fax to 1-800-FDA-0178.**
- **Complete a paper Voluntary MedWatch form and mail it to the FDA.**
- **To report adverse events in animals to the FDA's Center for Veterinary Medicine, please download and submit Form FDA 1932a found at: www.fda.gov/ReportAnimalAE.**


Alcohol

What is alcohol?

- # 1 Street Drug
- A low potency drug
- The alcohol we drink is ethanol (ethyl alcohol)
- Standard US drink: 14g of ethanol
  - Beer: 12oz of 5% alcohol
  - Wine: 5oz of 12% alcohol
  - Liquor: 1.5oz of 40% alcohol
- Other alcohols are toxic (e.g. isopropyl)
- BAC (blood alcohol content): % alcohol in someone's blood

Alcohol Use

- Fast Facts
  - 79,000 deaths annually attributed to excessive alcohol use
  - 3rd leading lifestyle-related cause of death in America
  - Cost
    - Est. $276 Billion/year (due to crime, healthcare, lost productivity, etc.)

What is alcohol?

Fermentation (Beer & Wine)

- Sugar + water in air, invaded by yeasts
- Yeasts eat the sugar→ethanol [CH3- CH2-OH or C2H5OH]+ CO2[bubbles up & escapes]
- Yeasts cannot survive in high alcohol concentration; at ~ 10-15% they die, so this can only produce beer or wine

Distillation (Spirits)

- Removes the water to increase the alcohol content
- Spirits come from different sources (e.g. Brandy—distilled wine, Whiskey—grains, etc.)

Pharmacokinetics

Ingestion: Oral

Distribution: total body water

- Affected by body composition (e.g. women have lower proportion of total body water)

Absorption:

- Absorbed primarily through duodenum in small intestines
- Rate varies depending on:
  - Food intake
  - Alcohol amount and concentration
  - Rate of drinking
  - First Pass Metabolism (e.g. Aspirin increases absorption by affecting first pass metabolism)

Metabolism: 10-14g ethanol/hour

Pharmacokinetics

- Metabolism
  - Genetic variations in metabolizing enzymes
    - ADH (alcohol dehydrogenase)
      - 5 classes with polymorphism occurring at ADH2 and ADH3
      - Each sub-unit is associated with a different ethnicity
        - e.g. ADH2-3: 15% prevalence in African American population
          - 25% higher metabolic rate
          - Could protect against alcohol-related birth defects
        - e.g. ADH2-2: 85% prevalence in Asian population

Pharmacokinetics

- Metabolism
  - Genetic variations in metabolizing enzymes
    - ALDH (aldehyde dehydrogenase)
      - ALDH2: responsible for ALDH activity
        - ALDH2-1/1: normal activity
        - ALDH2-1/2 or ALDH2-2/2: reduced activity
          - The “Flushing Response”
          - Common in Asian populations (10-65%)
          - Protective factor against alcoholism
      - Reduced ALDH activity → increased Acetylaldehyde → hangover symptoms/sickness

Pharmacodynamics

- Depressant
- “Messy drug”: diverse actions on the brain
- Responses: euphoria, impaired thought processes, decreased mechanical efficiency, reduced anxiety, disinhibition
- Alcohol myopia: compulsive activity; spontaneity; lack of forethought
- Dose dependent effects

Pharmacodynamics

GABA excitation

- GABA: inhibitory neurotransmitter
- Responsible for sedation/reduced anxiety

Glutamate inhibition

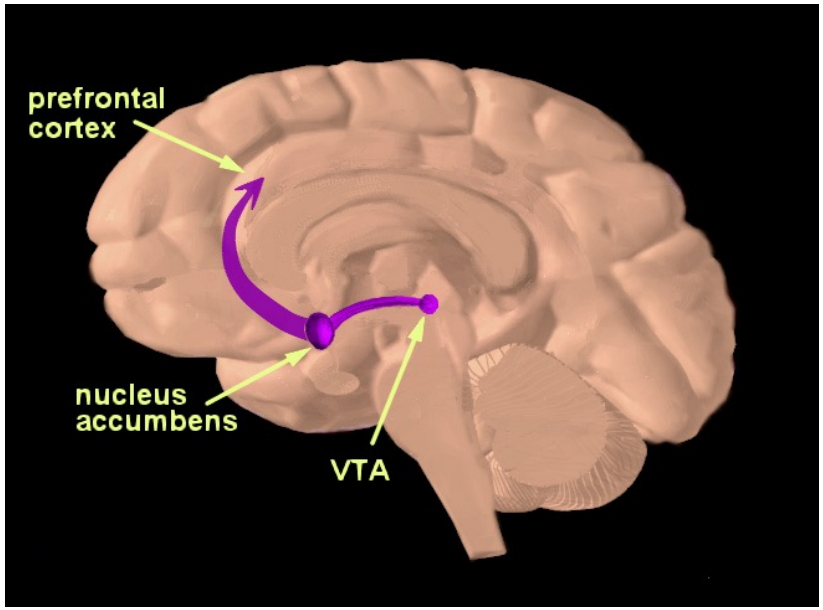
- Glutamate: excitatory neurotransmitter
- Blocks NMDA receptor
- Responsible for cognitive impairment, disinhibition, withdrawals

Opioid excitation

- Inhibits GABA neurons, which increases Dopamine
- Responsible for euphoric effects
- Activates Opioid peptide system
- Responsible for reinforcing and aversive effects (Mu- and Kappa- receptors) and cravings

Reinforcement

- Mesocorticolimbic system
  - Comprised of Ventral Tegmental Area, Nucleus Accumbens, Prefrontal Cortex
  - Activation → dopamine release → reinforcement/ reward/ pleasure



Alcohol Effects

BAC Effects

Table 9.5 Typical Acute Effects of Alcohol Associated with Different Ascending Blood Alcohol Concentrations (BACs)

BAC (%)	Effects
0.01–0.02	Slight changes in feeling; sense of warmth and well-being.
0.03–0.04	Feelings of relaxation, slight exhilaration, happiness; skin may flush, mild impairment in motor skills.
0.05–0.06	Effects become more noticeable. More exaggerated changes in emotion, impaired judgment, and lowered inhibitions. Coordination may be altered.
0.08–0.09	Reaction time increased, muscle coordination impaired. Sensory feelings of numbness in cheeks, lips, and extremities. Further impairment in judgment. Legal level of intoxication is .08% in all 50 of the United States, Puerto Rico, and the District of Columbia.
0.10	Deterioration in motor coordination and reaction time. Person may stagger and slow speech.
0.15	Major impairment in balance and movement. Large increase in reaction time. Large impairment in judgment and perception.

0.20	Difficulty staying awake; substantial reduction of motor and sensory capabilities; slurred speech, double vision, difficulty standing or walking without assistance.
0.30	Confusion and stupor. Difficulty comprehending what is going on; possible loss of consciousness (passing out).
0.40	Typically unconsciousness; sweatiness and clamminess of the skin. Alcohol has become an anesthetic.
0.45–0.50	Circulatory and respiratory functions may become totally depressed. LD 50 in humans.

How Long for Dependence?

- Ex. An average of 16 oz of Whiskey everyday for 2-3 weeks will cause physical dependence (i.e. tolerance, withdrawal, etc.)

Tolerance?

Decreased effect of a drug with prolonged use/exposure

Acute:

- Decreased effect of a drug within a single use/ exposure

Chronic:

- Decreased effect over multiple uses/ exposures

The Alcoholic

Five Types:

1. Remorseful, Resolute, no decision to stop
2. Unwilling to admit problem
3. Believes he can drink again after period of abstinence
4. Manic-depressive
5. Normal except for alcohol problem

Alcoholism

- Two Types:
  - Type I
    - Genetically & environmentally induced
    - Affects men & women
    - Onset after 25
    - Loss of control over drinking
    - Often drinks to relieve anxiety
  - Type II
    - Primarily genetic
    - Predominantly male
    - Onset before 25
    - Inability to abstain from drinking
    - Drinks to feel euphoria

Drug Testing for Alcohol

The most common test for alcohol exposure is a urine drug screen

A typical urine drug test screens for alcohol

A urine analysis detects the presence of ethyl glucuronide (EtG) – a metabolite found in alcoholic beverages

Alcohol and its metabolites can stay in the body for 2-3 days, depending on the quantity and length of time the alcohol was consumed

Drug Testing for Alcohol

- “High” positive: levels > 1,000 ng/mL of EtG
  - Indicates heavy drinking within the previous day or same day, or light drinking the day of the test
- “Low” positive: levels 500 – 1,000 ng/mL of EtG
  - Indicates heavy drinking within three days of the test, light drinking in the past 24 hours, or intense exposure to products containing alcohol recently
- “Very low: levels < 500 ng/mL but still detected
  - Indicates heavy drinking several days prior or light drinking 12 – 36 hours before, or that the person was exposed to alcohol-containing products

Drug Testing for Alcohol

Limitations of the drug test

- The EtG test can only confirm that a person has not consumed alcohol or alcohol containing products in the days leading up to the test
- Unfortunately, there are many items that contain alcohol people can encounter on a daily basis

False positive

- If a urine sample is not stored properly and remains too long at room temperature, EtG levels rise due to bacteria growth in the urine.
  - Refrigeration of samples is suggested for any EtG test that cannot be shipped within the recommended time frame.
- A person with diabetes who has a urinary tract infection may produce EtG and result in a positive test.
  - This can only occur in individuals who have diabetes.

Alcohol's Effects on Pregnancy

Alcohol Use in Pregnancy

- Prevalence in ♀ who know pregnant
  - 2%: ≥ 5 drinks/occasion 5+ days past mo
  - 28% ≥ 5 drinks typical drinking days
  - 21% ≥ 45 drinks per month
- ~50% pregnancies unplanned
  - 50% don't know pregnant early
  - 45% drink before know pregnant
  - ~5% ♀ drink ≥ 6 drinks/ week

Epidemiology: Rates of Alcohol Use among Women of Childbearing Age

CDC 2015 Morbidity and Mortality Report

- Non-pregnant women
  - Any Alcohol Use = 54%
  - Binge Drinking (4 or more) = 18%
- Pregnant women
  - Any Alcohol Use = 10% (1 in 10 consuming alcohol)
  - Binge drinking = 3% (1 in 33 binge drinking)

- Among Binge drinkers: Pregnant women have *higher frequency* of binge drinking than non-pregnant women
- Prevalence of alcohol use in pregnant women is higher for women with college degrees compared to less education

FASD Epidemiology

- **It is not known what percentage of babies will be born with FASD if the mother drinks alcohol during pregnancy.**

