Emerging Health Concerns in the Era of Cannabis Legalization

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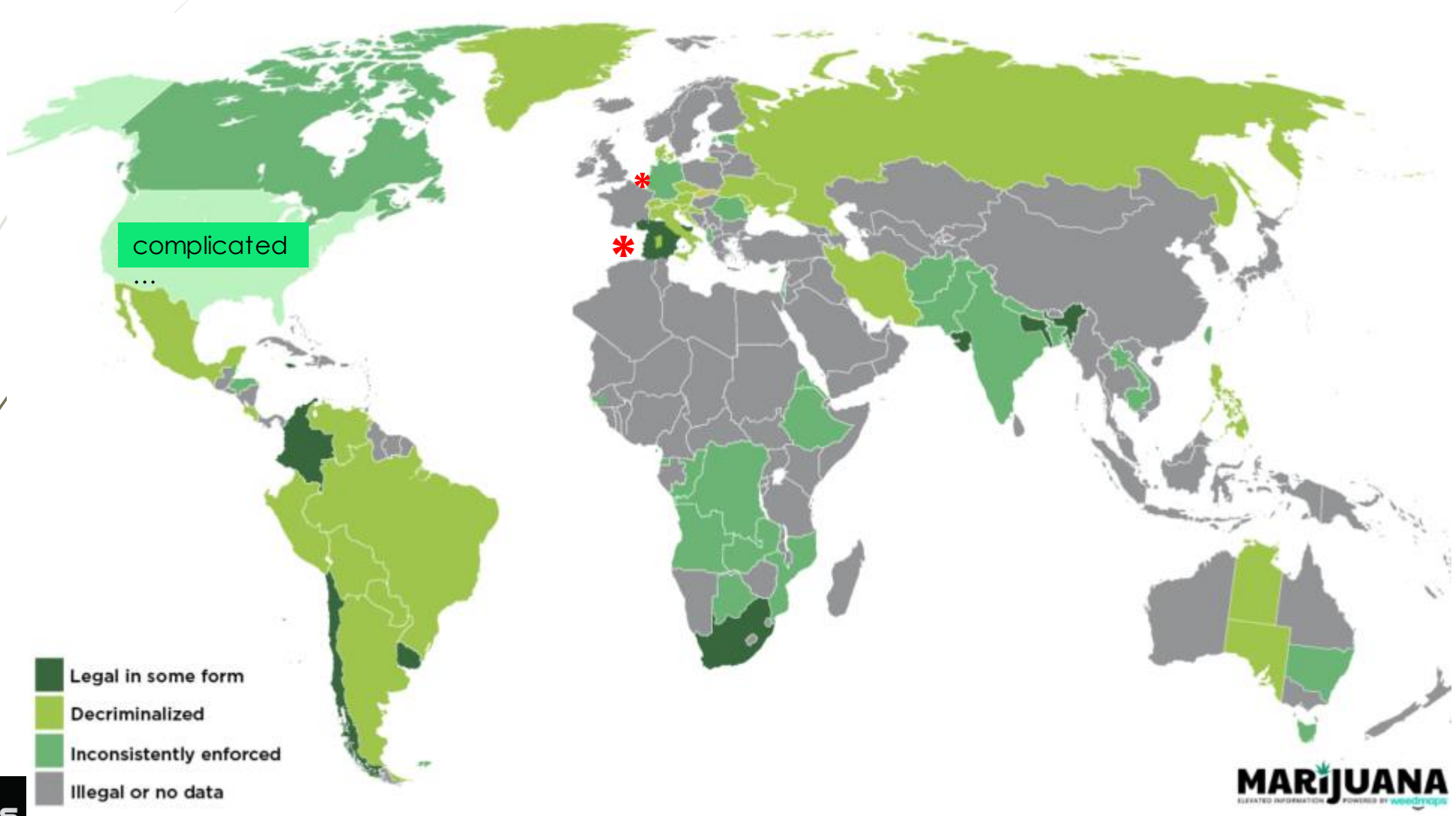
Cannabis legalization is advancing worldwide



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Legalization impact on population use and health hazards

- More first-time users
- More volume of consumption (more exposure)
- More matrices (smoke/vape/cookies/gummies/drinks)
- More access to vulnerable populations (young, elderly, cancer, immunocompromised, fertile females, pregnant)
- More potential for inappropriate/accidental use (young, driving, operating machinery)
- More apparent cannabis related medical problems (increased reporting)

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Cannabis population health impact is yet to be fully understood

- Limited US federal funding
- Restrictions on research even with private funds (stigma, loss of federal funding)
- Paucity of quality data (small numbers, case reports, no longitudinal studies, biases (reporting/publishing/authors/editors/reviewers)
- Post marketing studies NOT mandated at this time

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How do these concerns compare with alcohol?

