THE UNIVERSITY OF WESTERN AUSTRALIA

Associate Professor Dr. Stuart Reece
MBBS (Hons.), FRCS(Ed.), FRCS(Glas.), FRACGP, MD(UNSW).
School of Psychiatry and Clinical Neurosciences

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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Department of Health and Human Services, Food and Drug Administration [Docket No. FDA-2018-N-1072]: International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Cannabis Plant and Resin; Extracts and Tinctures of Cannabis; Delta-9-Tetrahydrocannabinol; Stereoisomers of Tetrahydrocannabinol; Cannabidiol; **Request for Comments** (FR Doc. 2018-07225).

Re: ***Novel Considerations for the FDA Evaluation of Re-scheduling Cannabinoids in United States: Cannabinoid Genotoxicity and Structural and Neurobehavioral Teratogenicity***

There exists sufficient empirical data from cellular to epidemiological studies to warrant caution in the use cannabinoids including cannabidiol as recreational and therapeutic agents.

Cannabinoids bind to CB1R receptors on neuronal mitochondrial membranes [1-7] where they can directly disrupt key functions [8-12] including cellular energy generation, DNA maintenance and repair, memory and learning [1-7,9,10,13-24].

Empirical literature associates cannabinoid use with CB1R-mediated vasospastic and vasothrombotic strokes, myocardial infarcts, arrhythmias [25-98] and arteritis [25,77,78,99-106]. Cannabis has been associated with increased cardiovascular stiffness and vascular aging, a major surrogate for organismal aging [107]. In the pediatric-congenital context CB1R-mediated cannabis vasculopathy forms a major pathway to teratogenesis including VSD, ASD, endocardial cushion defects, several other cardiovascular anomalies [75,108] and, via the omphalo-vitelline arterial CB1R's [25], gastroschisis [108-114]. Cannabis has been linked with several other malformations including hydrocephaly [108]. Cannabinoids also induce epigenetic perturbations [115-123]; and, like thalidomide [124-126], interfere with tubulin polymerization [127-132] and the stability of the mitotic spindle precipitating micronucleus formation [129,133-142], chromosomal shattering (chromothripsis) [129,143-157] providing further major pathways to genotoxicity .

Assuming validity of the above data, increased levels of both adult and neonatal morbidity should accompany increased cannabis use. The "Colorado Responds to Children with Special Needs" (CRCSN) program tracked congenital anomalies 2000-2013 [158]. Importantly this data monitors the teratological history of Colorado since 2001 when the state was first advised that intrastate cannabis would not be prosecuted by the Federal Government. In 2012 medical cannabis was legalized and in 2014 cannabis was completely legalized.

The University of Western Australia
Mooo, Perth WA 6009 Australia
T +61 7 3844-4000.
F +61 7 3844-4015
E stuart.reece@uwa.edu.au
E stuart.reece@bigpond.com

Over the period 2000-2013 Colorado almost doubled its already high congenital anomaly rate rising from 4,830 anomalies / 65,429 births (7.4%) to 8,165 / 65,004 (12.6%; Figure 1); the US mean is 3.1%. Major cardiovascular defects rose 61% (number and rate); microcephaly rose 96% (from 30 to 60 cases peaking at 72 in 2009); and chromosomal anomalies rose 28% (from 175 to 225, peaking at 264 in 2010; Figure 2-7). Over the whole period this totals to 87,772 major congenital anomalies from 949,317 live births (9.25%).

The use of cannabis in Colorado can be determined from the SAMHSA National Survey on Drug Use and Health. A close correlation is noted between major congenital anomaly rates and rates of cannabis use in Coloradans >12 years (R=0.8825; P=0.000029; Figure 8). Although data is not strictly comparable across U.S. registries, the Colorado registry is a passive rather than active case-finding registry and so might be expected to underestimate anomaly rates. Given the Colorado birth rate remained almost constant over the period 2000-2013, rising only 3.6%, a simple way to quantitate historical trends is to simply project forwards the historical anomaly rate and compare it to the rise in birth numbers. However rather than remaining relatively stable in line with population births, selected defects (left hand column Table 1) have risen several times more than the birth rate (right hand column).

