EVIDENCE ON THE CARCINOGENICITY OF

Marijuana Smoke

DRAFT

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PREFACE

The Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65, California Health and Safety Code 25249.5 *et seq*.) requires that the Governor cause to be published a list of those chemicals "known to the state" to cause cancer or reproductive toxicity. The Act specifies that "a chemical is known to the state to cause cancer or reproductive toxicity … if in the opinion of the state's qualified experts the chemical has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer or reproductive toxicity." The lead agency for implementing Proposition 65 is the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency. The "state's qualified experts" regarding findings of carcinogenicity are identified as the members of the Carcinogen Identification Committee (CIC) of the OEHHA Science Advisory Board (Title 27 Cal. Code of Regs. §25301; formerly Title 22, Cal. Code of Regs. §12301).

On September 7, 2007 OEHHA announced in the *California Regulatory Notice Register* that marijuana smoke was a chemical proposed for Committee consideration at their November 19, 2007 meeting. The September 7 notice also marked the start of a 60-day comment period during which interested parties could submit comments to OEHHA that would be forwarded to the members of the CIC prior to the November 2007 meeting. At their November 19, 2007 meeting, the Committee advised OEHHA to prepare hazard identification materials for marijuana smoke. A public request for information relevant to the assessment of the evidence on the carcinogenicity of this chemical was announced on December 12, 2007, in the *California Regulatory Notice Register*. No information was received as a result of this request.

These hazard identification materials were complied to provide the Committee with relevant information for use in its deliberations. A public meeting of the Committee to discuss this evidence is scheduled for **May 29, 2009**. At this meeting it is expected that the Committee will render an opinion on whether marijuana smoke has been clearly shown to cause cancer. Written public comments should be submitted to OEHHA by **May 19, 2009,** in order to be considered by the Committee in advance of the meeting. During the **May 29, 2009** meeting, the public will have an opportunity to present verbal comments to the Committee.

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1. EXECUTIVE SUMMARY

Marijuana smoke is formed when the dried flowers, leaves, stems, seeds and resins of plants in the genus *Cannabis* are burned. Marijuana smoke aerosol contains thousands of organic and inorganic chemicals, including psychoactive cannabinoids, which are unique to *Cannabis* plants. Inhaling marijuana smoke for is psychotropic properties became popular in western cultures in the 1960s, though marijuana has been used for medicinal and psychotropic purposes in other parts of the world for thousands of years. In California, use of marijuana for physician-recommended purposes has been legal under state law since 1996 when Proposition 215, the Compassionate Use Act, was passed by state voters. However, the vast majority of marijuana use continues to be for recreational purposes, which remains illegal.

Marijuana smoke and tobacco smoke share many characteristics with regard to chemical composition and toxicological properties. At least 33 individual constituents present in both marijuana smoke and tobacco smoke are already listed as carcinogens under Proposition 65.

In examining the potential carcinogenicity of marijuana smoke, a range of information was evaluated. Studies of cancer risk in humans and laboratory animals exposed to marijuana smoke were reviewed. Other relevant data, including studies investigating genotoxicity and effects on endocrine function, cell signaling pathways, and immune function caused by marijuana smoke, were all considered. Also of interest were the similarities in chemical composition and in toxicological properties between marijuana smoke and tobacco smoke, and the presence of numerous carcinogens in marijuana smoke. The findings of all these reviews are summarized below.

There is evidence from some epidemiological studies of people exposed to marijuana smoke suggestive of increased cancer risk from both direct and parental marijuana smoking. However, this evidence is limited by potential biases and small numbers of studies for most types of cancer. Studies reporting results for direct marijuana smoking have observed statistically significant associations with cancers of the lung, head and neck, bladder, brain, and testis. The strongest evidence of a causal association was for head and neck cancer, with two of three studies reporting statistically significant associations. The evidence was less strong but suggestive for lung cancer, with one of three studies conducted in populations that did not mix marijuana and tobacco reporting a significant association. Suggestive evidence also was seen for bladder cancer, with one of two studies reporting a significant association. For brain and testicular cancers, the single studies conducted of each of these endpoints reported significant associations. Among the epidemiological studies that reported results for parental marijuana smoking and childhood cancer, seven of eight found statistically significant associations. Maternal and paternal marijuana smoking were implicated, depending on the type of cancer. Childhood cancers that have been associated with maternal marijuana smoking are acute myeloid leukemia, neuroblastoma, brain astrocytoma, and rhabdomyosarcoma. Childhood cancers that have been associated with paternal marijuana smoking are leukemia, infant leukemia, acute lymphoblastic leukemia, and rhabdomyosarcoma.

A limitation common to the epidemiologic studies was potential bias from under-reporting of marijuana smoking due to its illegality, social stigma, lack of privacy during oral interviews, and

subject desire to please interviewers, and possibly different degrees of under-reporting between cancer patients and healthy controls. Another limitation of several studies was that they were conducted in geographic locations where marijuana and tobacco are commonly mixed before smoking (e.g., three of six lung cancer studies and one of two bladder cancer studies were conducted in northern Africa, and two of four oral cancer studies were conducted in England). Thus, the results of those studies may have been confounded by the effects of exposure to tobacco smoke.

In animal studies, increases in squamous cell papilloma of the skin were reported in mice exposed dermally to marijuana smoke condensate. Malignant mesenchymatous tumors were reported following six subcutaneous injections of marijuana smoke condensate to newborn rats. In a marijuana smoke inhalation study in female rats, benign tumors of the ovary (serous cytoma and follicular cysts) and benign and malignant tumors of the uterus (adenofibroma, adenosarcoma, and telengiectatic cyst and polyps) were observed. Marijuana smoke condensate also exhibited tumor promoting activity in a mouse skin tumor initiation-promotion assay.

Evidence indicating that marijuana smoke is genotoxic includes findings that marijuana smoke induces mutations in *Salmonella,* and several small cytogenetic studies in humans suggesting that exposure to marijuana smoke may be associated with increased mutations and chromosomal abnormalities. While the data on the genotoxicity of marijuana smoke *per se* is limited, many individual smoke constituents have been shown to form DNA adducts, induce gene mutations, and damage chromosomes.

Evidence indicating that marijuana smoke alters endocrine function includes findings for a number of different hormonal pathways. Marijuana smoke condensate has been shown to have estrogenic effects, including findings that it can activate the estrogen receptor (ER). Marijuana smoke also has been shown to have anti-estrogenic effects, through the induction of cytochrome P450 1A1 and the resultant increase in estrogen (E2) metabolism and through the inhibition of aromatase, an enzyme that converts testosterone to E2. Other studies indicate that marijuana smoke condensate has anti-androgenic effects, inhibiting binding of dihydrotestosterone (DHT) to the androgen receptor (AR). Studies of Δ^9 -tetrahydrocannabinol (Δ^9-THC) and other cannabinoids provide evidence for disruption of the hypothalamic-pituitary-gonadal axis, including evidence that Δ^9-THC inhibits the release of follicle stimulating hormone, luteinizing homone, prolaction, growth hormone, thyroid-stimulating hormone, and corticotrophin. These alterations in endocrine function can affect the growth of hormone responsive tissues, and might increase the risk of certain cancers (e.g., testes, ovary, uterus, and breast).

Evidence suggesting that marijuana smoke alters cell signaling pathways involved in cell cycle control comes from studies of the effects of Δ^9-THC and other cannabinoids on protein kinases. Depending upon the cell type and the dose administered, Δ^9-THC and other cannabinoids may either stimulate or inhibit cell proliferation.

There is evidence that marijuana smoke suppresses the innate and adaptive immune response. The bactericidal activity of rat alveolar macrophages was reduced by marijuana smoke *in vivo* and *in vitro*. Tumoricidal and bactericidal activities were reduced in alveolar macrophages from marijuana smokers, compared to non-smokers. In addition, in one study smoking marijuana was

associated with a more rapid progression of human immunodeficiency virus infection to acquired immunodeficiency syndrome. Δ^9-THC and other cannabinoids present in marijuana smoke have also been shown to suppress host resistance to microbial infection, macrophage function, natural killer and T cell cytolytic activity, cytokine production by macrophages and T cells, and to decrease antigen presentation by dendritic cells. These immunosuppressive effects could lead to an increased risk of cancer by reducing immunosurveillance capacity against neoplastic cells.

Prolonged exposures to marijuana smoke in animals and humans cause proliferative and inflammatory lesions in the lung, such as cellular disorganization, squamous metaplasia, and hyperplasia of basal and goblet cells (observed in the bronchial epithelial tissues of marijuana smokers).

In summary, there is some evidence from studies in humans that marijuana smoke is associated with increased cancer risk. Studies in animals also provide some evidence that marijuana smoke induces tumors, with benign and malignant tumors observed in rats exposed via inhalation, malignant tumors in rats exposed via subcutaneous injection as newborns, and benign tumors in mice exposed dermally. Studies investigating the genotoxicity, immunotoxicity, and effects on endocrine function and cell signaling pathways provide additional evidence for the carcinogenicity of marijuana smoke. Finally, the similarities in chemical composition and in toxicological activity between marijuana smoke and tobacco smoke, and the presence of numerous carcinogens in marijuana (and tobacco) smoke, provide additional evidence of carcinogenicity.

2. INTRODUCTION

2.1 Identity of Marijuana Smoke

Marijuana smoke is formed when the dried flowers, leaves, stems, seeds and resins of plants in the genus *Cannabis* are burned. *Cannabis sativa* and *Cannabis indica* are the species most commonly smoked. The following is a list of common marijuana plant products that are smoked:

- Bud. The flower tops of unpollinated female marijuana plants. Buds have the highest THC content of all parts of the plant. Bud is probably the most common form of marijuana smoked currently in the U.S.
- Ganja (India); kif, kief, kef, keef (Morocco and Algeria); tekrouri, takrouri (Tunisia); and dagga (southern Africa). A mixture of flowering tops and leaves from female plants, dried and diced or powdered.
- Hashish (Middle East) and charas (Far East). Crude resin from flowering tops of unfertilized female marijuana plants. Processed differently in different parts of the world. Often collected by rubbing onto hands, cloth, or leather jackets, or by sifting. Compressed into blocks.
- Leaf. Less potent than buds or flower tops with regard to THC content, leaves were commonly smoked in the U.S. when marijuana first became popular in the 1960s and 1970s.

- Bhang (India and Bangladesh). Generally prepared from the leaves of male plants. Most often used for making beverages but sometimes smoked.

Marijuana smoke contains several thousand different compounds (Sparacino *et al*., 1990). Some are released unchanged from the plant material as it burns, and the rest are products of either pyrolysis or incomplete combustion. Marijuana smoke consists of some chemicals present in the gas phase, some present in particulate matter, and some semi-volatile compounds that transition between the gas and particulate phase. Marijuana smoke includes a large variety of organic and inorganic chemicals, including amines, aromatic amines, aza-arenes, polycyclic aromatic hydrocarbons (PAHs), carbonyls, phenolics, pyrazines, pyrimidines, pyrroles, pyridines, isoxazoles, metals (arsenic, cadmium, chromium, lead, nickel, and selenium), hydrogen cyanide, carbon monoxide (CO), nitric oxide (N), other nitrogen oxides (NO_x), ammonia, and over 60 cannabinoid compounds (Hoffmann *et al.*, 1975; Lee *et al*., 1976; Sparacino *et al*., 1990; Moir *et al*., 2008).

Phytocannabinoid compounds are present in plants in the genus *Cannabis.* They are terpenophenolic compounds, commonly containing 21 carbons. The major cannabionoids present in marijuana smoke are Δ^9-tetrahydrocannabinol (Δ^9-THC), which is the most potent psychoactive compound present in marijuana (Elsohly, 2002), Δ^8 - THC, cannabinol (CBN), cannabidiol (CBD), cannabichromine and 11-OH-Δ^9 -THC. In the past, the levels of Δ^9-THC in marijuana smoked in the U.S. typically ranged from 1-3%. However, over the last 20 years levels of Δ^9-THC have been increasing as a result of the selective cultivation of plants. Typical levels of Δ^9-THC are now greater than 6%. Addition of hashish oil (a cannabinoid-rich extract from *Cannabis* plant material) to the dried material can boost Δ^9-THC levels even higher (e.g., 20%).

Approximately 350 of the thousands of chemicals present in marijuana smoke have been identified by various investigators (Moir *et al*., 2008, Gieringer *et al*., 2004, Sparacino *et al*., 1990; Hoffmann *et al*., 1975; Lee *et al*., 1976). These are shown in Table 1 below. Five main studies of the major constituents present in marijuana smoke were designed as follows:

- Moir *et al*. (2008) used standardized marijuana, which was harvested in May 2004 and produced by Prairie Plant Systems Inc., of Saskatoon, Canada, for Health Canada. The material tested consisted of flowering heads only (reference: H55-MS17/338-FH). Smoke was generated using a smoking machine, operating under two different smoking conditions. The first smoking condition involved a puff volume of 35 milliliters (ml), a puff duration of two seconds, and a puff interval of sixty seconds, while the second smoking condition, referred to as 'extreme,' involved a puff volume of 70 ml, a puff duration of two seconds, and a puff interval of 30 seconds.
- Gieringer *et al*. (2004) used standard National Institute on Drug Abuse (NIDA) marijuana obtained from an independent laboratory. The mean Δ^9-THC content was 4.15%. Smoke was generated by combusting the marijuana in a glass pipe bowl, and collected in a volatile gas trap.
- Sparacino *et al.* (1990) generated marijuana smoke from two samples of Mexican marijuana, one with a "low" Δ^9-THC content (1.3%) and another with a "high" Δ^9-THC content (4.4%). Smoking machines employed either a constant draft apparatus, or an intermittent puff smoking system.

- Hoffmann *et al*. (1975) analyzed marijuana leaves obtained from the Division of Cancer Cause and Prevention of the National Cancer Institute (NCI). The NCI material was prepared from confiscated Mexican marijuana. The low concentration of Δ^9-THC (0.61%) in the marijuana suggested to Hoffmann *et al*. (1975) that the material had been diluted with domestic marijuana. Smoke was generated using a smoking machine.
- Lee *et al*. (1976) obtained Mexican marijuana containing 2.8% Δ^9-THC from the National Institute of Mental Health, in Rockville, Maryland, and generated smoke using a smoking machine under conditions simulating that of an average tobacco cigarette smoker.

Differences in the analytical methods (e.g., sample preparation and fractionation, instrumentation, limit of detection) employed in these studies preclude reaching any conclusions regarding the comparability of marijuana smoke constituents from different samples of marijuana.

Many of the chemical constituents that have been identified in marijuana smoke are carcinogens. The following 33 marijuana smoke constituents included in Table 1 are listed under Proposition 65 as causing cancer: acetaldehyde, acetamide, acrylonitrile, 4-aminobiphenyl, arsenic, benz[*a*]anthracene, benzene, benzo[*a*]pyrene, benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, benzofuran, 1,3-butadiene, cadmium, carbazole, catechol, chromium (hexavalent compounds), chrysene, dibenz[*a,h*]anthracene, dibenz[*a,i*]pyrene, dibenzo[*a,e*]pyrene, diethylnitrosamine, dimethylnitrosamine, formaldehyde, indeno[*1,2,3,-c,d*]pyrene, isoprene, lead, mercury, 5-methylchrysene, naphthalene, nickel, pyridine, and quinoline.

Table 1. Chemicals detected in marijuana smoke.

acenaphthene
acenaphthylene
acetaldehyde
acetamide
acetone
8-acetoxy-pyrazolobenzo-as-triazine
3-acetylpyridine
acrolein
acrylonitrile
alkyl nitrile
aminobenzamide
3-aminobiphenyl
4-aminobiphenyl
aminodimethylpyrimidine
aminodiphenylene oxide
aminomethylquinoline
1-aminonaphthalene
2-aminonaphthalene
m-aminophenol
aminoquinoline
β-amiryn
ammonia
anthanthrene
anthracene
arsenic
1-azidonaphthalene
1,2,3,3a,4,5,6,7, 5-azulenemethanol
benz[*a*]anthracene
benzacenaphthylene
benzene
benzeneacetonitrile
1,2-benzenedicarboxylic acid, bis (2)
1,2-benzenediol
1,3-benzenediol, 2-(3,7-dimethyl-2
benzimidazole
benzo[*a*]fluorene
benzo[*a*]pyrene
benzo[*b*]fluoranthene
benzo[*b*]fluorene
benzo[*c*]fluorene
benzo[*e*]pyrene
benzo[*g,h,i*]perylene
benzo[*g,h,i*]perylene
benzo[*j*]fluoranthene
benzo[*k*]fluoranthene
benzofluoranthene
benzofuran
2H-1-benzopyran-5-ol, 2-methyl-2-(4
1,4-benzoquinone
benzyl acetate
benzyl acetophenone
N-benzyl-4-aminobutyronitrile
binaphthyl
α-bisabolol
1,3-butadiene
1-butoxy-2-propanol
tert-butyl-parahydroxybenzoate
butyraldehyde
butyroamide
cadmium
caffeine
DL-cannabichromene
cannabinol (CBN)
carbazole
β-carboline
carbon monoxide (CO)
caryophyllene
caryophyllene oxide
catechol
1-chloro-octadecane
cholesta-3,5-dien-7-one
cholesterol
cholesteryl acetate
chromium
chrysene
m,o,p-cresol
crotonaldehyde
p-cumyl phenol
cyclododecane
cyclohexadecane
4*H*-cyclopenta[*d,e,f*]phenanthrene
cyclopentadiene
1a,2,3,1H-cyclopropa[a]naphthalene
cyclopropanenanoic acid, 2-[(2-bu
4,7,10-cycloundecatriene
decahydro-4a-methyl-1-naphthalene
1-decanol
1-decene
dibenz[*a,h*]anthracene
dibenz[*a,i*]anthracene
dibenz[*a,i*]pyrene
dibenzo[*a,e*]pyrene
dibenzofuran
d-dibenzopyrene
dibutyl phthalate
diethyl biphenyl
2,2’-diethyl-1,1’-biphenyl
diethylnitrosamine
diethylphenylene diamine
1,2-dihydro-3-isobutyl-1-methylpyrazine-2-one
2,3-dihydrobenzofuran
dihydroxymethyl phenyl quinazoline
2,3-dihyroxyprohexadeacanoic acid
dimethoxybenzene isomer
dimethyl naphthyridine
dimethyl tetrazine
7,11-dimethyl-1,6,10-dodetatriene
dimethylbenzimidazole
3,4-dimethylbenzoic acid
3,3-dimethylcyclobutane-carbonitrile
10,10-dimethylenebicyc
dimethylethanamide imidazole
dimethylethylpyrrole
1-(1,5-dimethylhexyl) cyclohexane
1,2-dimethylimidazole
N,N-dimethyl-N-(p-methoxyphenyl) formamide
N,N'-dimethyl-N,N'-diethyl-p-phenylene diamine
dimethylnaphtho(2,3,6-)thiophene
dimethylnaphthyridine
dimethylnitrosamine
3,3-dimethyloxetase
2,4-dimethylphenol
2,5-dimethylphenol
dimethylpiperazine

dimethylpyrimidone
2,4-dimethylquinazoline
dimethyltrisulfide
dimethyl-β-carboline isomer
dioctyl phthalate
diphenylamine
diphenylethyne
diphenylpyridine isomer
2,6-diterbutylnaphthalene
ditolyl ethane
docosane
2-dodecen-1-yl (-)succinic anhydride
5-dodecyldihydro-2 (3H)-furanone
dronabinol (THC)
eicosane
(E)-3-eicosene
3-eicosene
ethoxy benzaldehyde
ethoxyquinazoline
ethyl hydroxyl acetophenone
ethyl-4*H*-cyclopenta[*d,e,f*]phenanthrene
ethylbinaphthyl
ethylindole
ethylmethylbiphenyl
ethylphenol, 4-
fluoranthene
fluorine
formaldehyde
glaucyl alcohol
heneicosane
henricosyl formate, 1-
heptacosane
heptadecane
2-heptadecanol
2-heptadecanone
hexacosane
hexadecanal
hexadecanamide
hexadecane
(Z)-3-hexadecane
hexadecanoic acid
hexadecanoic acid, hexadecyl ester
1-hexadecanol
2-hexadecanol
n-hexadecanol
cis-11-hexadecen-1-yl acetate
9-hexadecenoic acid eicosyl
9-hexadecenoic acid eicosyl ester
hexanedioic acid dioctyl ester
hexanenitrile 3(pyrrolidnylmethylene)
2-hexyl-1-decanol
hydrogen cyanide
hydroquinone
5-hydroxyindole
hydroxymethylquinoline
4,5,6,7-1H-indazole
indeno[*1,2,3,-c,d*]pyrene
indole
isoprene
lead
2-p-mentha-1,8-dien-3-y resocinol
mercury
1H-3a,7-methanoazulene, octahydro-1
methanol
methoxy propyl pyrazine
2-methoxy-3-methylpyrazine
methoxybenzaldehyde
methyl acetyl pyrrole
methyl benzimidazole
3-methyl benzoic acid
4-methyl carbostyril
methyl ethyl ketone
methyl ethyl pyrazine
methyl ethyl pyrrole
1-methyl imidazole
methyl palmitate
methyl phenyl cinnoline
methyl pyridine carboxylic acid
methyl pyrimidine
methyl stearate
16-methyl-, met heptadecanoic acid
2-methyl-1,4-benzenedoil
3-methyl-1,8-naphthyridine
2-methyl-1-hexadecanol
1-methyl-1H-indene
3-methyl-1H-indole
4-methyl-1H-indole
N-methyl-2-pyridinamine
1-methyl-4-(5-methyl-1-cylohexene
3-methyl-4-ethylpyrrole
3-methyl-5-triazolo(4,3-a)pyrazine
methylacenaphthylene
methylaminonaphthyridine
1-methylanthracene
2-methylanthracene
10-methylbenz[*a*]anthracene
2-methylbenz[*a*]anthracene
3-methylbenz[*a*]anthracene
4-methylbenz[*a*]anthracene
5-methylbenz[*a*]anthracene
6-methylbenz[*a*]anthracene
8-methylbenz[*a*]anthracene
9-methylbenz[*a*]anthracene
methylbenzoxazole
methylbinaphthyl
methylcarbazole
1-methylchrysene
2-methylchrysene
3-methylchrysene
5-methylchrysene
6-methylchrysene
N-methyldiphenylamine
methylethylnitrosamine
1-methylfluoranthene
2-methylfluoranthene
3-methylfluoranthene
7-methylfluoranthene
8-methylfluoranthene
1-methylfluorene
2-methylfluorene
2-methylfuran
3-methylheneicosane
methylindole
methyl-n-(pyrid-2-yl) dihydropyrrole
N-methyl-N-[4-[4-4-methoxy acetamide
N-methyl-N-[4[4-methoxy-acetamide
1-methylnaphthalene
2-methylnaphthalene
1-methylphenanthrene
2-methylphenanthrene
3-methylphenanthrene

9-methylphenanthrene
1-methylphenazine
methylphenyl quinoxaline
methylpropionyl furan
methyl-pteridinone isomer
methylpyrazine
1-methylpyrene
2-methylpyrene
4-methylpyrene
methylpyriloindole
methylquinoline
methylthiazolopyrimidine
methylthiopyridine
1-methyl-β-carboline
naphthalene
naptho-sydinone
nickel
nitric oxide (NO)
nitroacetanilide
nitrogen oxides (NO_x)
nitropicoline
nonacosane
nonadecane
nonadecene
1-nonadecene
octacosane
octadecane
1-octadecanethiol
2,3-octadecanoic acid, dihydroxypro
1-octadecene
5-octadecene
1,2,3,5,6,7,8,8a-octah naphthalene
1-octdecanethiol
6-octen-1-ol, 3,7-dimethyl acetate
1,1'-oxybis-octane
pentacosane
pentadecane
pentadecanoic acid
1-pentadecene
pentyl cannabinol, 3-n-
3-n-pentyl-delta-9-tetrahydrocannabinol
perylene
phenanthrene
1,2,1-phenanthrenecarboxylic acid
1-phenantthrenecarboxylic acid, 7-et
phenoxy ethanol
N-phenyl acrylamide
phenyl alcohol
phenyl benzothiazole
1-phenyl decane
phenyl methyl quanidine
phenyl methyl urea
phenyl pyrazoline
phenyl pyridine
phenyl urea
phenylbenzimidazole
(α-picolidene)-n-propylamine, N-
α-picoline
2-pmemtha-1,8-dien-3-y-resorcinol
propionaldehyde
propionamide
2-(propylamino)benzothiazole propylbenzimidazole
pyrene
pyridine
quaterphenyl
quaterphenyl diphenylacenaphtylene
quinoline
resorcinol
selenium
squalene
styrene
tetracosane
tetradecanoic acid
2- (tetradecyloxy)-ethanol
Δ,8-tetrahydrocannabinol
Δ,9-tetrahydrocannabinol
tetramethylcyclopentanedione
2,6,10,14-tetramethylhexadecane
3,5,6,7-tetra-s-indacen-1(2H)-one
2,3,5,6-tetra-s-indacene-1,7-dione
2-thiocyanatodiphenylamine
toluene
tolyl azide
tricosane
(Z)-9-tricosene
1,7,11-trimethyl cyclotetradecane
trimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine
trimethylnaphthyridine
2,2,4-trimethylpenta-1,3-diol-di-isobutyrate
1,3,5-trimethylpyrazole
2,6,10-trimethyl-tetradecane
tropolone
1-undecanol
valeramide
2-vinyl pyridine
vitamin E

2.1.1 Comparison of smoke constituents in marijuana from different sources

The chemical constituents of marijuana smoke do not appear to differ significantly with either the source or the Δ^9- THC content of the starting material. Rickert *et al*. (1982) compared the levels of tar (the resinous total particulate matter in marijuana smoke) and CO produced from two different lots of Columbian marijuana, containing either 1.3% or 4.5% Δ^9- THC. No differences were observed between the amounts of tar or CO present in the smoke from the two lots of marijuana. In another study, Chait and Pierri (1989) compared the amount of tar and CO generated from marijuana cigarettes obtained from the NIDA that contained either 0%, 1.4% or 2.7% Δ^9- THC. Δ^9- THC content had no effect on the amount of tar generated, or on the total weight of the smoke that was generated; however, the marijuana containing 2.7% Δ^9- THC generated a slightly lower amount of CO than the other two types of marijuana.

The study of Sparacino *et al*. (1990) compared the chemical constituents of marijuana smoke generated from "low" (1.3%) and "high" (4.4%) Δ^9- THC Mexican marijuana, using several rather crude analytical measures, such as elemental analysis, thermogravimetric analysis, and weight of chemical class fractions of the smoke condensates. The elemental analysis showed some slight differences in the percentage of carbon, hydrogen, nitrogen, sulfur, and oxygen between the two marijuana samples, with the "high" Δ^9- THC condensate containing slightly lower hydrogen (8.43% vs. 9.14%) and oxygen (17.84% vs. 20.65%) content, and higher nitrogen (6.48% vs. 4.17%) and sulfur (0.33% vs. 0.26%) content, as compared to the "low" Δ^9- THC condensate. The thermogravimetric analysis showed that a greater percentage of the constituents in the "low" Δ^9- THC condensate were volatile at a given temperature as compared with the "high" Δ^9- THC condensate (e.g., 78% in the "low" Δ^9- THC condensate vs. 68% in the "high" Δ^9- THC condensate at 270ºC). Comparing the weight percents of the acid, base, neutral and insoluble fractions of the condensates, the base and neutral fractions of the "low" Δ^9- THC condensate were somewhat heavier than those of the "high" Δ^9- THC condensate (base: 7.2% vs. 5.7%; neutral: 38.0% vs. 48.8%).

Hiller *et al*. (1984) compared the particle size distribution and particle concentration of marijuana smoke generated from marijuana containing various levels of Δ^9- THC (i.e., 0%, 0.89%, 1.61%, and 2.67% by weight of the plant material) that was obtained from the National Institute of Drug Abuse in Rockville, Maryland. Particle size distribution and concentration were analyzed by a single particle aerodynamic relaxation time analyzer. Δ^9- THC levels had no effect on marijuana smoke particle size distribution; however, as Δ^9- THC levels increased in the plant material, an increase in the total mass concentration of the marijuana smoke particles was observed.

2.2 Occurrence and Use

In the U.S., the popularity of marijuana smoking, as measured by first-time use rates, increased greatly in the late 1960s, reached a plateau in the 1970s, dropped to a mid-level in the 1980s, and increased again through the 1990s (Figure 1).

Figure 1. Marijuana first-time use incidence rates in the U.S. 1965-1998, per 1,000 person-years among persons aged 12 and older (Gfroerer *et al*., 2002).

Prior to the mid-1960s, the portion of the U.S. population that had ever smoked marijuana was relatively small, but possibly large enough for epidemiologic studies to detect excess cancer risk. For example, six percent of men and women who turned age 21 in the 1962-1966 time period had smoked marijuana at least once according to data from the National Household Survey on Drug Abuse (NHSDA) (Figure 2). Prior to the 1960s, the percent of the U.S. population that had ever smoked marijuana was in the range of 1-2%.

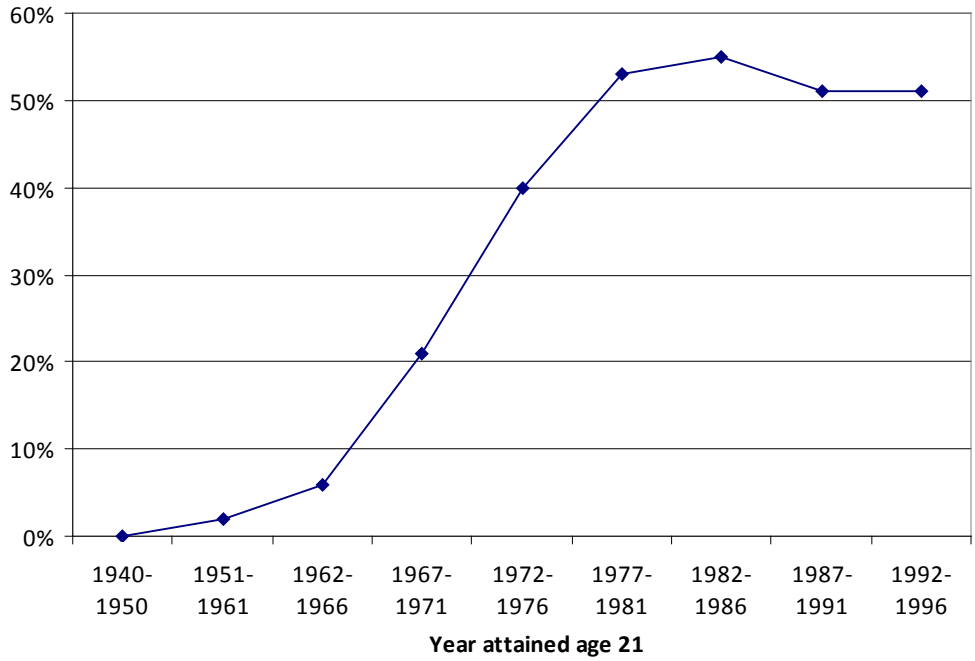

Figure 2. Percent of the U.S. population having smoked marijuana before age 21, by calendar year of attaining age 21 (Johnson and Gerstein, 1998).

The U.S. is one of few locations in the world where there has been little mixing of tobacco and marijuana prior to smoking, although blunt smoking (marijuana with a tobacco outer-wrapping, often a hollowed-out cigar) has become common among urban youth. The phenomenon is recent enough that tobacco smoke from blunts is unlikely to have confounded U.S. marijuana and cancer studies published to date.

In California, use of marijuana for physician-recommended purposes has been legal under state law since 1996 when Proposition 215, the Compassionate Use Act, was passed by state voters. Since then, 12 other states have legalized medical use of marijuana (Alaska, Colorado, Hawaii, Maine, Maryland, Michigan, Montana, Nevada, New Mexico, Oregon, Rhode Island, Vermont, and Washington). However, the vast majority of marijuana use in states in which medical use is legal has probably been for recreational purposes which remain illegal.

3. DATA ON CARCINOGENICITY

3.1 Carcinogenicity Studies in Humans

This section summarizes the currently available human data in the scientific literature related to the possible association of exposure to marijuana smoke and cancer observed among individuals who directly smoked marijuana or whose parents smoked marijuana. The literature includes controlled studies, case reports, literature reviews, commentaries, and editorials.

3.1.1 Literature Search and Review

3.1.1.1 Methods

Articles that reported or discussed observed cancers among people exposed to marijuana smoke or whose parents were exposed to marijuana smoke before or during gestation were identified by searching the PubMed database with the following search string: *(marijuana OR marihuana OR cannabis OR hash OR hashish OR kif OR kef OR kief OR keef OR ganja OR tekrouri OR bhang) AND (epidemiology OR epidemiologic* OR cohort* OR control OR controls OR mortality OR incidence OR rate OR rates OR odds OR risk OR ratio OR ratios)* with limitation to human studies, journal articles, and the topic of cancer. As of 10/17/08 this search string identified 463 articles. The PubMed search results were reviewed and copies of potentially relevant articles were obtained. Articles were additionally identified by examining the reference lists of obtained articles.

The literature search may have been biased toward finding articles that found an association between marijuana smoking and cancer. The potential bias is due to literature databases generally not containing the entire contents of articles. Instead, they contain only abstracts and selected basic information such as titles and keywords. If investigators are more likely to mention in abstracts factors found to be associated with disease than factors found to be not associated, a literature search may miss articles in which the results of interest are reported only in the body of the article.

Articles were examined to see if they were controlled studies, reviews, case reports, or commentaries. All controlled studies were then sorted by types of cancer reported. Aside from the case studies, those studies with rate ratios reported, or for which rate ratios could be calculated, are discussed in this report. In some articles, numbers that the Office of Environmental Health Hazard Assessment (OEHHA) wished to abstract were not directly presented, but could be calculated based on data in the article. OEHHA made the calculation and then added a footnote or explanatory note to indicate this.

Rate ratio estimates and 95% confidence intervals were abstracted to report values rounded to the nearest tenth in most cases. However, when a confidence limit would have rounded to 1.0, values were generally reported to the nearest hundredth.

3.1.1.2 Literature on Marijuana Smoking and Cancer Identified

The literature search identified 61 articles that reported results for marijuana smoking and cancer (Table 2). OEHHA identified 27 controlled studies of marijuana smoking and cancer published in 28 articles. Nineteen studies reported results for direct marijuana smoking only, seven reported results for parental smoking only, and one study reported results for both direct and parental marijuana smoking. OEHHA also identified 16 articles that described cancer cases who were marijuana smokers ("case reports"), eight articles that reviewed scientific literature on marijuana smoking and cancer, and nine commentaries/editorials on the topic.

Table 2. Types and Numbers of Scientific Journal Articles about Cancers Observed Among Marijuana Smokers and Among the Children of Marijuana Smokers.[§]

Type of article			
Controlled studies	**Case reports[#]**	**Reviews**	**Commentaries**
28 articles, 27 studies	16 articles	8 articles	9 articles
Direct smoking (22 articles, 20 studies) Aldington 2008a^ Aldington 2008b^ Bedwani 1997 Chacko 2006 Daling 1997 Daling 2009 Efird 2004 Gillison 2008 Hashibe 2006 Holly 1999 Hsairi 1993 Llewellyn 2004a Llewellyn 2004b Maden 1993 Nelson 1997 Rosenblatt 2004 Sasco 2002 Sidney 1997 Trivers 2006[@] Voirin 2006 Zhang 1999* Zhang 2000* Parental smoking (6 articles, 8 studies) *Maternal* Bluhm 2006 Kuijten 1990 *Paternal* Wen 2000 (data from 3 studies) *Maternal and paternal* Grufferman 1993 Robison 1989 Trivers 2006[@]	Almadori 1990 aWengen 1993 Caplan 1990 Dahlstrom 2008 Donald 1986 Donald 1991a Donald 1991b Endicott 1993 Ferguson 1989 Fung 1989 Lebeau 2005 Llewellyn 2003 Moiche Bokobo 2001 Nieder 2006 Richter 1995 Sridhar 1994 Taylor 1988	Carriot 2000 Firth 1997 Hall 2005 Hashibe 2002 Hashibe 2005 Johnson 2001 Kalant 2004 Mehra 2006	Brambilla 2008 Caplan 1991 Hall 2002 Henry 2003 Mao 1998 Quoix 2007 Sidney 2003 Taylor 2003 Weiss 2008

[§]Literature identified through October 17, 2008; listed by first author and year of publication.
[#]All case report articles were of direct smoking of marijuana.
^Two articles (Aldington 2008a and Aldington 2008b) reported results from the same study.
[@]One article (Trivers 2006) reported results for direct smoking and parental smoking.
*Two articles (Zhang 1999 and Zhang 2000) reported results from the same study.

The studies reported findings for several different types or categories of cancer: Nineteen different categories were examined in the studies reporting results for direct marijuana smoking, and seven categories were examined in the studies reporting results for marijuana smoking by parents of cases (Table 3). Some of the cancer categories overlapped considerably, e.g., the categories "head and neck" and "tobacco-related" included many of the same types of cancers. Some studies reported results for more than one type or category of cancer.

Table 3. Categories of Cancer Reported in Controlled Observational Studies of Marijuana Smoking.