Alcohol like

- first time users
- Increased exposure
- vulnerable populations (young, pregnant)
- inappropriate/accidental use (young, driving, operating machinery)
- More apparent

Cannabis specific

- Increased cannabis related medical problems (psychiatric, bad experience, contaminants)
- More matrices (smoke/vape/cookies/gummies/drinks)
- vulnerable populations (elderly, cancer, immunocompromised, fertile or pregnant females): contaminants

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Comparison to alcohol is useful but has limitations

- Cannabis and derived THC/CBD have medical applications.
- Addiction potential is not completely overlapping.
- Medical and psychiatric complications are different.
- Cannabis products medical risks are mostly (exceptions include CBD and liver toxicity) due to contaminants.

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Cannabis processing overview

Flower

- Pesticides
- Herbicides
- Fungicides
- Microbial agents
- Mold/fungi
- Heavy metals

Final Product

Extraction
- CO_2 (solvent-less)
- Propane
- Butane
- Acetone
- Ethanol

Purge/Remove Solvent
- Vacuum oven
- Rotary Evaporator

Extracted, Concentrated Oil

- Heavy metals

Final Product (vape oil, bubble hash, shatter, etc)

- Formulation
- Baking
- Mixing

Edibles, beverages, tinctures, topicals, etc.

Final Product

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How do we optimize the safety and quality of cannabis products?

Contaminants

- Foreign Material
- Water Activity
- Residual Solvents
- Residual Pesticides
- Heavy Metals
- Mycotoxins
- Microbials

Profiling

- Cannabinoids
- Terpenes

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Pesticides, herbicides and fungicides

How do plants get contaminated?

- Direct application
- Drifting from other fields (outdoor grows)
- Systemic (pesticides that are absorbed by the plant can be passed on in clones)

Pesticides of concern:

- Eagle 20 (Myclobutanil)
- Imidacloprid
- Abamectin
- Etoxazole
- Spiromesifen
- >60 different pesticides are tested for in California!

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Prevalence of cannabis pesticide contamination

- Pesticide use for the cultivation of cannabis crops (pre and post legalization) is well established.
- An early study of medicinal cannabis in California found excessive quantities of the pesticide Bifenthrin.
- Up to 85% of legalized cannabis products in Washington State were found in one study to contain significant quantities of insecticides, fungicides, miticides and herbicides.
- in vitro study showed that up to 60% of pesticide residues in smoke stream are transferred to end user as measured by gas chromatography.

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Potential toxicities of pesticides in cannabis

- A vast array of possible toxicities including malignancy, developmental issues, reproductive, neurological and endocrine disorders.
- Identified carcinogens present in cannabis include vinyl chloride, nitrosamines, reactive oxygen species and polycyclic aromatic hydrocarbons, notably benzopyrene and benzanthracene.
- When heated (smoked) myclobutanil degradation yields arsenic.
- Various pesticides, particularly organophosphate insecticides are recognized endocrine disruptors, and may interfere with normal fertility function and developmental processes.

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Legislative/regulatory issues

- Which pesticides are safe to use (if any) and which ones to test for (up to 66 in CA)
- What is the Maximal Residue Limit (MRL) of each pesticides used
- Where to test for pesticides (independent labs vs state labs)
- How to make sure that labs use accurate methods (LOD/LOQ, full spectrum testing, inter/intra obs. variability)

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Residual solvents in cannabis

Commonly used solvents to extract oils from cannabis flower:

- Acetone
- Propane
- Butane
- Ethanol

- CO_2 extraction is "solvent-free" but more costly

Possible health concerns:

- Impurities/contaminants in solvents themselves
- Incomplete purging of solvents by rotary evaporation or a vacuum oven

