

Cannabis, the Respiratory System and Cancers

An extract from Cannabis: ‘A General Survey of its Harmful Effects’ **Mary Brett updated August 2020**

There are several problems associated with the investigation of possible links between cannabis use and any carcinogenic effects it may have on human cells.

There are now some 140,000 or so scientific research papers on tobacco, while those on cannabis still amount only to about a tenth of that number. It is a relatively young science and, like tobacco, its side effects are usually not apparent for decades.

Cannabis smoking has only been widespread in Western society since the early 1970s and there would presumably be a 20 to 30 year latency period between the initiation of smoking and the development of cancer as is the case with tobacco.

Cannabis smokers often mix tobacco with their cannabis so they run all the well-documented risks of developing cancer associated with tobacco smoke. Relatively few of them smoke cannabis alone so any consequences and therefore causes are almost impossible to separate out. Marijuana smokers are more likely to under report their smoking, if they report it at all.

Large samples are required for case-control studies to take place. It is very difficult to get reliable information about an illegal substance from a large number of people. Questions about cannabis smoking are rarely asked of lung cancer patients.

On the other hand the similarities between tobacco and cannabis are many, the main difference being the presence of nicotine in tobacco and the 60 or so cannabinoids in cannabis (Hoffman et al 1975, Tashkin et al 1997, BMA 1997). So similar side effects may be expected.

Although the number of cannabis “cigarettes” consumed in a day would generally be much fewer than the daily total of tobacco cigarettes, the technique is different. Cannabis smoke is usually inhaled more deeply, held in the lungs for longer and smoked right down to the butt to get full money value. Cannabis cigarettes generally lack filters. (Wu et al 1988). More tar is inhaled from the cannabis butt than from its tip (Tashkin et al 1999).

Cannabis smoke contains 4 to 5 times as much tar as tobacco smoke so the amount of tar deposited in the lungs daily in a cannabis smoker is comparable to that of a tobacco smoker with a 20 a day habit (Benson et al, 1995).

Also the tar from cannabis contains 50% more of some of the carcinogens found in tobacco, notably benzpyrene, a potent carcinogen and a key factor in the promotion of lung cancer (Hoffman et al 1997, Tashkin et al 1997, Novotny et al 1976, Leuchtenberger et al 1983).

For lung cells to become cancerous, a particular combination of cell-growth regulating genes (oncogenes) must become activated or undergo mutation (suppressor genes of tumours).

Marijuana smoke has been reported to produce chromosome aberrations in bacteria as demonstrated by the Ames test (Busch et al 1979 and Wehner et al 1980).

Biopsies of bronchial mucosa have yielded interesting results. Abnormal proliferation of cells (goblet and reserve), transformation of normal ciliated cells to squamous metaplasia (skin-like cells), accumulation of inflammatory cells and abnormal cell nuclei have all been observed (Gong et al 1987, Fliegel et al 1997, Barsky et al 1998). A much higher proportion of these abnormalities was seen in marijuana smokers compared to non-smokers, the number was similar to that of tobacco smokers. Smokers of both tobacco and marijuana exhibited the highest number of all, suggesting the two have an additive effect. Precursors of the development of lung cancer in tobacco smokers include squamous metaplasia and abnormal nuclei (Auerbach et al 1961). Confirmation of these observations also came in 1980 from FS Tennant when he examined US servicemen who were heavy hashish smokers. The mutagenic properties of cannabis smoke were previously recorded in papers in the seventies (Magus

and Harris 1971 and Hoffman et al 1975). Human lung explants, exposed to marijuana smoke resulted in DNA and chromosomal alterations (Van Hoozen et al 1997).

Oncogenes and tumour suppressive genes, when mutated, produce proteins which cause cells to multiply rapidly and uncontrollably, resulting in tumours. Two of these proteins were found to be markedly increased in cannabis smokers compared to tobacco or non-smokers, the effects of tobacco and cannabis being additive (Roth et al 1998).

The mutagenic effects of marijuana smoke have also been observed by Chiesara and Rizzi 1983, Gilmore et al 1971, Herha and Obe 1974 and Stenchever et al 1974.

Benzpyrene can cause alteration of a gene, P53, one of the commonest tumour suppressor genes if acted on by a chemical particle, CYP1A1. THC has been shown to increase production of this particle so making possible the development of respiratory cancer. P53 is thought to play a part in 75% of lung cancers and it is expressed in 11% of cannabis and tobacco smokers (Dinissenko et al 1996, Marques-Magallanes et al 1997).

The immune system has a role to play in the development of cancer. Alveolar macrophages protect the lungs from infection, they also kill tumour cells. Marijuana and tobacco smokers produce two or three times as many of these cells as non-smokers. The effects of smoking both being additive (Barbers et al 1987). The macrophages in both tobacco and marijuana smokers were larger and had more inclusions, probably due to the ingestion of smoke particles (Beals et al 1989). A more recent paper by Baldwin et al in 1997 found significant impairment of the macrophage cells of both tobacco and marijuana smokers. These cells have been shown to have cannabis receptors (Bouaboula et al 1993). Anti-tumour immunity depends on antigen-presenting dendritic cells being able to stimulate the proliferation of T lymphocytes that identify and destroy tumour cells. In in-vitro studies in which dendritic cells and T lymphocytes were incubated with or without THC, the THC suppressed the T cell proliferation in a dose-dependent manner (Roth et al 1997). Two earlier papers on this subject were written in 1975, Peterson et al and Nahas et al. DNA alterations have been seen in the lymphocytes of pregnant marijuana smokers and their newborns. This study is particularly important as tobacco smokers were excluded (Ammenheuser et al 1998). Cannabis smoking also depressed pro-inflammatory cytokine production. Cytokines regulate macrophage function so this may account for the impairment of their ability to kill tumour cells (Baldwin et al 1997).

Experiments on animals have yielded confirmatory evidence for many of the previous observations. In 1979 Rosenkranz and Fleischman found changes in the bronchial epithelia of rats after they had inhaled marijuana smoke for several months. These changes were consistent with precancerous alterations in cells. In the same year Fried and Charlebois administered cannabis smoke to rats during pregnancy and discovered impaired development in the F2 generation, so not only was damage caused to the first but also the second generation. In 1997 Zhu and others treated mice for 2 weeks with THC prior to the implantation of Lewis lung cancer cells. Larger faster-growing tumours resulted suggesting that the THC impairs the development of anti-tumour immunity in vivo. Dubinett et al in 2000 also found that mice injected with THC had reduced capability to fight the growth of tumours.

Painting tar from marijuana smoke on the skins of mice produced lesions correlated with malignancies (Cottrell 1973).