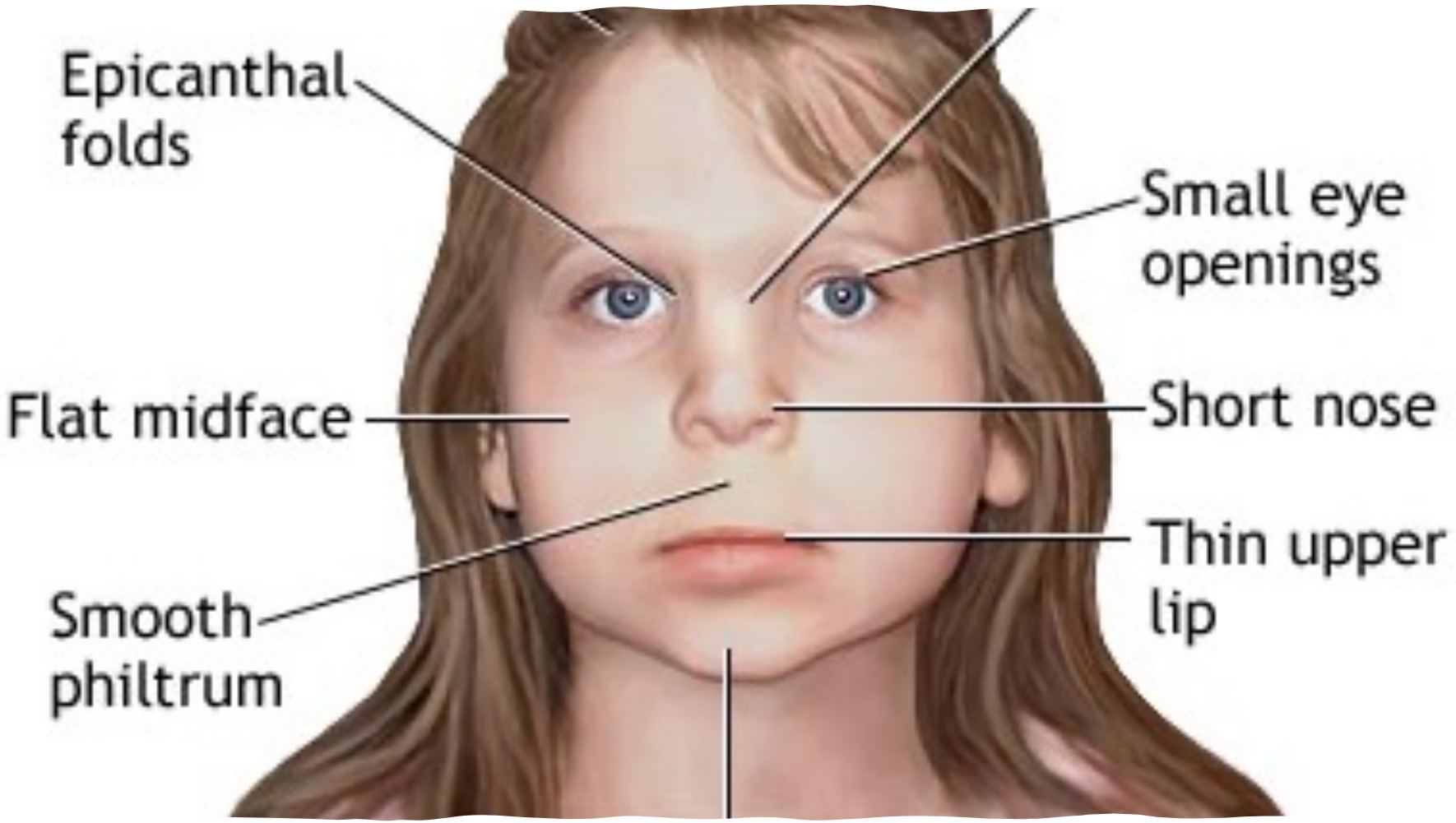
- **FASD is likely underdiagnosed**
  - **Dysmorphic features can be less noticeable in newborns**
  - **CNS deficits may not be recognized until preschool age**
  - **Less consideration for prenatal alcohol use to be underlying factor in behavioral and learning disorders**

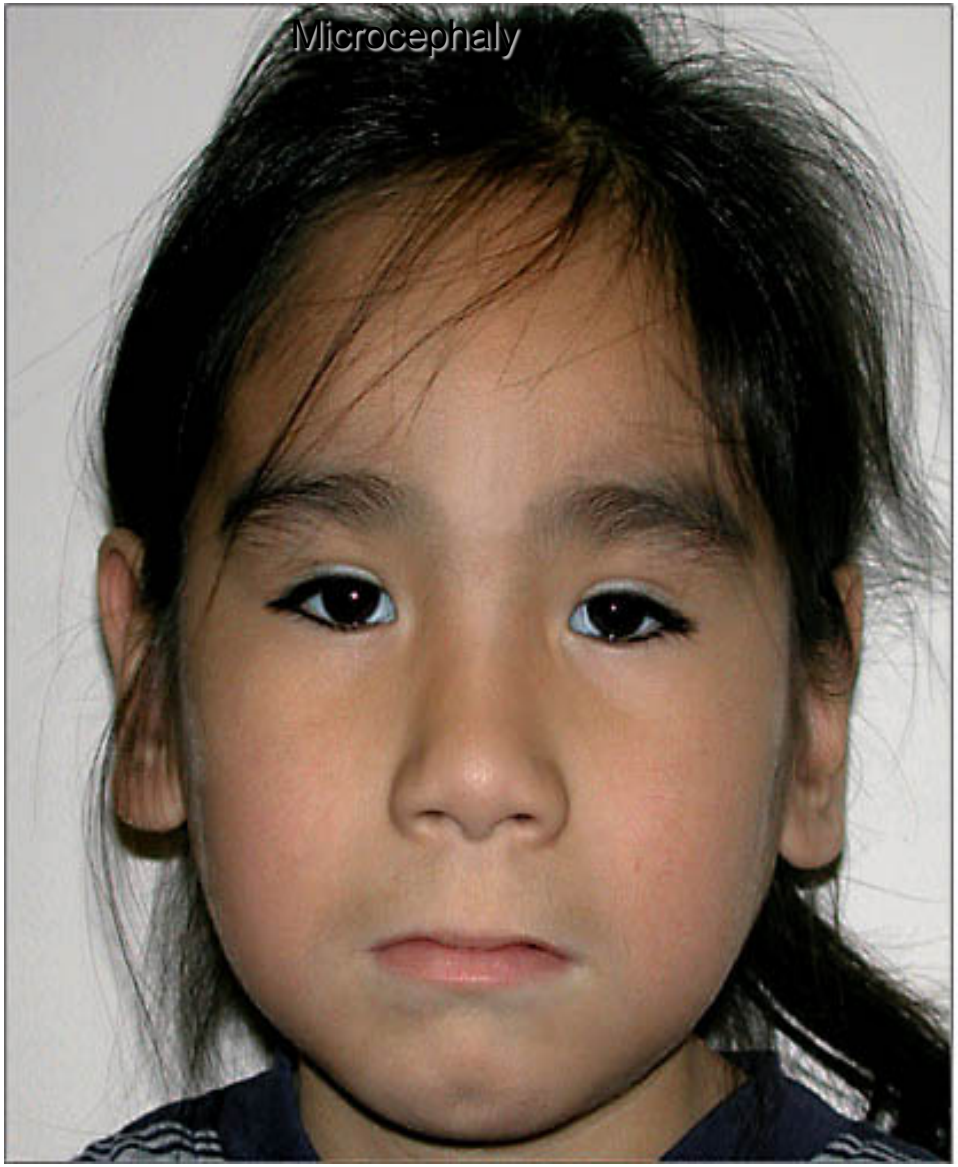
- **The CDC: up to 1.5 infants per 1000 births with FAS**
- **The CDC: 0.3 out of 1000 children from 7 to 9 years of age with FAS**
- **May et al. (2009): 10.9 to 25.2 cases of FAS/pFAS per 1000.**
- **May et al. (2014): 24 to 48 of FASD per 1000.**

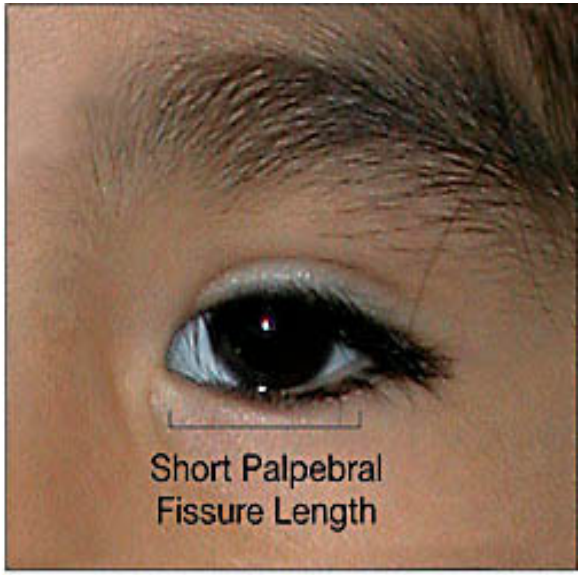
FAS Facts

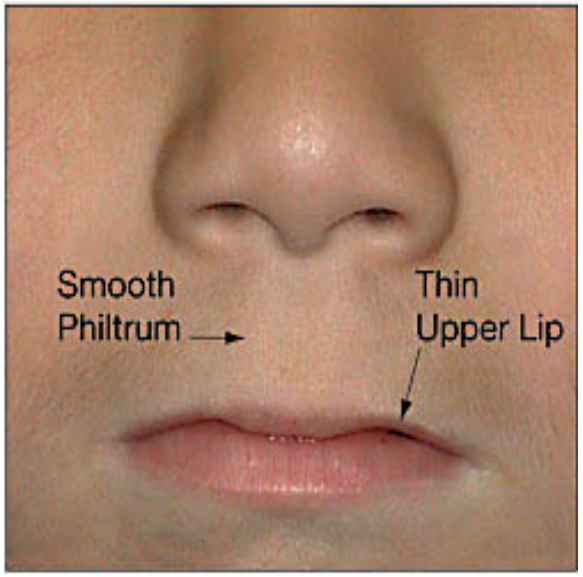
- Alcohol diffuses through placenta
- Concentration in fetal blood is the same as in the mother's blood within a few minutes
- The fetus is able to metabolize alcohol 10% as fast as the mother

Fetal Alcohol Spectrum Disorders (FASD)

