Response to RACGP Medicinal Cannabis Evaluation

All Cannabinoids,

Multigenerational

Genomic and Epigenomic Toxicity,

Food Chain Contamination:

Snake Oil

Preamble – *Preliminary Questionnaire*

What do the following issues all share in common:

i) Has no clinical trials to justify more than 80 alleged medical indications
ii) Dramatically accelerates aging
iii) Has been found in 80 / 80 recent mass murderers
iv) Is a major driver of poor mental health in young adults (18-25 years)
v) Is a major driver of poor mental health in older adults (> 26 years)
vi) Causes most major common mental disorders including anxiety, depression, PTSD, bipolar disorder, psychosis, schizophrenia
vii) Is linked with rising suicide rates
viii) Increases the rate of failed major adult relationships
ix) Increases the unemployment rate
x) Causes poverty and homelessness
xi) Drives drug overdoses from other drugs
xii) Drives overdoses in children directly and as the sole exposure
xiii) Drove a doubling in the rate of serious mental illness in USA in recent decades
xiv) Drives the exponentiating autism epidemics
xv) Drives the parabolically accelerating rate of USA congenital Atrial Septal Defects (secundum type)
xvi) Causes 12 congenital cardiac malformations in recent European epidemiological analysis
xvii) Drives Limbless birth defects rates elevated 60 times above background in France
xviii) Drives outbreaks of limblessness in Germany
xix) Shares 12 of 13 teratogenic mechanisms of action with thalidomide
xx) Shares 22 of 33 described birth defects with thalidomide
xxi) Concentrates certain environmental toxins in milk
xxii) Persistence of certain environmental toxins in milk for weeks
xxiii) Grossly inadequate Government assays of environmental toxins
xxiv) Disrupts the endocrine system particularly affecting the hypothalamic-pituitary-gonadal axis
xxv) Is estrogenizing
xxvi) A major driver of the commonest cancer in adults, breast cancer
xxvii) A major driver of the cancer responsible for the most years of life lost in adults, testicular cancer
xxviii) A major driver of the total childhood cancer
xxix) A major driver of the commonest cancer in children, acute lymphoid leukaemia
xxx) A major driver of inheritable cancer
xxxi) A major driver of two of the most rapidly increasing adult cancers, liver and pancreatic cancer
xxxii) Is known to be toxic to the genome and linked with DNA breaks
xxxiii) All its congeners and chemical family members are similarly implicated
xxxiv) Is known to be toxic to the epigenome and destroys the epigenetic machinery
xxxv) Damages the genes and epigenome for three to four generations
xxxvi) Is known to be toxic to the genome and linked with disruption of the mitotic machinery including kinetochores, centrosomes and mitotic spindles
xxxvii) Causes micronuclei
xxxviii) Damages sperm genetically [1]
xxxix) Damages sperm epigenetically [1]
xl) Damages sperm structurally and induces aging changes [1]
xli) Damages oocytes genetically [1]

xlii) Damages oocytes epigenetically [1]
xliii) Damages oocytes structurally and induces aging changes [1]
xliv) Causes 20% loss of fertilized oocytes (zygotes) after only a single cell division [2]
xlv) Poisons the soil
xlvi) Poisons the aquatic environment
xlvii) Contaminates the food chain
xlviii) Is linked with wildlife poisonings of eagles, bears, cougars, owls, falcons and (badger-like) fishers
xlix) Precipitates allergies in the respiratory tract and skin
l) Collects and concentrates heavy metal toxins in roots, stems, leaves and flowers
li) Is often contaminated with fungi, bacteria and viruses
lii) Inhibits mitochondrial function
liii) Inhibits mitophagy [3,4]
liv) Increases the rates of mortality, premature mortality and years of life lost [5-15]
lv) And constitutes the modern "snake oil" of an almost universally unproven remedy
lvi) And is a fast growing major global industry…

Cannabis!

Community Leadership

Since much of the data about cannabis is at once massive, confused, conflicted and highly technical there is a clear need for professional bodies such as RACGP, AMA, ACOG (American College of Obstetricians and Gynaecologists) [16,17], AAP (American Association of Pediatics) [18-21] and NIDA / NIH [22,23] to provide leadership and assistance to the community to navigate their way through this complex morass of information fraught with mixed motives and commercial actors whose interests are divergently and radically at variance with those of the general community. In places such as Amsterdam, Colorado, Oregon, Philadelphia, parts of Egypt, Morocco, Northern India and the northern rivers district of New South Wales where widespread cannabis use scenarios and commercial interests overwhelm those of the broader community the consequences are dire indeed by every metric [24]. According to one list Australia has at least 143 cannabis companies including several legal firms [A] and 43 licenced medical cannabis companies [B].

Overall Comment

The Queensland Health discussion paper [25] correctly highlights the dearth of clinical evidence for the myriad of indications for which cannabis is marketed in Australia. Given that the gold standard for clinical trials is the prospective randomized clinical trial (RCT), with a single exception, such evidence is notably lacking for so-called *"medicinal cannabis"*. The single group of exceptions for which randomized trials have demonstrated some role for cannabis is refractory rare forms of paediatric epilepsy of Lennox-Gastaut Syndrome (LGS), Dravet syndrome (DS) and Tuberous Sclerosis complex (TSC) [26-31]. In fact it would not be going too far to suggest that the nomenclature of *"medicinal cannabis"* is a radical misnomer as it implies that cannabis has been medically proven and it is use is therefore sound – which in general terms it is a grossly misleading and egregiously false misapprehension.

Numerous bodies have confirmed that commercialization of cannabis has far outstripped the present state of cannabinoid therapeutic research. In such a context the solution recommended by the Discussion paper of shuffling the administrative burden from one Government department to another is clearly inappropriate and serves merely to perpetuate the present health and administrative confusion.

Historical Context

It would appear the medical cannabis was legalized in Australia by a happy triple confluence of commercial interests, populist demand from its hallucinogenic, addictive and stuporific effects and a globalized movement sponsored by the mass media to this effect. A survey of 110 million patients in USA in 2022 showed that only 4,214 (0.0038%) were treated Epidiolex (cannabidiol) and in 40% none of the forms of paediatric epilepsy for which FDA had approved the medication were present [32]. Such statistics confirm the view that the original trials claiming a role as **fourth line** medication in refractory LGS/DS were an **overstatement of its importance** in the therapeutic armamentarium. Assuming a similar

[A] 135+ Australian Cannabis & Hemp Companies | Cannaus https://www.cannaus.com.au/companies/
[B] List of approved medicinal cannabis cultivators and producers in Australia | Office of Drug Control (ODC)

incidence of refractory paediatric epilepsy in Queensland with a population of 5 million people one would expect only 114 such patients. Given that Australia has 143 cannabis companies and 43 licensed medical cannabis companies it would appear that the great majority of cannabis scripts in this country are written for other indications which have not been validated by robust clinical trial evidence.

Any medication is evaluated by a risk benefit consideration. It is appropriate therefore to embark upon such an enquiry in this case.

Benefits

The sole exception to this is refractory paediatric epilepsy, often associated with profound intellectual disability, chromosomal disorders, or severe genetic abnormalities. RCT exist for Lennox-Gastaut Syndrome (LGS), Dravet syndrome (DS) and Tuberous Sclerosis complex (TSC) where cannabidiol has been shown to result in some reduction of seizure frequency of 25-50% in about 25% of patients [26-31]. Side effects including sedation, diarrhoea and an elevation of liver enzymes are common and are seen in 50-90% of participants. However even in such disorders its take up is remarkably low. The remarkably low patient incidence of cannabidiol scripts was mentioned above, at 0.0038% [32]. The experience described in a broader literature since the publication of these original clinical trials is broadly consistent with these results [33-45]. It would be fair to comment though that for its relatively mild clinical effect cannabis has been overly hyped by the mass media and its usually **fourth (or greater) line place** in the therapeutic armamentarium in this group of disorders has been substantially overstated.

Outside of this single group of indications the clinical evidence for any of the alleged benefits of cannabis is weak or anecdotal. This position has been confirmed by reviews from numerous authorities including AMA, RACGP and the group of the Director of NIDA at NIH in Bethesda Maryland Dr Nora Volkow and colleagues [22].

I run one of the largest private addiction medicine clinics in Queensland. The ONLY indication for which "medical" cannabis is prescribed in this large group of patients is to feed their long standing cannabis addiction without the interference of police. It is noted of course that in most cases patients have a "cover story" or excuse for their use which may be anxiety, depression, back pain, pain – or really virtually any real or imagined symptom – which – often enough are themselves symptoms of cannabis withdrawal or intoxication or brain or lung damage – but it only takes one or two questions to reveal the real nature of what is actually occurring.

That is to say that the effect of legalizing medical cannabis has just been to legitimate its long standing clandestine use albeit at a greatly inflated price and at a greatly elevated THC content. *"Medicinal cannabis"* far from being a misnomer, is actually just a legal fiction which effectively enables both the addiction in the patients and profiteering in the industry. As more and more classes of cannabis become subsidized by various public schemes this is actually a Government subsidized drug peddling Ponzi scheme for the primary benefit of organized business to the detriment of both the tax payer and the patients who are extorted for their generally exorbitant prices.

It should also be emphasized that the THC concentration of *"medicinal cannabis"* is much higher than the cannabis of former years. In the 1960's 1-2% THC content by weight was common. Now it is exceptional to see cannabis products of less than 19% - 30% being logged on QScript.

It should also be noted that cannabis addiction can be treated relatively easily with just 10mg diazepam in 98% of cases. Thus cannabis use syndrome (formerly known as cannabis dependence or cannabis addiction) is NOT by itself a valid medical indication for the continued use of cannabis.

Risks

The risks and side effects of cannabis on many organ systems have been well described and well known for years [22,46,47]. They were highlighted by recent AMA and RACGP position papers on this subject. Key organ systems affected by cannabis include the central nervous system, upper and lower respiratory systems, endocrine system, bones, cardiovascular , immune and the reproductive systems and tracts [47]. It is worth noting here that all major psychiatric syndromes have now been shown to be linked with cannabis use including depression, anxiety, PTSD, cannabis induced psychosis, schizophrenia, bipolar disorder, suicidal thoughts and actions, and recently mass homicides. References have been presented elsewhere [48,49].

A series of mass homicides have been presented from USA in ALL of which the offenders were found to have tested positive for cannabis [50]. Moreover there is also a substantial literature on cannabis and violence in several contexts [51-59].

Autism

It should also be noted that there is an increasing and robust literature from Australia, Canada and USA showing that cannabis is also linked with autism and ADHD-like syndromes in children in a causal manner. This has been demonstrated in space-time geospatiotemporal studies, using the statistics of formal causal inference [60-64], by longitudinal prospective clinical cohort studies [65-75] and is supported by fMRI brain imaging studies [76-78]. Many epigenetic changes have been described where prenatal cannabis exposure phenocopies autism-like epigenetic changes [79-91]. Autism-like synaptopathies have also been described from cannabis [83,92-104]. Cannabis has also been shown to alter neuroligins and neurexin epigenetically [88] which are key synaptic structural morphogens and also strongly implicated in autism [102,105-109]. Cannabis has been shown to epigenetically [88] perturb both the retinoid gradients [110,111] and both sides of the robo-slit ligand-receptor dyad which are some of the major factors controlling the massive forebrain outgrowth of the human rostral cerebrum [112-114]. Robo-Slit is also a key dyadic pair controlling axonal (and also arterial) guidance within the brain and spinal cord [115,116]. Cannabis also disrupts signalling by stathmin which is a key guidance molecule also involved in axonal guidance and growth cone steering and transduction of directional pathfinding cues in outgrowing axonal projections [117]. Cannabinoids also perturb both the neurogenesis and the differentiation of both inhibitory GABA-ergic and stimulatory glutamatergic cortical and hippocampal neurons of all types [1,48,64,118]. Cannabis disconnects key brain white matter tracts [119].

Therefore given the myriad of effects of cannabis on brain function and brain development in both the adult and developing organism, positive findings relating to severe neurodevelopmental outcomes in autism, ADHD and intellectual impairment generally must be considered expected and predictable and represent on-target neurotoxicity.

Overdose

An oft repeated but very misleading mantra is that *"no one ever died from cannabis"*. This is not true. There are numerous pathways from cannabis use to death including but not limited to:

i) Mental illness – depression, anxiety, suicidal thoughts and actions, bipolar affective disorder, psychosis, schizophrenia can all lead to death
ii) Gateway effects with death arising from drugs used secondarily for which cannabis was the gateway but not including cannabinoids at necropsy
iii) Polydrug overdose including cannabis
iv) Murder including mass murder – affects both perpetrator and victims
v) Cardiac arrest from arrhythmia
vi) Cardiac arrest from myocardial infarction
vii) Road traffic accidents
viii) Unemployment including homelessness
ix) Poverty including homelessness
x) Social isolation (exacerbated by failed relationships) including homelessness
xi) Cancers – adult and child
xii) Respiratory disease including chronic bronchitis, emphysema, lung cysts, asthmatic exacerbations
xiii) Complications of congenital anomalies including chromosomal anomalies
xiv) Accelerated aging syndromes
xv) Acute paediatric poisonings and overdoses

Several of these merit further comment. The role of cannabis as a gateway drug to other drug use is now well established [120-132]. Cannabis is frequently found at coronial postmortem but is usually discounted. This is a major methodological error and reflects medical fashion and ignorance more than public health trends. Therefore in patients who die from heroin use, but they began their drug using career with cannabis but are negative for cannabinoids at autopsy, cannabis was a primary and earlier cause of that mortality. In decedents who die with cannabis in their system cannabis was a contributing cause of that statistic. Moreover Colorado data shows convincingly that overdoses from other drugs, like heroin, amphetamine, fentanyl and cocaine also become much more common as cannabis use becomes more widespread and is inevitably accompanied by increases in the use of other drugs.

Direct links between cannabis and deaths involving interpersonal violence were mentioned above.

Cannabis use is well known to be linked with sudden cardiac death by abrupt myocardial infarction and malignant arrythmias. This has been documented in many reputable sources including the New England Journal of Medicine [46,133].

Cancer

Our group and others have written extensively on the links shown by modern epidemiological studies between cannabis and many cancers [1,47,134-153]. In spatiotemporal and causal inferential analysis it was shown that cannabis was the primary driver of the 50% rise in total pediatric cancer [145] which is a disorder whose prime genotoxic lesion is generally congenital or inherited [154,155]. It was shown that cannabis was the primary driver of the doubling in the rate of US testicular cancer which is the cause of the most years of life lost of any adult cancer [141,146]. We also showed that cannabis was the primary driver of recent surges in the rates of pancreatic and hepatic cancers in USA [89,136-138,147,156]. Cannabis was also shown to be a primary driver of rising breast cancer rates in USA which forms the commonest human cancer [139]. These findings in cancer epidemiology in USA were replicated in Europe [142,148,150]. We also showed in an analysis of European datasets that cannabis was a more powerful carcinogen than tobacco and alcohol, and in many analyses was more powerful than these two known carcinogens combined [148].

Aging

Cannabis has now been shown to be linked with accelerated aging at once by:

i) clinical syndromology [157],
ii) direct biophysical measurement of increased arterial hardening [158],
iii) elevated premature death rate [5-15],
iv) its induction of hepatic fibrosis and cirrhosis [159]
v) Impaired mitochondrial function (referenced above)
vi) Endocrine suppression especially affecting the hypothalamic – pituitary-gonadal axis [160,161]
vii) Elevated rates of mental illness (referenced elsewhere [48,49])
viii) Cellular changes in oocytes [162]
ix) Cellular changes in sperm [163-168]
x) Growth inhibition [1,169]
xi) DNA breakages (referenced elsewhere)
xii) Elevated rates of congenital anomalies (referenced elsewhere)
xiii) Elevated rates of cancer (referenced elsewhere)
xiv) Epigenetic derangement generally [85-89,170,171]
xv) human cellular epigenetic age [172]. Indeed this last is a dramatic effect with studies showing 29% advanced of biological epigenetic age by 30 years [172] and findings that this likely increases with time as a linear and quadratic function of age [158].

Paediatric Overdose

Adults do not overdose on cannabis because there are no cannabis receptors in the brain stem which controls breathing. However this is not true for children and toddlers who do have cannabinoid receptors in their brain stem. Thus cannabis can directly cause very serious respiratory depression in infants and toddlers who not infrequently require ventilation. Whilst statistics on this are difficult to locate they are kept in Colorado and Texas. Results there show uniformly that paediatric overdose deaths rise dramatically as cannabis use spreads. A 5-fold rise in paediatric (under five years) cannabis edible overdoses was reported in Texas 2017-2023 [173]. The overall overdose rate doubled in Texas 2012-2023 from

7.6 to 16.3 per 100,000 residents (114% rise [C]). In a USA national review of adolescent overdoses based on the CDC WONDER database after a decade of decreasing adolescent overdose rates 2010-2021 states with recreational programs saw overdose rates rise 88%, 479% and 115% in 2019, 2020 and 2021 respectively [174]. In a USA national poisons database review 2017-2021 overdoses from paediatric edible cannabis products increased from 207 in 2017 to 3,054 in 2021 an increase of 1,375% [175]. 98% of exposures occurred at home. Overdoses became more serious across this period with more patients requiring admission to hospital. Overdoses from both THC and cannabidiol are recognized as increasingly serious and a constitute a subject of increasing interest and concern for pediatric physicians [176].

Colorado legalized cannabis on January 1st 2014 [D]. A study of the overdose rate in Colorado performed from the Colorado Children's hospital in Aurora and the Regional Poisons Centre showed that the rate of paediatric overdoses increased dramatically across this period (January 1 2009 to December 31 2015) in children younger than ten, with a median age of 2 [177]. The rate of pediatric admissions to hospital doubled from 1.2 to 2.3 / 100,000 population from the two years prior to legalization to the two years thereafter demonstrating a causal relationship to the cannabis legalization event. Cannabis edibles and edible infused products were involved in half the exposures (52% and 48% respectively). Poison centre notifications for these products increased from 9 in 2009 to 47 in 2015 an annual average rise of 34% which was almost twice the rate of rise of the remainder of the USA (19%) [177]. Poor child supervision was implicated in more than half the cases (52%) presumably because the relevant adults were likely cannabis affected [177]. This elevated trend has continued in Colorado. Whereas in 2017 56 children younger than 5 years were reported with cannabis overdoses by 2021 this number had jumped further to 151 (169%) [E].

Another Colorado study found that the age groups where cannabis use rose the most was 18-25 years (from 19% to 34% 2003-04 to 2015-2016) and older than 26 years (5% to 15% 2003-04 to 2016-2017) [178]. Cannabis related hospitalizations rose from 575 /100,000 in 2000 to 2,413 in 2015 (319%). Adolescent emergency room visits rose from 172 to 780 (353%). The number of suicides with cannabis present rose from 40 to 158 2004-2015 (295%) and the percentage of suicides with cannabis present rose from 2.5% to 14.6% (484%) in the similar period [178]. Fatal drug overdoses in Colorado rose from 1999 to 2017 for prescription opioids from 73 to 372 (409%), for methamphetamine from 16 to 298 (1,652%), for heroin from 42 to 223 (420%) and for fentanyl from 0 to 81 (over 8,000%) [F]. Children's hospital visits for cannabis overdose rose from 1 in 2009 to 36 in 2017 (3,600%) and regional poisons centre notifications rose from 9 to 67 (644%) with a marked jump across the time of cannabis legalization (from 7 to 16 and 24 to 43, 128% and 79% 2013-2014) respectively [178].

These data show unequivocally that wherever reliable data exists increased cannabis use including cannabis legalization is associated with severe impacts on the weakest and most vulnerable members of the community in this case children and toddlers.

[C] Texas Health Data - Drug-Related Deaths https://healthdata.dshs.texas.gov/dashboard/drugs-and-alcohol/drug-related-deaths

[D] Cannabis in Colorado - Wikipedia https://en.wikipedia.org/wiki/Cannabis_in_Colorado#Results ; Colorado marijuana legalization timeline: 10 years of notable events https://www.denverpost.com/2023/12/31/colorado-marijuana-legalization-sales-timeline/

[E] Marijuana Exposures Among Colorado Children on the Rise | NarcononUS.org https://www.narcononus.org/articles/recent-news/marijuana-exposures-among-colorado-children-on-the-rise/

[F] co_poisoning_deaths_1518prov_qtr.xls - Google Drive https://drive.google.com/file/d/1vfi4kL9eD9rib7aEboteiGw67gOxXFpf/view

Genotoxicity

The outcomes of genotoxicity are well established to be congenital anomalies (birth defects), cancer formation and aging. Moreover many lines of evidence indicate that such genotoxic damage can be transmitted intergenerationally for at least four generations i.e. the next 100 years! [179] This is a major issue with cannabis and all cannabinoids albeit it is not widely understood, discussed or considered.

Cannabis and Δ9-THC has long been known to inhibit the synthesis of DNA, RNA and proteins [2,180-192] starting from 15 minutes after cannabis administration [189,193]. For the psychoactive metabolite 11-hydroxy-Δ9-THC (THC-COOH) this effect begins just five minutes after administration [189,193].

Moreover many cannabinoids are known to induce single and double stranded DNA breaks directly [194-199]. Indeed cannabis has long been known to test positive in the micronucleus assay which is a standard test for genotoxicity [152,198,200]. Micronucleus formation is a very serious genotoxic event with extremely serious downstream sequelae for cells, organs and organisms [201-210]. A PubMed search reveals that cannabis is now linked with epigenomic disruption in over 200 studies (207 hits; PubMed Entrez search conducted January 26th 2025). This is most commonly studied by alteration in patterns of DNA methylation. Not only is the epigenome disrupted and disorganized but so too are the critical readers, writers and erases of the epigenomic machinery including DNA methyltransferases 3 A and B, and TET1. The basic machinery of mitosis is grossly disrupted and disorganized by cannabis including proteins in the chromosomal centromeres, the kinetochores which bind the centrosomes to the mitotic spindle and even the tubulin which forms the microtubules of the mitotic spindle itself [169]. Thus cannabinoids disrupt all aspects of basic cell function.

Epigenetic disruption also extends to the histone proteins which package DNA inside the cell nucleus. DNA inside chromosomes in cells is wound around a core octamer of nucleosomal proteins which control which genes are made available to the transcription machinery and so determine cell type, cellular (neural, immune and metabolic) memory and a myriad of other key cellular functions. Many workers have shown that cannabis disrupts histone formation necessarily disrupting the epigenome [189,211]. Indeed extensive disruptions of histones themselves, and therefore necessarily the histone code, was described in detail 30 years before the epigenome was even discovered [189]. In the case of sperm heads this disorganization is so massive as to be very obvious at electron microscopy [212]. Obviously the implication of the sperm head in this issue raises the clear and present danger of transgenerational transmission of major indices of genotoxicity.

Olivetol - the Nucleus of All Cannabis

Importantly several studies now link this genotoxic effect with olivetol which is the C-ring nucleus structure common to all cannabinoids [2,213-219]. Thus all cannabinoids, including cannabidiol, cannabinol, cannabigerol, cannabichromene and all the congeners of Δ1-, Δ6-, Δ7-, Δ8-, Δ9-, Δ10-, Δ11- tetrahydrocannabinol are implicated. This becomes important from a regulatory point of view as it has been common practice around the world to legislate for

control of Δ9-THC levels whilst leaving the concentration, dose and amount of other known genotoxic cannabinoids, unregulated. This is counterfactual and counter-evidentiary.

Mitochondria

It should also be understood that many cannabinoids have long been known to inhibit mitochondrial function [164,220-236]. Mitochondria possess all of the cannabinoid receptor and transduction machinery found in the plasma membrane of the cell [234,237-243]. Moreover they concentrate lipophilic cannabinoids in their convoluted internal membrane structure in a manner which increases at least three-fold over time [2,212,244-246]. Mitochondria cluster around the nucleus as many of the processes of genome maintenance and transcription require energy. Mitochondria communicate with the nucleus via energy supply (as ATP), the supply of epigenomic substrates and via mitonuclear stress signalling pathways [247]. It is important to appreciate that many of the epigenetic substrates and cofactors arise from mitochondrial intermediate metabolism. Thus inhibition of mitochondrial metabolism necessarily perturbs and disrupts genomic and epigenomic function mandatorily.

It is also important to observe that whereas mitochondria are gathered around the normal cell nucleus to supply it with energy and cofactors for maintenance of the genome and epigenome, this similar clustering behaviour around the micronuclei (generated by cannabinoid interference with the normal machinery of cell division and the consequent induction of chromosomal mis-segregation) generates oxygen free radicals which mediate the rupture of the micronuclear membrane and catastrophic shattering of the micronuclear chromatin [208-210] inducing the genomic disaster of chromothripsis in the primary genome which is known to lead to major genotoxic outcomes including aging, the genesis of highly aggressive cancers, mental retardation and congenital anomalies in offspring and frequently cell death [248-251]. Far from being merely of theoretical interest, epidemiological evidence of chromosomal mis-segregation and deletion was found to be related primarily to cannabis exposure in human studies of both American and European paediatric populations [135-138,252].

