Alcohol and Cancer Burden In Uganda Government Interventions and Challenges



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Alcohol and Health risk:

- Alcohol consumption has been linked to more than 200 diseases and injury conditions, including, infectious diseases, cirrhosis, cancer, cardiovascular disease, early dementia and mental disorders.
- Worldwide consumption of alcoholic drinks in 2016 was equal to 6.4 litres of pure alcohol (ethanol) per person aged 15 years or older, which is equivalent to about one alcoholic drink per day.
- However, consumption varies widely, by country.
- Alcohol consumption is expected to continue to rise in half of the World Health Organization (WHO) regions unless effective policy reverses the trend.

Alcohol and Cancer risk: Evaluation of Human Carcinogens by IARC

Group	Definition	No. of agents
Group 1	Carcinogenic to humans	120
Group 2A	Probably carcinogenic to humans	82
Group 2B	Possibly carcinogenic to humans	311
Group 3	Not classifiable as to its carcinogenicity to humans	500

Alcohol and Cancer risk:

Evaluation of Human Carcinogens by IARC

Group	Example
Group 1	Formaldehyde, Benzo[a]pyrene, Alcoholic beverages, Benzene, Asbestos, Outdoor air pollution, Processed meat, Solar radiation, Tobacco use, Welding fumes, Wood dust, oncogenic infections such HPV, HBV, HCV, etc
Group 2A	DDT, Acrylamide, Glyphosate
Group 2B	Vinyl acetate, Pyridine, Lead, Digoxin
Group 3	Ampicillin, Ethylene, Fluorene, Coal dust, Coffee, drinking, Dental materials, Fluorescent lighting, Electric fields, Hepatitis D virus, Hair colouring products (personal use of), Human papillomavirus types 6 and 11, Paint manufacture (occupational exposure in), Silicone breast implants, Printing inks

What is the evidence that alcohol drinking can cause cancer?

- Alcohol consumption causes cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver and female breast (IARC, 2012) and
- possibly cancer of the stomach, pancreas, lung, and gallbladder (Cao at al. 2015).
- Alcohol consumption is carcinogenic to humans (Group 1).



What is the evidence that alcohol drinking can cause cancer?

- Ethanol in alcoholic beverages is carcinogenic to humans (Group 1).
- Acetaldehyde associated with the consumption of alcoholic beverages is carcinogenic to humans (Group 1).
- The carcinogenicity of alcoholic beverages does NOT seem to vary with the type of beverage; the effect appears to be caused by **ethanol** itself.
- Acetaldehyde, a genotoxic metabolite of ethanol leads to carcinogenesis (Scoccianti et al. 2015)

Contributions of Risk Factors to All Cancer Mortality

Risk factor		PAF (%)	
	Worldwide	LMICs	HICs
Smoking	21	18	29
Alcohol	5	5	4
Low fruit and vegetable intake	5	6	3
Overweight/obesity	2	1	3
Physical inactivity	2	2	2
Contaminated injection	2	2	<0.5
Unsafe sex	3	4	1
Air pollution	1	1	1
Indoor smoke from solid fuels	<0.5	<0.5	0

Danaei G, et al. Lancet 2005;366:1784-93

Common Causes of Cancer



Alcohol and Cancer risk

- Alcohol consumption is causally associated with many chronic diseases and deaths worldwide.
- Alcohol consumption accounts for about 3% and 10% of total cancers diagnosed in women and men, respectively.
- In both genders, the alcohol-attributable fraction is high for upper aero-digestive tract; lips, mouth, tongue, nose, throat, esophagus and trachea (25–44%), liver (18–33%), and colorectal (4–17%) cancers, and in women for breast cancer (about 5%) (Scoccianti et al. 2015).
- In liver cancer, for example, alcohol increases HCC risk at least twofold; some studies suggest at least a fivefold increase (Lafaro, Demirjian & Pawlik 2015)

Alcohol vs Esophageal Cancer Risk

- Alcohol consumption at any level is associated with an increased risk of a type of esophageal cancer called esophageal squamous cell carcinoma.
- The risks, compared with no alcohol consumption, range from 1.3-fold higher for light drinking to nearly 5-fold higher for heavy drinking (LoConte et al. 2018, Bagnardi et al. 2015).
- In addition, people who inherit a deficiency in an enzyme that metabolizes alcohol have been found to have substantially increased risks of esophageal squamous cell carcinoma if they consume alcohol (Wu et al. 2018).