There are a significant number of reports of human cancers which may be linked to the smoking of marijuana. FM Taylor in 1988 examined adults with upper respiratory tract cancer over a period of 4 years. Of 6 men and 4 women, average age 33.5 years, nine had carcinomas of the lungs tongue or larynx, five were heavy cannabis smokers, two smoked it regularly, one had possibly used other drugs and two were non cannabis smokers. It was complicated by the fact that six were heavy alcohol users and six were smokers of tobacco. He concluded that regular marijuana use was a potent factor especially in the presence of other risk factors. He conceded that alcohol and tobacco may have played a part, but pointed out that the peak incidence for cancers due to tobacco or alcohol is in the seventh decade of life. All of these victims were much younger.

In 1989 Caplan and Brigham reported two cases of tongue cancer. One was a man of 37 the other a man of 52. Both were heavy cannabis users, neither smoked tobacco or drank alcohol. Endicott and Skipper in 1991 conducted a 2-centre USA retrospective study. Twenty-six patients of age 41 or less

were diagnosed with throat or head tumours. The normal average age for tumours of this type is 57. All 26 were current or former marijuana smokers.

PJ Donald in 1993 examined patients with cancer of the head and throat over a 20-year period. He found 22 patients of age 40 or under on diagnosis, with squamous cell cancer. Their average age was 26. Nineteen of them were cannabis smokers, 16 being heavy users. In 13 the tumour was in the tongue or elsewhere in the oral cavity. Only half of them smoked tobacco.

110 private patients with lung cancer were studied. Nineteen (17%) of them were under 45. Thirteen of these had smoked marijuana of whom 12 reported current tobacco use. No tobacco-only smoking patients under 45 were noted (Sridhar et al 1994).

An epidemiological study to examine a possible association between cancer and marijuana was published in 1997 by Sidney and colleagues. 65,000 health plan members aged between 15 and 49 in 1979 to 1985 were followed for the development of new cancers till 1993. 182 tobacco-related cancers were detected, of which 97 were in the lungs. The study revealed no risk factors for cancers for lifetime or current use of marijuana.

The major limitation in this exercise is that those who were heavy or long-term users of cannabis were not followed up for long enough to detect cancers. Another criticism is that there may not have been sufficient of these long-term or heavy users to make the study effective. It must be remembered that most marijuana users quit before the level of exposure is sufficient to initiate the development of cancer and cannabis smoking has only been widespread in the USA since the 70s.

Zhang et al in 1999 studied 173 patients with carcinoma of the head and neck and compared them with 176 cancer-free controls. Age, sex, race, education, alcohol consumption and exposure to cigarette smoke either actively or passively, were all controlled for. Marijuana smoking increased the risk of squamous cell carcinoma of the head or neck, and a further increased risk was suggested with rising doses. Among people who smoked once a day the risk factor was 2.1 times compared with non-smokers, with those using it more than once a day the risk factor rose to 4.9. With patients who smoked cannabis and tobacco the risk was 36 times that for non-smokers.

It was reported in the press in January 2000 that a leading cardio-thoracic surgeon, Mr Alan Kirk of Glasgow's Western Infirmary was treating 12 patients aged 27 to 35 for lung cancer. Ten of them admitted they were regular cannabis smokers. Lung cancer normally develops in much older patients. All of them had also used tobacco but Mr Kirk said he thought it likely that cannabis had accelerated the process. He now routinely asks all his younger lung cancer patients whether they have smoked the drug. He has called for large scientific studies to be done.

The most prominent name and authority on cannabis and diseases of the respiratory system is that of Dr Donald Tashkin. He has researched the topic since the early seventies.

In 1993 he listed the factors suggesting that cannabis smoking may be associated with an increased risk of respiratory tract cancers.

1. Cannabis smoke has 50% more of certain carcinogens than tobacco smoke, especially the highly carcinogenic benz-pyrene.
2. Four times as much tar is produced by a cannabis cigarette than a tobacco one.
3. Experiments on animals have shown that cannabis smoke or tar from it is carcinogenic.
4. Heavy cannabis consumers have significantly higher numbers of cellular changes consistent with the preliminary stages of cancer.
5. There have been several reports of young cannabis-using people exhibiting the development of cancer. Tumours have appeared 10 to 30 years earlier than those who smoked tobacco alone.

In a review paper in 2002 he added that examination of the mucous membranes in long-term smokers suggests that THC weakens the immune defences against tumour cells.

In November 2002 the British Lung Foundation produced a paper "A Smoking Gun? The Impact of Cannabis Smoking on Respiratory Health". One of their recommendations was: "The British Lung Foundation recommends a public health education campaign aimed at young people to ensure that they

are fully aware of the increased risk of pulmonary infections and respiratory cancers associated with cannabis smoking”.

In September 2003 The Thoracic Society of Australia and New Zealand produced a position paper in The Internal Medicine Journal on the respiratory health effects of cannabis (Taylor and Hall). They also called for a campaign. “Public Health Education should dispel the myth that cannabis smoking is relatively safe by highlighting that the adverse respiratory effects of smoking cannabis are similar to those of smoking tobacco...that the respiratory hazards of smoking cannabis are significant...almost all studies indicate that the effects of cannabis and tobacco smoking are additive and independent”.

Gardner and others in 2003 found that a cannabinoid, methanandamide, resulted in an increased rate of tumour growth in murine lung cancer.

The death rate from lung cancer in Maori people is 3 times higher than in non-Maoris. In fact they have the highest lung-cancer death rate in the world. The average age of death is lower, 63 compared to 70 years. There is also a high incidence of tobacco smoking in these people, but equivalent rates are seen in areas of Asia and Europe where fewer succumb to cancer of the lung. A high rate of heavy marijuana use among the Maoris has led scientists to suggest that this may be a contributory factor. Research has shown that cannabis use has reached epidemic proportions and is rising (Harwood et al 2004). The Sydney Morning Herald on July 27th 2006 reported that, of the 142,144 people treated by Australia’s drug and alcohol treatment agencies in 2004-2005, 13,666 or almost 10% were Aboriginal or Torres Strait Islanders, amounting to nearly 5 times the proportion of indigenous people in the population. Among these people, 21% of males between 10 and 19 years were treated compared to 11% of other Australian males of the same age. With indigenous 10 to 19 year-old females the figures were 19% compared to 11% of the others. Cannabis was the commonest illicit drug for which treatment was sought.

Sarafian et al in 2005 suggested that THC contributes to DNA damage, inflammation and alterations in apoptosis (programmed cell death) in tracheo-bronchial epithelium and concluded that, “ THC delivered as a component of marijuana smoke, may induce a profile of gene expression that contributes to the pulmonary pathology associated with marijuana use”.