Similarly the epigenome controls sites of DNA breakage due to genomic disruption and controls DNA repair and DNA availability for such key functions as DNA transcription and replication [253-261]. In reciprocal manner the genome controls the epigenome as its genes provide the biological substrate from which the machinery of the epigenome is transcribed [169].

This leads to a key biological insight, namely that the genome-epigenome-mitochondrial mass are intimately, intricately and interdependently interrelated by myriad pathways and need to be considered and understood to function in a coordinated manner to control gene expression, cell phenotype, lineage commitment, aging and cell functions. Since the study of each of these layers of gene control necessarily requires different assays, tests and biometrics it is important always to appreciate that they are not separate but in fact different aspects of an intricately and intimately interconnected elegant and extremely sophisticated cellular regulatory network. This implies that to admit that cannabinoid mitochondriopathy is significant necessarily implies significant cannabinoid induced genotoxicity and cannabinoid induced epigenotoxicity. And by extension similar reciprocal concerns relate to cannabinoid genotoxicity and epigenotoxicity also.

Aging

Aging is widely understood to be the universal fate of all cells and all life forms. Radically transforming this general misperception is the recent demonstration of reversal of cellular and organismal aging by the use of stem cell factors by several leading research groups [262-267]. As noted above aging is one of the principal clinical stigmata of genotoxic lesions.

In a brilliant series of studies in a scientific *tour de force* the Sinclair laboratory from New York and their collaborators showed that the induction of just ten DNA breaks would cause the epigenome to rearrange itself to direct DNA repair at the breakage sites and that this epigenomic rearrangement then greatly accelerated the normal aging process [268]. Using stem cell reprogramming factors they were then able to reverse the epigenomic aging processes of cells including causing eye damage from optic nerve crush trauma, glaucoma and cataract to reverse and partially heal [263,268]. They were also able to reverse female ovarian aging in a mouse model of chemotherapy induced ovarian aging by dietary supplementation with nicotinamide mononucleotide to supplement cellular mitochondrial and nuclear levels of the critical metabolic co-factor nicotinamide adenine dinucleotide (NAD+) [269,270]. Ataxia telangectasia syndrome is a severe genetic disorder of deranged DNA repair characterized by increased DNA breaks and premature aging, senescence, many cancers and death. In mouse and worm models of this disorder they were able to show that nicotinamide supplementation improved mitochondrial function, mitophagy and DNA repair [271]. The work elegantly demonstrated the mechanistic convergence of the interrelationships between genome and mitochondrial balance through the mitonuclear communication described above. This dual relationship was further confirmed by the use of nicotinamide supplements to support defective mitochondrial metabolism due to a failure to generate some of the mitochondrially encoded oxidative phosphorylation components in a sirtuin-1- and hypoxia inhibitory factor (HIF)- dependent manner thereby inducing a pseudohypoxic metabolic state which mimicked the Warburg effect [272].

A clear conceptual understanding of this aging pathophysiology is of obvious relevance to the cellular and organismal pathophysiology induced by all common cannabinoids as they are concentrated in mitochondrial membranes and matrix and disrupt all three principal axes namely the genome, epigenome and mitochondrial compartments.

Given therefore that:

i) All cannabinoids are implicated in these processes
ii) Each layer is now very well documented
iii) These effects may persist through genetic and epigenetic inheritance to multiple generations and
iv) Cannabinoids typically persist in cell membranes for many months in chronic users
v) Exacerbation of aging processes alone is **common and ubiquitous** and likely dose related
vi) Bystander effects can occur through secondary and tertiary exposures

the conclusion becomes inescapable that the community has a major issue with cannabinoid related genotoxicity-epigenotoxicity-mitochondriopathy resulting from widespread cannabis usage, which can only be framed as a public health disaster.

Food Chain Contamination

International Experience

USA

California is said to have 6,881 registered cannabis farms [G] and likely more than ten times that number of unofficial illegal grow sites [H]. Local law enforcement is overwhelmed at the scale of the challenge [273]. Much of this new industry is concentrated in the rural north of the states in counties such as Shasta, Humboldt, Siskiyou, Mendocino, Butte and Trinity. Much has been written about environmental contamination by the pesticides commonly used to protect these crops and the effects of downstream contamination on small rodents and the higher predators which eat them including owls, bald eagles, bears, cougars and fishers (like badgers) [274-278]. Much has been written on the agricultural risks posed by cannabis farming including viral [279], bacterial [280-284] and fungal [284-301] infections the accumulation by the plant of heavy metals [284,302-314] and the excessive use of precious water resources in a frequently dry climate endangering aquatic habitats and fisheries [315-319].

Cannabis farms are known to use a lot of water for their rapidly growing crops which in large operations mature twice a week. It must therefore be considered that this water will run off from such plantations carrying in it concentrations of cannabinoids. Although these are known to be generally lipid soluble they will likely be carried on carrier molecules such as lipid droplets and organic debris which might be caught in such effluent in suspension. Indeed this is such a problem that the Californian Water Resources Control Board has established rules and guidelines in an effort to control this issue and protect the natural water resources [320-322]. Indeed it has also been shown that the concentrations of cannabinoids which are measured in Californian waterways can be detected in offshore molluscs and have been shown to be genotoxic at these concentrations to multicellular model organisms [323,324].

Quantities of cannabinoids have also been measured in the rivers of Canada [325,326] and in the Great Lakes region [327]. THC is metabolized in the liver first to hydroxy-THC (THC-OH) which is still psychoactive [328] and then to the carboxy derivative 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THC-COOH). Concentrations of THC-COOH have been measured as high as 12.5 ng/L in the soluble phase of the influent going into sewerage treatment works. Importantly they calculated distribution coefficients of 1,052 ng/L with particulate matter and 35,000 ng/L with organic matter for THC [326]. These authors detected THC-COOH at 1 ng/L in drinking water. From such data the authors were able to report average levels of cannabis use by residents of a small Canadian rural town of 53 mg/day/1,000 inhabitants respectively [326].

One review reported levels of THC-COOH as high as 2,590 ng/L in urban city wastewater effluent which fell to 169 (96.5%) in treated wastewater effluent [325]. Chlorine used in waste water treatment plants and swimming pools was shown to generate chlorinated and oxygenated breakdown products of THC-COOH which are more toxic than THC, THC-COOH or even registered solvents and disinfectants [325]. Thus swimming pools were

[G] Cannabis cultivation licenses, by state U.S. 2022 | Statista
https://www.statista.com/statistics/1108194/cannabis-cultivation-licenses-by-state-us/
[H] Reality of legal weed in California: Illegal grows, deaths - Los Angeles Times
https://www.latimes.com/california/story/2022-09-08/reality-of-legal-weed-in-california-illegal-grows-deaths

described as being a likely source of transdermal exposure to cannabinoids. Levels of 79.9 ng/L THC-COOH were found in surface water and 1 ng/L in drinking water. The salient point is made that in 2017 that Colorado consumed 187 tons of cannabis and in 2018 Canada used 370 tons all of which is subsequently released into the environment [325].

A key question relates to the transferability of dietary cannabinoids into animal products. A very worrying paper was published on this point in Nature Food which demonstrated that 20% of dietary THC and 11% of dietary cannabidiol were bioavailable in the milk of dairy cows fed cannabis stalks [329]. Worryingly this feed was derived from designate industrial *hemp* plants which were claimed to be low in THC content. The cannabinoid concentration of the silage feed was 1,254, 8,304, 39 and 450 mg/kg dry matter of Δ9-THC, cannabidiol, cannabinol and cannabidivarin respectively. Cows were fed 1mg/kg Δ9-THC during an initial one week adaptation period. Average ingested doses were 1.6 and 10.7 mg/kg and 3.1 and 20.4 mg/kg of Δ9-THC and cannabidiol in the low and high dose exposure groups respectively each for one week. Such doses resulted in steady state levels of Δ9-THC and cannabidiol after low- and high- dose exposures of 100 and 370, and 380 and 800 µg/kilogram of milk respectively. It was further observed that cows given this feed would appear sedated, almost asleep on their feet, would freeze their motion in time, would stop chewing and would appear to have an unsteady gait and be apparently giddy and "stoned". Treated cows fed less. Their milk yields cropped from 25 L/day to 19.8 L/day [329].

One week after hemp feeding Δ9-THC and cannabidiol were still detectable in the milk at 5 and 16 µg/kg respectively in the high dose group [329]. Both Δ9-THC and cannabidiol accumulated in the milk and were concentrated to levels 6-26 and 11-32 times those found in the plasma respectively.

For humans younger than 18 years it was found that consumption of milk from the low dose period would results in plasma levels exceeding the safe dose (known as the Average Reference Dose over 24 hours, ARfD) by a factor of 14 for average consumers but by 57-fold for high milk consumers [329]. For all demographic and population groups it was found that consumption of milk from the period of high hemp exposure would results in levels exceeding the ARfD by 120-fold. It was further shown that consumption of such cannabinoid contaminated milk could results in humans exceeding the ARfD in infants with high milk consumption even during the preliminary adaptation period [329].

It was also shown that the usual methods (gas chromatography with flame ionization detection, GC-FID) defined by official EU Government sources (Annex III Regulation EU Number 639/2014) for estimation of the cannabinoid content of the milk samples were incorrect in their readings as compared to state of the art techniques (high performance liquid chromatography coupled to tandem mass spectroscopy, HPLC/MS) by a factor of up to seven-fold [329]. This becomes very important given that hemp is defined as having a THC content of 0.3% dry weight by the US Farm Act and 0.2% in the EU. If this level is in error by seven-fold then serious consequences may ensue, particularly given the build up of cannabinoids in milk and in human fatty tissues including brain and gonads.

Atrial Septal Defect in USA

We reported in 2016 about a curious phenomenon in USA in relation to atrial septal defect secundum type (ASD) which is its commonest form [330]. At a time when the background rate

of ASD in the was around 20 /10,000 births a group of states with a higher ASD rate appeared to be emerging. At the time this seemed troubling and concerning to us although the full explanation was not apparent at that time. Most concerning of all was the state with the highest ASD rate, namely Kentucky. We have since understood that Senator Mitch McConnell, in 2018 the Senate majority leader, was from that state and was a powerful champion of the USA Agricultural Improvement Act (commonly known as the "Farm bill") at that time [331]. Whilst this bill was aimed to assist USA farmers Senator McConnell is said to have organized for the last minute insertion of clauses about cannabis and hemp which allowed and encouraged farmers exiting the tobacco industry to transfer to hemp cultivation. However these clauses are said to be so poorly written as to make their enforcement by the various Federal agencies almost impossible [331]. The massive USD$867,000,000,000 budget of this bill provided powerful financial sponsorship to stimulate this transition into cannabis farming making cannabis cultivation a Federally sponsored industry [I] [331]. This bill has been cited as the proximate cause of the flourishing USA cannabis farming industry and may have been a deliberate ploy by its sponsors [J]. Kentucky was therefore amongst the first to take advantage of these provisions and cannabis farming has since burgeoned in this state. Since then ASD became 15 times more common than elsewhere in the USA and the then reported rate across all races was 295.

Four year time span (thus quadrennial) data has since been released from the US National Birth Defects and Prevention Network (NBDPN) [332]. Nevada has since supplanted Kentucky as the leading state for ASD. The history of cannabis in Nevada is decriminalization in 2001 (Assembly Bill 453), medical cannabis allowed in 2013 (Senate Bill 374) and full legalization began January 1st 2017 following a state ballot [K]. For the 2016-2020 quadrennium Nevada reported an ASD rate of 773 across all races and 850 amongst African Americans. Kentucky's rate in this later period was 333 in all races and 568 amongst African Americans. ASD rates amongst African Americans in Louisiana and Kentucky in the 2012-2015 period were 867 and 466 respectively. ASD rates amongst American Indians / Alaska Natives for Nevada, New Mexico, Alaska and Kentucky in 2016-2020 were 595, 349, 296, and 276 respectively. In the 2012-2015 quadrennium rates in Mississippi, Kentucky, Oregon, Ohio, Alaska and Nevada in all races were 739, 357, 316, 267, 252, and 190. Cannabis has been legalized in Oregon, Nevada, and Alaska [L].

This data may be compared with data from the USA National Survey of Drug Use and Health which showed that past month cannabis use in the over 26 years age group across the period from 2008-2009 to 2018-2019 rose from 4.42% to 9.39% nationwide (P<0.001), from 4.63 to 9.78% in the northeast (P<0.001), from 5.56% to 12.49% in the west (P<0.001) and from 4.14% to 8.74% in the Midwest. In this period last month cannabis use tripled in Nevada from 7.74% to 22.04% (P<0.001) and rose significantly in Colorado (7.31% to 15.62%, P<0.001), Oregon (7.11% to 17.49%, P < 0.001), Mississippi (3.15% to 6.65%, P = 0.003), Alaska (9.3% to 16.25%, P = 0.37), Kentucky (3.40% to 6.42%, P =0.20), Louisiana (3.27%

[I] https://www.degruyter.com/document/doi/10.1515/jdpa-2020-0006/html
[J] Mitch McConnell's Cannabis Gambit: How The Farm Bill Unwittingly Fueled A THC Boom - Benzinga https://www.benzinga.com/markets/cannabis/24/05/35598477/mitch-mcconnells-cannabis-gambit-how-the-farm-bill-unwittingly-fueled-a-thc-boom
[K] https://nevadastatecannabis.org/laws
[L] Here's a Map of the U.S. States that Legalized Weed – HeyHelloHigh | Cannabis lifestyle for modern women https://heyhellohigh.com/2018/02/21/map-of-the-uss-states-that-legalized-weed-cannabis/

to 8.71% (P = 0.015), New Mexico (4.49% to 10.99%, P= 0.001), Washington (5.53% to 16.54%, P < 0.001) and Vermont (7.75% to 17.11%, P = 0.002) [M].

The real significance of this ASD data is that early termination of pregnancy for anomaly (ETOPFA) is not practised for this congenital anomaly. The simple reality is that if serious anomalies were becoming more common across USA we would really not be aware of it since there are relatively limited longitudinal data relating to ETOPFA practices by congenital anomaly type. If the real situation is that many congenital anomalies are increasing in the trajectory followed by ASD then the real state of neonatal epidemiology must be very dire indeed.

This parabolic increase in ASD rates exceeds even the now well documented exponential rise in the cannabis – autism link which has been demonstrated at both the epidemiological and mechanistic epigenetic levels [60-62,64,80,85,86,90,333-346].

Amelia in France and Germany

The major limb defects of amelia (no limbs) and phocomelia (flipper limbs) have been shown to be linked with cannabis use in both experimental animals [347-349] and in human epidemiological studies [142,350-357]. Detailed pathophysiological studies [88,116,358] provide possible and likely mechanistic bases for these observational findings [1,351-353,359,360].

The case of a recent outbreak of major limb defects in the province of Ain on the eastern edge of France on the Swiss border, and also in the Normandy region of France is of particular interest [361]. It was reported that the epidemiologist Emmanuelle Amar notified seven cases of amelia (limblessness) and phocomelia (flipper limb) in Ain about October 22nd 2018 which took the standardized incidence of this major defect to 60 times background [361]. The parents were known to live on communes in fields of sunflowers and corn [361]. Environmental factors were suspected. On October 18th 2018 a major drug haul of 135kg of cannabis resin was made in the region of Ain [362]. The seizure of so massive a quantity of concentrated cannabis product in this region implies significant drug use or perhaps production in the area. Just a few months earlier in June 2018 it was reported that a mayor in the southwest of France made application to the President of France to grow crops of legal cannabis [363]. This raises the very real possibility that the cases identified in France, which is reported to have amongst the highest rates of cannabis use in Europe [363] may have been associated with cannabis consumption, cannabis cultivation on the communes or potentially cannabinoid environmental contamination. In response to this report the French Government launched an enquiry - and terminated Dr Amar's employment [364]. More recently (2023) it is possible to find advice online about the best strains of cannabis to grow in the region of Ain [364].

A midwife in a hospital in Germany reported three cases of major limb defect in her institution [365]. As a result enquiry was made and over 30 more cases were identified. However as Germany has no national register of birth defects both the regional rate and the time trend of such major anomalies cannot be determined. It is known that cannabis use is

[M] Comparison of 2008-2009 and 2018-2019 Population Percentages (50 States and the District of Columbia) | CBHSQ Data
https://www.samhsa.gov/data/report/comparison-2008-2009-and-2018-2019-nsduh-state-prevalence-estimates

becoming much more common in Germany and medical use was allowed from April 1st 2024 [366].

Australia.

A significant cannabis operation is located at Caboolture north of Brisbane. At present it has 2,950 square meters under cultivation, harvests biweekly and produces 10,000 kg of cannabis annually. Plans are to double this in 2025 [N]. Another large grow site which is described as a $400 million venture, is being built in Toowoomba by Asterion Cannabis including a 40 hectare glass house aiming to produce 500,000kg annually with a value on the export market exceeding $1billion annually [O]. The hemp building company based in Victoria builds houses from hemp, advises that its products are non-toxic, and markets "hempcrete" a mixture of hemp fibre and lime used like concrete for walls and similar structures [P].

Toowoomba is located close to the headwaters of the Condamine river which flows into the Murray-Darling Basin. The Murray is Australia's largest waterway. Both the Murray and the Murrumbidgee river are heavily used for irrigation. In Australia's dry climate it often does not flow in its lower reaches but is reduced to a series of water holes. This implies that any cannabinoids emanating from Australia's enormous grow sites would become more concentrated as the amount of available water declines.

In 2014 Australia's richest person Gina Rinehart bought Bannister Downs Dairy in Northcliffe Western Australia. A state of the art creamery was built there in 2018 [Q]. The northern rivers area of New South Wales is a well known centre for alternate culture and cannabis cultivation. Gina Rinehart bought the 1918 hectare dairy farm there in 2023 called Split Rock Dairy. It was converted to Wagyu beef production which is a high end beef product commanding high prices on the international market [R]. In 2019 Ms. Rinehart invested $15 million in Little Green Pharma, an Australian medical cannabis company, for a capital raise aiming at penetrating the emerging cannabis market in Denmark and the EU [S]. The site included 21,500m^2 for cultivation and 4,000m^2 for post-harvest manufacturing aiming to produce 12,000kg cannabis flower annually and comprised Europe's largest cannabis production facility. Little Green pharma also has a large cannabis production facility in the Margaret river area of Western Australia [T]. Margaret river is a major centre for alternative lifestyle and hosts large cannabis farms [U]. Margaret River is 164 km from

---

[N] https://www.cannaus.com.au/companies/spring-sciences/

[O] Australia's biggest medicinal marijuana farm to be built in Queensland's conservative garden city - ABC News https://www.abc.net.au/news/rural/2021-04-15/australias-biggest-medicinal-cannabis-farm-toowoomba/100070770

[P] The Leaders In Hemp & Lime Construction https://www.thehempbuildingcompany.com.au/ Viewed 02.02.2025.

[Q] Our Partner | Bannister Downs Dairy https://bannisterdowns.com.au/about-us/partnerships?utm_source=chatgpt.com

[R] https://www.weeklytimesnow.com.au/subscribe/news/1/?sourceCode=WTWEB_WRE170_a&dest=https%3A%2F%2Fwww.weeklytimesnow.com.au%2Fproperty%2Fgina-rineharts-hancock-agriculture-purchases-split-rock-dairy%2Fnews-story%2F13713d5bbe523932aae0adf88fbcbee2&memtype=anonymous&mode=premium

[S] https://investlittlegreenpharma.com/site/about/company-overview

[T] https://www.abc.net.au/news/rural/2020-08-01/buy-local-trend-during-coronavirus-medicinal-cannabis-demand/1251533

[U] How To Grow Hemp In Australia - Growing Hemp In Our Great Country | Margaret River Hemp Co

Northcliffe where the beef cattle are raised. In both regions there may be concerns that the feed of the cattle may be contaminated from cannabis grown in the nearby vicinity.

Two major papers were released in 2011 from the International Birth Defects Surveillance Research and Clearing House, which is the major international collaboration of the birth defects registries relating to major limb defects of phocomelia (flipper limbs) and amelia (no limbs [367,368]. The only city in the world which was at the top of both incidence tables was Melbourne, Victoria. This is intriguing as Melbourne has a large immigrant population from many nations in Europe and Asia, none of which report high incidences of major limb defects. A simple google search reveals that the city is surrounded by cannabis farms. One Victorian cannabis farm is a $160million dollar project and another is a $184million dollar project [V]. Australian Primary Hemp based in Geelong grows and markets cannabis for food products [W].

The most famous Victorian amelic patient is Nick Vujicic who is tetra-amelic and is an internationally renowned motivational speaker [X]. At the time of his birth (December 1st 1982) no one in his family had this problem [Y]. His parents were very conservative and were church pastors. It is therefore unlikely that any known drug exposure occurred gestationally. Nick is now married and has four children. His children have all 16 limbs. Nick's parents were advised at the time of his birth that no genetic factor was implicated in the aetiopathogenesis of his condition [Z]. Together these factors point towards some environmental factor operating around the time of his conception or gestation which may have interfered with limb development.

Cannabis disrupts many major morphogens which together orchestrate and control body patterning and limb development [351-353]. The arm buds form at days 22-24, and leg buds form at days 24-26 of gestation [116]. It is therefore possible that some external teratogen may have been introduced at this period to interrupt and truncate limb development. Cannabis has been linked with amelia both by animal studies [347-349] and several epidemiological studies in humans [350-353]. In particular Δ9-THC and cannabidiol have been shown to directly interrupt sonic hedgehog which is one of the major body morphogens and is critically involved in limb formation [358]. Cannabis has also been shown to interfere with sonic hedgehog expression epigenetically [169,351-353]. Cannabis has also been shown to disrupt many morphogen gradients including bone morphogenetic proteins [369-371], retinoic acid [372-374], Wnt signalling [375-380], fibroblast growth factor [381,382], and sonic hedgehog [358]. It therefore becomes easy to see how gradient disruption at critical periods might interfere with this delicately balanced and finely choreographed sequential and orchestrated process.

Thalidomide

Although this is only one case it is interesting to recall that awareness of the thalidomide birth defect disaster was triggered by just three cases of the gestational use of thalidomide by

---

[V] Revealing where cannabis is growing in Australia | Cannaus
https://www.cannaus.com.au/national/where-cannabis-is-growing-in-australia/
[W] Australian Primary Hemp | ASX-Listed, Hemp Retail | Cannaus
https://www.cannaus.com.au/companies/australian-primary-hemp/
[X] Home - Nick Vujicic https://nickvujicic.com/
[Y] Nick Vujicic - Wikipedia https://en.wikipedia.org/wiki/Nick_Vujicic
[Z] Vujicic N. "Life without Limits: Inspiration for a Ridiculously Good Life." DoubleDay Press 2010.

nursing Sister Pat Sparrow who alerted the Dr William McBride to the effect [AA]. An early report to Lancet in 1962 referenced just five similar cases [383]. That was the starting point from which the modern drug regulatory regime emerged with a remarkably uniform emphasis on safety and genotoxicity testing trans-jurisdictionally and internationally [384,385].

Relevantly it has recently been shown that in fact cannabis shares 12 of the 13 described cellular mechanisms with thalidomide and 22 of its 33 described congenital anomalies [356].

Indeed in its context, given this well defined literature it must be surmized that the advocates and commercial entrepreneurs driving the present cannabis tsunami are well aware that cannabinoids are profoundly problematical in terms of genotoxicity and epigenotoxicity assays which is why they need cannabis legalization laws as a workaround to circumvent the global safeguards and systems which have been set in place to prevent a recurrence of exactly this nightmare of the widespread popularization of a hazardous known genotoxin.

AA

https://www.bing.com/images/search?view=detailV2&ccid=dmXSxVXP&id=10B730540B48C3CB8455CCA9F20BC893F7BDE0A5&thid=OIP.dmXSxVXPCAV3X4mUc_Es1gHaEK&mediaurl=https%3a%2f%2fi.ytimg.com%2fvi%2fUeglNxQ5gwg%2fmaxresdefault.jpg&exph=720&expw=1280&q=Thalidomide+scandal&simid=608052380960759895&FORM=IRPRST&ck=BBC6AFA95C948F1F7DBA5DD2E574FDE3&selectedIndex=0&itb=0&idpp=overlayview&ajaxhist=0&ajaxserp=0

Conclusion

It goes without saying that such food chain contamination occurs without population knowledge or consent. This removes the free choice from any supposed *"right to use drugs"* since the right not to be exposed to cannabinoids is removed from the target population. This includes such vulnerable populations as pregnant women, nursing mothers, the very old, the very young, the mentally ill, those allergic to cannabinoids or those suffering from virtually any chronic disease. Moreover given that cannabinoids and their congeners are known genotoxins and epigenotoxins with effects active for at least four generations not only is the target population's health degraded but so too is that of several subsequent generations yet to arrive.