Alcohol vs Liver Cancer Risk

- Liver cancer: Heavy alcohol consumption is associated with approximately 2-fold increased risks of two types of liver cancer:
- Hepatocellular carcinoma and
- Intrahepatic cholangiocarcinoma) (Petrick et al. 2018, Grewal et 2012).

Alcohol vs Breast Cancer Risk

- Light drinkers have a slightly increased (1.04-fold higher) risk of breast cancer, compared with nondrinkers.
- The risk increase is greater in moderate drinkers (1.23fold higher) and heavy drinkers (1.6-fold higher) (LoConte et al. 2018).
- An analysis of prospective data for 88,000 women participating in two US cohort studies concluded that for women who have never smoked, light to moderate drinking was associated with a 1.13-fold increased risk of alcohol-related cancers (mostly breast cancer) (Cao et al. 2015).

Alcohol vs Colorectal Cancer Risk

Moderate to heavy alcohol consumption is associated with 1.2- to 1.5-fold increased risks of cancers of the colon and rectum compared with no alcohol consumption (Fedirko et al, 2011).

Alcohol vs Head and Neck Cancer Risk

- Moderate drinkers have 1.8-fold higher risks of oral cavity (excluding the lips) and pharynx (throat) cancers and 1.4fold higher risks of larynx (voice box) cancers than nondrinkers, and
- Heavy drinkers have 5-fold higher risks of oral cavity and pharynx cancers and 2.6-fold higher risks of larynx cancers (LoConte et al. 2018, Bagnardi et al. 2015).
- Moreover, the risks of these cancers are substantially higher among persons who consume this amount of alcohol and also use tobacco (Hashibe et al. 2009).

Dose-response metaanalyses for the risk of cancer, per 10 grams increase in alcohol (as ethanol) consumed per day

Alcohol drinks and risk of cancer (WCRF & AICR, CUP 2018)

Cancer	Total no. of studies	No. of studies in meta- analysis	No. of cases	Risk estimate (95% CI)	² (%)	Conclusion ²	Date of CUP cancer report ³
Mouth, pharynx and larynx (oral cavity cancer)	12	6	5,617	1.15 (1.09–1.22)	88		
Mouth, pharynx and larynx (pharyngeal cancer)	8	4	342	1.13 (1.05-1.21)	61		
Mouth, pharynx and larynx (oral cavity and pharyngeal cancer combined)	10	5	954	1.19 (1.10-1.30)	83	Convincing:	004.0
Mouth, pharynx and larynx (laryngeal cancer)	13	6	781	1.09 (1.05-1.13)	33	Increases risk	2018
Mouth, pharynx and larynx (head and neck cancer) ⁴	3	-	-	Significant increased risk in 3 studies	-		
Mouth, pharynx and larynx (upper aerodigestive tract cancer)	10	9	1,826	1.18 (1.10-1.26)	95		
Oesophagus (squamous cell carcinoma)	8	6	1,079	1.25 (1.12-1.41)	95	Convincing: Increases risk	2016
Liver ^s	19	14	5,650	1.04 (1.02-1.06)	64	Convincing: Increases risk	2015
Colorectum ⁶	19	16	15,896	1.07 (1.05-1.08)	28	Convincing: Increases risk	2017
Breast (postmenopause) ⁷	34	22	35,221	1.09 (1.07–1.12)	71	Convincing: Increases risk	2017
Stomach ⁵	30	23	11,926	1.02 (1.00-1.04)	39	Probable: Increases risk	2016
Breast (premenopause) ⁷	16	10	4,227	1.05 (1.02-1.08)	0	Probable: Increases risk	2017
Lung	45	26	21,940	1.03 (1.01–1.05)	67	Limited – suggestive: Increases risk	2017
Pancreas ⁵	10	9	3,096	1.00 (0.99-1.01)	0	Limited – suggestive: Increases risk	2012
Skin (malignant melanoma)	7	6	7,367	1.08 (1.03-1.13)	66	Limited – suggestive: Increases risk	2017
Skin (basal cell carcinoma)	9	9	3,349	1.04 (0.99-1.10)	68	Limited – suggestive: Increases risk	2017
Kidney ⁸	8	7	3,525	0.92 (0.86-0.97)	55	Probable: Decreases risk	2015