Cancer Category Reported*	Number of Articles[+]	First Author, Year of Publication, Study Design	Number of Studies [+]
DIRECT MARIJUANA SMOKING			
Acute myeloid leukemia (AML)	1	Trivers 2006 case-control^	1
Anus	1	Daling 1987 case-control	1
Bladder	2	Bedwani 1997 case-control Chacko 2006 case-control	2
Brain (glioma)	1	Efird 2004 cohort	1
Breast	1	Sidney 1997 cohort	1
Cervix	1	Sidney 1997 cohort	1
Colorectal	1	Sidney 1997 cohort	1
Esophagus	1	Hashibe 2006 case-control	1
Head and neck (squamous cell)	4	Zhang 1999 case-control[+] Zhang 2000 case-control[+] Aldington 2008b case-control Gillison 2008 case-control	3
Larynx	1	Hashibe 2006 case-control	1
Lung	6	Aldington 2008a case-control Hashibe 2006 case-control Hsairi 1993 case-control Sasco 2002 case-control Sidney 1997 cohort Voirin 2006 case-control	6
Melanoma	1	Sidney 1997 cohort	1
Non-Hodgkin's lymphoma (NHL)	2	Holly 1999 case-control Nelson 1997 case-control	2
Oral cavity (squamous cell)	4	Hashibe 2006 case-control[@] Llewellyn 2004a case-control Llewellyn 2004b case-control Rosenblatt 2004 case-control	4
Penis	1	Maden 1993 case-control	1
Pharynx	1	Hashibe 2006 case-control	1
Prostate	1	Sidney 1997 cohort	1
Testis	1	Daling 2009 case-control	1

Cancer Category Reported*	Number of Articles[+]	First Author, Year of Publication, Study Design	Number of Studies [+]
Tobacco-related cancers (upper aerodigestive including esophagus, lung, pancreas, kidney, and bladder)	1	Sidney 1997 cohort	1
PARENTAL MARIJUANA SMOKING			
Maternal			
Childhood brain (astrocytoma) <15 years	1	Kuijten 1990 case-control	1
Paternal			
Childhood leukemia <18 years	1	Wen 2000 case-control[&]	3
Infant leukemia <18 months	1	Wen 2000 case-control	1
Childhood acute lymphoblastic leukemia <15 years	1	Wen 2000 case-control	1
Maternal and paternal			
Childhood acute myeloid leukemia <18 years	2	Robison 1989 case-control Trivers 2006 case-control^	2
Childhood neuroblastoma <19 years	1	Bluhm 2006 case-control	1
Childhood rhabdomyosarcoma <21 years	1	Grufferman 1993 case-control	1

* Some studies reported more than one type of cancer.
[+] Some studies were represented by multiple articles.
[@] 94% squamous cell.
[&] Wen *et al.*, 2000, reported results for childhood leukemia for data combined from three studies.
^ Trivers *et al.*, 2006, reported results for both direct (among children age 5-17) and parental marijuana smoking.

3.1.2 Issues of validity among studies of cancer and marijuana smoking

Validity issues that have been particularly important in the epidemiological studies reporting results for cancer and marijuana smoking have included:

- Under-reporting of marijuana use due to illegality and social stigma, lack of privacy during interviews, and lack of assurance of data confidentiality.
- Confounding bias from other risk factors for cancer (e.g., tobacco smoke).
- Selection bias from nonparticipation.
- Reporting bias within articles when authors present associations that were found rather than all results.
- Categorizing people with very little exposure (and thus little potential cancer risk) as exposed. Often, ever/never was the only marijuana exposure quantification in the epidemiologic studies.

3.1.2.1 Under-reporting of marijuana smoking

In case-control studies, if cases and controls under-report past marijuana smoking equally, then no bias in the rate ratio estimate occurs. However, if cases and controls under-report unequally, then bias can occur. For example, if there is less under-reporting among cases compared to controls, then marijuana use may appear to be associated with cancer when no cause-and-effect relationship exists.

All of the epidemiologic studies of cancer and marijuana smoking published to date have used questionnaires to obtain marijuana smoking histories from study subjects. In most of the studies the questionnaires were administered orally by interviewers, either in-person or over the phone, and study subjects answered the questions orally with various degrees of privacy. Some questionnaires were self-administered by subjects who answered the questions in writing.

Questionnaire-based studies of illicit drug use are frequently criticized because they rely on self-reporting of illegal and socially stigmatized behaviors (Harrison, 1997b). Study subjects may not be completely honest about past drug use in order to present themselves to interviewers and others in a favorable way (Harrell, 1997). This view is based on the social desirability theory in social sciences, which suggests that under-reporting occurs as a function of the perceived acceptability of the behavior in question. The degree of under-reporting of illegal drug use has been shown to vary by type of drug, time since last use of the drug, study population demographics, geographic location-specific legal and societal acceptability, level-of-detail of questions, method of responding to questions (e.g., oral vs. written answers), perceived level of anonymity/confidentiality, and employment requirements (Harrison and Hughes, 1997a).

Lack of privacy when subjects are answering questions can cause under-reporting. For example, it has been shown that subjects are less likely to divulge past use of illegal drugs if other members of a household are in hearing-range of a subject's answers during an oral interview (Harrell, 1997; Aquilino and LoSciuto, 1990; Aquilino, 1997).

Several social research studies have found that self-administered questionnaires (SAQ) yield higher reports of drug use than interviewer-administered questionnaires (Harrell, 1997). Computer assisted self-interviewing (CASI), particularly audio-CASI, has been shown to

produce higher rates of drug use reporting compared to the traditional SAQ and interviewer-administered procedures (Harrison and Hughes, 1997a; Lessler and O'Reilly, 1997).

Under-reporting of marijuana use by pregnant mothers has been objectively documented in several studies that have compared the results of maternal interviews with the results of chemical analyses of meconium for THC (delta 9 tetrahydrocannabinol) and its metabolites. For example, in a study of approximately 1,000 births occurring in the years 2002-2004 at a hospital in Barcelona, Spain, just 1.7% of the mothers disclosed during post-birth interview that they had ever used marijuana during the pregnancy in comparison to 5.3% of the babies having evidence of *in utero* marijuana exposure in their meconium (Lozano *et al*., 2007). The investigators noted that degree of maternal under-reporting is probably greater than these numbers would suggest because drug use during the first trimester is generally not detectable in meconium.

3.1.2.2 Potentially confounding variables

Bias could occur in cancer studies if marijuana smoking was associated with a factor that causes cancer, and that factor was not taken into account in the study design or analysis. For example, three of the studies of lung cancer and marijuana smoking were conducted in countries where tobacco is often mixed with marijuana prior to smoking. While the studies took into account tobacco-only smoking when calculating marijuana smoking results, they could not take into account for tobacco- marijuana-mixture smoking

Tobacco smoking

Tobacco smoke, a well-established cause of several types of cancer, is a potential source of confounding bias in studies of marijuana smoking and cancer. There are several ways in which tobacco smoke could be a confounding factor, as follows:

- Tobacco cigarette smoking is generally more common among marijuana smokers compared to marijuana nonsmokers.
- Some individuals simultaneously smoke tobacco and marijuana by:
    - Mixing tobacco and marijuana
    - Creating "blunts" (putting marijuana inside of a cigar wrapping or rolled tobacco leaf)
    - "Chasing" marijuana smoking with tobacco smoking.

Data on the degree of association between marijuana smoking and tobacco smoking have been provided by several epidemiological and social sciences studies. Rosenblatt *et al.*, 2004, in a case-control study in western Washington State, provided data showing that "ever marijuana smoking" was generally more frequent in controls with higher cumulative tobacco smoke exposure, except in the highest cumulative tobacco smoking category (30+ pack-years) (Rosenblatt *et al*. 2004). In an epidemiologic study of 64,855 members of a health plan in San Francisco and Oakland, California, who completed questionnaires during 1975-1985, "ever marijuana smoking" was more frequent in "ever tobacco smoking" subjects than in "never tobacco smoking" subjects (Sidney *et al*., 1997). The statistical association between ever-marijuana smoking and ever-tobacco smoking was statistically significant in both genders, but was stronger in females (OR=2.9, 95% CI 2.7-3.0) than in males (OR=1.9, 1.8-2.0). For the entire cohort the OR for the association of marijuana and tobacco use was 2.4 (95% CI = 2.3 – 2.5) (odds ratios and 95% confidence intervals calculated by OEHHA). A social sciences study

of tobacco and marijuana smoking among young adults (ages 15-24 in 2004 in Canada) found that the two behaviors were associated (Leatherdale *et al.*, 2007). For marijuana smoking in the past 12 months, the odds ratio for the association with current tobacco smoking was 6.4 (95% CI 5.7-7.1), and for former tobacco smoking was 3.1 (2.5-3.7).

Mixing of tobacco and marijuana prior to smoking has long been a common practice in many parts of the world, including Europe, Northern Africa, and Canada (Amos *et al.*, 2004; Johnson and Gerstein, 1998; Voirin *et al*., 2006). For example, a case-control study of lung cancer in Tunis, Tunisia, reported that mixing tobacco and marijuana has been common practice there (Voirin *et al*., 2006). In contrast, the historical practice in the U.S. of generally smoking marijuana without adding tobacco is arguably exceptional (Ream *et al*., 2008). New Zealand is another country where marijuana has been rarely mixed with tobacco according to Aldington *et al.* (2008a).

Another method of smoking marijuana that entails simultaneous exposure to tobacco smoke is the smoking of blunts. A blunt is either a rolled tobacco leaf with marijuana inside or, more commonly in the U.S., a cigar that has been hollowed out and filled with marijuana (the outer shell of a cigar is made of tobacco). Some marijuana smokers prefer blunts because of the concurrent nicotine effect, the large size (good for sharing), the easy addition of other drugs, and the secretiveness provided by the look of a cigar (Humfleet and Haas, 2004). In the U.S., blunt use has recently increased among urban youth and has been popularized by blunt-related rap music lyrics and T-shirts.

In the U.S., tobacco smoking immediately after marijuana smoking (called "chasing") has become a common ritual among some urban youths. For example, a survey in 2004-2005 of marijuana smokers in New York City found that blunt users often passed-around a cigarette or cigarillo "blunt chaser" immediately after a blunt was finished (Ream *et al*., 2008).

Alcohol consumption

Alcohol consumption is a known cause of several types of cancer. Alcohol consumption and marijuana smoking were strongly associated in the general population control group of the Rosenblatt *et al.* (2004) case-control study of oral cancer in western Washington State. "Ever marijuana smoking" ranged from 12% in subjects consuming less than one drink per week to approximately 50% in subjects consuming 20 or more drinks per week.

Sexual activity and sexually transmitted infections

Sexual activity is associated with several forms of cancer (e.g., anal cancer in men and women, penile cancer, cervical cancer, Kaposi's sarcoma, and Hodgkin's disease), and the associations are thought to be due primarily to infectious agents such as HPV (human papillomavirus), HIV (human immunodeficiency virus), and possibly HSV (herpes simplex virus). Cancer risk from sexual activity could bias studies of marijuana smoking if the sexual activity and marijuana smoking were associated. In the U.S., homosexual experience and marijuana smoking were associated in the 1996 NHSDA, with the association being stronger among women than among men (Cochran *et al*., 2004).

3.1.2.3 Effect modification by time since first exposure

An issue in epidemiologic studies of cancer and environmental exposures is whether there was sufficient length of time after first exposure to observe increased risk. Generally, five to 20 years must elapse before exposure-caused cancer cases begin to appear. For example, the lag time between increased tobacco cigarette smoking and increased lung cancer death rates in the U.S. was about 20-25 years (Kleinsmith *et al*., 2006). Thus, if marijuana smoke causes cancer by mechanisms that are similar to those of tobacco smoke, observation of study subjects more than 25 years after first marijuana smoking may be needed to epidemiologically detect increased cancer risk.

3.1.3 Controlled Studies

3.1.3.1 *Direct* marijuana smoking

Lung cancer

Six controlled studies reported results for lung cancer and marijuana smoking. The studies are discussed below in chronological order of publication, and are summarized in Appendix Table 1. The lung cancers in Sidney *et al.* (1997) below were also included in a cancer category called "tobacco-related cancer" in the same article (Appendix Table 4).

Hsairi et al. (1993) Etiologic factors in primary bronchial carcinoma in Tunisia (French language).

The first controlled study published on the topic of marijuana smoking and lung cancer risk was a case-control study by Hsairi *et al.* (1993) in the city of Tunis, Tunisia (Hsairi *et al*. 1993). The purpose of the study was to investigate the etiologic roles of marijuana smoking (by any method) and tobacco water pipe smoking. Male and female lung cancer cases were diagnosed during the years 1988-1989 at one hospital in Tunis, and controls were selected from the general population of Tunis (random or convenience selection not stated). Controls were matched to cases on tobacco cigarette smoking, age, and gender. The study reported a statistically significant association between marijuana smoking and lung cancer risk (OR=8.2, 95% CI 1.3-15.5).

The study had several important limitations. One limitation was the potential under-reporting of past marijuana smoking due to possible lack of privacy during interviews and lack of assurance of data confidentiality (the article does not address these issues). While 12% of lung cancer cases reported past marijuana smoking, only 1% of controls (one of 110) reported past marijuana smoking, a number that seems unrealistically low. Another limitation was that tobacco traditionally has been mixed into marijuana prior to smoking marijuana in northern Africa (Joseph 1973). While Hsairi *et al.* did not mention mixing of tobacco and marijuana, a later cancer study by Voirin *et al.* (2006), also based in Tunis, reported that "cannabis cigarettes are usually composed of a mixture of tobacco and cannabis." Since tobacco is a known cause of lung cancer, tobacco mixed into marijuana may have confounded the results for marijuana in the Hsairi *et al.* study. A third limitation was that the method of selecting controls (not described) could have caused bias (noted by investigators).

Sidney et al. (1997) Marijuana use and cancer incidence (California, U.S.).

Sidney *et al.* reported the results of a prospective cohort study of lung cancer and other cancers among members of a health plan in San Francisco and Oakland who were 15-49 years old when they voluntarily completed a written, self-administered questionnaire in 1979-1985 (Sidney *et al*., 1997). While the article stated that 64,855 members of the health plan participated, neither the number of members eligible to participate nor the participation rate was stated. Participants were divided into subcohorts of "ever" (>7 joints in lifetime, n=26,733) and "never" (0-7 joints in lifetime, n=38,122) marijuana smoking, and were followed for cancer incidence through 1993. After adjusting for tobacco cigarette smoking, alcohol consumption, age, race, and education, the rate ratios for any past marijuana smoking and lung cancer were 0.9 (95% CI = 0.5-1.7) among men and 1.1 (95% CI = 0.5-2.6) among women. The investigators reported that there was no significant association of lung cancer risk with either duration (continuous variable) or frequency (four categories) of marijuana smoking.

While Sidney *et al.* (1997) did not find increased risk of lung cancer, the cancers were diagnosed during the years 1979-1993, a period of time that may have been too soon after marijuana smoking became common in the late 1960s in the U.S. Cancers caused by environmental carcinogens often take more than 20 years from first exposure to be expressed (Kleinsmith *et al*. 2006). Another validity issue was possibly low participation by potential study subjects. The article did not present data on participation. A difference in participation between marijuana smokers and marijuana nonsmokers could have caused bias if participants had a lower or higher lung cancer risk than non-participants. A third limitation was that the investigators had no data on marijuana smoking (or other potential risk factors) subsequent to questionnaire administration at the beginning of the observation period.

Sasco et al. (2002) A case-control study of lung cancer in Casablanca, Morocco.

A case-control study of lung cancer cases diagnosed 1996-1998 at a hospital in Casablanca, Morocco, evaluated marijuana smoking among other potential environmental and occupational risk factors (Sasco *et al*., 2002). Included were 118 lung cancer cases out of an unstated total number of cases (participation rate not stated). Controls from the same hospital were matched to cases on age, gender, and place of residence. Among other topics, the participants were asked about past smoking of hashish or kif (a single question asked about past use of hashish or kif; separate data for hashish and kif smoking were not collected). Kif is a form of marijuana that has long been popular in Morocco and historically has contained approximately 30% tobacco (Joseph, 1973). After adjusting for tobacco cigarette smoking, the investigators reported an odds ratio of 2.0 (95% CI 0.6-6.3) for use of hashish or kif.

The study had several limitations, the most important of which was that tobacco was commonly mixed with the marijuana and may explain the elevated (albeit not statistically significant) odds ratio. Other limitations included no data on case- and control-specific participation (although participation for cases and controls combined was said to be approximately 90%) and under-

reporting of marijuana smoking due to possible lack of privacy in oral interviews and assurance of data confidentiality.

Voirin et al. (2006) Risk of lung cancer and past use of cannabis in Tunisia.

As a follow-up to the Hsairi *et al.* (1993) study (discussed above) that reported an association between marijuana smoking and lung cancer cases diagnosed 1988-1989 in Tunis, Voirin *et al.* (2006) conducted a case-control study of lung cancers diagnosed in the years 2000-2003 in Tunis (Voirin *et al*., 2006). The purpose of the study was to investigate potential risk from use of marijuana. Included were 149 lung cases out of an unstated total number of cases (participation rate not stated). Controls were selected from the same two hospitals as the cases plus a third hospital. After adjusting for tobacco cigarette smoking, the investigators reported significantly elevated odds ratios for ever marijuana smoking (OR=4.1, 95% CI 1.9-9.0), smoking >0-<1 joints/day (4.0, 1.6-10.2), smoking 1+ joints/day (4.2, 1.2-15.0), smoking >0-<5 years (4.7, 1.7-13.2), and smoking 5+ years (3.4, 1.1-10.1).

The authors acknowledged that tobacco was commonly mixed with the marijuana, saying that "cannabis cigarettes are usually composed of a mixture of tobacco and cannabis, and the strong (association with lung cancer may) be explained by exposure to the high levels of tar that are usually found in Tunisian tobacco." Other limitations included no information on participation rates and potential under-reporting of marijuana use due to possible lack of privacy during oral interviews. None of the 337 subjects reported that they were current marijuana smokers, which seems unlikely.

Hashibe et al. (2006) Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study.

The case-control study by Hashibe *et al.* (2006), in Los Angeles County included male and female lung cancer cases aged 18-62 and diagnosed during 1999-2004, a time period that extended to approximately 35 years after marijuana smoking became common in the U.S. in the late 1960s. Cases were identified by a population-based cancer registry, and controls were randomly selected from the general population of the county, matched on neighborhood, age, decade, and gender. For lung cancer, the investigators provided only dose-response analyses (they did not provide an odds ratio for ever/never or similar binary variable). No dose-response was found among cumulative joint-years categories (the odds ratios for all categories were less than 1.0), and no dose-response was found when cumulative joint-years was treated as a continuous variable (OR=1.0, 95% CI 0.7-1.4, for 50 joint years). (Note – joint-years are calculated by multiplying the number of joints smoked per day by the number of years smoked, e.g., smoking two joints per day for three years equals six joint-years). The odds ratios were adjusted for tobacco cigarette smoking, alcohol consumption, age, gender, race/ethnicity, and education. When the analysis was restricted to nonsmokers of tobacco cigarettes, the results were similar.

One limitation was substantially different participation rates for cases (39%) and controls (72%) which created potential for selection bias if participants and nonparticipants were different with regard to marijuana smoking history. Another limitation was possible under-reporting of marijuana smoking due to possible lack of privacy during oral interviews. A difference in under-reporting between cancer cases and healthy controls could have biased the odds ratios.

Aldington et al. (2008a) Cannabis use and risk of lung cancer: a case-control study.

In 2008, Aldington *et al.* published the results of a case control study of lung and head and neck cancers among men and women less than 56 years of age in New Zealand. The results were published in two articles; one that focused on lung cancer (discussed here) and one that focused on head and neck cancers (discussed later in this document). The lung cancer cases were diagnosed in the years 2001-2005 and were a mixture of new and historical diagnoses (Aldington *et al.*, 2008a). The cases were identified by a population-based cancer registry covering eight health districts (approximately half of the population of New Zealand), and controls were randomly selected from electoral rolls within age strata to represent the expected age distribution of cancer cases (controls were not individually matched to cases). The same control group was used for both the lung cancer and the head and neck cancer analyses. The participation rate for lung cancer cases was 77% and for controls was 66%. Data were collected via face-to-face oral interviews, usually at the subjects' homes.

The investigators reported an odds ratio for "ever" marijuana smoking and lung cancer of 1.2 (95% CI 0.5-2.6). They also reported odds ratios for three levels of cumulative marijuana smoking, of which only the highest exposure category (>10.5 joint-years) suggested increased risk (OR=5.7, 95% CI 1.5-21.6). All odds ratios were adjusted for tobacco cigarette smoking, age, gender, ethnicity, and family history of lung cancer.

A validity issue was possible under-reporting of marijuana use due to oral interviews in subjects' homes with possible lack of privacy. A difference in under-reporting between cancer cases and healthy controls could have caused bias in the odds ratios. Another potential source of bias was the inclusion of historical lung cancer cases (the percent that was historical was not stated). New cases are generally considered to be preferable in epidemiologic studies because historical cases who survive until interview may be different from cases who die with regard to the exposure of interest.

Oral cancer

Four studies have reported findings for oral cancer and marijuana smoking (Appendix Table 2). All four studies controlled for potential confounding from tobacco cigarette smoking, alcohol consumption, age, and gender.

Hashibe et al. (2006), as previously described.

The Hashibe *et al.* (2006) study described above studied oral and other cancers in a population-based case-control study in Los Angeles County. The study's objective was to determine whether marijuana smoking is a risk factor for cancer. For oral cancer, the investigators provided only dose-response analyses, that is, they did not provide an odds ratio for a binary variable such as ever/never. No dose-response was found across cumulative joint-years categories (the highest odds ratio in all categories was 1.1), and no dose-response was found when cumulative joint-years were treated as a continuous variable (OR=1.1, 95% CI 0.8-1.5, for 50 joint years). The odds ratios were adjusted for tobacco cigarette smoking, alcohol consumption, age, gender, race/ethnicity, and education. When the analysis was restricted to nonsmokers of tobacco cigarettes, a modest, non-significant increase in risk was found in the highest marijuana smoking category of 10+ joint-years (OR=1.8, 95% CI 0.7-4.7).

As noted above for lung cancer, limitations of the study include the potential for selection bias created by the different participation rates for cases (54%) and controls (72%), and possible under-reporting of marijuana smoking.

Llewellyn et al. (2004a) An analysis of risk factors for oral cancer in young people: a case-control study.
Llewellyn et al. (2004b) Risk factors for oral cancer in newly diagnosed patients aged 45 years and younger: a case-control study in Southern England.

Llewellyn *et al.* published two studies in 2004 that reported results for oral cancer and marijuana smoking in southern England (14 hospitals) (Llewellyn *et al*. 2004b; Llewellyn *et al*. 2004a). Both studies had the general objective of identifying risk factors for oral cancer. Marijuana smoking was not an *a priori* hypothesis and was not mentioned in the abstract of either article. The two studies were similar in design, but they differed in that cases were historical and occurred over 1990-1997 (with only 29% participation) in one study (2004a), and cases were new and occurred over 1999-2001 (with 80% participation) in the other study (2004b). Both studies selected controls without cancer from the medical practices of the cases' general physicians or nearby physicians (random or convenience selection not stated), matching to individual cases on age, sex, and area of residence. In the study that was based on historical diagnoses, the odds ratio for oral cancer and marijuana smoking was 1.0, and in the study based on new diagnoses, the odds ratio was 0.3.

Validity issues in both Llewellyn *et al.* studies included different questionnaire administration methods for cases and controls (all case questionnaires were administered via mail, while control questionnaires were administered via a mixture of mail and doctors' offices), non-systematic selection of controls (controls were recruited by contacting the cases' general medical practitioner and requesting patients from their practice who never had cancer, with no detail provided on how practitioners selected controls), and no definition of "cannabis smoker" presented in the articles. Whether "cannabis smoker" meant past, present, or ever marijuana smoking was not stated. In the data set based on historical diagnoses, selection bias could have occurred from the very low case participation rate.

Rosenblatt et al. (2004) Marijuana use and risk of oral squamous cell carcinoma.

Rosenblatt *et al.* (2004) combined data from two previous population-based case-control studies in western Washington State that were originally designed to examine possible associations of oral cancer and sexual activity and human papillomavirus (HPV) and herpes simplex virus (HSV) infections (Maden *et al*., 1992; Rosenblatt *et al.*, 2004; Schwartz *et al*., 1998). The previous studies had collected data on marijuana smoking but had not reported results for marijuana smoking. The Rosenblatt *et al.* analysis examined the marijuana data from the studies and found no association overall (OR=0.9 for ever marijuana use) and no dose-response trend with cumulative years of marijuana smoking or intensity of marijuana smoking measured as number of uses per week. The investigators adjusted for tobacco smoking, alcohol consumption, sex, education, birth year, and data set (the Maden 1992 data set versus the Schwartz 1998 data set). Validity issues included low participation and potential under-reporting of exposure due to possible lack of privacy during face-to-face interviews in subjects' homes.

Head and neck cancers

Three studies have reported findings for head and neck cancer and marijuana smoking (Appendix Table 3). Two were hypothesis testing in design for marijuana smoking (Aldington *et al*., 2008b; Zhang *et al*., 1999, Zhang *et al.*, 2000) and the third study was hypothesis generating (Gillison *et al*. 2008). All three studies controlled, via matching or statistical adjustment, for the potentially confounding effects of tobacco cigarette smoking, alcohol consumption, age, and gender. Other studies looked at individual types of head and neck cancers (e.g., pharyngeal, esophageal, laryngeal: Hashibe *et al.* (2006)) or subgroups (oral cancer: Hashibe *et al*. (2006); Llewellyn *et al.* (2004a & b), Rosenblatt *et al*. (2004)). Several types of head and neck cancers were also included in a study of "tobacco-related cancers" (Sidney *et al*., 1997).

Aldington et al. (2008b) Cannabis use and cancer of the head and neck: case-control study.

Aldington *et al.* published the results of a hypothesis testing case control study of marijuana smoking and cancers of the lung and head and neck among men and women less than 56 years of age in New Zealand. The study was published in two articles, one focused on head and neck cancer (discussed here) and one focused on lung cancer (discussed above). "Head and neck cancer" was defined by the investigators as cancers of the lip, tongue, floor of mouth, palate, mouth, tonsil, oropharynx, nasopharynx, hypopharynx, pharynx, nasal cavities, larynx, and head and neck unspecified (Aldington *et al*., 2008b). The design of the study is discussed above. The same control group was used for both the lung cancer and the head and neck cancer analyses. The participation rate for head and neck cancer cases was 77% and for controls was 66%. Data were collected via face-to-face oral interviews, usually at the subjects' homes.

The investigators reported that there was no increase in head and neck cancer risk for "ever" marijuana smoking (OR=1.0, 95% CI 0.5-2.6). They also reported that there were no statistically significantly elevations in risk among three levels of cumulative marijuana smoking (in joint-

years). When joint-years were analyzed as a continuous variable (rather than categories), there was a suggestion of increased risk that was not quite statistically significant (OR=1.04, 95% CI 0.97-1.11, for one joint-year). In the continuous variable analysis, counting only marijuana smoking 5 years or more before diagnosis increased the OR for one joint-year to 1.08, but widened the confidence interval to 0.77-1.53. All odds ratios were adjusted for tobacco cigarette smoking, age, gender, ethnicity, and health district.

As discussed above, potential sources of bias were possible under-reporting of marijuana smoking due to oral interviews in subjects' homes, and the inclusion of historical cases

Zhang et al. (1999) Marijuana use and increased risk of squamous cell carcinoma of the head and neck.
Zhang et al. (2000) Environmental tobacco smoking, mutagen sensitivity, and head and neck squamous cell carcinoma.

Zhang *et al.* (1999 and 2000) conducted a hypothesis-testing, hospital-based case-control study of marijuana smoking and squamous cell head and neck cancers diagnosed 1992-1994 at a cancer center in New York City (Zhang *et al*., 2000; Zhang *et al*., 1999). Controls were said to be blood donors at the cancer center, but the articles did not describe how the controls were selected (e.g., random selection or convenience sample). The controls were frequency-matched to cases on age and gender. Participation rates were excellent at 92% for cases and 80% for controls. Data on marijuana smoking and other potential risk factors were obtained in person at the hospital by a nurse interviewer using a structured questionnaire (personal communication with Dr. Zhang 11/18/2008).

The investigators reported an odds ratio of 2.6 (95% CI 1.1-6.6) for head and neck cancer and "ever marijuana use" after adjusting for tobacco cigarette smoking, alcohol consumption, age, gender, race, and education. When marijuana smoking was divided into categories of frequency of smoking (1 and 2+ times per day) there was a statistically significant increasing trend in the odds ratios (probability (p) =0.04), but neither of the individual odds ratios was statistically significant. When divided into categories of length of marijuana smoking (>0-5 and 6+ years), again there was a significant increasing trend (p=0.03), and again neither of the individual odds ratios was statistically significant. Apparent effect modification was reported for age (stronger association between marijuana smoking and head and neck cancer among subjects under age 55), cigarette smoking (stronger association among cigarette smokers), environmental tobacco smoke (ETS) (stronger association among ETS-exposed), mutagen sensitivity (stronger association among the sensitive), and to a lesser extent, alcohol use (stronger association among alcohol users). To determine mutagen sensitivity, blood samples were collected from cases and controls, lymphocytes were cultured for 67 hours, and the cultures were treated with the mutagen bleomycin for five hours (with colcemid added in the last hour to induce mitotic arrest). The frequency of chromatid breaks and exchanges was expressed as breaks per cell (exchanges were counted as two breaks). Mutagen "sensitive" was defined as >1 breaks per cell in the methods text and 1+ breaks per cell in the table showing results.

The investigators said that their results need to be interpreted with caution because of methodological limitations. One limitation that they noted was potential selection bias from the controls being blood donors. The investigators said "if use of marijuana were inversely associated with blood donation, the selection bias would lead to an overestimate of the marijuana effect." This limitation of the Zhang *et al.* study has been commented on by other researchers (Hall *et al*., 2005; Kalant 2004). Rosenblatt *et al*. (2004) used data from the NHSDA to estimate that the expected number of marijuana users among controls in the Zhang *et al*. study was 40.6, whereas only 17 users were observed, and commented that some or all of the 2.6-fold association could have been due to spuriously low exposure prevalence among the controls. Another limitation, acknowledged by the investigators, was low power and precision due to small sample size and low frequency of marijuana use. Possible under-reporting of marijuana smoking between cases and controls was noted by the investigators, who said that "the degree under-reporting of marijuana smoking might have been greater for healthy controls than cancer cases who might want to rationalize their disease."

Gillison et al. (2008) Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers.

Gillison *et al.* (2008) conducted a case-control study of head and neck cancers for which the tumors were categorized as positive or negative for human papillomavirus type 16 (HPV-16) DNA (Gillison *et al.*, 2008). The objective of the study was to examine whether the risk factors for HPV-16-positive head and neck cancers are similar to those for HPV-16-negative cancers. The investigators hypothesized that they are different cancers.

Newly diagnosed male and female cases age 18+ were identified during 2000-2006 at a hospital otolaryngology clinic in the city of Baltimore. Controls were randomly selected from non-cancer patients at the same clinic, matched on age and gender. Participation rates were relatively good at 77% and 70% for cases and controls, respectively. All odds ratios were adjusted for tobacco cigarette smoking, alcohol consumption, race, number of teeth lost, frequency of tooth brushing, and number of oral sex partners. Odds ratio analyses were conducted separately for the HPV-16-positive and HPV-16-negative cases. Marijuana use was defined as ever using marijuana at least once per month for one year or longer.

For HPV-16-positive head and neck cancer cases there was an association with marijuana smoking. The odds ratio for formerly smoking marijuana at least monthly for one year was 2.3 (95% CI 1.0-5.4), and for currently smoking marijuana and smoking marijuana at least monthly for one year was 4.7 (95% CI 1.3-17). When marijuana smoking was divided into cumulative exposure categories (1-4, 5-14, and 15+ joint-years), the odds ratios strongly increased with increasing exposure, and the test for trend was statistically significant (p=0.003). The odds ratio in the highest exposure category (15+ joint-years) was 6.4 (95% CI 1.6-26). Among nonsmokers of tobacco, the odds ratio for five or more joint-years of marijuana smoking was 11.0 (95% CI 1.6-74).

For HPV-16-negative cases there was less of an association between marijuana smoking and head and neck cancers. The odds ratio for formerly smoking marijuana at least monthly for one

year was 1.2 (95% CI 0.5-2.8) and for currently smoking marijuana and smoking marijuana at least monthly for one year was 2.0 (95% CI 0.6-6.5). When marijuana smoking was divided into cumulative exposure categories (1-4, 5-14, and 15+ joint-years), the odds ratios modestly increased with increasing exposure but the test for trend was not statistically significant (p=0.29).

The investigators suggested that marijuana may act directly or may promote HPV-positive head and neck cancers.

A potential validity issue in the Gillison *et al.* (2008) study was under-reporting of marijuana smoking. The questionnaire method was said to be "audio computer-assisted self-interview (ACASI) technology," but whether the subjects responded orally or had privacy in answering questions was not stated. Differential under-reporting of marijuana smoking between cases and controls could have biased the rate ratio estimates.

Pharyngeal cancer

Just one study has reported results for pharyngeal cancer and marij1uana smoking (Appendix Table 3). Other studies included pharyngeal cancer as a type of oral cancer (i.e., oropharynx in Llewellyn *et al.* (2004a & b) and Rosenblatt *et al*. (2004)) or head and neck cancer (i.e., Aldington *et al.* (2008b), Zhang *et al.* (1999 & 2000), and Gillison *et al. (*2008)). Pharyngeal cancer was also included as a type of "tobacco-related cancer" in the study of Sidney *et al*. (1997).

Hashibe et al. (2006), as previously described.

The Hashibe *et al.* (2006) study described above studied pharyngeal and other cancers in a population-based case-control study in Los Angeles County. The participation rate among pharyngeal cancer cases was low at 45% (100 were studied) and among controls was higher at 72% (1,040 were studied). Among never-users of tobacco, the odds ratio for pharyngeal cancer and "ever" marijuana smoking was 0.9 (95% CI 0.4-2.1) after adjusting for alcohol, age, gender, race/ethnicity, and education. (Odds ratios for "ever" marijuana smoking were not reported for all subjects or for tobacco users.) Among all subjects, no dose-response was found across cumulative joint-years categories (the odds ratios for all categories were less than 1.0), and no dose-response was found when cumulative joint-years were treated as a continuous variable (OR=0.8 95% CI 0.4-1.5, for 50 joint-years). The dose-response odds ratios were adjusted for tobacco smoking, alcohol, age, sex, race/ethnicity, and education. As noted above, validity issues included low participation of cases (45%), possible under-reporting of marijuana smoking due to possible lack of privacy during oral interviews, and possibly persons with little exposure (e.g., smoked marijuana only once in a lifetime) categorized as exposed in the ever/never analysis.

Esophageal cancer

One study has reported results for esophageal cancer and marijuana smoking (Appendix Table 3). Another study included esophageal cancer as a type of head and neck cancer (Zhang *et al*.

(1999 & 2000). Esophageal cancer was also included as a type of "tobacco-related cancer" in the study of Sidney *et al*. (1997).

Hashibe et al. (2006), as previously described.

The Hashibe *et al.* (2006) study described above, a population-based case-control study in Los Angeles County, also studied esophageal cancer. The participation rate among esophageal cancer cases was very low at 35% (108 were studied) and among controls was higher at 72% (1,040 were studied). Among never-users of tobacco, the odds ratio for esophageal cancer and "ever" marijuana smoking was 0.8 (95% CI 0.3-2.1) after adjusting for alcohol, age, gender, race/ethnicity, and education. (Odds ratios for "ever" marijuana smoking were not reported for all subjects or for tobacco users.) Among all subjects, no dose-response was found across cumulative joint-years categories (the odds ratios for all categories were less than 1.0), and no dose-response was found when cumulative joint-years were treated as a continuous variable (OR=1.1, 95% CI 0.8-1.5, for 50 joint-years). The dose-response odds ratios were adjusted for tobacco smoking, alcohol, age, sex, race/ethnicity, and education.

"Tobacco-related" cancers

One study has reported results for tobacco-related cancers (as a group) and marijuana smoking (Appendix Table 4).

Sidney et al. (1997), as previously described.

The Sidney *et al.* prospective cohort study described above also reported on "tobacco-related" cancers. Cancers categorized as tobacco-related included upper aerodigestive cancers (including esophagus) and cancers of the lung, pancreas, kidney, and bladder. After adjusting for tobacco cigarette smoking, alcohol consumption, age, race, and education, the rate ratios for "ever" marijuana smoking and tobacco-related cancers were 0.9 (95% CI 0.6-1.4) among men and 0.7 (95% CI 0.3-1.4) among women. The investigators reported that there was no significant association of tobacco-related cancers with either duration (continuous variable) or frequency (four categories) of marijuana smoking.

Limitations of the study are noted above, and include the potentially short observation period, possible selection bias because no data on participation rates were presented, and the absence of data on marijuana smoking or other exposures subsequent to completion of questionnaires at the beginning of the observation period.

Laryngeal cancer

One study has reported results for laryngeal cancer and marijuana smoking (Appendix Table 4). Other studies included laryngeal cancer as a type of head and neck cancer (i.e., Aldington *et al.* (2008b), Zhang *et al.* (1999, 2000), and Gillison *et al*. (2008)). Laryngeal cancer was also included as a type of "tobacco-related cancer" in the study of Sidney *et al.* (1997).

Hashibe et al. (2006), as previously described.

The Hashibe *et al.* (2006) population-based case-control study in Los Angeles County described above also reported on laryngeal cancer. This study had a low participation rate among cases of 42% (90 were studied), compared to 72% (1,040 were studied) in controls. Among never-users of tobacco, the odds ratio for laryngeal cancer and "ever" marijuana smoking was 1.2 (95% CI 0.3-5.5) after adjusting for alcohol, age, gender, race/ethnicity, and education. (Odds ratios for "ever" marijuana smoking were not reported for all subjects or for tobacco users.) Among all subjects, no dose-response was found across cumulative joint-years categories (the odds ratios for all categories were less than 1.0), and no dose-response was found when cumulative joint-years were treated as a continuous variable (OR=0.9, 95% CI 0.5-1.7, for 50 joint-years).

Bladder cancer

Two studies have reported results for bladder cancer and marijuana smoking (Appendix Table 4).

Bedwani et al. (1997) Epidemiology of bladder cancer in Alexandria, Egypt: tobacco smoking.

A case-control study of tobacco smoking and other potential risk factors (including hashish smoking) for bladder cancer among men in Alexandria, Egypt, was conducted by Bedwani *et al.* (1997). The 52 cases studied were diagnosed during the years 1993-1996. The total number of cases that occurred and the participation rate were not stated. While controls were said to be non-cancer patients from the same hospitals, the method of selecting the controls (random or convenience) was not stated, and apparently the controls were not matched to cases with regard to potentially confounding variables. After adjusting for tobacco cigarette smoking and other potential risk factors, the investigators reported a negative association between hashish smoking and bladder cancer (OR=0.4, 95% CI 0.1-2.5). The study had several limitations, including the possibility that tobacco and marijuana were sometimes mixed with marijuana (as it is elsewhere in northern Africa), no information on participation rates, and potential under-reporting of marijuana smoking due to possible lack of privacy in oral interviews.

Chacko et al. (2006) Association between marijuana use and transitional cell carcinoma.