In such a situation it becomes impossible to avoid the conclusion that cannabis is an unequivocal public health disaster and environmental catastrophe of the highest magnitude with multigenerational impacts.

Given the very limited number of clinical trials for various rare forms of pediatric epilepsy, and very low rate at which such prescriptions are issued in USA it becomes impossible not to conclude that cannabis is the completely unjustified modern *"snake oil"* of today. What is different about this is that its genotoxic risks have been known since at least 1969. Its epigenotoxic risks to histones have been known since 1976 which is well before the mechanics of the epigenome were themselves explicated.

It becomes impossible therefore not to conclude that the society broadly has succumbed to the seduction of the sedative - euphoric activities of this hallucinogen. The above review has been limited by time and space as I was only allowed ten days for its preparation. However it has been sufficient to document that the risk: benefit equation for cannabis is very different to its popularly understood air brushed public image as a *"soft drug"*. *"Soft"* is not an appropriate appellation to summarize the trail of destruction and woe outlined in the above commentary and the pages of references which follow.

What is urgently needed is for the medical profession to sound the alarm bells of the culture much better than we have done hithertofore. Our professional organs such as RACGP and AMA provide excellent routes for just this complete with wide open exposure in the mass media. Should we instead succumb to either the siren voices of chemical seduction and enslavement or commercial or community pressure we will have failed in our professional and fiduciary duty to the communities we serve and to their offspring to come for several generations; and makes us complicit in their egregious wholesale betrayal. To allow the continued desecration and denudation of our human, genetic, epigenetic, psychological, reproductive, social and natural environments is a great professional and moral crime against all seven.

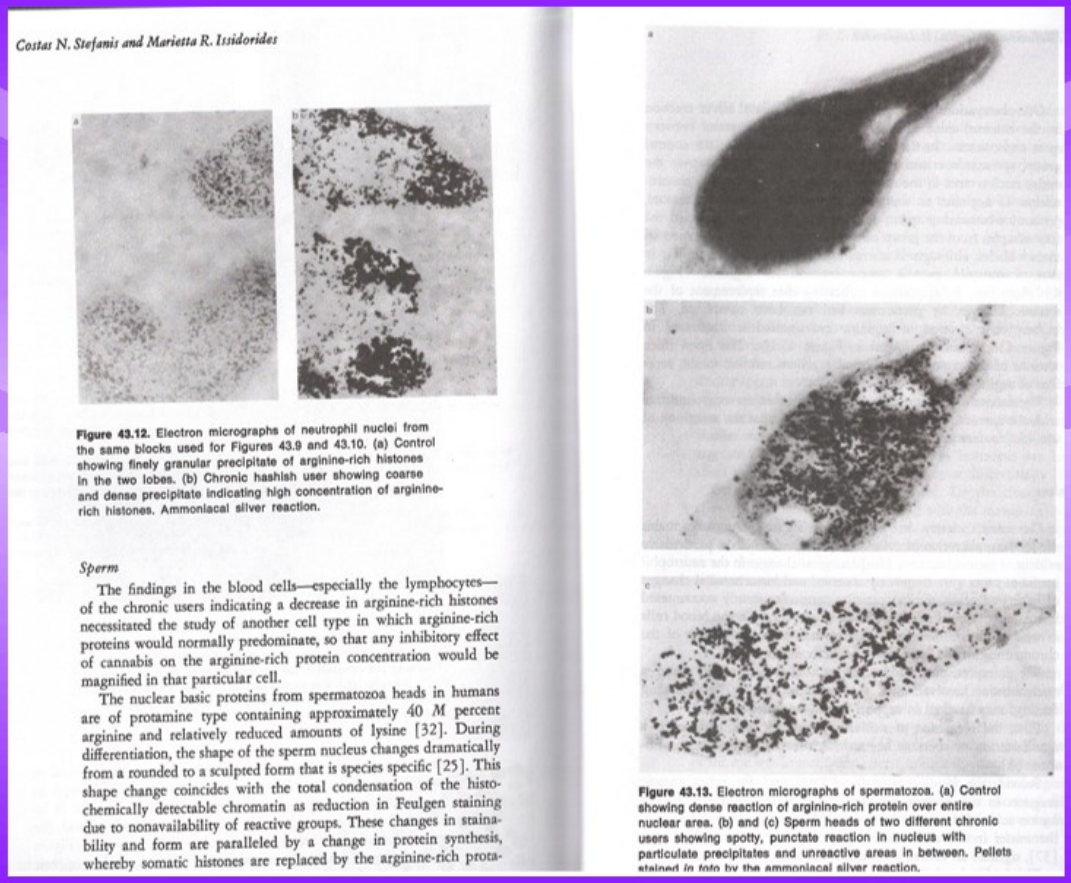
This we must not do.

We were told.

Our Duty now and the higher call of Honour is to tell all; community education as a matter of the highest urgency is now our imperative and emergent priority.

Human Sperm Head Histone Assay, 1976

Human Neutrophils



Costas N. Stefanis and Marietta R. Issidorides

Figure 43.12. Electron micrographs of neutrophil nuclei from the same blocks used for Figures 43.9 and 43.10. (a) Control showing finely granular precipitate of arginine-rich histones in the two lobes. (b) Chronic hashish user showing coarse and dense precipitate indicating high concentration of arginine-rich histones. Ammoniacal silver reaction.

Sperm

The findings in the blood cells—especially the lymphocytes—of the chronic users indicating a decrease in arginine-rich histones necessitated the study of another cell type in which arginine-rich proteins would normally predominate, so that any inhibitory effect of cannabis on the arginine-rich protein concentration would be magnified in that particular cell.

The nuclear basic proteins from spermatozoa heads in humans are of protamine type containing approximately 40 *M* percent arginine and relatively reduced amounts of lysine [32]. During differentiation, the shape of the sperm nucleus changes dramatically from a rounded to a sculpted form that is species specific [25]. This shape change coincides with the total condensation of the histochemically detectable chromatin as reduction in Feulgen staining due to nonavailability of reactive groups. These changes in stainability and form are paralleled by a change in protein synthesis, whereby somatic histones are replaced by the arginine-rich prota-

Figure 43.13. Electron micrographs of spermatozoa. (a) Control showing dense reaction of arginine-rich protein over entire nuclear area. (b) and (c) Sperm heads of two different chronic users showing spotty, punctate reaction in nucleus with particulate precipitates and unreactive areas in between. Pellets stained *in toto* by the ammoniacal silver reaction.

Human Sperm Heads

Stefanis C.N. & Issidorides M.R. (1976) "Cellular Effects of Chronic Cannabis Use in Man" In Marihunana: Chemistry, Biochemistry and Cellular Effects Vol. 1 (eds Nahas G.G., Paton W.D.M., & Idanpaan-Heikkla J.E.) Chapter. 43, 533-550 (Springer-Verlag).

Human Sperm Head Assay, 1999

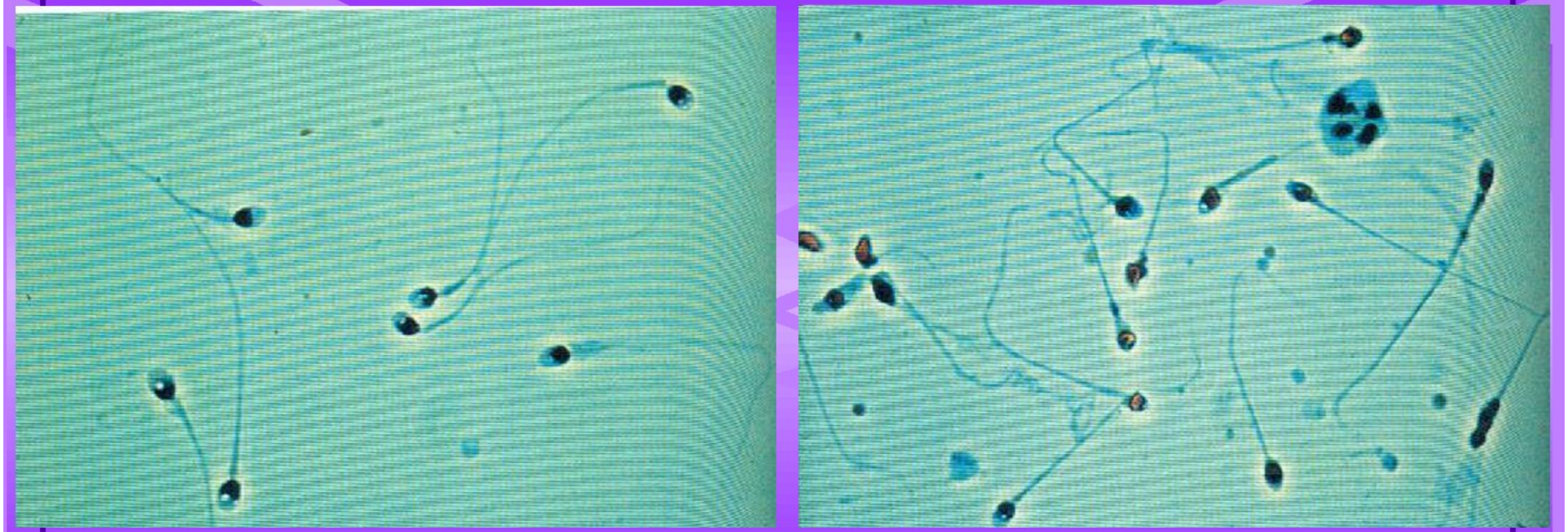


Fig. 8. *Top:* Normal ovoid shape human spermatazoa sampled from tobacco smoker and moderate alcohol drinker. *Bottom:* Nonovoid and immature form present among ovoid shape human spermatazoa sampled from daily marihuana smoker.

Hembree W.C. Nahas G.G., Zeidenberg P., Huang H.F.S. Changes in Human Spermatozoa Associated with High Dose Marihuana Smoking. In: Nahas G.G. SKM, Harvey D.J., Agurell S., ed. Marijuana and Medicine. Totowa, New Jersey: Humana Press; 1999:367-78

Oocyte - Chromosomal Damage, 1984

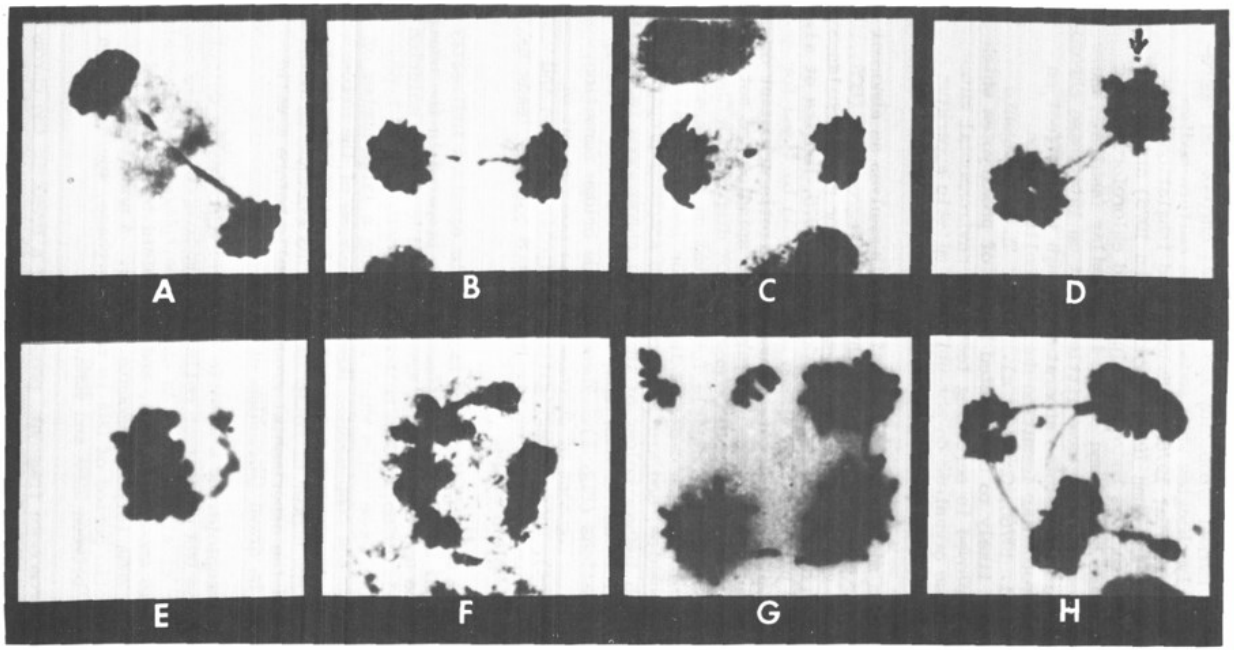


Figure 1. Errors of chromosome segregation (ECS). From Henrich et al. (1980). (A) Anaphase bridge. (B) Severed bridge. (C) Anaphase Zag. (D) Micronucleus (arrow) and multiple bridges. (E) Chromosome out of phase with others in metaphase. (F) Unequal segregation in bipolar diversion. (G) Multipolar division. (H) Multipolar division and bridges.

Effects of cannabis and natural cannabinoids on chromosomes and ova

A Morishima

NIDA Res Monogr. 1984;44:25-45.

In vitro induction of segregational errors of chromosomes by natural cannabinoids in normal human lymphocytes

Environ Mutagen. 1980;2(2):139-47. doi: 10.1002/em.2860020206.

R T Henrich, T Nogawa, A Morishima

References

1 Reece A.S. & Hulse G.K. Epigenomic and Other Evidence for Cannabis-Induced Aging Contextualized in a Synthetic Epidemiologic Overview of Cannabinoid-Related Teratogenesis and Cannabinoid-Related Carcinogenesis. *International Journal of Environmental Research and Public Health* **19**, 16721 - 16776 (2022).

2 Nahas, G. G., Morishima, A. & Desoize, B. Effects of cannabinoids on macromolecular synthesis and replication of cultured lymphocytes. *Federation proceedings* **36**, 1748-1752 (1977).

3 Si, J. *et al.* Cannabinoids improve mitochondrial function in skeletal muscle of exhaustive exercise training rats by inhibiting mitophagy through the PINK1/PARKIN and BNIP3 pathways. *Chem Biol Interact* **389**, 110855 (2024). https://doi.org/10.1016/j.cbi.2024.110855

4 Wang, Z., Zheng, P., Nagaratnam, N., Solowij, N. & Huang, X. F. Parkin Mediates Cannabidiol Prevention of Amyloid-Beta-Induced Senescence in Human Astrocytes. *Cannabis Cannabinoid Res* **8**, 309-320 (2023). https://doi.org/10.1089/can.2022.0186

5 Arendt, M., Munk-Jorgensen, P., Sher, L. & Jensen, S. O. Mortality among individuals with cannabis, cocaine, amphetamine, MDMA, and opioid use disorders: a nationwide follow-up study of Danish substance users in treatment. *Drug Alcohol Depend* **114**, 134-139 (2011). https://doi.org/10.1016/j.drugalcdep.2010.09.013

6 Davstad, I., Allebeck, P., Leifman, A., Stenbacka, M. & Romelsjo, A. Self-reported drug use and mortality among a nationwide sample of Swedish conscripts - a 35-year follow-up. *Drug Alcohol Depend* **118**, 383-390 (2011). https://doi.org/10.1016/j.drugalcdep.2011.04.025

7 Muhuri, P. K. & Gfroerer, J. C. Mortality associated with illegal drug use among adults in the United States. *Am J Drug Alcohol Abuse* **37**, 155-164 (2011). https://doi.org/10.3109/00952990.2011.553977

8 Pavarin, R. M. & Berardi, D. Mortality risk in a cohort of subjects reported by authorities for cannabis possession for personal use. Results of a longitudinal study. *Epidemiol Prev* **35**, 89-93 (2011).

9 Callaghan, R. C. *et al.* All-cause mortality among individuals with disorders related to the use of methamphetamine: a comparative cohort study. *Drug Alcohol Depend* **125**, 290-294 (2012). https://doi.org/10.1016/j.drugalcdep.2012.03.004

10 Hser, Y. I., Kagihara, J., Huang, D., Evans, E. & Messina, N. Mortality among substance-using mothers in California: a 10-year prospective study. *Addiction* **107**, 215-222 (2012). https://doi.org/10.1111/j.1360-0443.2011.03613.x

11 Frost, L., Mostofsky, E., Rosenbloom, J. I., Mukamal, K. J. & Mittleman, M. A. Marijuana use and long-term mortality among survivors of acute myocardial infarction. *Am Heart J* **165**, 170-175 (2013). https://doi.org/10.1016/j.ahj.2012.11.007

12 Desai, R. *et al.* Recreational Marijuana Use and Acute Myocardial Infarction: Insights from Nationwide Inpatient Sample in the United States. *Cureus* **9**, e1816 (2017). https://doi.org/10.7759/cureus.1816

13 DeFilippis E.M. *et al.* Cocaine and Marijuana Use among Young Adults Presenting with Myocardial Infarction: The Partners YOUNG-MI Registry. *Journal of the American College of Cardiology* **In Press** (2018). https://doi.org/10.1016/j.jacc.2018.02.047

14 von Greiff, N., Skogens, L., Berlin, M. & Bergmark, A. Mortality and Cause of Death-A 30-Year Follow-Up of Substance Misusers in Sweden. *Substance use & misuse*, 1-9 (2018). https://doi.org/10.1080/10826084.2018.1452261

15 Fridell, M. *et al.* Prediction of psychiatric comorbidity on premature death in a cohort of patients with substance use disorders: a 42-year follow-up. *BMC psychiatry* **19**, 150 (2019). https://doi.org/10.1186/s12888-019-2098-3

16 Gynecologists, A. C. o. O. a. *ACOG Committee Opinion: Marijuana Use During Pregnancy and Lactation*, <https://www.acog.org/en/Clinical/Clinical%20Guidance/Committee%20Opinion/Articles/2017/10/Marijuana%20Use%20During%20Pregnancy%20and%20Lactation> (2017).

17 American College of Obstetricians and Gynecologists. *Substance Abuse and Pregnancy*, <https://www.acog.org/About-ACOG/ACOG-Departments/State-Legislative-Activities/Substance-Abuse-and-Pregnancy?IsMobileSet=false> (2019).

18 The impact of marijuana policies on youth: clinical, research, and legal update. *Pediatrics* **135**, 584-587 (2015). https://doi.org/10.1542/peds.2014-4146

19 Ammerman, S., Ryan, S. & Adelman, W. P. The impact of marijuana policies on youth: clinical, research, and legal update. *Pediatrics* **135**, e769-785 (2015). https://doi.org/10.1542/peds.2014-4147

20 Dharmapuri, S., Miller, K. & Klein, J. D. Marijuana and the Pediatric Population. *Pediatrics* **146** (2020). https://doi.org/10.1542/peds.2019-2629

21 Wong, S. S. & Wilens, T. E. Medical Cannabinoids in Children and Adolescents: A Systematic Review. *Pediatrics* **140** (2017). https://doi.org/10.1542/peds.2017-1818

22 Hoch, E. *et al.* Cannabis, cannabinoids and health: a review of evidence on risks and medical benefits. *European archives of psychiatry and clinical neuroscience* (2024). https://doi.org/10.1007/s00406-024-01880-2

23 Volkow, N. D., Baler, R. D., Compton, W. M. & Weiss, S. R. Adverse health effects of marijuana use. *N Engl J Med* **370**, 2219-2227 (2014). https://doi.org/10.1056/NEJMra1402309

24 Reece A. S. Chronic Immune Stimulation as a Contributing Cause of Chronic Disease in Opiate Addiction Including Multi-System Ageing *Medical hypotheses* **75**, 613-619 (2010). https://doi.org/10.1016/j.mehy.2010.07.047. Epub 2010 Aug 25.

25 Queensland Health. *Medicinal Cannabis in Queensland: A Report on Stakeholder Feedback*, <https://www.health.qld.gov.au/__data/assets/pdf_file/0031/1366267/Medicinal-cannabis-in-Queensland-A-report-on-stakeholder-feedback.pdf> (2024).

26 Thiele, E. A. *et al.* Add-on Cannabidiol Treatment for Drug-Resistant Seizures in Tuberous Sclerosis Complex: A Placebo-Controlled Randomized Clinical Trial. *JAMA Neurology* **78**, 285-292 (2021). https://doi.org/10.1001/jamaneurol.2020.4607

27 Devinsky, O. *et al.* Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *New England Journal of Medicine* **376**, 2011-2020 (2017). https://doi.org/doi:10.1056/NEJMoa1611618

28 Devinsky, O. *et al.* Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome. *New England Journal of Medicine* **378**, 1888-1897 (2018). https://doi.org/doi:10.1056/NEJMoa1714631

29 Thiele E., E.M., B., Bhathal H., Jansen F. & Kotulska-Jozwiak K. *Cannabidiol (CBD) Treatment in Patients with Seizures Associated with Tuberous Sclerosis Complex: A Randomized, Double-blind, Placebo-Controlled Phase 3 Trial (GWPCARE6)*, <https://aesnet.org/abstractslisting/cannabidiol-%28cbd%29-treatment-in-patients-with-seizures-associated-with-tuberous-sclerosis-complex--a-randomized--double-

blind--placebo-controlled-phase-3-trial-%28gwpcare6%29?utm_source=chatgpt.com> (2019).

30 Thiele, E. A. *et al.* Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* (2018). https://doi.org/10.1016/S0140-6736(18)30136-3

31 Tang, R. & Fang, F. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *N Engl J Med* **377**, 699 (2017). https://doi.org/10.1056/NEJMc1708349

32 Lin, B. Y. *et al.* Cannabidiol prescribing in the United States: An analysis of real-world data. *Drug Alcohol Depend Rep* **13**, 100303 (2024). https://doi.org/10.1016/j.dadr.2024.100303

33 Koubeissi, M. Anticonvulsant Effects of Cannabidiol in Dravet Syndrome. *Epilepsy Curr* **17**, 281-282 (2017). https://doi.org/10.5698/1535-7597.17.5.281

34 Samanta, D. *et al.* Antiseizure medications for Lennox-Gastaut Syndrome: Comprehensive review and proposed consensus treatment algorithm. *Epilepsy Behav* **164**, 110261 (2025). https://doi.org/10.1016/j.yebeh.2024.110261

35 Varadkar, S. Cannabidiol for drop seizures in Lennox-Gastaut syndrome. *Lancet* (2018). https://doi.org/10.1016/S0140-6736(18)30135-1

36 Mellis, C. Cannabidiol for drug-resistant seizures in the Dravet syndrome. *J Paediatr Child Health* **54**, 101-102 (2018). https://doi.org/10.1111/jpc.13803

37 Moore, Y. & Robinson, R. Cannabidiol reduced frequency of convulsive seizures in drug resistant Dravet syndrome. *Arch Dis Child Educ Pract Ed* (2017). https://doi.org/10.1136/archdischild-2017-313700

38 Wechsler, R. T. *et al.* Consensus panel recommendations for the optimization of EPIDIOLEX® treatment for seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex. *Epilepsia Open* **9**, 1632-1642 (2024). https://doi.org/10.1002/epi4.12956

39 Miller, I. *et al.* Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial. *JAMA Neurology* **77**, 613-621 (2020). https://doi.org/10.1001/jamaneurol.2020.0073

40 Aderinto, N. *et al.* The efficacy and safety of cannabidiol (CBD) in pediatric patients with Dravet Syndrome: a narrative review of clinical trials. *Eur J Med Res* **29**, 182 (2024). https://doi.org/10.1186/s40001-024-01788-6

41 Elbadri, M. *et al.* Is adjunctive Cannabidiol effective in controlling seizures for adult patients with Lennox-Gastaut Syndrome? - A single centre long term follow up study. *Epilepsy Behav* **157**, 109904 (2024). https://doi.org/10.1016/j.yebeh.2024.109904

42 Besag, F. M. C., Vasey, M. J. & Brown, R. J. Promising therapeutic strategies for Lennox-Gastaut syndrome: what's new? *Expert Rev Neurother* **25**, 15-27 (2025). https://doi.org/10.1080/14737175.2024.2439512

43 Espinosa-Jovel, C. *et al.* Real-world evidence on the use of cannabidiol for the treatment of drug resistant epilepsy not related to Lennox-Gastaut syndrome, Dravet syndrome or Tuberous Sclerosis Complex. *Seizure* **112**, 72-76 (2023). https://doi.org/10.1016/j.seizure.2023.09.015

44 Auvin, S., Nortvedt, C., Fuller, D. S. & Sahebkar, F. Seizure-free days as a novel outcome in patients with Lennox-Gastaut syndrome: Post hoc analysis of patients receiving cannabidiol in two randomized controlled trials. *Epilepsia* **64**, 1812-1820 (2023). https://doi.org/10.1111/epi.17618

45 Silvinato, A., Floriano, I. & Bernardo, W. M. Use of cannabidiol in the treatment of epilepsy: Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex. *Rev Assoc Med Bras (1992)* **68**, 1345-1357 (2022). https://doi.org/10.1590/1806-9282.2022d689

46 Volkow, N. D., Compton, W. M. & Weiss, S. R. Adverse health effects of marijuana use. *N Engl J Med* **371**, 878-879 (2014). https://doi.org/10.1056/NEJMc1407928

47 Reece, A. S. Chronic toxicology of cannabis. *Clin Toxicol (Phila)* **47**, 517-524 (2009). https://doi.org/10.1080/15563650903074507

48 Reece A.S. & Hulse G.K. in *Epidemiology of Cannabis: Genotoxicity and Neurotoxicity, Epigenomics and Aging* Vol. 1 (eds Reece A.S. & Hulse G.K.) Ch. 1-570, 570 (Elsevier, 2025).