reviews

Annals of Oncology 24: 301–308, 2013 doi:10.1093/annonc/mds337 Published online 21 August 2012

Light alcohol drinking and cancer: a meta-analysis

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Background: There is convincing evidence that alcohol consumption increases the risk of cancer of the colorectum, breast, larynx, liver, esophagus, oral cavity and pharynx. Most of the data derive from studies that focused on the effect of moderate/high alcohol intakes, while little is known about light alcohol drinking (up to 1 drink/day). **Patients and methods:** We evaluated the association between light drinking and cancer of the colorectum, breast, larynx, liver, esophagus, oral cavity and pharynx, through a meta-analytic approach. We searched epidemiological studies using PubMed, ISI Web of Science and EMBASE, published before December 2010. **Results:** We included 222 articles comprising ~92 000 light drinkers and 60 000 non-drinkers with cancer. Light drinking was associated with the risk of oropharyngeal cancer [relative risk, RR = 1.17; 95% confidence interval (Cl) 1.06–1.29], esophageal squamous cell carcinoma (SCC) (RR = 1.30; 95% Cl 1.09–1.56) and female breast cancer (RR = 1.05; 95% Cl 1.02–1.08). We estimated that ~5000 deaths from oropharyngeal cancer, 24 000 from esophageal SCC and 5000 from breast cancer were attributable to light drinking in 2004 worldwide. No association was found for colorectum, liver and larynx tumors.

Conclusions: Light drinking increases the risk of cancer of oral cavity and pharynx, esophagus and female breast.



How does alcohol cause cancer? 1. Acetaldehyde

- When we drink alcohol, it is turned in to a chemical called acetaldehyde.
- Acetaldehyde is a genotoxic metabolite of ethanol.
- □ This happens mainly in the liver.
- Acetaldehyde can cause cancer by damaging DNA and stopping our cells from repairing this damage.

How does alcohol cause damage? 2. Hormone changes

- Hormones act as messengers in the body, giving our cells instructions - including when to grow and divide.
- Alcohol can increase the blood levels of some hormones such as oestrogen and insulin.
- Oestrogen, a sex hormone, is linked to the risk of breast cancer.

How does alcohol cause damage? 3. Increased absorption

Alcohol can affect the cells between the mouth and throat, which may make it easier for other carcinogens to be absorbed. How does alcohol cause damage? 4. Impairing absorption of a variety of nutrients

- Alcohol impairs the body's ability to break down and absorb a variety of nutrients that may be associated with cancer risk.
- Notably, vitamin A; nutrients in the vitamin B complex, such as folate; vitamin C; vitamin D; vitamin E; and carotenoids.

How does alcohol cause damage? 4. Folate absorption

- Ex. ethanol disrupts folate metabolism regulated by methylenetetrahydrofolate reductase (MTHFR),
- Low level of folate in presence of TT genotype variant modulates breast cancer risk (Scoccianti et al. 2015).
- □ The TT variant decreases MTHFR activity by 70% and appears to modulate risks of breast cancer (Platek et al. 2009), in association with low folate intake, and of oral cancer, at daily consumption of ≥2 drinks (Supic et al. 2011).