Chacko *et al.* (2006) performed a case-control study of transitional cell carcinoma of the bladder among urological clinic patients at two Veterans Administration facilities in the U.S. Marijuana smoking was hypothesized to be a risk factor for bladder cancer because of case reports in the scientific literature. Fifty-two cases under age 60 were age-matched to 104 non-cancer controls from the same urological clinics. Data were obtained via self-administered written questions and answers. The investigators reported an odds ratio of 3.4 ($p = 0.008$) for "ever smoked" marijuana, but the result was not adjusted for tobacco smoking, a well-established cause of transitional cell carcinoma of the bladder. When tobacco smokers were excluded from the analysis, the study again found a positive association with marijuana smoking (odds ratio 3.3),

but the precision of the estimate (e.g., hypothesis test probability or 95% confidence interval) was not reported and the association was based on small numbers (six exposed cases and four exposed controls).

While the study did not report adjusted odds ratios, it did report a significant trend across three categories of cumulative marijuana smoking (joint-years) (p=0.01) in a regression analysis that adjusted for tobacco smoking, smoked meat, Agent Orange, radiation, and dyes.

A strength of the study was its use of self-administered, written questionnaires, a method that may have collected relatively reliable self-reported marijuana smoking data. A limitation of the study was that the odds ratio for which precision was calculated (3.4, p=0.008) was not adjusted for tobacco cigarette smoking. Another limitation was no information on case participation (control participation was said to be 79%). Also, 46% of the control group had erectile dysfunction, "to which tobacco smoking is a common contributor" (noted by authors). If the control group had an unusually high proportion of tobacco smokers, the effect on the odds ratio would be to make it smaller than it otherwise would be, so the large number of erectile dysfunction patients in the control group is unlikely to be responsible for the positive association found with marijuana smoking. Curiously, tobacco smoking, a known cause of bladder cancer, was not associated with bladder cancer in this study. Finally, there is a data error in the article in that the numbers of cases stratified into tobacco and marijuana smoking categories (created by tobacco yes/no and marijuana yes/no variables) do not sum correctly. The three categories for which numbers of cases are presented sum to 55 cases, which is more than the 52 total cases.

Prostate cancer

One study has reported results for prostate cancer and marijuana smoking (Appendix Table 5).

Sidney et al. (1997), as previously described.

The Sidney *et al.* prospective cohort study described above also reported on prostate cancer among members of a health plan in San Francisco and Oakland. As noted above, subjects were 15-49 years old when they voluntarily completed a written, self-administered questionnaire in 1979-1985 (Sidney *et al.*, 1997). While the article stated that 27,920 men participated, neither the number of men eligible to participate nor the participation rate was stated. Participants were divided into subcohorts of "ever" (>7 joints in lifetime, n=13,577) and "never" (0-7 joints in lifetime, n=14,343) marijuana smoking, and were followed for cancer occurrence through 1993. After adjusting for tobacco cigarette smoking, alcohol consumption, age, race, and education, the rate ratio for "ever" marijuana smoking was slightly elevated at 1.3 (95% CI 0.6-2.6). The investigators reported that there was no significant association of prostate cancer with either duration (continuous variable) or frequency (four categories) of marijuana smoking. When the cohort was restricted to subjects who had never smoked tobacco cigarettes, the rate ratio for "ever" marijuana smoking and prostate cancer was elevated and of borderline statistical significance (rate ratio (RR) =3.1, 95% CI 1.0-9.5).

As noted above, limitations of the study included the potentially short observation period possible selection bias because no data on participation rates were presented, and lack of data on marijuana smoking or other exposures subsequent to completion of questionnaires at the beginning of the observation period.

Penile cancer

One study has reported results for penile cancer and marijuana smoking (Appendix Table 5).

Maden et al. (1993) History of circumcision, medical conditions, and sexual activity and risk of penile cancer.

Marijuana smoking was among many potential risk factors for penile cancer studied by Maden *et al.* (1993) in a case-control study conducted in 13 counties in western Washington State, U.S., and in the Lower Mainland and Vancouver Island in British Columbia, Canada. Marijuana smoking was not an *a priori* hypothesis and was not mentioned in the abstract or introduction of the article. Cases occurring 1979-1990 under age 75 were identified through population-based cancer registries, and controls were randomly selected (using random digit phone dialing) from the general populations of the areas covered by the cancer registries, with matching on age and date of diagnosis. Participation rates were 50% for cases and 74% for controls. Questionnaires were administered via face-to-face oral interviews at subjects' homes or another place of their choosing. After adjusting for tobacco cigarette smoking, alcohol consumption, age, and number of sexual partners, the odds ratio for "ever" marijuana smoking was elevated but not statistically significant (OR=1.5, 95% CI 0.7-3.2). When marijuana smoking was categorized by cumulative frequency, the odds ratios were 1.7 (95% CI 0.8-3.9) for 1-< 51 times and 1.0 (95% CI 0.3-3.6) for 51+ times.

Limitations of the study included possible under-reporting of marijuana smoking due to lack of privacy during oral interviews in subjects' homes, selection bias from low participation among the cases (50%), and use of historical cases (18% of the cases could not be interviewed due to being deceased).

Cervical cancer

One study has reported results for cervical cancer and marijuana smoking (Appendix Table 5).

Sidney et al. (1997), as previously described.

Sidney *et al.* also reported the results for cervical cancer in their prospective cohort study among San Francisco and Oakland members of a health plan. As noted above, subjects were 15-49 years old when they voluntarily completed a written, self-administered questionnaire in 1979-1985 (Sidney *et al.*, 1997). While the article stated that 36,935 women participated, neither the number of women eligible to participate nor the participation rate was stated. Participants were divided into subcohorts of "ever" (>7 joints in lifetime, n=13,156 women) and "never" (0-7

joints in lifetime, n=23,779) marijuana smoking, and were followed for cervical cancer occurrence through 1993. After adjusting for tobacco cigarette smoking, alcohol consumption, age, race, and education, the rate ratio for "ever" marijuana smoking was 1.1 (95% CI 0.9-1.5). The investigators also calculated a rate ratio for "current" marijuana smoking and cervical cancer that was elevated and of borderline significance (RR=1.6, 95% CI 1.0-2.5). When the cohort was restricted to subjects who had never smoked tobacco cigarettes, the rate ratio for "ever" marijuana smoking and all cervical cancer was elevated and of borderline significance 1.4 (95% CI 1.0-2.1) and for invasive cervical cancer was elevated but not statistically significant (RR=2.4, 95% CI 0.8-6.7).

As noted above, limitations of the study included the potentially short observation period, possible selection bias because no data on participation rates were presented, and lack of data on marijuana smoking or other exposures subsequent to completion of questionnaires at the beginning of the observation period.

Breast cancer

One study has reported results for breast cancer and marijuana smoking (Appendix Table 5).

Sidney et al. (1997), as previously described.

Sidney *et al*. also reported results for breast cancer in women in their prospective cohort study. After adjusting for tobacco cigarette smoking, alcohol consumption, age, race, and education, the rate ratio for "ever" marijuana smoking was 1.0 (95% CI 0.8 – 1.3). There was no significant association found with either duration (continuous variable) or frequency (four categories) of marijuana smoking.

Colorectal cancer

One study has reported results for colorectal cancer and marijuana smoking (Appendix Table 6).

Sidney et al. (1997), as previously described.

Sidney *et al.* also reported results for colorectal cancer in their prospective cohort study. After adjusting for tobacco cigarette smoking, alcohol consumption, age, race, and education, the rate ratios for "ever" marijuana smoking and colorectal cancer were 0.9 (95% CI 0.5-1.8) among men and 0.6 (95% CI 0.2-1.3) among women. There was no significant association found with either duration (continuous variable) or frequency (four categories) of marijuana smoking.

Anal cancer

One study has reported results for anal cancer and marijuana smoking (Appendix Table 6).

Daling et al. (1987) Sexual practices, sexually transmitted diseases, and the incidence of anal cancer.

Using anal cancer cases reported to cancer registries in western Washington State and British Columbia, Daling *et al.* (1987) conducted a case-control study of potential environmental and lifestyle risk factors for anal cancer (Daling *et al.*, 1987). Male and female cases diagnosed in the years 1979-1985 were compared to colon cancer controls from the same registries, matched to cases on age, gender, year of diagnosis, and country. The analysis for marijuana smoking, which excluded men who were not strictly heterosexual, found an elevated but not statistically significant risk among men (OR=2.5, 95% CI 0.7-9.2) and found no elevation in risk among women (OR=0.8, 95% CI 0.2 – 4.0).

While the study did not find a statistically significant association with marijuana smoking, it may have identified cases too soon after marijuana use became common in the U.S. to detect excess risk. The study's most recent cases were diagnosed in 1985 and marijuana smoking became common in the U.S. in the late 1960s, less than 20 years earlier (see discussion of issues of validity specific to studies of cancer and marijuana smoke). Another limitation was that about 10% of subjects died prior to interviewing and were not included. Historical patients who survived until interview may have been different with regard to marijuana smoking history than patients who died. A third limitation was potential lack of privacy during oral interviews that could have affected the accuracy of answers to questions about past marijuana use. In the study's favor, however, the controls also had cancer, so there probably would not have been a difference in accuracy between cases and controls due to a difference in health status (the controls were similarly ill).

Melanoma

One study has reported results for melanoma and marijuana smoking (Appendix Table 6).

Sidney et al. (1997), as previously described.

In Sidney *et al.*, a prospective cohort study of members of a health plan in San Francisco and Oakland, the rate ratios for "ever" marijuana smoking and malignant melanoma were 1.2 (95% CI 0.7-2.1) among men and 1.1 (95% CI 0.6-1.9) among women. There was no significant association found with either duration (continuous variable) or frequency (four categories) of marijuana smoking.

Brain cancer

One study has reported results for brain cancer and marijuana smoking (Appendix Table 6).

Efird et al. (2004) The risk for malignant primary adult-onset glioma in a large, multiethnic, managed-care cohort: cigarette smoking and other lifestyle behaviors.

Efird *et al.* (2004) conducted a cohort study of risk factors for malignant primary adult-onset glioma (MPAG) among members of the health plan in northern California that was studied for other types of cancer by Sidney *et al.* (1997). Of 142,085 health plan members who in the years 1977-1985 were 25+ years old and were eligible to fill-out a questionnaire that included questions about past marijuana smoking, 105,005 (74%) participated. Incident cases of MPAG among members were observed through March 1999. The investigators estimated rate ratios for six definitions of past marijuana smoking, and reported statistically significantly elevated rate ratios for the definitions of "once a month" (RR=3.6, 1.3-10.2), "once a month or more" (RR=2.8, 1.3-6.2), and "weekly" (RR=3.2, 1.1-9.2). The investigators concluded that the results suggest a modestly increased risk for MPAG among marijuana smokers.

One limitation to the study was small numbers of cases in some marijuana smoking categories. For example, no cases occurred in the category of "daily" marijuana smoking (cohort size 2,823), and only one case occurred in the category of "less than once a month" (cohort size 5,768). Another limitation was that subjects were categorized into marijuana smoking categories based solely on their history prior to filling-out the questionnaires in the years 1977-1985. The marijuana smoking-behavior of the subjects could have changed over the study follow-up period (acknowledged by the authors).

Testicular cancer

One study has reported results for testicular cancer and marijuana smoking (Appendix Table 7). Most (95%) testicular cancers are germ cell tumors (GCTs), indicating that they originate from primordial germ cells. Among testicular germ cell tumors (TGCTs), the most common histological type is seminoma, followed by malignant teratoma, embryonal carcinoma, choriocarcinoma, and other specified types.

Daling et al. (2009). Association of marijuana use and the incidence of testicular germ cell tumors.

Daling *et al.* (2009) analyzed data on marijuana use from the Adult Testicular Cancer Lifestyle and Blood Specimen (ATLAS) study, a population-based case-control study conducted in the Seattle/Puget Sound region of Washington State. The purpose of the ATLAS study was not described by Daling *et al*., but an earlier publication indicated that the study had the general purpose of investigating potential demographic, medical, and lifestyle risk factors (Biggs *et al.*, 2008). Cases were new TGCT patients aged 10-44 who were diagnosed January 1999, through January 2006. Controls were randomly selected from the general population using random digit phone dialing, with matching on age and year of diagnosis. Participation rates were 67% for cases and 52% for controls. Questionnaires were administered via face-to-face oral interviews at subjects' homes, workplaces, and other convenient places. After adjusting for tobacco cigarette smoking, alcohol consumption, age, and history of cryptorchidism, the odds ratio for "ever" marijuana smoking and TGCT was 1.3 (95% CI 1.0-1.8). When the cases were divided into categories of pure seminoma (n=230) and non-seminoma or mixed (n=139), the odds ratios for "ever" marijuana smoking were 1.2 (0.9-1.8) for pure seminoma and 1.5 (0.9-2.4) for non-seminoma or mixed. While further analysis of marijuana history found no statistically

significant associations with pure seminoma, "current" marijuana smoking was found to be significantly associated with non-seminoma/mixed cancers (OR=2.3, 95% CI 1.3-4.0). Within "current" marijuana smoking and non-seminoma/mixed cancers the association was strongest for starting smoking marijuana before age 18 (OR=2.8, 1.6-5.1), more than 10 years (OR=2.7, 1.5-5.0), and more than once per week (OR=3.0, 1.5-5.6). No significant associations with non-seminoma/mixed cancers were reported for former marijuana smokers.

The authors noted that the incidence rates for all histological types of TGCTs have been increasing in the U.S. and they speculated that marijuana smoking might be a cause of the non-seminoma/mixed portion of the increase. However, they offered no explanation for the association existing only for current marijuana smokers. The lack of association among former marijuana smokers was not discussed. Limitations of the study included possible under-reporting of marijuana smoking due to lack of privacy during oral interviews in subjects' homes and selection bias from unequal participation by cases (67%) and controls (52%).

Acute myeloid leukemia (AML)

One study has reported results for AML and marijuana smoking (Appendix Table 7).

Trivers et al. (2006) Parental marijuana use and risk of childhood acute myeloid leukaemia: a report from the Children's Cancer Group (U.S. and Canada).

While the title of the Trivers *et al.* (2006) article mentions only parental use of marijuana, the article also includes results for children's direct marijuana smoking at ages 5-17 as reported by the children's mothers. A total of 638 AML cases age 0 - 17 years and diagnosed in 1989-1993 in the U.S. and Canada were identified by the Children's Cancer Group. Random digit phone dialing identified 711 control children who were matched to cases on age at case diagnosis, race, and residential location. While the numbers of cases and controls who were age 5-17 and thus eligible for the direct smoking part of the study were not stated, the article said that 277 case mothers and 325 control mothers answered questions about their child's marijuana smoking.

Eleven (4%) of the case children and 10 (3.1%) of the control children were reported by their mothers to have ever smoked marijuana. After adjusting for case age, race, gender, and residential location, and parental income, education, and age at child's birth, the odds ratio for ever smoking marijuana by the children was not significantly elevated (OR=1.16, 95% CI 0.34-3.93).

Limitations of the study included potential selection bias because participation rates for the mothers asked to report marijuana smoking by their children were not stated. However, there was no indication that their participation was different than the overall (all case ages) participation rates of 81% for case mothers and 79% for control mothers. A difference in participation between cases and controls could cause bias if participants and nonparticipants were different with regard to marijuana smoking history. Another potential limitation was under-reporting of marijuana smoking due to oral interviews with possible lack of privacy. Differential under-reporting between case and control mothers could have biased the rate ratio

estimate. Other potential limitations included categorizing very little exposure (e.g., smoked marijuana only once) as exposed and short observation time after exposure (e.g., the oldest cases were age 17 and first marijuana smoking often occurs at ages 14-16).

Non-Hodgkin's lymphoma (NHL)

Two studies have reported results for NHL and marijuana smoking (Appendix Table 7).

Holly et al. (1999) Case-control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay Area, California.

Marijuana smoking was among many exploratory analyses in a case-control study of risk factors for NHL among women and heterosexual men conducted in the San Francisco Bay area (six counties) by Holly *et al.* (1999). Homosexual men were excluded because infection with the human immunodeficiency virus (HIV) is a known risk factor for NHL and is associated with male homosexuality. The study had several *a priori* hypotheses based on results of previous studies, but marijuana smoking was not among them. Cases occurring 1978-1985 and age 21-74 were identified through a population-based cancer registry, and controls were randomly selected from the general population using random digit phone dialing, matching on age, gender, and county of residence. A total of 2,812 cases were identified, 1,593 (57%) were interviewed, and 1,281 (701 men and 580 women) were studied after excluding homosexual men. A total of 3,224 eligible controls were identified, 2,515 (78%) were interviewed, and 2,095 (1,257 men and 838 women) were studied after excluding homosexual men. Questionnaires were administered via face-to-face oral interviews at subjects' homes or other convenient place of their choosing.

Among men, after adjusting for age and county of residence, marijuana smoking was statistically significantly associated with decreased risk of NHL, with odds ratios of 0.6 (95% CI 0.5-0.8) for having smoked 1-<40 times, 0.5 (0.4-0.7) for 40-999 times, and 0.5 (0.3-0.8) for 1,000+ times. The results were similar among women, with odds ratios of 0.6 (0.4-0.8) for having smoked 1-<40 times, 0.6 (0.4-1.0) for 40-999 times, and 0.7 (0.3-1.5) for 1,000+ times. When the investigators combined the data for men and women, they found odds ratios of 0.7 (0.6-0.8) for 1-<40 times and 0.6 (0.4-0.7) for 40+ times after adjusting for age, county of residence, gender, and education. The authors concluded that marijuana smoking was associated with decreased risk of NHL.

Lower participation of cases (57%) compared to controls (78%) in the study could have caused bias if participants and nonparticipants were different with regard to marijuana smoking history. A large portion of case nonparticipation was due to cases being deceased (21% of all cases), despite use of the registry's rapid case ascertainment system. Historical patients who survived until interview may have been different than patients who died with regard to marijuana smoking history. Another potential source of bias was the oral face-to-face interviews in subjects' homes or public places with possible lack of privacy. The authors said "Response bias can occur with the reporting of sensitive information such as sexual behavior and drug use." Differential under-reporting of marijuana smoking between cases and controls could have biased the rate ratio estimates.

Nelson et al. (1997) Alcohol, tobacco and recreational drug use and the risk of non-Hodgkin's lymphoma.

Nelson *et al.* (1997) analyzed alcohol, tobacco, and recreation drug data collected in a case-control study of risk factors for NHL among HIV-negative men and women in Los Angeles County, U.S. (Nelson *et al*. 1997). The authors did not say why they excluded HIV-positive cases, but presumably for the same reason that Holly *et al*. (1999) excluded homosexual men, which was that HIV infection is a known risk factor for NHL and other potential risk factors were of interest. Marijuana smoking was apparently not an *a priori* hypothesis, as indicated, in part, but the absence of findings for marijuana in the article's abstract. Cases occurring 1989-1992 and age 18-75 were identified through a population-based cancer registry, and controls were randomly selected from the general population using neighborhood controls with matching on age, gender, race/ethnicity, and language. A total of 1,429 cases were identified by the cancer registry, 525 (37%) were interviewed, and 377 (184 male and 193 female) were studied after excluding cases that did not have confirmed pathology and who were HIV positive.
The total number of eligible controls contacted was not stated, but 377 (184 male and 193 female) were studied, the same as for cases because of pair matching. Questionnaires were administered via oral interview, but the method of interview (telephone or face-to-face) was not stated.

Among men, the odds ratio for ever having smoked marijuana was 0.9 (0.5-1.5) after adjusting for neighborhood, age, race/ethnicity, and language. When marijuana smoking among men was examined by total number times of past use, the odds ratios were 0.7 (0.3-1.4) for 1-5 times, 0.9 (0.5-1.9) for 6-800 times, and 1.1 (0.5-2.5) for 901+ times. Among women, the odds ratio for ever having smoked marijuana was 0.7 (0.4-1.3), and odds ratios for categories of number of times used were not calculated. The authors concluded that a history of marijuana smoking was not associated with increased risk of NHL.

The low participation of cases (37%) could have caused bias if participants and nonparticipants were different with regard to marijuana smoke history. Most of the case nonparticipation was due to 658 (46%) of the 1,429 cases being deceased, despite the fact that the study was based on newly diagnosed patients. Historical patients who survived until interview may have been different than patients who died with regard to marijuana smoking history. Another limitation of the study was potential under-reporting of marijuana smoking due to oral interviews (locations not stated) with possible lack of privacy when answering questions. Differential under-reporting of marijuana smoking between cases and controls could have biased the rate ratio estimates.

3.1.3.2 *Parental* marijuana smoking and cancers in offspring

Childhood leukemia (all types combined), infant leukemia (all types combined), and childhood acute lymphoblastic leukemia (ALL)

One study has reported results for parental marijuana smoking and childhood leukemia of all types combined, parental marijuana smoking and infant leukemia (all types combined), and

parental marijuana smoking and childhood acute lymphoblastic leukemia (ALL) (Appendix Table 8).

Wen et al. (2000) Paternal military service and risk for childhood leukemia in offspring.

Wen *et al.* (2000) conducted a case-control analysis of childhood (age <18 years) leukemia that focused on the fathers' military service but that also reported results for the fathers' marijuana smoking (Wen *et al*. 2000). The data on 2,343 cases and 2,723 controls were pooled from three populations studied by the Children's Cancer Group (CCG), a cooperative network of approximately 100 institutions in the U.S. and Canada. The three populations had different case eligibility criteria, as follows:

- Protocol E-09 included infant (under age 19 months) leukemia of all types diagnosed 1983-1988 (275 cases; 12% of all cases in the study).
- Protocol E-14 included childhood (under age 15 years) acute lymphoblastic leukemia (ALL) diagnosed 1989-1993 (1,618 cases; 69% of all cases in the study).
- Protocol E-15 included childhood (under age 18 years) acute myeloid leukemia (AML) diagnosed 1989-1993 (450 cases; 19% of all cases in the study).

In all three populations, questionnaires were administered via telephone interviews directly with the fathers or mothers as acting as surrogates for fathers (mothers answered the fathers' questions for 16% of the cases and 32% of the controls in the combined data) with the general purpose of identifying risk factors for childhood leukemia. Marijuana smoking was among many potential risk factors for which questions were asked and was not an *a priori* hypothesis, as indicated, in part, by the results for marijuana smoking not appearing in the article's abstract.

The article's paternal marijuana smoking variable of "ever smoked marijuana" was not further defined, but a more recent article by Trivers *et al.* (2006) based on some of the same children indicated that the time period of the father's marijuana smoking in the Wen *et al*. (2000) article was most likely the 12 months prior to the child's birth (Trivers *et al*., 2006).

For the study of childhood leukemia (all types combined), out of an unstated number of cases that occurred, 3,101 cases met initial eligibility criteria (phone in home and mother available and English or Spanish speaking), and the fathers (or mothers acting as surrogates for fathers) of 2,343 cases participated (76% of eligible cases). Control children were selected using random digit phone dialing, but the matching variables were somewhat different. While all three studies matched on residential location (based on phone number), study protocol E-09 additionally matched on year of diagnosis and study protocols E-14 and E-15 additionally matched on age at diagnosis, race, and gender. A total of 4,111 eligible controls were identified, and the fathers (or mothers acting as surrogates for fathers) of 2,723 controls (66%) participated. After adjusting for the matching variables, the odds ratio for childhood leukemia (all types combined) and fathers having smoked marijuana in the 12 months prior to the child's birth was significantly elevated (OR=1.5, $p<0.01$, 95% CI not reported).

For the study of infant leukemia (defined as occurring in children under 19 months of age, and diagnosed 1983-1988), 275 case and 478 control fathers participated (72% and 64% of eligible,

respectively). Proxy interviews (mothers answered the father's interview questions) occurred for 11% of the case fathers and 29% of the control fathers (Shu *et al*., 1996). After adjusting only for the matching variables of residential location and year of diagnosis, the odds ratio for infant leukemia (all types combined) and fathers having ever smoked marijuana in the 12 months prior to the child's birth was significantly elevated (OR=2.0, $p<0.05$, 95% CI not reported).

For the study of ALL (under age 15 and diagnosed 1989-1993), 1,618 cases and 1,722 control fathers participated (78% and 66% of eligible, respectively). Proxy interviews (mothers answered the father's interview questions) occurred for 17% of the case fathers and 32% of the control fathers (Shu *et al*., 1999). After adjusting only for the matching variables of residential location, age at diagnosis, race, and gender, the odds ratio for ALL and fathers having ever smoked marijuana in the 12 months prior to the child's birth was significantly elevated (OR=1.5, $p<0.05$, 95% CI not reported).

One limitation of the data included in the Wen *et al.* (2000) article was under-reporting of marijuana smoking due to possible lack of privacy during oral interviews. Differential under-reporting between case and control fathers could have biased rate ratio estimates. Another limitation was categorizing very little exposure (e.g., smoked marijuana only once) as exposed.

Childhood acute myeloid leukemia (AML)

Two studies have reported results for childhood AML and parental marijuana smoking (Appendix Table 8).

Robison et al. (1989) Maternal drug use and risk of childhood nonlymphoblastic leukemia among offspring. An epidemiologic investigation implicating marijuana (a report from the Children's Cancer Study Group).

Robison *et al.* (1989) conducted a case-control study of childhood (under age 18) AML (called acute non-lymphoblastic leukemia in the article) cases identified by the CCG in the years 1980-1984 in the U.S. and Canada (Robison *et al*. 1989). A total of 331 cases of childhood AML were identified, and 262 cases met further eligibility criteria (phone in home and mother available and English speaking). The mothers of 204 cases (78% of eligible) and the fathers of an unstated number of cases participated. Control children were selected using random digit phone dialing, matching on the case's age, race, and residential location (based on phone area code and exchange). A total of 260 control children were initially identified and 203 mothers (78%) and an unstated number of fathers participated.

Questionnaires were administered to the parents of the cases and controls via telephone interview. The questionnaires had the general purpose of identifying risk factors for childhood AML, and marijuana smoking was among many potential risk factors for which questions were asked. Maternal marijuana smoking, defined as smoking five or more times in the year before pregnancy or during pregnancy, was reported by 5% of case mothers and 0.5% of control mothers, yielding an odds ratio described as "tenfold" and statistically significant ($p=0.005$). The actual value of the odds ratio and its 95% confidence interval were not provided. Paternal

marijuana smoking, defined as smoking five or more times in the year before pregnancy, was reported by 12% of case fathers and 8% of control fathers, yielding an odds ratio of 1.47 (p=0.32) (95% CI not provided). The odds ratios were adjusted for case age at diagnosis, race, and residential location, and maternal education, tobacco use, and alcohol consumption.

A limitation of the study was possible under-reporting of marijuana smoking due to the oral interviews with possible lack of privacy. The authors said that the frequencies of maternal marijuana smoking (5% for cases and 0.5% for controls) in their study were "considerably lower" than in previous studies. They acknowledged that differential under-reporting between case and control parents may have biased the rate ratio estimates. A limitation of the maternal marijuana smoking analysis was the small number of exposed control mothers; only one of the 203 control mothers reported having smoked marijuana five or more times in the year before or during pregnancy.

Trivers et al. (2006) Parental marijuana use and risk of childhood acute myeloid leukemia: a report from the Children's Cancer Group (U.S. and Canada).

Trivers *et al.* (2006) analyzed childhood AML case-control data for cases diagnosed 1989-1993 to confirm the association with maternal marijuana smoking reported by Robison *et al.* (1989) for cases diagnosed 1980-1984 (Trivers *et al*. 2006). Out of an unstated number of cases that occurred, 638 met eligibility criteria (phone in home and mother available and English speaking), and 517 mothers (81% of eligible) and 450 fathers (71% of eligible) participated by completing an orally administered questionnaire. Control children were identified by random digit phone dialing, matching on the case's age, race, and residential location. Approximately 711 control children were initially identified (711 is estimated by OEHHA based on numbers in the article), and 610 (79%) of the control mothers and 523 (68%) of the control fathers participated. Marijuana smoking was among many potential risk factors for childhood AML for which questions were asked.

Odds ratio analyses for parental marijuana smoking were calculated separately for the mothers and fathers, adjusting for the children's age, race, gender, and residential location, and parents' income, education, and age at child's birth. For maternal exposure, the odds ratio for marijuana smoking "ever" was 0.89 (95% CI 0.66-1.19), for marijuana smoking in the 12 months before the child's birth was 0.43 (0.23-0.80), and for marijuana smoking in the year after the child's birth was 0.61 (0.32-1.13). For paternal exposure, the odds ratio for marijuana smoking "ever" was 1.37 (1.02-1.83), for marijuana smoking in the 12 months before the child's birth was 1.02 (0.67-1.53), and for marijuana smoking in the year after the child's birth was 1.03 (0.66-1.61). The authors concluded that the association between maternal marijuana smoking and childhood AML reported by Robison *et al.* (1989) was not confirmed. Interestingly, the authors made no mention in the article's text of the finding of a significant association with paternal "ever" marijuana smoking. "Ever" marijuana smoking was not defined in the article with regard to when it occurred, but the high percentages of controls reporting ever marijuana smoking (45% of control mothers and 53% of control fathers) indicate that the variable may have included ever in the parent's lifetime.

Limitations of the study included possible under-reporting of marijuana smoking due to the oral interviews with possible lack of privacy. Differential under-reporting between case and control parents could have caused bias in the rate ratio estimates (acknowledged by the authors).

Childhood brain cancer (astrocytoma)

One study has reported results for childhood brain cancer (astrocytoma) and parental marijuana smoking (Appendix Table 9). Astrocytomas account for about half of all brain tumors in children under age 15.

Kuijten et al. (1990) Gestational and familial risk factors for childhood astrocytoma: results of a case-control study.

Maternal marijuana smoking was one of many exploratory analyses of gestational risk factors for childhood astrocytoma conducted by Kuijten *et al*. (1990). Male and female cases diagnosed in 1980-1986 and less than 15 years of age were identified at eight hospitals in Pennsylvania, New Jersey, and Delaware. A total of 217 cases were identified, and 205 cases met further eligibility criteria (physician consent, U.S. residence, phone in home, and biological mother available and English speaking). The mothers of 163 cases (80% of eligible) participated by completing an orally administered questionnaire. Control children were selected using random digit phone dialing, matching on the case's age, race, and residential location (based on phone area code and exchange). Approximately 211 control children were initially identified, and 163 control mothers (77%) participated.

The odds ratio for ever maternal marijuana smoking in the 10 months before the child's birth was 2.8 (95% CI 0.9-9.9) after adjusting for the matching variables of age at diagnosis, race, and residential location. When the analysis was limited to the nine months before the child's birth (i.e., marijuana smoking during the pregnancy only), the odds ratio for maternal marijuana smoking was 4.0 (p=0.11) (95% CI not provided).

A limitation of the study noted by the investigators was potential bias from under-reporting of marijuana smoking by the mothers. The authors said "The possibility that a bias in reporting the use of an illegal drug during a telephone interview caused the observed case excess must be considered."

Childhood neuroblastoma

One study has reported results for childhood neuroblastoma and parental marijuana smoking (Appendix Table 9). Neuroblastoma is a cancer of the sympathetic nervous system that most commonly begins in the abdomen and is diagnosed in children before age five.

Bluhm et al. (2006) Maternal use of recreational drugs and neuroblastoma in offspring: a report from the Children's Oncology Group (U.S.).

Bluhm *et al.* (2006) analyzed data on recreational drug use from a case-control study of childhood neuroblastoma conducted by the Children's Oncology Group (Bluhm *et al*., 2006). Male and female cases diagnosed in 1992-1994 and less than 19 years of age were identified at 139 medical institutions in North America. Of an unstated number of cases that occurred, 741 met eligibility criteria (physician and parent consent, phone in home, and mother available and English or Spanish speaking), and 538 mothers (73% of eligible) and an unstated number of fathers participated by completing an orally administered questionnaire. Controls were randomly selected using random digit phone dialing, individually matching controls to cases on the first eight digits of the case's household phone number (which are associated with residential location) and the case's age at diagnosis (Olshan *et al*., 1999). A total of 703 eligible controls were identified, and 504 (72%) control mothers and an unstated number of fathers participated.

The odds ratio for maternal marijuana smoking ever in the 10 months before the child's birth was 1.4 (95% CI 0.8-2.5) after adjusting for case age at diagnosis, household income, and maternal use of other recreational drugs. When examined by pregnancy time intervals, the odds ratios for maternal marijuana smoking were 0.9 (0.4-1.9) in the month before pregnancy, 4.8 (1.6-16.5) in the first trimester, 1.4 (0.2-9.7) in the second trimester, 1.5 (0.2-10.2) in the third trimester, and 0.7 (0.4-1.4) in the interval between birth and diagnosis. Thus, maternal marijuana smoking was significantly associated with increased risk only in the first trimester of pregnancy. Dose-response in the first trimester was investigated by creating two marijuana smoking intensity categories. For smoking less than one pipeful per day in the first trimester the odds ratio was 4.2 (1.5-14.6), and for smoking one or more pipefuls per day the odds ratio was similar at 4.4 (1.1-29.6).

While maternal marijuana smoking was the focus of the marijuana use analysis, the authors also reported an odds ratio for "paternal marijuana use around pregnancy" of 2.0 (1.2-3.2) after adjusting for case age at diagnosis and household income.

One limitation of the study was possible bias from differential under-reporting of marijuana smoking between case and control parents. The investigators said that "Parents of cases may recall and report exposures more fully than parents of controls, seeking explanations for a child's illness," and that "parents of controls are thought to have comparatively less motivation to report stigmatized behaviors." Differential under-reporting between case and control parents could have biased the rate ratio estimates. A limitation that was specific to the results for fathers was missing data (no paternal questionnaire data for 403 (46%) of 741 eligible cases and 301 (60%) of eligible controls) (a concern acknowledged by Dr. Bluhm, personal communication). Another limitation to the results for fathers was that the time period of marijuana smoking that was assessed was not clear (the article described the time period as "around pregnancy").

Childhood rhabdomyosarcoma

One study reported results for childhood rhabdomyosarcoma and parental marijuana smoking (Appendix Table 9). Rhabdomyosarcoma is an aggressive soft tissue tumor that can arise virtually anywhere in the body. It is the most common soft tissue tumor in children.

Grufferman et al. (1993) Parents' use of cocaine and marijuana and increased risk of rhabdomyosarcoma in their children.

Grufferman *et al.* (1993) analyzed recreational drug use data that were collected in a case-control study of childhood rhabdomyosarcoma in which the main purpose was investigation of risk from fathers' tobacco smoking during the year preceding the child's birth (Grufferman *et al*., 1993). Male and female cases diagnosed in 1982-1988 and less than 21 years of age were identified at 69 hospitals in the U.S. that participated in the CCG or the Pediatric Oncology Group networks of treatment centers. A total of 511 cases of childhood rhabdomyosarcoma were identified, and 440 cases met further eligibility criteria (diagnosed at an institution with Institutional Review Board approval, U.S. resident, phone in home, and mother available and English or Spanish speaking). The mothers of 322 cases (73% of eligible) and the fathers of 312 cases (71% of eligible) participated by completing an orally administered questionnaire. Control children were selected using random digit phone dialing, matching on the case's age, race, gender and residential location (based on the first eight digits of the case's telephone number). Approximately 413 control children were initially identified, and the mothers of 322 (78%) and the fathers of 304 (74%) participated. (Note - some of these participation numbers were estimated by OEHHA based on data in the article; see Appendix Table 9 for which numbers were estimated).

Questionnaires were administered to the parents of the cases and controls via telephone interview. Maternal marijuana smoking, defined as ever in the year before the child's birth, was reported by 9% of case mothers and 4% of control mothers. The odds ratio for maternal marijuana smoking and child rhabdomyosarcoma was statistically significantly elevated at 3.0 (95% CI 1.4-6.5) after adjusting for children's age at diagnosis, race, gender, birthmarks, prematurity, and mothers' bleeding or cramping during pregnancy. Paternal marijuana smoking ever in the year before the child's birth was reported by 22% of case fathers and 14% of control fathers. The odds ratio for paternal marijuana smoking was statistically significantly elevated at 2.0 (1.3-3.3) after adjusting for child age at diagnosis, race, and gender.

The investigators found a significant correlation between mothers' and fathers' use of marijuana and concluded that it was not possible to separate differences in risk from mothers' or fathers' use. The authors expressed concern about bias from differential reporting of marijuana smoking between case and control parents. They said that "Parents of children with cancer might be more forthcoming in reporting an illegal activity than parents of community controls."

3.1.4 Case Reports

Fifteen articles reported cancer cases who had a history of smoking marijuana (case reports) (Table 3). Some of the cases were remarkable in that the cancers occurred at young ages and/or occurred in the lung or upper aerodigestive tract of patients who denied use of tobacco and alcohol. Cancer sites for which case reports have been published are tongue (Almadori *et al.*, 1990; aWengen, 1993; Fung *et al*., 1999), oral cavity (aWengen, 1993; Llewellyn *et al.*, 2003), pharynx (aWengen, 1993; Fung *et al.*, 1999; Richter *et al*., 1995), head and neck (Dahlstrom *et al*., 2008; Donald, 1991b; Endicott *et al.*, 1993), lung (Ferguson *et al*., 1989; Fung *et al*., 1999; Lebeau and Genot, 2005; Sridhar *et al.*, 1994; Taylor, 1988), bladder (Nieder *et al.*, 2006),

larynx (Taylor, 1988), kidney (Moiche Bokobo *et al*., 2001), liver (Richter *et al*., 1995), and colon (Richter *et al.*, 1995). While sometimes useful for hypothesis generation, case reports are limited in their usefulness for hazard identification because they usually lack complete ascertainment of all cases in populations, lack enumeration of populations at risk, and do not provide statistical measures of association. According to the Preamble to the International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans, the uncertainties in interpretation of case reports make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship (IARC, 2006). The Preamble also says, however, that when taken together with epidemiologic studies, case reports may add materially to the judgement that a causal relationship exists.