49 Reece, A. S. & Hulse, G. K. Co-occurrence across time and space of drug- and cannabinoid- exposure and adverse mental health outcomes in the National Survey of Drug Use and Health: combined geotemporospatial and causal inference analysis. *BMC Public Health* **20**, 1655-1669 (2020). https://doi.org/10.1186/s12889-020-09748-5

50 Radio.US, W. t. P. *Shooters, Terrorists and Mass Killers who Used Marijuana (Month / Year)*, <https://www.wethepeopleradio.us/pot---shooter-list.html> (2022).

51 Mok, P. L. *et al.* Parental Psychiatric Disease and Risks of Attempted Suicide and Violent Criminal Offending in Offspring: A Population-Based Cohort Study. *JAMA Psychiatry* **73**, 1015-1022 (2016). https://doi.org/10.1001/jamapsychiatry.2016.1728

52 Miller N.S. & Oberbarnscheidt T. Marijuana Violence and Law. *Journal of Addiction Research & Therapy* **2017**, S11-S16 (2017).

53 Service, U. S. S. *US Secret Service Report on Mass Attacks in Public Places*, 2018).

54 Shorey, R. C. *et al.* Marijuana use is associated with intimate partner violence perpetration among men arrested for domestic violence. *Transl Issues Psychol Sci* **4**, 108-118 (2018). https://doi.org/10.1037/tps0000140

55 Dellazizzo, L. *et al.* Cannabis use and violence in patients with severe mental illnesses: A meta-analytical investigation. *Psychiatry Res* **274**, 42-48 (2019). https://doi.org/10.1016/j.psychres.2019.02.010

56 Devine M. *The link between pot and mass shootings may be closer than we think*, <https://calmca.org/calmcablog/2019/8/8/the-link-between-pot-and-mass-shootings-may-be-closer-than-we-think?ss_source=sscampaigns&ss_campaign_id=5d4c3f20755775398d1df26d&ss_email_id=5d4c4edcdf4ba44ca217c8db&ss_campaign_name=The+link+between+pot+and+mass+shootings+may+be+closer+than+we+think&ss_campaign_sent_date=2019-08-08T16%3A33%3A47Z> (2019).

57 Gobbi, G. *et al.* Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood: A Systematic Review and Meta-analysis. *JAMA Psychiatry* **76**, 426-434 (2019). https://doi.org/10.1001/jamapsychiatry.2018.4500

58 Miller, N. S., Ipeku, R. & Oberbarnscheidt, T. A Review of Cases of Marijuana and Violence. *Int J Environ Res Public Health* **17** (2020). https://doi.org/10.3390/ijerph17051578

59 Service, U. S. S. *US Secret Service Report on Mass Attacks in Public Places 2019*, <https://www.secretservice.gov/sites/default/files/reports/2020-09/MAPS2019.pdf> (2020).

60 Reece A. S. & Hulse G.K. Epidemiological Associations of Various Substances and Multiple Cannabinoids with Autism in USA. *Clinical Pediatrics: Open Access* **4**, 1-20 (2019). https://doi.org/10.24105/2572-0775.4.155

61 Reece A.S. & Hulse G.K. Effect of Cannabis Legalization on US Autism Incidence and Medium Term Projections. *Clinical Pediatrics: Open Access* **4**, 1-17 (2019). https://doi.org/10.4172/2572-0775.1000154

62 Reece, A. S. & Hulse, G. K. Gastroschisis and Autism-Dual Canaries in the Californian Coalmine. *JAMA Surg* **154**, 366-367 (2019). https://doi.org/10.1001/jamasurg.2018.4694

63 Reece A.S. & Hulse G.K. Impact of Converging Sociocultural and Substance-Related Trends on US Autism Rates: Combined Geospatiotemporal and Causal Inferential Analysis. *European Archives of Psychiatry and Clinial Neuroscience* **19**, 7726-7752 (2022). https://doi.org/10.1007/s00406-022-01446-0

64 Reece A.S. & Hulse G.K. in *Epidemiology of Cannabis: Genotoxicity and Neurotoxicity, Epigenomics and Aging* Vol. 1 (eds Reece A.S. & Hulse G.K.) Ch. 2, 570 (Elsevier, 2025).

65 Corsi, D. J. *et al.* Maternal cannabis use in pregnancy and child neurodevelopmental outcomes. *Nat Med* **26**, 1536-1540 (2020). https://doi.org/10.1038/s41591-020-1002-5

66 Fried, P. A. & Smith, A. M. A literature review of the consequences of prenatal marihuana exposure. An emerging theme of a deficiency in aspects of executive function. *Neurotoxicol Teratol* **23**, 1-11 (2001).

67 Fried, P., Watkinson, B., James, D. & Gray, R. Current and former marijuana use: preliminary findings of a longitudinal study of effects on IQ in young adults. *CMAJ* **166**, 887-891 (2002).

68 Smith, A., Fried, P., Hogan, M. & Cameron, I. The effects of prenatal and current marijuana exposure on response inhibition: a functional magnetic resonance imaging study. *Brain Cogn* **54**, 147-149 (2004).

69 Smith, A. M., Fried, P. A., Hogan, M. J. & Cameron, I. Effects of prenatal marijuana on response inhibition: an fMRI study of young adults. *Neurotoxicol Teratol* **26**, 533-542 (2004). https://doi.org/10.1016/j.ntt.2004.04.004

70 Fried, P. A., Watkinson, B. & Gray, R. Neurocognitive consequences of marihuana--a comparison with pre-drug performance. *Neurotoxicol Teratol* **27**, 231-239 (2005). https://doi.org/10.1016/j.ntt.2004.11.003

71 Porath, A. J. & Fried, P. A. Effects of prenatal cigarette and marijuana exposure on drug use among offspring. *Neurotoxicol Teratol* **27**, 267-277 (2005). https://doi.org/10.1016/j.ntt.2004.12.003

72 Smith, A. M., Fried, P. A., Hogan, M. J. & Cameron, I. Effects of prenatal marijuana on visuospatial working memory: an fMRI study in young adults. *Neurotoxicol Teratol* **28**, 286-295 (2006). https://doi.org/10.1016/j.ntt.2005.12.008

73 Smith, A. M., Longo, C. A., Fried, P. A., Hogan, M. J. & Cameron, I. Effects of marijuana on visuospatial working memory: an fMRI study in young adults. *Psychopharmacology (Berl)* **210**, 429-438 (2010). https://doi.org/10.1007/s00213-010-1841-8

74 Smith, A. M. *et al.* Prenatal marijuana exposure impacts executive functioning into young adulthood: An fMRI study. *Neurotoxicol Teratol* **58**, 53-59 (2016). https://doi.org/10.1016/j.ntt.2016.05.010

75 Brents L. in *Handbook of Cannabis and Related Pathologies: Biology, Pharmacology, Diagnosis and Treatment* Vol. 1 (ed Preedy V.R.) Ch. 17, 160-170 (Academic Press, 2017).

76 Baranger, D. A. A. *et al.* Association of Mental Health Burden With Prenatal Cannabis Exposure From Childhood to Early Adolescence: Longitudinal Findings From the Adolescent Brain Cognitive Development (ABCD) Study. *JAMA Pediatrics* **176**, 1261-1265 (2022). https://doi.org/10.1001/jamapediatrics.2022.3191

77 Lepow, L. *et al.* Independent and Interactive Impacts of Prenatal Exposure to Legal Substances and Childhood Trauma on Emotion Processing in Pre-Adolescents:

Preliminary Findings From the ABCD Study. *JAACAP Open* **2**, 274-289 (2024). https://doi.org/10.1016/j.jaacop.2024.04.009

78 Paul, S. E. *et al.* Associations Between Prenatal Cannabis Exposure and Childhood Outcomes: Results From the ABCD Study. *JAMA Psychiatry* **78**, 64-76 (2021). https://doi.org/10.1001/jamapsychiatry.2020.2902

79 Banerjee, S. *et al.* Phytocannabinoids in neuromodulation: From omics to epigenetics. *J Ethnopharmacol* **330**, 118201 (2024). https://doi.org/10.1016/j.jep.2024.118201

80 Bortoletto, R. & Colizzi, M. Cannabis Use in Autism: Reasons for Concern about Risk for Psychosis. *Healthcare (Basel)* **10** (2022). https://doi.org/10.3390/healthcare10081553

81 Colizzi, M., Bortoletto, R., Costa, R., Bhattacharyya, S. & Balestrieri, M. The Autism-Psychosis Continuum Conundrum: Exploring the Role of the Endocannabinoid System. *Int J Environ Res Public Health* **19** (2022). https://doi.org/10.3390/ijerph19095616

82 Murphy, S. K. *et al.* Cannabinoid exposure and altered DNA methylation in rat and human sperm. *Epigenetics* **13**, 1208-1221 (2018). https://doi.org/10.1080/15592294.2018.1554521

83 Noble, A. J., Adams, A. T., Satsangi, J., Boden, J. M. & Osborne, A. J. Prenatal cannabis exposure is associated with alterations in offspring DNA methylation at genes involved in neurodevelopment, across the life course. *Mol Psychiatry* (2024). https://doi.org/10.1038/s41380-024-02752-w

84 Reece, A. S. & Hulse, G. K. Impacts of cannabinoid epigenetics on human development: reflections on Murphy et. al. 'cannabinoid exposure and altered DNA methylation in rat and human sperm' epigenetics 2018; 13: 1208-1221. *Epigenetics* **14**, 1041-1056 (2019). https://doi.org/10.1080/15592294.2019.1633868

85 Schrott, R. *et al.* Cannabis use is associated with potentially heritable widespread changes in autism candidate gene DLGAP2 DNA methylation in sperm. *Epigenetics* **15**, 161-173 (2020). https://doi.org/10.1080/15592294.2019.1656158

86 Schrott, R. *et al.* Cannabis alters DNA methylation at maternally imprinted and autism candidate genes in spermatogenic cells. *Syst Biol Reprod Med* **68**, 357-369 (2022). https://doi.org/10.1080/19396368.2022.2073292

87 Schrott, R. *et al.* Sperm DNA methylation alterations from cannabis extract exposure are evident in offspring. *Epigenetics Chromatin* **15**, 33 (2022). https://doi.org/10.1186/s13072-022-00466-3

88 Schrott, R. *et al.* Refraining from use diminishes cannabis-associated epigenetic changes in human sperm. *Environ Epigenet* **7**, dvab009 (2021). https://doi.org/10.1093/eep/dvab009

89 Schrott, R. *et al.* Sperm DNA methylation altered by THC and nicotine: Vulnerability of neurodevelopmental genes with bivalent chromatin. *Sci Rep* **10**, 16022 (2020). https://doi.org/10.1038/s41598-020-72783-0

90 Shorey-Kendrick, L. E. *et al.* Prenatal delta-9-tetrahydrocannabinol exposure is associated with changes in rhesus macaque DNA methylation enriched for autism genes. *Clin Epigenetics* **15**, 104 (2023). https://doi.org/10.1186/s13148-023-01519-4

91 Smith, A., Kaufman, F., Sandy, M. S. & Cardenas, A. Cannabis Exposure During Critical Windows of Development: Epigenetic and Molecular Pathways Implicated in Neuropsychiatric Disease. *Curr Environ Health Rep* **7**, 325-342 (2020). https://doi.org/10.1007/s40572-020-00275-4

92 Besseling, R. *et al.* Functional network abnormalities consistent with behavioral profile in Autism Spectrum Disorder. *Psychiatry Res Neuroimaging* **275**, 43-48 (2018). https://doi.org/10.1016/j.pscychresns.2018.02.006

93 Brose, N., O'Connor, V. & Skehel, P. Synaptopathy: dysfunction of synaptic function? *Biochemical Society transactions* **38**, 443-444 (2010). https://doi.org/10.1042/BST0380443

94 Christensen, D. L. *et al.* Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years--Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. *MMWR Surveill Summ* **65**, 1-23 (2016). https://doi.org/10.15585/mmwr.ss6503a1

95 Dolen, G. & Sahin, M. Editorial: Essential Pathways and Circuits of Autism Pathogenesis. *Front Neurosci* **10**, 182 (2016). https://doi.org/10.3389/fnins.2016.00182

96 Kang, J., Park, H. & Kim, E. IRSp53/BAIAP2 in dendritic spine development, NMDA receptor regulation, and psychiatric disorders. *Neuropharmacology* **100**, 27-39 (2016). https://doi.org/10.1016/j.neuropharm.2015.06.019

97 Keil, K. P. & Lein, P. J. DNA methylation: a mechanism linking environmental chemical exposures to risk of autism spectrum disorders? *Environmental Epigenetics* **2** (2016). https://doi.org/10.1093/eep/dvv012

98 Lorenzetti, V., Solowij, N. & Yucel, M. The Role of Cannabinoids in Neuroanatomic Alterations in Cannabis Users. *Biol Psychiatry* **79**, e17-31 (2016). https://doi.org/10.1016/j.biopsych.2015.11.013

99 McKowen, J. *et al.* Characterizing autistic traits in treatment-seeking young adults with substance use disorders. *The American Journal on Addictions* **n/a** https://doi.org/https://doi.org/10.1111/ajad.13247

100 Noroozi, R. *et al.* Glutamate receptor, metabotropic 7 (GRM7) gene variations and susceptibility to autism: A case-control study. *Autism Res* **9**, 1161-1168 (2016). https://doi.org/10.1002/aur.1640

101 Oliveira, B., Mitjans, M., Nitsche, M. A., Kuo, M. F. & Ehrenreich, H. Excitation-inhibition dysbalance as predictor of autistic phenotypes. *J Psychiatr Res* **104**, 96-99 (2018). https://doi.org/10.1016/j.jpsychires.2018.06.004

102 Radyushkin, K. *et al.* Neuroligin-3-deficient mice: model of a monogenic heritable form of autism with an olfactory deficit. *Genes Brain Behav* **8**, 416-425 (2009). https://doi.org/10.1111/j.1601-183X.2009.00487.x

103 Schrott, R. *et al.* Cannabis alters DNA methylation at maternally imprinted and autism candidate genes in spermatogenic cells. *Syst Biol Reprod Med*, 1-13 (2022). https://doi.org/10.1080/19396368.2022.2073292

104 Won, H., Mah, W. & Kim, E. Autism spectrum disorder causes, mechanisms, and treatments: focus on neuronal synapses. *Front Mol Neurosci* **6**, 19 (2013). https://doi.org/10.3389/fnmol.2013.00019

105 Anderson, G. R. *et al.* beta-Neurexins Control Neural Circuits by Regulating Synaptic Endocannabinoid Signaling. *Cell* **162**, 593-606 (2015). https://doi.org/10.1016/j.cell.2015.06.056

106 Hishimoto, A. *et al.* Neurexin 3 polymorphisms are associated with alcohol dependence and altered expression of specific isoforms. *Hum Mol Genet* **16**, 2880-2891 (2007). https://doi.org/ddm247 [pii]
10.1093/hmg/ddm247

107 Wang, H. Endocannabinoid Mediates Excitatory Synaptic Function of β-Neurexins. Commentary: β-Neurexins Control Neural Circuits by Regulating Synaptic Endocannabinoid Signaling. *Frontiers in Neuroscience* **10** (2016). https://doi.org/10.3389/fnins.2016.00203

108 Foldy, C., Malenka, R. C. & Sudhof, T. C. Autism-associated neuroligin-3 mutations commonly disrupt tonic endocannabinoid signaling. *Neuron* **78**, 498-509 (2013). https://doi.org/10.1016/j.neuron.2013.02.036

109 Sun, C., Zhang, L. & Chen, G. An unexpected role of neuroligin-2 in regulating KCC2 and GABA functional switch. *Mol Brain* **6**, 23 (2013). https://doi.org/1756-6606-6-23 [pii]
10.1186/1756-6606-6-23

110 Shibata, M. *et al.* Regulation of prefrontal patterning and connectivity by retinoic acid. *Nature* **598**, 483-488 (2021). https://doi.org/10.1038/s41586-021-03953-x

111 Ziffra, R. S. *et al.* Single-cell epigenomics reveals mechanisms of human cortical development. *Nature* **598**, 205-213 (2021). https://doi.org/10.1038/s41586-021-03209-8

112 Alpar, A. *et al.* Endocannabinoids modulate cortical development by configuring Slit2/Robo1 signalling. *Nat Commun* **5**, 4421 (2014). https://doi.org/10.1038/ncomms5421

113 Cardenas, A. *et al.* Evolution of Cortical Neurogenesis in Amniotes Controlled by Robo Signaling Levels. *Cell* **174**, 590-606 e521 (2018). https://doi.org/10.1016/j.cell.2018.06.007

114 Yeh, M. L. *et al.* Robo1 modulates proliferation and neurogenesis in the developing neocortex. *J Neurosci* **34**, 5717-5731 (2014). https://doi.org/10.1523/JNEUROSCI.4256-13.2014

115 London, N. R. & Li, D. Y. Robo4-dependent Slit signaling stabilizes the vasculature during pathologic angiogenesis and cytokine storm. *Curr Opin Hematol* **18**, 186-190 (2011). https://doi.org/10.1097/MOH.0b013e328345a4b9

116 Carlson, B. M. *Human Embryology and Developmental Biology*. 6 edn, Vol. 1 1-506 (Elsevier, 2019).

117 Tortoriello, G. *et al.* Miswiring the brain: Δ9-tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway. *Embo j* **33**, 668-685 (2014). https://doi.org/10.1002/embj.201386035

118 Reece A.S. & Hulse G.K. European Epidemiological Patterns of Cannabis- and Substance- Related Congenital Neurological Anomalies: Geospatiotemporal and Causal Inferential Study. *International Journal of Environmental Research and Public Health* **20**, 441-475 (2022).

119 Zalesky, A. *et al.* Effect of long-term cannabis use on axonal fibre connectivity. *Brain* **135**, 2245-2255 (2012). https://doi.org/aws136 [pii]
10.1093/brain/aws136

120 Lynskey, M. T., Fergusson, D. M. & Horwood, L. J. The origins of the correlations between tobacco, alcohol, and cannabis use during adolescence. *Journal of child psychology and psychiatry, and allied disciplines* **39**, 995-1005 (1998).

121 Fergusson, D. M., Horwood, L. J. & Swain-Campbell, N. Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction* **97**, 1123-1135 (2002). https://doi.org/103 [pii]

122 Fergusson, D. M., Horwood, L. J. & Beautrais, A. L. Cannabis and educational achievement. *Addiction* **98**, 1681-1692 (2003). https://doi.org/573 [pii]

123 Fergusson, D. M., Horwood, L. J., Lynskey, M. T. & Madden, P. A. Early reactions to cannabis predict later dependence. *Arch Gen Psychiatry* **60**, 1033-1039 (2003). https://doi.org/10.1001/archpsyc.60.10.1033
60/10/1033 [pii]

124 Fergusson, D. M., Swain-Campbell, N. R. & Horwood, L. J. Arrests and convictions for cannabis related offences in a New Zealand birth cohort. *Drug Alcohol Depend* **70**, 53-63 (2003). https://doi.org/S0376871602003368 [pii]
125 Fergusson, D. M., Boden, J. M. & Horwood, L. J. Cannabis use and other illicit drug use: testing the cannabis gateway hypothesis. *Addiction* **101**, 556-569 (2006).
126 Fergusson, D. M. & Boden, J. M. Cannabis use and later life outcomes. *Addiction* **103**, 969-976; discussion 977-968 (2008). https://doi.org/ADD2221 [pii]
10.1111/j.1360-0443.2008.02221.x
127 Marie, D., Fergusson, D. M. & Boden, J. M. Links between ethnic identification, cannabis use and dependence, and life outcomes in a New Zealand birth cohort. *The Australian and New Zealand journal of psychiatry* **42**, 780-788 (2008). https://doi.org/901464301 [pii]
10.1080/00048670802277289
128 Le Strat, Y. *et al.* First positive reactions to cannabis constitute a priority risk factor for cannabis dependence. *Addiction* **104**, 1710-1717 (2009). https://doi.org/ADD2680 [pii]
10.1111/j.1360-0443.2009.02680.x
129 Horwood, L. J. *et al.* Cannabis use and educational achievement: findings from three Australasian cohort studies. *Drug Alcohol Depend* **110**, 247-253 (2010). https://doi.org/S0376-8716(10)00109-2 [pii]
10.1016/j.drugalcdep.2010.03.008
130 Swain, N. R., Gibb, S. J., Horwood, L. J. & Fergusson, D. M. Alcohol and cannabis abuse/dependence symptoms and life satisfaction in young adulthood. *Drug and alcohol review* **31**, 327-333 (2012). https://doi.org/10.1111/j.1465-3362.2011.00339.x
131 Fergusson, D. M., Boden, J. M. & Horwood, L. J. Psychosocial sequelae of cannabis use and implications for policy: findings from the Christchurch Health and Development Study. *Social psychiatry and psychiatric epidemiology* **50**, 1317-1326 (2015). https://doi.org/10.1007/s00127-015-1070-x
132 Hall, W. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? *Addiction* **110**, 19-35 (2015). https://doi.org/10.1111/add.12703
133 Menahem S. in *Handbook of Cannabis and Related Pathologies* Vol. 1 (ed Preedy V.) Ch. 50, 481-485 (Elsevier, 2017).
134 Reece A.S. Rapid Response: Cannabinoid Genotoxic Trifecta - Cancerogenesis, Clinical Teratogenesis and Cellular Ageing. *British Medical Journal* **376**, n3114 Rapid Response (2022). https://doi.org/ https://doi.org/10.1136/bmj.n3114
135 Reece A.S. & Hulse G.K. Epidemiological Overview of Multidimensional Chromosomal and Genome Toxicity of Cannabis Exposure in Congenital Anomalies and Cancer Development *Scientific Reports* **11**, 13892-13912 (2021). https://doi.org/10.10389/s41598-021-93411-5
136 Reece A.S. & Hulse G.K. Geotemporospatial and Causal Inferential Epidemiological Overview and Survey of USA Cannabis, Cannabidiol and Cannabinoid Genotoxicity Expressed in Cancer Incidence 2003–2017: Part 1 – Continuous Bivariate Analysis. *Archives of Public Health* **80**, 99-133 (2022). https://doi.org/doi.org/10.1186/s13690-022-00811-8
137 Reece A.S. & Hulse G.K. Geotemporospatial and Causal Inferential Epidemiological Overview and Survey of USA Cannabis, Cannabidiol and Cannabinoid Genotoxicity Expressed in Cancer Incidence 2003–2017: Part 2 – Categorical Bivariate Analysis and Attributable Fractions. *Archives of Public Health* **80**, 100-135 (2022). https://doi.org/doi.org/10.1186/s13690-022-00812-7

138 Reece A.S. & Hulse G.K. Geotemporospatial and Causal Inferential Epidemiological Overview and Survey of USA Cannabis, Cannabidiol and Cannabinoid Genotoxicity Expressed in Cancer Incidence 2003–2017: Part 3 – Spatiotemporal, Multivariable and Causal Inferential Pathfinding and Exploratory Analyses of Prostate and Ovarian Cancers. *Archives of Public Health* **80**, 100-136 (2022). https://doi.org/doi.org/10.1186/s13690-022-00813-6

139 Reece A.S. & Hulse G.K. Geospatiotemporal and Causal Inference Study of Cannabis and Other Drugs as Risk Factors for Female Breast Cancer USA 2003-2017. *Environmental Epigenetics* **2022**, 1-22 (2022).

140 Reece A.S. & Hulse G.K. Novel Insights into Potential Cannabis-Related Cancerogenesis from Recent Key Whole Epigenome Screen of Cannabis Dependence and Withdrawal: Epidemiological Comment and Explication of Schrott et.al. *Genes (Basel)* **14**, 1-14 (2022).