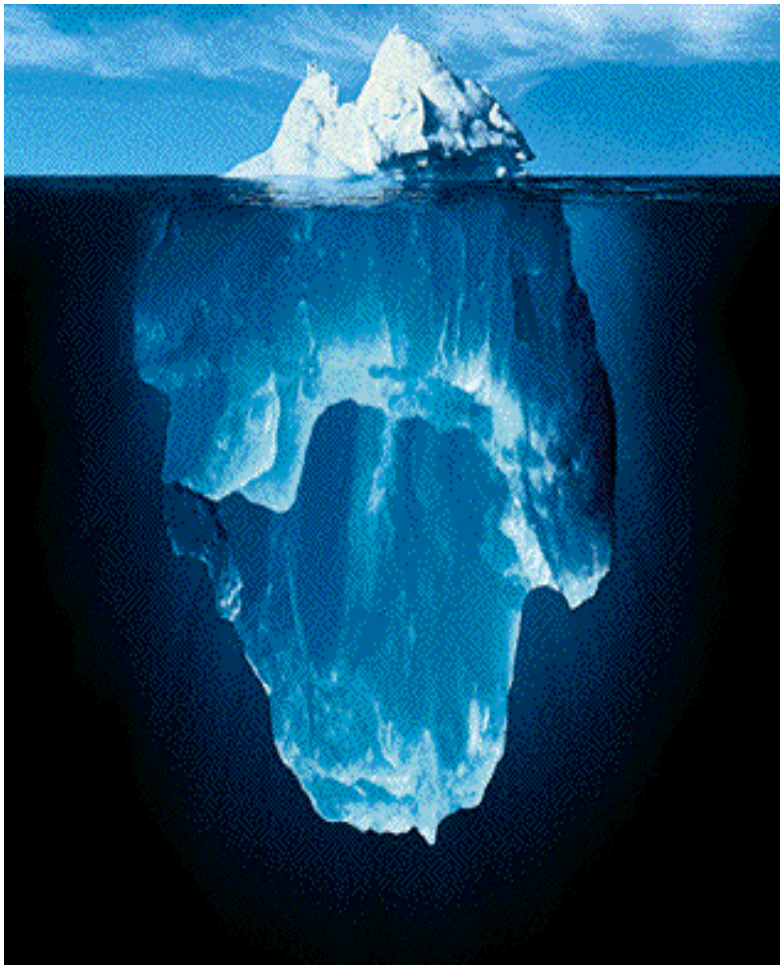



Microcephaly


Short Palpebral
Fissure Length


Smooth
Philtrum
Thin
Upper Lip

FAS – Only the Tip of the Iceberg

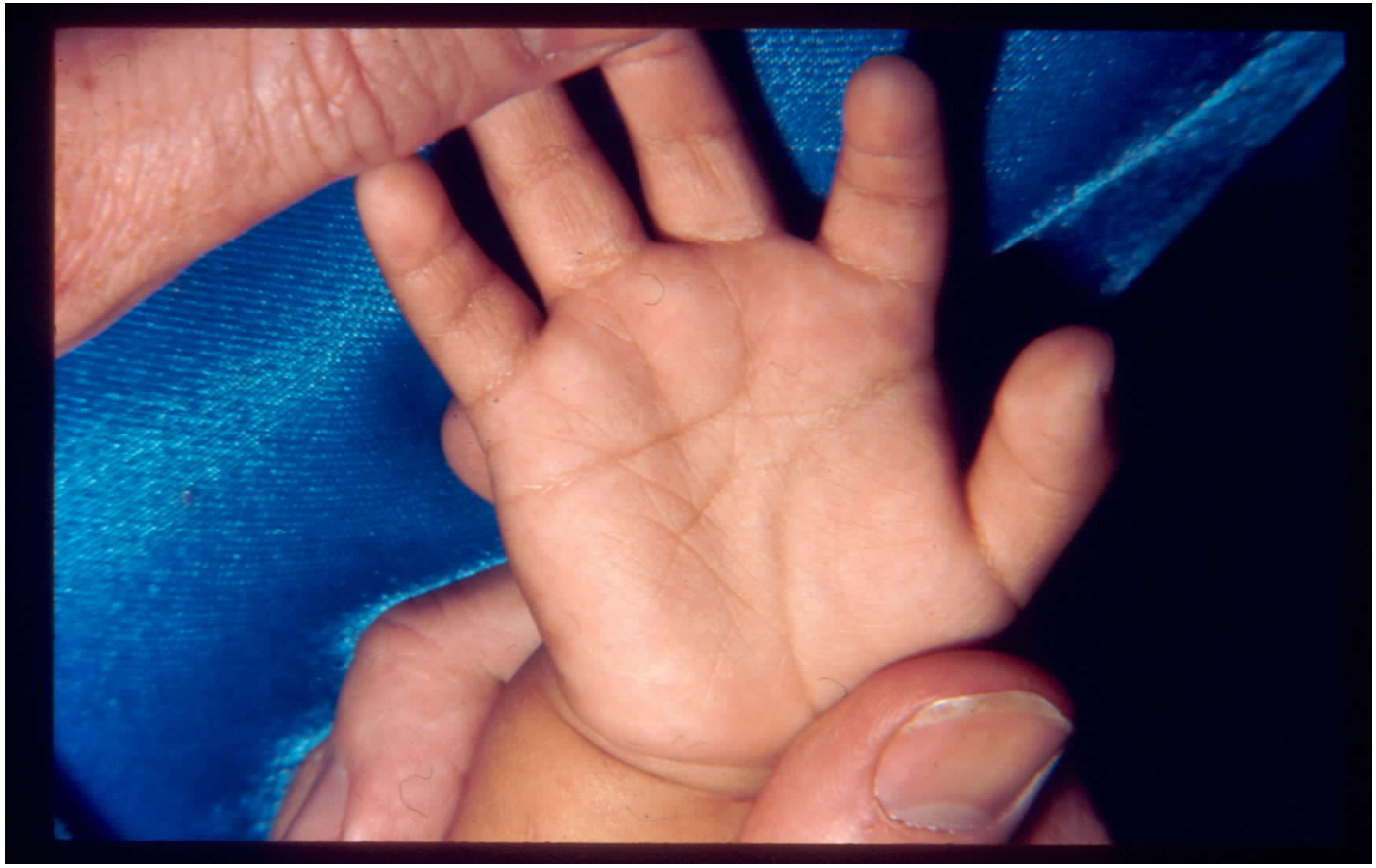


- PFAS –Partial Fetal Alcohol Syndrome (PFAS)
- Alcohol-Related Birth Defects (ARBD)
- Alcohol-Related Neurodevelopmental Disorders (ARND)

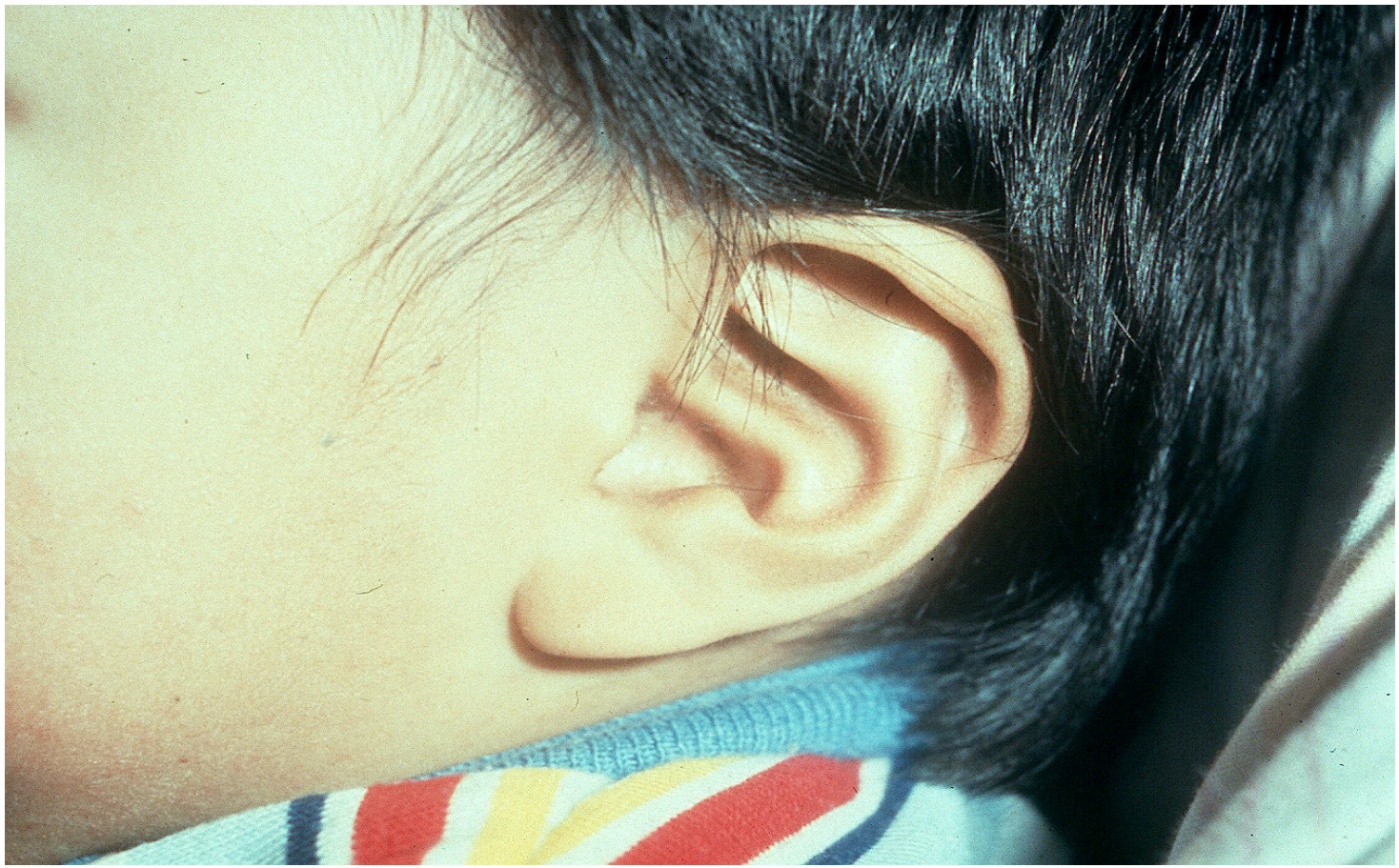
Associated congenital anomalies, malformations, & dysplasias:

Cardiac	**ASD**	**Aberrant great vessels**
	VSD	**Conotruncal heart defects**
Skeletal	**Hypoplastic nails**	**Clinodactyly of 5th fingers**
	Short 5th digits	**Pectus carinatum/excavatum**
	Radioulnar synostosis	**Vertebral segmentation defects**
	Lg joint contractures	**Scoliosis**
	Camptodactyly	**"Hockey stick" palmar creases**
Renal	**Aplastic/hypoplastic/ Dysplastic kidneys**	**"Horseshoe" kidneys/ Ureteral duplications**
Eyes	**Strabismus**	**Refractive errors**
	Retinal vascular anomalies	**Optic nerve hypoplasia**
Ears	**"Railroad track" ears**	**Conductive/ neurosensory hearing loss**

Hockey Stick Palmar Crease



Railroad Track Ears



Partial FAS

Confirmed ETOH exposure in utero

2+ characteristic minor facial anomalies

1+ of:

- Growth retardation
- Deficient brain growth
- Behavioral/cognitive abnormalities

How pFAS differs from FAS

Alcohol-Related Neurodevelopmental Disorder

- **3+ CNS impairments**
- **Few or no facial abnormalities**
- **Growth deficiency**
- **Prenatal alcohol exposure**
- **Differs from other FASD by:**
  - **Focus on CNS deficits**
  - **Minimal to no growth or facial abnormalities**

Alcohol-Related Birth Defects

- Not fit other FASD category
- Maternal ETOH exposure
- Minor facial anomalies
- 1+ Congenital defects:
  - Cardiac
  - Renal
  - Skeletal
  - Eye, ear