Table 4. Case reports of cancer patients who previously smoked marijuana**.**

First Author and Year of Publication	Geographic Location	Type of Cancer	Number of Cases	Age Range
Taylor 1988	Tampa, Florida, U.S.	respiratory	7 (no data on tobacco)	28-36
Ferguson 1989	Hartford, Connecticut, U.S.	lung	1 (smoked tobacco)	27
Almadori 1990	Rome, Italy	tongue	1 (smoked tobacco)	23
Caplan 1990	Randwick, Australia	tongue	2 (did not smoke tobacco or drink alcohol)	37-52
Donald 1991b*	Sacramento, California, U.S.	head and neck	11 (2 did not smoke tobacco or drink alcohol)	19-38
aWengen 1993	Sacramento, California, U.S.	upper aerodigestive	34 (no data on tobacco)	20-40
Endicott 1993	Tampa, Florida, U.S.	head and neck	20 (no data on tobacco)	17-40
Sridhar 1994	Miami, Florida, U.S.	lung	13 (12 smoked tobacco)	27-44
Richter 1995	Germany	hypopharynx, colon, and liver (simultaneous primary cancers)	1 (smoked tobacco)	28
Fung 1999	Philadelphia, Pennsylvania, U.S.	lung, nasopharynx, and tongue	3 (did not smoke tobacco)	31-37
Moiche Bokobo 2001	Madrid, Spain	kidney	1 (did not smoke tobacco or drink alcohol)	36
Llewellyn 2003	South East of England	oral	15 (no data on tobacco)	<46
LeBeau 2005	Paris, France	lung	1 (smoked tobacco)	22
Nieder 2006	Stony Brook, New York, U.S.	bladder	1 (did not smoke tobacco)	45
Dahlstrom 2008	Houston, Texas, U.S.	head and neck	105 (3 did not smoke tobacco or drink alcohol)	range not stated

*Included cases reported by Donald (1986) and Donald (1991a).

3.1.5 Reviews of Literature

Firth (1997) Marijuana use and oral cancer: a review.

Firth (1997) nicely summarized six case report articles about aerodigestive cancer patients who had smoked marijuana (Firth 1997). However, the usefulness of the review was limited because it included only case reports. It did not discuss epidemiological studies, of which five had been published prior to 1997.

Carriot and Sasco (2000) Cannabis and cancer (French language).

Carriot and Sasco (2000) reviewed literature on cannabis and cancer identified by a manual and computerized bibliographic search (Carriot and Sasco 2000). The authors discussed three epidemiological studies of direct marijuana smoking (by Hsairi *et al.*, 1993, Sidney *et al.*, 1997, and Zhang *et al.* 1999), two epidemiological studies of parental marijuana smoking (Robison *et al.*, 1989 and Kuijten *et al.*, 1990), 10 case report articles, and one commentary. The authors concluded that several publications have suggested an association between marijuana smoking and cancer. They noted in particular the dose-response relationships reported by Zhang *et al.* (1999) between head and neck cancer and duration (p=0.03) and frequency (p=0.04) of marijuana smoking.

Johnson (2001) Tobacco use and oral cancer: a global perspective.

Johnson (2001) wrote a review that focused on tobacco and oral cancer, but that briefly discussed marijuana and oral cancer (Johnson 2001). It cited only the review of case reports by Firth (1997). Johnson noted that marijuana and tobacco are often mixed and concluded "It is thus impossible at present to discern an independent risk for the smoking of cannabis."

Kalant (2004) Adverse effects of cannabis on health: an update of the literature since 1996.

The review by Kalant (2004) of adverse effects of marijuana discussed just two cancer studies: 1) the cohort study by Sidney *et al.* (1997) of cancer rates 1979-1993 among San Francisco Bay-area health plan members, and 2) the case-control study by Zhang *et al.* (1999) of head and neck cancer cases diagnosed 1992-1994 at a hospital in New York City and controls who were blood donors at the hospital (Kalant 2004). Regarding Sidney *et al.* (1997), Kalant highlighted that the study reported associations of borderline statistical significance between marijuana smoking and prostate cancer (RR==3.1, 1.0-9.5) and cervical cancer (RR=1.4, 1.0-2.1). He said that there were two problems with the study. One problem was that the majority of the subjects classified as marijuana users may have had little exposure because "exposed" included marijuana use as little as six times in subjects' lives. The other problem he noted was that the duration of the study may have been too short if the time to cancer diagnosis after marijuana smoking is similar to that for tobacco smoking. Regarding Zhang *et al*. (1999), Kalant highlighted the overall

association between head and neck cancer and marijuana smoking (OR=2.6, 1.1-6.6) and the statistically significant associations of head and neck cancer risk with duration and frequency of marijuana smoking. Kalant concluded that the Zhang *et al.* study must be regarded as strongly suggestive of a causal association.

Hall et al. (2005) Cannabinoids and cancer: causation, remediation, and palliation.

Hall *et al.* (2005) included cancer causation in a review of marijuana and potential adverse and beneficial medical effects (Hall *et al*. 2005). In a section on causation, the authors discussed five studies that reported results for direct marijuana smoking and cancer risk. Regarding the Sidney *et al.* (1997) cohort study, they noted that the study reported elevated risk for prostate cancer and commented that a limitation of the study was lack of data on marijuana smoking after questionnaire administration at the beginning of follow-up. Regarding the Zhang *et al.* (1999) case-control study of head and neck cancer, they noted the association with marijuana smoking that was found, but also noted that bias could have occurred if the blood donor control group had an unusually low history of marijuana smoking. Regarding the Llewellyn *et al.* (2004a) and Rosenblatt *et al.* (2004) case-control studies of oral cancer, they noted lack of association with marijuana smoking in those studies. Regarding the Efird *et al.* (2004) cohort study of brain cancer, they noted that a significant association was reported (RR=2.8, 1.3-6.2) and that the study was hypothesis generating in design with respect to marijuana smoking.

Hall *et al.* also reviewed three studies reporting results for parental marijuana smoking and childhood cancer (AML: Robison *et al.*, 1989; brain astrocytoma: Kuijten *et al.*, 1992; and rhabdomyosarcoma: Grufferman *et al.*, 1993). They commented that all three studies reported associations with parental marijuana smoking during pregnancy, but noted that none of the studies was designed to investigate risk from parental marijuana smoking. They said that an alternative explanation for the associations was differential reporting bias between the case and controls parents. Hall *et al.* concluded that the epidemiological studies of direct and parental marijuana smoking and cancer have reported inconsistent associations, and that the limitations of self-reporting of illegal drug use will need to be addressed in future studies. They commented that "Risks may become clearer as baby-boomer birth cohorts (who were the first to smoke cannabis in substantial numbers) enter the age groups in which cancer incidence begins to rise steeply."

Hashibe et al. (2002) Marijuana smoking and head and neck cancer.
Hashibe et al. (2005) Epidemiologic review of marijuana use and cancer risk.

Hashibe *et al.* (2002 and 2005) reviewed, in two publications, a total of 16 epidemiological studies of direct exposure (12 studies) and parental exposure (four studies) to marijuana smoking (Hashibe *et al*., 2002; Hashibe *et al*., 2005). The first publication (Hashibe *et al.*, 2002) included two epidemiological studies, one of which was the prospective cohort study by Sidney *et al.* (1997) of health plan members who had completed a self-administered questionnaire. The reviewers noted that the Sidney *et al.* study found that marijuana use was not associated with cancer risk, with the exception of weak associations with prostate and cervical cancers. They

also noted two limitations of the study: low statistical power due to few cases of cancer, and chance findings due to multiple comparisons.

The other study reviewed by Hashibe *et al.* (2002) was the case-control study of head and neck cancer by Zhang *et al.* (1999). (Note – the same Dr. Zhang was a coauthor of the Hashibe *et al.* 2002 and 2005 reviews.) The reviewers noted that marijuana smoking and head and neck cancer risk were associated overall (OR=2.5, 1.1-6.60) as well as in a dose-response manner with both frequency ($p<0.05$) and duration ($p<0.05$) of use in the Zhang *et al.* (1999) study. They said that results need to be interpreted with caution, however, because of methodological limitations.

Hashibe *et al.* summarized the main features and the main findings of the 12 studies of direct marijuana smoking, and made comments about several of them. Regarding the discrepant results from the two studies of head and neck cancer (Zhang *et al.*, 1999, that found an association, and Rosenblatt *et al.*, 2004, that did not find an association), Hashibe *et al.* said that the discrepancy may have been due to differences in biases between the two studies. They noted, in particular, that the blood donor control subjects in the Zhang *et al.* (1999) study may have had healthier lifestyle behaviors than the general population, which could have caused a spuriously elevated rate ratio estimate for marijuana smoking. They also noted, however, that the blood donors might have been, in part, friends and relatives of the head and neck cancer cases and thus have shared lifestyle factors with the patients, which could have biased the rate ratio estimate to be closer to the null. They concluded that "the possible direction of bias owing to having blood donor control subjects would not necessarily be away from the null and is, in fact, difficult to predict."

None of the four studies of parental marijuana smoking and cancer in offspring included in the Hashibe *et al.* (2005) review had been included in previous reviews. The four studies were: Robison *et al.* (1989) (acute myeloid leukemia and maternal marijuana use), Kuijten *et al.* (1990) (brain astrocytoma and maternal marijuana use), Grufferman *et al.* (1993) (rhabdomyosarcoma and maternal and paternal marijuana use), and Wen *et al.* (2000) (leukemia and paternal marijuana use). The reviewers noted that all four of the studies reported significant associations with parental marijuana smoking, but that the number of exposed cases in the studies was small, resulting in unstable estimates. The reviewers speculated that the associations could have been due to multiple comparisons, publication bias, confounding by other drug use, and differential reporting accuracy between case and control parents. The reviewers concluded that sufficient studies are not available to adequately evaluate the impact of marijuana on cancer risk.

Mehra et al. (2006) The association between marijuana smoking and lung cancer: a systematic review.

Mehra *et al.* (2006) conducted a systematic review of the literature on marijuana smoking and lung cancer that found two of the three studies of lung cancer that had been published prior to 2006. They noted that the Sidney *et al.* (1997) cohort study in northern California did not find increased risk of lung cancer, and that the Sasco *et al.* (2002) case-control study of lung cancer in Casablanca did find significantly increased risk but did not completely control for exposure to

tobacco smoke. The reviewers concluded that the two studies were not able to demonstrate a relationship between marijuana smoking and lung cancer.

3.1.6 Commentaries and Editorials

Mao and Oh (1998), in an editorial in the *Journal of the National Cancer Institute*, discussed whether marijuana smoking might cause cancer. They discussed the large body of circumstantial evidence that existed at the time that suggested that risk might be increased, but commented that the recent (at the time) cohort study by Sidney *et al.* (1997) did not find any strong associations. They said that the Sidney *et al.* (1997) study had two critical defects: 1) it classified subjects with small amounts of past marijuana smoking as exposed, and 2) it obtained marijuana smoking histories only at the beginning of the study.

In a letter to the *Journal of the Royal Society of Medicine*, Caplan (1991) wrote that the larger number of case reports for upper airway cancers compared to lower airway cancers suggested that marijuana smoking has a greater carcinogenic effect on the upper airways.

Hall and MacPhee (2002) published an editorial about marijuana use and cancer in the journal *Addiction*. They commented that the epidemiological evidence was still too meager to warrant strong conclusions, and that the evidence that marijuana smoking during pregnancy increases the risk of childhood cancer is "much weaker" than the evidence for adult cancers.

Henry *et al.* (2003) estimated, in an editorial in the *British Medical Journal*, that marijuana smoking may eventually cause about 30,000 deaths per year (including cancer and other causes of death) in the United Kingdom if marijuana smoke and tobacco smoke have similar effects.

Sidney (2003) published an editorial in the *British Medical Journal* as a follow-up to the Henry *et al.* (2003) editorial in the same journal. Sidney suggested that the estimate by Henry *et al.* of 30,000 deaths per year in the UK due to marijuana smoking was probably too high, for several reasons. One reason was that, compared to tobacco smokers, most people who try marijuana do not become long term users. Another reason was that the quantity of substance smoked per day is generally much greater for tobacco than for marijuana.

Taylor and Hall (2003), in a position statement for the *Thoracic Society of Australia and New Zealand* in the *Internal Medicine Journal*, said that the association of tobacco smoking and marijuana smoking makes it difficult to separate their independent effects. The statement said that "there are few data as yet to confirm that *cannabis* smoking causes malignancy in the respiratory tract."

Quoix (2007) commented in the French journal *Revue Des Maladies Respiratoires* that the role of marijuana smoking as a risk for lung cancer is difficult to assess as most *cannabis* smokers are also tobacco smokers. Quoix also said that epidemiological studies suggest that marijuana smoking is not carcinogenic.

Weiss (2008), in a commentary in the *Clinical Journal of Oncology Nursing*, said that marijuana smoking cessation is common and may explain the lack of association with lung cancer. The

commentary was apparently written before the Aldington *et al.* (2008a) study of lung cancer (that reported increased risk) was published.

Brambilla and Colonna (2008), in an editorial in the *European Respiratory Journal*, commented that the study of lung cancer by Aldington *et al.* (2008a) "confirms" that marijuana smoking increases the risk of developing lung cancer.

3.1.7 Discussion of Human Data

OEHHA's search for scientific journal articles on the topic of marijuana smoking and cancer identified a total of 60 relevant articles representing 27 controlled epidemiological studies (19 of direct marijuana smoking and eight of parental marijuana smoking), 16 case report articles (all regarding direct marijuana smoking), eight review articles, and nine commentaries/editorials (Table 1). The following discussion focuses on categories of cancer for which a statistically significant association with marijuana smoking has been reported.

3.1.7.1 Discussion of direct marijuana smoking

Lung cancer

Six controlled studies reported results for marijuana smoking and lung cancer (Appendix Table 1), and all six adjusted for tobacco cigarette smoking. Three of the studies reported statistically significant elevated rate ratio estimates (Aldington *et al*., 2008a; Hsairi *et al*., 1993; Voirin *et al*., 2006). Two of the three significant studies, however, were conducted in northern Africa (both studies were in Tunis, Tunisia) where tobacco is commonly mixed with marijuana prior to smoking, thus tobacco may have confounded the results (Hsairi *et al*.; Voirin *et al*.). The third study reporting significantly increased risk, by Aldington *et al.* (2008a), was conducted in New Zealand where tobacco is rarely mixed with marijuana, and, thus, it is the study that most strongly suggests increased risk of lung cancer (Aldington *et al*., 2008a). Risk was elevated only in the highest of three cumulative exposure levels, however. The odds ratios were 0.3 (95% CI 0.1-1.7) for >0-<1.39 joint-years, 0.5 (0.1-2.0) for 1.39-10.5 joint-years, and 5.7 (1.5-21.6) for >10.5 joint-years. As with most case-control studies published to date, the Aldington *et al.* (2008) study obtained data on marijuana smoking by orally interviewing cancer cases and healthy controls, and substantial social science literature suggests that use of recreational drugs is under-reported in interviews due to their illegality and social stigma. As expressed by several cancer investigators, bias could occur if cancer cases were more forthcoming about past marijuana use than healthy controls.

Of the three studies that did not report statistically significant increased risk, one, by Sasco *et al.* (2002), reported nonsignificantly elevated risk (OR=2.0, 0.6-6.3) (Sasco *et al*., 2002). The study was conducted in northern Africa (Morocco), however, where tobacco is commonly mixed with marijuana. The other two studies that did not find significantly increase risk were conducted in the U.S. where, like New Zealand, tobacco is not commonly mixed with marijuana. Neither of the studies in the U.S., reported elevated risk. One of the studies in the U.S., by Sidney *et al.* (1997), was a cohort study that may have ended too soon after marijuana smoking became common in the U.S. to detect excess risk (follow-up ended in 1993) (Sidney *et al*., 1997). The other study in the U.S. was a case-control study by Hashibe *et al.* (2006) of newly diagnosed

cases in Los Angeles County in the years 1999-2004 (Hashibe *et al*., 2006). Strengths of the Hashibe *et al.* (2006) study included: 1) location in the U.S. where tobacco is not commonly mixed with marijuana, and 2) inclusion of cases through 2004, which was up to 36 years after marijuana smoking became popular in the U.S. (in approximately 1969). The odds ratios for dose categories in the Hashibe *et al.* (2006) study that were in the range where Aldington *et al.* (2008a) found increased risk (above 10 joint-years) were 0.6 (0.3-1.0) for 10-<30 joint-years, 0.8 (0.4-1.7) for 30-<60 joint-years, and 0.6 (0.3-1.2) for 60+ joint-years. Thus the Hashibe *et al.* (2006) and Aldington *et al.* (2008a) studies, both apparently of good quality, reported results that disagree.

All six studies had potential for bias from under-reporting of marijuana smoking due to lack of privacy during questionnaire administration. If lung cancer patients in studies were more forthcoming in answering questions about past marijuana smoking than non-cancer controls, then the odds ratios for marijuana smoking may have been artificially increased.

Head and neck cancer

Two of three studies of head and neck cancers reported statistically significant associations with marijuana smoking (Appendix Table 3). One of the two studies, a case-control study by Zhang *et al.* (1999 and 2000), collected data via face-to-face oral interviews at a hospital in New York City and reported an odds ratio of 2.6 (1.1-6.6) for "ever marijuana smoking" (Zhang *et al*., 2000; Zhang *et al*., 1999). The association was stronger among subjects who were tobacco smokers, consumed alcohol, were exposed to ETS, or were mutagen sensitive, but the interaction analyses were based on small numbers and lacked precision according to the investigators. Limitations of the study included potential bias from controls being blood donors if they had different use of marijuana than the general population, and potential bias from differential under-reporting of marijuana use between cases and control.

The other study that reported an association was a case-control study by Gillison *et al.* (2008) of patients with squamous cell head and neck cancer who had tissue available for DNA analysis (94% of all patients) at a hospital in Baltimore (Gillison *et al*., 2008). Data on many potential risk factors were collected from subjects via ACASI, a method that might have relatively less under-reporting of marijuana smoking than traditional interview methods. The odds ratio was significantly elevated at 6.4 (1.6-26) for 15+ joint-years of cumulative exposure among patients with tumor tissue that was human papillomavirus (HPV)-16-positive (38% of patients in their study). Among patients with tumor tissue that was HPV-16-negative, the odds ratio for 15+ joint-years was elevated but smaller (2.0, 0.5-7.8). Odds ratios for all head and neck cancer patients combined were not calculated. The purpose of the study was to compare risk factors in general for HPV-16-positive and HPV-16-negative head and neck cancers. According to the authors, a subgroup of head and neck cancers is caused by HPV and is characterized by the presence of high-risk HPV genomic DNA sequences in the tumors (approximately 95% contain HPV-16 DNA). The investigators found no evidence of multiplicative interactions between marijuana and tobacco or alcohol.

The Hashibe *et al.* (2006) case-control study of marijuana smoking and tobacco-related cancers provided results for specific sites that are considered to be within the category of "head and

neck," but did not provide results for head and neck as a single category. The study found no association between marijuana smoking and specific head and neck cancers.

All three of the studies had limitations that could have biased the odds ratios, including selection bias (e.g., use of blood donors for controls in the Zhang *et al.* studies) and possible differential under-reporting of marijuana smoking between cases and controls.

Bladder cancer

Of two studies that reported results for bladder cancer and marijuana smoking, one reported significantly increased risk in the form of a hypothesis-test probability (p=0.01) from a multivariate linear regression model (Appendix Table 4) (Chacko *et al*., 2006). The regression model adjusted for potential confounding from exposure to tobacco cigarette smoking, smoked meat, Agent Orange, radiation, and dyes. Marijuana use in joint-years was entered into the model as a continuous term of median values of the following categories: <20 joint-years, 20-40 joint-years and >40+ joint-years. The study reported crude odds ratios but did not report adjusted odds ratios. Lack of adjusted odds ratios and an error in the article's data presentation limit the data's usefulness.

Brain cancer

The one study that reported results for brain cancer, a cohort study by Efird *et al.* (2004), found statistically significant associations for marijuana smoking categories of once a month (RR=3.6, 1.3-10.2), once a month or more (RR=2.8, 1.3-6.2), and weekly (RR=3.2, 1.1-9.2) (Efird *et al*., 2004). A strength of the study was its use of self-administered, written questionnaires, a method that may have collected relatively reliable self-reported marijuana smoking data. A weakness of the study was lack of exposure data after questionnaire administration at the beginning of follow-up.

Testicular cancer

The one study that reported results for testicular cancer, a case-control study by Daling *et al.* (2009), found statistically significant associations with marijuana smoking in the histological sub-group of non-seminoma/mixed cancers, and only for current marijuana smoking (OR=2.3, 95% CI 1.3-4.0). The investigators inexplicably did not mention the lack of association among former marijuana smokers in the discussion section of the article. Limitations of the study included potential bias from under-reporting of marijuana smoking due to lack of privacy during oral interviews in homes and workplaces and unequal participation by cases and controls.

Other cancers

Statistically significant associations with marijuana smoking have not been reported for oral cancer (four studies), NHL (two studies), and pharyngeal cancer, esophageal cancer, "tobacco-related cancers," laryngeal cancer, prostate cancer, penile cancer, cervical cancer, breast cancer, colorectal cancer, anal cancer, melanoma, and acute myeloid leukemia (one study each).

The only suggestion of increased oral cancer risk was among non-smokers of tobacco cigarettes in the Hashibe *et al.* (2006) study, among whom there was a nonsignificant increase in oral cancer risk in the highest cumulative marijuana smoking category (10+ joint-years OR=1.8, 95%

CI 0.7-4.7). Issues of validity in the oral cancer studies included possible lack of privacy during oral interviews in two studies, different questionnaire administration methods for cases and controls in two studies, an ill-defined exposure measure ("cannabis smoker") in two studies, and a very low case participation rate (29%) in one study.

Two studies have reported results for NHL and direct smoking of marijuana. The studies were consistent in showing no association with marijuana smoking. One of the studies showed statistically significantly decreased risk among men (Holly *et al*., 1999). The limitations of the studies were similar. They both had low case participation rates due to large numbers of deaths among the cases, despite using newly diagnosed cases, creating potential for bias if cases interviewed and not interviewed were different with regard to marijuana smoking history. Both studies also had the limitation of potential bias from differential under-reporting of marijuana use between cancer cases and controls.

3.1.7.2 Discussion of parental marijuana smoking

Eight studies reported results for seven categories of childhood cancer. Six of the categories were significantly associated with parental marijuana smoking, as follows: 1) childhood leukemia (all types combined) and paternal exposure, 2) infant leukemia (all types combined) and paternal exposure, 3) childhood ALL and paternal exposure, 4) childhood AML and maternal exposure, 5) childhood neuroblastoma and maternal exposure, and 6) childhood rhabdomyosarcoma and maternal and paternal exposure. The seventh cancer category, childhood brain astrocytoma, was also reported to be associated, but the 95% confidence interval for the odds ratio did not exclude 1.0 (OR=2.8, 95% CI 0.9-9.9, for maternal marijuana smoking ever in the 10 months before childbirth).

The eight studies shared a common foundation in that all were conducted under the auspices of the NCI-funded Children's Oncology Group or its predecessors, the CCG and the Pediatric Oncology Group (Robison *et al*., 1995). The eight studies thus had similarities in design and shared strengths and weaknesses with regard to control selection and other methods. Parental marijuana smoking was among many potential risk factors investigated and was apparently not a focus of any of the data collection efforts.

A limitation of all of the childhood cancer studies was possible under-reporting due to social stigma and lack of privacy during oral interviews with parents. Differential under-reporting between case and control parents could have biased rate ratio estimates. Grufferman *et al.* (1993) said that "Parents of children with cancer might be more forthcoming in reporting an illegal activity than parents of community controls," and Bluhm *et al.* (2006) said that "Parents of cases may recall and report exposures more fully than parents of controls, seeking explanations for a child's illness … Parents of controls are thought to have comparatively less motivation to report stigmatized behaviors."

The Hashibe *et al.* (2005) review commented that the number of exposed cases in some of the childhood cancer studies was small, resulting in unstable estimates. The reviewers speculated that the significant associations reported for parental marijuana smoking may have been due to

multiple comparisons, publication bias, confounding by other drug use, or differential reporting accuracy between case and control parents.

Fathers' marijuana smoking was addressed in five of the childhood cancer articles (Bluhm *et al*., 2006; Grufferman *et al.*, 1993; Robison *et al*., 1989; Trivers *et al*., 2006; Wen *et al*., 2000). A limitation of the studies was that mothers often completed questionnaires for fathers (proxy interviews). For example, in the Wen *et al.* (2000) study of childhood leukemia, questionnaires for fathers were administered to mothers acting as surrogates for fathers for 16% of case children and 32% of control children. Another limitation of the studies was relatively low participation by fathers (father's availability was not required as it was for mothers). For example, in the Bluhm *et al.* (2006) study of childhood neuroblastoma, fathers' questionnaires were completed for just 54% of eligible cases and 43% of eligible controls. Proxy interviews and low response rates created potential for bias in these studies.

The two studies that reported results for childhood AML had different results. The study by Robison *et al.* (1989) found a significant association with maternal marijuana smoking (OR="tenfold," p=0.005) while the study by Trivers *et al.* (2006), found a significant association with paternal marijuana smoking (OR=1.4, 95% CI 1.02-1.8). The methods of the two studies were similar, but they differed in time period of case ascertainment and questionnaire design. Trivers *et al.* (2006) suggested that the differences in findings may have been due to more detailed questions about marijuana smoking and stronger assurance of data confidentiality in their study.

3.1.8 Conclusions Regarding Human Studies

3.1.8.1 Direct marijuana smoking

Among 19 categories of cancer for which rate ratio estimates were reported for direct marijuana smoking, statistically significant associations were reported in five categories: lung cancer, head and neck cancer, bladder cancer, brain cancer, and testicular cancer.

Three of six studies of lung cancer were conducted in northern Africa where marijuana and tobacco are commonly mixed, thus the results of those studies may have been confounded by tobacco smoke. Among the three studies conducted in populations that did not commonly mix marijuana and tobacco, two found no association and one found a statistically significant association. That study, by Aldington *et al.* (2008) in New Zealand, reported an odds ratio of 5.7 (95% CI 1.5-22) for the highest cumulative marijuana smoking category (>10.5 joint-years). A limitation of the study was possible bias from under-reporting of marijuana smoking due to lack of privacy during interviews.

Three studies reported results for head and neck cancers and marijuana smoking, of which two found statistically significant associations. A case-control study by Zhang *et al.* (1999 and 2000) in New York City reported an odds ratio of 2.6 (95% CI 1.1-6.6) for any marijuana smoking. Limitations of the study included potential bias from under-reporting of marijuana smoking due to lack of privacy during interviews and use of blood donors as controls (marijuana use may be inversely associated with blood donation, according to the authors). A case-control study by

Gillison *et al.* (2008) in Baltimore reported an association that was stronger among patients who's tumor tissue was HPV-16-positive (OR=6.4, 95% CI 1.6-26, for 15+ joint-years) than among patients who's tumor tissue was HPV-16-negative (OR=2.0, 95% CI 0.5-7.8). The investigators suggested that marijuana may act directly or may promote HPV-positive head and neck cancers. The study's ACASI may have reduced under-reporting of marijuana smoking, but the article did not say whether the subjects had privacy when responding.

Of two studies that reported results for bladder cancer and marijuana smoking, one, a case-control study by Chacko *et al.* (2006) at Veteran's Administration facilities in the U.S., found a significant association. The association was reported in the form of a hypothesis-test probability (p=0.01) for cumulative joint-years in a regression model that adjusted for tobacco cigarette smoking and other potential risk factors. A strength of the study was that data were obtained from subjects via self-administered written questionnaires. Limitations included errors in the data presentation and no data on case participation.

The only study that reported results for brain cancer, a cohort study of adult onset glioma by Efird *et al.* (2004) in northern California, found significant associations for three overlapping definitions of past marijuana smoking: once a month (RR=3.6, 95% CI 1.3-10.2), once a month or more (RR=2.8, 1.3-6.2), and weekly (RR=3.2, 1.1-9.2). A strength of the study was its use of self-administered, written questionnaires, but a limitation was lack of exposure data after questionnaire administration at the beginning of the study.

The only study that reported results for testicular cancer, a case-control study of testicular GCTs by Daling *et al.* (2009), found statistically significant associations with marijuana smoking, but only in the histological sub-group of non-seminoma/mixed cancers, and only for current marijuana smoking (OR=2.3, 95% CI 1.3-4.0). Limitations of the study included possible under-reporting of marijuana smoking due to lack of privacy during oral interviews and unequal participation by cases and controls.

In conclusion, the strongest evidence for a causal association between direct marijuana smoking and cancer comes from studies of head and neck cancer, among which two of three studies reported a statistically significant association. The evidence is less strong but suggestive for lung cancer (one of three studies of populations that did not mix marijuana and tobacco reported a significant association), bladder cancer (one of two studies reported a significant association), and brain cancer (the only study reported a significant association). A limitation of many of the studies was potential bias from under-reporting of past marijuana smoking that could occur if there was a difference in degree of under-reporting between cancer patients and controls.

3.1.8.2 Parental marijuana smoking

Seven of the eight studies of childhood cancers that reported results for parental marijuana smoking before or during gestation found statistically significant associations, and the eighth study's odds ratio was elevated and of borderline statistical significance. The types of cancer that were significantly associated with marijuana smoking by mothers were acute myeloid leukemia (age <18 years), neuroblastoma (age <15 years), brain astrocytoma (age < 15 years), and rhabdomyosarcoma (age <21 years). The types of cancer that were significantly associated with marijuana smoking fathers were leukemia (age <18 years), infant leukemia (age < 19

months), acute lymphoblastic leukemia (age <15 years), and rhabdomyosarcoma (age <21 years). For acute myeloid leukemia, a significant association with mother's but not father's marijuana smoking was observed in Robison *et al.* (1989), while Trivers *et al.* (2006) reported a significant association with father's but not mother's smoking.

It was remarkable that such a variety of types of childhood cancer were associated with parental marijuana smoking. It may not be a coincidence that the studies had similar designs and shared strengths and limitations with regard to methods. All were conducted under the auspices of the NCI-funded Children's Oncology Group or its predecessors.

One limitation common to the studies was potential bias from under-reporting of marijuana smoking by parents due to marijuana's illegality and social stigma. The bias could occur if there was a difference in degree of under-reporting between parents of cancer patients and parents of controls. Concern about this bias was expressed by Bluhm *et al.* (2006) who said "Parents of cases may recall and report exposures more fully than parents of controls, seeking explanations for a child's illness."

Validity issues that were specific to studies that reported results for fathers were that participation by fathers was not required for case eligibility (as it was for mothers) and that mothers often acted as proxies for fathers. Some articles did not state the level of participation by fathers or say whether proxy interviews were employed. Bias could have occurred if the percent of proxy interviews differed between case and control fathers and the mothers were less knowledgeable or more or less forthcoming about the fathers' marijuana use than the fathers themselves.

In conclusion, all of the studies of childhood cancer reported an association with parental marijuana smoking before or during gestation. Both maternal and paternal marijuana smoking were implicated, depending on the type cancer. The associations may be causal, but the wide variety of types of cancer that were associated and the similarity of the limitations of the studies regarding under-reporting of marijuana smoking and use of proxy interviews suggest that the associations may be due to methodological limitations.

3.2 Carcinogenicity Studies in Animals

Three animal carcinogenicity studies have been reported in the literature using either marijuana smoke or its condensate, each using a different route of administration. In one study, female Swiss mice were exposed to marijuana smoke condensate by skin painting. In the second study, newborn Charles River rats were injected subcutaneously with marijuana condensate and in the third study female Wistar rats were exposed via inhalation to marijuana smoke. The study design of these experiments and results seen are shown in Table 5. The studies are further described below.

3.2.1 Studies in Mice

Hoffman *et al*. (1975) compared the carcinogenic potential of marijuana smoke condensate to tobacco smoke condensate in a skin-painting study with female Swiss albino mice (Ha/ICR/Mil). Marijuana and tobacco were obtained from the NCI. Marijuana cigarettes were made with leaf

cuttings while tobacco cigarettes were made with the standard SEB-1 blend of the tobacco working group of NCI. Marijuana and tobacco smokes were generated using automatic smoking machines with multiple units. Condensates were collected on glass fiber filters.

Smoke condensate dissolved in acetone was painted on the shaved backs of female mice (100/group) three times per week for 74 weeks. An average of 75 milligrams (mg) of "tar" (particulate matter from marijuana or tobacco smoke) was applied per application. The first skin tumor among marijuana smoke condensate-treated groups occurred at 17 weeks, and the first skin tumor among mice treated with tobacco smoke condensate occurred about one week later. Tumor incidences were 6/99 for the marijuana smoke condensate group and 14/97 for the tobacco smoke condensate group (Table 5). All tumors were benign squamous cell papillomas of the skin, except for two squamous cell carcinomas among the tobacco smoke condensate treated group. Although no concurrent control group was used, the authors noted that skin tumors were "rarely observed" among acetone-treated controls from other studies in their laboratory. Thus both marijuana and tobacco smoke were considered active in this experiment, with marijuana being somewhat less active than tobacco smoke.

3.2.2 Studies in Rats

Repetto *et a*l. (1979) studied the composition of marijuana smoke condensate collected in ethanol and its carcinogenic effects in a subcutaneous injection study in newborn Charles River CD rats. Marijuana smoke was generated by an automatic smoking device, commonly used for tobacco cigarette research, and by a manual smoking device, which the authors felt was more representative of the pattern of smoking by a marijuana smoker. Condensates were collected and measured for total weight, particulate matter weight, and benzo[a]pyrene content. Different dilutions in ethanol/olive oil of the condensates (actual dilutions not reported) were administered to groups of newborn Charles River CD rats (numbers and sex not reported) via subcutaneous injection in the cervical region on days 1, 4, 7, 11, 14 and 18 of life. A vehicle control group was also employed. The authors did not report the observation period before the animals were sacrificed. The results were noted by study authors as follows: "From the lots of animals treated with different concentrations of condensate only those receiving amounts of 194 mg/kg i.e., 5.7 μg of benzo[a]pyrene/ml, showed tumor evolution. The animals treated with more diluted solutions did not show any affliction." Tumors formed among treated newborn rats were described as 'mesenchimatous (mixed mesenchymal tumors composed of two or more cell types) with giant anaplastic (undifferentiated) cells invading the dermis and infiltrating skeletal muscle (Table 5).

In the inhalation study by Murthy *et al.* (1985) female Wistar rats were exposed to marijuana smoke for 15 minutes per day, six days per week for up to 36 months. The smoke was generated by burning 0.6 grams of marijuana plant material and then drawing it into a Plexiglas smoking chamber with a respiratory pump. The number of treated animals and the controls is not clear from the report, but appears to be 20 rats per group. Although the paper did not report tumor incidence data, the authors stated that 50 percent of the marijuana smoke-treated rats developed tumors, where as none of the control animals did (Table 5). The tumors were described as benign serous cystoma of the ovary, follicular cysts of the ovary, adenofibroma and

telengiectatic cysts and polyps with atypical glands of the uterus, and malignant adenosarcoma of the uterus.

Table 5. Carcinogenicity studies of marijuana smoke and smoke condensate in animals.

Study author (Test substance)	Species (sex) Group size	Dose groups	Tumor Type	Tumor Incidence
Hoffman *et al*., 1975 (marijuana or tobacco smoke condensate in acetone)	Swiss albino mice (F) 100/group	Marijuana[1]	Squamous cell papillomas of the skin	6/99
		Tobacco[1]	Squamous cell papillomas and two carcinomas of the skin	(14/98)
		Laboratory historical controls	Skin tumors	Rarely observed[2]
Repetto *et al*., 1979 (marijuana smoke condensate in ethanol/ olive oil)	Newborn CD rats (sex not specified)	0, 194 mg/ml s.c. injection on days 1,4,7,11,14 and 18 of life	Mesenchimatous tumors (malignant)	Incidence not reported
Murthy *et al*., 1985 (marijuana smoke)	Wistar rats (F) 20/group	Inhalation of smoke 15 minutes/ day, six days/ week, for 36 months Controls	<u>Ovary</u> Benign serous cytoma[3] Follicular cysts <u>Uterus</u> Adenofibroma Telengiectatic cysts and polyps Adenosarcoma	50% of animals 0%

[1] 75 mg tar/ application, three applications/week for 75 weeks.
[2] "rarely observed" is typically used to indicate ≤ 1 percent incidence.
[3] surface epithelial stromal tumor.

3.2.3 Tumor Promotion Studies

Hoffman *et al.* (1975) conducted a tumor promotion study of marijuana smoke condensate. Groups of 60 female Swiss albino mice were dermally administered a single 75 micrograms (µg) dose of 7, 12-dimethylbenz[a]-anthracene (DMBA) as an initiating dose. Ten days following initiation, suspensions of marijuana smoke or tobacco smoke condensates were painted onto the shaved backs of the mice, three times per week for 56 weeks. About 75 µg of each condensate was administered per application. A control group of DMBA-initiated mice received dermal applications of acetone three times per week for 56 weeks.

There were 26 skin tumor-bearing mice among the 60 mice treated with marijuana smoke condensate: 48 squamous cell papillomas, three squamous cell carcinomas, and three fibrosarcomas were observed. Among the tobacco smoke condensate treated group, 34/60 had skin tumors (72 squamous cell papillomas, and six squamous cell carcinomas were observed among tumor-bearing animals). Five of 60 DMBA-initiated control mice exhibited skin tumors. Eight squamous cell papillomas and two squamous cell carcinomas were observed. The authors concluded that marijuana smoke condensate possessed tumor-promoting activity at a somewhat lower level than that of tobacco smoke condensate.

3.3 Other Relevant Data

3.3.1 Pharmacokinetics and Metabolism

Marijuana smoke is a complex aerosol mixture of thousands of chemicals present in the gas and particulate phases. The available information on the pharmacokinetics and metabolism of this complex mixture is limited, although there is some information on the pharmacokinetics of Δ^9-THC in marijuana smoke. Pharmacokinetic studies of individual smoke constituents administered singly provide limited information regarding the mixture, as interactions between the various constituents in marijuana smoke are expected to occur, and are not discussed here.

3.3.1.1 Absorption

The aerodigestive tract (lips and mouth tissues, tongue, nose, throat, vocal cords, and portions of the esophagus and trachea) and the lungs are directly exposed to marijuana smoke constituents during the inhalation of marijuana smoke. Absorption of gaseous constituents of marijuana smoke may occur at multiple sites within the aerodigestive tract and the lungs, dependent upon solubility and vapor pressure. With regard to marijuana smoke particulates, deposition may occur throughout the aerodigestive tract and the lungs, dependent upon the aerosol or particle size. It has been estimated that 80.7 to 86.7% of the inhaled resinous total particulate matter (i.e., tar) in marijuana smoke would be deposited in the lung (Wu *et al*., 1988). This estimate was based on a mean median aerodynamic diameter of marijuana smoke tar of 0.35 to 0.43 μm. Some particles deposited within the aerodigestive tract will enter the gastrointestinal tract, as will some particles deposited in the lungs and then cleared by mucociliary transport. Thus while the principal sites of absorption are the lungs and the aerodigestive tract, some absorption of marijuana smoke constituents is expected to occur via the gastrointestinal tract.