141 Reece A.S. & Hulse G.K. State Trends of Cannabis Liberalization as a Causal Driver of Increasing Testicular Cancer Rates across the USA. *International Journal of Environmental Research and Public Health* **19**, 12759 – 12796 (2022).

142 Reece A.S. & Hulse G.K. in *Cannabis, Cannabinoids and Endocannabinoids* Vol. 1 (eds BMartin C.R., Preedy. V., & Patel V.) Ch. 5, 570 (Elsevier, 2023).

143 Reece A.S. & Hulse G.K. Clinical Epigenomic Explanation of the Epidemiology of Cannabinoid Genotoxicity Manifesting as Transgenerational Teratogenesis, Cancerogenesis and Aging Acceleration. *International Journal of Environmental Research and Public Health* **20**, 3360-3383 (2023).

144 Reece , A. S. Cannabinoid Genotoxic Trifecta - Cancerogenesis, Clinical Teratogenesis and Cellular Ageing. *British Medical Journal* **376**, n3114 (2022). https://doi.org/https://doi.org/10.1136/bmj.n3114

145 Reece, A. S. & Hulse, G. K. A geospatiotemporal and causal inference epidemiological exploration of substance and cannabinoid exposure as drivers of rising US pediatric cancer rates. *BMC Cancer* **21**, 197-230 (2021). https://doi.org/10.1186/s12885-021-07924-3

146 Reece, A. S. & Hulse, G. K. Causal inference multiple imputation investigation of the impact of cannabinoids and other substances on ethnic differentials in US testicular cancer incidence. *BMC Pharmacol Toxicol* **22**, 40-71 (2021). https://doi.org/10.1186/s40360-021-00505-x

147 Reece, A. S. & Hulse, G. K. Sociodemographically Stratified Exploration of Pancreatic Cancer Incidence in Younger US Patients: Implication of Cannabis Exposure as a Risk Factor. *Gastroenterology Insights* **14**, 204-235 (2023).

148 Reece A.S. & Hulse G.K. Cannabis- and Substance-Related Carcinogenesis in Europe: A Lagged Causal Inferential Panel Regression Modelling Study. *Journal of Xenobiotics* **13**, 323-385 (2023).

149 Reece A.S. & Hulse G.K. Cannabis Could Be the Missing Environmental Carcinogen Hiding in Plain View. *Gastroenterology* **165**, 1092-1093 (2023). https://doi.org/https://doi.org/10.1053/j.gastro.2023.02.050

150 Reece A.S. & Hulse G.K. in *Epidemiology of Cannabis: Genotoxicity and Neurotoxicity, Epigenomics and Aging* Vol. 1 (eds Reece A.S. & Hulse G.K.) Ch. 4, 570 (Elsevier, 2025).

151 Reece A.S. & Hulse G.K. in *Epidemiology of Cannabis: Genotoxicity and Neurotoxicity, Epigenomics and Aging* Vol. 1 Ch. 1-2500, 2500 (Elsevier, In Press).

152 Reece, A. S. & Hulse, G. K. Chromothripsis and epigenomics complete causality criteria for cannabis- and addiction-connected carcinogenicity, congenital toxicity and

heritable genotoxicity. *Mutat Res* **789**, 15-25 (2016). https://doi.org/10.1016/j.mrfmmm.2016.05.002

153 Reece, A. S. & Hulse, G. K. Epidemiology of Δ8THC-Related Carcinogenesis in USA: A Panel Regression and Causal Inferential Study. *International Journal of Environmental Research and Public Health* **19**, 7726-7752 (2022).

154 Grobner, S. N. *et al.* The landscape of genomic alterations across childhood cancers. *Nature* **555**, 321-327 (2018). https://doi.org/10.1038/nature25480

155 Ma, X. *et al.* Pan-cancer genome and transcriptome analyses of 1,699 paediatric leukaemias and solid tumours. *Nature* **555**, 371-376 (2018). https://doi.org/10.1038/nature25795

156 Reece, A. S. & Hulse, G. K. Cannabis Could Be the Missing Environmental Carcinogen Hiding in Plain View. *Gastroenterology* **165**, 1092-1093 (2023). https://doi.org/10.1053/j.gastro.2023.02.050

157 Phillips, K. T. *et al.* Chronic health conditions, acute health events, and healthcare utilization among adults over age 50 in Hawai'i who use cannabis: A matched cohort study. *Drug Alcohol Depend* **234**, 109387 (2022). https://doi.org/10.1016/j.drugalcdep.2022.109387

158 Reece, A. S., Norman, A. & Hulse, G. K. Cannabis exposure as an interactive cardiovascular risk factor and accelerant of organismal ageing: a longitudinal study. *BMJ Open* **6**, e011891-e011901 (2016). https://doi.org/10.1136/bmjopen-2016-011891

159 Patsenker, E. & Stickel, F. Cannabinoids in liver diseases. *Clin Liver Dis (Hoboken)* **7**, 21-25 (2016). https://doi.org/10.1002/cld.527

160 NIDA. Marijuana effects on the endocrine and reproductive systems. *NIDA Res Monogr* **44**, 1-130 (1984).

161 Borowska, M. *et al.* The effects of cannabinoids on the endocrine system. *Endokrynol Pol* **69**, 705-719 (2018). https://doi.org/10.5603/EP.a2018.0072

162 Morishima, A. Effects of cannabis and natural cannabinoids on chromosomes and ova. *NIDA Res Monogr* **44**, 25-45 (1984).

163 Rossato, M., Pagano, C. & Vettor, R. The cannabinoid system and male reproductive functions. *Journal of neuroendocrinology* **20 Suppl 1**, 90-93 (2008).

164 Rossato, M., Ion Popa, F., Ferigo, M., Clari, G. & Foresta, C. Human sperm express cannabinoid receptor Cb1, the activation of which inhibits motility, acrosome reaction, and mitochondrial function. *The Journal of clinical endocrinology and metabolism* **90**, 984-991 (2005). https://doi.org/10.1210/jc.2004-1287

165 Chioccarelli, T. *et al.* Cannabinoid receptor 1 influences chromatin remodeling in mouse spermatids by affecting content of transition protein 2 mRNA and histone displacement. *Endocrinology* **151**, 5017-5029 (2010). https://doi.org/10.1210/en.2010-0133

166 Chioccarelli, T. *et al.* The Cannabinoid Receptor CB1 Stabilizes Sperm Chromatin Condensation Status During Epididymal Transit by Promoting Disulphide Bond Formation. *Int J Mol Sci* **21** (2020). https://doi.org/10.3390/ijms21093117

167 Zimmerman A.M., Zimmerman S. & Raj A.Y. in *Marijuana and Medicine* Vol. 1 (eds G. G. Nahas, Sutin K.M., Harvey D.J., & Agurell S.) Ch. 27, 347-358 (Humana Press, 1999).

168 Huang H.F.S., Nahas G.G. & Hembree W.C. in *Marijuana in Medicine* Vol. 1 (eds G. G. Nahas, Sutin K.M., Harvey D.J., & Agurell S.) Ch. 28, 359-366 (Human Press 1999).

169 Schrott, R. *et al.* Refraining from use diminishes cannabis-associated epigenetic changes in human sperm. *Environmental Epigenetics* **7**, 1-10 (2021). https://doi.org/10.1093/eep/dvab009

170 Watson, C. T. *et al.* Genome-Wide DNA Methylation Profiling Reveals Epigenetic Changes in the Rat Nucleus Accumbens Associated With Cross-Generational Effects of Adolescent THC Exposure. *Neuropsychopharmacology* **40**, 2993-3005 (2015). https://doi.org/10.1038/npp.2015.155

171 Dempster, E. L. *et al.* Methylomic signature of current cannabis use in two first-episode psychosis cohorts. *Mol Psychiatry* (2024). https://doi.org/10.1038/s41380-024-02689-0

172 Allen, J. P. *et al.* Lifetime marijuana use and epigenetic age acceleration: A 17-year prospective examination. *Drug and Alcohol Dependence* **233**, 109363 (2022). https://doi.org/https://doi.org/10.1016/j.drugalcdep.2022.109363

173 Powers V. *Marijuana addiction and overdose in texas*, <https://www.utphysicians.com/marijuana-addiction-and-overdose-in-texas/> (2023).

174 Bleyer, A., Barnes, B., Stuyt, E., Voth, E. A. & Finn, K. Cannabis and the overdose crisis among US adolescents. *Am J Addict* (2024). https://doi.org/10.1111/ajad.13669

175 Tweet, M. S., Nemanich, A. & Wahl, M. Pediatric Edible Cannabis Exposures and Acute Toxicity: 2017-2021. *Pediatrics* **151** (2023). https://doi.org/10.1542/peds.2022-057761

176 Stoner, M. J. *et al.* Marijuana use in children: An update focusing on pediatric tetrahydrocannabinol and cannabidiol use. *J Am Coll Emerg Physicians Open* **3**, e12770 (2022). https://doi.org/10.1002/emp2.12770

177 Wang, G. S. *et al.* Unintentional Pediatric Exposures to Marijuana in Colorado, 2009-2015. *JAMA Pediatr* **170**, e160971 (2016). https://doi.org/10.1001/jamapediatrics.2016.0971

178 Roberts, B. A. Legalized Cannabis in Colorado Emergency Departments: A Cautionary Review of Negative Health and Safety Effects. *West J Emerg Med* **20**, 557-572 (2019). https://doi.org/10.5811/westjem.2019.4.39935

179 Hughes V. Epigenetics: The Sins of the Father. *Nature* **507**, 22-24 (2014).

180 Blevins R.D. & Regan J.D. in *Marihunana: Chemistry, Biochemistry and Cellular Effects* Vol. 1 (eds Nahas G.G., Paton W.D.M., & Idanpaan-Heikkla J.E.) Ch. 19, 213-222 (Springer-Verlag, 1976).

181 Blevins, R. D. & Regan, J. D. delta-9-Tetrahydrocannabinol: effect on macromolecular synthesis in human and other mammalian cells. *Archives of toxicology* **35**, 127-135 (1976).

182 Carchman, R. A., Harris, L. S. & Munson, A. E. The inhibition of DNA synthesis by cannabinoids. *Cancer Res* **36**, 95-100 (1976).

183 Huot J. in *Marihunana: Chemistry, Biochemistry and Cellular Effects* Vol. 1 (eds Nahas G.G., Paton W.D.M., & Idanpaan-Heikkla J.E.) Ch. 27, 313-328 (Springer-Verlag, 1976).

184 Jakubovic A. & McGeer P.L. in *Marihunana: Chemistry, Biochemistry and Cellular Effects* Vol. 1 (eds Nahas G.G., Paton W.D.M., & Idanpaan-Heikkla J.E.) Ch. 20, 223-242 (Springer-Verlag, 1976).

185 Jung, K. M. *et al.* Uncoupling of the endocannabinoid signalling complex in a mouse model of fragile X syndrome. *Nat Commun* **3**, 1080 (2012). https://doi.org/10.1038/ncomms2045

186 McClean, D. K. & Zimmerman, A. M. Action of delta 9-tetrahydrocannabinol on cell division and macromolecular synthesis in division-synchronized protozoa. *Pharmacology* **14**, 307-321 (1976).

187 Mon, M. J., Haas, A. E., Stein, J. L. & Stein, G. S. Influence of psychoactive and nonpsychoactive cannabinoids on cell proliferation and macromolecular biosynthesis in human cells. *Biochemical pharmacology* **30**, 31-43 (1981). https://doi.org/10.1016/0006-2952(81)90281-1

188 Mon, M. J., Jansing, R. L., Doggett, S., Stein, J. L. & Stein, G. S. Influence of delta9-tetrahydrocannabinol on cell proliferation and macromolecular biosynthesis in human cells. *Biochemical pharmacology* **27**, 1759-1765 (1978).

189 Nahas G.G., Desoize B., Hsu J. & Morishima A. in *Marihunana: Chemistry, Biochemistry and Cellular Effects* Vol. 1 (eds Nahas G.G., Paton W.D.M., & Idanpaan-Heikkla J.E.) Ch. 26, 299-312 (Springer-Verlag, 1976).

190 Thomas, J., Tilak, S., Zimmerman, S. & Zimmerman, A. M. Action of delta 9-tetrahydrocannabinol on the pool of acid soluble nucleotides. *Cytobios* **40**, 71-85 (1984).

191 Zimmerman A.M. & Zimmerman S.B. in *Marihunana: Chemistry, Biochemistry and Cellular Effects* Vol. 1 (eds Nahas G.G., Paton W.D.M., & Idanpaan-Heikkla J.E.) Ch. 17, 195-206 (Springer-Verlag, 1976).

192 Zimmerman, S. & Zimmerman, A. M. Genetic effects of marijuana. *The International journal of the addictions* **25**, 19-33 (1990).

193 Perez-Reyes M. *et al.* in *Marihunana: Chemistry, Biochemistry and Cellular Effects* Vol. 1 (eds Nahas G.G., Paton W.D.M., & Idanpaan-Heikkla J.E.) Ch. 15, 179-186 (Springer-Verlag, 1976).

194 Gilmour, D. G., Bloom, A. D., Lele, K. P., Robbins, E. S. & Maximilian, C. Chromosomal aberrations in users of psychoactive drugs. *Arch Gen Psychiatry* **24**, 268-272 (1971). https://doi.org/10.1001/archpsyc.1971.01750090074011

195 Leuchtenberger, C. & Leuchtenberger, R. Morphological and cytochemical effects of marijuana cigarette smoke on epithelioid cells of lung explants from mice. *Nature* **234**, 227-229 (1971). https://doi.org/10.1038/234227a0

196 Leuchtenberger, C., Leuchtenberger, R. & Schneider, A. Effects of marijuana and tobacco smoke on human lung physiology. *Nature* **241**, 137-139 (1973). https://doi.org/10.1038/241137a0

197 Stenchever, M. A., Kunysz, T. J. & Allen, M. A. Chromosome breakage in users of marihuana. *Am J Obstet Gynecol* **118**, 106-113 (1974). https://doi.org/10.1016/s0002-9378(16)33653-5

198 Russo, C. *et al.* Low doses of widely consumed cannabinoids (cannabidiol and cannabidivarin) cause DNA damage and chromosomal aberrations in human-derived cells. *Archives of toxicology* **93**, 179-188 (2019). https://doi.org/10.1007/s00204-018-2322-9

199 Zimmerman, A. M., Zimmerman S., Raj A.Y. in *Marihuana and medicine* (eds Nahas G.G., Sutin K.M., Harvey D.J., & Agurell S.) Ch. 27, 347-358 (Humana Press, 1999).

200 Hall, W. & Degenhardt, L. Adverse health effects of non-medical cannabis use. *Lancet* **374**, 1383-1391 (2009). https://doi.org/S0140-6736(09)61037-0 [pii]
10.1016/S0140-6736(09)61037-0

201 Fenech, M. *et al.* Molecular mechanisms of micronucleus, nucleoplasmic bridge and nuclear bud formation in mammalian and human cells. *Mutagenesis* **26**, 125-132 (2011). https://doi.org/10.1093/mutage/geq052

202 Knouse, K. A. & Amon, A. Cell biology: The micronucleus gets its big break. *Nature* **522**, 162-163 (2015). https://doi.org/10.1038/nature14528

203 Waldron, D. Genome stability: Chromothripsis and micronucleus formation. *Nat Rev Genet* **16**, 376-377 (2015). https://doi.org/10.1038/nrg3970

204 Zhang, C. Z. *et al.* Chromothripsis from DNA damage in micronuclei. *Nature* **522**, 179-184 (2015). https://doi.org/10.1038/nature14493

205 Mackenzie, K. J. *et al.* cGAS surveillance of micronuclei links genome instability to innate immunity. *Nature* **548**, 461-465 (2017). https://doi.org/10.1038/nature23449

206 Terradas, M., Martín, M. & Genescà, A. Detection of Impaired DNA Replication and Repair in Micronuclei as Indicators of Genomic Instability and Chromothripsis. *Methods Mol Biol* **1769**, 197-208 (2018). https://doi.org/10.1007/978-1-4939-7780-2_13

207 Fenech, M. *et al.* Micronuclei as biomarkers of DNA damage, aneuploidy, inducers of chromosomal hypermutation and as sources of pro-inflammatory DNA in humans. *Mutat Res* **786**, 108342 (2020). https://doi.org/10.1016/j.mrrev.2020.108342

208 Di Bona, M. *et al.* Micronuclear collapse from oxidative damage. *Science* **385**, eadj8691 (2024). https://doi.org/doi:10.1126/science.adj8691

209 Maddaluno, M. & Settembre, C. Micronuclear collapse mechanisms in cancer. *Science* **385**, 930-931 (2024). https://doi.org/10.1126/science.adr7417

210 Martin, S. *et al.* A p62-dependent rheostat dictates micronuclei catastrophe and chromosome rearrangements. *Science* **385**, eadj7446 (2024). https://doi.org/doi:10.1126/science.adj7446

211 Mon, M. J., Haas, A. E., Stein, J. L. & Stein, G. S. Influence of psychoactive and nonpsychoactive cannabinoids on chromatin structure and function in human cells. *Biochemical pharmacology* **30**, 45-58 (1981). https://doi.org/10.1016/0006-2952(81)90282-3

212 Stefanis C.N. & Issidorides M.R. in *Marihunana: Chemistry, Biochemistry and Cellular Effects* Vol. 1 (eds Nahas G.G., Paton W.D.M., & Idanpaan-Heikkla J.E.) Ch. 43, 533-550 (Springer-Verlag, 1976).

213 Morishima A., Henrich R., Jou S. & Nahas G.G. in *Marihunana: Chemistry, Biochemistry and Cellular Effects* Vol. 1 (eds Nahas G.G., Paton W.D.M., & Idanpaan-Heikkla J.E.) Ch. 23, 265-273 (Springer-Verlag, 1976).

214 Henrich, R. T., Nogawa, T. & Morishima, A. In vitro induction of segregational errors of chromosomes by natural cannabinoids in normal human lymphocytes. *Environ Mutagen* **2**, 139-147 (1980).

215 Green, K., Symonds, C. M., Oliver, N. W. & Elijah, R. D. Intraocular pressure following systemic administration of cannabinoids. *Current eye research* **2**, 247-253 (1982). https://doi.org/10.3109/02713688209011626

216 McClanahan, R. H. & Robertson, L. W. Biotransformation of olivetol by Syncephalastrum racemosum. *Journal of natural products* **47**, 828-834 (1984). https://doi.org/10.1021/np50035a013

217 Appendino, G. *et al.* Antibacterial cannabinoids from Cannabis sativa: a structure-activity study. *Journal of natural products* **71**, 1427-1430 (2008). https://doi.org/10.1021/np8002673

218 Brizzi, A. *et al.* Synthetic bioactive olivetol-related amides: The influence of the phenolic group in cannabinoid receptor activity. *Bioorganic & medicinal chemistry* **28**, 115513 (2020). https://doi.org/10.1016/j.bmc.2020.115513

219 Fisar, Z., Singh, N. & Hroudova, J. Cannabinoid-induced changes in respiration of brain mitochondria. *Toxicology letters* **231**, 62-71 (2014). https://doi.org/10.1016/j.toxlet.2014.09.002

220 Bino, T., Chari-Bitron, A. & Shahar, A. Biochemical effects and morphological changes in rat liver mitochondria exposed to 1 -tetrahydrocannabinol. *Biochim Biophys Acta* **288**, 195-202 (1972). https://doi.org/10.1016/0005-2736(72)90238-6

221 Ryan, D., Drysdale, A. J., Lafourcade, C., Pertwee, R. G. & Platt, B. Cannabidiol targets mitochondria to regulate intracellular Ca2+ levels. *J Neurosci* **29**, 2053-2063 (2009). https://doi.org/10.1523/jneurosci.4212-08.2009

222 Wu, H. Y., Huang, C. H., Lin, Y. H., Wang, C. C. & Jan, T. R. Cannabidiol induced apoptosis in human monocytes through mitochondrial permeability transition pore-mediated ROS production. *Free Radic Biol Med* **124**, 311-318 (2018). https://doi.org/10.1016/j.freeradbiomed.2018.06.023

223 Winklmayr, M. *et al.* Dose-Dependent Cannabidiol-Induced Elevation of Intracellular Calcium and Apoptosis in Human Articular Chondrocytes. *J Orthop Res* **37**, 2540-2549 (2019). https://doi.org/10.1002/jor.24430

224 Olivas-Aguirre, M., Torres-López, L., Pottosin, I. & Dobrovinskaya, O. Phenolic Compounds Cannabidiol, Curcumin and Quercetin Cause Mitochondrial Dysfunction and Suppress Acute Lymphoblastic Leukemia Cells. *Int J Mol Sci* **22** (2020). https://doi.org/10.3390/ijms22010204

225 Chan, J. Z. & Duncan, R. E. Regulatory Effects of Cannabidiol on Mitochondrial Functions: A Review. *Cells* **10**, 1251 (2021). https://doi.org/10.3390/cells10051251

226 Drummond-Main, C. D. *et al.* Cannabidiol Impairs Brain Mitochondrial Metabolism and Neuronal Integrity. *Cannabis Cannabinoid Res* (2022). https://doi.org/10.1089/can.2022.0011

227 Rupprecht, A., Theisen, U., Wendt, F., Frank, M. & Hinz, B. The Combination of Δ(9)-Tetrahydrocannabinol and Cannabidiol Suppresses Mitochondrial Respiration of Human Glioblastoma Cells via Downregulation of Specific Respiratory Chain Proteins. *Cancers (Basel)* **14** (2022). https://doi.org/10.3390/cancers14133129

228 Costa, B. & Colleoni, M. Changes in rat brain energetic metabolism after exposure to anandamide or Delta(9)-tetrahydrocannabinol. *European journal of pharmacology* **395**, 1-7 (2000).

229 Sarafian, T. A., Kouyoumjian, S., Khoshaghideh, F., Tashkin, D. P. & Roth, M. D. Delta 9-tetrahydrocannabinol disrupts mitochondrial function and cell energetics. *American journal of physiology* **284**, L298-306 (2003).

230 Sarafian, T. A. *et al.* Inhaled marijuana smoke disrupts mitochondrial energetics in pulmonary epithelial cells in vivo. *American journal of physiology* **290**, L1202-1209 (2006).

231 Badawy, Z. S. *et al.* Cannabinoids inhibit the respiration of human sperm. *Fertil Steril* **91**, 2471-2476 (2009). https://doi.org/10.1016/j.fertnstert.2008.03.075

232 Volkow N.D., Compton W.M. & Weiss S.R.B. Adverse Health Effects of Marijuana Use. *New England Journal of Medicine* **371**, 878-879 (2014). https://doi.org/doi:10.1056/NEJMc1407928

233 V. Wolff *et al.* Étude de l'effet du THC sur la respiration mitochondriale du cerveau de rat. Une piste de réflexion pour expliquer le lien entre la consommation de cannabis et la survenue d'infarctus cérébral chez l'homme

Study of the effect of THC on mitochondrial respiration of the rat brain. One line of thought to explain the link between cannabis use and the occurrence of cerebral infarction in men

Revue Neurologique, Neurological Review **170**, A19-A20 (2014). https://doi.org/10.1016 / j.neurol.2014.01.081

234 Wolff, V. *et al.* Tetrahydrocannabinol induces brain mitochondrial respiratory chain dysfunction and increases oxidative stress: a potential mechanism involved in cannabis-related stroke. *Biomed Res Int* **2015**, 323706 (2015). https://doi.org/10.1155/2015/323706

235 Heintzman, D. R. *et al.* Subset-specific mitochondrial stress and DNA damage shape T cell responses to fever and inflammation. *Science Immunology* **9**, eadp3475 (2024). https://doi.org/doi:10.1126/sciimmunol.adp3475

236 Rossato, M. Endocannabinoids, sperm functions and energy metabolism. *Molecular and cellular endocrinology* **286**, S31-35 (2008). https://doi.org/10.1016/j.mce.2008.02.013

237 Mahoney, J. M. & Harris, R. A. Effect of 9 -tetrahydrocannabinol on mitochondrial processes. *Biochemical pharmacology* **21**, 1217-1226 (1972).

238 Bartova, A. & Birmingham, M. K. Effect of delta9-tetrahydrocannabinol on mitochondrial NADH-oxidase activity. *J Biol Chem* **251**, 5002-5006 (1976).

