Implications of Non-Consensual Unleashing Cannabis Teratogenesis and Neuroteratogenesis on Whole Unsuspecting Populations in North America

Cannabis in the USA Food Chain

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Introduction

I am advised that the present US farm bill will essentially legalize cannabis across the USA, including its ability to be sold for animal feed, which will introduce cannabinoids into the food chain via meat and dairy food and eggs. It would appear that no proper public debate has occurred on this issue. I am further advised that Europe has allowed cannabis to be used freely as stockfeed for several years now. However, Switzerland has not allowed this to occur due to concerns of unbridled and unmeasured amounts of cannabis in the food supply, and its access to pregnant females and growing children. Then Swiss concern is apparently that cannabinoids might have effects on the developing foetus or growing children, and in particular in their brain growth, development and wiring during their formative years. A good question therefore is which approach is correct – the European approach or the Swiss approach?? And why do we really need to have an open discussion anyway?? With 22% of Californian teenagers recently testing positive for cannabis, the issue is far from trivial [1].

Current Scenario

Consider the following frightening scenario, readily documented on a quick internet search. In 2007 some US researchers working in Hawaii reported an increased rate of babies being born without arms or with dramatically reduced arms which was 21.9 times elevated above control levels, with uncertainty (confidence) intervals from 4 to 65 times increased above background [2-6]. In the small French town of Ain near the swiss border about July 2018 a seizure of 135 cannabis resin occurred, likely about 99% pure THC concentration. Cows in the region were born without their legs. And the rate of babies born with tiny or completely absent arms in the same region near Ain was reported at 58 times the usual rate – that is within the confidence and uncertainty interval reported by the Hawaiian researchers in 2007 [7]. Could cannabis be implicated??? Or is it just the pesticides?? When I pointed these facts out to the French Health Minister and Prime Minister, the previously closed investigation was re-opened. The results of that investigation are not available at the time of writing.

Cannabis Teratogenesis

Consider the following table which shows the number of 59 selected congenital birth defects in Colorado by type in the years 2000 and 2013. The data was current from Colorado Department of Health and Environment as of October 2018 [8]. The number of births in Colorado over this period was essentially unchanged from 65,429 in year 2000 to 65,004 in year 2013.

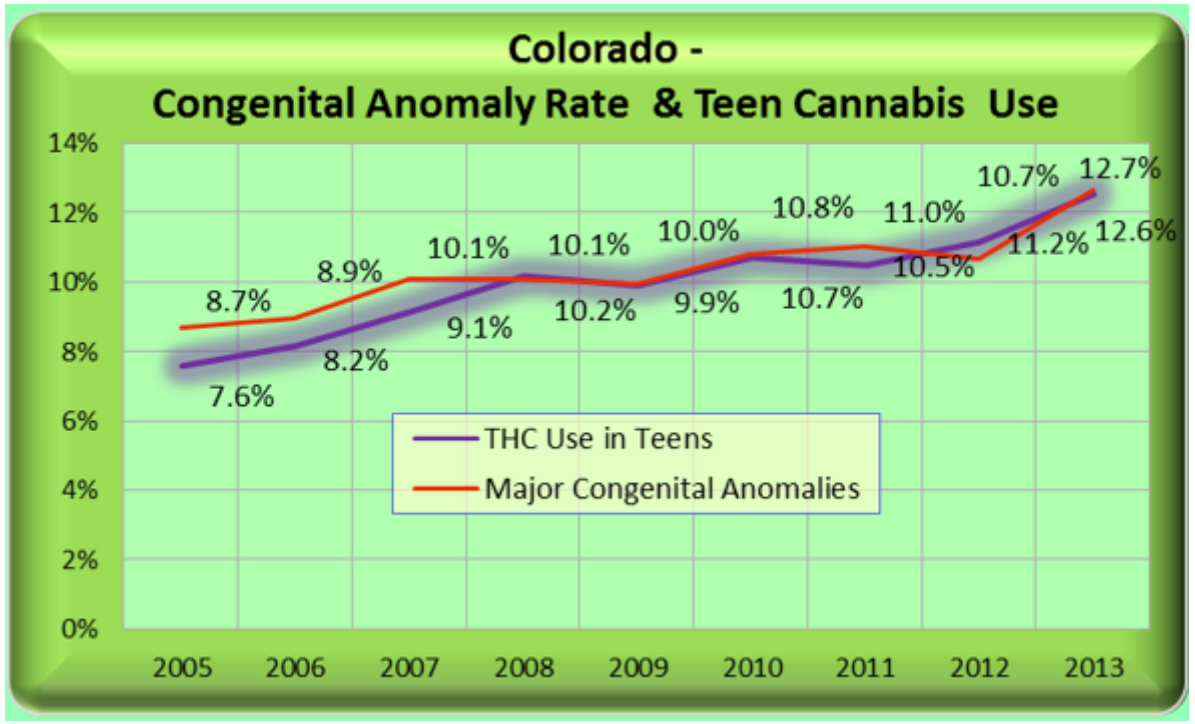
The defects in question are remarkable – microcephaly is on the list and shows a near doubling of the number of cases. Microcephaly became famous in association with Zika virus infection [9]. Anencephaly is also listed – which is a near absence of the brain, and is usually fatal at or within an hour or two of birth. 11 heart defects are shown, 4 defects each of brain, organs and limbs, 3 head defects and two genetic defects.