By way of leaching and dissolution, some of the adsorbed chemicals on smoke particles will traverse the plasma membrane and gain entry into epithelial cells and other cells of the lung. Many chemicals in marijuana smoke are readily absorbed, including the cannabinoids. Highly lipophilic substances, such as the PAHs, are more slowly absorbed in the thicker epithelium of the conducting airways (Gerde *et al*., 1991).

Studies have shown that the bioavailability within the lungs of Δ^9-THC and other cannabinoids present in marijuana smoke can vary considerably, depending upon the burning characteristics of the marijuana cigarette, the depth of inhalation, the inhalation volume, the holding time and the level of experience of the smoker (Chiang and Rapaka, 1987; Huestis, 2007). The bioavailability

of other constituents of marijuana smoke would also be expected to vary depending upon these same factors. Δ^9-THC is readily absorbed from the oral cavity (Huestis and Cone, 2004).

3.3.1.2 Distribution

Distribution studies of marijuana smoke have not been conducted. The distribution of Δ^9-THC present in marijuana smoke has been investigated, however. Δ^9-THC is lipophilic and the majority absorbed is sequestered in tissues, with only a small fraction present in the blood. In blood, Δ^9-THC is extensively bound to plasma protein (97 to 99 percent), with a limited amount of free Δ^9-THC present in the blood (NTP, 1996). The concentration of Δ^9-THC in the brain is similar to that in plasma, suggesting that transport of Δ^9-THC into the brain is not hindered by any "blood-brain" barrier. Studies in dogs and sheep have shown that Δ^9-THC crosses the placenta and reaches the fetus (Lindgren, 1983). The Δ^9-THC levels present in fetal tissues and blood were lower than those in maternal tissues (Lindgren, 1983). In studies in humans, Δ^9-THC was shown to accumulate in the breast milk, with levels in breast milk eight times higher in than those in plasma (Ellenhorn, 1996).

Pharmacokinetic studies of marijuana smoke in humans have shown that cannabinoids are quickly absorbed from the lungs, reaching peak plasma levels within seven to eight minutes. In a study by Huestis *et al*. (1992), Δ^9-THC plasma concentrations were measured in two individuals following exposure to a single marijuana cigarette, containing either 1.75 or 3.55% Δ^9-THC. Measured plasma Δ^9-THC concentrations after a single inhalation of the low and high Δ^9-THC content cigarettes were 7.0±8.1 ng/ml and 18.1±12.0 ng/ml, respectively. Plasma Δ^9-THC concentrations measured after smoking the entire cigarette peaked at 84.3 ng/ml for the low Δ^9-THC content cigarette, and 162.2 ng/ml for the high Δ^9-THC content cigarette.

3.3.1.3 Metabolism

The chemical constituents of marijuana smoke can be metabolized directly upon absorption in tissues of the aerodigestive tract or the lungs. They may also be metabolized in the blood or in other organs, subsequent to systemic distribution. A variety of Phase I and Phase II enzymes are expected to be involved in the metabolism of marijuana smoke, based on what is known about the metabolism of many of the individual chemicals presents in marijuana smoke, such as the aromatic amines and PAHs.

Exposure to marijuana smoke has been shown to induce some of the same enzymes that are involved in its metabolism, such as cytochrome P450 1A1. Marcottee *et al*. (1975) found that lung cytochrome P450 1A1 levels in rats exposed to marijuana smoke generated by the burning of four marijuana cigarettes (3.4 g) were induced two to four-fold above basal levels at six hours post-exposure. Liver levels were never more than two times that of basal levels. Roth *et al*. (2001) reported that marijuana tar was more potent than tobacco tar in inducing cytochrome P4501A1 expression in Hepa 1 cells, and attributed this to the activation of the AhR by Δ^9 –THC.

Metabolism studies of Δ^9-THC indicate that it is extensively metabolized by microsomal enzymes in the liver. The metabolism of Δ^9-THC involves oxidation, decarboxylation and

conjugation reactions (Chiang and Rapaka, 1987). Phase I reactions include allelic oxidation at the C-8 and C-9 positions to yield 11-hydroxy-THC, which is more psychoactively potent than the parent compound (Allenhorn, 1998). This is further metabolized to 8-11-dihydroxy-THC, and then to 11-nor-9-carboxy-THC. More than 100 THC metabolites including di and tri hydroxy compounds, ketones, aldehydes and carboxylic acids have been identified; however, 11-nor-9-carboxy-THC and the glucuronic acid conjugate are the major end products of biotransformation in most species including humans (Huestis, 2007). Δ^9-THC metabolites bind to plasma protein, and the plasma elimination half life of Δ^9-THC metabolites in humans can range from five to six days 50 hours (Huestis, 2007). This slower rate of elimination of Δ^9-THC metabolites is due to the slow release of Δ^9-THC from sequestered tissues. Studies of CBD indicate that it is also quickly absorbed from marijuana smoke into the systemic circulation. The plasma profile of CBD is similar to that of Δ^9-THC.

3.3.1.4 Excretion

Excretion of marijuana smoke constituents occurs in the breath, breast milk, urine, and feces, and is dependent upon the specific constituent chemical.

3.3.2 Genotoxicity

The majority of available information on the genotoxicity of marijuana smoke comes from cytogenetic studies conducted in marijuana smokers. Genotoxicity studies of marijuana smoke condensate in *Salmonella* and marijuana smoke exposure in monkeys have also been published. In addition, marijuana-derived cannabinoids have been tested in a few genotoxicity assays, and information is available on the genotoxicity of several other chemicals present in marijuana smoke. This information is briefly summarized below.

Marijuana smoke condensates were mutagenic in the *Salmonella* reverse mutation assay (strains TA 98 and TA 100) in the presence of metabolic activation (Busch *et al.*, 1979; Sparacino *et al*., 1990). Talaska *et al*. (1992) investigated the effect of marijuana smoke on lung DNA adduct levels in six rhesus monkeys exposed to marijuana smoke for one year, using P^{32}-postlabeling techniques. The monkeys were assessed seven months after the cessation of marijuana smoke exposure. No increase in total lung DNA adducts was observed in exposed monkeys, as compared with controls. The authors noted that the lengthy period between last exposure and tissue collection and assessment may be the reason a significant increase in DNA adducts was not observed in the treated animals.

One study has compared mutation frequency in lymphocytes from marijuana smokers and non-smokers. Specifically, Ammenheuser *et al*. (1998) compared the frequency of hypoxanthine-guanine phosphoribosyl transferase (*hprt)* mutations in marijuana smoking mothers (n = 5) and their newborn infants with that in non-smoking mothers (n=5) and newborns, and found an increased frequency of mutations in both the marijuana smoking moms and in their newborns.

Several studies have compared levels of DNA or chromosome damage in marijuana smokers and non-smokers. Chiesara (1983) investigated the frequency of chromosome damage in peripheral blood lymphocytes obtained from marijuana smokers, heroin-marijuana addicts, and non-

smoking controls (15 subjects per group, aged 19-21 years). The frequency of chromosome anomalies in marijuana smokers was three times higher than in controls, while in heroin-marijuana addicts the frequency was 21.3 times higher than in controls. In another study, Stenchever *et al*. (1974) compared the frequency of chromosome abnormalities in peripheral blood lymphocytes from 49 marijuana smokers with an average age of 23.3 years to that in 20 non-smoking controls with an average age of 28 years. Marijuana smokers had an increased number of chromosome breaks in peripheral blood lymphocytes than controls (3.4 cells with breaks per 100 cells in smokers vs. 1.2 cells with breaks per 100 cells in controls). Matsuyama *et al*. (1977) compared the effects of smoking marijuana cigarettes containing 0, 1, or 2% Δ^9–THC on chromosomal break frequencies in peripheral blood lymphocytes of 21 volunteers. Blood was drawn before, during and after a 28-day smoking period in which subjects smoked one marijuana cigarette per day. Some of the blood samples were cultured in two different laboratories using different techniques. Neither laboratory found a significant increase in break frequencies associated with marijuana smoking. In another study, chromosomal abnormalities in bone marrow lymphocytes obtained from seven long-term (15-20 year) marijuana smokers (ages 40 - 57 years) were compared with those observed in 25 non-smoking controls (age 21-57) (Kumar and Kunwar, 1971). The authors examined a total of 157 bone marrow cells from the marijuana smokers and a total of 500 cells from controls. A significantly higher increase in the frequency of chromosome abnormalities was found in the marijuana smokers as compared to that in controls. Another study reported an increase in DNA single strand breaks in alveolar macrophages recovered from the marijuana smokers, compared to controls. This occurred whether the smokers solely used marijuana or if they also smoked tobacco (Sherman *et al*., 1991, as reviewed in Li and Lin, 1998).

Zimmerman and Zimmerman (1990) reviewed genotoxicity studies conducted on cannabinoids, and noted that Δ^9-THC was not mutagenic in the *Salmonella* reverse mutation assay, nor did it increase the frequency of sister chromatid exchanges *in vitro* in cultured human fibroblasts obtained from normal or DNA repair deficient (i.e., xeroderma pigmentosum) individuals. Significant increases in bone marrow micronuclei were observed in mice given 10 milligrams per kilogram body weight (mg/kg bw) doses of Δ^9-THC, CBN or CBD (as reviewed in Zimmerman and Zimmerman, 1990).

Several other chemical constituents of marijuana smoke are genotoxic, including 4-aminobiphenyl (Saletta *et al.*, 2007), benz[a]anthracene, chrysene, benzo[b]fluoranthene (ATSDR, 1995), benzo[a]pyrene (Straif *et al*., 2005), dibenz[a,i]pyrene, dibenz[a,e]pyrene (IARC, 1983), cadmium (IARC, 1997), nickel (ATSDR, 2005), lead (IARC, 2006), formaldehyde (Cogliano *et al*., 2004), and styrene (IARC, 1994).

3.3.3 Animal Tumor Pathology

In the 74-week Swiss albino mouse skin painting study of Hoffmann *et al*. (1975), marijuana smoke condensate induced squamous cell papillomas of the skin. The study authors stated that skin tumors were rarely observed in acetone-treated controls in their laboratory in other skin-painting studies conducted with this strain of mouse. The less-than-lifetime duration of the study may have been insufficient to observe progression of the squamous cell papillomas to carcinomas in the marijuana smoke condensate treated animals.

Malignant mesenchimatous tumors were reported by Repetto *et al*. (1979) in their subcutaneous injection study of marijuana smoke condensate in newborn CD rats. These tumors were described as being "mixed" mesenchimatous tumors, composed of two or more cells, with "giant anaplastic (undifferentiated) cells invading the dermis and infiltrating skeletal muscle." These malignant tumors may develop from multipotent mesenchymal stem cells, or as a result of transformation of skin epithelial cells (Nieto, 2008).

In the marijuana smoke inhalation study conducted in female Wistar rats by Murthy *et al*. (1985), a number of different types of tumors of the ovary and uterus were reported to be treatment related. In the ovary benign serous cystoma were observed. These are tumors of the surface epithelial stroma of the ovary. Ovarian follicular cysts, formed from follicles that fail to ovulate, were also observed. Ovarian follicular cysts can secrete estrogens in excessive amounts and can be neoplastic, although the report by Murthy *et al*. (1985) does not provide sufficient information on these cysts to determine their neoplastic status. Uterine tumors included adenofibroma, adenosarcoma, and telengiectatic cysts and polyps. Uterine adenofibromas are benign mesenchymal neoplasms, and uterine adenosarcomas are malignant tumors. Both are rare in rats (Leininger and Jokinen, 1990). Uterine cysts and polyps are benign lesions. Insufficient information was provided in the report by Murthy *et al*. (1985) to evaluate the potential for these lesions to progress to malignancy.

3.3.4 Effects on Endocrine Systems

3.3.4.1 Hypothalamic-pituitary-gonadal (HPG) axis

Marijuana smoke affects the hypothalamic-pituitary-gonadal (HPG) axis in several ways, resulting in alterations in sex hormone levels. In both males and females, the secretion of sex hormones is directly controlled by the pituitary and indirectly influenced by the hypothalamus. From cells in the medial basal hypothalamus, gonadotropin releasing hormone (GnRH) is secreted in a pulsatile fashion under the influence of a variety of other factors, including endogenous opiates, catecholamines, prolactin, corticotropin-releasing hormone (CRH), and neuropeptide Y. GnRH stimulates the production of gonadotropins, such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the anterior pituitary. In both males and females, FSH and LH act on the gonads, leading to the secretion of testosterone in males and estradiol and progesterone in females. These hormones feed back to the hypothalamus and anterior pituitary to modulate GnRH and gonadotropin release. The functional interconnections between these three organs are referred to as the HPG axis. The effects of marijuana smoke on the male HPG axis are shown in Figure 3. Increased levels of sex hormone—estrogen or androgen—are associated with increased risk of breast, prostate, testis and uterine cancer in humans and experimental animals (Blank *et al*., 2008; Chlebowski *et al*., 2009). There is some evidence from one study in female rats and one study in humans that exposure to marijuana smoke is associated with tumors at some of these same sites. Specifically, increases in ovarian and uterine tumors were observed in female rats exposed via inhalation (Murthy *et al*., 1985), and increased risk for testicular germ cell tumors was reported by Daling *et al*. (2009).

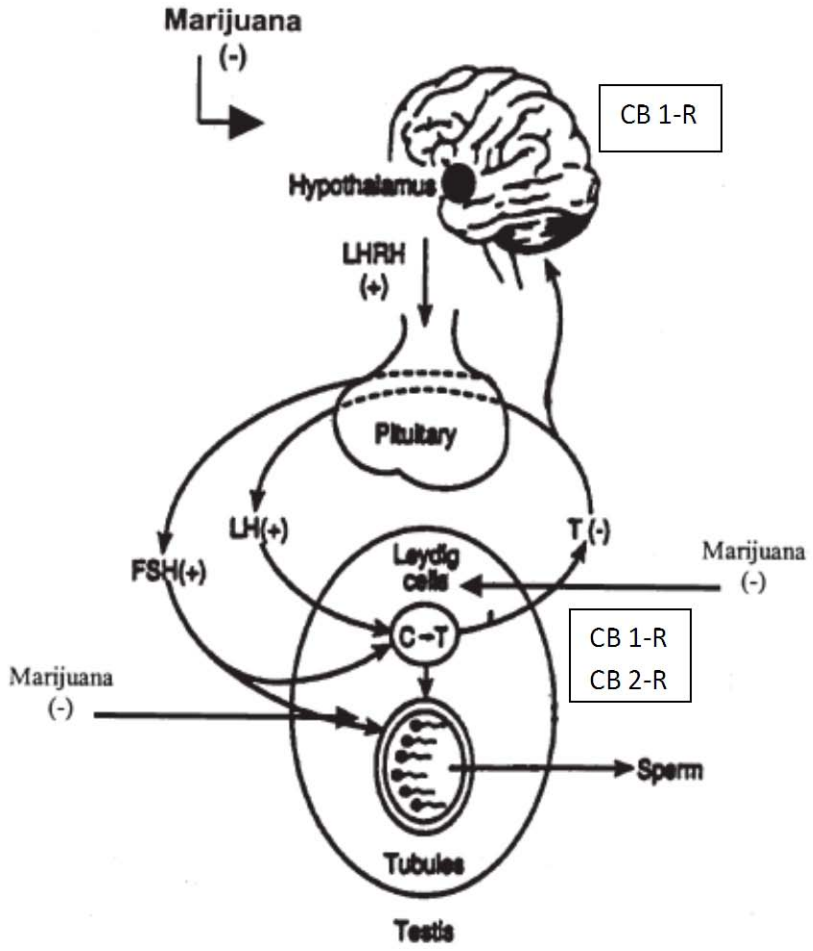

Figure 3. Effects of marijuana smoke on male hypothalamic-pituitary-gonadal (HPG) axis function. LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone; GHRH, growth hormone-releasing hormone; FSH, follicle-stimulating hormone; C, cholesterol; T, testosterone. CB 1-R and CB 2-R, cannabinoid receptors 1 and 2. Adapted from Brown and Dobs (2002) and modified by OEHHA.

Cannabinoid receptor-mediated effects on the HPG axis

Marijuana smoke condensates, Δ^9-THC, and other cannabinoids acutely alter the integrity of the HPG axis and affect reproductive function by acting at the hypothalamus either directly through GnRH or indirectly through other modulators (Brown and Dobs, 2002). These effects are likely mediated by central cannabinoid (CB1) receptors in the hypothalamus (Steiner and Wotjak, 2008). This in turn is thought to affect anterior pituitary hormone secretion. Exposure to Δ^9-THC inhibits gonadotropin (e.g., FSH, LH), prolactin (Scorticati *et al*., 2004), growth hormone, and thyroid-stimulating hormone release, and stimulates the release of corticotropin. Consequently, cannabinoid exposure could have profound effects on metabolism, lactation, the function of the reproductive system, and on the endocrine stress axis — the hypothalamic-pituitary-adrenal axis. In addition, animal studies have shown that CB1 receptors are present in

the testes, uterus, and ovaries, suggesting a possible direct effect of cannabinoids on the gonads (Wang *et al*., 2006).

While the mechanism by which cannabinoids affect anterior pituitary hormone secretion is not clear, the observation that these are acute effects suggests that cannabinoids are acting on brain neurotransmitter systems. Although cannabinoid receptors appear to play a major role in the ability of cannabinoids to influence hormone release, further work is needed to characterize their function in the neuroendocrine regulation of sex hormone secretion (Murphy *et al*., 1998).

Non-cannabinoid receptor-mediated effects on the HPG axis

As discussed in more detail below, under the sections on Direct Estrogen Receptor (ER)-Mediated Effects and Androgen Receptor (AR) Antagonism, non-cannabinoid components of marijuana smoke condensate have been shown to bind to the ER, and marijuana smoke condensate and Δ^9-THC have been shown to inhibit binding of dihydrotestosterone (DHT) to the AR. The extent to which these non-CB1-mediated pathways contribute to marijuana's effects on the HPG axis has not been clarified.

3.3.4.2 Direct estrogen receptor (ER)-mediated effects

Marijuana smoke condensate

Lee *et al*. (2006) evaluated the estrogenic effect of marijuana smoke condensate using several classical ER-mediated pathway assays, including *in vitro* bioassays, the cell proliferation assay, the reporter gene assay, and the ER competitive binding assay. Marijuana smoke condensate was positive for estrogenic activity in each of the assays. The estrogenic effect of marijuana smoke condensate was also observed in the immature female rat uterotrophic assay. Obvious changes in the appearance of uterine epithelial cells were observed in animals treated with a single dose of 10 mg/kg body weight marijuana smoke condensate, and a greater uterine response was observed at a 25 mg/kg body weight dose. Lee *et al*. (2006) also found that marijuana smoke condensate enhanced in a dose-dependent manner the expression of the Insulin Growth Factor Binding Protein-1(IGFBP-1) gene, which is an estrogen responsive gene.

Phenols

Lee *et al*. (2006) identified certain constituents of marijuana smoke condensate responsible for its estrogenicity. First, they fractionated the condensate into the following seven fractions: organic bases, organic acids, aliphatic compounds, aromatic compounds, slightly polar compounds, moderately polar compounds, and highly polar compounds. Then, they assessed the estrogenic activity of each fraction in a cell proliferation assay, and analyzed active fractions using gas chromatography-mass spectrometry (GC-MS). The fraction with the strongest estrogenic activity was an organic acid fraction containing the phenols 4-methylphenol and 4-ethylphenol. Both compounds have previously been shown to bind to the ER and to elicit ER-mediated estrogenic responses (Terasaka *et al*., 2006).

Cannabinoids

The interaction of cannabinoids with the ER has been studied with inconsistent results. Lee *et al*. (2006) evaluated the estrogenic effect of three major cannabinoids, i.e., Δ^9-THC, CBD, and CBN, in the same ER-mediated pathway assays in which they tested marijuana smoke condensate. None were positive in the ER-mediated pathway assays. Rawitch *et al*. (1977) reported that Δ^9-THC competed with [^{3}H] estradiol for binding to rat uterine ER in cytosolic preparations. Similarly, Sauer *et al.* (1983) demonstrated the competition of either crude marijuana extract or CBD for binding of [^{3}H] estradiol to the ER from rat uterine cytosol. However, in the same study, Δ^9-THC or 10-hydroxylated metabolites of Δ^9-THC failed to compete (Sauer *et al*., 1983). In contrast, Okey and Bondy (1978) failed to observe any displacement of [^{3}H] estradiol from the ER complex in the rat uterus by either Δ^9-THC or cannabis resin. Chakravarty and Naik (1983) were also unable to find any evidence for Δ^9-THC interaction with rat ER, in a variety of different tissues. On the other hand, estrogenic responses of Δ^9-THC were observed in the mouse uterus by Paria *et al*. (1992; 1994). Thus, the data regarding binding of cannabinoids and cannabis constituents to the ER are rather conflicting.

Flavonoid phytoestrogens

Phytoestrogens are compounds present in plants that possess estrogenic activity. Marijuana plants contain flavonoids phytoestrogens, however, the amount present varies between subspecies and with growing season. The flavonoids vary not only in their distribution between subspecies of *Cannabis sativa,* but also in their distribution within the leaves, flowers, and stems of a single plant (Turner *et at.,* 1976; Paris *et al.,* 1976). Saur *et al*. (1983) reported that apigenin, one of several flavonoid phytoestrogens known to exist in marijuana leaves, displayed high affinity for the ER. The amount of flavonoid phytoestrogens present in marijuana smoke condensates is very small, however, and the extent to which these compounds might contribute to ER activation by marijuana smoke is unclear.

3.3.4.3 Indirect ER-mediated effects

Interaction with the aryl hydrocarbon receptor (AhR)

Marijuana smoke

Marijuana smoke contains numerous PAHs, which bind to the AhR, and result in enzyme induction. Cytochrome P450 1A1, also known as aryl hydrocarbon hydroxylase, is induced by PAHs in marijuana smoke. The induction of P450 1A1 has the potential to down-regulate endogenous estrogen, as follows: since cytochrome P450 1A1 metabolizes the estrogen 17β-estrodiol (E2) to metabolites that do not bind to the ER, induction of P450 1A1 lowers the level of E2 available to bind to and activate the ER.

Activation of the AhR by marijuana smoke was demonstrated by Marcottee *et al*. (1975) in experiments in which rats were exposed to marijuana smoke produced from four marijuana cigarettes (containing 3.4 g marijuana). A two- to four-fold increase in P450 1A1 activity in the lung was reported six hours post-exposure. Also, marijuana tar has been shown to induce CYP 1A1 expression in Hepa-1 cells (Roth *et al.*, 2001). In the same study, Δ^9-THC acted through the AhR to activate transcription of CYP1A1. A 2 μ/ml concentration of Δ^9-THC produced an average 2.5-fold induction of CYP1A1 mRNA, whereas a 10 μ/ml concentration of Δ^9-THC produced a 4.3-fold induction. Marijuana tar was more potent than tobacco tar in inducing CYP

1A1 expression in this cell system, and the authors attributed this to the presence of Δ^9-THC in the marijuana tar (Roth *et al*., 2001).

Lee *et al*. (2005) employed the ethoxyresorufin-O-deethylase (EROD) assay to measure P450 1A1 activity. They also measured the rate of E2 metabolism in two cell types (rat H4IIE hepatoma cells and human MCF-7 breast cancer cells) exposed to marijuana smoke condensate. They found that marijuana smoke condensate induced CYP1A1 activity and E2 metabolism.

Cannabinoids
Lee *et al.* (2005) also investigated the effects of Δ^9-THC, CBD, and CBN on P450 1A1 activity and E2 metabolism in rat H4IIE hepatoma cells and human MCF-7 breast cancer cells, using the EROD and E2 metabolism assays. No effects of these cannabinoids were observed in these cell lines.

AhR cross-talk with the ER

There are three plausible mechanisms by which exposure to marijuana smoke may result in cross-talk between the AhR and the ER, given the evidence discussed above that marijuana smoke activates both receptors. These mechanisms, as discussed by Beischlag *et al*. (2008), are as follows: in the first mechanism, AhR ligands, such as PAHs present in marijuana smoke, induce the recruitment of ER to ligand-activated AhR/aryl hydrocarbon receptor nuclear translocator (ARNT) heterodimer complex and other coreregulators in the nucleus. This recruitment of ER is enhanced in the presence of ER agonists, which are also present in marijuana smoke. Once recruited, ER can modulate AhR transcriptional activity. Ligand-activated or inactivated ER can occupy AhR-responsive promoter regions in the DNA, thereby reducing the pool of ER available to regulate estrogen-responsive promoter regions. This results in a decrease in the transcriptional activity of estrogen responsive genes. In the second mechanism, recruitment of ER to ligand-actived AhR triggers ubiquination of cytosolic ER. Ubiquination of proteins leads to protein degradation, thus this proposed cross-talk mechanism also results in fewer ER available to regulate estrogen-responsive genes. In the third mechanism, activated ER results in the recruitment of activated AhR in the nucleus. Once recruited, the activated AhR modulates ER transcriptional activity by occupying proposed AhR-responsive sites in the promoter region of the ER gene. This will inhibit transcription of the gene, and reduce ER protein expression levels.

Inhibition of aromatase

Marijuana smoke
Aromatase (CYP 19A1) is an enzyme that converts testosterone to E2. Like the induction of CYP 1A1 described above, inhibition of aromatase would also result in less formation of E2, and lower levels of E2 overall. Lee *et al.* (2005) reported that marijuana smoke condensate inhibited aromatase activity in human JEG-3 choriocarcinoma cells.

Cannabinoids
Lee *et al*. (2005) also investigated the effect of Δ9-THC, CBD, and CBN on aromatase activity in human JEG-3 choriocarcinoma cells. None of these cannabinoid compounds had any effect on aromatase activity in this cell system. This suggests that something other than the

cannabinoids present in marijuana smoke is responsible for marijuana smoke's inhibition of aromatase.

3.3.4.4 Cannabinoid receptor-mediated effects

Cannabinoid receptor cross talk with epidermal growth factor (EGF) receptor signaling pathways

Hart *et al*. (2004) discovered the link between the CB1-R/CB2-R G protein couple receptor (GPCR) signaling pathway and the epidermal growth factor (EGF) receptor signaling pathway. They demonstrated that Δ^9- THC and other cannabinoid receptor ligands promote mitogenic kinase signaling in cancer cells. Communication between these two independent signaling pathways is mediated by metalloprotease and EGF. In their study, treatment of two cell lines (glioblastoma U373-MG and lung carcinoma NCIH292) with low levels of Δ^9- THC led to accelerated cell proliferation. The proliferation was completely dependent on metalloprotease and EGF receptor activity. EGF receptor signal transactivation was identified as the mechanistic link between cannabinoid receptors and the activation of prosurvival protein kinase B (also known as Akt/PKB) signaling (the mitogen-activated protein kinases extracellular signal-regulated kinase). However, it is well documented that EGF receptors can cross talk with the ER signaling pathway (Yanger and Davidson, 2006). It is also likely that cannabinoid-induced estrogenic-like effects are modulated through mitogenic kinase signaling and epidermal growth factor receptor (EGFR) signaling in cancer cells.

Taken together, their data show that concentrations of Δ^9- THC comparable with those detected in the serum of patients after Δ^9- THC administration accelerate the proliferation of cancer cells at these levels. Apoptosis is apparently not induced at these levels but instead at much higher levels of Δ^9- THC in the cell culture (*in vitro*). These results suggest that low doses of Δ^9- THC may contribute to cancer progression in patients. They provide another potential mechanism that cannabinoids could work through the complexity of signal transduction networking communication between ER, EGFR, Akt/PKB signaling and CB1-R/CB2-R receptors (GPCRs) to accelerate proliferation of glioblastoma and lung cancers.

3.3.4.5 Androgen receptor (AR)-mediated effects

AR Antagonism

Marijuana smoke condensate and Δ^9-THC inhibit binding of DHT to the androgen receptor (Purohit *et al*., 1980). In their study, marijuana smoke condensate and its constituents Δ^9-THC and CBN were tested for their ability to interact with the AR in rat prostate cytosol. All three inhibited the specific binding of DHT to the AR. In addition, other metabolites of Δ^9-THC were also androgen antagonists. These data suggest that the anti-androgenic effects associated with marijuana use result, at least in part, from inhibition of androgen action at the receptor level.

Effects of cannabinoids on androgen metabolism

A study by Watanabe *et al*. (2005), conducted with crude extracts of the marijuana plant, rather than with marijuana smoke, suggests that cannabinoids can affect steroid metabolism in the

testes. In their study, incubation of crude extracts of marijuana with rat testis microsomes resulted in the inhibition of cytochrome P450c17, also known as cytochrome P450-dependent 17 α-hydroxylase. This enzyme is present in Leydig cells of the testes, ovarian follicles, and in the adrenal gland. It is critical in steroidogenesis, as the production of all sex steroids and cortisol is dependent upon cytochrome P450c17 activity. This enzyme catalyzes the conversion of pregnenolone to 17-hydroxypregnenolone, the precursor of dehydroepiandrosterone, and the conversion of progesterone to 17-hydroxyprogesterone, the precursor of androstenedione. Δ9-THC, CBD and CBN also inhibited the activity of cytochrome P450c17 in rat testis microsomes at relatively higher concentrations than those present in crude extract.

3.3.4.6 Summary of endocrine effects

Marijuana smoke and its cannabinoid components affect the HPG axis at multiple levels. These effects result in alterations in sex hormone levels, which in turn can affect the growth and function of hormone responsive tissues, and by these mechanisms might increase the risk of certain cancers (e.g., testes, ovary, uterus, and breast). On the other hand, the anti-estrogenic effect of PAHs may contribute to decreased cancer risk at these sites.

The neuroendocrine effects are likely mediated by central CB1 receptors in the hypothalamus and other non-cannabinoid receptor-mediated effects on the HPG Axis. The estrogenic/antiestrogenic effects of marijuana smoke are mediated through both direct ER and indirect ER dependent pathways. Several constituents of marijuana smoke condensate may have estrogenic/antiestrogenic effects. They include 4-ethylphenol and 4-methylphenol, which bind directly to the ER, and are active in direct ER-dependent assays. In addition, ER-AhR cross-talk might be related to the antiestroginicity as a result of the enhancement of E2 metabolism and the depletion of E2. These findings suggest that pyrogenic products including PAHs, which are at greater amounts in marijuana smoke than in tobacco smoke, are responsible for the antiestrogenic effect of marijuana smoke condensate. Further, aromatase activities are inhibited by marijuana smoke, resulting in lower levels of E2 in the circulation. The anti-androgenic effects associated with marijuana use and interactions with steroid metabolism have the potential to result in significant alterations in hormonal levels. Recent reports indicate the possibility of cannabinoid receptor cross talk with EGF receptor and GPCR signaling pathways. This might increase the risk of cell proliferation and subsequent cancer development. More research is needed to explore this possibility.

3.3.5 Effects on Immunological Systems

The effect of marijuana smoke on immune function has been investigated in only a few studies, while the effects of Δ^9-THC and other cannabinoids on multiple aspects of immune function have been investigated in several different assays. These studies, which are briefly discussed below, indicate that marijuana smoke and cannabinoids suppress immune function by a number of different mechanisms.

3.3.5.1 Marijuana smoke

Macrophages play an important role in initiating and maintaining innate and adaptive immune response. Rat alveolar macrophages obtained by pulmonary lavage were incubated with *Staphylococcus albus* in the presence of increasing doses of marijuana smoke. A dose-dependent decrease in macrophage bactericidal activity was observed. It was further observed that the active component in marijuana smoke responsible for this effect was a water-soluble compound present in the gas phase of fresh marijuana smoke. No effect was observed with Δ^9-THC or Δ^9-THC-extracted marijuana (Huber *et al*., 1975). In an *in vivo* study, these same investigators examined the intrapulmonary inactivation of aerosolized *S. aureus* in rats exposed to increasing doses of fresh marijuana smoke. Intrapulmonary bacterial inactivation was impaired by marijuana smoke in a dose-dependent manner (Huber *et al.,* 1980). No effect was observed with Δ^9-THC, suggesting that smoke constituents other than cannabinoids are responsible for the immunosuppressive effects observed.

Baldwin *et al*. (1997) investigated the bactericidal and tumoricidal activity of alveolar macrophages obtained from the lungs of 10 habitual smokers of marijuana (MS), and compared this activity to that observed in macrophages obtained from 22 non-smokers (NS), 11 tobacco smokers (TS), and 13 cocaine smokers (CS). Alveolar macrophages from marijuana smokers were deficient in the ability to phagocytose *S. aureus* and were also limited in their ability to kill bacteria and tumor cells, as compared to the macrophages from NS. No differences in bactericidal or tumoricidal activity were observed in macrophages obtained from TS or CS. Alveolar macrophages from MS were not able to use nitrogen oxide to kill bacteria, and when stimulated with lipopolysaccharide (LPS), they produced less tumor necrosis factor, less granulocyte-macrophage colony stimulating factor and less interleukin-6 (IL-6) than macrophages from NS. In the tumoricidal assay, macrophages from MS lysed significantly fewer (24 to 40 percent fewer) tumor cells than did macrophages from NS.

In a study of individuals infected with the human immunodeficiency virus (HIV), a more rapid progression to acquired immunodeficiency syndrome (AIDS), which was associated with greater changes in T cell subsets, was observed in marijuana users, compared to non-users (Tindall *et al.,* 1988).

3.3.5.2 Δ^9-THC and other cannabinoids

Cannabinoid receptors are expressed in various tissues within the body, including the immune system. Specifically, CB1-R is expressed at high levels in the brain and to a lesser extent in peripheral tissues such as the adrenal gland, reproductive organs and immune cells (Pertwee *et al.,* 2008). CB2-R is expressed in varying amounts in cells of the immune system in the following rank order, from highest expression to lowest: B cells> natural killer cells> monocytes> polymorphonuclear neutrophils>CD8+ T cells >CD4+ T cells (Buckley, 2008). Ligand binding to these receptors affects various signaling pathways, including the adenyl cyclase and ERK/MAPK pathways, regulating functions such as cell growth, transformation and apoptosis (Parolaro *et al*., 2008).

Δ^9-THC has been shown to disrupt all aspects of the immune response, including host resistance to microbial infection, macrophage function, natural killer (NK) and T cell cytolytic activity, cytokine production by macrophages and T cells, and decreased antigen presentation by dendritic cells (Cabral and Staab, 2005; Kaminski, 1994; Massi *et al.*, 2006). Studies in mice have shown that Δ^9-THC reduces thymus and spleen cellularity (McKallip *et al*., 2002). Δ^9-THC also induces apoptosis in mouse T and B cells, reducing the ability of these cells to proliferate when activated (McKallip *et al*., 2002). These effects are thought to be mediated through CB2-R, based on experiments showing that the synthetic CB2-R agonist JWH015 decreases splenocyte cell proliferation in response to challenge with anti-CD-3 mAbs, concanavalin A (ConA), or LPS, in a dose-dependent manner (Lombard *et al*., 2007). This decrease in cell proliferation was associated with an increase in apoptosis. A similar dose-related increase apoptosis in cultured thymocytes, accompanied by a dose-related increase in caspase -3/7 activity, was observed in cultured thymocytes treated with the CB2-R agonist JWH015 (Lombard *et al*., 2007). Buchweitz *et al.* (2007) found that *in vivo* administration of the CB2-R agonist JWH015 resulted in thymic atrophy, apoptosis and decreased T cell response to mitogens, further confirming the role of cannabinoid receptors in regulating immune function.

A number of studies have demonstrated a differential sensitivity of T cells to mitogen stimulation in the presence of Δ^9-THC (3 to 7 μg/ml). This sensitivity was due to the direct effect of Δ^9-THC on T cells and was not abrogated by addition of interleukin-2 (IL-2). Similar results were observed in peripheral blood lymphocytes treated with Δ^9-THC or OH-THC (Kaminski, 1994). Recently, the effect of Δ^9-THC on various parameters of immune response was investigated in CB1 (-/-), CB2 (-/-), and wild type mice. Δ^9-THC treatment of wild type, CB1 (-/-), and CB2 (-/-) mice produced no difference in the percentage of T cells, B cells and macrophages in the spleen, lymphocyte proliferation, IL-2 production, or interferon- γ (IFN- γ) production. However, Δ^9-THC suppressed the *in vivo* antibody response to sheep red blood cells (SRBC) and to CD40 antibody in wild type mice, but not CB receptor negative mice. Δ^9-THC did not suppress LPS-induced response regardless of the genotype. This suggests a limited role for the CB-1 and CB-2 receptor in the modulation of the immune response parameters (Springs *et al.*, 2008). Using cannabinoid receptor knock-out mice, Buckly (2008) reported that CB1-R and CB2-R are not involved in the inhibition by 2-AG or WIN 55,212-2 of splenocyte and CD4 T cell proliferation stimulated by con A, anti-CD3 and anti-CD 28 antibodies. 2-AG and Win 55,212-2 also inhibited the production of IL-2 and IFN-γ in wild type and CB2 (-/-) splenocytes and CD4+ T cells in a dose dependent manner. In a recent study, Rockwell *et al*. (2006) reported that the suppression of IL-2 is mediated via peroxisome proliferator-activated receptor gamma (PPARγ) that is independent of CB1-R and CB2-R.

Δ^9-THC and 11-OH THC suppressed the proliferation and NK cell killing of murine NK B61A2 cells and suppressed the cytolytic activity of lymphocyte activated killer cells against both YAC-1 and EL-4 tumor targets (Kawakami *et al*., 1998). In contrast, another study showed that NK cell cytolytic activity was inhibited without affecting Con A-induced cell proliferation (Massi *et al*., 2000). Kishimoto *et al*. (2005) reported that 2-AG induced the migration of KHYG-1 cells (an NK leukemia cell line), which is abolished by the CB2 receptor antagonist SR 144528. Neither Δ^9-THC nor anandamide (AEA) induced migration. However, 2-AG and Δ^9-THC together abolished the 2-AG-induced migration.

In a study of primary and second antibody response to SRBC in Heb/FeJ mice spleen cells, Δ^9-THC and anandamide produced dose-dependent immunosuppression (Eisenstein *et al.*, 2007). The suppression was blocked by a CB2-R antagonist (SR144528) but not by a CB1-R antagonist (SR141716). These effects were observed in the 10^{-13} to 10^{-7} M range for Δ^9-THC and the 10^{-14} to 10^{-7} M range for AEA. The role of CB2-R in immune suppression was also shown in autoimmune encephalomyelitis (EAE)- induced in wild type and CB2 (-/-) knockout mice on B10.PL background (Maresz *et al*., 2007). The expression of CB1-R on neurons, but not on T cells, was necessary for cannabinoid induced suppression of EAE. The CB2-R knockout mice, however, exhibited a higher incidence of disease and a reduced recovery rate compared to their wild-type counterparts. Further induction of EAE in wild type mice with CB2 (-/-) T cells by adoptive transfer of encephalogenic T cells resulted in more severe clinical disease and more proliferation, an increased production of inflammatory cytokine, and decreased apoptosis of CB2 (-/-) cells.