239 Benard, G. *et al.* Mitochondrial CB(1) receptors regulate neuronal energy metabolism. *Nat Neurosci* **15**, 558-564 (2012). https://doi.org/10.1038/nn.3053

240 Hebert-Chatelain, E. *et al.* Cannabinoid control of brain bioenergetics: Exploring the subcellular localization of the CB1 receptor. *Mol Metab* **3**, 495-504 (2014). https://doi.org/10.1016/j.molmet.2014.03.007

241 Koch, M. *et al.* Hypothalamic POMC neurons promote cannabinoid-induced feeding. *Nature* **519**, 45-50 (2015). https://doi.org/10.1038/nature14260

242 Hebert-Chatelain, E. *et al.* A cannabinoid link between mitochondria and memory. *Nature* **539**, 555-559 (2016). https://doi.org/10.1038/nature20127

243 Jimenez-Blasco, D. *et al.* Glucose metabolism links astroglial mitochondria to cannabinoid effects. *Nature* **583**, 603-608 (2020). https://doi.org/10.1038/s41586-020-2470-y

244 Birmingham M.K. & Bartova A. in *Marihunana: Chemistry, Biochemistry and Cellular Effects* Vol. 1 (eds Nahas G.G., Paton W.D.M., & Idanpaan-Heikkla J.E.) Ch. 35, 425-440 (Springer-Verlag, 1976).

245 Stefanis C.N. & Issidorides M.R. in *Marihunana: Chemistry, Biochemistry and Cellular Effects* Vol. 1 (eds Dewey W.L., Martin B.R., Beckner J.S., & Harris L.S.) Ch. 29, 349-366 (Springer-Verlag, 1976).

246 Zimmerman A.M. & Zimmerman S.B. in *Marihunana: Chemistry, Biochemistry and Cellular Effects* Vol. 1 (eds Nahas G.G., Paton W.D.M., & Idanpaan-Heikkla J.E.) Ch. 17, 195-206 (Springer-Verlag, 1976).

247 Canto, C., Menzies, K. J. & Auwerx, J. NAD(+) Metabolism and the Control of Energy Homeostasis: A Balancing Act between Mitochondria and the Nucleus. *Cell Metab* **22**, 31-53 (2015). https://doi.org/10.1016/j.cmet.2015.05.023

248 Liu, S. *et al.* Nuclear envelope assembly defects link mitotic errors to chromothripsis. *Nature* **561**, 551-555 (2018). https://doi.org/10.1038/s41586-018-0534-z

249 Selmecki, A. M. *et al.* Polyploidy can drive rapid adaptation in yeast. *Nature* **519**, 349-352 (2015). https://doi.org/10.1038/nature14187

250 Tang, S., Stokasimov, E., Cui, Y. & Pellman, D. Breakage of cytoplasmic chromosomes by pathological DNA base excision repair. *Nature* **606**, 930-936 (2022). https://doi.org/10.1038/s41586-022-04767-1

251 Umbreit, N. T. & Pellman, D. Cancer biology: Genome jail-break triggers lockdown. *Nature* **550**, 340-341 (2017). https://doi.org/10.1038/nature24146

252 Reece A.S. & Hulse G.K. Cannabis- and Substance- Related Epidemiological Patterns of Chromosomal Congenital Anomalies in Europe: Geospatiotemporal and Causal Inferential Study. *International Journal of Environmental Research and Public Health* **19**, 11208-11258 (2022).

253 Harrod, A., Lane, K. A. & Downs, J. A. The role of the SWI/SNF chromatin remodelling complex in the response to DNA double strand breaks. *DNA Repair (Amst)* **93**, 102919 (2020). https://doi.org/10.1016/j.dnarep.2020.102919

254 Tsai, L. J. *et al.* RNF8 has both KU-dependent and independent roles in chromosomal break repair. *Nucleic Acids Res* **48**, 6032-6052 (2020). https://doi.org/10.1093/nar/gkaa380

255 Vasilyeva, T. A., Marakhonov, A. V., Sukhanova, N. V., Kutsev, S. I. & Zinchenko, R. A. Preferentially Paternal Origin of De Novo 11p13 Chromosome Deletions Revealed in Patients with Congenital Aniridia and WAGR Syndrome. *Genes (Basel)* **11** (2020). https://doi.org/10.3390/genes11070812

256 Yamazoe, T., Mori, T., Yoshio, S. & Kanto, T. Hepatocyte ploidy and pathological mutations in hepatocellular carcinoma: impact on oncogenesis and therapeutics. *Glob Health Med* **2**, 273-281 (2020). https://doi.org/10.35772/ghm.2020.01089

257 Ben Yamin, B. *et al.* DNA polymerase zeta contributes to heterochromatin replication to prevent genome instability. *Embo j* **40**, e104543 (2021). https://doi.org/10.15252/embj.2020104543

258 Cheloshkina, K. & Poptsova, M. Comprehensive analysis of cancer breakpoints reveals signatures of genetic and epigenetic contribution to cancer genome rearrangements. *PLoS Comput Biol* **17**, e1008749 (2021). https://doi.org/10.1371/journal.pcbi.1008749

259 García Fernández, F. *et al.* Modified chromosome structure caused by phosphomimetic H2A modulates the DNA damage response by increasing chromatin mobility in yeast. *J Cell Sci* **134** (2021). https://doi.org/10.1242/jcs.258500

260 Jamsen, J. A. *et al.* Structural basis for proficient oxidized ribonucleotide insertion in double strand break repair. *Nat Commun* **12**, 5055 (2021). https://doi.org/10.1038/s41467-021-24486-x

261 Llorens-Agost, M. *et al.* POLθ-mediated end joining is restricted by RAD52 and BRCA2 until the onset of mitosis. *Nat Cell Biol* **23**, 1095-1104 (2021). https://doi.org/10.1038/s41556-021-00764-0

262 Chen, Y. *et al.* Reversible reprogramming of cardiomyocytes to a fetal state drives heart regeneration in mice. *Science* **373**, 1537-1540 (2021). https://doi.org/10.1126/science.abg5159

263 Lu, Y. *et al.* Reprogramming to recover youthful epigenetic information and restore vision. *Nature* **588**, 124-129 (2020). https://doi.org/10.1038/s41586-020-2975-4

264 Ocampo, A. *et al.* In Vivo Amelioration of Age-Associated Hallmarks by Partial Reprogramming. *Cell* **167**, 1719-1733.e1712 (2016). https://doi.org/10.1016/j.cell.2016.11.052

265 Takahashi, K. & Yamanaka, S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* **126**, 663-676 (2006). https://doi.org/10.1016/j.cell.2006.07.024

266 Yu, J. *et al.* Induced pluripotent stem cell lines derived from human somatic cells. *Science* **318**, 1917-1920 (2007). https://doi.org/10.1126/science.1151526

267 Du, J. *et al.* A small-molecule cocktail promotes mammalian cardiomyocyte proliferation and heart regeneration. *Cell Stem Cell* **29**, 545-558.e513 (2022). https://doi.org/10.1016/j.stem.2022.03.009

268 Yang, J. H. *et al.* Loss of epigenetic information as a cause of mammalian aging. *Cell* **186**, 305-326.e327 (2023). https://doi.org/10.1016/j.cell.2022.12.027

269 Bertoldo, M. J. *et al.* NAD(+) Repletion Rescues Female Fertility during Reproductive Aging. *Cell Rep* **30**, 1670-1681.e1677 (2020). https://doi.org/10.1016/j.celrep.2020.01.058

270 Ho, W. J. *et al.* Fertility protection during chemotherapy treatment by boosting the NAD(P)(+) metabolome. *EMBO Mol Med* **16**, 2583-2618 (2024). https://doi.org/10.1038/s44321-024-00119-w

271 Fang, E. F. *et al.* NAD(+) Replenishment Improves Lifespan and Healthspan in Ataxia Telangiectasia Models via Mitophagy and DNA Repair. *Cell Metab* **24**, 566-581 (2016). https://doi.org/10.1016/j.cmet.2016.09.004

272 Gomes, A. P. *et al.* Declining NAD(+) induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. *Cell* **155**, 1624-1638 (2013). https://doi.org/10.1016/j.cell.2013.11.037

273 Paige St. John. *The reality of legal weed in California: Huge illegal grows, violence, worker exploitation and deaths*, <https://www.latimes.com/california/story/2022-09-08/reality-of-legal-weed-in-california-illegal-grows-deaths > (2022).

274 Hofstadter, D. *et al.* High rates of anticoagulant rodenticide exposure in California Barred Owls are associated with the wildland–urban interface. *Ornithological Applications* **123** (2021). https://doi.org/10.1093/ornithapp/duab036

275 Martin, M., Delheimer, M., Gabriel, M., Wengert, G. & Moriarty, K. Combined field and clinical methods clarify mortality causes and survival patterns of Pacific martens. *Journal of Wildlife Management* (2022). https://doi.org/10.1002/jwmg.22131

276 Medel, I., Gabriel, M., Wengert, G., Filigenzi, M. & Clifford, D. Passive monitoring of soluble pesticides linked to cannabis cultivation: a multi-scale analysis. *Water Quality Research Journal* **57** (2022). https://doi.org/10.2166/wqrj.2022.101

277 Wengert, G. *et al.* Distribution of trespass cannabis cultivation and its risk to sensitive forest predators in California and Southern Oregon. *PLOS ONE* **16**, e0256273 (2021). https://doi.org/10.1371/journal.pone.0256273

278 Wiens, J. *et al.* Anticoagulant rodenticides in Strix owls indicate widespread exposure in west coast forests. *Biological Conservation* **238**, 108238 (2019). https://doi.org/10.1016/j.biocon.2019.108238

279 Hézode, C. *et al.* Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. *Hepatology* **42**, 63-71 (2005). https://doi.org/10.1002/hep.20733

280 Le, Q. N. *et al.* Validation of the Soleris® Coliform Method for Detection of Coliform Bacteria in Dried Cannabis Flower: AOAC Performance Tested MethodSM 010302. *J AOAC Int* **105**, 1423-1427 (2022). https://doi.org/10.1093/jaoacint/qsac057

281 Le, Q. N. *et al.* Validation of the Soleris® NF-TVC Method for Detection of Aerobic, Mesophilic Microorganisms in Dried Cannabis Flower: AOAC Performance Tested MethodSM 071203. *J AOAC Int* **105**, 1418-1422 (2022). https://doi.org/10.1093/jaoacint/qsac055

282 Le, Q. N. *et al.* Validation of the Soleris®Enterobacteriaceae Method for Detection of Enterobacteriaceae in Dried Cannabis Flower: AOAC Performance Tested MethodSM 121901. *J AOAC Int* **105**, 1671-1676 (2022). https://doi.org/10.1093/jaoacint/qsac063

283 Rosauer, M. L., Lopez-Velasco, G., Silbernagel, K. M., Horine, L. & Tudor, A. Validation of the 3MTM Molecular Detection Assay 2-Salmonella for detection of Salmonella in Dried Cannabis Flower and Dried Hemp Flower: AOAC Performance Tested MethodsSM 091501. *J AOAC Int* **105**, 1684-1690 (2022). https://doi.org/10.1093/jaoacint/qsac068

284 Seltenrich, N. Cannabis Contaminants: Regulating Solvents, Microbes, and Metals in Legal Weed. *Environmental health perspectives* **127**, 82001 (2019). https://doi.org/10.1289/ehp5785

285 Llewellyn, G. C. & O'Rear, C. E. Examination of fungal growth and aflatoxin production on marihuana. *Mycopathologia* **62**, 109-112 (1977). https://doi.org/10.1007/bf01259400

286 Kagen, S. L. Aspergillus: an inhalable contaminant of marihuana. *N Engl J Med* **304**, 483-484 (1981). https://doi.org/10.1056/nejm198102193040812

287 Kagen, S. L., Kurup, V. P., Sohnle, P. G. & Fink, J. N. Marijuana smoking and fungal sensitization. *J Allergy Clin Immunol* **71**, 389-393 (1983). https://doi.org/10.1016/0091-6749(83)90067-2

288 Schwartz, I. S. Fungal sinusitis and marijuana. *Jama* **257**, 2914-2915 (1987). https://doi.org/10.1001/jama.1987.03390210062012

289 Hamadeh, R., Ardehali, A., Locksley, R. M. & York, M. K. Fatal aspergillosis associated with smoking contaminated marijuana, in a marrow transplant recipient. *Chest* **94**, 432-433 (1988). https://doi.org/10.1378/chest.94.2.432

290 Verweij, P. E., Kerremans, J. J., Voss, A. & Meis, J. F. Fungal contamination of tobacco and marijuana. *Jama* **284**, 2875 (2000). https://doi.org/10.1001/jama.284.22.2875

291 Citterio, S. *et al.* The arbuscular mycorrhizal fungus Glomus mosseae induces growth and metal accumulation changes in Cannabis sativa L. *Chemosphere* **59**, 21-29 (2005). https://doi.org/10.1016/j.chemosphere.2004.10.009

292 Cescon, D. W. *et al.* Invasive pulmonary aspergillosis associated with marijuana use in a man with colorectal cancer. *J Clin Oncol* **26**, 2214-2215 (2008). https://doi.org/10.1200/jco.2007.15.2777

293 Pérez-Moreno, M., Pérez-Lloret, P., González-Soriano, J. & Santos-Álvarez, I. Cannabis resin in the region of Madrid: Adulteration and contamination. *Forensic science international* **298**, 34-38 (2019). https://doi.org/10.1016/j.forsciint.2019.02.049

294 Punja, Z. K. *et al.* Pathogens and Molds Affecting Production and Quality of Cannabis sativa L. *Front Plant Sci* **10**, 1120 (2019). https://doi.org/10.3389/fpls.2019.01120

295 Benedict, K., Thompson, G. R., 3rd & Jackson, B. R. Cannabis Use and Fungal Infections in a Commercially Insured Population, United States, 2016. *Emerg Infect Dis* **26**, 1308-1310 (2020). https://doi.org/10.3201/eid2606.191570

296 Le, Q. N. *et al.* Emergency Response Validation of the Soleris® Direct Yeast and Mold Method for Detection of Yeast and Mold in Dried Cannabis Flower: AOAC Performance Tested MethodSM 051301. *J AOAC Int* **105**, 848-854 (2022). https://doi.org/10.1093/jaoacint/qsab135

297 Goodnight, K. M., Tian, P. & Bissonnette, K. M. First Report of Charcoal Rot Caused by Macrophomina phaseolina on Hemp (Cannabis sativa) in Missouri. *Plant Dis* (2023). https://doi.org/10.1094/pdis-02-23-0385-pdn

298 Gwinn, K. D., Leung, M. C. K., Stephens, A. B. & Punja, Z. K. Fungal and mycotoxin contaminants in cannabis and hemp flowers: implications for consumer health and directions for further research. *Front Microbiol* **14**, 1278189 (2023). https://doi.org/10.3389/fmicb.2023.1278189

299 Katchman, B. A., Tomchaney, M., Rueda, A., Stice, S. & Hogan, M. PathogenDx DetectX Combined Demonstrates Equivalent Performance in Comparison to Four AOAC Certified Methods for the Detection of Aspergillus Species, Salmonella Species, and STEC in Dried Hemp Flower. *J AOAC Int* **106**, 949-955 (2023). https://doi.org/10.1093/jaoacint/qsad027

300 Punja, Z. K., Ni, L., Lung, S. & Buirs, L. Total yeast and mold levels in high THC-containing cannabis (Cannabis sativa L.) inflorescences are influenced by genotype, environment, and pre-and post-harvest handling practices. *Front Microbiol* **14**, 1192035 (2023). https://doi.org/10.3389/fmicb.2023.1192035

301 Sun, S. *et al.* Arbuscular mycorrhizal fungi influence the uptake of cadmium in industrial hemp (Cannabis sativa L.). *Chemosphere* **330**, 138728 (2023). https://doi.org/10.1016/j.chemosphere.2023.138728

302 Mallampati, S. R., McDaniel, C. & Wise, A. R. Strategies for Nonpolar Aerosol Collection and Heavy Metals Analysis of Inhaled Cannabis Products. *ACS Omega* **6**, 17126-17135 (2021). https://doi.org/10.1021/acsomega.1c02740

303 McDaniel, C., Mallampati, S. R. & Wise, A. Metals in Cannabis Vaporizer Aerosols: Sources, Possible Mechanisms, and Exposure Profiles. *Chem Res Toxicol* **34**, 2331-2342 (2021). https://doi.org/10.1021/acs.chemrestox.1c00230

304 Gardener, H., Wallin, C. & Bowen, J. Heavy metal and phthalate contamination and labeling integrity in a large sample of US commercially available cannabidiol (CBD) products. *Sci Total Environ* **851**, 158110 (2022). https://doi.org/10.1016/j.scitotenv.2022.158110

305 Liebling, J. P., Clarkson, N. J., Gibbs, B. W., Yates, A. S. & O'Sullivan, S. E. An Analysis of Over-the-Counter Cannabidiol Products in the United Kingdom. *Cannabis Cannabinoid Res* **7**, 207-213 (2022). https://doi.org/10.1089/can.2019.0078

306 Meehan-Atrash, J. & Rahman, I. Novel Δ(8)-Tetrahydrocannabinol Vaporizers Contain Unlabeled Adulterants, Unintended Byproducts of Chemical Synthesis, and Heavy Metals. *Chem Res Toxicol* **35**, 73-76 (2022). https://doi.org/10.1021/acs.chemrestox.1c00388

307 Nelson, J., Jones, C., Heckle, S. & Anderson, L. Determination of Heavy Metals in a Variety of Cannabis and Cannabis-Derived Products, First Action 2021.03. *J AOAC Int* **105**, 1640-1651 (2022). https://doi.org/10.1093/jaoacint/qsab173

308 Okoroafor, P. U., Ogunkunle, C. O., Heilmeier, H. & Wiche, O. Phytoaccumulation potential of nine plant species for selected nutrients, rare earth elements (REEs), germanium (Ge), and potentially toxic elements (PTEs) in soil. *Int J Phytoremediation* **24**, 1310-1320 (2022). https://doi.org/10.1080/15226514.2021.2025207

309 Suraev, A., Benson, M. J., Martin, L., Lintzeris, N. & McGregor, I. S. Determination of contaminants in artisanal cannabis products used for childhood epilepsy in the Australian community: A sub-analysis of the 'PELICAN' study. *Epilepsy Behav* **127**, 108496 (2022). https://doi.org/10.1016/j.yebeh.2021.108496

310 Wieczorek, J., Kaczor, M. & Boryło, A. Determination of (210)Po and (210)Pb in cannabis (Cannabis sativa L.) plants and products. *J Environ Radioact* **246**, 106834 (2022). https://doi.org/10.1016/j.jenvrad.2022.106834

311 McGraw, K. E. *et al.* Blood and Urinary Metal Levels among Exclusive Marijuana Users in NHANES (2005-2018). *Environmental health perspectives* **131**, 87019 (2023). https://doi.org/10.1289/ehp12074

312 Singh, K., Tripathi, S. & Chandra, R. Bacterial assisted phytoremediation of heavy metals and organic pollutants by Cannabis sativa as accumulator plants growing on distillery sludge for ecorestoration of polluted site. *J Environ Manage* **332**, 117294 (2023). https://doi.org/10.1016/j.jenvman.2023.117294

313 Afridi, A. J., Zuberi, A., Yousafzai, A. M. & Kamran, M. Therapeutic Role of Hemp (Cannabis sativa) Against Copper-Induced Toxicity in Labeo rohita and Cirrhinus mrigala. *Biol Trace Elem Res* **202**, 307-318 (2024). https://doi.org/10.1007/s12011-023-03650-y

314 Čechová, L. *et al.* Study of plasma activated water effect on heavy metal bioaccumulation by Cannabis sativa Using Laser-Induced Breakdown Spectroscopy. *Ecotoxicol Environ Saf* **283**, 116807 (2024). https://doi.org/10.1016/j.ecoenv.2024.116807

315 Bauer, S. *et al.* Impacts of surface water diversions for marijuana cultivation on aquatic habitat in four northwestern California watersheds. *PLoS One* **10**, e0120016 (2015). https://doi.org/10.1371/journal.pone.0120016

316 Cannabis Research Centre, U. o. C., Berkeley. *Water Use in Cannabis Agriculture*, <https://crc.berkeley.edu/wp-content/uploads/2020/12/CRC_Brief_WaterUse_2020_1205.pdf?utm_source=chatgpt.com> (2020).

317 South Yuba River Citizens League. *Water Use in Agriculture: Exploring Residential and Cannabis Water Consumption*, <https://yubariver.org/posts/water-use-in-agriculture-exploring-residential-and-cannabis-water-consumption/> (2024).

318 Zheng, Z., Fiddes, K. & Yang, L. A narrative review on environmental impacts of cannabis cultivation. *Journal of Cannabis Research* **3**, 35 (2021). https://doi.org/10.1186/s42238-021-00090-0

319 Zipper, S. *et al.* Cannabis and residential groundwater pumping impacts on streamflow and ecosystems in Northern California. *Environmental Research Communications* **1**, 125005 (2019). https://doi.org/10.1088/2515-7620/ab534d

320 California Water Boards: State Water Resources Control Board. *Cannabis Cultivation Policy - Principles and Guidelines (Requirements) for Cannabis Cultivation*, <https://www.waterboards.ca.gov/water_issues/programs/cannabis/cannabis_policy.html> (2024).

321 California Water Boards: State Water Resources Control Board. *State Board - Cannabis Cultivation Water Quality*, <https://www.waterboards.ca.gov/water_issues/programs/cannabis/cannabis_water_quality.html?utm_source=chatgpt.com> (2025).

322 California Water Boards: State Water Resources Control Board. *Water Boards Cannabis Cultivation*, <https://www.waterboards.ca.gov/water_issues/programs/cannabis/> (2025).

323 Parolini, M. & Binelli, A. Oxidative and genetic responses induced by Δ-9-tetrahydrocannabinol (Δ-9-THC) to Dreissena polymorpha. *Sci Total Environ* **468-469**, 68-76 (2014). https://doi.org/10.1016/j.scitotenv.2013.08.024

324 Parolini, M., Castiglioni, S., Magni, S., Della Torre, C. & Binelli, A. Increase in cannabis use may indirectly affect the health status of a freshwater species. *Environ Toxicol Chem* **36**, 472-479 (2017). https://doi.org/10.1002/etc.3575

325 How, Z. T. & Gamal El-Din, M. A critical review on the detection, occurrence, fate, toxicity, and removal of cannabinoids in the water system and the environment. *Environmental Pollution* **268**, 115642 (2021). https://doi.org/https://doi.org/10.1016/j.envpol.2020.115642

326 Palardy, A., Gagné, J. P. & Tremblay, L. Presence of Illicit Drugs and Pharmaceutical Residues in the Wastewaters of an Eastern Canadian City. *J Xenobiot* **5**, 5773 (2015). https://doi.org/10.4081/xeno.2015.5773

327 Werschler T. & Brennan A. *Wastewater-based Estimates of Cannabis and Drug Use in Canada: Pilot test Detailed Results*, <https://www150.statcan.gc.ca/n1/pub/11-621-m/11-621-m2019004-eng.htm> (2019).

328 Chayasirisobhon Sirichai. Mechanisms of Action and Pharmacokinetics of Cannabis. *The Permanente Journal* **25**, 1-3 (2021). https://doi.org/doi:10.7812/TPP/19.200

329 Wagner, B. *et al.* Transfer of cannabinoids into the milk of dairy cows fed with industrial hemp could lead to Δ9-THC exposure that exceeds acute reference dose. *Nature Food* (2022). https://doi.org/10.1038/s43016-022-00623-7

330 Reece, A. S. & Hulse, G. K. Contemporary epidemiology of rising atrial septal defect trends across USA 1991-2016: a combined ecological geospatiotemporal and causal inferential study. *BMC Pediatr* **20**, 539-550 (2020). https://doi.org/10.1186/s12887-020-02431-z

331 Coleman, J. J. Did the 2018 Farm Bill's Hemp Provisions Decriminalize Marijuana? *Journal of Drug Policy Analysis* **14**, 1-21 (2021). https://doi.org/doi:10.1515/jdpa-2020-0006

332 Natoinal Birth Defects Prevention Network. *Major Birth Defects Data from Population-Based Birth Defects Surveillance Programs in the United States, 2016-2020*, <https://nbdpn.org/wp-content/uploads/2024/07/Birth_Defects_Data_and_Directory_Jan2024.pdf> (2024).