In June 2005 Roth and Tashkin of UCLA, the two leading authors of many papers linking cannabis and cancer for over 10 years, described an epidemiological study at the meeting of the International Cannabinoid Research Society in Tampa, Florida. This paper has yet to appear on the ICRS website. Tashkin reported that they had failed to substantiate the link. Needless to say the press immediately issued banner headlines like “Marijuana is safer than tobacco”. However it has emerged that the study lacked statistical power. Tashkin and Roth explained that they had very few patients smoking more than 6 joints a day, a very mild level of consumption. They said that had they had more moderate and heavy smokers, their outcomes would almost certainly have been different. The study was originally designed to have 3 controls for each cancer case, in reality the ratio was around 0.7. Statistics are powerful but not powerful enough to account for gross flaws in sampling errors and study design.

Tashkin also in June 2005, reviewed the literature on lung injury caused by smoking marijuana. He concluded, “Regular marijuana smoking produces a number of long-term pulmonary consequences including chronic cough and sputum, histopathologic evidence of widespread airway inflammation and injury and immunohistochemical evidence of dysregulated growth of respiratory epithelial cells that may be pre-cursors of cancer.....Habitual use of marijuana is also associated with abnormalities in structure and function of alveolar macrophages including impairment in microbial phagocytosis and killing that is associated with defective production of immunostimulatory cytokines and nitric oxide thereby potentially predisposing to pulmonary infection”.

Dr Martha Terris et al, of Georgia’s Medical College and the Veterans Affairs Medical Centre Augusta, writing in Urology January 2006 reported that, of 52 men between 44 and 60 with transitional cell bladder cancer, 88.5% had a history of marijuana smoking. Almost 31% were still using the drug. 104 controls were seekers of urological care other than bladder cancer. Tobacco smoking is the major risk for bladder cancer but is only common in the over 60s. Since marijuana metabolites have a half-life in urine about 5 times greater than tobacco metabolites, they warned that, “Marijuana smoking may be an even more potent stimulant of malignant transformation in transitional epithelium than tobacco smoking”.

A systematic review of 19 studies into the impact of marijuana smoking on the development of pre-malignant lung changes and lung cancer was carried out by Mehra et al in 2006. Deficiencies in the methodology of some of the studies were noted. The conclusion was as follows: “ Given the prevalence of marijuana smoking and studies predominantly supporting biological plausibility of an association of marijuana smoking with lung cancer on the basis of molecular, cellular, and histopathologic findings, physicians should advise patients regarding potential adverse health outcomes until further rigorous studies are performed that permit definitive conclusions”.

Other adverse respiratory effects are seen with cannabis smoking. In 2004 Moore et al looked at over 6500 adults aged 20 to 59. Current marijuana use was defined as 100+ lifetime use and at least one day of use in the past month. Self-reported respiratory symptoms included chronic bronchitis, frequent phlegm and wheezing, shortness of breath, pneumonia and chest sounds in the absence of a cold. They concluded that efforts to reduce and prevent marijuana use may have substantial public health benefits associated with decreased respiratory health problem.

In 2006 the risk of lung cancer and past use of cannabis was studied in Tunisia by Berthiller et al. They found that the odds ratio for the past use of cannabis and lung cancer was 4.1 after adjustment for age, tobacco use and occupational exposures. No clear dose-response relationship was observed between the risk of lung cancer and the intensity or duration of cannabis use. “This study suggests that smoking cannabis may be a risk factor for lung cancer”.

Bluhm and others in 2006 found that maternal use of recreational drugs increased the risk of neuroblastoma in offspring. 538 children with the cancer were studied, and compared with 504 age-matched controls. They concluded that maternal use of any illicit or recreational drug around pregnancy increased the risk of neuroblastoma in offspring, particularly marijuana use in the first trimester of pregnancy. Evaluation of other recreational drugs was limited by infrequent use.

A systematic review of 34 studies on pulmonary function and respiratory complications was carried out in 2007 by Tetrault et al. The summarized findings are as follows:

Short-term marijuana smoking was associated with improved airway response in 10 of 11 challenge studies (effects assessed immediately or shortly afterwards, 15 mins or 1 hour). However the results of the other one suggested a reversal of this effect after 1.5 to 2 months of marijuana smoking. Longer-term marijuana smoking was inconsistently associated with airflow obstruction. Results from pulmonary function tests were worse in marijuana smokers than in controls in 8 of 14 studies. Longer-term marijuana smoking was associated with an increased risk of various respiratory complications (cough, sputum production, wheezing, dyspnea, pharyngitis, worsening of asthma symptoms) in 14 of 14 studies. The overall quality of studies varied, many failed to control for tobacco smoking and none defined a standardized measure of marijuana dose.

A story in BBC News on 3rd June 2007 reported a case of emphysema in a 37-year-old woman who had smoked cannabis for 20 years when it was diagnosed at the age of 34. She had progressed from 2/day to up to 10/day. Dr Onn Min Kon of St Mary’s Hospital London believes her cannabis smoking may be to blame for her condition. He has several other young cannabis-smoking patients who have lungs normally seen in 65 year-olds. The woman said, “If I don’t stop smoking I won’t be around much longer – there is no cure for emphysema, the holes in my lungs are getting bigger.... There should be adverts showing people like me”. Dr Kon is planning a study to compare the lungs of cannabis smokers with those of tobacco-only users., he will use lung-function tests and CT scans.

Marijuana worsens breathing problems in current smokers with chronic obstructive pulmonary disease (COPD) according to a paper presented at The American Thoracic Society 2007 International Conference in May 2007. Among people of 40 and over, tobacco smokers were 2.5 times as likely to develop COPD as non-smokers, while smoking cigarettes and marijuana together the risk rose to 3.5 times. The odds of someone smoking tobacco and cannabis developing *any* respiratory symptoms were 18 times more than a person who used neither. The study involved 648 adults of 18 and over (Tan W 2007).

On March 26th 2007, Dr Sarah Aldington of The Medical Research Institute in Wellington presented a paper to The Thoracic Society conference in Auckland. She said that “Approximately 5% of lung

cancer cases in those aged 55 and under may be attributable to cannabis, equating to 15 new cases a year. In 2002 306 people were diagnosed in New Zealand with lung cancer. “The younger someone starts smoking cannabis, the higher the risk of lung cancer”, she said. The risk of developing the disease increased by about 8% per year for people whose cumulative exposure equated to smoking one joint a day, about the same as a person with a pack a day tobacco habit.