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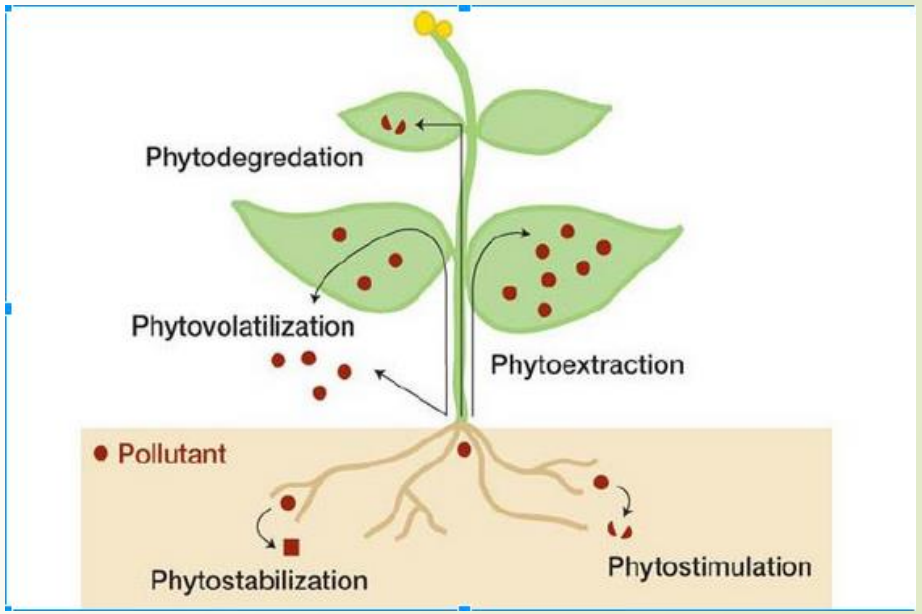
Heavy metals in cannabis

Cannabis/Hemp

are metal hyperaccumulators

- Historically, hemp has been used to prepare soil for planting food crops.
- Cannabis plant can grow despite high metal soil content.
- Absorbs and concentrates metals.
- Cannabis and hemp plant may be used as “phytoremediator” of heavy metals and other pollutants.

Phytoremediation



Can you spot the difference?

Grown with Advanced Nutrients

Grown with Cadmium, Mercury, Lead, Arsenic, Nickel

Cannabis can contain heavy metals such as cadmium, mercury, lead, arsenic and nickel.

Discover the dangers of heavy metal toxicity at:
AdvancedNutrients.com/HeavyMetal

And remember to always ask,
"Was it grown with Advanced Nutrients?"
for safety before you smoke.

Advanced Nutrients
Raising the Bud Weights... and Reputations... of Top Growers

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Specific heavy metals and their sources

Heavy metals found in cannabis

- Cadmium
- Arsenic
- Lead
- Mercury

- Misc. others: nickel, barium, silver

Metal sources

- Soil
- Water
- Nutrients
- Fertilizers (myclobutanil: arsenic, organophos: cadmium)

- Processing (drying)
- Packaging (vape)
- Intentional (street cannabis)

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Heavy metals toxicity from cannabis use:

- Broadly, heavy metals cross GI lumen via para/transcellular routes into the circulation where they may accumulate in various organs.
- Most heavy metals are recognized endocrine disruptors, interfering with fertility and developmental processes.
- Mercury and lead at toxic levels affect neurological development and function.
- Cadmium and arsenic are highly volatile and become carcinogenic under pyrolytic conditions.
- Arsenic is classified by the IARC as Group 1 substance (carcinogenic to humans) due to its causal association with skin, liver and GU cancers.
- Arsenic contamination associated with "cannabis arteritis", a form of thrombitis obliterans.

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Cannabis arteritis: Similar to Buerger's

- Arsenic may be a factor in vascular thrombosis and inflammatory arteritis.
- Possibly inhibits vascular endothelial growth factor and induce endothelial cell apoptosis.
- Case report of 26 year old female heavy cannabis user

El Omri, Naoual et al. "Cannabis arteritis." *The Pan African medical journal* vol. 26 53. 1 Feb. 2017, doi:10.11604/pamj.2017.26.53.11694

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Microbial contaminants in cannabis

Common organisms

- Salmonella
- E. Coli
- Aspergillus niger
- Aspergillus terreus
- Aspergillus fumigatus
- Aspergillus flavus

- Others: Klebsiella, Enterobacter, Acinetobacter, Stenotrophomonas, Pseudomonas, Bacillus, Cryptococcus