Groups of C57BL/6 mice were administered 0, 25, 50, or 75 mg/kg Δ^9-THC for five days. On the third day of the treatment, mice were given influenza virus (PR8) intranasally four hours before Δ^9-THC treatment and were killed 7 and 10 days post infection. Treatment resulted in a dose-dependent increase in viral hemagglutinin mRNA levels. However, Δ^9-THC treated mice also had a dose-dependent decrease in macrophage, CD4+, and CD8+ cells in bronchoalveolar lavage fluid compared to controls. The observed reduction in inflammation suggested that Δ^9-THC increased viral load by decreasing the recruitment of macrophage and lymphocytes to the lungs (Buchweitz *et al*., 2007). Roth *et al.* (2005) implanted $1\text{-}2x10^7$ human peripheral blood lymphocytes (PBL) into severe combined immunodeficient mice (SCID). Animals were infected i.p. with HIV virus containing a 300-400 reporter virus vector (NL-r-HSAs). Δ^9-THC (10 mg/kg-day) was given four to five days post-infection. The number of CD+ cells was decreased in Δ^9-THC treated mice not treated with the virus, caused either by reduction of CD+ cells proliferation or apoptosis. There was a two- to four-fold increase in HIV infection and a 50-fold increase in HIV RNA copy number in peripheral blood lymphocytes in the Δ^9-THC -treated and HIV- infected mice compared to controls. Also, there was a reduction in IFNχ production in Δ^9-THC treated mice.

In microglial cells (macrophages in the central nervous system (CNS), CB1-R is expressed constitutively at a relatively low level. CB2-R is not expressed in resting microglial cells, but it is present at high levels in primed cells and is involved in cannabinoid-mediated inhibition of the processing of select antigens and chemotaxis. In response to *Acanthamoeba culbertsoni*, responsible for granulomatous amoebic encephalitis, endocannabinoids are pro-chemotactic. Δ^9-THC inhibits the chemotactic effects of endocannabinoids via CB2-R (Cabral *et al.*, 2008). Thus, Δ^9-THC disrupts endocannabinoid–mediated homeostasis of the immune response.

Dendritic cells, which are antigen-presenting cells similar to macrophages, play an important role in initiating and maintaining adaptive immune responses. Wacnik *et al.* (2008) reported that arachidonylcycloropylamide (ACPA), a structural analogue of anandamide, significantly reduced Kv channel function in dendritic cells via CB1-R pathways in a pertusis toxin sensitive manner. This was associated with reduced expression of major histocompatibility (MHC) class II molecules, as well as their capacity to stimulate T cells in a mixed lymphocyte reaction (MLR).

The authors suggest that both exogenous and endogenous cannabinoids may modulate the Kv channel, which alters the stimulatory function of dendritic cells.

Zhu *et al.* (2000) evaluated the host immune reactivity in two murine cancer models: Lewis lung carcinoma (3LL) in C57BL/6 and alveolar cell carcinoma (LiC2) in Balb/c mice. In mice administered 5 mg/kg Δ^9-THC four times per week for 35 days beginning two weeks before the implantation of tumor cells, treatment with Δ^9-THC increased the growth of tumor cells relative to those not treated. Δ^9-THC treatment did not, however, affect the growth of LiC2 cells in BALB/c SCID mice. Δ^9-THC treatment increased IL-10, increased TGF-β, and decreased IFN-γ in tumor homogenates and spleen cells. Administration of CB2 antagonist blocked the effects of Δ^9-THC, suggesting a role for CB2-R in mediating the inhibition of tumor immunity.

McKallip *et al*. (2005) showed that mice exposed to Δ^9-THC exhibited suppressed antitumor immune response to mammary tumor cells (4T1) and that this suppression was mediated via the CB2-R. Furthermore, Δ^9-THC suppresses the Th1 immune response by enhancing Th2-associated cytokines through up-regulation of several Th2-regulated genes. This suggests that exposure to marijuana smoke may potentially increase susceptibility to breast and other cancers that do not express cannabinoid receptors. Disruption of the Th1/Th2 cytokine balance could play a role in promoting tumor growth since Th1 cytokines activate cell-mediated immune response while Th2 cytokines inhibits cell-mediated immune response. Hart *et al*. (2004) suggested that Δ^9-THC might increase the proliferation of cancer cells via the mitogenic kinase signaling pathway. Lee *et al.* showed that there was no significant difference between cannabinoid-induced apoptosis in thymocytes and EL-4 thymoma cells. Furthermore, marijuana tar produced inhibition of Fas-induced caspase-3 activity and induction of necrotic cell death in A459 lung tumor cells. Marijuana tar was found to be more potent than tobacco tar in this study. The author stated that exposure to whole smoke more likely reflect the environment in the lungs of smokers (Sarafian, 2001).

On the other hand, cannabinoids have also been proposed to be a potential antitumor agents based on experiments performed both in cultured cells and in animal models of cancer. A number of plant-derived (Δ^9-THC, CBD), synthetic (Win 55,212-2, Hu-210) and endogenous cannabinoids are known to exert antiproliferative action on a wide spectrum of cells in cultures (Guzman, 2003). Cannabinoid administration to nude mice has been shown to reduce the growth of various types of tumor zenografts, including lung carcinoma (Munson, 1975), skin carcinoma (Casanova, 2003), and lymphoma (McKallip, 2002). In a clinical trial in nine patients with actively growing recurrent glioblastoma multiforme, 20-40 µg THC was given intratumorally at Day 1 and increased progressively to 80-180 µg/day over two to five days. The mean survival of the cohort from the beginning of the study was only 24 weeks (CI, 15-33). Δ^9-THC was reported to decrease tumor cell proliferation and to increase tumor cell apoptosis (Velasco, 2007; Guzman, 2006). Ligresti *et al*. (2006) observed a significant reduction in tumor growth of xenograft tumors induced by subcutaneous injection of cannabidiol and cannabidiol rich extract in athymic mice. The authors state that observed effects were due to the induction of apoptosis by direct or indirect activation of CB2 and vanilloid receptors, and by independent elevation of Ca^{2+} and reactive oxygen species.

A series of reports suggest that cannabinoids demonstrate potent anti-inflammatory action by modulating cytokine production. They increase the production of TNF, IL-1, IL-6 and IL-10 when given in conjunction with antigens (Costa, 2007). In the murine model of Con A- induced hepatitis, Δ^9-THC suppressed immune-mediated liver damage including autoimmune hepatitis and viral hepatitis, when Δ^9-THC was administered intraperitoneally after Con A challenge. This was followed by an increase in the absolute number of Forehead helix transcription factor P3+T regulatory cells (suppressor T cells). Con A-induced hepatitis was reversed by both CB1 and CB2 antagonists (Hedge *et al*., 2008).

From the foregoing discussion it is clear that many aspects of innate and adaptive immune response and tumor growth are targeted by cannabinoids. While the inhibition of tumor growth is mediated via CB2-R, the inhibition of immune response parameters is mediated by multiple mechanisms including CB1-R and CB2-R mediated inhibition of cAMP, protein kinase pathways (Kaminiski *et al*., 1980), induction of apoptosis (Do *et al*., 2004), by PPARγ dependent inhibition of NF-AT (Rockwell *et al*. 2006), and by affecting potassium (Kv) channel function (Wacnik *et al*., 2008). While the immunosuppressive properties of cannabinoids may be useful in the treatment of autoimmune diseases, the effect on tumor growth may be limited to tumors with high levels of CB2-R. The fact that similar mechanisms seem to be operating to decrease thymus cellularity, an important secondary organ for T cell subset generation, raises concerns. It is well established that individuals with primary immunodeficiency, acquired immunodeficiency disorders, and patients undergoing prolonged and intensive immunotherapy following organ transplantation are at increased risk of developing cancer (Penn, 2000).

3.3.6 Effects on Other Systems

Data from humans and animals indicating that marijuana smoke causes histologic changes in the lung are summarized below. An animal study reporting metaplastic effects of marijuana smoke condensate on the skin is also described.

3.3.6.1 Human studies

Gong *et al*. (1987) examined bronchial epithelial tissues from 16 marijuana smokers (MS), six tobacco smokers (TS), 13 smokers of both marijuana and tobacco (MTS), and four nonsmokers (NS), and observed histopathologic changes in the tissues of all individuals in the MS, TS, and MTS groups. Squamous metaplasia of the bronchial epithelium was observed in 53% of the MS group, 50% of the TS group, 100% of the MTS group, and none of the NS group. Hyperplasia of basal and goblet cells was significantly greater in the MS group (80%) than in the NS group (0%), and cellular disorganization was more prevalent in the MS group than in either the NS or the TS groups. The authors concluded that young, heavy marijuana smokers have "a high prevalence of abnormal airway appearance and histologic findings, irrespective of concomitant tobacco smoking."

The effects of marijuana and tobacco smoke on tracheobronchial histopathology was evaluated in 40 marijuana smokers, 31 tobacco smokers and 53 nonsmokers with a mean age of 35, 38 and 32, respectively (Fligiel *et al*., 1997). The participants were recruited from an ongoing study investigating the pulmonary effects of smoking marijuana, tobacco, and/or cocaine. The results discussed here concern only those seen in marijuana and tobacco smokers. Marijuana and tobacco smoking each produced significant bronchial mucosal histopathology, including a

significant increase in basal cell hyperplasia, stratification, goblet cell hyperplasia, basement membrane thickening and squamous cell metaplasia. The effects of marijuana and tobacco smoke on the histopathology were found to be additive.

Hii *et al.* (2008) reported on lung changes present in a series of ten patients (mean age 41±9 years) who smoked marijuana regularly for more than one year. Nine of the ten marijuana smokers had emphysematous bullae (areas where the lung tissue has been severely damaged, creating an airspace ≥1cm in diameter) in the upper and mid zones of the lung on high resolution computed tomography (CT) scans. The occurrence of emphysematous bullae is associated with exposure to toxic chemicals, including exposure to tobacco smoke (Hii *et al*., 2008).

Barsky *et al.* (1998) assessed the presence of several molecular markers associated with pre-neoplastic or neoplastic changes in bronchial biopsies obtained from 12 marijuana smokers, 13 cocaine smokers, 14 tobacco smokers (tobacco only, or some combination of tobacco and marijuana or cocaine), and 28 nonsmokers. The mean age of all subjects was 39 years. The molecular markers evaluated included Ki 67 (a proliferative marker), EGFR (epidermal growth factor receptor), Her-2/Neu (a member of the growth factor receptor tyrosine kinase family), P53 (a tumor suppressor gene product), DNA ploidy (genetic instability) and G-actin (a cytoskeleton protein involved in cell morphology). Abnormal expression of many of these markers was observed in bronchial biopsies from marijuana smokers, as compared to the nonsmokers. The authors concluded that molecular alterations seen in the bronchial epithelium of marijuana smokers were similar in nature and magnitude to those seen in tobacco smokers.

3.3.6.2 Animal studies

Marijuana smoke was administered to groups of Fischer rats (30 animals/sex/dose group; with 50 animals/sex in the high dose groups) at concentrations of 0, 0.4, 0.9, or 1.5 mg/kg, six to seven days per week for one year (Fleischman *et al*., 1979). Animals were examined thirty days after cessation of exposure. A spectrum of dose-related inflammatory and proliferative lesions of the respiratory system were observed in treated animals, including focal hypertrophy and hyperplasia of the alveolar lining cells, and focal thickening of the alveolar septa and pleura. The severity of marijuana smoke induced inflammation was greater in females than in males.

Roy *et al*. (1976) exposed dogs to either marijuana smoke (3.0 gram/dog), or tobacco smoke (3.2 gram/dog) at a rate of four cigarettes a day seven days a week via tracheostomy tube for 900 days. Fourteen dogs were exposed to marijuana smoke, six to tobacco smoke, and fourteen dogs served as unexposed controls. The region of the respiratory tract most commonly affected in both treatment groups was the trachea, with squamous cell metaplasia observed in 83% of the dogs exposed to marijuana smoke, and 50% of the dogs exposed to tobacco smoke. Chronic inhalation of marijuana and tobacco smoke also produced bronchiolitis (inflammation of the bronchioles) with macrophage infiltration of the walls of the terminal air-passages.

In a study by Fligiel *et al.* (1991) rhesus monkeys (15-16 per group) were exposed to various doses of marijuana smoke for one year (e.g., smoke from one marijuana cigarette seven days per week; smoke from one marijuana cigarette two days per week, or smoke from one ethanol-extracted “placebo control” marijuana cigarette seven days per week). A control group was

treated under "sham smoke" conditions seven days per week, for one year. Animals were sacrificed seven months after cessation of exposure, and the lungs were examined. There was a greater degree of inflammatory fibrosis and bronchiolar squamous cell metaplasia in marijuana smoke-treated monkeys relative to sham smoke controls, and alveolar epithelia cell hyperplasia was observed only in marijuana smoke exposed monkeys (Fligiel *et al.*, 1991).

Cottrell *et al*. (1973) conducted skin painting studies of marijuana smoke condensate in two strains of mice (Swiss and "black and white hybrid" mice). Groups of 10 mice each received five applications of either marijuana smoke condensate, 0.5% benzo[a]pyrene, or acetone vehicle. Metaplasia of the sebaceous glands of the skin, a pre-neoplastic change observed in mouse skin-painting studies of tobacco smoke condensate, was observed in animals treated with either marijuana smoke condensate or benzo[a]pyrene.

3.3.7 Comparison of Marijuana and Tobacco Smoke

Marijuana and tobacco smoke share many characteristics, as they are both complex gaseous and particulate mixtures formed from the burning of plant material. Both mixtures contain products of pyrolysis and incomplete combustion, as well as compounds released unchanged from the starting plant material. The primary differences between the two mixtures are that cannabinoids and cannabinoid-derived products are present only in marijuana smoke and nicotine and nicotine-derived products are present only in tobacco smoke (Hoffmann *et al*., 1975). Other than cannabinoid- and nicotine-derived compounds, comparisons of the individual chemical constituents of marijuana smoke with those in tobacco smoke indicate that the two smokes are qualitatively very similar, although quantitative differences in the levels of individual chemical constituents were apparent (Moir *et al*., 2008; Lee *et al*., 1976, Hoffman *et al*., 1975).

The particle size distributions of marijuana and tobacco smoke are similar, with the mass median aerodynamic diameter of marijuana smoke particulates ranging from 0.35 to 0.43 μm, compared to 0.38 μm for tobacco smoke particulate (Hiller *et al*., 1984). This same study found that particle number and mass was greater in marijuana smoke than in tobacco smoke, and that marijuana smoke particle number and mass concentration increased as Δ^9 -THC concentration increased.

As discussed in Section 3.3.1 Pharmacokinetics and Metabolism, Wu *et al*. (1988) estimated that 80.7 to 86.7% of the inhaled resinous total particulate matter (*i.e*., tar) in marijuana smoke would be deposited in the human lung, based on a mean median aerodynamic diameter of marijuana smoke tar of 0.35 to 0.43 μm. Using the same methodology, these authors estimated that 64.0% of tobacco smoke tar would be deposited in the lung. Follow-up studies conducted with marijuana and tobacco smokers and the use of a smoking apparatus capable of measuring puff volume and inhaled tar showed that the intake of marijuana smoke tar by smokers is four times greater than the intake of tobacco smoke tar (Taskin *et al*., 1991).

The increased amount of tar deposited in the lungs from smoking equal amounts of marijuana, as compared with tobacco, may partly be due to differences in the way the two substances are smoked. Marijuana cigarettes (joints) and pipes are non-filtered and are smoked by taking longer puffs (larger puff volume) and holding the smoke in the lungs for a longer duration than

tobacco cigarettes (Taskin *et al*., 2002). These smoking differences will also result in a greater absorption of marijuana smoke constituents into the lungs and aerodigestive tract than with tobacco smoke.

The total volume of smoke inhaled by typical marijuana smokers may be quite different than the quantity inhaled by typical tobacco smokers, however. For example, smoking two to three packs of tobacco cigarettes per day (40 to 60 cigarettes) has been historically common in the U.S., while the number of marijuana cigarettes smoked per day has been considerably lower. Also, as the Δ^9-THC content in marijuana has risen, leaf content in marijuana products has dropped over time, possibly requiring fewer puffs to achieve the same psychoactive effect.

As discussed in Section 2 (Identity of Marijuana Smoke), many of the constituents in marijuana smoke are carcinogenic. Each of the 33 marijuana smoke constituents identified as Proposition 65 carcinogens are also present in tobacco smoke, which is itself a Proposition 65 carcinogen. Table 6 lists these carcinogenic constituents and compares the levels (if available) of each carcinogen reported in the marijuana and tobacco smoke comparison studies of Moir *et al.* (2007), Lee *et al*. (1976), and Hoffman *et al*. (1975). For many of the carcinogenic smoke constituents, the levels were similar in marijuana and tobacco smoke. For acrylonitrile, 4-aminobiphenyl, benzo[*a*]pyrene, benzo[*b*]fluoranthene, 1, 3-butadiene, and carbazole, the levels in marijuana smoke were significantly elevated above those in tobacco smoke. For other constituents, including acetaldehyde, formaldehyde, and several of the PAHs, the levels were significantly lower than those in tobacco smoke.

Table 6. Quantitative comparison of thirty-three carcinogenic constituents in marijuana and tobacco smoke.

Carcinogenic Smoke Constituent	**Marijuana Smoke (µg/cigarette)**	**Tobacco Smoke (µg/cigarette)**	*** P < 0.05**
Acetaldehyde	448±44	872±101	*
Acetamide[(1)]	Not quantified	Not quantified	
Acrylonitrile	36.6±4.3	13±1.2	*
4-Aminobiphenyl	0.00617±0.00044	0.00156±0.00013	*
Arsenic	0.00244±0.00113	0.00549±0.00033	*
Benz[*a*]anthracene	0.0262±0.0034	0.0305±0.0025	*
Benzene	58.3±5.9	62.2±3.5	
Benzo[*a*]pyrene	0.00867±0.00112	0.0143±0.0012	*
Benzo[*b*]fluoranthene	0.00718±0.00112	0.0108±0.0006	*
Benzo[*j*]fluoranthene	0.00427±0.00083	0.00581±0.00044	*
Benzo[*k*]fluoranthene	0.00152±0.00026	0.00342±0.00032	*
Benzofuran[(1)]	Not quantified	Not quantified	
1,3-Butadiene	79.5±7.4	64.8±2.2	*
Cadmium	0.00691±0.00134	0.145±0.008	*
Carbazole[(2)]	0.065	0.0007	*
Catechol	63.9±7.3	170±15	*
Chromium[(5)]	0.01287±0.00693	0.01287±0.00693	

Chrysene	0.0262±0.0014	0.0388±0.0023	*
Dibenz[*a,h*]antharacene	0.00141±0.00019	0.00115±0.00021	*
Dibenzo[*a,i*]pyrene	0.000356±0.000192	0.000987±0.000145	*
Dibenzo[*a,e]*pyrene	0.000339±0.000183	0.000531±0.000198	
Diethylnitrosamine[3]	<0.0035	<0.0035	
Dimethylnitrosamine[3]	0.05213	0.05918	
Formaldehyde	25.1±2.7	200±28	*
Indeno[*1,2,3-cd*]pyrene	0.0036±0.00048	0.00458±0.00089	****
Isoprene	74±6.5	286±15	****
Lead[5]	0.00833±0.00468	0.0211±0.0011	*
Mercury[4]	0.00351±0.00031	0.00535±0.00052	*
5-Methylchrysene	<0.000035	<0.000035	
Naphthalene	2.07±0.29	2.907±0.159	****
Nickel[5]	0.01404±0.00757	0.01404±0.00757	
Pyridine	34.6±4.3	31.1±1.7	
Quinoline	1.06±0.26	1.31±0.08	****

Data from Moir *et al.* (2007) under standard smoking conditions, unless otherwise noted.
[1] Detected but not quantified by Gieringer *et al*. (2004).
[2] Data for marijuana smoke from Lee *et al*. (1976) converted to μg/cigarette by OEHHA; data for tobacco smoke from Warner *et al*. (1989).
[3] Data from Hoffman *et al.* (1975) converted to μg/cigarette by OEHHA.
[4] Data from the extreme smoking conditions reported in Moir *et al.* (2007).
[5] Mean and standard deviation of the range presented in Moir *et al.* (2007), calculated by OEHHA.

In studies comparing the carcinogenicity of dermally applied marijuana and tobacco smoke condensates in the mouse, both smoke condensates induced squamous cell tumors of the skin (Hoffman *et al*., 1975). These authors also found that marijuana and tobacco smoke condensates both exhibited tumor promoting activity in a mouse skin tumor initiation-promotion assay. In studies comparing the mutagenicity of marijuana and tobacco smoke condensates in *Salmonella*, marijuana smoke condensates were found to be equivalently (Busch *et al*., 1979) or more (Sparacino *et al*., 1990) mutagenic than tobacco smoke condensates. Tobacco smoke is considered to be a systemic human mutagen, having been shown to be genotoxic in nearly all systems tested, and to be mutagenic in many of the organs and tissues in which tobacco smoke-induced cancers occur, including the oral cavity, nasal tissues, esophagus, lung, and pancreas (DeMarini, 2004). Given the similar results from the studies of marijuana and tobacco smoke in the *Salmonella* assay, the similarity in chemical composition between marijuana and tobacco smoke, and the presence of numerous genotoxic constituents in both (e.g., 4-aminobiphenyl, benz[a]anthracene, chrysene, benzo[b]fluoranthene, benzo[a]pyrene, dibenz[a,i]pyrene, dibenz[a,e]pyrene, cadmium, nickel, lead, formaldehyde, and styrene, See Section 3.3.2 Genotoxicity), it is expected that marijuana smoke would also be a systemic mutagen.

Similarities in the ability to induce histopathologic changes have been reported for marijuana and tobacco smoke, as discussed in Section 3.3.6 (Effects on Other Systems). Specifically, marijuana smoke induced similar histopathologic changes in human (Gong *et al*., 1987; Fligiel *et al*., 1997; Barsky *et al.*, 1998) and dog (Roy *et al*., 1976) lungs as tobacco smoke. In mouse

skin, marijuana and tobacco smoke condensate induced similar metaplastic changes in sebaceous glands (Cottrell *et al*., 1973).

4. MECHANISMS

Marijuana smoke is a complex mixture of thousands of chemical constituents, at least 33 of which have been identified individually as carcinogens. Given the complexity of the mixture, it is difficult to determine the mechanisms by which marijuana smoke may induce cancer. Based on the available studies on marijuana smoke and what is known about individual smoke constituents, it is possible that several mechanisms are operative. These possibilities include genotoxicity, alterations in endocrine function, alterations in multiple cell signaling pathways, and immune suppression. The similarity in the composition and observed effects of marijuana and tobacco smoke also suggests that these two complex mixtures likely share several common mechanisms of action.

Data supporting genotoxic mechanisms for marijuana smoke include findings that marijuana smoke induces mutations in *Salmonella* (Busch *et al.,* 1979; Sparacino *et al.,* 1990), and several small cytogenetic studies in humans suggesting that exposure to marijuana smoke may be associated with increased mutations (Ammenheuser *et al.,* 1998) and chromosomal abnormalities (Chiesara, 1983, Stenchever *et al*., 1974; Kumar and Kunwar, 1971; Li and Lin, 1998). While the data on the genotoxicity of marijuana smoke *per se* is limited, many individual smoke constituents have been shown to form DNA adducts, induce gene mutations, and damage chromosomes. Genotoxic constituents include 4-aminobiphenyl (Saletta *et al.,* 2007), benz[*a*]anthracene, chrysene, benzo[*b*]fluoranthene (ATSDR, 1995), benzo[*a*]pyrene (Straif *et al*., 2005), dibenz[*a,i*]pyrene, dibenz[*a,e*]pyrene (IARC, 1983), cadmium (IARC, 1997), nickel (ATSDR, 2005), lead (IARC, 2006), formaldehyde (Cogliano *et al*., 2004), and styrene (IARC, 1994). Benzo[*a*]pyrene, a component of both marijuana and tobacco smoke, induces p53 mutations identical to those induced by tobacco smoke, suggesting the possibility that they are caused by benzo[*a*]pyrene (Feng *et al*., 2006; Phillips *et al*., 1990). It is reasonable to assume that the benzo[*a*]pyrene in marijuana smoke could induce the same mutations.

Data supporting mechanisms involving alterations in endocrine function include findings for a number of different hormonal pathways. For example, marijuana smoke condensate has been shown to have estrogenic effects, including findings that it can activate the ER (Lee *et al*., 2006) and induce expression of the estrogen responsive gene IGFBP-1 (Lee *et al*., 2006). Two individual chemicals present in marijuana smoke, 4-methylphenol and 4-ethylphenol, have also been shown to bind with the ER and elicit ER-mediated estrogenic responses (Terasaka *et al.,* 2006). Marijuana smoke also has been shown to have anti-estrogenic effects, through its induction of cytochrome P450 1A1 and the resultant increase in E2 metabolism (Lee *et al*., 2005, Roth *et al.,* 2001). Other anti-estrogenic effects include the inhibition of aromatase, an enzyme that converts testosterone to E2 by marijuana smoke condensate (Lee *et al*., 2005). Aromatase inhibition results in formation of less E2 by this pathway, and lower levels of E2 overall. Other studies indicate that marijuana smoke condensate has anti-androgenic effects, inhibiting binding of DHT to the AR (Purohit *et al*., 1980). Δ^9-THC also inhibited the binding of DHT to the AR (Purohit *et al*., 1980). Δ^9-THC, CBD and CBN also were shown to inhibit cytochrome P450c17 in the testes, one of the enzymes necessary for sex steroid synthesis (Watanabe *et al*., 2005). Additional studies with Δ^9-THC provide evidence for disruption of the HPG axis mediated via

CB1-R in the hypothalamus (Steiner and Wotjak 2008), and CB1-R and CB2-R in the testes, ovaries and uterus (Wang *et al*., 2006). These provide evidence that Δ^9-THC inhibits the release of FSH, LH, prolaction, growth hormone, thyroid-stimulating hormone , and corticotropin (Scorticati *et al*., 2004).

Data supporting mechanisms involving alterations in cell signaling pathways include observations in cancer cell lines that Δ^9-THC and other cannabinoids activate protein kinases, resulting in increased cell proliferation of cancer cell lines (Hart *et al*., 2004). More specifically, protein kinase activation occurs as a result of cannabinoid binding to GPCRs (CB1-R and CB2-R). CB1-R activates calcium and potassium ion channels, inhibits adenyl cyclase, and activates the extracellular signal-regulated kinases/microtubule-associated protein kinase (ERK/MAPK) pathways, thereby affecting cell cycle control. CB2-R regulates the activity of several signal transduction pathways that operate through adenyl cyclase/cyclic adenosine monophosphate and the ERK/MAPK pathways (Parolaro *et al*., 2008).

Data supporting immunosuppressive mechanisms for marijuana smoke include findings from one study each that marijuana smoke suppresses the immune response to bacterial challenge in rats (Huber *et al*., 1980) and rat alveolar macrophages *in vitro* (Huber *et al*., 1975), that tumoricidal and bactericidal activities of alveolar macrophages obtained from marijuana smokers were reduced, compared to non-smokers (Baldwin *et al*., 1997), and that smoking marijuana was associated with a more rapid progression of HIV infection to AIDS (Tindall *et al*., 1988). Numerous studies with Δ^9-THC and other cannabinoids present in marijuana smoke (see Section 3.3.5 Effects on the Immune System) demonstrate their ability to induce a variety of immunosuppressive effects. These include suppression of host resistance to microbial infection, suppression of macrophage function, suppression of NK and T cell cytolytic activity, suppression of cytokine production by macrophages and T cells, and decreased antigen presentation by dendritic cells (Cabral and Staab, 2005; Kaminski, 1994, Massi *et al*., 2006). These immunosuppressive effects could lead to an increased risk of cancer by reducing immunosurveillance capacity against neoplastic cells.

5. SUMMARY AND CONCLUSIONS

5.1 Summary of Evidence

There is evidence from some epidemiological studies of marijuana smoke suggestive of increased cancer risk from both direct and parental marijuana smoking. However, this evidence is limited by potential biases and small numbers of studies for most types of cancer.

For direct marijuana smoking, statistically significant associations were reported for head and neck cancer, lung cancer, bladder cancer, brain cancer, and testicular cancer. The strongest evidence of a causal association is for head and neck cancer, for which two of three studies reported statistically significant associations. One of the two significant studies may have been biased, however, by under-reporting of marijuana smoking due to lack of privacy during interviews and use of blood donors as controls (if marijuana use was inversely associated with blood donation). The other significant study found the association to be much stronger among cases with tumor tissue that was HPV-16-positive than HPV-16-negative, and suggested that

there may have been an interaction between marijuana smoke and infection with the virus (HPV is a known cause of head and neck cancers). The study's use of audio computer-assisted self interviews may have reduced under-reporting of marijuana smoking. The third study found no association with "ever" marijuana smoking, but found a modest, nonsignificant association in the highest category of cumulative exposure (8+ joint-years). The evidence was less strong but suggestive for lung cancer (one of three studies conducted in populations that did not mix marijuana and tobacco reported a significant association), bladder cancer (one of two studies reported a significant association), and brain and testicular cancers (the single studies reported significant associations).

A limitation common to these epidemiologic studies was potential bias from under-reporting of marijuana smoking due to its illegality and social stigma, combined with lack of privacy during oral interviews, subject desire to please interviewers, and possibly different degrees of under-reporting between cancer patients and healthy controls. Another limitation of several studies was geographic location where marijuana and tobacco are commonly mixed (e.g., three of six lung cancer studies and one of two bladder cancer studies were conducted in northern Africa, and two of four oral cancer studies were conducted in England), thus, the results of those studies may have been confounded by tobacco smoke.

Among the epidemiological studies that reported results for parental marijuana smoking and childhood cancer, seven of eight found statistically significant associations. Maternal and paternal marijuana smoking were implicated, depending on the type of cancer. For marijuana smoking by mothers, the categories of cancer that were significantly associated were acute myeloid leukemia, neuroblastoma, brain astrocytoma, and rhabdomyosarcoma. For marijuana smoking by fathers, the categories of cancer that were significantly associated were leukemia, infant leukemia, acute lymphoblastic leukemia, and rhabdomyosarcoma. All of the studies were conducted under the auspices of the NCI-funded Children's Oncology Group or its predecessors and shared methodological strengths and limitations. The associations may have been causal, but the wide variety of types of cancer that were associated and the similarity of the methods of the studies suggest that the associations may have been due to methodological limitations. Limitations that were specific to studies with results for fathers' marijuana smoking were low participation by fathers and use of proxy interviews (mothers often acted as surrogates for fathers). Bias could have occurred if the participation of the fathers or the percent of proxy interviews differed between case and control fathers. The problem with low participation is that participants may be different than non-participants in a way (e.g., marijuana use) that affects the results. The problem with proxy interviews is that mothers may be less knowledgeable and more or less forthcoming about the fathers' marijuana use than the fathers themselves.

In animal studies, increases in squamous cell papilloma of the skin were reported in Swiss mice exposed dermally to marijuana smoke condensate. Malignant mesenchimatous tumors were reported following six subcutaneous injections of marijuana smoke condensate to newborn CD rats. In a marijuana smoke inhalation study in female Wistar rats, benign tumors of the ovary (serous cytoma and follicular cysts) and benign and malignant tumors of the uterus (adenofibroma, adenosarcoma, and telengiectatic cyst and polyps) were observed. Marijuana smoke condensate also exhibited tumor promoting activity in a mouse skin tumor initiation-

promotion assay, increasing the incidence of squamous cell papillomas, squamous cell carcinomas, and fibrosarcomas in Swiss mice initiated with 7, 12-dimethylebenz(a)anthracene.

Evidence indicating that marijuana smoke is genotoxic includes findings that marijuana smoke induces mutations in *Salmonella,* and several small cytogenetic studies in humans suggesting that exposure to marijuana smoke may be associated with increased mutations and chromosomal abnormalities. While the data on the genotoxicity of marijuana smoke *per se* is limited, many individual smoke constituents have been shown to form DNA adducts, induce gene mutations, and damage chromosomes. These include 4-aminobiphenyl, benz[*a*]anthracene, chrysene, benzo[*b*]fluoranthene, benzo[*a*]pyrene, dibenz[*a,i*]pyrene, dibenz[*a,e*]pyrene, cadmium, nickel, lead, formaldehyde, and styrene.

Evidence indicating that marijuana smoke alters endocrine function includes findings for a number of different hormonal pathways. Marijuana smoke condensate has been shown to have estrogenic effects, including findings that it can activate the ER. Marijuana smoke also has been shown to have anti-estrogenic effects, through the induction of cytochrome P450 1A1 and the resultant increase in E2 metabolism and through the inhibition of aromatase, an enzyme that converts testosterone to E2. Other studies indicate that marijuana smoke condensate has anti-androgenic effects, inhibiting binding of DHT to the AR. Studies of Δ^9-THC and other cannabinoids provide evidence for disruption of the HPG axis, including evidence that Δ^9-THC inhibits the release of FSH, LH, prolactin, growth hormone, thyroid-stimulating hormone, and corticotrophin. These alterations in endocrine function can affect the growth of hormone responsive tissues, and might increase the risk of certain cancers (e.g., testes, ovary, uterus, and breast).

Evidence indicating that marijuana smoke alters cell signaling pathways involved in cell cycle control includes observations in cancer cell lines that Δ^9-THC and other cannabinoids can activate protein kinases, and this may result in increased cell proliferation.

There is evidence that marijuana smoke suppresses the innate and adaptive immune response. The bactericidal activity of rat alveolar macrophages was reduced by marijuana smoke *in vivo* and *in vitro*. Tumoricidal and bactericidal activities were reduced in alveolar macrophages from marijuana smokers, compared to non-smokers. In addition, in one study smoking marijuana was associated with a more rapid progression of HIV infection to AIDS. Δ^9-THC and other cannabinoids present in marijuana smoke have also been shown to suppress host resistance to microbial infection, macrophage function, NK and T cell cytolytic activity, cytokine production by macrophages and T cells, and to decrease antigen presentation by dendritic cells. These immunosuppressive effects could lead to an increased risk of cancer by reducing immunosurveillance capacity against neoplastic cells.

Histopathological changes observed in marijuana smokers' bronchial epithelial tissues include cellular disorganization, squamous metaplasia, and hyperplasia of basal and goblet cells. In addition, a number of abnormal molecular markers associated with pre-neoplastic or neoplastic changes have been observed in bronchial biopsies obtained from marijuana smokers. In animal studies of marijuana smoke, dose-related inflammatory and proliferative lesions of the respiratory system have been observed in rats, metaplasia of the sebaceous glands in mice,

bronchiolitis with macrophage infiltration in the terminal air passages of dogs, and alveolar epithelial hyperplasia in monkeys.

Marijuana smoke and tobacco smoke are both complex mixtures of thousands of chemicals. Both mixtures share many characteristics with regard to chemical composition and toxicological activity. Tobacco smoke is a Proposition 65 carcinogen, and at least 33 individual constituents present in both marijuana smoke and tobacco smoke are Proposition 65 carcinogens. The similarity in the composition and observed effects of marijuana and tobacco smoke suggests that these two complex mixtures likely share several common mechanisms of action.

5.2 Conclusion

There is evidence from some epidemiological studies of marijuana smoke suggestive of increased cancer risk from both direct and parental marijuana smoking. However, this evidence is limited by validity issues and small numbers of studies for most types of cancer. Direct marijuana smoking has been statistically significantly associated with cancer of the lung, head and neck, bladder, brain, and testis. Parental marijuana smoking before or during gestation has been statistically significantly associated with childhood cancer. Childhood cancers that have been associated with maternal marijuana smoking are acute myeloid leukemia, neuroblastoma, brain astrocytoma, and rhabdomyosarcoma. Childhood cancers that have been associated with paternal marijuana smoking are leukemia, infant leukemia, acute lymphoblastic leukemia, and rhabdomyosarcoma.

In animal studies, increases in squamous cell papilloma of the skin were reported in mice exposed dermally to marijuana smoke condensate. Malignant mesenchimatous tumors were reported following six subcutaneous injections of marijuana smoke condensate to newborn rats. In a marijuana smoke inhalation study in female rats, benign tumors of the ovary and benign and malignant tumors of the uterus were observed.

There is evidence that marijuana smoke is genotoxic, immunosuppressive, and can alter endocrine function. Studies of Δ^9-THC and other cannabinoids provide evidence for alterations of multiple cell signaling pathways, in endocrine function, and suppression of the innate and adaptive immune response. Prolonged exposures to marijuana smoke in animals and humans cause proliferative and inflammatory lesions in the lung.

Marijuana smoke and tobacco smoke share many characteristics with regard to chemical composition and toxicological activity. Tobacco smoke is a Proposition 65 carcinogen, and at least 33 individual constituents present in both marijuana smoke and tobacco smoke are Proposition 65 carcinogens.