CNS Abnormalities

Memory problems

Attachment disorder

Impaired motor skills

Learning disabilities

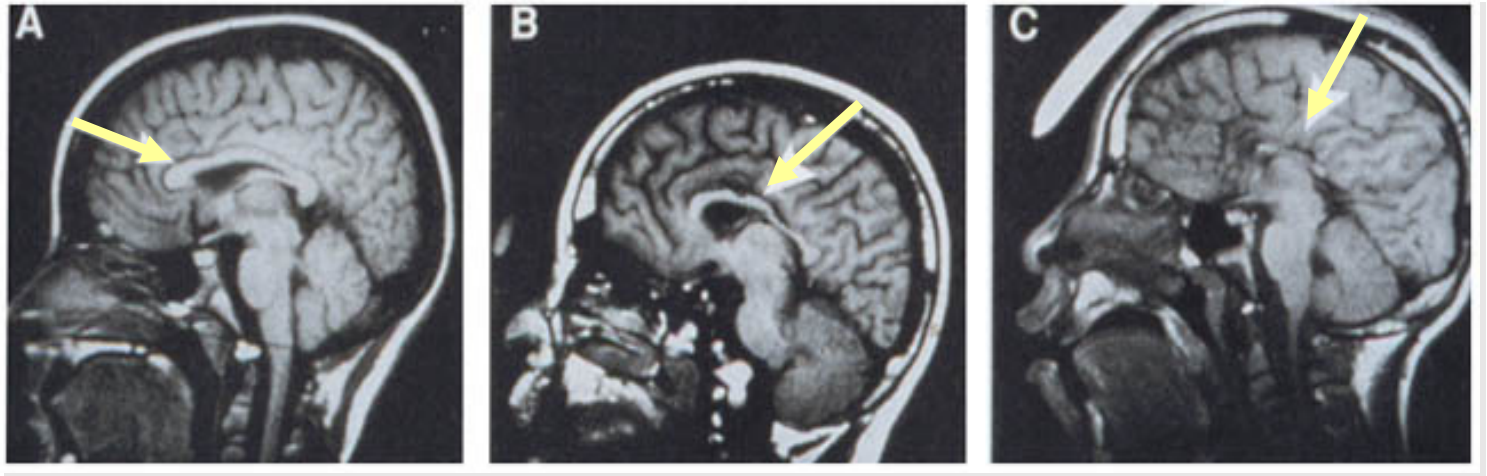
Problems with reasoning and judgment

- **Neurodevelopmental Disorders**

Inability to discern consequences of actions

Intellectual impairment

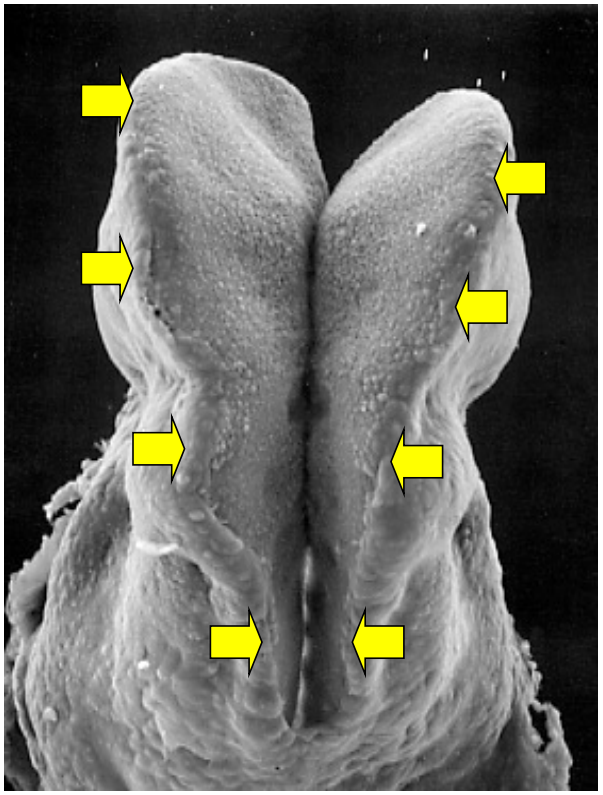
Visualization of the brain of a normal individual (A) and two with FAS (B,C) shows permanent loss of the tissue indicated by the arrows (portions of the corpus callosum).



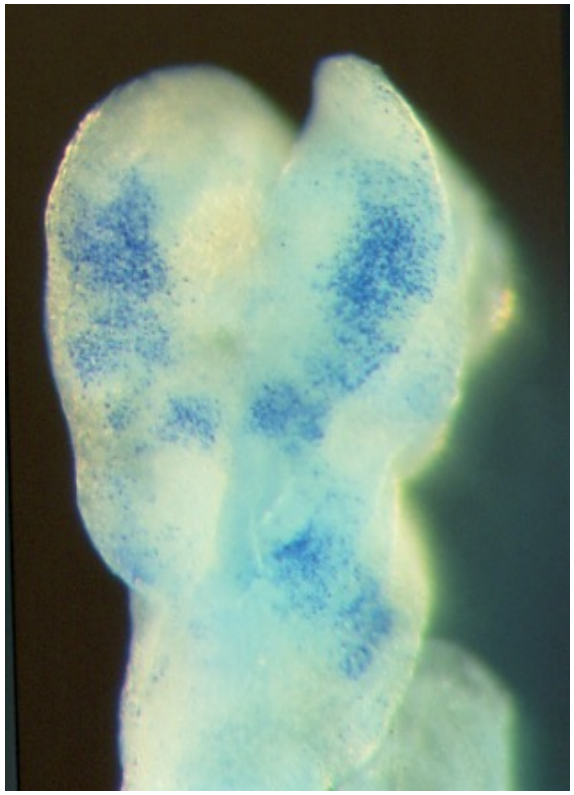
Normal FAS FAS

Images courtesy of Dr. S. Mattson

ALCOHOL KILLS SPECIFIC CELLS IN THE DEVELOPING BRAIN

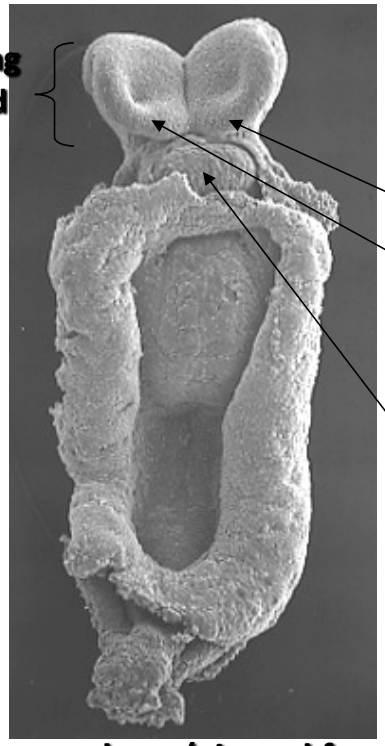


Arrows surround a portion of the brain of a mouse embryo (viewed from the back) that is at a developmental stage corresponding to a 22-23 day human.

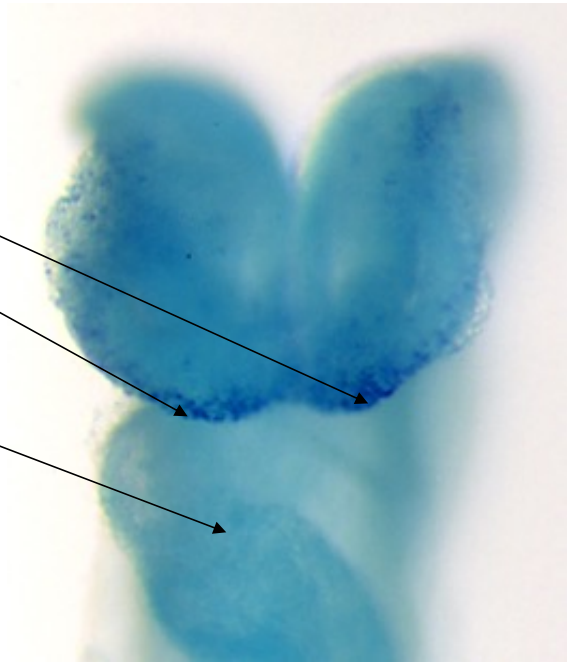


Cells killed by alcohol in the brain of a mouse embryo (at a comparable stage of development to that on the left) have taken up a dark blue stain.

CELLS THAT SHOULD FORM MIDLINE STRUCTURES OF THE BRAIN AND FACE ARE KILLED BY ALCOHOL

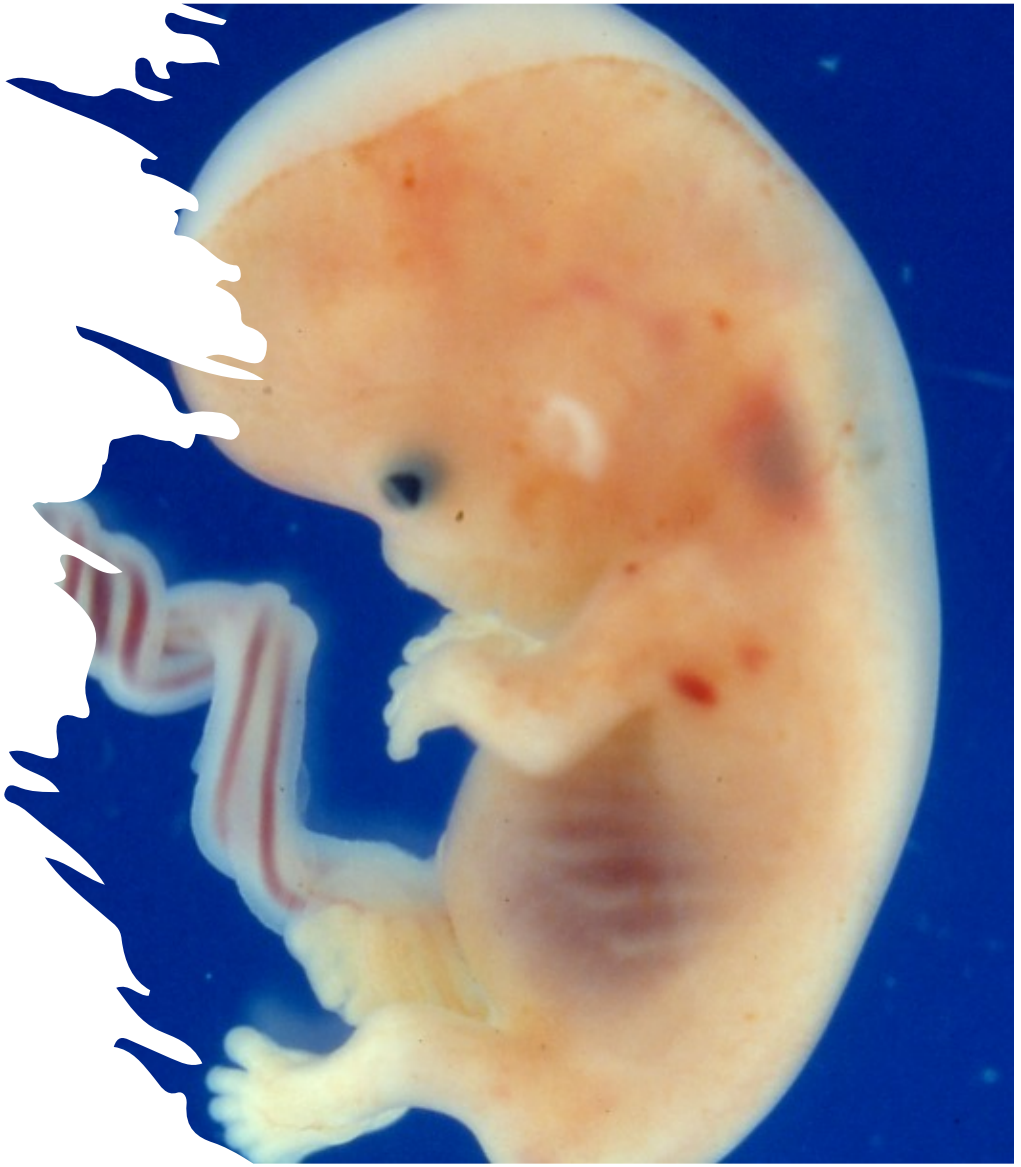


Mouse embryo (viewed from the front) at a stage corresponding to a 22-23 day old human.