333 Schanen, N. C. Epigenetics of autism spectrum disorders. *Hum Mol Genet* **15 Spec No 2**, R138-150 (2006). https://doi.org/10.1093/hmg/ddl213

334 Pinto, D. *et al.* Convergence of genes and cellular pathways dysregulated in autism spectrum disorders. *Am J Hum Genet* **94**, 677-694 (2014). https://doi.org/10.1016/j.ajhg.2014.03.018

335 Varadinova, M. & Boyadjieva, N. Epigenetic mechanisms: A possible link between autism spectrum disorders and fetal alcohol spectrum disorders. *Pharmacol Res* **102**, 71-80 (2015). https://doi.org/10.1016/j.phrs.2015.09.011

336 Keil, K. P. & Lein, P. J. DNA methylation: a mechanism linking environmental chemical exposures to risk of autism spectrum disorders? *Environ Epigenet* **2** (2016). https://doi.org/10.1093/eep/dvv012

337 Cattane, N., Richetto, J. & Cattaneo, A. Prenatal exposure to environmental insults and enhanced risk of developing Schizophrenia and Autism Spectrum Disorder: focus on biological pathways and epigenetic mechanisms. *Neuroscience and biobehavioral reviews* (2018). https://doi.org/10.1016/j.neubiorev.2018.07.001

338 Duffney, L. J. *et al.* Epigenetics and autism spectrum disorder: A report of an autism case with mutation in H1 linker histone HIST1H1E and literature review. *Am J Med Genet B Neuropsychiatr Genet* **177**, 426-433 (2018). https://doi.org/10.1002/ajmg.b.32631

339 Eshraghi, A. A. *et al.* Epigenetics and Autism Spectrum Disorder: Is There a Correlation? *Front Cell Neurosci* **12**, 78 (2018). https://doi.org/10.3389/fncel.2018.00078

340 Nevison, C., Blaxill, M. & Zahorodny, W. California Autism Prevalence Trends from 1931 to 2014 and Comparison to National ASD Data from IDEA and ADDM. *J Autism Dev Disord* **48**, 4103-4117 (2018). https://doi.org/10.1007/s10803-018-3670-2

341 Waye, M. M. Y. & Cheng, H. Y. Genetics and epigenetics of autism: A Review. *Psychiatry and clinical neurosciences* **72**, 228-244 (2018). https://doi.org/10.1111/pcn.12606

342 Schrott, R. *et al.* Cannabis use is associated with potentially heritable widespread changes in autism candidate gene DLGAP2 DNA methylation in sperm. *Epigenetics* **15**, 161-173 (2019). https://doi.org/10.1080/15592294.2019.1656158

343 Zhang, X. C., Shu, L. Q., Zhao, X. S. & Li, X. K. Autism spectrum disorders: autistic phenotypes and complicated mechanisms. *World J Pediatr* (2019). https://doi.org/10.1007/s12519-018-0210-2

344 Avalos, L. A. *et al.* Maternal Prenatal Cannabis Use and Child Autism Spectrum Disorder. *JAMA Netw Open* **7**, e2440301 (2024). https://doi.org/10.1001/jamanetworkopen.2024.40301

345 Tadesse, A. W., Ayano, G., Dachew, B. A., Betts, K. & Alati, R. Exposure to maternal cannabis use disorder and risk of autism spectrum disorder in offspring: A data linkage cohort study. *Psychiatry Res* **337**, 115971 (2024). https://doi.org/10.1016/j.psychres.2024.115971

346 Tadesse, A. W., Dachew, B. A., Ayano, G., Betts, K. & Alati, R. Prenatal cannabis use and the risk of attention deficit hyperactivity disorder and autism spectrum disorder in

offspring: A systematic review and meta-analysis. *J Psychiatr Res* **171**, 142-151 (2024). https://doi.org/10.1016/j.jpsychires.2024.01.045

347 Fournier E., Rosenberg E., Hardy N. & Nahas G.G. in *Marihunana: Chemistry, Biochemistry and Cellular Effects* Vol. 1 (eds Nahas G.G., Paton W.D.M., & Idanpaan-Hekkkila J.E.) Ch. 37, 457-468 (Springer-Verlag, 1976).

348 Geber, W. F. & Schramm, L. C. Effect of marihuana extract on fetal hamsters and rabbits. *Toxicology and applied pharmacology* **14**, 276-282 (1969).

349 Geber, W. F. & Schramm, L. C. Teratogenicity of marihuana extract as influenced by plant origin and seasonal variation. *Arch Int Pharmacodyn Ther* **177**, 224-230 (1969).

350 Forrester, M. B. & Merz, R. D. Risk of selected birth defects with prenatal illicit drug use, Hawaii, 1986-2002. *Journal of toxicology and environmental health* **70**, 7-18 (2007).

351 Reece A.S. & Hulse G.K. Effects of Cannabis on Congenital Limb Anomalies in 14 European Nations: A Geospatiotemporal and Causal Inferential Study. *Environmental Epigenetics* **8**, 1-34 (2022).

352 Reece , A. S. Limblessness: Cannabinoids Inhibit Key Embryonic Morphogens both Directly and Epigenomically. *British Medical Journal* **376**, n3114 (2022). https://doi.org/ https://doi.org/10.1136/bmj.n3114

353 Reece, A. S. & Hulse, G. K. Epidemiological association of cannabinoid- and drug-exposures and sociodemographic factors with limb reduction defects across USA 1989–2016: A geotemporospatial study. *Spatial and Spatio-temporal Epidemiology* **41**, 100480-100490 (2022). https://doi.org/https://doi.org/10.1016/j.sste.2022.100480

354 Reece A.S. & Hulse G.K. Cannabinoid- and Substance- Relationships of European Congenital Anomaly Patterns: A Space-Time Panel Regression and Causal Inferential Study. *Environmental Epigenetics* **8**, 1-40 (2022).

355 Reece A.S. & Hulse G.K. in *Cannabis, Cannabinoids and Endocannabinoids* Vol. 1 (eds Martin C.R., Preedy V., & Patel V.) Ch. 5, 570 (Elsevier, 2022).

356 Reece A.S. & Hulse G.K. in *Epidemiology of Cannabis: Genotoxicity and Neurotoxicity, Epigenomics and Aging* Vol. 1 (eds Reece A.S. & Hulse G.K.) Ch. 1-570, 570 (Elsevier, 2025).

357 Reece, A. S. & Hulse, G. K. Geotemporospatial and causal inference epidemiological analysis of US survey and overview of cannabis, cannabidiol and cannabinoid genotoxicity in relation to congenital anomalies 2001–2015. *BMC Pediatrics* **22**, 47-124 (2022). https://doi.org/10.1186/s12887-021-02996-3

358 Fish, E. W. *et al.* Cannabinoids Exacerbate Alcohol Teratogenesis by a CB1-Hedgehog Interaction. *Sci Rep* **9**, 16057-16075 (2019). https://doi.org/10.1038/s41598-019-52336-w

359 Reece, A. S. & Hulse, G. K. Perturbation of 3D nuclear architecture, epigenomic dysregulation and aging, and cannabinoid synaptopathy reconfigures conceptualization of cannabinoid pathophysiology: part 1-aging and epigenomics. *Frontiers in psychiatry* **14**, 1182535 (2023). https://doi.org/10.3389/fpsyt.2023.1182535

360 Reece, A. S. & Hulse, G. K. Perturbation of 3D nuclear architecture, epigenomic aging and dysregulation, and cannabinoid synaptopathy reconfigures conceptualization of cannabinoid pathophysiology: part 2-Metabolome, immunome, synaptome. *Frontiers in psychiatry* **14**, 1182536 (2023). https://doi.org/10.3389/fpsyt.2023.1182536

361 Gant J. Scientists are baffled by spatter of babies born without hands or arms in France, as investigation fails to discover a cause. *Daily Mail* **Sunday 13th July**

(2019). <https://www.dailymail.co.uk/news/article-7242059/Scientists-baffled-babies-born-without-hands-arms-France-probe-fails-discover-cause.html>.

362 24 Heures. Seizure of 135 kg of cannabis in Ain. *24 Heures* (2018). <https://www.24heures.ch/geneve/Saisie-de-135-kg-de-cannabis-dans-l-Ain/story/17353874>.

363 Connexion Journalist. Mayor wants to grow and sell cannabis in French fields. (2018). <https://www.connexionfrance.com/French-news/legalisation-of-cannabis-in-France>.

364 Voser S. *Best Outdoor Cannabis Strains to Grow in France*, <https://www.zamnesia.com/us/blog-best-cannabis-strains-to-grow-outdoors-in-france-n1256> (2023).

365 Robinson M. *Babies born with deformed hands spark investigation in Germany*, <https://edition.cnn.com/2019/09/16/health/hand-deformities-babies-gelsenkirchen-germany-intl-scli-grm/index.html> (2019).

366 BBC News. *Germany Partially Decriminalizes Cannabis*, <https://www.bing.com/videos/riverview/relatedvideo?q=what+are+the+rules+in+germany+about+cannabis&mid=D43053AAC39F41B0FB9ED43053AAC39F41B0FB9E&FORM=VIRE> (2024).

367 Bermejo-Sanchez, E. *et al.* Amelia: a multi-center descriptive epidemiologic study in a large dataset from the International Clearinghouse for Birth Defects Surveillance and Research, and overview of the literature. *Am J Med Genet C Semin Med Genet* **157C**, 288-304 (2011). https://doi.org/10.1002/ajmg.c.30319

368 Bermejo-Sanchez, E. *et al.* Phocomelia: a worldwide descriptive epidemiologic study in a large series of cases from the International Clearinghouse for Birth Defects Surveillance and Research, and overview of the literature. *Am J Med Genet C Semin Med Genet* **157C**, 305-320 (2011). https://doi.org/10.1002/ajmg.c.30320

369 Birerdinc, A., Jarrar, M., Stotish, T., Randhawa, M. & Baranova, A. Manipulating molecular switches in brown adipocytes and their precursors: a therapeutic potential. *Prog Lipid Res* **52**, 51-61 (2013). https://doi.org/10.1016/j.plipres.2012.08.001

370 Richard, D. & Picard, F. Brown fat biology and thermogenesis. *Front Biosci (Landmark Ed)* **16**, 1233-1260 (2011). https://doi.org/10.2741/3786

371 Xu, T. R., Yang, Y., Ward, R., Gao, L. & Liu, Y. Orexin receptors: multi-functional therapeutic targets for sleeping disorders, eating disorders, drug addiction, cancers and other physiological disorders. *Cellular signalling* **25**, 2413-2423 (2013). https://doi.org/10.1016/j.cellsig.2013.07.025

372 Fraher, D. *et al.* Lipid Abundance in Zebrafish Embryos Is Regulated by Complementary Actions of the Endocannabinoid System and Retinoic Acid Pathway. *Endocrinology* **156**, 3596-3609 (2015). https://doi.org/10.1210/en.2015-1315

373 Kučukalić, S. *et al.* Genetic Susceptibility to Posttraumatic Stress Disorder: Analyses of the Oxytocin Receptor, Retinoic Acid Receptor-Related Orphan Receptor A and Cannabinoid Receptor 1 Genes. *Psychiatr Danub* **31**, 219-226 (2019). https://doi.org/10.24869/psyd.2019.219

374 Lee, Y. S. & Jeong, W. I. Retinoic acids and hepatic stellate cells in liver disease. *Journal of gastroenterology and hepatology* **27 Suppl 2**, 75-79 (2012). https://doi.org/10.1111/j.1440-1746.2011.07007.x

375 Vallee, A., Lecarpentier, Y., Guillevin, R. & Vallee, J. N. Effects of cannabidiol interactions with Wnt/beta-catenin pathway and PPARgamma on oxidative stress and neuroinflammation in Alzheimer's disease. *Acta Biochim Biophys Sin (Shanghai)* **49**, 853-866 (2017). https://doi.org/10.1093/abbs/gmx073

376 Nallathambi, R. *et al.* Identification of Synergistic Interaction Between Cannabis-Derived Compounds for Cytotoxic Activity in Colorectal Cancer Cell Lines and Colon Polyps That Induces Apoptosis-Related Cell Death and Distinct Gene Expression. *Cannabis Cannabinoid Res* **3**, 120-135 (2018). https://doi.org/10.1089/can.2018.0010

377 Petko, J., Tranchina, T., Patel, G., Levenson, R. & Justice-Bitner, S. Identifying novel members of the Wntless interactome through genetic and candidate gene approaches. *Brain research bulletin* **138**, 96-105 (2018). https://doi.org/10.1016/j.brainresbull.2017.07.004

378 Xian, X., Tang, L., Wu, C. & Huang, L. miR-23b-3p and miR-130a-5p affect cell growth, migration and invasion by targeting CB1R via the Wnt/beta-catenin signaling pathway in gastric carcinoma. *OncoTargets and therapy* **11**, 7503-7512 (2018). https://doi.org/10.2147/ott.S181706

379 McKenzie, M. G. *et al.* Non-canonical Wnt Signaling through Ryk Regulates the Generation of Somatostatin- and Parvalbumin-Expressing Cortical Interneurons. *Neuron* **103**, 853-864 e854 (2019). https://doi.org/10.1016/j.neuron.2019.06.003

380 Nalli, Y. *et al.* Analyzing the role of cannabinoids as modulators of Wnt/beta-catenin signaling pathway for their use in the management of neuropathic pain. *Bioorganic & medicinal chemistry letters* **29**, 1043-1046 (2019). https://doi.org/10.1016/j.bmcl.2019.03.013

381 Aguado, T. *et al.* The CB1 cannabinoid receptor mediates excitotoxicity-induced neural progenitor proliferation and neurogenesis. *J Biol Chem* **282**, 23892-23898 (2007). https://doi.org/10.1074/jbc.M700678200

382 Williams, E. J., Walsh, F. S. & Doherty, P. The FGF receptor uses the endocannabinoid signaling system to couple to an axonal growth response. *J Cell Biol* **160**, 481-486 (2003). https://doi.org/10.1083/jcb.200210164

383 Linz W. Thalidomide and Congenital Abnormalities. *Lancet* **7223**, 271-272 (1962).

384 Rehman, W., Arfons, L. M. & Lazarus, H. M. The rise, fall and subsequent triumph of thalidomide: lessons learned in drug development. *Ther Adv Hematol* **2**, 291-308 (2011). https://doi.org/10.1177/2040620711413165

385 Zhou, S., Wang, F., Hsieh, T. C., Wu, J. M. & Wu, E. Thalidomide-a notorious sedative to a wonder anticancer drug. *Current medicinal chemistry* **20**, 4102-4108 (2013).

Other Cannabis References

1. Reece A.S., Hulse G.K. "Chromothripsis and Epigenomics Complete Causality Criteria for Cannabis- and Addiction- Connected Carcinogenicity, Congenital Toxicity and Heritable Genotoxicity." Mutation Research (2016); 789: 15-25. PMID: 27208973. DOI:10.1016/j.mrfmmm.2016.05.002 http://www.sciencedirect.com/science/article/pii/S0027510716300574?via%3Dihub

2. Reece A.S., Norman A., Hulse G.K. "Cannabis Exposure as an Interactive Cardiovascular Risk Factor and Accelerant of Organismal Ageing – A Longitudinal Study" 6(11):e011891. Accepted BMJ Open 20th October 2016. PubMed ID: 27821595. DOI: http://dx.doi.org/10.1136/bmjopen-2016-011891. Published *BMJ Open* 01/11/2016. http://bmjopen.bmj.com/content/6/11/e011891.full.pdf+html

3. Reece A.S., Hulse G.K. Letter in Response to: "Medicinal Cannabis in Australia: The Missing Links" Martin J.H. and Bonomo Y.A., Medical Journal of Australia 205 (9): 425. Published 07.11.2016. Accepted 28.06.2016. PubMed ID : 27809740 DOI: 10.5694/mja16.00709. Published 7th November 2016. https://www.mja.com.au/journal/2016/205/9/medicinal-cannabis-australia-missing-links?utm_source=MJA+news+alerts&utm_campaign=c8082025ed-EMAIL_CAMPAIGN_2016_11_03&utm_medium=email&utm_term=0_8c7e70a099-c8082025ed-41326421 .

4. Reece A.S., Norman A., Hulse G.K. "Acceleration of Cardiovascular - Biological Age by Amphetamine Exposure is a Power Function of Chronological Age." (2017) 9 (1): 30-38. Accepted by Heart Asia 8th November 2016. 2017, 9 (1): 30-38. PubMed ID: 28243315.
doi: http://dx.doi.org/10.1136/heartasia-2016-010832 .
http://heartasia.bmj.com/content/9/1/30
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5307374/

5. Reece A.S., Wang W., Hulse G.K. "Pathways from Epigenomics and Glycobiology towards Novel Biomarkers of Addiction and its Radical Cure". Medical Hypotheses. Published 17th April 2018. Vol 116: 10-21.
https://doi.org/10.1016/j.mehy.2018.04.011 .

6. Reece A.S. "Known Cannabis Teratogenicity Should be Carefully Considered" BMJ Rapid Response. Accepted 06/08/2018. URL:
https://www.bmj.com/content/362/bmj.k3357/rr-0
Chosen as Editors Choice for BMJ 23/10/2018.

7. Rapid Response to Cardenas A, Villaba A., de Juan Romero C., Pico E., Kyrousi C., Tzika A.C., Tessier-Lavigne M., Ma L., Drukker M., Borrell V. (2018) "Evolution of cortical neurogenesis in amniotes is controlled by robo signaling levels." Cell 174(3): 590-606. Published on Cell website.

https://www.cell.com/cell/fulltext/S0092-8674(18)30732-3?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867418307323%3Fshowall%3Dtrue#comments-heading

8. Reece A.S., Hulse G.K. "Explaining Contemporary Patterns of Cannabis Teratology". Accepted in Clinical Pediatrics 18th January 2019. https://pdfs.semanticscholar.org/09b5/40b74212f3fc2a5d2e9d4a86a12021d05658.pdf doi: 10.4172/2572-0775.1000146

9. Reece A.S. "Cannabis Problematics Include but are not Limited to Pain Management" JAMA. Published online 3rd February 2019. https://jamanetwork.com/journals/jama/fullarticle/2723649 . doi: doi:10.1001/jama.2019.0077 .

10. Reece A.S., Hulse G.K. "Gastroschisis and Autism—Dual Canaries in the Californian Coalmine" Published online February 6th 2019. doi: 10.1001/jamasurg.2018.4694 PMID: 30725103 JAMA Surgery https://jamanetwork.com/journals/jamasurgery/article-abstract/2723261

11. Reece A.S., Hulse G.K. "Effect of Cannabis Legalization on US Autism Incidence and Medium Term Projections." Clinical Pediatrics: Open Access. Accepted 27th April 2019. 4(2): 1-17. https://www.longdom.org/open-access/effect-of-cannabis-legalization-on-us-autism-incidence-and-medium-term-projections.pdf ePublished 3rd May 2019.
DOI: 10.24105/2572-0775.4.154 .

12. Reece A.S. Rapid Response to "When the Law Fails Patients." by Hurley R. in British Medical Journal. "Billionaires v Babies." Published 10th May 2019. 2019; 365:1980 https://www.bmj.com/content/365/bmj.l1980/rr doi: https://doi.org/10.1136/bmj.l1980

13. Reece A.S. Rapid Response to "Why Medical Cannabis is still out of Patient's Reach." By Nutt D. BMJ 2019; 365:1903. https://www.bmj.com/content/365/bmj.l1903/rr-1. doi: https://doi.org/10.1136/bmj.l1903. Published 10th May 2019.

14. Reece A.S., Hulse G.K. "Epidemiological Associations of Various Substances and Multiple Cannabinoids with Autism in USA". Accepted 22nd May 2019. Clinical Pediatrics: Open Access. Published 31st May 2019. https://www.longdom.org/open-access/epidemiological-associations-of-various-substances-and-multiple-cannabinoids-with-autism-in-usa.pdf
doi: 10.24105/2572-0775.4.155

15. Reece A.S., Hulse G.K. "Impacts of Cannabinoid Epigenetics on Human Development: Reflections on Murphy et. al. "Cannabinoid Exposure and Altered DNA Methylation in Rat and Human Sperm" Epigenetics 2018; 13: 1208-1221." Accepted Epigenetics 14th June 2019. doi: https://doi.org/10.1080/15592294.2019.1633868 .

16. Reece A.S. Should We Legalize Cannabis: "Cannabis Debates and Cannabis Debacles: Serious Downstream Implications of Cannabis Neurotoxicity and Genotoxicity" British Medical Journal, Rapid Responses, Published 7th July 2019 https://www.bmj.com/content/366/bmj.l4507/rapid-responses.

17. Reece A.S. Hulse G.K. "Cannabis Teratology Explains Current Patterns of Coloradan Congenital Defects: The Contribution of Increased Cannabinoid Exposure to Rising Teratological Trends." Clinical Pediatrics. Published online 9th July 2019. https://doi.org/10.1177/0009922819861281

18. Reece A.S., Hulse G.K., "Impacts of Cannabinoid Epigenetics on Human Development: Reflections on Murphy et. al. "Cannabinoid Exposure and Altered DNA Methylation in Rat and Human Sperm" Epigenetics 2018; 13: 1208-1221. 13th July 2019. https://www.tandfonline.com/doi/full/10.1080/15592294.2019.1633868

19. Reece A.S. "Cannabis Threatens Oocytes, a Non-Renewable National Genomic Resource – and Implications of Prostacyclin Vasodilation and Anti-thrombogenesis" British Medical Journal Rapid Response. Accepted 19th July 2019. https://www.bmj.com/content/366/bmj.l4507/rr-5

20. Reece A.S. "Unrolling and Unravelling Far-Reaching Implications of Cannabis Use in Pregnancy Study." Comment in JAMA Network Online Accepted 31st July 2019. See Comments Tab. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2738343

21. Reece A.S., Hulse G.K., "Cannabis Consumption Patterns Parallel the East-West Gradient in Canadian Neural Tube Defect Incidence: An Ecological Study" Accepted for Global Pediatric Health 20th October 2019. https://journals.sagepub.com/doi/pdf/10.1177/2333794X19894798 https://doi.org/10.1177/2333794X19894798 Volume 6 (1): 1-12.

22. Reece A.S., Hulse G.K. "Canadian Cannabis Consumption and Patterns of Congenital Anomalies: An Ecological Geospatial Analysis" . Accepted in Journal of Addiction Medicine, 6th January 2020. MS No. JAM-D-00715R3. https://journals.lww.com/journaladdictionmedicine/Abstract/publishahead/Canadian_Cannabis_Consumption_and_Patterns_of.99248.aspx ePublished 13th March 2020.

23. Reece A.S., Hulse G.K. "Response to Lane". Rapid Response to Ian A Lane. "Re: Cannabis exposure as an interactive cardiovascular risk factor and accelerant of organismal ageing: A longitudinal study" BMJ Open. ePublished 27th March 2020. https://bmjopen.bmj.com/content/6/11/e011891.responses

24. Reece A.S., Hulse G.K. America Addresses Two Epidemics Dataset – Cannabis and Coronavirus and their Interactions: Combined Geospatial and Causal Inference Study Dataset held on Mendeley data repository. May 2020. https://data.mendeley.com/drafts/x22mm7bh34

25. Reece A.S., Hulse G.K. "Cannabis in Pregnancy – Rejoinder, Exposition and Cautionary Tales." Accepted for Publication in Psychiatric Times, 18/07/2020.

ePublished 10/10/2020. https://www.psychiatrictimes.com/view/cannabis-pregnancy-rejoinder-exposition-cautionary-tales

26. Reece A.S., Hulse G.K. "Broad Spectrum Epidemiological Contribution of Cannabis and Other Substances to the Teratological Profile of Northern New South Wales: Geospatial and Causal Inference Analysis" Published in BMC Pharmacology and Toxicology 13/11//2020. (2020) 21:75 doi.org/10.1186/s40360-020-00450-1 https://link.springer.com/article/10.1186/s40360-020-00450-1

27. Reece A.S., Hulse G.K. "Response to Polocaro and Vettraino" Accepted in Missouri Medicine 04/10/2020. https://www.omagdigital.com/publication/?m=11307&i=685331&p=36&pre=1

28. Reece A.S., Hulse G.K. "Co-Occurrence Across Time and Space of Drug- and Cannabinoid- Exposure and Adverse Mental Health Outcomes in the National Survey of Drug Use and Health: Combined Geotemporospatial and Causal Inference Analysis" Accepted in BMC Public Health 22nd October 2020. https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-020-09748-5 Published 04/11/2020. 20:1655 https://doi.org/10.1186/s12889-020-09748-5 .

29. Reece A.S., Hulse G.K. "Contemporary epidemiology of rising atrial septal defect trends across USA 1991–2016: a combined ecological geospatiotemporal and causal inferential study." BMC Pediatrics 2020; 20:539-550. https://bmcpediatr.biomedcentral.com/track/pdf/10.1186/s12887-020-02431-z.pdf

30. Reece A.S., Hulse G.K. "A geospatiotemporal and causal inference epidemiological exploration of substance and cannabinoid exposure as drivers of rising US pediatric cancer rates." BMC Cancer. 2021; 21: (1) 197- 230. https://bmccancer.biomedcentral.com/track/pdf/10.1186/s12885-021-07924-3.pdf .