Colorado had an average of 67,808 births over the period 2000-2013 and experienced a total of 87,772 birth defects, 20,152 more than would have been predicted using 2000 rates. Given the association between cannabis use and birth defects and the plausible biological mechanisms, cannabis may be a major factor contributing to birth congenital morbidity in Colorado. If we accept this and apply the "Colorado effect" to the over 3,945,875 births in USA in 2016 we calculate an excess of 83,762 major congenital anomalies annually nationwide if cannabis use rises in the US to the level that it was in Colorado in 2013.

In reality both cannabis use and cannabis concentration is rising across USA following legalization which further implies that the above calculations represent significant underestimations [159,160]. This CRCSN data series terminates in 2013 prior to full legalization in 2014. Moreover parents of children harbouring severe anomalies may frequently elect for termination, which will again underestimate numbers of abnormal live births.

In California 7% of all pregnant mothers were recently shown to test positive for cannabis exposure, including almost 25% of teenage mothers in 2015 so cannabinoids clearly constitute a significant population-wide teratological exposure [161]. This is particularly relevant to cannabis genotoxicity as many studies show a dramatic up-tick in genotoxic effect in the dose-response curve for both tetrahydrocannabinol and cannabidiol above a certain threshold dose as higher, sedating levels are reached [132,136,162-166]. Cannabis is usually used amongst humans for its sedative effects.

Other examples of high congenital anomaly rates accompanying increased cannabis use include North Carolina [167-169], Mexico [170-175], Northern Canada [111,176-178], New Zealand and the Nimbin area in Australia [179-182].

The above data leave open the distinct possibility that the rate of congenital anomalies from significant prenatal paternal or maternal cannabis exposure may become substantial.

With over 1,000 trials listed on clincaltrials.gov the chance of a type I experimental error for cannabinoid therapeutics and a falsely positive trial finding is at least 25/1,000 trials at the 5% level.

The major anomaly rate is just the "tip of the iceberg" of the often subtle neurobehavioral teratology of Foetal Cannabinoid Syndrome (FCS) following antenatal cannabinoid exposure characterized by attention, learning, behavioral and social deficits which in the longer term impose significant educational, other addiction and welfare costs - and is clearly more common [121,183-225]. Foetal Alcohol Syndrome (FAS) is known to be epigenetically mediated [226-251] and foetal alcohol is known to act via CB1R's [186,203,206-208,210,216,252-259]. Cannabis has significant and heritable epigenetic imprints in neural, immune and germ cell (sperm) tissues [20,117,119,120,122,260-262], and epigenomic disruption has been implicated in FCS [241]. CB1R-mediated disruption by disinhibition of the normal gamma and theta oscillatory rhythms of the forebrain which underpin thinking, learning and sanity have been implicated both in adult psychiatric disease and the neurodevelopmental aspects of FCS [211].

All of this implies that in addition to usually short-term therapy-oriented clinical trials, longer term studies and careful twenty-first century next generation studies will be required to carefully review inter-related genotoxic, teratologic, epigenetic, transcriptomic, metabolomic, epitranscriptomic and long term cardiovascular outcomes which appears to have been largely overlooked in extant studies – effects which would appear rather to have taken Coloradans by surprise. Congenital registry data also needs to be open and transparent which it presently is not. We note that cannabidiol is now solidly implicated in genotoxicity [134,263-269]. Governments are duty-bound to carefully weigh and balance the implications of their social policies; lest like Colorado, we too unwittingly create a "Children with Special Needs Program" [158].

These data also directly imply that young adults, as the very group which most consumes cannabis [160,161,270-273] is the very group which most requires protection from its reproductive, genotoxic and teratogenic effects.

Yours sincerely,

Assoc. Prof. Dr. Stuart Reece.
University of Western Australia and
Edith Cowan University,
Perth,
Australia.

