

### Summary of Cannabis Genotoxicity Papers

There are several principal pathways to inheritable genotoxicity, mutagenicity and teratogenesis induced by cannabis which are known and well established at this time including the following. These three papers discuss different aspects of these effects.

- 1) **Stops Brain Waves and Thinking** The brain has both stimulatory and inhibitory pathways. GABA is the main brain inhibitory pathway. Brain centres talk to each other on gamma (about 40 cycles/sec) and theta frequencies (about 5 cycles/sec), where the theta waves are used as the carrier waves for the gamma wave which then interacts like harmonics in music. The degree to which the waves are in and out of phase carries information which can be monitored externally. GABA ( $\gamma$ -aminobutyric acid) inhibition is key to the generation of the synchronized firing which underpins these various brain oscillations. These GABA transmissions are controlled presynaptically by type 1 cannabinoid receptors (CB1R's) and CB1R stimulation shuts them down. This is why cannabis users forget and fall asleep.
- 2) **Blocks GABA Pathway and Brain Formation** GABA is also a key neurotransmitter in brain formation in that it guides and direct neural stem cell formation and transmission and development and growth of the cerebral cortex and other major brain areas. Gamma and theta brain waves also direct neural stem cell formation, sculpting and connectivity. Derangements then of GABA physiology imply that the brain will not form properly. Thin frontal cortical plate measurements have been shown in humans prenatally exposed to cannabis by fMRI. This implies that their brains can never be structurally normal which then explains the long lasting and persistent defects identified into adulthood.
- 3) **Epigenetic Damage** DNA not only carries the genetic hardware of our genetic code but it also carries the software of the code which works like traffic lights along the sequence of DNA bases to direct when to switch the genes on and off. This is known as the "epigenetic code". Fetal alcohol syndrome is believed to be due to damage to the software epigenetic code. The long lasting intellectual, mood regulation, attention and concentration defects which have been described after in utero cannabis exposure in the primary, middle and high schools and as college age young adults are likely due to these defects. Epigenetics "sets in stone" the errors of brain structure made in (2) above.
- 4) **Arterial Damage**. Cannabis has a well described effect to damage arteries through (CB1R's) (American Heart Association 2007) which they carry in high concentration (Nature Reviews Cardiology 2018). In adults this causes heart attack (500% elevation in the first hour after smoking), stroke, severe cardiac arrhythmias including sudden cardiac death; but in developing babies CB1R's acting on the developing heart tissues can lead to at least six major cardiac defects (Atrial- ventricular- and mixed atrio-ventricular and septal defects, Tetralogy of Fallot, Epstein's deformity amongst others), whilst constriction of various babies' arteries can lead to serious side effects such as gastroschisis (bowels hanging out) and possibly absent limbs (in at least one series).
- 5) **Disruption of Mitotic Spindle**. When cells divide the separating chromosomes actually slide along "train tracks" which are long chains made of tubulin. The tubulin chains are called "microtubules" and the whole football-shaped structure is called a "mitotic spindle". Cannabis inhibits tubulin formation, disrupting microtubules and the mitotic spindle causing the separating chromosomes to become cut off in tiny micronuclei, where they eventually become smashed up and pulverized into "genetic junk", which leads to foetal malformations, cancer and cell death. High rates of Down's syndrome, chromosomal anomalies and cancers in cannabis exposed babies provide clinical evidence of this.
- 6) **Defective Energy Generation & Downstream DNA Damage** DNA is the crown jewel of the cell and its most complex molecule. Maintaining it in good repair is a very energy

intensive process. Without energy DNA cannot be properly maintained. Cannabis has been known to reduce cellular energy production by the cell's power plants, mitochondria, for many decades now. This has now been firmly linked with increased DNA damage, cancer formation and aging of the cells and indeed the whole organism. As it is known to occur in eggs and sperm, this will also damage the quality of the germ cells which go into forming the baby and lead directly to damaged babies and babies lost and wasted through spontaneous miscarriage and therapeutic termination for severe deformities.

- 7) **Cancer induction** Cannabis causes 12 cancers and has been identified as a carcinogen by the California Environmental Protection agency (2009). This makes it also a mutagen. 4 of these cancers are inheritable to children; i.e. inheritable carcinogenicity and mutagenicity. All four studies in testicular cancer are strongly positive (elevation by three fold). Carcinogen = mutagen = teratogen.
- 8) **Colorado's Teratology Profile**. From the above described teratological profile we would expect exactly the profile of congenital defects which have been identified in Colorado (higher total defects and heart defects, and chromosomal defects) and Ottawa in Canada (long lasting and persistent brain damage seen on both functional testing and fMRI brain scans in children exposed in utero) where cannabis use has become common. Gastroschisis was shown to be higher in all seven studies looking at this; and including in Canada, carefully controlled studies. Moreover in Australia, Canada, North Carolina, Colorado, Mexico and New Zealand, gastroschisis and sometimes other major congenital defects cluster where cannabis use is highest. Colorado 2000-2013 has experienced an extra 20,152 severely abnormal births above the rates prior to cannabis liberalization which if applied to the whole USA would equate to more than 83,000 abnormal babies live born annually (and probably about that number again therapeutically aborted); actually much more since both the number of users and concentration of cannabis have risen sharply since 2013, and cannabis has been well proven to be much more severely genotoxic at higher doses.
- 9) **Cannabidiol is also Genotoxic** and tests positive in many genotoxicity assays, just as tetrahydrocannabinol does.
- 10) **Births defects registry data needs to be open and transparent and public**. At present it is not. This looks too much like a cover up.