Aldington et al in Thorax 2007, in a study of 339 subjects, divided into 4 smoking groups, tobacco only, cannabis only, cannabis and tobacco and non-smokers of either substance. They concluded that, “Smoking cannabis was associated with a dose-related impairment of large airways function resulting in airflow obstruction and hyperinflation. In contrast cannabis smoking was seldom associated with macroscopic emphysema. The 1:2.5 to 6 dose equivalence between cannabis joints and tobacco cigarettes for adverse effects on lung function is of major public health significance”.

A connection between cannabis smoking and emphysema was described in a paper by Beshay and others in October 2007. It concluded, “In case of emphysema in young individuals, marijuana use has to be considered in the differential diagnosis. The period of marijuana smoking seems to play an important role in the development of lung emphysema. This obviously quite frequent condition in young and so far asymptomatic patients will have medical, financial and ethical impact, as some of these patients may be severely handicapped or even become lung transplant candidates in the future”.

In 2008, Moir et al compared marijuana and tobacco smoke. Ammonia was present in mainstream marijuana smoke at up to 20 times that in tobacco smoke, hydrogen cyanide, NO, NOx, and some aromatic amines were 3 to 5 times greater. Sidestream marijuana smoke had more polycyclic aromatic hydrocarbons (PAHs) than sidestream tobacco smoke. ‘The confirmation of the presence, in both mainstream and sidestream smoke of marijuana cigarettes of known carcinogens and other chemicals implicated in respiratory diseases is important information for public health and communication of the risk related to exposure to such materials’.

Hii et al in January 2008 found that marijuana smokers face rapid lung destruction, approximately 20 years earlier than tobacco smokers. Bullous lung disease (bullae) is a condition where air trapped in the lungs causes an obstruction to breathing and eventual destruction of the lungs. The condition can often go undetected, not showing up on chest x-rays. The average age of marijuana smokers with lung problems is 41 compared with tobacco smokers at 65. One of the authors said, “What is outstanding about this study is the relatively young ages of the lung disease patients, as well as the lack of abnormality on chest x-rays and lung functions in nearly half the patients we tested. Marijuana is inhaled as extremely hot fumes to the peak inspiration and held for as long as possible before slow exhalation. This predisposes to greater damage to the lungs and makes marijuana smokers more prone to bullous disease as compared to cigarette smokers”.

A comparison of the carcinogenic effects of cannabis versus tobacco was carried out in New Zealand by Aldington et al January 2008. They found that the lung cancer risk of one marijuana joint a day equals that of a daily packet of cigarettes. For every one joint/day smoked for a year the risk factor rose 8%. This association was similar to the 7% risk seen for a pack/day for a year of tobacco smoking.

Daling et al in 2009, found an association between marijuana smoking and testicular cancer. 369 men between 18 and 44 with testicular germ cell tumours were investigated in Washington State. Men who smoked the drug once a week or started long-term when they were adolescents were twice as likely to develop the particularly aggressive form, nonseminoma which accounts for about 40% of all cases. Current marijuana use was linked to a 70% increase for the disease.

Tan WC et al, 2009 (April) found that smoking marijuana and tobacco increases the risk of COPD. People over 40 who used both tobacco and marijuana were almost 3 times more likely to suffer from COPD. The use of marijuana alone was not linked to this increase in risk. It appears that the marijuana may act as a kind of “primer” in the airways, augmenting the effects of tobacco.

June 2009, Singh R et al found that cannabis use increases the risk of cancer. They unearthed “convincing evidence” that cannabis smoke damages DNA in ways that could potentially increase the risk of cancer in humans. They discovered that the smoking of 3 to 4 cannabis cigarettes/day would cause the same degree of damage to bronchial mucus membranes as 20 or more tobacco cigarettes/day.

Cannabis smoke, because of its lower combustability compared to tobacco, contains 50% more carcinogenic polycyclic aromatic hydrocarbons than tobacco smoke.

June 2009 The CIC (Carcinogen Identification Committee) of The OEHHA (Office of Environmental Health Hazard Assessment) of the California Environmental Protection Agency, determined that marijuana smoke was clearly shown, through scientifically validated testing, according to generally accepted principles, to cause cancer.

2012 Pletcher looked at the association between marijuana exposure and pulmonary function over 20 years. He concluded that 'occasional and low cumulative marijuana use' (2-3 joints/month) was not associated with adverse effects on pulmonary function', but also that there was increasing evidence of lung trouble among smokers of 20 or more/month. However his research was widely criticised. The comparison was made with a tobacco smoker of 8-9cigarettes/day. They did not compare 2-3/month tobacco users with 2-3/month cannabis smokers, or heavy with heavy. They only looked at limited lung function parameters, FeV1 (Forced expiratory Volume) and FVC (Forced Vital Capacity). No microscopic analysis of tissue was carried out. No other area of potential damage was addressed. Marijuana smokers inhale more deeply than tobacco smokers and hold their breaths longer. This may stretch the lungs so resulting in larger volumes. How much air you can force out of your lungs was the only measurement taken. Other studies have produced different results and can be read in this chapter:

2012 British Lung Foundation C.E.O. Dame Helena Shovelton said that cannabis smoking poses a 20 times greater risk of lung cancer per cigarette than tobacco smoking. Used by more than a third of young people under 24, but 88% believe it's less dangerous than tobacco. A third said it did not harm health. The average puff on a joint is two thirds longer and held in lungs for 4 times longer. So Cannabis smoker inhales 4 times as much tar and 5 times as much carbon monoxide. With each puff the smoke particles become more concentrated and harmful.

Because cannabis can suppress the immune system, smokers are at risk of respiratory problems: coughing, wheezing, sputum production, acute bronchitis and airway obstruction. Also infective lung conditions, TB and legionaire's disease. As well as pneumothorax – collapsed lung and lung cancer. It is estimated that 5% of lung cancers in those aged 55 or under may be caused by smoking cannabis.

2012 Sept Lacson et al, Looked at the possible increase of testicular cancer in marijuana users. Testicular cancer is the commonest cancer diagnosed in young men of 15-45 and is increasing. The self-reported recreational use among 163 young men with diagnosed testicular cancer and compared it with 292 healthy controls. Men with a history of marijuana use were twice as likely to have sub-types of testicular cancer called non-seminoma, and mixed germ cell tumours. These tumours carry a worse prognosis than the seminoma type

2014 Chinnappa and others investigated emphysema in North Wales. Eight patients (aged 35-48) In an emergency department for exacerbation of COPD were found to have precocious COPD associated with high cannabis use. All had signs of advanced emphysema. All had at least 10-20 years smoking more than 5 joints/day. Four required long-term oxygen therapy, one is actively listed for a lung transplant. This was all independent of genetic susceptibility. They concluded that the addition of cannabis to tobacco, and high usage at a young age, is leading to an increase of COPD in general and bullous emphysema as a phenotype in particular.