Table 1.:

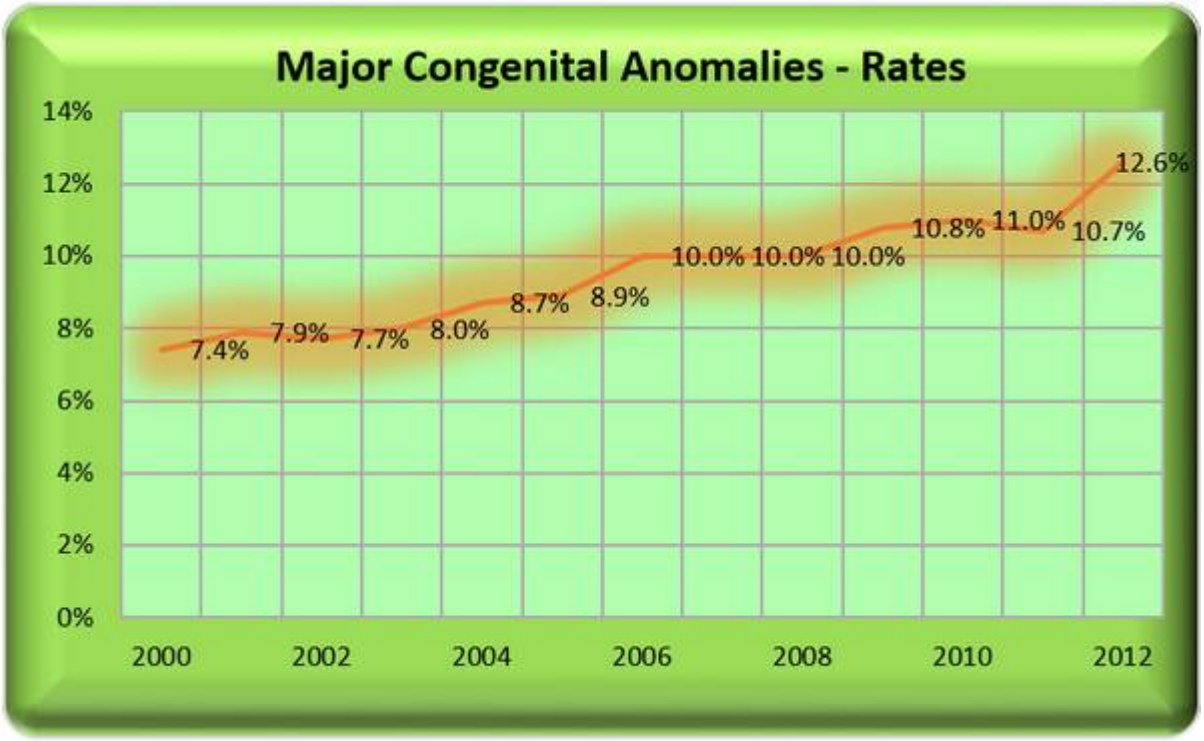
Cumulative Data for Colorado

Birth Defects 2000-2013 *

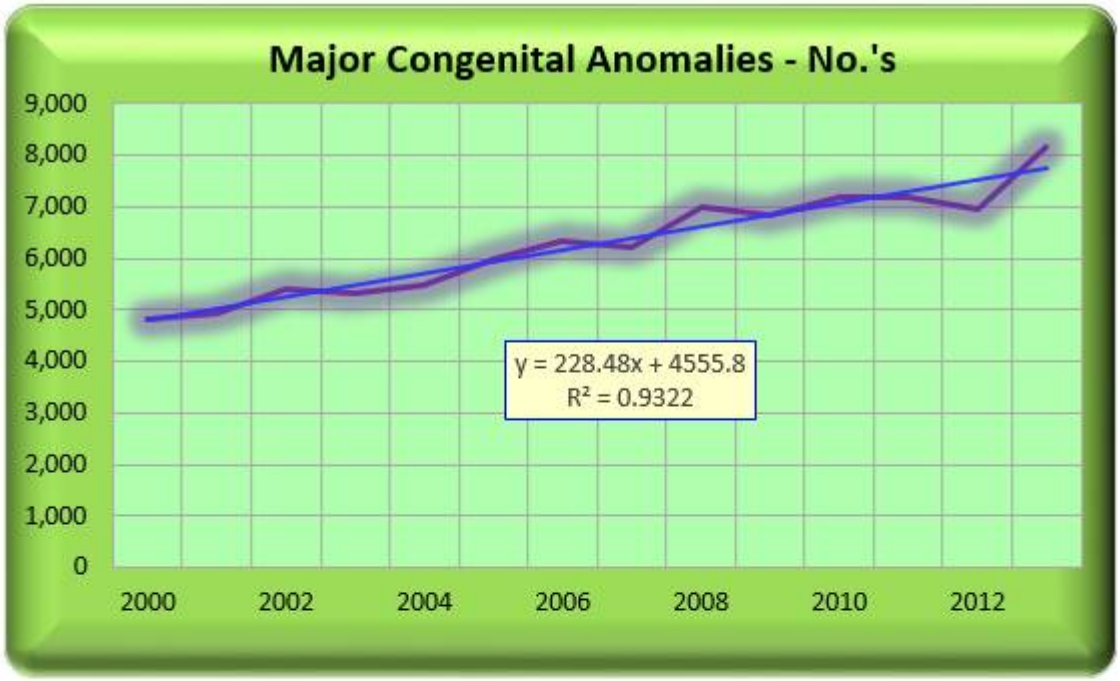
Anomaly	Cumulative Total 2000-2013	Projected Total from Baseline	Excess Above Baseline	% Change 2000-2013	Times (x) Increase Relative to Births
Births	949,317	916,006	33,311	3.6%	1.00
