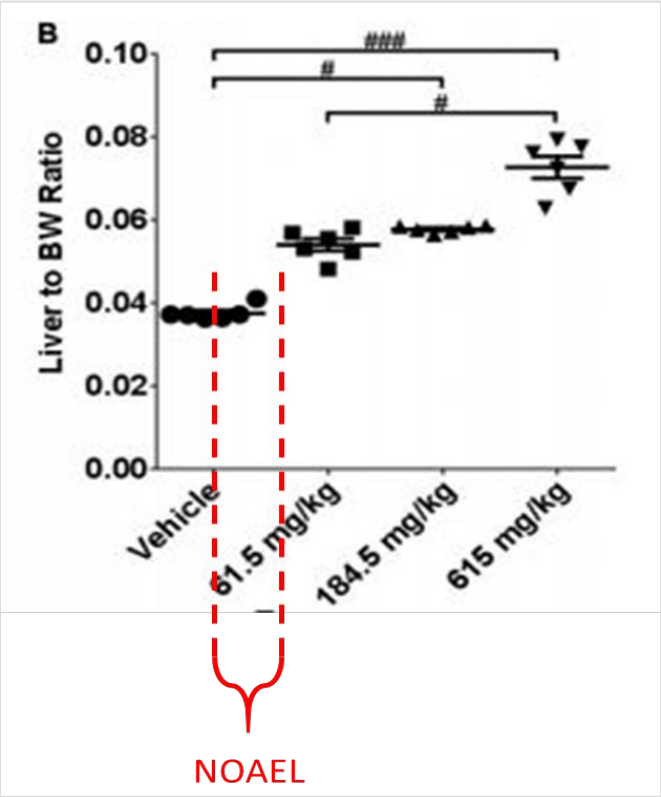
NPA Current Market Analysis

- FDA can stabilize and effectively regulate the market via an HHE-precedent on red yeast rice and monacolin K.
- Approximately 1,500 products have come to market in the past 3 years reportedly containing CBD.
- Agency is not currently screening products for THC or inspecting for GMPs or reviewing NDIs or GRAS notices for hemp products containing CBD.
- Mouse study (NOAEL estimate: 8-10 mg/kg)
- Humans (WHO Report) – safe use up to 600 mg, no place preference, no indication of hepatotoxicity.



"frequency of liver tumors observed in a gene therapy study with AAV vectors in male mice of the B6C3F1 hybrid background, which are known to have a high frequency of spontaneous liver tumors"

Bell P. et al. (2006). Analysis of Tumors Arising in Male B6C3F1 Mice with and without AAV Vector Delivery to Liver. *Molecular Therapy* 14: Issue 1, P34-44

Female B6C3F1 mice have 14 % incidence of spontaneous liver tumors vs. males (52% spontaneous liver tumors)

Moser G.J. et al. (2008). Furan-induced dose-response relationships for liver cytotoxicity, cell proliferation, and tumorigenicity (furan-induced lived tumorigenicity). *Experimental and Toxicologic Pathology* 61 (2009): 101 - 111

B6C3F1 mice

Ewing L.E. et al. (2019). Hepatotoxicity of a cannabidiol-rich cannabis extract in the mouse model. *Molecules* 24: 24091694.

- B6C3F1 mice - appropriate animal model for mouse cancer bioassay (Gold Standard for National Cancer Institute)
- Tumor was not an endpoint of the study
- Not an ideal animal model for acute hepatotoxicity (2 wk admin of CBD on liver histomorph)
- No NOAEL reported in the mouse study
- *Molecules* is not ideal for publishing tox studies (open source)

B6C3F1 mice have been adopted by the U.S. government (namely the National Cancer Institute), as the mouse for use in the cancer bioassay program

- It is susceptible to high spontaneous/background rates of liver tumors
- It is used because early tumors are indicative of test article related tumors while spontaneous tumors show up late in B6C3F1.

HOWEVER….

The article “Hepatotoxicity of a Cannabidiol-Rich Cannabis Extract in the Mouse Model”:

- It was not using this mouse strain for a tumor bioassay.
- It was looking at acute hepatotoxicity (2 weeks of CBD administration)
- The article does not even mention the term tumor anywhere.

WHO Cannabidiol (CBD) Critical Review Report

An orally administered dose of 600mg of CBD did not differ from placebo on the scales of the Addiction Research Centre Inventory, a 16 item Visual Analogue Mood Scale, subjective level of intoxication or psychotic symptoms.

Cannabidiol (CBD) Critical Review Report – World Health Organization https://www.who.int/medicines/access/controlled-substances/CannabidiolCriticalReview.pdf