2015 Macleod et al looked at cannabis smoking and its effects on the lungs. Participants consisted of 500 individuals, 242 of them males. The mean age of tobacco-only smokers was 45 and median tobacco exposure 25 pack years. The mean age of cannabis and tobacco smokers was 37 years, median tobacco exposure 19 years rising to 22.5 when tobacco smoked with cannabis. Although tobacco and cannabis use were associated with increased reporting of respiratory symptoms, this was higher in those who also smoked cannabis. Each additional joint year of cannabis use was associated with a 0.3% increase in (COPD) Coronary Obstructive Pulmonary Disease. They concluded that, 'In adults who predominantly smoked resin cannabis mixed with tobacco, additional adverse effects were observed on respiratory health relating to cannabis use'.

2015 Hancox et al Looked at the effects of quitting cannabis on respiratory symptoms.

Associations between changes in cannabis use and respiratory symptoms in a population-based cohort of 1037 young adults (Dunedin Study) were assessed. Participants were asked about cannabis and tobacco use at ages 18, 21, 26, 32 and 38 years. Symptoms of morning cough, sputum production, wheeze, dyspnoea on exertion and asthma diagnoses were ascertained at the same ages. Reducing or quitting cannabis use was associated with reductions in the prevalence of cough, sputum and wheeze to levels similar to nonusers. Frequent cannabis use is associated with symptoms of bronchitis in young adults. Reducing cannabis use often leads to a resolution of these symptoms.

2015 American Lung Association (March 2015). Marijuana smoke has been shown to contain many of the same toxins, irritants and carcinogens as tobacco smoke. The smoke is inhaled more deeply and held in the lungs for longer. Second hand marijuana smoke contains many of the same toxins and carcinogens found in inhaled smoke, in similar amounts, if not more! Children in the home may be at risk. It causes chronic bronchitis and injures the cell linings of the large airways possibly explaining chronic cough, phlegm productions and wheezing. An immune-compromised person is more susceptible to lung infections (immune system is impaired).

In 1981 the WHO report on cannabis use said, “It is instructive to make comparisons with the study of effects of other drugs, such as tobacco or alcohol. With these drugs, “risk factors” have been freely identified, although full causality has not yet been established. Nevertheless such risk factors deserve and receive serious attention with respect to the latter drugs. It is puzzling that the same reasoning is often not applied to cannabis”... “To provide rigid proof of causality in such investigations is logically and theoretically impossible, and to demand it is unreasonable”.

2015 Dr Lisa Charles, Medical Director Victoria Hospital, Castries, St Lucia said that mixing marijuana and tobacco is a dangerous practice and is turning people into ‘respiratory cripples’. Over the last 10 years she has seen an increasing epidemic of young people suffering from COPD (Chronic Obstructive Pulmonary Disease). Young people in their 30s have end-stage lung disease. COPD is irreversible and progressive. Patients are literally confined to bed with oxygen cylinders and need full care. Bed space was severely compromised. The cost of treatment is horrendous. The Pan American Health Organisation has said that COPD is a leading cause of morbidity and mortality in the Americas and it is both preventable and treatable.

2016 Wilson et al found that 1 in 6 children hospitalized (Colorado hospital) for lung inflammation (coughing, wheezing and other symptoms of bronchiolitis) tested positive for marijuana exposure. More of the children were positive for THC after legalisation (21% compared with 10% before). Secondhand smoke may be a rising child health concern.

2016 Martinasek et al undertook a systematic review of the respiratory effects of inhalational marijuana. Forty-eight articles were collected and categorized by respiratory effects. In particular, lung cancer, bullous emphysema/COPD, and other respiratory symptoms were the primary categories. The research indicates that there is a risk of lung cancer from inhalational marijuana as well as an association between inhalational marijuana and spontaneous pneumothorax, bullous emphysema, or COPD. A variety of symptoms have been reported by inhalational marijuana smokers, including wheezing, shortness of breath, altered pulmonary function tests, cough, phlegm production, bronchodilation, and other symptoms

2017 Mishra et al looked at cannabis-induced bullous lung disease leading to pneumothorax. ‘A 30-year-old man with spontaneous pneumothorax associated with marijuana use was admitted. The patient had no medical conditions and presented to the emergency room with chest pain. The physical examination revealed decreased breath sound on the right side of the chest. Bed side ultrasound of chest showed stratosphere sign, absent lung sliding; consistent with right-sided pneumothorax. The patient underwent placement of a chest tube. Computed tomography chest scans performed on day two also showed bullous lung disease in the right lung. Serial x-rays of the chest showed re-expansion of the lung. Despite the beneficial effects of Marijuana there are deleterious effects which are emphasized here. This case highlights the need for further studies to establish the relationship between marijuana use and lung diseases in the absence of nicotine use’.

2017 National Cancer Institute gave findings on cannabis and cannabinoids in relation to cancer.

2018 Wilson et al found second-hand smoke in kids' lungs. The impact of secondhand marijuana smoke exposure on children is unknown. New methods allow for the detection of marijuana smoke exposure in children. **Abstract:** We studied children who were hospitalized in Colorado and had a parent participating in a smoking cessation study; all children had urine samples remaining from the original study as well as consent for future research. Parents completed a survey and urine samples were analyzed for cotinine and marijuana metabolites, including 11-hydroxy- Δ 9-tetrahydrocannabinol (COOH-THC), by using liquid chromatography-tandem mass spectrometry. The median age of the children was 6.0 years (range 0-17 years); 57% were boys. Half (55%) were white, 12% were African American, and 33% were of another race; 39% identified as Hispanic. Approximately 46% had detectable COOH-THC, and 11% had detectable THC. Of those with detectable THC, 3 were teenagers, and 6 were <8 years of age. There were no significant differences in urinary COOH-THC concentrations by age, sex, race and/or ethnicity, or socioeconomic status. Children with positive results for COOH-THC were more likely to have parents who use marijuana daily, smoke marijuana versus other forms of use, use daily in the home, and smoke marijuana in another room if the children are around compared with smoking outside. Approximately half of the children who qualified for our study had biological evidence of exposure to marijuana. Researchers in studies such as this provide valuable data on secondhand exposure to children from parents using tobacco and marijuana and can inform public health policies to reduce harm.