Major Congenital Defects	87,772	67,620	20,152	29.8%	8.20
Major CVS	19,288	14,028	5,260	37.5%	10.31
VSD	4,447	3,794	653	17.2%	4.73
ASD-Secundum	9,833	4,970	4,863	97.8%	26.91
Microcephaly	761	420	341	81.2%	22.33
Chromosomal	3,134	2,450	684	27.9%	7.68

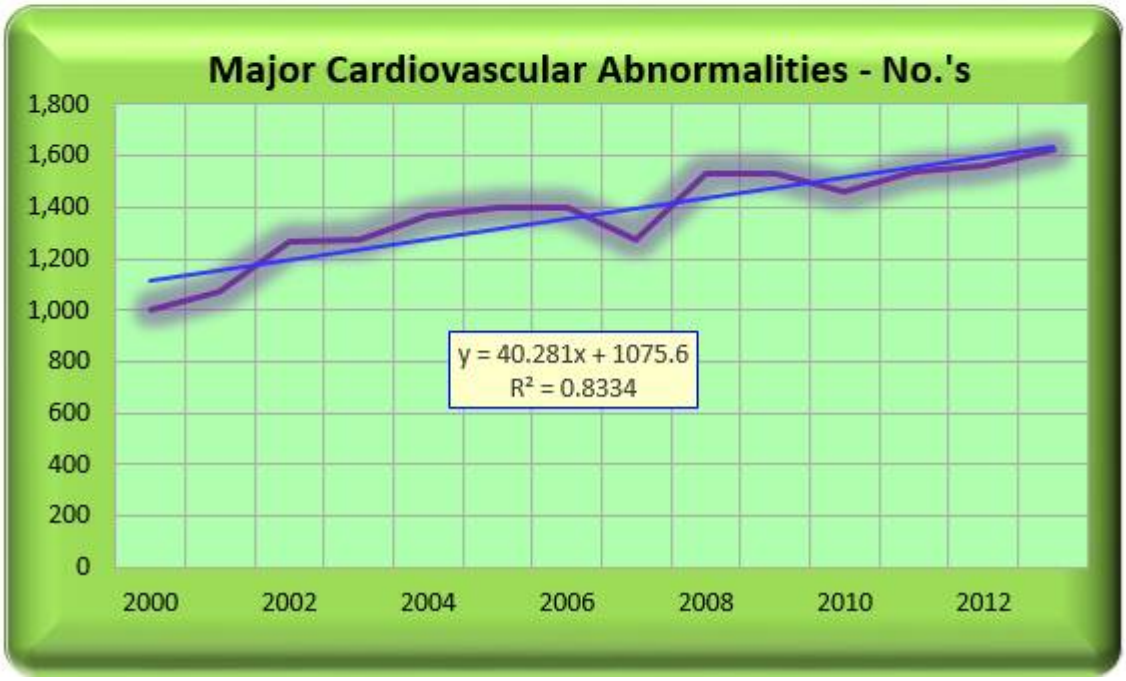
* - From Reference (4)

Figure 1.