A close-up view of an alcohol-exposed mouse embryo shows cells killed by alcohol that have taken up a dark blue stain.

By the ninth week of development the human fetus is about 24mm. long. Damage caused by alcohol to the brain at this time and until birth can result in abnormal brain function.



Excessive alcohol exposure can cause damage during all stages of prenatal development.

- **Pre-implantation: first 2 weeks**
- **Embryonic: 3-8 weeks after conception**
- **Fetal: from week 9 until birth**

Alcohol and Breastfeeding

- **When you drink alcohol, it passes into your breast milk at concentrations similar to those found in your bloodstream**.
- Although a breastfed baby is exposed to just a fraction of the alcohol his or her mother drinks, a newborn eliminates alcohol from his or her body at only half the rate of an adult.
- The amount of alcohol taken in by a nursing infant through breast milk is estimated to be **5% to 6% of the weight-adjusted maternal dose**.
- Alcohol can typically be detected in breast milk for about 2 to 3 hours after a single drink is consumed.

Alcohol and Breastfeeding

- Ideally it is best to avoid breastfeeding for about **2 hours** after drinking one alcoholic beverage.
- Women may want to express breast milk to relieve any engorgement for their own comfort.
- **They are minor and unlikely to have any long-term impact on your baby**.
- The only way they would potentially cause problems is if you were to drink heavily throughout the day.
- The amount of alcohol that passes into breast milk is miniscule, less than a tenth of a percent of what you drink

Alcohol and Breastfeeding

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

- “**There's nothing you can do to remove the alcohol from your milk once pumped;**
- Since alcohol is not “trapped” in breastmilk (it returns to the bloodstream as mother's blood alcohol level declines), **pumping and dumping will not remove it**.
- Drinking a lot of water, resting, or drinking coffee will not speed up the rate of the elimination of alcohol from your body either.
- "If a mom is going to drink alcohol, she should wait **at least three to four hours** until breastfeeding the baby," said Dr. Herway. (The CDC says to wait a minimum of two hours.)
- "The amount of alcohol in breast milk is very similar to the amount in the woman's blood and alcohol is a fast-acting drug,"

Alcohol and Breastfeeding

- Waiting **two hours after each alcoholic drink to breastfeed** should allow the alcohol to leave your breast milk whether or not you pump and dump.
- The half-life of alcohol is four to five hours. A half-life is how long it takes for your body to get rid of half of it.
- It takes about five half-lives to get rid of alcohol completely.
- So, it takes about **25 hours** for your body to clear all the alcohol

Treatment

Treatment

Natural Recovery

- Most people recover without formal treatment

Self-Help group

- E.g. Alcoholics Anonymous

Professional Treatment

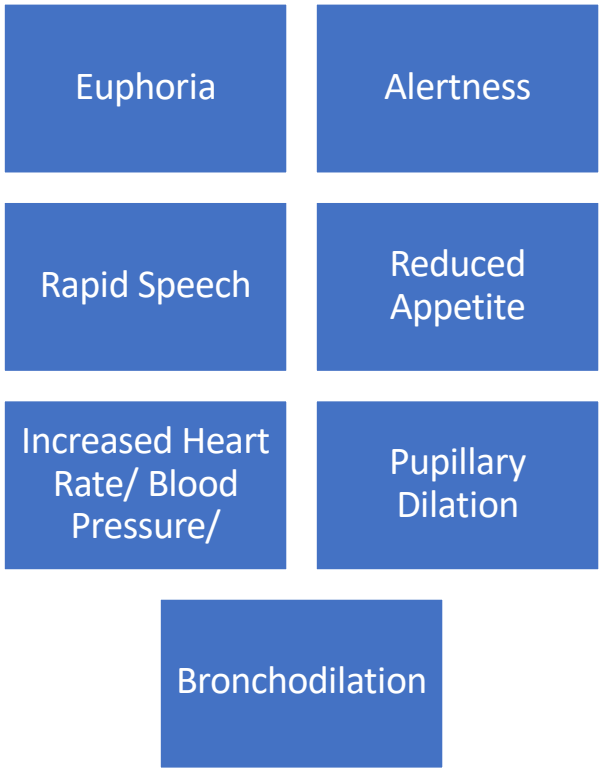
- Geared around a theoretical orientation
- Models:
  - Moral
  - Disease
  - Biological
  - Social Learning
  - Sociocultural
  - Biopsychosocial

Amphetamines & Methamphetamine

What are Amphetamines?

- Amphetamines are man made medications that stimulate the central nervous system.
- The primary medical uses of amphetamines include:
  - The treatment of attention deficient hyperactivity disorder (ADHD)
  - The treatment of narcolepsy - a sleep disorder where an individual has the inability to stay awake

Amphetamine Effects



- Wakefulness
- Mood Elevation
- A Feeling of Power
- Slight Tremors
- Increased Respiration
- Insomnia

- These effects last 4-12hrs

Withdrawal Effects

- Sleep disturbances, Depression
- Fatigue, Headache
- Nausea/vomiting, Diarrhea, Abdominal cramps
- Fever, Dizziness, Chills
- Hypo- or hypertension

Meth Crystals

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

Methamphetamine

This drug is a long-acting amphetamine

Its duration of action is 12-36 hours

It can be highly addictive

Methamphetamine causes high body temperatures which can lead to brain damage and sudden cardiac death

Dr. Merrill Norton Pharm.D.,D.Ph.,CMAC

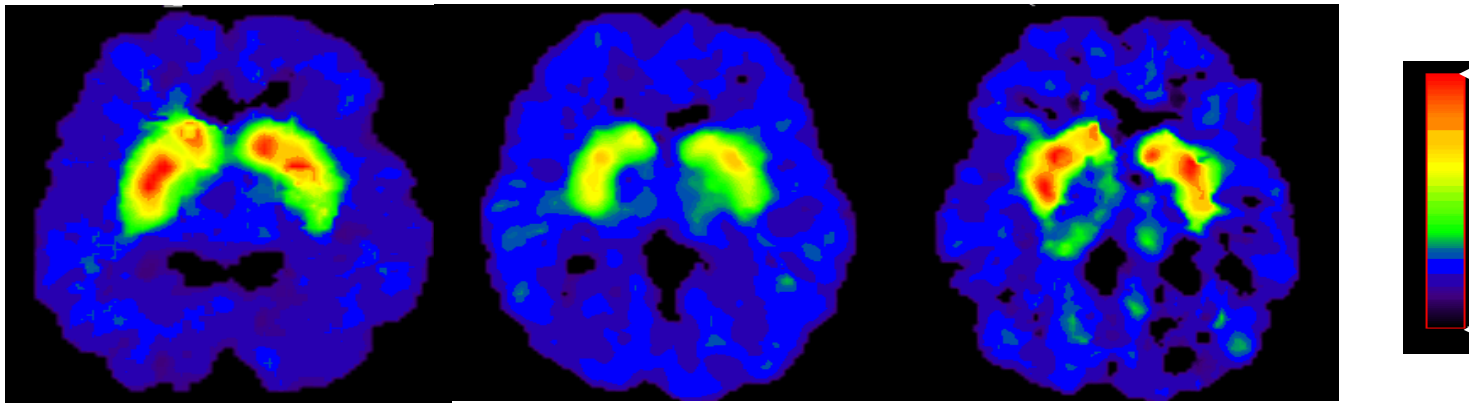
Methamphetamine Toxicity

Dehydration can lead to serious effects including stroke, seizure, heart attack, kidney failure, and heat exhaustion

Excessive dehydration can lead to the loss of essential electrolytes necessary for heart function

Eventual overstimulation of brain cells leads to cell death

Partial Recovery of Brain Dopamine Transporters in Methamphetamine (METH) Abuser After Protracted Abstinence



Normal Control

METH Abuser
(1 month abstinent)

METH Abuser
(24 months abstinent)

Overamping With Methamphetamine

- **You hit, your body because you had so much energy, your body can't take it. Your body will just shut the fuck down. Your heart cannot take that physical …… rush and people will shut down, they go to sleep."**
- **Overdose deaths involving methamphetamine nearly tripled from 2015 to 2019 among people ages 18-64 in the United States, according to a study by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health.**
- **In 2020, more than 93,000 Americans died from drug overdoses, marking the largest one-year increase in overdose deaths ever recorded, according to provisional data from the U.S. Centers for Disease Control and Prevention.**
- **Overdose deaths involving psychostimulants, and particularly methamphetamine, have also risen steeply in recent years, and many of these deaths involved use of an opioid at the same time. However, questions remain on how trends in methamphetamine use contribute to greater risk for overdose deaths.**

- Harding, R.W., Wagner, K.T., Fiuty, P. *et al.* "It's called overamping": experiences of overdose among people who use methamphetamine. *Harm Reduct J* **19,** 4 (2022). https://doi.org/10.1186/s12954-022-00588-7

Drug Testing for Amphetamines and Methamphetamine

- A common test for amphetamine exposure is a urine drug screen
- A typical urine drug test screens for amphetamines
- Amphetamine is a metabolite of methamphetamine – both can be found in the urine after methamphetamine use

How long do amphetamines stay in your system?	
Urine	Up to 5 days
Blood	Up to 2 days
Saliva	Up to 5 days
Hair	Up to 3 months

Drug Testing for Amphetamines and Methamphetamine

- False positives
  - These are the two most commonly reported false positive tests
  - Can be caused by: Brompheniramine, bupropion, chlorpromazine, clomipramine, dextromethorphan, diphenhydramine, doxylamine, ibuprofen, naproxen, promethazine, quetiapine, quinolones (ofloxacin and gatifloxacin), ranitidine, sertraline, thioridazine, trazodone, venlafaxine, verapamil

- For amphetamines, most incidents of false positives can be related to a drug's structure, but case reports and retrospective reviews have associated many drugs with false positives.
- Following a positive drug screening, the possibility of a false positive always should be considered.
- A thorough review of the patient's vital signs, relevant history, and recent medications should be conducted, with additional analysis with more specific tests if warranted.