2019 Winhusen et al found that cannabis use, with or without tobacco co-use, is associated with respiratory disease. **Abstract:** Cannabis use is a potential risk factor for respiratory disease but its role apart from tobacco use is unclear. We evaluated the association between regular cannabis use, with and without tobacco co-use, and onset of asthma, chronic obstructive pulmonary disease (COPD), and pneumonia. **METHODS:** Analysis of a limited data set obtained through IBM Watson Health Explorers, an electronic-health-record-integration platform. Matched controls using Mahalanobis distance within propensity score calipers were defined for: 1) cannabis-using patients (n = 8932); and subgroups of cannabis-using patients: 2) with an encounter diagnosis for tobacco use disorder (TUD; n = 4678); and 3) without a TUD diagnosis (non-TUD; n = 4254). Patients had at least: one recorded blood pressure measurement and one blood chemistry lab result in the MetroHealth System (Cleveland, Ohio). Cannabis-using patients had an encounter diagnosis of cannabis abuse/dependence and/or ≥ 2 cannabis-positive urine drug screens (UDSs). Control patients, not having cannabis-related diagnoses or cannabis-positive UDSs, were matched to the cannabis-using patients on demographics, residential zip code median income, body mass index, and, for the total sample, TUD-status. **RESULTS:** Regular cannabis use was significantly associated with greater risk for asthma (odds ratio (OR) = 1.44; adjusted odds ratio (aOR) = 1.50; OR = 1.32), COPD (OR = 1.56; aOR = 1.44; OR = 2.17), and pneumonia (OR = 1.80; OR = 1.84; OR = 2.13) in the total sample and TUD and non-TUD subgroups, respectively. TUD-patients had the greatest prevalence of respiratory disease, regardless of cannabis-use indication. **CONCLUSIONS:** Regular cannabis use is associated with significantly greater risk of respiratory disease regardless of TUD status. Future research to understand the impact of cannabis use on respiratory health is warranted.

2020 Gracie and Hancox looked at Cannabis use disorder and the lungs. **Abstract:** Cannabis is one of the world's most widely used recreational drugs and the second most commonly smoked substance. Research on cannabis and the lungs has been limited by its illegal status, the variability in strength and size of cannabis cigarettes (joints), and the fact that most cannabis users also smoke tobacco, making the effects difficult to separate. Despite these difficulties, the available evidence indicates that smoking cannabis causes bronchitis and is associated with changes in lung function. The pattern of effects is surprisingly different from that of tobacco. Whereas smoking cannabis appears to increase the risk of severe bronchitis at quite low exposure, there is no convincing evidence that this leads to chronic obstructive pulmonary disease. Instead, cannabis use is associated with increased central airway resistance, lung hyperinflation and higher vital capacity with little evidence of airflow obstruction or impairment of gas transfer. There are numerous reports of severe bullous lung disease and pneumothorax among heavy cannabis users, but convincing epidemiological data of an increased risk of emphysema or alveolar destruction are lacking. An association between cannabis and lung cancer remains unproven, with studies providing conflicting findings.

References

Aldington S *Cannabis links to lung cancer*

Paper to The Thoracic Society Conference Auckland, New Zealand March 26th 2007.

Thorax 2007; 0:1-7. doi: 10.1136/thx.2006.077081

Aldington S, Williams M, Nowitz M, Weatherall M, Pritchard A, Mc Naughton A, Robinson G, Beasley R,

The effects of cannabis on pulmonary structure, function and symptoms.

Online First 31st July 2007. doi:10.1136/thx.2006.077081

Aldington S et al, *Cannabis use and risk of lung cancer: a case-control study* European Respiratory Journal 2008; 31: 280-6.

American Lung Association, March 23rd 2015 statement.

Ammenheuser MM Berenson AB Babiak AK Singleton CR Whorton Jr EB *Frequencies of hprt mutant lymphocytes in marijuana-smoking mothers and their newborns* Mutation Research 403:55-64 1998.

Auerbach O Stout AP Hammond ED Garfinkel A *Changes in bronchial epithelium in relation to cigarette smoking and in relation to lung cancer* New England Journal of Medicine 265:253-267 1961.

Baldwin GC Tashkin DP Buckley DM Park AN Dubinett SM Roth MD *Habitual smoking of marijuana and cocaine impairs alveolar macrophage function and cytokine production* Am. J. Respir. Crit. Care Med. 156:1606-1613.1997.

Barbers RG Gong H Jr Tashkin DP Oishi J Wallace JM *Differential examination of bronchioalveolar lavage cells in tobacco cigarette and marijuana smokers* Am. Rev. Respir. Dis.135: 1271-1275 1987.

Barsky SH Roth MD Kleerup EC Simmon M Tashkin DP *Molecular Alterations in bronchial epithelium of habitual marijuana, cocaine and/or tobacco* J Natl Cancer Instit. 1998.

BBC News 03/06/07. <http://news.bbc.co.uk/go/pr/fr/-/hi/health/6551327.stm>

Beals TF Fligiel SEG Stuth S Tashkin DP *Morphological alterations of alveolar macrophages from marijuana smokers* Am. Rev. Respir. Dis. 139 (Part 2) A336. 1989.

Benson M Bentley AM *Lung disease induced by drug addiction* Thorax 50:1125-1127 1995.

Berthiller VN, Benhaim-Luzon V, Boniol M, Straif K, Ayoub WB, Ayed FB, Sasco AJ *Risk of Lung cancer and past use of cannabis in Tunisia* J. Thorac Oncol 2006 Jul; 1(6): 577-9.

Beshay M, Kaiser H, Niedhart D, Reymond MA, Schmid RA, *Emphysema and secondary pneumothorax in young adults smoking cannabis.* Eur J Cardiothorac Surg October 9th 2007 32; 834-8.

Bluhm EC, Daniels J, Pollock BH, Olshan AF *Maternal use of recreational drugs and neuroblastoma in offspring: a report from the Children's Oncology Group (United States)* Cancer Causes Control 2006; 17: 663-9.

BMA (British Medical Association) *Therapeutic Uses of Cannabis* Amsterdam, The Netherlands: Academic Publishers, 1998.

Bouaboula M Rinaldi M Carayon P Carillon C Delpuch B Shire D Lefur G Casellas P *Cannabinoid-recepto expression in human leukocytes* Eur.J. Biochem. 214: 173-180 1993.

British Lung Foundation *A Smoking Gun? The Impact of Cannabis Smoking on Respiratory Health* 2002.

British Lung Foundation June 2012 *Report into Cannabis smoking and Health*

Busch FW Seid DA Wei EJ *Mutagenic activity of marijuana smoke condensates* Cancer lett. 6: 319-324 1979.