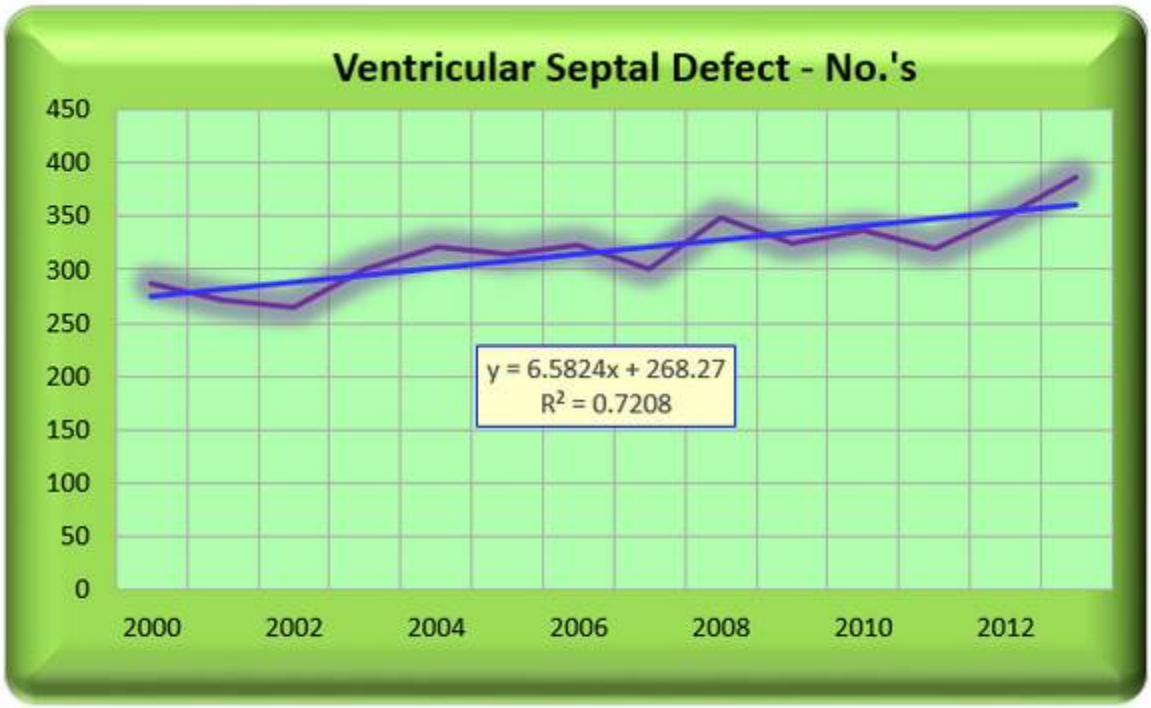

Major Congenital Anomalies - Rates
14%
12%
10%
8%
6%
4%
2%
0%
2000
2002
2004
2006
2008
2010
2012
7.4%
7.9%
7.7%
8.0%
8.7%
8.9%
10.0%
10.0%
10.0%
10.8%
11.0%
10.7%
12.6%