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7. APPENDIX TABLES

7.1 Epidemiological studies reporting results for *direct* marijuana smoking

7.1.1 Appendix Table 1 – Lung Cancer

Appendix Table 1	Lung Cancer					
Study Parameter	**Aldington 2008a**	**Hashibe 2006**	**Hsairi 1993**	**Sasco 2002**	**Sidney 1997**	**Voirin 2006**
Study Design	Case-control	Case-control	Case-control	Case-control	Cohort	Case-control.
Case Definition[#]	Lung cancer	Trachea, bronchus, and lung (ICD-O-2 C33.9-C34)	Lung cancer	Lung cancer	Lung cancer (ICD-9, codes not stated)	Lung cancer
Purpose of Data Collection	To determine if lung and head and neck cancers are associated with marijuana use.	To determine if marijuana use is associated with lung & upper aero-digestive cancer.	To determine whether smoking marijuana increases risk of lung cancer.	To evaluate established and suspected risk factors for lung cancer.	To test hypothesis that marijuana use is associated with tobacco-related cancers.	To investigate the effect of marijuana use on the etiology of lung cancer.
Study Population	Location: New Zealand. Cases: population-based cancer registry, mix of historical and new diagnoses 2001-2005, male & female, age <56. Controls: randomly selected from electoral rolls within age strata to be similar in age to cases. Same controls used in head & neck cancer analysis.	Location: Los Angeles, U.S. Cases: population-based cancer registry, new diagnoses 1999-2004, male and female, age 18-62. Controls: randomly selected from general population, matched on neighborhood, age, and gender. Analysis dropped matching and included controls for other cancers.	Location: Tunis, Tunisia. Cases: one hospital, male and female, new diagnoses 1988-1989, age range not stated. Controls: general population (random or convenience selection not stated), matched to individual cases on tobacco cigarette smoking, age, and gender.	Location: Casablanca, Morocco. Cases: one hospital, new diagnoses 1996-1998, male and female, age 35-82. Controls: non-cancer patients at same hospital (random or convenience selection not stated), matched to individual cases on age, gender, and place of residence.	Location: San Francisco and Oakland, U.S. Cohort: male and female health plan members, age 15-49, who volunteered to complete a questionnaire in 1979-1985. Cases were new diagnoses 1979-1993. Maximum case age was 63.	Location: Tunis, Tunisia. Cases: two hospitals, new diagnoses 2000-2003, male only, age range not stated. Controls: patients at same two hospitals as cases plus a third hospital (random or convenience selection not stated). No matching to individual cases.

Appendix Table 1	Lung Cancer					
Study Parameter	**Aldington 2008a**	**Hashibe 2006**	**Hsairi 1993**	**Sasco 2002**	**Sidney 1997**	**Voirin 2006**
Participation	Cases: unstated number occurred, 102 eligible and contacted, 79 (77%) of contacted interviewed. Controls: unstated number eligible, 493 contacted, 324 (66%) of contacted interviewed.	Cases: 1,567^ occurred, 611 (39%) interviewed. Controls: 1,444^ eligible, 1,040 (72%) interviewed.	Cases: 110 occurred, 110 (100%) interviewed. Controls: unstated eligible, 110 interviewed.	Cases: unstated number occurred, 118 interviewed. Controls: unstated number eligible, 235 interviewed. Participation ~90% for cases and controls combined.	Unstated number eligible, 64,855 interviewed. Subcohorts: Ever ms: 26,733 (22 cases) Never ms: 38,122 (75) cases	Cases: Unstated number occurred, 149 interviewed. Controls: unstated number eligible, 188 interviewed.
Questionnaire Administration Methods	Oral interviews, face-to-face, usually at the subjects' homes.	Oral interviews, face-to-face, locations not stated.	Oral interviews, face-to-face or phone not stated, locations not stated.	Oral interviews, face-to-face, at hospital.	Self-administered written questions and answers, at health care facilities.	Methods not stated but probably oral interviews at hospitals.
Privacy of Oral Answers	Not stated	Not stated	Not stated	Not stated	Not applicable	Not stated
Assurance of Data Confidentiality*	Yes	Yes	Not stated	Not stated.	Yes	Yes

Appendix Table 1	Lung Cancer					
Study Parameter	**Aldington 2008a**	**Hashibe 2006**	**Hsairi 1993**	**Sasco 2002**	**Sidney 1997**	**Voirin 2006**
Results (% cases/controls exposed if case-control study, rate ratio estimate, 95% confidence interval, and adjustments for potentially confounding variables)	*Ever ms*: 27%/12% OR=1.2 (0.5-2.6) *Cumulative ms (categories):* *>0-<1.39 jy:* OR=0.3 (0.1-1.7) *1.39-10.5 jy:* OR=0.5 (0.1-2.0) *>10.5 jy:* OR=5.7 (1.5-21.6) *Cumulative ms (continuous) 1 jy:* OR=1.08 (1.02-1.15) Adjusted for tobacco cigarette smoking, age, gender, ethnicity, family history of lung cancer, and health district.	<u>All subjects</u> *Ever ms:* 51%/54%[+] *Cumulative ms:* *>0-<1 jy:* OR=0.6 (0.5-0.9) *1-<10 jy:* OR=0.7 (0.5-1.1) *10-<30 jy:* OR=0.6 (0.3-1.0) *30-<60 jy:* OR=0.8 (0.4-1.7) *60+ jy:* OR=0.6 (0.3-1.2) *Cumulative ms (continuous) 50 jy:* OR=1.0 (0.7-1.4) Adjusted for tobacco cigarette smoking, alcohol, age, gender, race, and education. <u>Never tobacco cigarettes</u> *Ever ms:* 17%/40%[+] *Cumulative ms:*[$] *>0-<1 jy:* OR=0.4 (0.2-0.9) *1+ jy:* OR=1.1 (0.5-2.6)	*Habitual marijuana smoker:* 12%/1% OR=8.2 (1.3-15.5) Adjusted for tobacco cigarette smoking, age, and gender.	*Use of hashish or kiff:* 13%/5% OR=2.0 (0.6-6.3) Adjusted for tobacco cigarette smoking, age, gender, and place of residence.	*Ever ms (7+ joints lifetime):* <u>Men</u> RR=0.9 (0.5-1.7) <u>Women</u> RR=1.1 (0.5-2.6) *Frequency of ms (categories of times per month/week):* "Not associated." *Length of ms (continuous)*: "Not associated." Adjusted for tobacco cigarette smoking, alcohol, age, race, and education.	*Ever ms:* 20%/6% OR=4.1 (1.9-9.0) *Frequency of ms:* *>0-<1 joints/day*: OR=4.0 (1.6-10.2) *1+ joints/day:* OR=4.2 (1.2-15.0) *Length of ms:* *>0-<5 years:* OR=4.7 (1.7-13.2) *5+ years:* OR=3.4 (1.1-10.1) Adjusted for tobacco cigarette smoking, age, and occupational exposures.

Appendix Table 1	Lung Cancer					
Study Parameter	**Aldington 2008a**	**Hashibe 2006**	**Hsairi 1993**	**Sasco 2002**	**Sidney 1997**	**Voirin 2006**
Validity Issues Specific to This Study	*Under-reporting of marijuana smoking:* the oral interviews in subjects' homes with possible lack of privacy may have led to under-reporting of ms. Differential under-reporting of ms between cases and controls could have biased the rate ratio estimates. *Selection bias:* cases were a mixture of historical and new cancer patients, but the percent that were historical was not stated. Historical patients who survived until interview may have been different than patients who died with regard to ms history.	*Under-reporting of marijuana smoking:* the face-to-face interviews in subjects' homes with possible lack of privacy may have led to under-reporting of ms. Differential under-reporting of ms between cases and controls could have biased the rate ratio estimates. *Selection bias:* case participation was low at 39% while control participation was higher at 72%. The difference in participation between cases and controls could have caused bias if participants and nonparticipants were different with regard to ms history (noted by investigators).	*Under-reporting of marijuana smoking:* only one of 110 controls reported habitual ms, a low number that may reflect lack of interview privacy or lack of assurance of data confidentiality. *Confounding bias:* tobacco and marijuana are often mixed prior to smoking in Tunisia according to Voirin 2006 (not mentioned in Hsairi 1993). *Selection bias:* the method of selecting controls from the greater Tunis area was not described, thus the potential for selection bias cannot be assessed.	*Under-reporting of marijuana smoking:* possible lack of privacy and assurance of data confidentiality may have led to under-reporting. Differential under-reporting between cases and controls can bias rate ratio estimates (noted by investigators). *Confounding bias:* tobacco and marijuana are often mixed prior to smoking in northern Africa. *Selection bias:* case- and control-specific rates of participation were not stated. Different rates of participation could cause bias if participants and nonparticipants differed in their ms history.	*Short time since first ms exposure: w*idespread marijuana smoking began in the U.S. in approximately 1969 and study follow-up ended in 1993 (25 years later), possibly not enough time for an epidemiologically detectable number of cancers caused by ms to occur. *Selection bias:* participation rates were not stated and could have been low, creating bias if participants and nonparticipants were different with regard to ms history. *Incomplete ms data:* no ms data after questionnaire administration at beginning of follow-up (noted by investigators).	*Under-reporting of marijuana smoking:* none of the 337 subjects reported that they were current marijuana smokers, which seems unlikely and which suggests under-reporting of ms. *Confounding bias:* tobacco was "usually" mixed into marijuana before smoking according to the authors. *Selection bias:* participation rates were not stated and could have been low, creating potential for bias if participants and nonparticipants were different with regard to ms history.

[#]Case definition as described in article. ICD=International Classification of Diseases. O=Oncology.
*Assurance of data confidentiality was assumed if the article stated that the investigators obtained approval from an institutional review board or informed consent from the subjects.
^Estimated by OEHHA based on numbers in the Hashibe *et al.* (2006) article.
[+]Adjusted odds ratios for "ever" marijuana smoking were not presented in the Hashibe *et al.* (2006) article and were not calculable from data in article.
[$]Adjusted for alcohol, age, gender, race/ethnicity, and education.

7.1.2 Appendix Table 2 – Oral Cancer

Appendix Table 2	Oral Cancer			
Study Parameter	**Hashibe 2006**	**Llewellyn 2004a**	**Llewellyn 2004b**	**Rosenblatt 2004**
Study Design	Case-control	Case-control	Case-control	Case-control (2 previous data sets combined)
Case Definition[#]	Squamous cell carcinoma of the tongue, gums, floor of mouth, palate, other and unspecified mouth, salivary glands, and tonsils (ICD-O-2 C01.9-C09)	Squamous cell carcinomas of the lip, tongue, gums, floor of mouth, palate, other and unspecified mouth, tonsils, and oropharynx (ICD-10 C00-C06, C09-C10)	Squamous cell carcinomas of the lip, tongue, gums, floor of mouth, palate, other and unspecified mouth, tonsils, and oropharynx (ICD-10 C00-C06, C09-C10)	Squamous cell carcinoma of the tongue, gum, floor of mouth, oropharynx, and other intraoral sites." (ICD-O-1 141, 143-146).
Purpose of Data Collection	To determine whether marijuana use is associated with lung & upper aerodigestive tract cancers.	To evaluate the major risk factors for oral cancer in young people.	To identify the risk factors for oral cancer in patients age 45 and younger.	To determine whether HPV/HSV infections and sexual history are related to risk of oral cancer.
Population	Location: Los Angeles County, U.S. Cases: population-based cancer registry, new diagnoses 1999-2004, male and female, age 18-62. Controls: randomly selected from general population, matched to individual cases on neighborhood, age, and gender. Analysis dropped matching and included controls for other cancers.	Location: Southern England Cases: 14 hospitals, historical diagnoses 1990-1997, male and female, age <46. Controls: practices of cases' general physicians or nearby physicians (random or convenience selection not stated), matched on age, sex, and area of residence.	Location: Southern England Cases: 14 hospitals, new diagnoses 1999-2001, male and female, age <46. Controls: practices of cases' general physicians or nearby physicians (random or convenience selection not stated), matched on age, sex, and area of residence.	Location: Three counties in western Washington State Cases: Dataset 1 was all historical or a mix of historical and new diagnoses 1985-1989, age <66, male. Dataset 2 was new diagnoses 1990-1995, male & female, age 18-65. Controls: random digit dialing of general population, matched on age (and sex in dataset 2).
Participation	Cases: 777^ occurred, 303 (54%) interviewed. Controls: 1,444^ eligible, 1,040 (72%) interviewed.	Cases: 404 occurred, 116 (29%) interviewed Controls: unstated eligible, 207 interviewed.	Cases: 70 occurred, 53 (80%) interviewed Controls: unstated eligible, 91 interviewed.	Cases: 703 occurred, 407 (58%) interviewed Controls: 939 eligible, 615 (65%) interviewed

Appendix Table 2	Oral Cancer			
Study Parameter	**Hashibe 2006**	**Llewellyn 2004a**	**Llewellyn 2004b**	**Rosenblatt 2004**
Questionnaire Administration Methods	Oral interviews, face-to-face, locations not stated.	Self-administered written questionnaires and answers, at home for cases and a mix of at home and doctors' offices for controls.	Self-administered written questionnaires and answers, at home for cases and a mix of at home and doctors' offices for controls.	Oral interviews, face-to-face, usually at the subjects' homes.
Privacy of Oral Answers	Not stated	Not applicable	Not applicable	Not stated
Assurance of Data Confidentiality*	Yes	Yes	Yes	Yes

Appendix Table 2	Oral Cancer			
Study Parameter	**Hashibe 2006**	**Llewellyn 2004a**	**Llewellyn 2004b**	**Rosenblatt 2004**
Results (% cases/controls exposed if case-control study, rate ratio estimate, 95% confidence interval, and adjustments for potentially confounding variables)	<u>All subjects</u> *Ever ms:* 62%/54%[+] *Cumulative ms:* *>0-<1 jy:* OR=1.1 (0.7-1.5) *1-<10 jy:* OR=1.1 (0.7-1.7) *10-<30 jy:*OR=0.9 (0.5-1.7) *30-<60 jy:*OR=0.9 (0.4-2.0) *60+ jy:* OR=1.1 (0.6-2.1) *Cumulative ms (continuous) 50 jy:* OR=1.1 (0.8-1.5) Adjusted for tobacco cigarette smoking, alcohol, age, gender, race/ethnicity, and education. <u>Never tobacco cigarettes</u> *Ever ms:* 44/ 40%[+] *Cumulative ms:* *>0-<1 jy:* OR=0.9 (0.5-1.6) *1-<10 jy:* OR=1.5 (0.7-3.5) *10+ jy:* OR=1.8 (0.7-4.7) Adjusted for alcohol, age, gender, race/ethnicity, and education.	*"Cannabis smoker":* 9%/ 15% OR=1.0 (0.5-2.2) Adjusted for tobacco cigarette smoking, alcohol consumption, age, gender, and ethnicity.	*"Cannabis smoker":* 13%/10% OR=0.3 (0.1-1.8) Adjusted for tobacco cigarette smoking, alcohol consumption, age, gender, and ethnicity.	*Ever ms:* 26%/24% OR=0.9 (0.6-1.3) *Years of use* *>0-<1 y:* OR=0.8 (0.4-1.2) *1-<2 y:* OR=0.2 (0.1-0.7) *2-<6 y:* OR=1.3 (0.6-2.6) *6-<16 y:* OR=0.7 (0.4-1.4) *16+ y:* OR=1.2 (0.6-2.2) *Frequency of use* *<1 time/year:* OR=1.0 (0.6-1.8) *<1 times/week:* OR=0.8 (0.5-1.4) *1-<8 times/week:* OR=0.8 (0.4-1.6) *8+ times/week:* OR=0.5 (0.2-1.6) Adjusted for tobacco cigarette smoking, alcohol consumption, gender, education, birth year, and data set.

Appendix Table 2	Oral Cancer			
Study Parameter	**Hashibe 2006**	**Llewellyn 2004a**	**Llewellyn 2004b**	**Rosenblatt 2004**
Validity Issues Specific to This Study	*Under-reporting of marijuana smoking:* the face-to-face interviews in subjects' homes with possible lack of privacy may have led to under-reporting of ms. Differential under-reporting of ms between cases and controls could have biased the rate ratio estimates. *Selection bias:* oral cancer case participation was somewhat low at 54%, while control participation was higher at 72%. The difference in participation between cases and controls could have caused bias if participants and nonparticipants were different with regard to ms history (noted by investigators).	*Selection bias from low case participation.* The participation rate of oral cancer cases was 29%. Low participation could have caused bias if those who participated were different from non-participants with respect to ms history (noted by investigators). *Different methods for cases and controls.* While all questionnaires for cases were mailed, control questionnaires were administered via a mixture of mail and at doctors' offices. *Non-random selection of controls.* Controls were recruited by the cases' general practitioners from among patients without cancer. No detail provided on selection methods. *"Cannabis smoker" not defined.* Whether past, present, or ever marijuana smoking was not stated.	*Different methods for cases and controls.* While the case questionnaires were administered via mail, control questionnaires were administered via a mixture of mail and doctors' offices. *Non-random selection of controls.* Controls were recruited by the cases' general practitioners from among patients without cancer. No detail provided on selection methods. *"Cannabis smoker" not defined.* Whether past, present, or ever marijuana smoking not stated.	*Under-reporting of marijuana smoking:* the face-to-face interviews in subjects' homes with possible lack of privacy may have led to under-reporting of ms. Differential under-reporting of ms between cases and controls could have biased the rate ratio estimates. *Selection bias.* One of the two datasets (Maden 1992) used in the analysis used solely historical diagnoses or a mixture of historical and new diagnoses (method not clearly stated), resulting in 24% of cases being deceased by the time of interview, and a low overall participation rate of 50% in that dataset. The surviving and participating cases may have been different than the non-participating and deceased cases with regard to ms history (noted by investigators).

[#]Case definition as described in article. ICD=International Classification of Diseases. O=Oncology.
[@]Hypothesis testing or generating for marijuana smoke.

*Assurance of data confidentiality was assumed if the article stated that the investigators obtained approval from an institutional review board or informed consent from the subjects.
^Estimated by OEHHA based on numbers in the Hashibe *et al.* (2006) article.
[+]Adjusted odds ratios for "ever" marijuana smoking were not presented in the Hashibe *et al.* (2006) article and were not calculable from data in article.

7.1.3 Appendix Table 3 – Head and Neck, Pharyngeal, and Esophageal Cancers

Appendix Table 3	Head and Neck Cancer			Pharyngeal Cancer	Esophageal Cancer
Study Parameter	**Aldington 2008b**	**Zhang 1999 & 2000**	**Gillison 2008**	**Hashibe 2006**	**Hashibe 2006**
Study Design	Case-control	Case-control	Case-control	Case-control	Case-control
Case Definition[#]	Cancers of lip, tongue, floor of mouth, palate, mouth, tonsil, oropharynx, nasopharynx, hypopharyx, pharynx, nasal cavities, larynx, and head and neck unspecified) ("ICD" C00-C02, C04-C06, C09-C11, C13-C14, C30, C32)	Cancers of lip, tongue, salivary glands, gum, floor of mouth, other parts of mouth, oropharynx, nasopharynx, hypopharynx, other oral cavity, esophagus, nasal cavities, and larynx (ICD-9 140-150, 160-161).	Squamous cell carcinomas of oral cavity, paranasal sinus, pharynx, larynx, and unknown primary of head and neck.	Cancers of oropharynx, nasopharynx, hypopharynx, nasal cavity, middle ear, and sinuses (ICD-O-2 C10-C14.0, C30-C31.1)	Cancers of esophagus (except cervical) and junction of esophagus and cardia of stomach (ICD-O-2 C15.1-C16.0)
Purpose of Data Collection	To determine whether lung and head and neck cancers are associated with cannabis smoking.	To determine if there is an association between marijuana use and head and neck cancers.	To compare risk factors for HPV-positive and HPV-negative squamous cell carcinomas of head & neck.	To determine whether marijuana use is associated with lung & upper aerodigestive tract cancers.	To determine whether marijuana use is associated with lung & upper aerodigestive tract cancers.

Appendix Table 3	Head and Neck Cancer			Pharyngeal Cancer	Esophageal Cancer
Study Parameter	**Aldington 2008b**	**Zhang 1999 & 2000**	**Gillison 2008**	**Hashibe 2006**	**Hashibe 2006**
Population	Location: ~half of New Zealand. Cases: population-based cancer registry, mix of historical and new diagnoses 2001-2005, male & female, age <56. Controls: randomly selected from electoral rolls within age strata to create similar age distribution to cases. Same controls used in lung cancer analysis.	Location: New York City, U.S. Cases: one hospital, new diagnoses 1992-1994, male and female, age range not stated. Controls: blood donors at the same hospital, random or convenience selection not stated, 4frequency-matched on age and gender.	Location: Baltimore, U.S. Cases: one otolaryngology clinic, new diagnoses 2000-2006, male and female, age 18+. Controls: randomly selected from non-cancer patients at the same clinic, matched on age and gender.	Location: Los Angeles County, U.S. Cases: population-based cancer registry, new diagnoses 1999-2004, male and female, age 18-62. Controls: randomly selected from general population, matched to individual cases on neighborhood, age, and gender. Analysis dropped matching and included controls for other cancers.	Location: Los Angeles County, U.S. Cases: population-based cancer registry, new diagnoses 1999-2004, male and female, age 18-62. Controls: randomly selected from general population, matched to individual cases on neighborhood, age, and gender. Analysis dropped matching and included controls for other cancers.
Participation	Cases:106 contacted, 75 (71%) eligible and interviewed. Controls: 493 eligible, 324 (66%) interviewed.	Cases: 192 occurred, 173 (92%) interviewed. Controls: 196 selected, 176 (88%) interviewed.	Cases: unstated number occurred, 256 (77%) agreed to participate, of whom 240 had tumor tissue available for HPV-16 status testing. 92 (38% of 240) were HPV-16-positive and interviewed, and 148 were HPV-16-negative and interviewed. Controls: unstated number eligible, 322 (70%) interviewed.	Cases: 222^ occurred, 100 (45%) interviewed. Controls: 1,444^ eligible, 1,040 (72%) interviewed.	Cases: 309^ occurred, 108 (35%) interviewed. Controls: 1,444^ eligible, 1,040 (72%) interviewed.

Appendix Table 3	Head and Neck Cancer			Pharyngeal Cancer	Esophageal Cancer
Study Parameter	**Aldington 2008b**	**Zhang 1999 & 2000**	**Gillison 2008**	**Hashibe 2006**	**Hashibe 2006**
Questionnaire Administration Methods	Oral interviews, face-to-face, usually at the subjects' homes.	Oral interviews, face-to-face, at hospital~	Audio computer-assisted self-interviews.	Oral interviews, face-to-face, locations not stated.	Oral interviews, face-to-face, locations not stated.
Privacy of Oral Answers	Not stated	Not stated	Not applicable	Not stated	Not stated
Assurance of Data Confidentiality*	Yes	Yes	Yes	Yes	Yes

Appendix Table 3	Head and Neck Cancer			Pharyngeal Cancer	Esophageal Cancer
Study Parameter	**Aldington 2008b**	**Zhang 1999 & 2000**	**Gillison 2008**	**Hashibe 2006**	**Hashibe 2006**
Results (% cases/controls exposed if case-control study, rate ratio estimate, 95% confidence interval, and adjustments for potentially confounding variables)	*Ever ms:* 21%/12% OR=1.0 (0.5-2.6) *Cumulative ms:* *>0-<1 jy:* OR=0.4 (0.1-2.2) *1-8.3 jy:* OR=1.2 (0.3-4.2) *>8.3 jy:* OR=1.6 (0.5-5.2) *Cumulative ms (continuous) 1 jy:* OR=1.04 (0.97-1.11) *Cumulative ms to 5 years before diagnosis (continuous variable) one jy:* OR=1.08 (0.77-1.53) Adjusted for tobacco cigarette smoking, age, gender, ethnicity, income, and health district.	<u>All subjects</u> *Ever ms:* 14%/10% OR=2.6 (1.1-6.6) *Frequency (0, 1, 2+ times per day):* p=0.04 for trend *Length (0, 1-5, 6+ yrs):* p=0.03 for trend <u>Age < 55</u> *Ever ms:* 36%/19% OR=3.1 (1.0- 9.7) *Frequency (times per day):* p=0.04 for trend *Length (years):* p=0.08 for trend <u>Age 55 +</u> "No association" <u>ETS[$] exposed</u> *Ever ms:* OR=7.1 (1.5-34.5) <u>Not ETS exposed</u> *Ever ms:* OR=3.5 (0.4-29.4) Adjusted for tobacco, alcohol, age, gender, race, and education.	<u>HPV-16-positive[&]</u> *Former 1+ yr:* 22%/14% OR=2.3 (0.98-5.4) *Current 1+ yr:* 11/3% OR=4.7 (1.3-17) *Cumulative ms:* *1-<4 jy:* OR=2.0 (0.8-5.2) *5-14 jy:* OR=6.0 (1.2-29) *15+ jy:* OR=6.4 (1.6-26) <u>HPV-16-negative</u> *Former 1+ yr:* 13%/11% OR=1.2 (0.5-2.8) *Current 1+ yr:* 7%/4% OR=2.0 (0.6-6.5) *Cumulative ms:* *1-<4 jy:* OR=1.0 (0.4-2.5) *5-14 jy:* OR=1.7 (0.4-7.4) *15+ jy:* OR=2.0 (0.5-7.8) Adjusted for tobacco, alcohol, race, tooth loss & brush, & no. oral sex partners.	<u>All subjects</u> *Ever ms:* 40%/54%[+] *Cumulative ms:* *>0-<1 jy:* OR=0.7 (0.4-1.2) *1-<10 jy:* OR=0.7 (0.3-1.7) *10-<30 jy:* OR=0.4 (0.1-1.5) *30+ jy:* OR=0.6 (0.2-1.6) *Cumulative ms (continuous) 50 jy:* OR=0.8 (0.4-1.5) Adjusted for tobacco cigarette smoking, alcohol, age, gender, race/ethnicity, and education. <u>Never tobacco</u> *Ever ms:* 30%/40%[+] OR=0.9 (0.4-2.1) Adjusted for alcohol, age, gender, race/ethnicity, and education.	<u>All subjects</u> *Ever ms:* 53%/54%[+] *Cumulative ms:* *>0-<1 jy:* OR=0.7 (0.4-1.2) *1-<10 jy:* OR=0.8 (0.4-1.6) *10-<30 jy:* OR=0.4 (0.2-1.3) *30+ jy:* OR=0.5 (0.2-1.3) *Cumulative ms (continuous) 50 jy:* OR=1.1 (0.8-1.5) Adjusted for tobacco cigarette smoking, alcohol, age, gender, race/ethnicity, and education. <u>Never tobacco</u> *Ever ms:* 39%/40%[+] OR=0.8 (0.3-2.1) Adjusted for alcohol, age, gender, race/ethnicity, and education.

Appendix Table 3	Head and Neck Cancer			Pharyngeal Cancer	Esophageal Cancer
Study Parameter	**Aldington 2008b**	**Zhang 1999 & 2000**	**Gillison 2008**	**Hashibe 2006**	**Hashibe 2006**
Validity Issues Specific to This Study	*Under-reporting of marijuana smoking:* the oral interviews in subjects' homes with possible lack of privacy may have led to under-reporting of ms. Differential under-reporting of ms between cases and controls could have biased the rate ratio estimates. *Selection bias:* cases were a mixture of historical and new cancer patients, but the percent of cases that were historical was not stated. Historical patients who survived until interview may have been different than patients who died with regard to ms history.	*Under-reporting of marijuana smoking:* the face-to-face interviews at hospitals with possible lack of privacy may have led to under-reporting of ms. Differential under-reporting of ms between cases and controls could have biased the rate ratio estimates. *Selection bias*: Controls were selected from blood donors at the cancer center who were "possibly less likely" to have been marijuana users (noted by the investigators).	*Under-reporting of marijuana smoking*. The questionnaire method was said to be "audio computer-assisted self-interview (ACASI) technology," but whether the subjects responded orally or had privacy in answering questions was not stated. Differential under-reporting of ms between cases and controls could have biased the rate ratio estimates.	*Under-reporting of marijuana smoking:* the face-to-face interviews in subjects' homes with possible lack of privacy may have led to under-reporting of ms. Differential under-reporting of ms between cases and controls could have biased the rate ratio estimates. *Selection bias:* case participation was low at 45% while control participation was higher at 72%. The difference in participation between cases and controls could have caused bias if participants and nonparticipants were different with regard to ms history (noted by investigators).	*Under-reporting of marijuana smoking:* the face-to-face interviews in subjects' homes with possible lack of privacy may have led to under-reporting of ms. Differential under-reporting of ms between cases and controls could have biased the rate ratio estimates. *Selection bias:* case participation was low at 35% while control participation was higher at 72%. The difference in participation between cases and controls could have caused bias if participants and nonparticipants were different with regard to ms history (noted by investigators).

[#]Case definition as described in article. ICD=International Classification of Diseases. O=Oncology.

*Assurance of data confidentiality was assumed if the article stated that the investigators obtained approval from an institutional review board or informed consent from the subjects.

^Estimated by OEHHA based on numbers in the Hashibe *et al.* (2006) article.

[+]An adjusted odds ratios for "ever" marijuana smoking was not presented for all subjects by Hashibe *et al.* (2006) but was presented for nonsmokers of tobacco cigarettes.
[$]ETS = environmental tobacco smoke.
[&]HPV = human papillomavirus.
[~]The Zhang *et al.* articles (1999 and 2000) did not provide detail about the methods of interviewing, but Dr. Zhang said in personal correspondence that nurse interviewers administered the questionnaires in-person at the hospital.

7.1.4 Appendix Table 4 – Tobacco-Related, Laryngeal, and Bladder Cancers

Appendix Table 4	Tobacco-Related Cancers	Laryngeal Cancer	Bladder Cancer	
Study Parameter	**Sidney 1997**	**Hashibe 2006**	**Bedwani 1997**	**Chacko 2006**
Study Design	Cohort	Case-control	Case-control	Case-control
Case Definition[#]	"Upper aerodigestive" (including esophagus), lung, pancreas, kidney, and bladder cancers (ICD 9, codes not stated)	Laryngeal cancer (ICD-O-2 C32)	Bladder cancer	Transitional cell cancer of the bladder
Purpose of Data Collection	To test hypothesis that marijuana use is associated with tobacco-related cancers.	To determine whether marijuana use is associated with lung & upper aerodigestive tract cancers.	To investigate the relationship between tobacco smoking and bladder cancer	To compare marijuana use among cases and controls.
Population	Location: San Francisco and Oakland, U.S. Cohort: male and female health plan members, age 15-49, who volunteered to complete a questionnaire in 1979-1985. Cases were new diagnoses 1979-1993. Maximum possible case age was 63.	Location: Los Angeles County, U.S. Cases: population-based cancer registry, new diagnoses 1999-2004, male and female, ages 18-62. Controls: randomly selected from general population, matched to individual cases on neighborhood, age, and gender. Analysis dropped matching and included controls for other cancers.	Location: Alexandria, Egypt Cases: network of hospitals in Greater Alexandria, new diagnoses 1993-1996, male only, age <75. Controls: non-cancer patients in same network of hospitals, selection method not stated, no matching.	Location: Augusta, Georgia, and Palo Alto, California, U.S. Cases: two Veterans Administration hospitals, new diagnoses (years of diagnoses not stated), male only, age < 61. Controls: other urological clinic patients at the same hospitals, random or convenience selection not stated, matched on age.
Participation	Unstated number eligible, 64,855 studied. Subcohorts: Ever ms: 26,733 (41 cases) Never ms: 38,122 (141 cases)	Cases: 214^ occurred, 90 (42%) interviewed. Controls: 1,444^ eligible, 1,040 (72%) interviewed.	Cases: unstated number occurred, 151 interviewed. Controls: unstated number eligible, 157 interviewed.	Cases: unstated number occurred, 52 interviewed. Controls: 168 identified, 131 eligible, 104 (79% of eligible) interviewed.

Appendix Table 4	Tobacco-Related Cancers	Laryngeal Cancer	Bladder Cancer	
Study Parameter	**Sidney 1997**	**Hashibe 2006**	**Bedwani 1997**	**Chacko 2006**
Questionnaire Administration Methods	Self-administered written questions and answers, at health care facilities.	Oral interviews, face-to-face, locations not stated.	Oral interviews, probably face-to-face, location not stated.	Self-administered written questions and answers, location not stated
Privacy of Oral Answers	Not applicable	Not stated	Not stated	Not applicable
Assurance of Data Confidentiality*	Yes	Yes	Not stated	Yes

Appendix Table 4	Tobacco-Related Cancers	Laryngeal Cancer	Bladder Cancer	
Study Parameter	**Sidney 1997**	**Hashibe 2006**	**Bedwani 1997**	**Chacko 2006**
Results (% cases/controls exposed if case-control study, rate ratio estimate, 95% confidence interval, and adjustments for potentially confounding variables)	*Ever ms (7+ joints lifetime):* <u>Men</u> RR=0.9 (0.6-1.4) <u>Women</u> RR=0.7 (0.3-1.4) *Frequency of ms (categories of times per month/week):* "Not associated." *Length of ms (continuous)*: "Not associated." Adjusted for tobacco cigarette smoking, alcohol, age, race, and education.	<u>All subjects</u> *Ever ms:* 57%/54%[+] *Cumulative ms:* *>0-<1 jy:* OR=0.8 (0.4-1.6) *1-<10 jy:* OR=0.4 (0.2-1.2) *10-<30 jy:* OR=0.9 (0.3-2.5) *30-<60 jy:* OR=0.7 (0.2-2.7) *60+ jy:* OR=0.8 (0.3-2.5) *Cumulative ms (continuous) 50 jy:* OR=0.9 (0.5-1.7) Adjusted for tobacco cigarette smoking, alcohol, age, gender, race/ethnicity, and education. <u>Non-smokers of tobacco</u> *Ever ms:* 46%/40%[+] OR=1.2 (0.3-5.5) Adjusted for alcohol, age, gender, race/ethnicity, and education.	*Smoked hashish at least once a day for at least one year:* 8.6%/8.3% OR=0.4 (0.1-2.5) Adjusted for tobacco cigarette smoking, age, education, type of house, history of schistosomiasis, and high-risk occupation.	*Ever habitual ms:* 89%/67% Adjusted OR not calculated *Current habitual ms:* 31/20% Adjusted OR not calculated *Upper tertile of joint-years (>40 jy):* 40%/15% Adjusted OR not calculated *Cumulative ms ("continuous term of median values of the following categorizations: < 20 jy, 20-40 jy, 40+ jy"):* P trend = 0.01 Adjusted for tobacco cigarette smoking, smoked meat, Agent Orange, radiation, and dyes.

Appendix Table 4	Tobacco-Related Cancers	Laryngeal Cancer	Bladder Cancer	
Study Parameter	**Sidney 1997**	**Hashibe 2006**	**Bedwani 1997**	**Chacko 2006**
Validity Issues Specific to This Study	*Short time since first ms exposure: w*idespread smoking of marijuana began in the U.S. in approximately 1969 and the study's follow-up ended in 1993 (25 years later), possibly not enough time for an epidemiologically detectable number of cancers caused by ms to have occurred. *Selection bias:* participation rates were not stated and could have been low, creating potential for bias if participants and nonparticipants were different with regard to ms history. *Incomplete ms data:* no ms data after questionnaire administration at beginning of follow-up (noted by investigators).	*Under-reporting of marijuana smoking:* the face-to-face interviews in subjects' homes with possible lack of privacy may have led to under-reporting of ms. Differential under-reporting of ms between cases and controls could have biased the rate ratio estimates. *Selection bias:* case participation was low at 42% while control participation was higher at 72%. The difference in participation between cases and controls could have caused bias if participants and nonparticipants were different with regard to ms history (noted by investigators).	*Confounding bias:* tobacco and marijuana may have been mixed prior to smoking as has been reported elsewhere in northern Africa (topic not mentioned in Bedwani 1997). *Under-reporting of marijuana smoking:* the face-to-face interviews at health care facilities with possible lack of privacy and possible lack of assurance of data confidentiality (the article is silent on both issues) may have led to under-reporting of ms. Differential under-reporting of ms between cases and controls could have biased the rate ratio estimate. *Selection bias:* participation rates were not stated and could have been low, creating potential for bias.	*Confounding bias:* 46% of the control group had erectile dysfunction, "to which tobacco smoking is a common contributor" (noted by authors). Curiously, tobacco smoking, a known cause of bladder cancer, was not associated with bladder cancer in this study. *Selection bias:* the case participation rates was not stated and could have been low, creating potential for bias if participants and nonparticipants were different with regard to ms history. *Data error.* The article's numbers of cases stratified into tobacco and marijuana smoking categories (created by tobacco yes/no and marijuana yes/no variables) do not sum correctly. The three categories for which numbers of cases are presented sum to 55 cases, which is more than the 52 total cases.

[#] Case definition as described in article. ICD=International Classification of Diseases. O=Oncology.

*Assurance of data confidentiality was assumed if the article stated that the investigators obtained approval from an institutional review board or informed consent from the subjects.
^Estimated by OEHHA based on numbers in the Hashibe *et al.* (2006) article.
[+]An adjusted odds ratios for "ever" marijuana smoking was presented only for nonsmokers of tobacco cigarettes by Hashibe *et al.* (2006).

7.1.5 Appendix Table 5 – Prostate, Penile, Cervical, and Breast Cancers

Appendix Table 5	Prostate Cancer	Penile Cancer	Cervical Cancer	Breast Cancer
Study Parameter	**Sidney 1997**	**Maden 1993**	**Sidney 1997**	**Sidney 1997**
Study Design	Cohort	Case-control	Cohort	Cohort
Case Definition[#]	Prostate cancer (ICD-9, codes not stated)	Penile cancer (ICD-O-1 187.1-187.4)	Cervical cancer (ICD-9, codes not stated)	Breast cancer (ICD-9, codes not stated)
Purpose of Data Collection	To test hypothesis that marijuana use is associated with tobacco-related cancers.	To further clarify risk factors for penile cancer.	To test hypothesis that marijuana use is associated with tobacco-related cancers.	To test hypothesis that marijuana use is associated with tobacco-related cancers.
Population	Location: San Francisco and Oakland, U.S. Cohort: male health plan members, age 15-49, who volunteered to complete a questionnaire in 1979-1985. Cases were new diagnoses 1979-1993. Maximum case age was 63.	Location: Washington State (13 western counties), U.S., and British Columbia (Vancouver Island & Lower Mainland), Canada. Cases: population-based cancer registry, new and historical, diagnosed 1979-1990, age <75. Controls: general population (random-digit dialing), matched on age and date of diagnosis.	Location: San Francisco and Oakland, U.S. Cohort: female health plan members, age 15-49, who volunteered to complete a questionnaire in 1979-1985. Cases were new diagnoses 1979-1993. Maximum case age was 63.	Location: San Francisco and Oakland, U.S. Cohort: female health plan members, age 15-49, who volunteered to complete a questionnaire in 1979-1985. Cases were new diagnoses 1979-1993. Maximum case age was 63.
Participation	Unstated number eligible, 27,920 interviewed. Subcohorts: Ever ms: 13,577 (12 cases) Never ms: 14,343 (30 cases)	Cases: 219 occurred , 110 (50%) interviewed Controls: 481 eligible, 355 (74%) interviewed.	Unstated number eligible, 36,935 interviewed. Subcohorts: Ever ms: 13,156 (130 cases) Never ms: 23,779 (172 cases)	Unstated number eligible, 36,935 interviewed. Subcohorts: Ever ms: 13,156 (76 cases) Never ms: 23,779 (284 cases)
Questionnaire Administration Methods	Self-administered written questions and answers, at health care facilities.	Oral interviews, face-to-face, at subjects' homes or another place of their choosing.	Self-administered written questions and answers, at health care facilities.	Self-administered written questions and answers, at health care facilities.