- Caplan GA Brigham BA *Marijuana smoking and carcinoma of the tongue: is there an association?* Cancer 66: 1005-1006 1989.
- Chiesara E Rizzi R *Chromosome damage in heroin-marijuana and marijuana addicts* Archives of Toxicology Supplement 6:128-130 1983.
- Chinnappa NB, Zalewska K, Mckeon D. P60 Cannabis Lung Causing Debilitating Emphysema: Are We On The Verge of an Epidemic? Thorax 2014;69:A101 doi: 10.1136/thoraxjnl-2014-206260.201.
- Cottrell JC Sohn SS Vogel WH *Toxic effects of marijuana tar on mouse skins* Archives of Environmental Health 26(5): 277-278 1973.
- Daling JR, Doody DR, Sun X, Britton L, et al, *Association of marijuana use and the incidence of testicular germ cell tumors Cancer: Early View*, published online 9 Feb 2009. DOI: 10.1002/cncr24159
- Dinissenko MF Pao A Tang M-S Pfeifer GP *Preferential formation of benz-pyrene adducts at lung cancer mutational hotspots in P53* Science 274:430-432. 1996.
- Donald PJ *Marijuana and upper aerodigestive tract malignancy in young patients* in Nahas GG Latour C (eds) Cannabis: Physiology, Epidemiology, Detection. Ann Arbor CRC Press 165-183 1993.
- Dubinett SM et al (UCLA) Journal of Immunology June 2000.
- Endicott J Skipper P *Marijuana and the upper aerodigestive tract: Malignancy in young subjects* in Internationales Symposium Gegen Drogen Zurich:Verlag Menchenkenntnis 547-551 1991.
- Fligiel SEG Beals TF Venkat H Stuth S Gong H Tashkin DP *Pulmonary pathology in marijuana smokers* in Chesher G Consroe P Musty R (eds) An International Research Report: National Campaign Against Drug Abuse Monograph 7 Canberra Australian Government Publication Service 1988.
- Fried PA Charlebois AT *Cannabis administered during pregnancy: First and second generation effects in rats* Physiol. Psychol. 7 307-310 1979.
- Gardner B, Zhu LX, Sharma S, Tashkin DP, Dubinett SM *Methanandamide increases COX-2 expression and tumor growth in murine lung cancer*. FASEB J Nov 2003; 17(14):2157-9.
- Gilmore DG Blood AD Lele KP Robbins ES Maximillian C *Chromosomal aberrations in users of psychiatric drugs* Archives of General Psychiatry 24:268-272 1971.
- Gong HJ Fligiel S Tashkin DP Barbers RG *Tracheobronchial changes in habitual heavy smokers of marijuana with and without tobacco* American Review of Respiratory Disease 136:142-147 1987.
- Gracie K, Hancox RJ, Cannabis use disorder and the lungs Addiction :14 April 2020 <https://doi.org/10.1111/add.15075>
- Hancox, R. J., Shin, H.H., Gray, A.R., Poulton, R. , Sears, M.R. | 2015 Effects of quitting cannabis on respiratory symptoms European Respiratory Journal, 2015, Published ahead of print 2 April 2015, doi: 10.1183/09031936.00228914.
- Harwood M, Aldington S, Beasley R *Lung Cancer in Maori: a Neglected Priority* Journal of the New Zealand Medical Association 15th April 2005; 118:1213.
- Herha J Obe G *Chromosomal damage in chronic users of cannabis: in vivo investigation with two-day lymphocyte cultures* Pharmacopsychiatric 7:328-337 1974.
- Hii SW, Tam JDC, Thompson BR, Naughton M, *Bullous lung disease due to marijuana* Respiriology Jan 2008; 13 (1): 122-7.

- Hoffmann D Brunnemann KD Gori GB Wynder EL *On the carcinogenicity of marijuana smoke*. Recent Advances Phytochem. 9:63-8 1975.
- Kirk A, Consultant in cardio-thoracic surgery, Glasgow Western Infirmary. " *Cancer Threat from Cannabis*" The Sunday Post (Scotland) January 23rd 2000.
- Lacson JCA, Carroll JD, Ellenie Tuazon, Castelao EJ, Bernstein L, Cortessis VK, *Testicular Cancer and Marijuana Use*. Cancer; Published online: September 10th 2012 (doi:10.1002/cncr.27554)
- Leuchtenberger C *Effects of marijuana (cannabis) smoke on cellular biochemistry utilizing "in vitro" test systems* In Fehr KO Kalant H (eds) *Adverse Health and Behavioral Consequences of Cannabis Use* ARF Toronto 1982.
- Macleod J, Robertson R, Copeland L, McKenzie J, Elton R, Reid P, Cannabis, tobacco smoking, and lung function: a cross-sectional observational study in a general practice population. DOI: 10.3399/bjgp15X683521 Pub 1st February 2015.
- Magus RD Harris LS *Carcinogenic Potential of Marijuana Smoke Condensate* Fed. Proc.30: 279 abs.1971
- Marques-Magallanes JA Tashkin DP Serafian T Stegeman J and Roth MD In vivo and in vitro activation of cytochrome P4501A1 by marijuana smoke Presented by Tashkin at the symposium of the International Cannabinoid Research Society Stone Mountain GA June 1997.
- Martinasek MP, McGrogan JB, Maysonet A. Systematic Review of the Respiratory Effects of Inhalational Marijuana. *Respir. Care* 2016 Nov;61(11):1543-1551. Epub. 2016 Aug 9th.
- Mehra R, Moore BA, Crothers K, Tetrault J, Fiellin DA *The Association between Marijuana Smoking and Lung Cancer: A Systematic Review* Arch Intern. Med. 2006; 166: 1359-67.
- Mishra R, Patel R, Khaja M. Cannabis-induced bullous lung disease leading to pneumothorax: Case report and literature review. *Medicine (Baltimore)*. 2017 May;96(19):e6917. doi: 10.1097/MD.00000000000006917.
- Moir D, Rickert S, Lévassieur G, Larose Y et al, *A Comparison of mainstream and Sidestram Marijuana and Tobacco Cigarette Smoke Produced under Two Machine Smoking Conditions* Chem. Res. Toxicol. 2008; 21: 494-502
- Moore BA, Augustson EM, Moser RP, Budney AJ *Respiratory Effects of Marijuana and Tobacco Use in a US Sample* J Gen Intern Med 2004; 20: 33-37.
- Nahas GG Desoize B Armand JP Hsu J Morishima A *Natural Cannabinoids: Apparent depression of nucleic acids and protein synthesis in cultures of human lymphocytes* Szara S Brande X (eds) Raven NY 177-188
- Novotny M Lee ML Bartle KD *A possible chemical base for the higher mutagenicity of marijuana smoke as compared to tobacco smoke* Experientia 32:280-282 1976.
- Peterson BH Lemberger L Graham J Dalton B *Alterations in the cellular-mediated immune responsiveness of chronic marijuana smokers* Psychopharmacol Communic 1 67-74 1975.
- Pletcher MJ, Vittinghoff E, Kalhan R, Richmann J, Safford M, Sidney S, Feng L, Kertesz S, *Association Between Marijuana Exposure and Pulmonary Function Over 20 Years*. JAMA Jan 11th 2012; 307(2):173-181

Rosenkrantz H Fleischman RW *Effects of cannabis on lungs* in Nahas GG Paton WDM (eds) *Advances in the Biosciences* vols 22 and 23 *Marijuana: Biological Effects, Analysis, Metabolism, Cellular Responses, Reproduction and Brain* pp 279-299 Pergamon Press Oxford 1979.