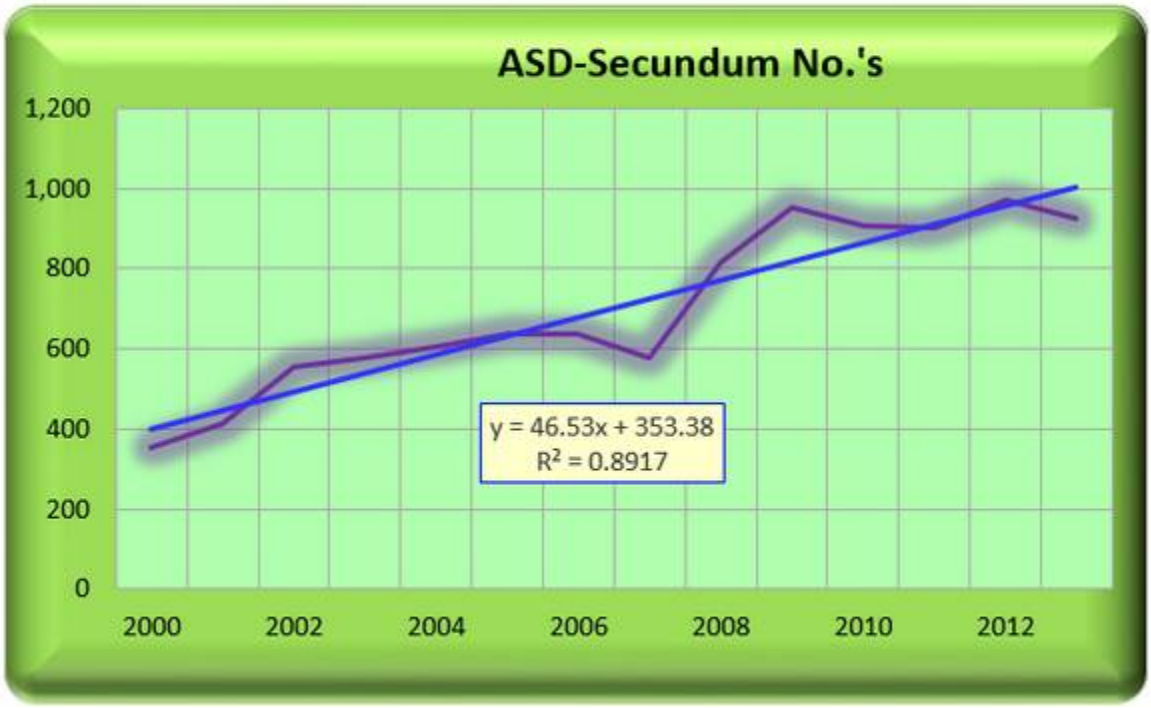
Figures 2, 3.


Major Congenital Anomalies - No.'s
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
0
2000
2002
2004
2006
2008
2010
2012
y = 228.48x + 4555.8
R² = 0.9322