How does alcohol cause damage? 5. Mitochondrial injury

- Ethanol potentiates mitochondrial injury by further increasing reactive oxygen species (ROS) production and enhancing oxidation, ex. hepatic glutathione oxidation.
- ROS are chemically reactive molecules that contain oxygen.
- ROS can damage DNA, proteins, and lipids (fats) in the body through a process called oxidation
- Thus, resulting in increased apoptosis and cell injury (Singal & Anand 2007)

How does alcohol cause damage? 6. Carcinogenic contaminants

- Alcoholic beverages may also contain a variety of carcinogenic contaminants that are introduced during fermentation and production, such as:
- Nitrosamines,
- □ Asbestos fibers,
- Phenols, and
- Hydrocarbons.

The levels of metals (μ g/L) in each brand of alcohol and their associated health indices (HI). HI is listed from the most significant (top) to the least (bottom).

Sachet brand	Metal content ^a	HI metals	Ratio ^b	The 13
Ethanol	_	4.1 (1.0) ^c	$>1(1)^{c}$	brands were Big 5
TEB	12143 ^d	7.3x10 ^{-2 e}	1/14	Vodka (B5V),
AWE	4342 ^d	2.6x10 ^{-2 e}	1/38	(BEG) Bond 7
REX	794.5	1.3x10 ⁻²	1/83	Whisky (B7W).
NSB	1479 ^d	1.1x10 ^{-2 e}	1/91	Brigade Spirit
BOL	1340 ^d	9.6x10 ^{-3 e}	1/104	(BRG), Chief Waragi
TGL	538.0 ^d	5.7x10 ^{-3 e}	1/192	Spirit (CW1 and
B5V	200.8	1.9x10 ⁻³	1/529	CVV2, duplicates
B7W	64.8	1.5x10 ⁻³	1/714	apart) Goal Vodka
BEG	148.4	1.3x10 ⁻³	1/769	(GOV), Kick Spirit
GOV	123.3	1.1x10 ⁻³	1/909	Pineapple Waragi
KPW	166.5	1.1x10 ⁻³	1/1000	(KPW), Relax
BRG	123.3	8.9x10 ⁻⁴	1/1136	(REX), Royal Vodka
CW1	43.3	8.7x10 ⁻⁴	1/1176	(ROV), Salongo Spirit (SAG)
ROV	164.1	8.3x10 ⁻⁴	1/1266	Uganda Waragi
CW2	113.6	7.8x10 ⁻⁴	1/1300	(UGW), and V6
SAG	138.9	6.9x10 ⁻⁴	1/1493	Tangawizi Vodka
UGW	16.1	6.3x10 ⁻⁴	1/1639	(V6T).
V6T	148.5	5.8×10^{-4}	1/1818	

Otim O, Juma T, Otunnu O (2019) Assessing the health risks of consuming 'sachet' alcohol in Acoli, Uganda. PLoS ONE 14(2): e0212938. <u>https://doi.org/10.1371/journal</u>. pone.0212938

How does the combination of alcohol and tobacco and or other carcinogen affect cancer risk?

- Research shows that people who use both alcohol and tobacco have higher risks of developing cancers of the oral cavity, pharynx (throat), larynx, and esophagus than people who use either alcohol or tobacco alone.
- For oral and pharyngeal cancers, the risks associated with using both alcohol and tobacco are multiplicative; that is, they are greater than would be expected from adding the individual risks associated with alcohol and tobacco together (Turati et al. 2013, Hashibe et al. 2009).
- Synergistic mechanism has also been observed with HBC and HCV.
- EX. greater HCV replication in the presence of alcohol, increased oxidative stress & inhibition of hepatic expression of Bcl-2 (Singal & Anapd 2007)

How does alcohol cause damage?