Colorado Birth Defects Numbers 2000 – 2013,

Data - October 2018

Defect	2000	2013	Elevation 2000-2013	Heart	Brain	Organs	Limbs	Head	Genetic	Forrester 2007
Congenital Buphthalmos - Very swollen eyes	2	6	300.0%					300.0 %		
Atrial Septal Defect - Secundum	355	926	260.8%	260.8 %						**Yes**
Hypoplastic Left Heart	14	29	207.1%	207.1 %						**Yes**
Microcephaly - Shrunken Brain - like Zika virus	30	59	196.7%		196.7 %					**Yes**
Hirschsprung's disease - Lazy Bowel	16	30	187.5%			187.5%				
Anencephaly - Missing brain	4	7	175.0%		175.0 %					**Yes**
Reduction Deformities of Leg	10	17	170.0%				170.0 %			
Major Congenital defects	4830	8165	169.0%							**Yes**
Anophthalmia / Microphthalmia - No eyes	6	10	166.7%					166.7 %		
Reduction Deformity of Limbs	9	15	166.7%				166.7 %			
Respiratory Abnormality	217	354	163.1%			163.1%				
Major Cardiovascular Anomalies	1002	1622	161.9%	161.9 %						**Yes**
Renal Agenesis - No kidney	23	35	152.2%			152.2%				
Pulmonary Artery Defects	143	212	148.3%	148.3 %						
Major Genitourinary defects	1132	1676	148.1%			148.1%				

Major Musculoskeletal defects	958	1373	143.3%				143.3 %			**Yes**
Common Truncus of Heart	5	7	140.0%	140.0 %						
Ventricular Septal Defect of Heart	287	386	134.5%	134.5 %						**Yes**
Major Central Nervous System Defects	201	269	133.8%		133.8 %					**Yes**
Encephalocoele	6	8	133.3%		133.3 %					**Yes**
Endocardial Cushion Defects of Heart	20	26	130.0%	130.0 %						**Yes**
Chromosomal Defects	175	225	128.6%						128.6%	**Yes**
Trisomy 21 / Downs Syndrome	87	108	124.1%						124.1%	**Yes**
Total Anomalous Pulmonary Venous Connection of Heart	9	11	122.2%	122.2 %						
Patent Ductus Arteriosus near Heart	765	916	119.7%	119.7 %						
Abdominal Wall Defects	51	60	117.6%							**Yes**
Polysyndactyly - Extra / Joined fingers	170	197	115.9%				115.9 %			**Yes**
Common Ventricle of Heart	13	15	115.4%	115.4 %						
Transposition of the Great Vessels of the Heart	23	26	113.0%	113.0 %						
Orofacial Defects	121	134	110.7%					110.7 %		**Yes**
Number			30	11	4	4	4	3	2	16


Colorado -
Congenital Anomaly Rate & Teen Cannabis Use
14%
12%
10%
8%
6%
4%
2%
0%
2005
2006
2007
2008
2009
2010
2011
2012
2013
7.6%
8.2%
9.1%
10.2%
9.9%
10.7%
10.5%
11.2%
12.6%
8.7%
8.9%
10.1%
10.1%
10.0%
10.8%
11.0%
10.7%
12.7%
THC Use in Teens
Major Congenital Anomalies

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Risk of Selected Birth Defects with Prenatal Illicit Drug Use, Hawaii, 1986–2002