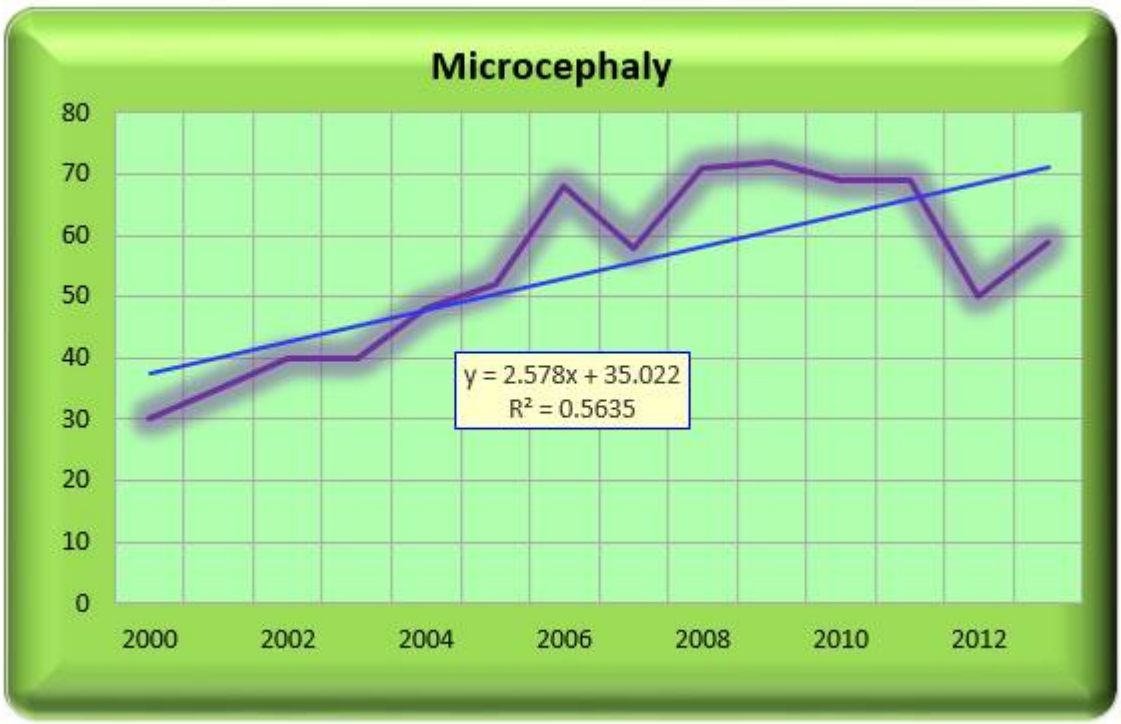

Major Cardiovascular Abnormalities - No.'s
1,800
1,600
1,400
1,200
1,000
800
600
400
200
0
2000
2002
2004
2006
2008
2010
2012
y = 40.281x + 1075.6
R² = 0.8334

Figures 4, 5.


Ventricular Septal Defect - No.'s
450
400
350
300
250
200
150
100
50
0
2000
2002
2004
2006
2008
2010
2012
y = 6.5824x + 268.27
R² = 0.7208


ASD-Secundum No.'s
1,200
1,000
800
600
400
200
0
2000
2002
2004
2006
2008
2010
2012
y = 46.53x + 353.38
R² = 0.8917

Figures 6. 7.


Microcephaly
80
70
60
50
40
30
20
10
0
2000
2002
2004
2006
2008
2010
2012
y = 2.578x + 35.022
R² = 0.5635