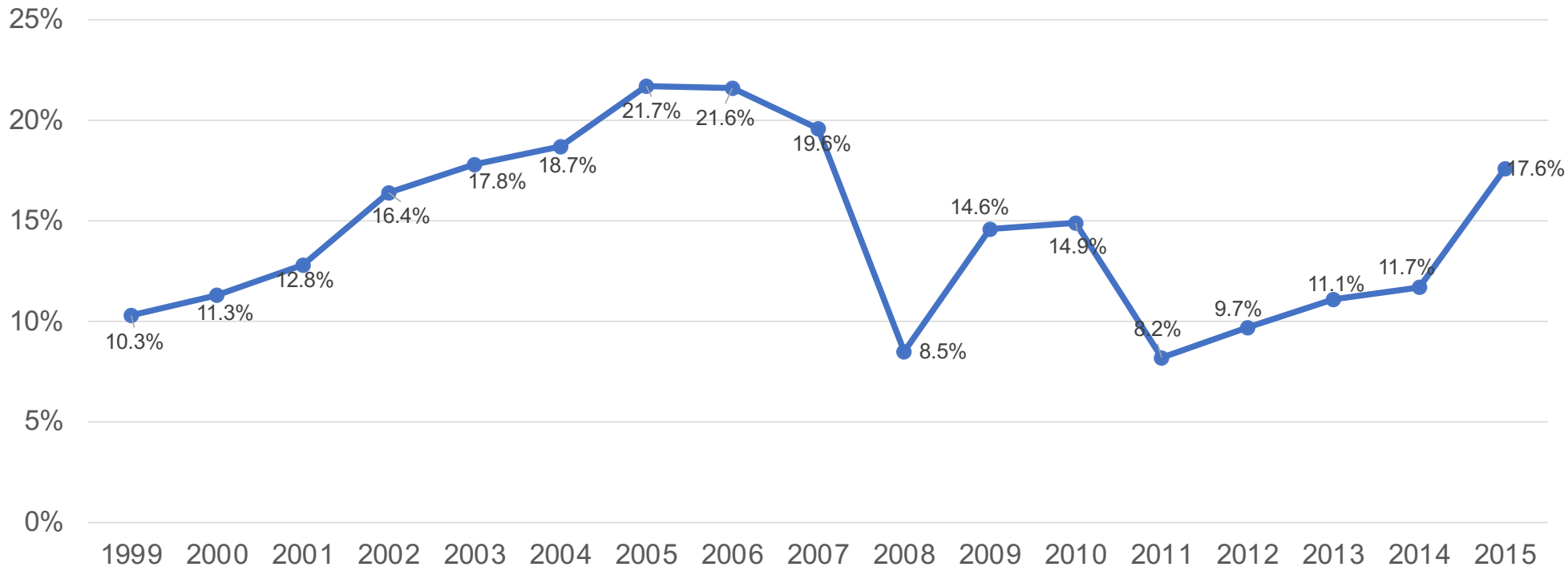
Amphetamines Effects on Pregnancy

Women and Methamphetamine

- Compared with male methamphetamine users, female methamphetamine users:
  - Use methamphetamine more days in a 30-day period
  - Smoke rather than snort or inject the drug
  - Are more likely to be single parents who live alone with their children
  - Have worse medical, psychiatric, and employment profiles
- 70% of methamphetamine-dependent women report histories of physical and sexual abuse
- Research points to women being drawn to methamphetamine as a way to lose weight, aid self-confidence, and increase energy to deal with childrearing

(Brecht et al., 2004; Galanter et al., 2014; Polcin et al., 2012; Semple et al., 2005)

The Prevalence of Methamphetamine Use Disorder as a Primary Substance Problem Among Pregnant Women at Substance Abuse Treatment Admission



*Note: Estimates based on **pregnant women who entered SUD treatment** during the fiscal year.*

Source: TEDS-A Data, 1999–2015

Prenatal Exposure to Methamphetamine

- Methamphetamine easily crosses the placenta
- The fetal brain is very sensitive to any level of methamphetamine
- Metabolism of methamphetamine in the fetus is not the same as in adults
- We must have a high index of suspicion to adequately test moms and infants exposed to methamphetamine

In pregnancy…

- Very little data.
- Growth restriction occurs with full-term infants, (constriction of the umbilical artery?)
- 4% have a recognizable withdrawal syndrome.
- Evidence of cognitive deficit in children born to mothers who use meth
- Weak evidence for physical defects in children

  whose mothers used meth.

Amphetamines Effects on Pregnancy

- **Continuous methamphetamine use during pregnancy is associated with preterm delivery and low-birth weight, both of which contribute to neonatal morbidity and mortality.**
- The majority of women in the study stopped using MA (86%), which is extremely reassuring.
- The women that did stop engaged in prenatal care more often and had normal birth outcomes.
- Stopping MA use at any time during pregnancy improves birth outcomes, thus resources should be aimed at treatment of addiction and promotion of prenatal care.

Wright, T. E., Schuetter, R., Tellei, J., & Sauvage, L. (2015). Methamphetamines and pregnancy outcomes. *Journal of addiction medicine*, *9*(2), 111–117. https://doi.org/10.1097/ADM.0000000000000101

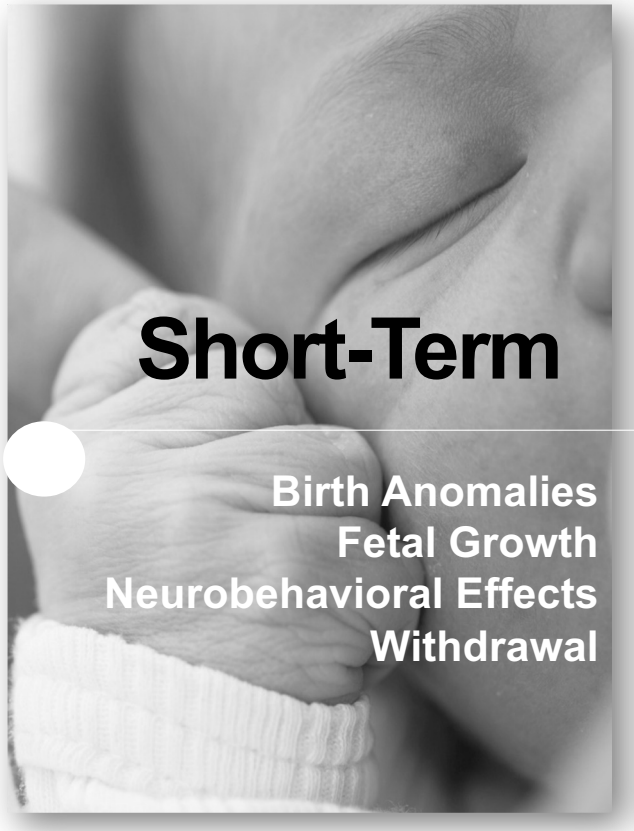
Amphetamines Effects on Pregnancy

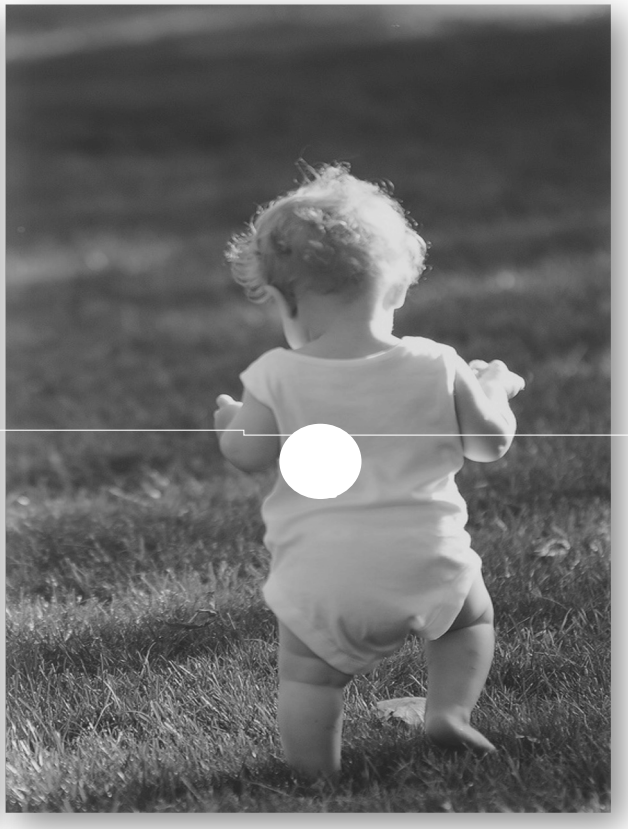
- **Maternal Effects of Methamphetamine During Pregnancy**
- **Increased maternal blood pressure**
- **Increased maternal heart rate**
- **Increased risk of premature birth**
- **Constricts blood flow in the placenta, thereby impacting oxygen flow to the fetus**

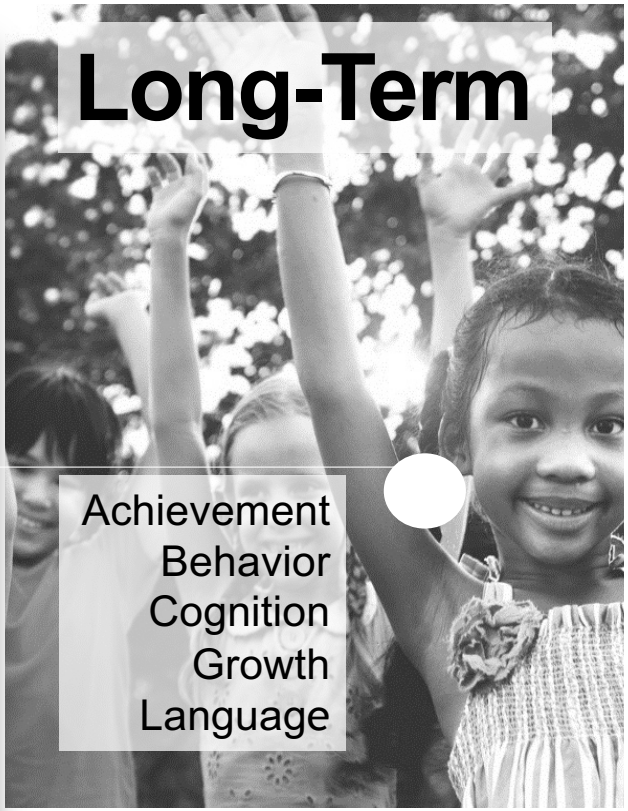
Effects of Prenatal Substance Exposure

American Academy of Pediatrics Technical Report

Comprehensive review of ~275 peer-reviewed articles over 40 years (1968–2006)







(Behnke & Smith, 2013)

Methamphetamine and Prenatal Exposure: Long-Term Outcomes

- Children prenatally exposed to methamphetamine are at higher risk for emotional and behavioral issues compared to their peers, exhibiting symptoms as early as age 3
- Symptoms include anxiety, depression, aggressiveness, hyperactivity, impulsivity, and inattention
- Prenatal exposure to methamphetamine can alter children's cognitive functioning
- Children ages 6 to 7 who are exposed to methamphetamine have lower IQs when compared to their peers, as well as learning and memory deficiencies, fine-motor developmental delays, and visual-motor integration impairment

(LaGasse et al., 2012; Kwiatkowski et al., 2018)

Amphetamines Effects on Pregnancy

- **Amphetamine Pregnancy and Breastfeeding Warnings**
- Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight; these infants should be monitored for feeding difficulties, irritability, agitation, excessive drowsiness and other withdrawal symptoms.
- Not recommended to breast feed; Excreted into human milk: Yes

- The effect on the neurological development of the breastfed infant has not been well studied.
- Large dosages might interfere with milk production, especially in women whose lactation is not well established.
- Based on limited data, this drug is estimated to be present in human milk at approximately 2% to 13.8% of the maternal weight-adjusted dose (milk/plasma ratio 1.9 to 7.5). This drug does not appear to effect breastfeeding infants adversely in doses prescribed for medical indications, however, the effects on neurological development have not been well studied.