Mathias B. Forrester and Ruth D. Merz
Hawaii Birth Defects Program, Honolulu, Hawaii, USA

Deformity	*Rate Ratio*	*95%C.I.*
Encephalocoele	39.98	9.03-122.29
Hypoplastic Left Heart Syndrome	32.29	3.81-122.65
Syndactyly	24.33	10.40-48.63
Gastroschisis	23.11	4.69-69.34
Reduction Deformity Upper Limbs	21.90	4.45-65.63
Hydrocephly	16.65	6.65-34.66
Cleft Palate	14.73	3.98-38.23
Anotia / Microtia	13.99	1.68-51.66
Tetralogy of Fallot	13.65	1.64-50.37
Pyloric Stenosis	13.17	3.56-34.13
Microcephaly	12.80	4.13-30.17
Pulmonary Valve Atresia / Stenosis	11.46	3.10-29.66
Anal, Rectal, Large Bowel Atresia / Stenosis	10.36	1.25-38.05
Obstructive Genito-Urinary Defect	9.23	2.98-21.69
Polydactyly	8.87	3.24-19.42
Ventricular Septal Defect	8.83	4.82-14.87
Anopthalmia / Microphthalmia	8.31	0.21-47.38
Cleft Lip with / without Cleft Palate	8.19	2.22-21.13
Atrial Septal Defect	6.12	1.98-14.35
Trisomy 21	5.26	1.08-15.46

Data Taken from Table 3 – Re-formatted

39 of the 59 defects listed, or 66%, defects rose, and for 30 of those defects they rose more than 10%. This in itself is of interest. Note however that many of these babies will be aborted, a trend which has become more marked in recent years, so that the numbers seen and recorded as live births likely represent a lower bound of the rising effect in question. For many of these defects the abortion rate is a major confounding factor in interpreting the results.

These 30 defects are listed in the following table. Importantly 16 of these defects had been previously identified by the important Hawaiian study as being likely linked with cannabis use, as indicated [7]. Or, put another way, 12 of the 21 defects, or 57%, previously shown to be more common in Hawaii amongst mothers prenatally exposed to cannabis, have also shown up in the Colorado congenital defects series as rising in frequency in association with cannabis legalization.

What is striking about this table is that many of the commonest defects have become more common after cannabis legalization: Total congenital defects, atrial; septal defects secundum, ventricular septal defects, major cardiovascular abnormalities, chromosomal abnormalities, major central nervous system defects, major musculoskeletal abnormalities have all become more common under the influence of cannabis. One would be brave to argue that atrial septal defect, showing a 261% rise 2000-2013 in Colorado, bears no causal relationship whatsoever to maternal and / or paternal cannabis use.

And it is important to appreciate that it is unlikely that these effects were due to the use of other drugs which were uniformly falling across this period as quantitated in the National Survey of Drug Use and Health (NSDUH) conducted each year by the Substance abuse and Mental Health Services Administration (SAMHSA) [10].

It should be said at this point that many of the defects reported as elevated in Hawaii have not been confirmed by other case series. Notwithstanding this feature of the data, the close parallels in the experience of Hawaii and Colorado is striking indeed, and should well give us pause in terms of the widespread roll out of an agent which may potentially have teratogenic potential.

Known Cannabis-Related Teratogenicity

The literature on cannabis is voluminous so it is useful just to summarize its main features here for the sake of brevity and conciseness.

A major paper by the National Birth Defects Prevention Network based out of the Centres for Disease Control in Atlanta Georgia [11] determined that cannabis was likely to be causally associated with increased rates of :

1) Anencephaly (Odds Ratio 1.9 times elevated, 95% Credible interval 1.1-3.2)
2) Oesophageal atresia (Odds Ratio 1.7 times elevated, 95% Credible interval 1.0-2.9)
3) Diaphragmatic hernia (Odds Ratio 1.8 times elevated, 95% Credible interval 1.1-3.0)
4) Gastroschisis (Odds Ratio 1.7 times elevated, 95% Credible interval 1.2-2.3).

To this impressive list can be added two congenital heart defects as defined by the American Academy of Pediatrics in a position paper [12]:

5) Ventricular septal defect (1.9 times elevated) and
6) Ebsteins pulmonary valvopathy (2.4 times elevated)

It is noteworthy that the findings in relation to gastroschisis have been confirmed by numerous other investigators, including the senior Canadian Paediatric Surgical Network in multiple studies [11,13-36]. Numerous replicated studies clearly show that cannabis is associated with both an increased incidence [7,28,36-40] and increased severity [32,33,40] of gastroschisis.