Excessive alcohol consumption

Heavy drinking:

 is defined as more than two drinks per day on average for men or more than one drink per day on average for women.

Binge drinking:

- is defined as five or more drinks during a single occasion for men, or four or more drinks during a single occasion for women.
 - Any drinking by pregnant women or underage youth

CPSTF 2013

Light Alcohol Drinking



What happens to cancer risk after a person stops drinking alcohol?

- Stopping alcohol consumption is not associated with immediate reductions in cancer risk.
- The cancer risks eventually decline, although it may take years for the risks of cancer to return to those of never drinkers.
- This was demonstrated in study on head and neck cancers and on esophageal cancer.

What happens to cancer risk after a person stops drinking alcohol?

- For example, ex-drinkers still had higher risks of oral cavity and pharyngeal cancers than never drinkers even 16 years after they stopped drinking alcohol, although it was lower than before they stopped drinking (Rehm et al. 2007).
- One study estimated that it would take more than 35 years for the higher risks of laryngeal and pharyngeal cancers associated with alcohol consumption to decrease to the level of never drinkers (Ahmad Kiadaliri et al. 2013).

Estimated age-standardized incidence and mortality rates (World) in 2020, Uganda, both sexes, all ages (excl. NMSC) Cervix uteri Prostate Breast Oesophagus Kaposi sarcoma Liver Non-Hodgkin lymphoma Colorectum Ovary Incidence Penis Mortality 10 2030 0 40 50 International Agency for Research on Cancer Data source: Globocan 2020 ASR (World) per 100 000 Graph production: Global Cancer World Health Observatory (http://gco.iarc.fr)

Trends of the most common Cancers in Uganda:



Trends in agestandardized incidence rates per 100,000 (3year moving averages) Vs other cancers-**KPBCR** (Bukirwa et al 2020)



- Alcohol consumption is also linked to infectious diseases such as HIV in Uganda (Kim et al. 2016, Zablotska et al. 2006).
- Alcohol impairs judgment and may influence the risk of sexually transmitted oncogenic infections such as HPV (risk factor for cervical, anal, penile and head and neck cancers), HBV and HCV (risk factor for liver cancer), HIV (risk factor and co-factor for several cancers such cervical cancer, KS, and certain types of lymphoma), and HHV-8 (risk factor of KS).
- The infection-associated cancers such as cervical, KS, liver, lymphoma, and penile cancers are among the top 10 cancers in Uganda.

Study	Aim(s) / Focus	Design / method	Findings
Okello et al. 2016	Population attributable fraction (PAF) of Esophageal squamous cell carcinoma due to smoking and alcohol in Uganda	Case-control study	PAF of ESCC due to smoking, alcohol intake and a combination of alcohol & smoking were 16, 10 , and 13 % respectively.
Boffetta Et al. 2006	The burden of cancer attributable to alcohol drinking, Worldwide, including Africa, Uganda included in the sample of surveys conducted in 69 countries.	Data from meta- and pooled analyses and from the WHO Global Burden of Disease survey.	PAF of 6.5% in men and 2 % in women in East and central Africa for of cancers of the oral cavity, pharynx, esophagus, liver, colon, rectum, larynx and female breast.

Study	Aim(s) / Focus and Scope	Design / method	Findings
Okello et al. 2015	Risk Factors of Esophageal Squamous Cell Cancer in Southwestern Uganda.	Case- Control Study.	History of both alcohol and smoking were associated with ESCC (AOR 4.10 , 95%Cl 1.14 - 14.78).
Okello et al. 2023	Dietary Heterocyclic Amine Intake and Risk of Esophageal Squamous Cell Carcinoma in Rural Uganda	Case- Control Study.	Drinking 3 to 4 alcoholic drinks daily was associated with ESCC (AOR 8.00 , 95% CI 2.31 - 27.74)