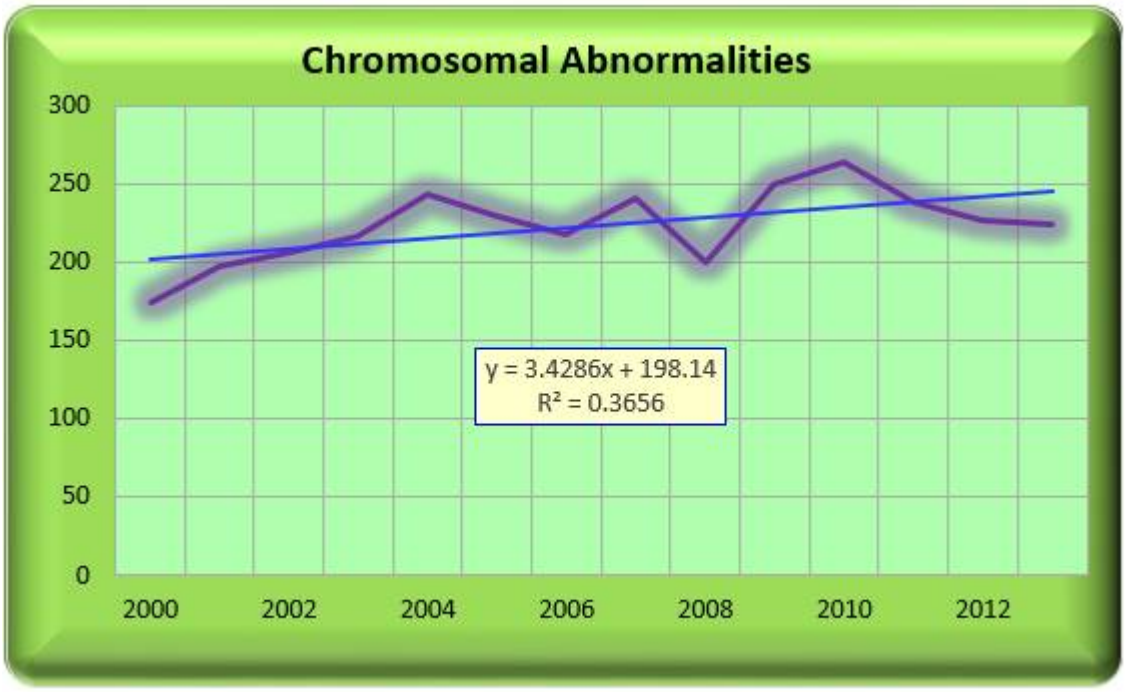
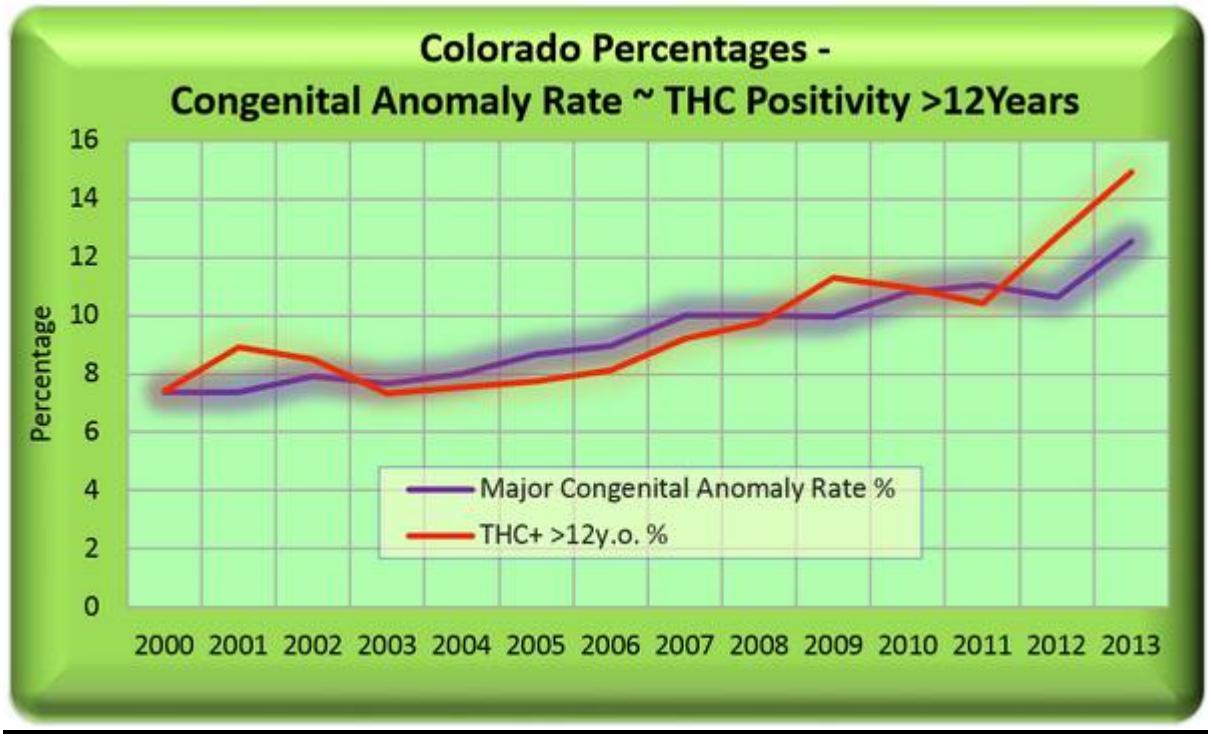

Chromosomal Abnormalities
300
250
200
150
100
50
0
2000
2002
2004
2006
2008
2010
2012
y = 3.4286x + 198.14
R² = 0.3656

Figure 8


Colorado Percentages -
Congenital Anomaly Rate ~ THC Positivity >12Years
Percentage
16
14
12
10
8
6
4
2
0
2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013
Major Congenital Anomaly Rate %
THC+ >12y.o. %

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