Contamination source

- Growing
  - Water
  - Nutrients
  - Soil & compost
  - Air

- Processing/storage/sales
  - Hands
  - Coughing, sneezing

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Reported and potential impact of cannabis contamination with bacteria

- Enteritis outbreak traced to Salmonella Muenchen in cannabis
- E.coli/Salmonella/Shigella: GI, bloody diarrhea, HUS, Reiter's
- Other enterobacter: GI
- Pseudomonas: PNA
- Aspergillus: PNA, systemic infections, immunocompromized

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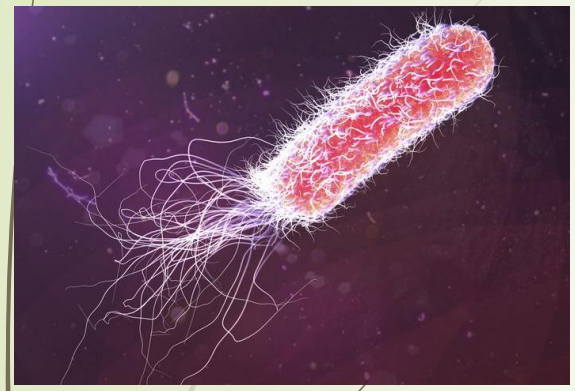
Case report: Pseudomonas aeruginosa



- 23 y/o male, daily cannabis smoker for 4 years (preferred method of inhalation: bong/water pipe)
- 3 days of fever, haemoptysis, and dyspnea
- Labs showed high WBC and CRP
- CT scan showed LUL necrotizing PNA with hydropneumothorax
- *P. aeruginosa* recovered from:
  - Sputum
  - pleural fluid
  - bong

Respirol Case Rep. 2018 Feb; 6(2): e00293. Published online 2017 Dec 22. "Marijuana "bong" Pseudomonas lung infection: a detrimental recreational experience"

Fungal contaminants

- Wet/humid conditions during harvesting can lead to fungal growth and infections after consumption.
- Several toxigenic species of Aspergillus, Penicillium as well as Cryptococcus liquefaciens have been found in commercial cannabis samples.
- Multiple reports of fungal spore contaminants in cannabis products, including mycotoxin-producing strains of Aspergillus.
- Vaporized fungal spores are likely to survive smoking temperatures and may cause fungal pneumonia at even very low numbers.
- Several case reports of opportunistic infection with fungi, commonly Aspergilli, in immunocompromised patients linked to findings of cannabis contaminated by fungal spores.

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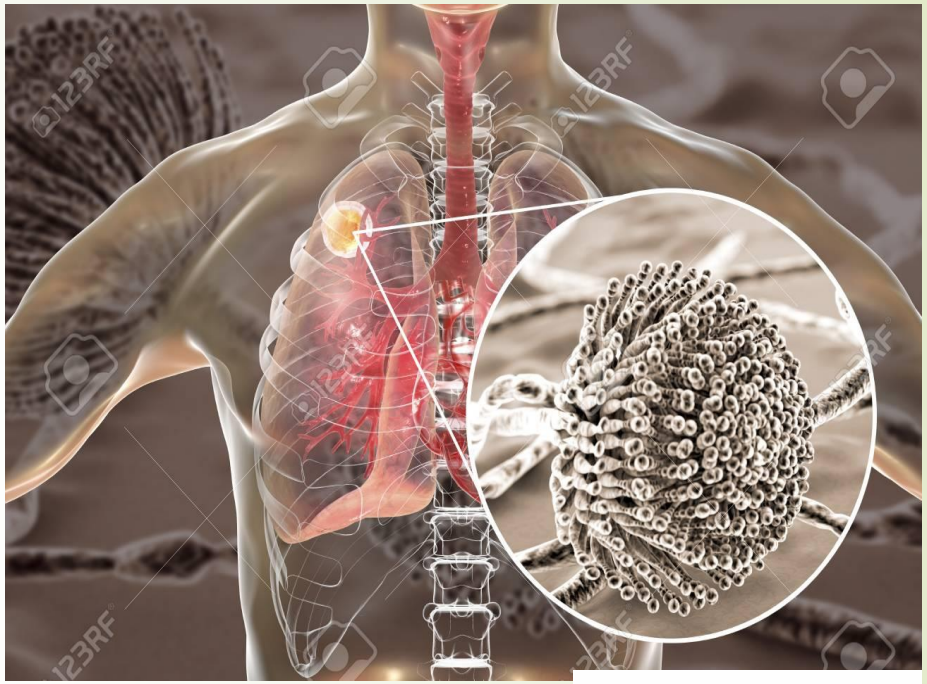
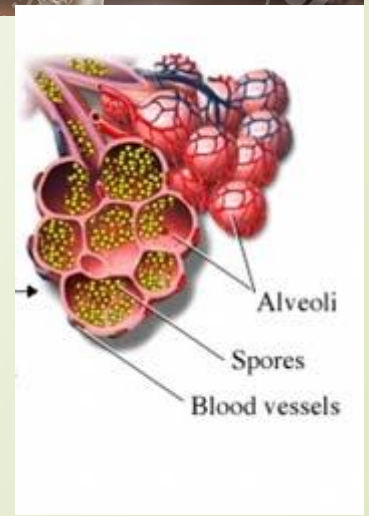
Aspergillus spp. Infections traced to cannabis use