Appendix Table 5	Prostate Cancer	Penile Cancer	Cervical Cancer	Breast Cancer
Study Parameter	**Sidney 1997**	**Maden 1993**	**Sidney 1997**	**Sidney 1997**
Privacy of Oral Answers	Not applicable	Not stated	Not applicable	Not applicable
Assurance of Data Confidentiality*	Yes	Not stated	Yes	Yes
Results (% cases/controls exposed if case-control study, rate ratio estimate, 95% confidence interval, and adjustments for potentially confounding variables)	<u>All subjects</u> *Ever ms (7+ joints lifetime):* RR=1.3 (0.6-2.6). *Frequency of ms (categories of times per month/week):* "Nonsignificant twofold increase" in highest exposure category of 1+ times/week." *Length of ms (continuous)*: "Not associated." Adjusted for tobacco cigarette smoking, alcohol, age, race and education. <u>Nonsmokers of tobacco</u> *Ever ms:* RR=3.1 (1.0-9.5) Adjusted for alcohol, age, race, and education.	*Ever ms:* 17%/11% OR=1.5 (0.7-3.2) *Cumulative ms frequency 1-< 51 times:* 13%/7% OR=1.7 (0.8-3.9) *51+ times:* 5%/4% OR=1.0 (0.3-3.6) Adjusted for tobacco cigarette smoking, alcohol consumption, age, and number of sexual partners.	<u>All subjects</u> *Ever ms (7+ joints lifetime):* RR=1.1 (0.9-1.5) *Frequency of ms (categories of times per month/week):* "Not associated." *Length of ms (continuous)*: "Not associated." Adjusted for tobacco cigarette smoking, alcohol, age, race and education. <u>Nonsmokers of tobacco</u> All cervical cancer *Ever ms:* RR=1.4 (1.0-2.1) Invasive cervical cancer *Ever ms:* RR=2.4 (0.8-6.7) Adjusted for alcohol, age, race, and education.	*Ever ms (7+ joints lifetime):* RR=1.0 (0.8 – 1.3) *Frequency of ms (categories of times per month/week):* "Not associated." *Length of ms (continuous)*: "Not associated." Adjusted for tobacco cigarette smoking, alcohol, age, race and education.

Appendix Table 5	Prostate Cancer	Penile Cancer	Cervical Cancer	Breast Cancer
Study Parameter	**Sidney 1997**	**Maden 1993**	**Sidney 1997**	**Sidney 1997**
Validity Issues Specific to This Study	*Short time since first ms exposure: w*idespread smoking of marijuana began in the U.S. in approximately 1969 and the study's follow-up ended in 1993 (25 years later), possibly not enough time for an epidemiologically detectable number of cancers caused by ms to have occurred. *Selection bias:* participation rates were not stated and could have been low, creating potential for bias if participants and nonparticipants were different with regard to ms history. *Incomplete ms data:* no ms data after questionnaire administration at beginning of follow-up (noted by investigators).	*Under-reporting of marijuana smoking:* the interviews in subjects' homes with possible lack of privacy or assurance of data confidentiality (the article is silent on those issues) may have led to under-reporting of ms. Different under-reporting between cases and controls could bias rate ratio estimates. *Selection bias:* case participation was 50% while control participation was higher at 70%. The difference in participation could have caused bias if those who participated were different with regard to marijuana smoke history (noted by investigators). *Selection bias:* cases were apparently all historical or a mix of historical and new cancer patients. 18% were deceased and could not be interviewed. Patients who survived until interview may have been different than the deceased with regard to ms history.	*Short time since first ms exposure: w*idespread smoking of marijuana began in the U.S. in approximately 1969 and the study's follow-up ended in 1993 (25 years later), possibly not enough time for an epidemiologically detectable number of cancers caused by ms to have occurred. *Selection bias:* participation rates were not stated and could have been low, creating potential for bias if participants and nonparticipants were different with regard to ms history. *Incomplete ms data:* no ms data after questionnaire administration at beginning of follow-up (noted by investigators).	*Short time since first ms exposure: w*idespread smoking of marijuana began in the U.S. in approximately 1969 and the study's follow-up ended in 1993 (25 years later), possibly not enough time for an epidemiologically detectable number of cancers caused by ms to have occurred. *Selection bias:* participation rates were not stated and could have been low, creating potential for bias if participants and nonparticipants were different with regard to ms history. *Incomplete ms data:* no ms data after questionnaire administration at beginning of follow-up (noted by investigators).

[#] Case definition as described in article. ICD=International Classification of Diseases. O=Oncology.
*Assurance of data confidentiality was assumed if the article stated that the investigators obtained approval from an institutional review board or informed consent from the subjects.
^Calculated by OEHHA based on numbers in the article.
[$]This type of cancer was not classified as tobacco-related by Sidney *et al.* (1997).

7.1.6 Appendix Table 6 – Colorectal, Anal, Melanoma, and Brain Cancers

Appendix Table 6	Colorectal Cancer	Anal Cancer	Melanoma	Brain Cancer
Study Parameter	**Sidney 1997**	**Daling 1987**	**Sidney 1997**	**Efird 2004**
Study Design	Cohort	Case-control	Cohort	Cohort
Case Definition[#]	Colorectal cancer (ICD 9, codes not stated)	Anal cancer (including in situ (21%))	"Melanoma" (ICD 9, codes not stated)	Malignant primary adult onset glioma (ICD-O 938X/3 - 948X/3)
Purpose of Data Collection	To test hypothesis that marijuana use is associated with tobacco-related cancers.	To elucidate risk factors for anal cancer.	To test hypothesis that marijuana use is associated with tobacco-related cancers.	To determine risk from cigarette smoking and other lifestyle behaviors.
Population	Location: San Francisco and Oakland, U.S. Cohort: male and female health plan members, age 15-49, who volunteered to complete a questionnaire in 1979-1985. Cases were new diagnoses 1979-1993. Maximum case age was 63.	Location: 3 counties in western Washington State, U.S., and the province of British Columbia, Canada. Cases: population-based cancer registries, historical diagnoses 1978-1985, male and female, age <70. Controls: colon cancer cases randomly selected from same cancer registries, matched to individual cases on age, gender, and country.	Location: San Francisco and Oakland, U.S. Cohort: male and female health plan members, age 15-49, who volunteered to complete a questionnaire in 1979-1985. Cases were new diagnoses 1979-1993. Maximum case age was 63.	Location: northern California, U.S. Cohort: male and female health plan members, age 25+, who volunteered to complete a questionnaire in 1979-1985. Cases were new diagnoses 1979-1999.

Appendix Table 6	Colorectal Cancer	Anal Cancer	Melanoma	Brain Cancer
Study Parameter	**Sidney 1997**	**Daling 1987**	**Sidney 1997**	**Efird 2004**
Participation	Unstated number eligible, 64,855 interviewed. Subcohorts of ms: Never: 38,122 (30 cases) Ever: 26,733 (12 cases)	Cases:208 occurred, 148 (71%) interviewed. Controls:220 eligible, 166 (76%) interviewed. Marijuana analysis excluded ever-homosexual men, resulting in 126 cases & 165 controls.	Unstated number eligible, 64,855 interviewed. Subcohorts of ms: Never: 38,122 (74 cases) Ever: 26,733 (49 cases)	142,085 eligible, 105,005 (74%) interviewed. Subcohorts of ms: Never ms: cohort size not stated, 60 cases Ever ms: cohort size not stated, 9 cases Less than once a month; 5,768, 1 case Once a month: 4,699, 4 cases Once a month or more: cohort size not stated, 8 cases. Weekly: 6,002, 4 cases Daily: 2,823, 0 cases
Questionnaire Administration Methods	Self-administered written questions and answers, at health care facilities.	Oral interviews, face-to-face or phone not stated, locations not stated.	Self-administered written questions and answers, at health care facilities.	Self-administered written questions and answers, at health care facilities.
Privacy of Oral Answers	Not applicable	Not stated	Not applicable	Not applicable
Assurance of Data Confidentiality*	Yes	Not stated	Yes	Yes

Appendix Table 6	Colorectal Cancer	Anal Cancer	Melanoma	Brain Cancer
Study Parameter	**Sidney 1997**	**Daling 1987**	**Sidney 1997**	**Efird 2004**
Results (% cases/controls exposed if case-control study, rate ratio estimate, 95% confidence interval, and adjustments for potentially confounding variables)	*Ever ms (7+ joints lifetime):* <u>Men</u> RR=0.9 (0.5-1.8) <u>Women</u> RR=0.6 (0.2 – 1.3) *Frequency of ms (categories of times per month/week):* "Not associated." *Length of ms (continuous)*: "Not associated." Adjusted for tobacco cigarette smoking, alcohol, age, race, and education.	<u>Men (heterosexual only)</u> *Ever ms:* 25%/13% OR=2.5 (0.7-9.2) <u>Women</u> *Ever ms:* 4%/5% OR=0.8 (0.2 – 4.0) Adjusted for tobacco cigarette smoking, age, and country.	*Ever ms (7+ joints lifetime):* <u>Men</u> RR=1.2 (0.7 – 2.1) <u>Women</u> RR=1.1 (0.6 – 1.9) *Frequency of ms (categories of times per month/week):* "Not associated" *Length of ms (continuous)*: "Not associated" Adjusted for tobacco cigarette smoking, alcohol, age, race, and education.	*Ever ms:* RR=1.9 (0.9-4.0) *Frequency of ms* *Less than once a month:* RR=0.6 (0.1-4.4) *Once a month:* RR=3.6 (1.3-10.2) *Once a month or more:* RR=2.8 (1.3-6.2) *Weekly:* RR=3.2 (1.1-9.2) *Daily:* RR not calculable (no exposed cases) Adjusted for age, gender, race, education, alcohol, coffee consumption, and tobacco smoking (cigarette, pipe, and cigar).

Appendix Table 6	Colorectal Cancer	Anal Cancer	Melanoma	Brain Cancer
Study Parameter	**Sidney 1997**	**Daling 1987**	**Sidney 1997**	**Efird 2004**
Validity Issues Specific to This Study	*Short time since first ms exposure: w*idespread smoking of marijuana began in the U.S. in approximately 1969 and the study's follow-up ended in 1993 (25 years later), possibly not enough time for an epidemiologically detectable number of cancers caused by ms to have occurred. *Selection bias:* participation rates were not stated and could have been low, creating potential for bias if participants and nonparticipants were different with regard to ms history. *Incomplete ms data:* no ms data after questionnaire administration at beginning of follow-up (noted by investigators).	*Short time since first exposure: w*idespread smoking of marijuana began in the U.S. in approximately 1969 and the study's case-ascertainment ended in 1985 (17 years later), possibly not enough time for an epidemiologically detectable number of cancers caused by ms to have occurred. *Selection bias:* cases and controls were historical cancer diagnoses and ~10% of subjects died prior to interviewing and were not included. Historical patients who survived until interview may have been different than patients who died with regard to ms history.	*Short time since first ms exposure: w*idespread smoking of marijuana began in the U.S. in approximately 1969 and the study's follow-up ended in 1993, possibly not enough time for an epidemiologically detectable number of cancers caused by ms to have occurred. *Selection bias:* participation rates were not stated and could have been low, creating potential for bias if participants and nonparticipants were different with regard to ms history. *Incomplete ms data:* no ms data after questionnaire administration at beginning of follow-up (noted by investigators).	*Small numbers of exposed cases for some marijuana smoking categories:* a rate ratio could not be estimated for the category "daily marijuana smoking" because no cases occurred, and the rate ratio for "less than once a month" was based on just one exposed case. *Incomplete ms data:* subjects were categorized into ms categories based solely on history prior to filling-out questionnaires in 1977-1985; marijuana smoking-behavior could have changed over the study follow-up period (noted by investigators).

[#] Case definition as described in article. ICD=International Classification of Diseases. O=Oncology.

*Assurance of data confidentiality was assumed if the article stated that the investigators obtained approval from an institutional review board or informed consent from the subjects.

^Calculated by OEHHA based on numbers in the article.

7.1.7 Appendix Table 7 – Testicular Cancer, AML, and Non-Hodgkin's Lymphoma

Appendix Table 7	Testicular Cancer	Acute Myeloid Leukemia (AML)	Non-Hodgkin's Lymphoma (NHL)	
Study Parameter	**Daling 2009**	**Trivers 2006**	**Holly 1999**	**Nelson 1997**
Study Design	Case-control	Case-control	Case-control	Case-control
Case Definition[#]	Testicular germ cell tumors (TGCTs), ICD-O topography C62 and histology 9060-9091.	Childhood AML	Non-Hodgkin's lymphoma	Non-Hodgkin's lymphoma, high or medium grade
Purpose of Data Collection	To investigate risk factors for testicular cancer.	To test the hypothesis that parental marijuana use increases risk of childhood AML.	To investigate *a priori* hypotheses (that did not include marijuana smoking) based on earlier studies.	To examine risk factors for NHL.
Population	Location: Seattle/Puget Sound region (3 counties), U.S. Cases: population-based cancer registry, new diagnoses 1999-2006, age 20-44. Controls: general population (random-digit dialing), matched on age and year of diagnosis.	Location: U.S. and Canada. Cases:. "more than100 institutions involved in pediatric cancer care," new diagnoses 1989-1993, male and female, age 5-17 (for analysis of direct marijuana smoking by children) . Controls: randomly selected from source populations, matched on age, race, and residential location.	Location: San Francisco Bay area (6 counties), U.S. Cases: population-based cancer registry, new diagnoses 1978-1985, male (heterosexual only) and female, age 21-74. Controls: general population (random-digit dialing), matched on age, gender, and county of residence.	Location: Los Angeles County, U.S. Cases: population-based cancer registry, new diagnoses 1989-1992, HIV negative, male and female, age 18-75. Controls: randomly selected neighborhood controls, matched on age, gender, race/ethnicity, and language (English or Spanish).

Appendix Table 7	Testicular Cancer	Acute Myeloid Leukemia (AML)	Non-Hodgkin's Lymphoma (NHL)	
Study Parameter	**Daling 2009**	**Trivers 2006**	**Holly 1999**	**Nelson 1997**
Participation	Cases: 548 occurred, 369 (67%) interviewed (230 pure seminoma and 139 non-seminoma or mixed). Controls: 1,875 eligible, 979 interviewed (52%).	Cases: unstated number of cases occurred, unstated number of mothers eligible, 277 mothers interviewed. Controls: unstated number of controls eligible, unstated number of mothers eligible, 325 mothers interviewed.	Cases: 2,812 occurred, 1,593 (57%) interviewed, 1,281 analyzed after excluding homosexual men. Controls: 3,224 eligible, 2,515 (78%) interviewed, 2,095 analyzed after excluding homosexual men.	Cases: 1,429^ male and female occurred, 525 (37%)^ initially interviewed, 377 (184 male and 193 female) included after excluding non-confirmed pathology and HIV positive. Controls: unstated number eligible, 377 (184 male and 193 female) interviewed.
Questionnaire Administration Methods	Oral, face-to-face interviews in subjects' homes, workplaces, and other convenient places.	Oral interviews via telephone.	Oral, face-to-face interviews in subjects' homes or at places convenient to subjects.	Oral interviews, telephone or face-to-face not stated.
Privacy of Oral Answers	Not stated	Not stated	Not stated	Not stated
Assurance of Data Confidentiality*	Yes	Yes	Yes	Yes

Appendix Table 7	Testicular Cancer	Acute Myeloid Leukemia (AML)	Non-Hodgkin's Lymphoma (NHL)	
Study Parameter	**Daling 2009**	**Trivers 2006**	**Holly 1999**	**Nelson 1997**
Results (% cases/controls exposed if case-control study, rate ratio estimate, 95% confidence interval, and adjustments for potentially confounding variables)	<u>Pure seminoma</u> *Ever ms:* 72%/68% OR=1.2 (0.9-1.8) *Former ms:* 53%/48% OR=1.2 (0.8-1.8) *Current ms:* 19%/20% OR=1.3 (0.8-2.1) *…and first use at age <18:* OR=1.2 (0.7-2.0) *… and length 10+ years:* OR=1.2 (0.7-2.1) *…and frequency 1+ days/week:* OR=1.3 (0.7-2.4) <u>Non-seminoma/mixed</u> *Ever ms:* 74%/68% OR=1.5 (0.9-2.4) *Former ms:* 46%/48% OR=1.2 (0.9-1.7) *Current ms:* 38%/20% OR=2.3 (1.3-4.0) *…and first use at age <18:* OR=2.8 (1.6-5.1) *… and length 10+ years:* OR=2.7 (1.5-5.0) *…and frequency 1+ days/week:* OR=3.0 (1.5-5.6) Adjusted for age, year, alcohol, cigarette smoking, and cryptorchidism.	*Ever ms by children at ages 5-17 reported by mothers:* 4%/3% OR=1.2 (0.3-3.9) Adjusted for age at diagnosis, race, and residential location, and parents' income, education, and age at child's birth.	<u>Men (heterosexual only)</u> *Total number of times ms* *1-<40 times:* 16%/21% OR=0.6 (0.5-0.8) *40-999 times:* 9%/16% OR=0.5 (0.4-0.7) *1,000+ times:* 4%/8% OR=0.5 (0.3-0.8) Adjusted for age and county of residence <u>Women</u> *Total number of times ms* *1-<40 times:* 13%/20% OR=0.6 (0.4-0.8) *40-999 times:* 5%/7% OR=0.6 (0.4-1.0) *1,000+ times:* 2%/2% OR=0.7 (0.3-1.5) Adjusted for age and county of residence <u>Men (heterosexual only) & women</u> *Total number of times ms:* *1-<40 times:* OR=0.7 (0.6-0.8) *40+ times:* OR=0.6 (0.4-0.7) Adjusted for age, county of residence, gender, and education.	<u>Men (HIV negative cases only)</u> *Ever ms:* 40%/42% OR=0.9 (0.5-1.5) *Total number of times ms* *1-5 times:* 11%/16% OR=0.7 (0.3-1.4) *6-800 times:* 18/17% OR=0.9 (0.5-1.9) *901+ times:* 10/9% OR=1.1 (0.5-2.5) Adjusted for neighborhood, age, race/ethnicity, and language. <u>Women (HIV negative cases only)</u> *Ever ms:* (percent cases/controls exposed not stated) OR=0.7 (0.4-1.3) Adjusted for neighborhood, age, race/ethnicity, and language.

Appendix Table 7	Testicular Cancer	Acute Myeloid Leukemia (AML)	Non-Hodgkin's Lymphoma (NHL)	
Study Parameter	**Daling 2009**	**Trivers 2006**	**Holly 1999**	**Nelson 1997**
Validity Issues Specific to This Study	*Selection bias:* the low participation of controls (52%) compared to cases (67%) could have caused bias if participants and nonparticipants were different with regard to ms history (acknowledged by the authors). *Under-reporting of marijuana smoking:* oral interviews with possible lack of privacy when answering questions may have led to under-reporting of ms. Differential under-reporting of ms between cases and controls could have biased the rate ratio estimates.	*Selection bias:* participation rates for mothers of cases aged 5-17 and respective control mothers were not stated, but there was no indication that participation was different than the overall (cases aged >0-17) rates of 81% for case mothers and 79% for control mothers. A difference in participation between cases and controls could cause bias if participants and nonparticipants were different with regard to ms history. *Under-reporting of marijuana smoking:* oral interviews with possible lack of privacy when answering questions may have led to under-reporting of ms. Differential under-reporting of ms between case and control parents could have biased the rate ratio estimate (acknowledged by the authors).	*Selection bias:* the low participation of cases (57%) compared to controls (78%) could have caused bias if participants and nonparticipants were different with regard to ms history. Many cases were deceased (21% of all cases). Historical patients who survived until interview may have been different than patients who died with regard to ms history. *Under-reporting of marijuana smoking:* oral face-to-face interviews in subjects' homes or public places with possible lack of privacy when answering questions may have led to under-reporting of ms. The authors said "Response bias also can occur with the reporting of sensitive information such as sexual behavior and drug use." Differential under-reporting between cases and controls could have biased the rate ratio estimates.	*Selection bias:* the very low participation of cases (37%) compared to controls (70%) could have caused bias if participants and nonparticipants were different with regard to ms history. Some of the case nonparticipation was due to cases being deceased (46% of all cases); patients who survived until interview may have been different than patients who died with regard to ms history. *Under-reporting of marijuana smoking:* oral interviews (locations not stated) with possible lack of privacy when answering questions may have led to under-reporting of ms. Differential under-reporting of ms between cases and controls could have biased the rate ratio estimates.

[#] Case definition as described in article. ICD=International Classification of Diseases. O=Oncology.

*Assurance of data confidentiality was assumed if the article stated that the investigators obtained approval from an institutional review board or informed consent from the subjects.
^Calculated by OEHHA based on numbers in the article.

7.2 Epidemiological studies reporting results for *parental* marijuana smoking

Summary of controlled studies that have reported results for parental marijuana smoking (ms) and childhood cancers as of October 17, 2008.

7.2.1 Appendix Table 8 – Child Leukemia, ALL, and AML

Appendix Table 8	**Childhood Leukemia (paternal exposure)**	**Infant Leukemia (paternal exposure)**	**Childhood Acute Lymphoblastic Leukemia (ALL) (paternal exposure)**	**Childhood Acute Myeloid Leukemia (AML) (maternal and paternal exposure)**	
Study Parameter	**Wen 2000**	**Wen 2000**	**Wen 2000**	**Robison 1989**	**Trivers 2006**
Study Design	Case-control	Case-control	Case-control	Case-control	Case-control
Case Definition[#]	Leukemia (any type) age < 18 years	Leukemia (any type) age < 19 months[&]	Acute lymphoblastic leukemia age < 15 years	Acute myeloid leukemia age < 18 years	Acute myeloid leukemia age < 18 years
Purpose of Data Collection	To identify risk factors for childhood leukemia.	To identify risk factors for infant leukemia.	To identify risk factors for childhood ALL.	To identify risk factors for childhood AML.	To identify risk factors for childhood AML.

Appendix Table 8	Childhood Leukemia (paternal exposure)	Infant Leukemia (paternal exposure)	Childhood Acute Lymphoblastic Leukemia (ALL) (paternal exposure)	Childhood Acute Myeloid Leukemia (AML) (maternal and paternal exposure)	
Study Parameter	**Wen 2000**	**Wen 2000**	**Wen 2000**	**Robison 1989**	**Trivers 2006**
Population	Location: U.S. and Canada. Cases: three studies at approximately 100 institutions in the Children's Cancer Group (combined data from protocols E-09, E-14, and E-15), new diagnoses 1983-1993, male and female. Controls: selected by random digit phone dialing, matched on residential location (area code & exchange), year of diagnosis (protocol E-09 only), and age at diagnosis, race, and gender (protocols E-14 and E-15 only).	Location: U.S. and Canada. Cases: approximately 100 institutions in the Children's Cancer Group (protocol E-09), new diagnoses 1983-1988, male and female. Controls: selected by random digit phone dialing, matched on residential location (area code & exchange) and year of diagnosis.	Location: U.S. and Canada. Cases:. approximately 100 institutions in the Children's Cancer Group (protocol E-15), new diagnoses 1989-1993, male and female. Controls: selected by random digit phone dialing, matched on residential location (area code & exchange), age at diagnosis, race, and gender.	Location: U.S. and Canada. Cases: approximately 100 institutions in the Children's Cancer Group, new diagnoses 1980-1984, male and female. Controls: selected by random digit phone dialing, matched on residential location (area code & exchange), age at diagnosis, and race.	Location: U.S. and Canada. Cases: more than100 institutions in the Children's Cancer Group (protocol E-14), new diagnoses 1989-1993, male and female. Controls: selected by random digit phone dialing, matched on residential location (area code & exchange), age at diagnosis, race, and gender.[%]

Appendix Table 8	Childhood Leukemia (paternal exposure)	Infant Leukemia (paternal exposure)	Childhood Acute Lymphoblastic Leukemia (ALL) (paternal exposure)	Childhood Acute Myeloid Leukemia (AML) (maternal and paternal exposure)	
Study Parameter	**Wen 2000**	**Wen 2000**	**Wen 2000**	**Robison 1989**	**Trivers 2006**
Participation	Cases: 3,101 children eligible (phone in home, mother available and English speaking), 2,343 (76%) of paternal questionnaires completed.[#] Controls: 4,111 children eligible, 2,723 (66%) of paternal questionnaires completed.[#]	Cases: 382 children eligible (phone in home, mother available and English speaking), 275 (72%) of paternal questionnaires completed.[#] Controls: 743 children eligible, 478 (64%) of paternal questionnaires completed.[#]	Cases: 2,081 children eligible (phone in home, mother available and English speaking), 1,618 (78%) of paternal questionnaires completed.[#] Controls: 2,597 children eligible, 1,722 (66%) of paternal questionnaires completed.[#]	Cases: 262 children eligible (phone in home, mother available and English speaking), 204 (78%) of maternal and an unstated number of paternal questionnaires completed.[#] Controls: 260 children eligible, 203[^] (78%) of maternal and an unstated number of paternal questionnaires completed.[#]	Cases: 638 eligible (phone in home, mother available and English speaking), 517 (81%) of maternal and 450 (71%) of paternal questionnaires completed.[#] Controls: 771[^] children eligible, 610 (79%) of maternal and 523 (68%) of paternal questionnaires completed.[#]
Questionnaire Administration Methods	Oral interview via telephone. Mothers answered father's questions for 16% of case and 32% of control paternal questionnaires.	Oral interview via telephone. Mothers answered father's questions for 11% of case and 29% of control paternal questionnaires.	Oral interview via telephone. Mothers answered father's questions for 17% of case and 32% of control paternal questionnaires.	Oral interview via telephone. No mention of mothers acting as proxies for fathers.	Oral interview via telephone. Mothers answered father's questions for 12% of case and 24% of control paternal questionnaires.
Privacy of Oral Answers	Not stated	Not stated	Not stated	Not stated	Not stated
Assurance of Data Confidentiality*	Yes	Yes1	Yes	Yes	Yes

Appendix Table 8	Childhood Leukemia (paternal exposure)	Infant Leukemia (paternal exposure)	Childhood Acute Lymphoblastic Leukemia (ALL) (paternal exposure)	Childhood Acute Myeloid Leukemia (AML) (maternal and paternal exposure)	
Study Parameter	**Wen 2000**	**Wen 2000**	**Wen 2000**	**Robison 1989**	**Trivers 2006**
Results (% cases/controls exposed if case-control study, rate ratio estimate, 95% confidence interval, and adjustments for potentially confounding variables)	*Ever paternal ms in year before birth:* [$] 16%/12% OR=1.5 (95% CI not provided), p<0.01 Adjusted for matching variables only. The matching variables varied between subpopulations (see text).	*Ever paternal ms in year before birth:* [$] 18%/10% OR=2.0 (95% CI not provided), p<0.05 Adjusted for matching variables only. The matching variables were residential location (based on phone number) and year of diagnosis.	*Ever paternal ms in year before birth* [$] 16%/12% OR=1.5 (95% CI not provided), p<0.05 Adjusted for matching variables only. The matching variables were residential location (based on phone number), age at diagnosis, race, and gender.	<u>Maternal ms</u> *5+ times in year before or during pregnancy:* 5/0.5% OR="tenfold" (95% CI not provided), p=0.005 <u>Paternal ms</u> *5+ times in year before pregnancy:* 12%/8% OR=1.5 (95% CI not provided), p=0.32 Adjusted for residential location, age at diagnosis, and race, and maternal education, tobacco use, and alcohol consumption.	<u>Maternal ms</u> *Ever:* 45%/45%, OR =0.9 (0.7-1.2) *Ever in year before birth:* 4/7%, OR =0.4 (0.2-0.8) *Ever in year after birth:* 5/6%, OR=0.6 (0.3-1.1) <u>Paternal ms</u> *Ever:* 60%/53%, OR =1.4 (1.02-1.8) *Ever in year before birth:* 16/14%, OR=1.0 (0.7-1.5) *Ever in year after birth:* 15/13%, OR=1.0 (0.7-1.6) Adjusted for residential location, age at diagnosis, race, and gender, and parents' income, education, and age at child's birth.

Appendix Table 8	Childhood Leukemia (paternal exposure)	Infant Leukemia (paternal exposure)	Childhood Acute Lymphoblastic Leukemia (ALL) (paternal exposure)	Childhood Acute Myeloid Leukemia (AML) (maternal and paternal exposure)	
Study Parameter	**Wen 2000**	**Wen 2000**	**Wen 2000**	**Robison 1989**	**Trivers 2006**
Validity Issues Specific to This Study	*Under-reporting of marijuana smoking:* oral interviews with possible lack of privacy when answering questions may have led to under-reporting of ms. Differential under-reporting of ms between case and control parents could have biased the rate ratio estimate. *Proxy interviews:* the differing percents of proxy interviews for case (16%) and control (32%) fathers could cause bias if the mothers were more or less forthcoming or knowledgeable about the fathers' marijuana use than the fathers themselves.	*Under-reporting of marijuana smoking:* oral interviews with possible lack of privacy when answering questions may have led to under-reporting of ms. Differential under-reporting of ms between case and control parents could have biased the rate ratio estimate. *Proxy interviews:* the differing percents of proxy interviews for case (11%) and control (29%) fathers could cause bias if the mothers were more or less forthcoming or knowledgeable about the fathers' marijuana use than the fathers themselves.	*Under-reporting of marijuana smoking:* oral interviews with possible lack of privacy when answering questions may have led to under-reporting of ms. Differential under-reporting of ms between case and control parents could have biased the rate ratio estimate. *Proxy interviews:* the differing percents of proxy interviews for case (17%) and control (32%) fathers could cause bias if the mothers were more or less forthcoming or knowledgeable about the fathers' marijuana use than the fathers themselves.	*Under-reporting of marijuana smoking:* oral interviews with possible lack of privacy when answering questions may have led to under-reporting of ms. The reported frequencies of marijuana smoking were "considerably lower" than in previous studies, according to the authors. Differential under-reporting of ms between case and control parents could have biased the rate ratio estimates (acknowledged by authors).	*Under-reporting of marijuana smoking:* oral interviews with possible lack of privacy when answering questions may have led to under-reporting of ms. Differential under-reporting between case and control parents could have biased the rate ratio estimates (acknowledged by the authors). *Proxy interviews:* the differing percents of proxy interviews for case (12%) and control (24%) fathers could cause bias if the mothers were more or less forthcoming or knowledgeable about the fathers' marijuana use than the fathers themselves.

*Assurance of data confidentiality was assumed if the article stated that the investigators obtained approval from an institutional review board or informed consent from the subjects.
[^]Calculated by OEHHA based on numbers in the article.
[$]Ever smoking marijuana was not further defined in the Wen *et al.* (2000) article, but a subsequent article by Trivers *et al.* (2006) based on some of the same children indicated that the results were most likely for any marijuana smoking in the year prior to the child's birth.
[&]While the Wen *et al.* (2000) article said the infant leukemia cases were diagnosed before 18 months of age, a preceding article that provided greater detail about the study's methods by Shu *et al.* (1996) said that the cases were 18 months of age or younger.
[%]The Trivers *et al.* (2006) article did not mention matching controls to cases on gender, but the Wen *et al.* (2000) article said that gender was a matching variable in this population (subjects in CCG protocol E-14).
[#]A father could participate only if the mother participated.

7.2.2 Appendix Table 9 – Child Brain Cancer, Neuroblastoma, & Rhabdomyosarcoma

Appendix Table 9	Childhood Brain Astrocytoma (maternal exposure)	Childhood Neuroblastoma (maternal and paternal exposure)	Childhood Rhabdomyosarcoma (maternal and paternal exposure)
Study Parameter	**Kuijten 1990**	**Bluhm 2006**	**Grufferman 1993**
Study Design	Case-control	Case-control	Case-control
Case Definition[#]	Brain astrocytoma age < 15 years	Neuroblastoma age < 19 years	Rhabdomyosarcoma age < 21 years
Purpose of Data Collection	To identify risk factors for childhood astrocytoma.	To identify risk factors for childhood neuroblastoma.	To identify risk factors for childhood rhabdomyosarcoma
Population	Location: U.S. (states of Pennsylvania, New Jersey, and Delaware). Cases: 8 hospitals, new diagnoses 1980-1986, male and female. Controls: selected by random digit phone dialing, matched on residential location (phone area code and exchange), age at diagnosis, and race.	Location: North America. Cases:. 139 institutions in Children's Oncology Group (merged Children's Cancer Group and Pediatric Oncology Group), new diagnoses 1992-1994**,** male and female. Controls: selected by random digit phone dialing, matched on residential location (first eight digits of phone number[+]) and age at diagnosis.	Location: U.S. (42 states and District of Columbia). Cases:. 60 hospitals in Children's Cancer Group and Pediatric Oncology Group, new diagnoses 1982-1988, male and female. Controls: selected by random digit phone dialing, matched on residential location (first eight digits of phone number), age at diagnosis, race, and gender.
Participation	Cases: 205 children eligible (physician consent, U.S. residence, phone in home, and biological mother available and English speaking), 163 (80%) of maternal questionnaires completed. Controls: 211[^] children eligible, 163 (77%) of maternal questionnaires completed.	Cases: 741 children eligible (physician and parent consent, phone in home, mother available and English or Spanish speaking), 538 (73%) of maternal and 403 (54%) of paternal questionnaires completed.[#] Controls: 703 children eligible; 504 (72%) of maternal and 301 (43%) of paternal questionnaires completed.[#$]	Cases: 440 children eligible (U.S. residence, phone in home, mother available and English or Spanish speaking), 322[^] (73%) of maternal and 312[^] (71%[^]) of paternal questionnaires completed.[#] Controls: 413[^] children eligible; 322[^] (78%[^]) of maternal and 304[^] (74%[^]) of paternal questionnaires completed.[#]
Questionnaire Administration Methods	Oral interviews of mothers via telephone.	Oral interviews of mothers and fathers via telephone. No mention of mothers answering questions for unavailable fathers.	Oral interviews of mothers and fathers via telephone. No mention of mothers answering questions for unavailable fathers.

Appendix Table 9	Childhood Brain Astrocytoma (maternal exposure)	Childhood Neuroblastoma (maternal and paternal exposure)	Childhood Rhabdomyosarcoma (maternal and paternal exposure)
Study Parameter	**Kuijten 1990**	**Bluhm 2006**	**Grufferman 1993**
Privacy of Oral Answers	Not stated	Not stated	Not stated
Assurance of Data Confidentiality*	Yes	Yes	Yes

Appendix Table 9	Childhood Brain Astrocytoma (maternal exposure)	Childhood Neuroblastoma (maternal and paternal exposure)	Childhood Rhabdomyosarcoma (maternal and paternal exposure)
Study Parameter	**Kuijten 1990**	**Bluhm 2006**	**Grufferman 1993**
Results (% cases/controls exposed if case-control study, rate ratio estimate, 95% confidence interval, and adjustments for potentially confounding variables)	*Ever maternal ms in 10 months before birth:* % case/control mothers exposed not provided OR=2.8 (0.9-9.9) *Ever maternal ms in 9 months before birth:* % case/control mothers exposed not provided OR=4.0 (p=0.11) (95% CI not provided) Adjusted for age at diagnosis, race, and residential location.	<u>Maternal ms</u> *Ever in 10 months before birth:* 9%/5%, OR=1.4 (0.8-2.5) Adjusted for case age, income, and other recreational drugs. --- *Ever in month before pregnancy:* 8%/5%, OR=0.9 (0.4-1.9) *Ever in first trimester:* 6%/1% OR=4.8 (1.6-16.5) *<1 pipeful/day*: OR=4.2 (1.5-14.6) *1+ pipeful/day:* OR=4.4 (1.1-29.6) *Ever in second trimester:* 2%/1% OR=1.4 (0.2-9.7) *Ever in third trimester:* 2%/1% OR=1.5 (0.2-10.2) Adjusted for case age, income, residential location, and ms in other pregnancy time intervals. <u>Paternal ms</u> *Ever around time of pregnancy:* (% exposed not provided or calculable from article) OR=2.0 (1.2-3.2) Adjusted for age at diagnosis, income, and residential location.	<u>Maternal ms</u> *Ever in year before birth:* 9%/4% OR=3.0 (1.4-6.5) Adjusted for age at diagnosis, race, gender, residential location, birthmarks, prematurity, and mothers' bleeding or cramping during pregnancy. <u>Paternal ms</u> *Ever in year before birth:* 22%/14% OR=2.0 (1.3-3.3) Adjusted for age at diagnosis, race, gender, and residential location.

Appendix Table 9	Childhood Brain Astrocytoma (maternal exposure)	Childhood Neuroblastoma (maternal and paternal exposure)	Childhood Rhabdomyosarcoma (maternal and paternal exposure)
Study Parameter	**Kuijten 1990**	**Bluhm 2006**	**Grufferman 1993**
Validity Issues Specific to This Study	*Under-reporting of marijuana smoking:* oral interviews with possible lack of privacy when answering questions may have led to under-reporting of ms. Differential under-reporting between case and control mothers could have biased the rate ratio estimates (noted by investigators).	*Under-reporting of marijuana smoking:* oral interviews with possible lack of privacy may have led to under-reporting of ms. Differential under-reporting between case and control parents could have biased rate ratio estimates (noted by investigators). *Unclear paternal marijuana smoking time period:* the time period with respect to mothers' pregnancies in which fathers' marijuana smoking was assessed was not clear. The article said simply "around pregnancy." *Selection bias among fathers:* paternal participation with regard to drug use questions was relatively low at 54% for cases and 43% for controls.[#] Differential participation between case and control fathers could cause bias if participants and nonparticipants were different with regard to ms history.	*Under-reporting of marijuana smoking:* oral interviews with possible lack of privacy when answering questions may have led to under-reporting of ms. Differential under-reporting between case and control parents could have biased the rate ratio estimates (noted by investigators).

*Assurance of data confidentiality was assumed if the article stated that the investigators obtained approval from an institutional review board or informed consent from the subjects.

[^]Calculated by OEHHA based on numbers in the article.

[+]Bluhm *et al.* (2006) did not mention matching controls to cases on the first eight digits of the case's household telephone number, but a preceding article about the same study population by Olshan *et al.* (1999) said that this was done.

[#]A father could participate only if the mother participated.

[$]Participation numbers for fathers in Bluhm et al. 2006 were supplied by Dr. Bluhm in a personal communication.