Cannabis-Related Neurobehavioural Teratology

In addition to this good starting list it has now been well and adequately documents from three longitudinal studies from Ottawa, Pittsburgh and Amsterdam than children prenatally exposed to cannabis have worse performance indices on multiple cerebral and cortical tests of higher functioning, memory, concentration, executive processing and visual processing speeds and agility, and where tasks are performed in similar times it takes much more brain to perform similar operations [41]. The longest running of these studies is in Ottawa where these persistent defects of cortical function have been shown to persist into young adult life in the early twenties. As the other studies are not so advanced as the Ottawa longitudinal case series this major and concerning feature has not been independently confirmed at the time of writing. However since all the major findings of the Ottawa group have been confirmed by later investigators, it is also expected that these major and very concerning functions will be similarly confirmed by subsequent studies.

Effects of Cannabis on Pregnancy outcomes.

It is well established from the antenatal literature that children congenitally exposed to cannabis have increased rates of prematurity smaller heads throughout life, and lower body weight. These findings are reflects in most but not all studies of this subject and was confirmed to be so by no less a figure that Dr Nora Volkow, Director of the National Institute of Drug Abuse writing in such eminent medical journals as JAMA [42-45].

Shortcomings of the Extent Research

It is well acknowledged that the present body of research data has two major shortcomings which have not been well addressed to date.

1) These studies are almost uniformly based on self-report which is known to be highly erroneous (about 80%) in most cases. Hence the denominator and exposure determination is highly flawed in most extant studies in a manner which tends to reduce the observed effect. For this reason the reported effects represent lower bounds on the true likely effect.
2) All of the extant epidemiology has been performed in prior decades in a predominantly low THC concentration milieu. Hence it may be that none of these studies are relevant to the modern high concentration environment.

These dose related concerns achieve particular significance when one understands that many studies of cannabis genotoxicity actually show an exponential effect of cannabis exposure on genetic outcomes so that a doubling of cannabis dose cause a quadrupling or greater of genotoxic damage rather than a simple doubling of effect [46-53].

All of these factors together imply clearly that the extant literature represents a lower bound of cannabis teratology, rather than a definitive description and delineation of what is and is not cannabis related. The real news could be much worse.

This implies that one needs to take an intelligent and informed approach to what has been published and take careful thought on the matter, rather than simply parrot off the above defects as if one could realistically pretend it was the final word.

Neurobehavioural and Neuroteratological spectrum

If one conducts a thoughtful consideration of the above pattern of neuropathology one discovers a distinct progression of the spectrum of disease which might be listed from least serious to most serious as:

1) Impairment of higher executive and cortical functioning
2) Impaired neural processing times and
3) Increased recruitment of widespread neural machinery in computational exercises
4) Smaller brain and head size
5) Microcephaly – small / tiny brain
6) Anencephaly – no brain
7) Foetal death before, during or shortly after birth.

This spectrum of disease clearly implies a progression from mild to moderate. It seems self-evident that as cannabis becomes more concentrated, more and more people are exposed, and particularly if there is an exponential dose-response relationship between exposure and genotoxic damage. The implications of such an exposure occurring population wide can only be considered as horrific.

Moreover a mechanism has recently been described whereby cannabis has been shown to adversely affect the ratio of the two genes which control brain growth [54]. The slit/robo ratio has been shown to directly regulate the growth of the large brain cortex in man and great apes which is responsible for our higher intellectual function. Cannabis has been shown to raise the level of robo (the "Roundabout" gene) and drop the level of the dll ("Distal-less") gene which are the reverse of the changes which induce and control the growth of the growth of the massive cerebral cortex in man [54-57].

Cardiovascular toxicity and CB1R Mediated effects

The above table shows clearly that one of the major organs bearing the brunt of cannabis teratology in both Colorado and Hawaii is the heart and blood vessels. In both cases this has been traced to high numbers of cannabinoid type 1 receptors (CB1R's) in the central heart – a region known as the "endocardial cushions" - and present on the embryonic vessels from very early in the first weeks of foetal growth [58-60].