Amphetamines Effects on Pregnancy

- Effects of Methamphetamine on the Developing fetus/infant
- Poor fetal growth—small for gestational age
- Elevated fetal blood pressure (stroke)
- Birth defects (6 times the normal rate)
  - Cleft palate/lip
  - Heart disease
  - Kidney disease
  - Intestines born outside the body
  - Premature birth
- Placental hemorrhage

Amphetamines Effects on Pregnancy

- Newborn signs of meth exposure
- Withdrawal
  - Jittery
  - Poor feeding
  - Poor wake /sleep cycle
  - Irritable
  - High pitched cry
  - Tremors
  - Hypertonia

- These symptoms may last as long as 6 weeks, in contrast to withdrawal from other drugs which may only last the first week of life

Amphetamines Effects on Pregnancy

- A study from the Centers for Disease Control and Prevention (CDC) found that **an increasing number of pregnant women are taking attention-deficit/hyperactivity disorder (ADHD) medicine.**
- Taking ADHD medicine in early pregnancy may be related to these birth defects:
  - Gastroschisis
  - Omphalocele
  - Transverse limb deficiency
- Anderson KN, Dutton AC, Broussard CS, Farr SL, Lind JN, Visser SN, Ailes EC, Shapira SK, Reefhuis J, Tinker SC, the National Birth Defects Prevention Study. ADHD Medication Use During Pregnancy and Risk for Selected Birth Defects: National Birth Defects Prevention Study, 1998-2011. *Journal of Attention Disorders.* 2020; 24 (3): 479-489.

Synthetic Cannabinoids (Bath Salts, Black Mamba, Spice)

What Are Synthetic Cannabinoids?

- Chemistry and Pharmacology
  - The chemical structure of synthetic cannabinoids shares similarities with THC, but they are not classified as a THC
  - Synthetic cannabinoids bind to the brain cannabinoid receptor CB1 and peripheral receptor CB2 with higher affinity than THC, suggesting it would have the same effects as THC in vivo

Case Example: Synthetic Cannabinoid Use among Pregnant Woman

- A woman (35 weeks pregnant) suffered a seizure and appeared agitated
  - High blood pressure and protein in urine, treated for eclampsia
  - An emergency C-section was performed (baby in distress)
- The woman screened negative for drugs, but an anonymous caller reported the woman regularly smoked "Spice Gold," a synthetic cannabinoid.
  - Spice Gold cannot be detected with a standard urine test.
- The baby tested negative for drugs.
- The woman required psychiatric care for psychotic behavior the day after delivery.
  - "*This was not a pregnancy problem but a drug problem. Eclampsia is cured with delivery of the baby, but she did not get better after delivery.*" (Dr. Cindy Lee)

SOURCE: Join Together Online, May 8, 2013.

Synthetic Cannabinoid Use Leads to Dangerous Symptoms in Pregnant Women

- Leads to symptoms similar to those caused by dangerous conditions known as preeclampsia and eclampsia
  - Preeclampsia is marked by high blood pressure and a high level of protein in the urine;
  - Preeclampsia can lead to eclampsia, which can cause a pregnant woman to develop seizures or coma, and in rare cases is fatal.

SOURCE: Join Together Online, May 8, 2013.

Bath Salts

- Bath Salts are synthetic stimulants sold as alternate products such as plant food, jewelry cleaner, or phone cleaner, similar to synthetic Cannabinoids;
- The effects seen are similar to cocaine or amphetamines;
- Bath Salts come as a white or brown crystal-like powder that can be swallowed, smoked, snorted, or injected;
- Bath Salts can be detected in the urine with specific testing

Bath Salts

- Short-term effects of Bath Salts include:
  - Paranoia, leading to thoughts that others are “out to get them”
  - Terrifying hallucinations
  - Panic attacks
  - Increased sociability and sex drive

Bath Salts

Other names for Bath salts are Bloom, Cloud Nine, and Scarface

It is often sold online or in gas stations

Packages are labeled as “not for human consumption” to conceal the contents inside

Bath Salts

- Long-term effects include :
  - Depression and/or Anxiety
  - Tremors
  - Problems sleeping
  - Addiction potential - in part due to the intense cravings that occur when use is discontinued
  - Intoxication leading to death

Bath Salts in the News

Face-Eating Attack Possibly Prompted by 'Bath Salts,' Authorities Suspect

Miami police suspect that what caused a 31-year-old man to rip off his clothes and viciously gnaw on the face of another man in a daylight attack on a busy highway is a new and extremely dangerous street drug known as "bath salts."

"The cases are similar minus a man eating another. People taking off their clothes. People suddenly have superhuman strength," says Aguilar. "They become violent and they are burning up from the inside. Their organs are reaching a level that most would die. By the time police approach them they are a walking dead person."

Bath Salts and Pregnancy

Bath Salts and Pregnancy

- Drug abuse during pregnancy is not uncommon.
- Health care providers are commonly not aware which substances their patients are using.
- Unfortunately, timely screening tests for bath salts are not available, making diagnosis difficult.
- Due to their increased use, bath salts should be considered in the differential, particularly if a patient presents in a psychotic and aggressive state.

- Schloemerkemper N. (2018). Psychotic due to bath salts and methamphetamines: emergency cesarean section under general anesthesia. *Journal of biomedical research*, *32*(4), 311–313. https://doi.org/10.7555/JBR.32.20180023

Black Mamba

Black Mamba is a synthetic cannabinoid that can be swallowed or smoked

It is fast acting and “skunk-like”

The short-term effects include uncomfortable distortions in reality and vivid hallucinations

Black Mamba Long-Term Effects

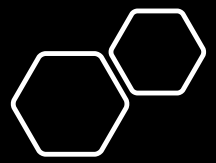
Black Mamba users can experience outbursts of extreme violence towards others

Self-harming also occurs with Black Mamba users, potentially leading to hospitalization

Suicidal thoughts may occur with Black Mamba use

Spice: a Synthetic Cannabinoid

- Spice is also known as K2, Fake Weed, or Bliss
- Spice is marketed as an “herbal incense”
- Packages claim that Spice is a blend of traditionally used medicinal herbs, but instead it is laced with synthetic cannabinoids that are not naturally in the herbs it is labeled to possess



Spice

Spice can be smoked in pipes, bongs, or joints

The high from Spice lasts an average of 10 minutes, and no longer than 30 minutes

As of March 1, 2011, synthetic cannabinoids have been temporarily placed in Schedule I federally, but has been illegal on a state level in Georgia since May 2010

Spice

The addiction potential of Spice is unknown. However, based on the similarity to THC in vivo, it can be hypothesized that the addiction potential is similar to marijuana

No official information is available on the withdrawal or tolerance associated with Spice, though one case of withdrawal after daily use of Spice Gold for 3 months is reported. Physicians treating the user noted his use showed signs associated with addiction

Drug Testing for Synthetic Cannabinoids

- The synthetic cannabis is a completely artificial substance and has nothing to do with the usual cannabis/marijuana
- Their only common point is to activate the same receptors in the human body (CB1 and CB2 receptors)
- The molecules of synthetic cannabis and "natural" cannabis are very different
- This is why it is necessary to use a very specific test to detect any use or abuse of this new drug

Drug Testing for Synthetic Cannabinoids

- There was a study (Salmone, 2014) done looking at the use of a hair test that screens for 23 synthetic cannabinoids
- There is a urine drug screen by Redwood Toxicology that screens for 37 synthetic cannabinoids and their metabolites
  - Average window of detection is 72 hours following a single low dose; in case of chronic use the window may be much longer

Fetal Effects: Possible

Growth restriction

- Confounded by tobacco
- If there is an effect, likely small and unclear consequences

Stillbirth

- Most studies exclude due to history of stillbirth
- Increased risk of stillbirth (THC in umbilical cord)
- Possibly confounded by tobacco use

Metz, AJOG 2015

Fetal Effects: Possible

- **Preterm Birth**
  - **Conflicting results**
  - **Confounders (history of PTB, iatrogenic)**
  - **Positive biologic screen seems more correlated**
  - **Unclear the effects (early versus late preterm)**

- Metz, AJOG 2015

Neurodevelopment: Human Studies

Decreased language comprehension
Difficulty with attention
Memory impairment
Increased hyperactivity
Increased impulsivity
Younger age at onset of substance use

Metz, AJOG 2015

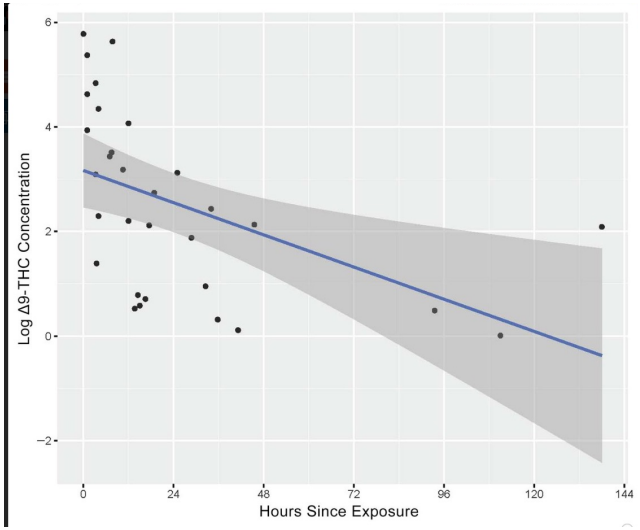
Breastfeeding

Marijuana is detected in breastmilk

Bertrand, Pediatrics 2018

Breastfeeding

- Detection for up to 6 days
- Related to dose and frequency of use
- Decreased approximately 3% per hour after exposure



- Half life of approximately 27 hours
- Extremely variable concentrations, likely due to lipophilic nature

Bertrand, Pediatrics 2018


Benzodiazepines

Benzodiazepines

Benzodiazepines are prescription medications used to induce sedation and reduce the occurrence of seizures

These drugs are sometimes called “Benzos”

Benzos treat anxiety and difficulty sleeping with their sedating effects

Examples of Benzodiazepines include Valium, Xanax, Klonopin, and Ativan

Benzodiazepines Short-Term Effects

- Drowsiness
- Sleepiness
- Fatigue
- Impaired thinking
- Memory loss
- Confusion
- Blurred vision
- Impaired coordination

Benzodiazepines Long-Term Effects

- Personality changes
- Impaired thinking or memory loss
- Addiction
- From injecting: increased risk of contracting Hepatitis B or C, HIV

Benzodiazepines

- Abrupt discontinuation of Benzodiazepines can lead to withdrawal. Symptoms of Benzo withdrawal include:
  - Bizarre dreams
  - Difficulty sleeping
  - Fatigue
  - Anxiety
  - Irritability
  - Delusions
  - Hallucinations
  - Paranoia
  - Seizures

Benzodiazepines

Benzodiazepines can cause an additive effect with other drugs which can lead to an overdose

Drugs that will interact with benzodiazepines and can lead to an overdose are alcohol, barbiturates, opioids, and some antidepressants

Overdose symptoms:

- Over-sedation or sleep
- Mood swings, aggression
- Shallow, slow breathing
- Unconsciousness, coma, death