- CASE 1
  - 47 y/o male, tobacco smoker 40 pack-year, 5 joints per day.
  - RA patient
  - 4 year history of dyspnea, weight loss, coughing thick sputum
  - High CRP
  - CT scan showed COPD with multiple bullae.
  - Bullae extracted via surgery showed an Aspergilloma (fungal ball)
- CASE 2
  - 43 y/o male, smoked 20 joints per day.
  - Predisposing heart condition
  - CT showed emphysema and aspergilloma





Mediterr J Hematol Infectious Disease; 2011. Epub 2011 Jan 14
"Too Many Moldy Joints – Marijuana and Chronic Pulmonary Aspergillosis"

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Aspergilloma in cannabis user

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Prevention and remediation for microbial contaminants in cannabis

- Pharmaceutical grade standards and procedures need to be developed and adopted (inter)nationally.
- This may be achieved at multiple points in the production process:
  - ensuring clean growing media
  - hygienic handling and storing
  - gamma-irradiation of final products
- Accurate production and supply chain tracking
- Public health monitoring for suspected outbreaks
- Adequate education of immunocompromised patients about contaminant risks

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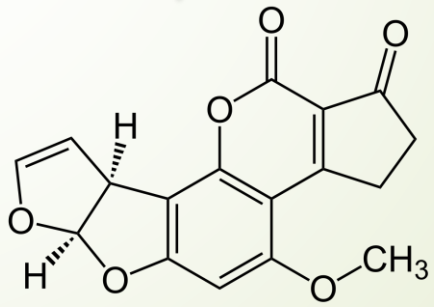
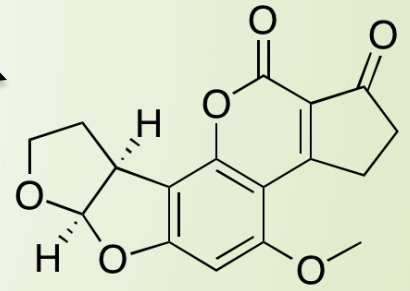
Mycotoxins/Aflatoxins in cannabis products

- Mycotoxins are secondary toxic metabolites resulting from fungal contamination and growth.
- Production of mycotoxins can be mitigated by ensuring products are properly dried and stored.
- Mycotoxins of concern in cannabis:
  - Aflatoxin B1, B2, G1, G2 (*A. flavus, A. parasiticus*)
  - Ochratoxin A (*A. ochraceus)*



Aflatoxin B1



Aflatoxin B2

Health risks due to aflatoxins in cannabis

- Aflatoxins are classified by the International Agency for Research on Cancer (IARC) as Group 1 substances (carcinogenic to humans) due to their causal association with hepatocellular carcinoma.
- Aflatoxins have been detected in cannabis preparations and smoke.
- Two species of Aspergillus (flavus and parasiticus) showed aflatoxin B1 and G1 production when grown on cannabis versus natural flora substrate.
- Aflatoxins may not be denatured by pasteurization or smoking processes.

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Closing comments

- Cannabis legalization driven by public opinion and political will is advancing worldwide.
- Full spectrum of health risks not well defined or included in the legalization process.
- Post marketing/legalization studies needed with the backing of public funds and resources.
- Reevaluation in 5-10 years would yield a more accurate picture.

- Yeast-derived cannabinoids a solution or a different problem?

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