Indeed the effect of cannabis to cause gastroschisis has similarly been ascribed to damage to the vessels of the abdominal wall [13,21]. Cannabis has been shown to cause inflammation and constriction of blood vessels in a way which is likely to be well able to cause major downstream effects [58]. In this respect it can act somewhat like cocaine.

Whilst the effect of thalidomide to cause major damage to limbs is well known, it is not so widely known that thalidomide actually acts on the blood vessels. By biding to angiophilin, it inhibits the growth of blood vessels [61-71]. Since the blood vessels form the framework of the developing limb the limb does not and cannot form.

Similar mechanisms may pertain to cannabis-related vasculopathy. Indeed in this respect the occurrence of gastroschisis in the developing baby is directly analogous to stroke and heart attack observed in adults exposed to cannabis [44,45,72,73].

Phocomelia / Micromelia

And of course cannabis vasculopathy also accounts for the loss of limbs – which doctors call phocomelia or micromelia – just like thalidomide [69]. One notes concerning findings in this respect from both Hawaii [7] and Colorado [8] – and now it would appear – also from France [3,6].

Chromosomal Defects and the Chromosomal Trisomies

Cannabis has been shown to interfere directly with the machinery of cell division and in particular to disrupt the mitotic spindle which guides chromosomal separation during mitosis. It also disrupts actin formation which is the other major building block of the cytoskeletal machinery. This process has been described at length by our group in this reference [74].

Hence the finding in both the Hawaiian study, and in Colorado, of an increased incidence of the relatively common Down's syndrome trisomy 21 [75] despite an abortion rate of around 70% [76-83], can be well explained on the basis of the known mechanisms of action of cannabinoids.

Other Cannabinoids

THC is not the only derivate of the cannabis plant which has been shown to be genotoxic. Genotoxic and epigenotoxic actions have also been shown for cannabidiol, cannabinol, cannabidivarin and cannabichromene [49,84-92].

This implies that the action taken to limit the level of THC per se in agricultural and livestock feed is completely irrelevant and egregiously misses the point relating to the generalizability of many cannabinoids in genotoxic assays and downstream cellular and organismal effects.

Summary

It is well established that prenatal cannabis exposure causes:

1) Defective cortical and executive functioning into young adulthood
2) Anencephaly – no brain
3) Smaller brains, likely including microcephaly,
4) Gastroschisis
5) Diaphragmatic hernia
6) Oesophageal atresia
7) Ventricular septal defect
8) Ebstein's anomaly damage to the pulmonary valves
9) Smaller babies and
10) Increased prematurity

However these well described findings in the present literature represent a lower bound on cannabis-related teratology and neuroteratology in view of:

1) the very serious pattern of teratology described in animals not unlike thalidomide [93-95];
2) the rapidly rising concentration of THC in modern cannabis products
3) The exponential dose-response relationship between cannabis exposure and genotoxic effects described in many studies [46-48,50-53]
4) The powerful effect of the father's cannabis exposure in addition to the mothers.

Moreover the known teratological mechanisms of cannabis, to cause and inflammatory and vasoconstrictive arteriopathy of tiny foetal vessels, along with a predominantly CB1R dependent pattern of tropism directly explains the majority of the pattern of cannabis teratology. This close concordance between known teratological patterns, and the known and proven mechanisms of action of cannabis make widespread use foolhardy in the extreme and the very opposite and antithesis of all sound public health principles. In particular use of cannabis products by young adults of the reproductive age group should be strictly disallowed.

The well described epigenetic toxicity of cannabis is believed to have effects for up to four generations – or around 100 years [49,96-101]. None of these matters has been spelled out in the public debate to this point.

It is stressed again that what is established in the scientific literature on this point to date represents a lower bound of likely cannabis effects rather than a definitive final description for all the reasons outlined. If this advice is not heeded it it not clear to this author that the fabric of society could withstand the enormous health, social and medical imposts imposed by the tsunami of congenital toxicology and neurotoxicology in particular – the least of which implications would be financial.

Hence it is this author's view that the Swiss approach to these problems is medically correct, namely to ban cannabis and hemp products from the food chain – and the European approach to allow it is deeply flawed and indeed may account for the pattern of teratology presently observed in France. **It is not sensible to allow cannabis, hemp or cannabinoids of any description or at any concentration to be added to the food supply chain where populations will be forced to consume them against their will and without their knowledge or *informed* consent.**

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