31. Reece A.S., Hulse G.K. "Causal Inference Multiple Imputation Investigation of the Impact of Cannabinoids and Other Substances on Ethnic Differentials in US Testicular Cancer Incidence" Accepted BMC Public Health 13th April 2021. https://bmcpharmacoltoxicol.biomedcentral.com/articles/10.1186/s40360-021-00505-x

32. Reece A.S., Hulse G.K. "Epidemiological Overview of Multidimensional Chromosomal and Genome Toxicity of Cannabis Exposure in Congenital Anomalies and Cancer Development." Accepted in Scientific Reports June 13th 2021. https://www.nature.com/articles/s41598-021-93411-5

33. Reece A.S., Hulse G.K. "Quadruple Convergence – Rising Cannabis Prevalence, Intensity, Concentration and Use Disorder Treatment". Lancet Regional Health Europe October 22nd 2021. 100245. https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00231-3/fulltext .

34. Reece A.S. "Neurological, Epigenomic and Multigenerational Adverse Outcomes of Prenatal Cannabis Exposure". Comment on "Association of Comorbid Behavioral and Medical Conditions With Cannabis Use Disorder in Pregnancy" by Meinhofr A.,

Hinde J.M., Keyes K.M. JAMA Psychiatry. Published October 5th 2021. https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2785860

35. Reece A.S., Hulse G.K. "Geotemporospatial and Causal Inference Epidemiological Analysis of US Survey and Overview of Cannabis, Cannabidiol and Cannabinoid Genotoxicity in Relation to Congenital Anomalies 2001–2015." Accepted in BMC Pediatrics 3rd November 2021. Published January 19th 2022. URL: https://rdcu.be/cFksL

36. Reece A.S., Hulse G.K. "Cannabinoid- and Substance- Relationships of European Congenital Anomaly Patterns: A Space-Time Panel Regression and Causal Inferential Study". Environmental Epigenetics Published 5th February 2022. https://academic.oup.com/eep/article-abstract/doi/10.1093/eep/dvab015/6521073

37. Reece A.S., Hulse G.K. "Epidemiological Association of Cannabinoid- and Drug-Exposures and Sociodemographic Factors with Limb Reduction Defects Across USA 1989-2016: A Geotemporospatial Study." Published Spatial and Spatiotemporal Epidemiology February 1st 2022. https://www.sciencedirect.com/science/article/pii/S1877584522000041?via%3Dihub

38. Reece A.S. "Rapid Response: Cannabinoid Genotoxic Trifecta - Cancerogenesis, Clinical Teratogenesis and Cellular Ageing" Rapid Response to Why doctors have a moral imperative to prescribe and support medical cannabis—an essay by David Nutt. British Medical Journal. Published 30th January 2022. URL: https://www.bmj.com/content/376/bmj.n3114/rr-1

39. Reece A.S., Hulse G.K. "Geotemporospatial and Causal Inferential Epidemiological Overview and Survey of USA Cannabis, Cannabidiol and Cannabinoid Genotoxicity Expressed in Cancer Incidence 2003–2017: Part 1 – Continuous Bivariate Analysis". Archives of Public Health, Published 1st April 2022. Volume 80 Pages 99-128. URL: https://rdcu.be/cKfKp . doi: doi.org/10.1186/s13690-022-00811-8 .

40. Reece A.S., Hulse G.K. "Geotemporospatial and Causal Inferential Epidemiological Overview and Survey of USA Cannabis, Cannabidiol and Cannabinoid Genotoxicity Expressed in Cancer Incidence 2003–2017: Part 2 – Categorical Bivariate Analysis and Attributable Fractions." Published 1st April 2022. Archives of Public Health, Volume 80: 100-135. doi: doi.org/10.1186/s13690-022-00812-7 URL: https://rdcu.be/cKfKq .

41. Reece A.S., Hulse G.K. "Geotemporospatial and Causal Inferential Epidemiological Overview and Survey of USA Cannabis, Cannabidiol and Cannabinoid Genotoxicity Expressed in Cancer Incidence 2003–2017: Part 3 – Spatiotemporal, Multivariable and Causal Inferential Pathfinding and Exploratory Analyses of Prostate and Ovarian Cancers." Published 1st April 2022 Archives of Public Health, 80:101-131. URL: https://rdcu.be/cKfOH

42. Reece A.S. "Limblessness: Cannabinoids Inhibit Key Embryonic Morphogens both Directly and Epigenomically" Rapid Response to Why doctors have a moral imperative to prescribe and support medical cannabis—an essay by David Nutt.

British Medical Journal. Published 31th January 2022. URL: https://www.bmj.com/content/376/bmj.n3114/rr-2

43. Reece A.S. "Recent Epigenomic Insights into Mechanisms of Severe Cannabinoid Genotoxicity". British Medical Journal. Rapid Response to Why doctors have a moral imperative to prescribe and support medical cannabis—an essay by David Nutt. Published 7th February 2022. URL: https://www.bmj.com/content/376/bmj.n3114/rr-6

44. Reece A.S. "Epigenomic and Other Mechanisms Underlying Cannabis Neurotoxicity". British Medical Journal. Rapid Response to Why doctors have a moral imperative to prescribe and support medical cannabis—an essay by David Nutt. Published 7th February 2022. URL: https://www.bmj.com/content/376/bmj.n3114/rr-7

45. Reece A.S., Hulse G.K. "Geospatiotemporal and Causal Inference Study of Cannabis and Other Drugs as Risk Factors for Female Breast Cancer USA 2003-2017." Environmental Epigenetics Published 07.04.2022. Vol. 1 pp1-22. https://academic.oup.com/eep/article/8/1/dvac006/6539905

46. Reece A.S., Hulse G.K. "Chapter 7: Cannabinoid Genotoxicity and Congenital Anomalies: A Convergent Synthesis of European and USA Datasets", In: Martin, Patel, & Preedy – "Cannabis Use, Neurobiology, Psychology, and Treatment" Accepted 12th March 2022.

47. Reece A.S., Hulse G.K. "Chapter 8: Cannabis Genotoxicity and Cancer Incidence: A Highly Concordant Synthesis of European and USA Datasets" In Martin, Patel, & Preedy – "Cannabis Use, Neurobiology, Psychology, and Treatment" Accepted 12th March 2022.

48. Reece A.S., Hulse G.K. "Congenital Anomaly Epidemiological Correlates of Δ8THC Across USA 2003-2016: Panel Regression and Causal Inferential Study". Published Environmental Epigenetics 17th May 2022. https://academic.oup.com/eep/advance-article/doi/10.1093/eep/dvac012/6586812

49. Reece A.S., Hulse G.K. "Impact of Converging Sociocultural and Substance-Related Trends on US Autism Rates: Combined Geospatiotemporal and Causal Inferential Analysis European Archives of Psychiatry and Clinical Neuroscience". European Archives of Psychiatry and Clinical Neuroscience. Published 03.07.2022. https://rdcu.be/cQShO https://doi.org/10.1007/s00406-022-01446-0 or as a PDF here https://link.springer.com/content/pdf/10.1007/s00406-022-01446-0.pdf

50. Reece A.S., Hulse G.K. "Epidemiology of Δ8THC–Related Carcinogenesis in USA: A Panel Regression and Causal Inferential Study" International Journal of Environmental Research and Public Health. 2022; 19(13): 7726. Published 23.06.2022 http://www.mdpi.com/1660-4601/19/13/7726/

51. Reece A.S., Hulse G.K. "European Epidemiological Patterns of Cannabis- and Substance- Related Congenital Cardiovascular Anomalies: Geospatiotemporal and Causal Inferential Study". Accepted Environmental Epigenetics 29.06.2022. https://watermark.silverchair.com/dvac015.pdf?token=AQECAHi208BE49Ooan9kkh

W_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAtMwggLPBgkqhkiG9w0BBwagggLAMII
CvAIBADCCArUGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQMSrGYLTO
PHWdjpqVWAgEQgIIChrGW0KhiOZ9kgNjej8fhS6fWVDpDvwr3EaPwDvoxxgyZy
1UohMpAVD9dbEdEQvC50UD9obCyyEs37mKzoss3hkcHVsqTtTWbikpDSj-
n5ujTOGb--
e78cZXmJfwInlf8JcqlUhtigEaTQtiJTi6nAcRyBF1zXhWAFbZ4BFd4CEEPsp4MaB
H-
f5joEehdzmd2GkXhQGDLX6kiAU24Olb8P1eUTDp5hrK9sfpralAD6OGQmskvDI6
d4XXqtLoA9IZfjdWiq3sfLq2AZyPddeMTOlCF2H20CcHw1iOstOTtgolstD5mj0VfjI
e44oSY8X2iM7ThBAf4mYRE80CjYX1mAboZanjgdj2XnJxmcEkuwkX9UnurH8gc
9RDb2B1-JAYlKD5BPdF-
ZNzrjj7cxDMrTazeywZHAJIXzEtdZPU_cLDFGEPp2fROHG1Bep7mF0jg18vJms4
O55ABQy_-BeEi7Ol7qEYG4BRHSxwL_kaMC5CxckSM4-nucr-
1PeHmUnSBnQEypgffMyD79j-P1brlXrq76bx9flMB3W-
t5jbvYsyGYtnUmSiTx5sZSlRViytzcVSIMlp5g87tqzIwjkz5mwZd-2_n5Yf-
RMCFnfxa8Glp9Q0D8vpyRWgY6VI-
y9dKcsy4wTkjAMVTT_wsfaAdIB6fpzC5soaav6LT77a6xytpJDnA88l2AAjaobVOi
XBn6TfqdUZpORknq8n7w85svtppGY543AkSYtqY1ABeyUXcnZtby9FD36cYZgk
HyRC_sHN2Sxm9RpGRJpzWoUpLwjtXOzw82Yq7KvjNgX7iKiIPB8y6eaVnrnRyja
isRGN31x9kyGLvmXGYVJeIBDR5Ub4QEdQWD00

52. Reece A.S., Hulse G.K. "Effects of Cannabis on Congenital Limb Anomalies in 14 European Nations: A Geospatiotemporal and Causal Inferential Study". Accepted Environmental Epigenetics June 30th 2022.
https://watermark.silverchair.com/dvac016.pdf?token=AQECAHi208BE49Ooan9kkh
W_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAtMwggLPBgkqhkiG9w0BBwagggLAMII
CvAIBADCCArUGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQMNHNmS_r
eKcvwoKTJAgEQgIIChq6d3nWsYxJcwkgstque1Yd6h6CrpZ9ajam8m4juGtZU3Xr_
YP_k8XnQcKnm_PzpF5l5Ma1HsO5tBIDcnMA9oIvhQEYGNATMkQpxoYUNy7V
3Uj6pCGRAhpiAA1fODM4mqgeGdJGcYXCRkWel4LoTgdW7dgZIwhymlkpHrhN
gOwXUs98f6wHz3fBxYyldrwGtLIcD6UuXiTL05JGqNhaImA6SafaUkRWRKQUo8
uOb0Y4ZPAJnVHm6xrLiqjhicOOKhhhpxjz4-
0aXuZYhhgKXxoQNaiJPrbgV0hlT2BwVjsivhSFrPqR3otVGThCPVr06cbhGexf7wL
ndnLUZNMesLrNaT1t5NMcNC8sk8KsilVx4PHF27bo9zwotLp0yL8CiRaliIIeVt-
hcb21dYWVykRoJ3lihaJewGP2tSMS0vfvMxoceUXrYU1-
zI0UoSJYQDb4mcRkEziCS1zylRwu20HQrEVZwnbhqOW3qfVUpJlcJ4HLPK4-
AXFvt5zpHeItMsnxJStmsdXwfWby4_dI3_vq_msUbITLV6cQC9417lbAw_c7ht33V
nqycoOJjndOwb5mv8WO0pPdBIqxhxrj6TvpzRMP7xfQr6qhkosQy77XKlw562igAv
vdwwAHBsCwJvKTm6VntXOSfmEEfPlnwJPjk6Qgnpit67nOMBe_yGqXsFu5vfg3s
Wiw5gblK8KB1nGQP78sRnC6S_V9aibgVdYVGbDTgEd_Xuna7c-
9dpIS2zfE0mhUlorkf_IpRD9PGKuy1d3GdBOeDK12xzyw7fLb-
GmQX7nqj8r5l3wVJ2B-
oKaXpXTY8RINtJvE14R06idJRE7bSMxnlFTXL20rXAUS13Y80Zi0

53. Reece A.S. "Disruption of Interlocking Synchrony Between Metabolome and Epigenome Key to Understanding Widespread Embyrotoxicity and Carcinogenicity of Diverse Cannabinoids" Published in The BMJ July 7th 2022.
https://www.bmj.com/content/377/bmj.o1567/rr-0

54. Reece A.S., Hulse G.K. "Extending the "Paracentral Dogma" of biology with the metabolome: Implications for understanding genomic-glycomic-metabolic-epigenomic synchronization". Accepted Engineering 20th July 2022.

55. Reece A.S., Hulse G.K. "European Epidemiological Patterns of Cannabis- and Substance- Related Body Wall Congenital Anomalies: Geospatiotemporal and Causal Inferential Study". Published International Journal of Environmental Research and Public Health 26th July 2022. Vol. 19: pp9027 – 9064. https://www.mdpi.com/1660-4601/19/15/9027/pdf

56. Reece A.S., Hulse G.K. "Cannabis, Cannabidiol, Cannabinoids and Multigenerational Policy". Accepted Engineering 21st July 2022.

57. Reece A.S., Hulse G.K. "European Epidemiological Patterns of Cannabis- and Substance- Related Body Wall Congenital Anomalies: Geospatiotemporal and Causal Inferential Study". Published International Journal of Environmental Research and Public Health 19(15): 9027 - 9064. 25th July 2022. https://www.mdpi.com/1660-4601/19/15/9027/pdf

58. Reece A.S., Hulse G.K. "Cannabis, Cannabidiol, Cannabinoids and Multigenerational Policy". Published Engineering 2nd September 2022. https://doi.org/10.1016/j.eng.2022.07.012 doi: https://doi.org/10.1186/s13690-022-00986-0

59. Reece A.S., Hulse G.K. "Response to Chen et. al." Archives of Public Health. Archives of Public Health 80(1): 235-236. Published November 16th 2022. https://archpublichealth.biomedcentral.com/articles/10.1186/s13690-022-00986-0

60. Reece A.S., Hulse G.K "Cannabis- and Substance- Related Epidemiological Patterns of Chromosomal Congenital Anomalies in Europe: Geospatiotemporal and Causal Inferential Study". International Journal of Environmental Research and Public Health 2022; 19(18): 11208-11258. Published September 6th 2022. https://www.mdpi.com/1660-4601/19/18/11208

61. Reece A.S., Hulse G.K. "State Trends of Cannabis Liberalization as a Causal Driver of Increasing Testicular Cancer Rates across the USA". Published October 5th 2022 International Journal of Environmental Research and Public Health 19(19): 12759 – 12796. https://www.mdpi.com/1660-4601/19/19/12759/htm

62. Reece A.S., Hulse G.K. "Socioeconomic, Ethnocultural, Substance- and Cannabinoid-Related Epidemiology of Down Syndrome USA 1986-2016: Combined Geotemporospatial and Causal Inference Investigation". Accepted in International Journal of Environmental Research and Public Health 19(20): 13340 - 13376. 16th October 2022. https://www.mdpi.com/1660-4601/19/20/13340/pdf https://www.mdpi.com/1660-4601/19/20/13340

63. Reece A.S., Hulse G.K. "European Epidemiological Patterns of Cannabis- and Substance- Related Congenital Uronephrological Anomalies: Geospatiotemporal and

Causal Inferential Study". Accepted in International Journal of Environmental Research and Public Health 19th October 2022. Published October 23rd 2022. 19(21): 13769 – 13828. https://doi.org/10.3390/ijerph192113769 doi: 10.3390/ijerph192113769 .

64. Reece A.S., Hulse G.K "Epigenomic and Other Evidence for Cannabis-Induced Aging Contextualized in a Synthetic Epidemiologic Overview of Cannabinoid-Related Teratogenesis and Cannabinoid-Related Carcinogenesis". Published in International Journal of Environmental Research and Public Health 19(24): 16721 - 16776. 13th December 2022. https://www.mdpi.com/1660-4601/19/24/16721 doi: https://doi.org/10.3390/ijerph192416721 .

65. Reece A.S., Hulse G.K. "Novel Insights into Potential Cannabis-Related Cancerogenesis from Recent Key Whole Epigenome Screen of Cannabis Dependence and Withdrawal: Epidemiological Commentary and Explication of Schrott et.al.". Published in "Genes" 41(1): 32 - 45. December 22st 2022. https://www.mdpi.com/2073-4425/14/1/32 https://doi.org/10.3390/genes14010032 .

66. Reece A.S., Hulse G.K. "European Epidemiological Patterns of Cannabis- and Substance- Related Congenital Neurological Anomalies: Geospatiotemporal and Causal Inferential Study." Published in International Journal of Environmental Research and Public Health December 27th 2022. 20(1): 441 - 475. https://www.mdpi.com/1660-4601/20/1/441. doi: 10.1093/eep/dvac015 .

67. Reece A.S., Hulse G.K. "Geospatiotemporal and Causal Inferential Study of European Epidemiological Patterns of Cannabis- and Substance-Related Congenital Orofacial Anomalies" J. Xenobiotics. 2023. 13(1): 42-74. https://www.mdpi.com/2039-4713/13/1/6 . Doi: https://doi.org/10.3390/jox13010006 .

68. Reece A.S., Hulse G.K. "Patterns of Cannabis- and Substance- Related Congenital General Anomalies in Europe: A Geospatiotemporal and Causal Inferential Study". Pediatric Reports. Accepted February 3rd 2023. Published February 8th 2023. 2023. 15(1) 69-121. https://www.mdpi.com/2036-7503/15/1/9 doi: https://doi.org/10.3390/pediatric15010009

69. Reece A.S., Hulse G.K. "Congenital Gastrointestinal Anomalies in Europe 2010–2019: A Geo-Spatiotemporal and Causal Inferential Study of Epidemiological Patterns in Relationship to Cannabis- and Substance Exposure " Accepted Gastroenterology Insights. February 7th 2023. 2023; 14(1): 64-109. https://www.mdpi.com/2036-7422/14/1/7

70. Reece A.S., Hulse G.K "Clinical Epigenomics Explains Epidemiology of Cannabinoid Genotoxicity Manifesting as Transgenerational Teratogenesis, Cancerogenesis and Aging Acceleration". International Journal of Environmental Research and Public Health 2023; 20(4): 3360-3383. https://www.mdpi.com/1660-4601/20/4/3360

71. Reece A.S., Hulse, G.K. "Cannabis Could be the Missing Environmental Carcinogen Hiding in Plain View". Gastroenterology 165 (4) 1092-1093 ePub April 11th 2023

2023. https://www.gastrojournal.org/article/S0016-5085(23)00587-5/fulltext?referrer=https%3A%2F%2Fpubmed.ncbi.nlm.nih.gov%2F doi: https://doi.org/10.1053/j.gastro.2023.02.050

72. Reece A.S. "Cannabis Neurotoxicity and Genotoxicity" British Medical Journal. Letter to the Editor 2023, 380: p407. https://www.bmj.com/content/380/bmj.p407/rapid-responses

73. Reece A.S. "Cannabis Genotoxicity" Online Encyclopaedia. Published March 6th 2023. https://encyclopedia.pub/entry/41883 E Scholarly Community Encyclopaedia.

74. Reece A.S., Hulse G.K. "Sociodemographically Stratified Exploration of Pancreatic Cancer Incidence in Younger US Patients: Implication of Cannabis Exposure as a Risk Factor". Gastroenterology Insights, Published May 12th 2023. https://www.mdpi.com/2036-7422/14/2/16 https://doi.org/10.3390/gastroent14020016

75. Reece A.S. Comment on "Addiction Medicine Physicians and Medicinal Cannabinoids" in JAMA Psychiatry May 16th 2023. https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2804266

76. Reece A.S., Hulse G.K. "Cannabis- and Substance-Related Carcinogenesis in Europe: A Lagged Causal Inferential Panel Regression Study" Published March 18th 2023. Journal of Xenobiotics, 13(3): 325-385. https://www.mdpi.com/2039-4713/13/3/24

77. Reece A.S., Hulse G.K. "Perturbation of 3D Nuclear Architecture, Epigenomic Aging, and Dysregulation, and Cannabinoid Synaptopathy Reconfigures Conceptualization of Cannabinoid Pathophysiology: Part 1 – Aging and Epigenomics" Frontiers in Psychiatry Vol 14: 1-23. Published 05.09.2023. doi: https://doi.org/10.3389/fpsyt.2023.1182535 https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1182535/full

78. Reece A.S., Hulse G.K. "Perturbation of 3D Nuclear Architecture, Epigenomic Aging, and Dysregulation, and Cannabinoid Synaptopathy Reconfigures Conceptualization of Cannabinoid Pathophysiology: Part 2 – Metabolome, Immunome, Synaptome." 03.10.2023 Frontiers in Psychiatry. Volume 14, Pages 1-25. https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1182536/full

79. Reece A.S., Hulse G.K. "Key Insights into Cannabis-Cancer Pathobiology and Genotoxicity." Accepted Addiction Biology September 26th 2024.

COMMISSIONED BOOK CHAPTERS

80. Reece A.S., Hulse G.K. "Cannabinoid Genotoxicity and Congenital Anomalies: Convergent Synthesis of European and USA Datasets" In Preedy V. "Cannabis, Cannabinoids and Endocannabinoids." Elsevier Press, 2022. Accepted January 2022.

81. Reece A.S., Hulse G.K. "Cannabis Genotoxicity and Cancer Incidence: A Highly Concordant Synthesis of European and USA Datasets" In Preedy V. "Cannabis, Cannabinoids and Endocannabinoids." Elsevier Press, 2022. Accepted January 2022.

82. Reece A.S., Hulse G.K. "Close Parallels between Cannabis Use and Deteriorating US Mental Health at Four Levels Supports and Extends the Epidemiological Salience of Demonstrated Causal Mental Health Relationships: A Geospatiotemporal Study". Chapter 1 in Cannabinoid Epidemiology: Neurotoxicity, Genotoxicity, Teratogenicity and Carcinogenicity, Elsevier Press. Accepted 27th September 2022.

83. Reece A.S., Hulse G.K. "Linked Rise of Cannabis Use and Autism Incidence Demonstrated by Close Three Level Geospatiotemporal Relationships, USA, 1990-2011". Chapter 2 in Cannabinoid Epidemiology: Neurotoxicity, Genotoxicity, Teratogenicity and Carcinogenicity, Elsevier Press. Accepted 27th September 2022.

84. Reece A.S., Hulse G.K. "Geospatiotemporal and Causal Inferential Analysis of United States Congenital Anomalies as a Function of Multiple Cannabinoid- and Substance- Exposures: Phenocopying Thalidomide and Hundred Megabase-Scale Genotoxicity". Chapter 3 in Cannabinoid Epidemiology: Neurotoxicity, Genotoxicity, Teratogenicity and Carcinogenicity, Elsevier Press. Accepted 27th September 2022.

85. Reece A.S., Hulse G.K. "Geospatiotemporal and Causal Inferential Epidemiological Survey and Exploration of Cannabinoid- and Substance- Related Carcinogenesis in USA 2003-2017". Chapter 4 in Cannabinoid Epidemiology: Neurotoxicity, Genotoxicity, Teratogenicity and Carcinogenicity, Elsevier Press. Accepted 27th September 2022.

86. Reece A.S., Hulse G.K. "Multivalent Cannabinoid Epigenotoxicities and Multigenerational Aging". Chapter 5 in Cannabinoid Epidemiology: Neurotoxicity, Genotoxicity, Teratogenicity and Carcinogenicity, Elsevier Press. Accepted 27th September 2022.

87. Reece A.S. "Cannabinoid Epigenotoxicity and Genotoxicity" JAMA. Published November 7th 2022. Comment on "Closing the Loophole on Hemp-Derived Cannabis Products" https://jamanetwork.com/journals/jama/fullarticle/2798426

88. Reece A.S., Hulse G.K., "Key Insights into Cannabis-Cancer Pathobiology" eLetter to Science journal in reply to "Micronuclear collapse from oxidative damage" by Di Bona M., Bakhoum S.F. et.al. Science 2024 August 30, 385(6712): eadj8691. doi: 10.1126/science.adj8691. ePublished 24.09.2024.

https://www.science.org/doi/10.1126/science.adj8691?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed#elettersSection

89. Reece A.S., Hulse G.K., "Key Insights into Cannabis-Cancer Pathobiology" eLetter to Science journal in reply to "A p62-dependent rheostat dictates micronuclei catastrophe and chromosome rearrangements" by Martin S., Santaguida S et.al. Science 2024 August 30, 385(6712): eadj7446. doi: 10.1126/science.adj7446. ePublished 24.09.2024. https://www.science.org/doi/10.1126/science.adj7446?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed#elettersSection

90. Reece A.S., Hulse G.K. "Perspective: Key Insights into Cannabis-Cancer Pathobiology and Genotoxicity" In Addiction Biology. Accepted September 25th 2024.