Drug Testing for Benzodiazepines

- A common test for benzodiazepine exposure is a urine drug screen
- A typical urine drug test screens for benzodiazepines
- Benzodiazepines are extensively metabolized by the liver, and the parent compounds are not detected in urine – their metabolites are

Benzodiazepines	LOQ (ng/mL)	Detection Time* up to
Long-Acting		10 days
Diazepam as metabolites	100	
Nordiazepam	100	
Intermediate-Acting		5 days
Alprazolam as metabolite	100	
Lorazepam	100	
Oxazepam	100	
Temazepam	100	
Chlordiazepoxide as metabolite	100	
Clonazepam as metabolite	100	
Flunitrazepam as metabolite	50	
Short-Acting		2 days
Triazolam as metabolite	100	
Flurazepam as metabolite	100	

Drug Testing for Benzodiazepines

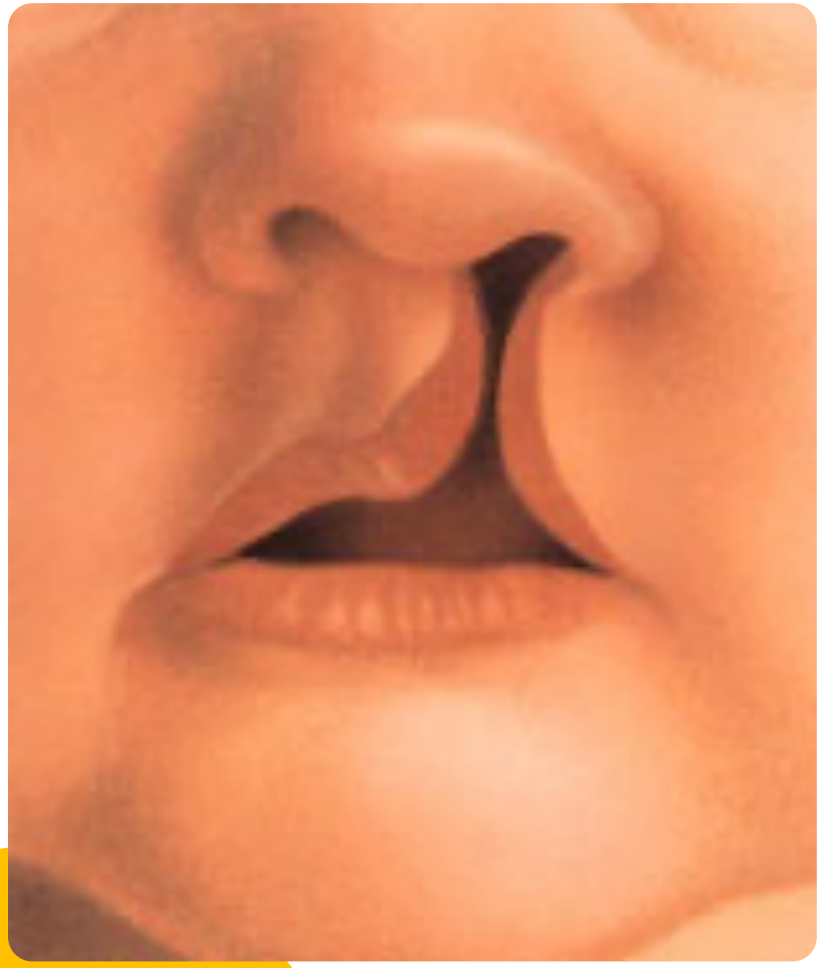
- False positives
  - Tolmetin
  - Naproxen
  - Etodolac
  - Fenoprofen
  - Oxaprozin
  - Sertraline

Benzodiazepines and Pregnancy

- Most benzodiazepines have a **category D** rating within the U.S. Food and Drug Administration (FDA) Pregnancy Categories.
- This means that there is some positive evidence of human fetal risk, but the potential benefits may warrant use of benzodiazepines in pregnant women
- There are also several benzodiazepine medications that currently have a category X rating.
- This means that the risk involved with their use clearly outweigh the potential benefits and they are contraindicated during pregnancy. These drugs include:[2]
- **Flurazepam (Dalmane)**
- **Estazolam (ProSom)**
- **Temazepam (Restoril)**
- **Quazepam (Doral)**
- **Triazolam (Halcion)**

Benzodiazepines

- Small increased risk for cardiac/oral cleft malformations with first-trimester exposure.
- Neonatal toxicity (“floppy infant syndrome”) /withdrawal
- Avoid in the first trimester, late in the third trimester
- Other adverse outcomes such as:
- Preterm birth
- Low birth weight
- Neonatal respiratory distress
- Symptoms of benzodiazepine toxicity have been reported in newborns, including sedation, decreased muscle tone (floppiness), and breathing problems.



Benzodiazepines (BMJ 1998;317:839-43)

- Meta-analysis
- Cohort studies showed no association between fetal exposure to BZDs and risk for major malformations or oral cleft
- Case-control studies showed that risk for major malformations or oral cleft alone was increased
- Use around delivery - “floppy infant”

Benzodiazepines

- Milk levels of benzodiazepines not excessive but rarely sedation has been reported in breastfed infants;
- If sedative required, shorter half-life drugs such as lorazepam and midazolam preferred;
- Long term exposure not recommended.

Neonatal Benzodiazepine Withdrawal

- These symptoms are not commonly seen and are likely to occur in women taking higher doses of benzodiazepines.
- There have also been reports of benzodiazepine withdrawal occurring in newborns exposed to benzodiazepines during pregnancy.
- Symptoms of neonatal benzodiazepine withdrawal include irritability, sleep disruption, restlessness, depression, tremors, and seizures.

Benzodiazepines Withdrawal

- To minimize neonatal withdrawal, gradually taper the mother's benzodiazepine before delivery
  - Taper 3 to 4 weeks before the due date and discontinue at least 1 week before delivery.
  - If benzodiazepines cannot be tapered
    - use a short acting agent
    - advise the mother to discontinue benzodiazepine use as soon as she thinks she is going into labour.

Caffeine Pills and Drinks

What Is Caffeine?

- Caffeine is a central nervous system stimulant drug
- It is found in the seeds, nuts, and leaves of a number of different plants
- Products with caffeine include: coffee, tea, cocoa, and chocolate
- Caffeine increases alertness and make you feel less worn out
- 85% of the US population consumes ≥ 1 cup of a coffee a day

Caffeine Pills and Drinks

- Caffeine affects everyone differently, based on factors such as:
  - Size, weight, and health – larger, heavier people tend to require more caffeine to produce similar effects in smaller, lighter people
  - How often the person consumes caffeine
  - Whether other drugs are taken around the same time
  - The amount of caffeine taken

Caffeine Pills and Drinks

- Doses > 400 mg are considered unsafe. This is equivalent to 3-5 cups of coffee or 2-4 caffeine pills
  - Some energy drinks can contain as much as 320mg of caffeine (equivalent to 2–3 cups of coffee) - this is a reason for concern.
- Overdoses can occur with 1-5 grams of caffeine
  - Caffeine overdose can lead to coma and death

Caffeine and ADOLESCENTS

- Studies show caffeine consumption can affect a **teenager's concentration and ability to sleep**, which in turn may slow the maturing process of their brains
- Because of their smaller body weight (on average), caffeine has more than twice the impact on children than it does on adults
- This means children and young adolescents are more susceptible to caffeine-related symptoms such as anxiety, insomnia and nervousness.
- Studies have suggested that the adolescent brain is more susceptible to stress and addiction due to the way the developing brain is wired.

Caffeine and Health Problems

- Cigarette smoking doubles the rate of caffeine clearance by increasing liver enzyme activity, which may explain the higher rate of caffeine consumption among smokers.
- Mixing alcohol and energy drinks results in higher rates of binge drinking, reductions in perceived intoxication, faster rates of self-paced alcohol consumption, or increases in risk taking behavior.
- Adolescents under 14 should avoid caffeine where possible, and teenagers between 14 and 17 years of age should limit their intake to 100mg or less a day.

Caffeine Pills and Drinks

- High caffeine doses can cause:
  - Gastrointestinal issues such as acid reflux and diarrhea
  - Increased mental stimulation leading to anxiety, jitters, and irritability
  - Dehydration which can lead to headaches and migraines
  - Heart palpitations
  - Insomnia

Caffeine Long-Term Effects

- Irregular heartbeat and/or heart problems
- Anxiety
- Addiction
- Stomach ulcers
- Heartburn

Drug Testing for Caffeine

- A caffeine screen could be indicated in patients with moderate-to-severe symptoms of caffeine toxicity (hemodynamic instability, dysrhythmias, seizures, altered mental status)
- It could also be used to monitor caffeine concentrations in newborns
- Caffeine and its metabolites can be found in detectable amounts in the urine and blood

What Products Contain Caffeine—and How Much?

Item	Milligrams Caffeine: Typical	Milligrams Caffeine: Range
• Coffee (8 oz)	**100**	60 – 180
• Tea (8 oz)	**40**	20 – 90
• Some soft drinks (8 oz)	**24**	20 – 40
• Cocoa beverage (8 oz)	**6**	3 – 32
• Chocolate milk (8 oz)	**5**	2 – 7
• Milk chocolate (1 oz)	**6**	1 – 15
• Baker's chocolate (1 oz)	**26**	26

Caffeine

- Water soluble - Vd ↑, []↓
- Metabolized by CYP1A2* - Metabolism ↓ during pregnancy

Weeks	Clearance	Half-Life
• 11	100%	5.3h
• 17	68%	9.9h
• 24	54%	12.6h
• 32	37%	10h
• PP	100%	5.5h

* Induced by cigarette smoking

Caffeine Metabolism in Pregnancy

Metabolic Step		Change in Pregnancy
• Transport proteins		?
• Phase I metabolism		
• CYP1A2 (M>F)		↓
• XO (M=F)		↔
• 8-Hydroxylation (M?F)		↑
• Phase II metabolism		
• N Acetyltransferase	(M=F)	↓

CYP3A4

- Most abundant CYP450 in liver and GI
  - 30% of total cytochrome P450
- Broad substrate specificity
  - Metabolizes >50% of drugs
- Activity/amount increased during pregnancy
- Caveats
  - Substrate overlap with P-gp
  - ? Unbound plasma concentration
  - Time course across pregnancy undefined

Caffeine and Pregnancy

- The risk of excess infant growth and overweight in childhood—important risk factors for later cardiometabolic disease—is increasing with maternal caffeine intake;
- Maternal caffeine intake >200 mg/day during pregnancy was associated with high weight gain velocity beginning from the first months of life and higher BMI throughout childhood.
- Papadopoulou E, Botton J, Brantsæter A*, et al*
- Maternal caffeine intake during pregnancy and childhood growth and overweight: results from a large Norwegian prospective observational cohort study
- *BMJ Open* 2018;**8:**e018895. doi: 10.1136/bmjopen-2017-018895

Caffeine & Reproductive Health

- Fertility: No association between total caffeine consumption and reduced fertility
- Miscarriage: Ongoing research and numerous existing studies find no evidence that moderate caffeine intake has adverse effects on pregnancy or pregnancy outcome

Breast Changes

- No association between caffeine and breast changes, tumors, or tenderness

Breastfeeding

- 1-3 cups of coffee a day OK
- 3+ can lead to increased wakefulness and poor feeding for the baby

Thank You For Your Time

Any Questions?