Roth MD Kleerup EC Arora A Barsky S Taskin DP *Airway inflammation in young marijuana and tobacco smokers* *Am. Rev. Respir. Crit. Care. Med* 157: 928-937 1998.

Roth MD Zhu L Sharma S Stolina M Chen K Park A Tashkin DP Dubinett SM *D-9-tetrahydrocannabinol inhibits antigen presentation in vitro and anti-tumor immunity in vivo*. Symposium International Cannabinoid Research Society Stone Mountain GA June 1997.

Sarafian T, Habib N, Mao JT, Tsu IH, Yamamoto ML, Hsu E, Tashkin DP, Roth MD *Gene expression changes in human small airway epithelial cells exposed to Delta-9-tetrahydrocannabinol*. *Toxicol Lett.* August 14th 2005; 158(2): 95-107.

Sidney S Beck JE Tekawa IS Quesenberry CP Jr *Marijuana use and cancer incidence* *Am. J. Public Health* 585-590 1997.

Singh R, Sandhu J, Kaur B, Juren T, Steward WP, Segerback D, Farmer PB, *Evaluation of the DNA Damaging Potential of Cannabis Cigarette Smoke by the Determination of Acetaldehyde Derived N2-Ethyl-2'-deoxyguanosine Adducts*. *Chemical Research in Toxicology*, 22, 1181-1188.

Sridhar KS Raub WA Weatherby NL Metsch LR Surratt HL Inciardi JA Duncan RC Anwyl RS McCoy CB *Possible role of marijuana smoking as a carcinogen in the development of lung cancer at a young age* *J. Psychoactive Drugs* 26:285-288 1994.

Stenchever MA Kunysz TJ Allen MA *Chromosome breakage in users of marijuana* *American Journal of Gynecology* 118:106-113 1974.

Tan W, *The Impact of Cigarette and Marijuana Smoking in Chronic/Obstructive Pulmonary Disease Study in Vancouver, Canada*. Presentation to The American Thoracic Society 2007 International Conference, May 22nd 2007. (Session C38; Abstract # 681; Poster Board #L4)

Tan WC, Lo C, Jong A, Xing L, FitzGerald MJ Vollmer WM, Buist SA, Sin DD, *Marijuana and Chronic obstructive lung disease: a population-based study*. *CMAJ* 2009; 180(8). doi: 10.1503/cmaj.081040.

Tashkin DP Simmons MS Sherrill DL Coulson AH *Heavy habitual marijuana smoking does not cause an accelerated decline in FEV1 with age*. *American Journal of Respiratory and Critical Care Medicine* 155:141-148 1997.

Tashkin DP *Effects of marijuana smoking profile on respiratory deposition of tar and absorption of CO and D-9 tetrahydrocannabinol* Pulmonary pathophysiology and immune consequences of smoked substance abuse FESEB Summer Research Conference July 18-23 Copper Mountain CO 1999.

Tashkin DP *Is frequent marijuana smoking harmful to health?* *Western J Medicine* 158:635-637 1993.

Tashkin DP Baldwin GC Sarafian T Dubinett S Roth MD *Respiratory and immunologic consequences of marijuana smoking* *J. Clinical Pharmacology* 42 (11 suppl): 715-781 2002.

Tashkin DP and Roth MD ICRS Presentation Tampa Florida June 2005 (in press).

Tashkin DP *Smoked marijuana as a cause of lung injury* *Monaldi Arch Chest Dis* June 2005; 63(2): 93-100.

Taylor FM *Marijuana as a potential respiratory tract carcinogen: a retrospective analysis of a community hospital population* *Southern Medical Journal* 81:1213-1216 1988.

Tennant FS *Histopathologic and clinical abnormalities of the respiratory system in chronic hashish smokers* in Harris LS (ed) *Problems of Drug Dependence* 27:309-315 1979 NIDA Rockville MD 1980.

Terris M et al "Marijuana use linked to early bladder cancer" Urology January 2006.

Tetrault JM, Crothers K, Moore BA et al, *Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review*. Arch Intern Med 2007; 167(3): 221-8.

Thoracic Society of Australia and New Zealand Position Statement (Taylor DR and Hall W) Internal Medicine Journal 33:310-313 2003

Van Hoozen BE Cross CE *Respiratory tract effects of marijuana* Clinical Reviews in Allergy and Immunology 15: 243-269 1997.

Wehner FC van Rensburg SJ Thiel PG *Mutagenicity of marijuana and Transkei smoke condensates in the Salmonella/microsome assay* Mutat. Res. 77: 135-142 1980.

WHO/ARF(Addiction Research Foundation)Report: *Adverse Health and Behavioral Consequences of Cannabis Use* Addiction Research Foundation Toronto Canada March 30/April 3rd 1981

Wilson KM, et al, Marijuana Exposure in children Hospitalised for Bronchiolitis.
<https://www.sciencedaily.com/releases/2016/04/160430100247.htm>

Wilson KM, Torok MR, Wei B, Wang L, Lowary M, Blount B. Marijuana and Tobacco Co-exposure in Hospitalized Children Pediatrics 2018.

Winhusen T, Theobald J, Kaelber DC, Lewis D Regular cannabis use, with and without tobacco co-use, is associated with respiratory disease. Drug Alcohol Depend. 2019 Sep 16;204:107557. doi: 10.1016/j.drugalcdep.2019.107557. [Epub ahead of print]

Wu TC Tashkin DP Djahed B Rose JE *Pulmonary hazards of smoking marijuana as compared with tobacco* New England Journal of Medicine 318:347-351 1988.

Zhang ZF Morgenstern H Spitz MR Tashkin DP Yu GP Marshall JR Hsu TC Schantz SP *Marijuana use and increased risk of squamous cell carcinoma of the head and neck* Cancer Epidemiol. Biomarkers Prev. 8: 1071-1078 1999.

Zhu L Sharma S Stolina M Chen K Park A Roth M Tashkin DP Dubinett SM *THC-mediated inhibition of the anti-tumor immune response* 19th South California Pulmonary Research Conference, Palm Springs CA January 1997.