Study	Aim(s) / Focus and Scope	Design / method	Findings
Qian et al. 2014	Alcohol Consumption and Breast Cancer Risk among Women in Three Sub- Saharan African Countries. Uganda inclusive.	Case- Control Study	In all the study sites (Uganda, Nigeria, and Cameroon), both past (AOR = 1.54 ; 95% CI: 1.19–2.00) and current drinking (AOR = 1.71 ; 95% CI: 1.30–2.23) were associated with breast cancer risk. However, Uganda alone, exhibited statistically insignificant association

Study	Aim(s) / Focus and Scope	Design / method	Findings
Rukundo et al. 2014	The association between red blood folate levels and breast cancer among women seen at a tertiary Ugandan hospital.	Case- Control Study	Alcohol drinking was associated with breast cancer risk (2.1 (1.1- 4.1). The odds of having breast cancer among women with normal folate levels compared to those with low folate levels were 1.4 (95% Cl 0.7 to 2.9)
Wekha et al. 2021	Prevalence and factors associated with CRC among patients hospitalized with lower gastrointestinal complaints at a tertiary health facility in Uganda.	10-year retrospec tive chart review	Alcohol consumption, smoking, diet, and family history of malignancies, combined as any risk factor of CRC, was associated with the CRC risk (AOR: 5.3 (2.9–9.9).

Study	Aim(s) / Focus and Scope	Design / method	Findings
Olasubo mi et al. 2022	association between benign breast disease (BBD) and breast cancer (BC) in a heterogeneous population of African women: Nigeria Cameroon, and Uganda.	Case- Control Study between 1998– 2018	Alcohol consumption mediated BBD and BC risk by 3.3 % with total mediation effect of (AOR: 1.508 (1.204–1.889)*)
Otim, Juma,and Otunnu. 2019	Investigation into the link between 'sachet' alcohol intake and health risk in Uganda , Acholi Sub- region – assessed the health risk associated with consuming heavy metal contaminated alcoholic products	A cross- sectional study based on the US Environm ental Protectio n Agency (US EPA)	A strong correlation was observed between ingestion of spirits and health risks and in. At >2.5 sachets/day for 240 day/ year over a lifetime for example, the risk of developing cancer due to exposure to As, Pb and Cr alone is 1 in 102,041 .

Recommended Public policy and prevention strategies at national level

- The WHO 2010 global strategy on harmful use of alcohol supports ten target areas for national actions such as:
- Health sector response,
- Community actions,
- Drink-driving policies,
- Limitation of the availability of alcohol,
- Action on marketing and pricing policies,
- Reducing the negative consequences of intoxication and
- Reducing the public health effect of illegally and informally produced alcohol

The three best public policy and prevention interventions at national level

- WHO recently identified the three best interventions to tackle harmful alcohol use at national level.
- Restricted access to retailed alcohol
- Limitation of alcohol advertising, and
- Taxes on alcohol.

Public health recommendation: Avoid alcohol, if you cannot, limit alcohol

- Not drinking alcohol is better for cancer prevention.
- Even little amounts of alcohol pose cancer risk, so for lowest risk, it is recommended not drinking alcohol at all.
- However, if you do drink alcohol and cannot not quit drinking, limit your intake to not more than two drinks a day for a man and one drink a day for a woman.
- Pregnant women and children should not drink alcohol at all.

Government Interventions: What mechanisms are present to monitor alcohol consumption in Uganda?

WHO Stepwise Approach to Surveillance (STEPS): Uganda STEPS Survey of Non-communicable Disease (NCD) Risk Factors-2014. Participants = 3987 adults

Results for adults aged 18-69 years (incl. 95% CI)	Both Sexes	Males	Females
% currently drink (drank alcohol in the past 30 days)	28.5	40.1	17.9
	(26.2-30.8)	(36.5-43.6)	(15.3-20.5)
% engage in heavy episodic drinking (6 or more drinks on any occasion in the past 30 days)	16.7 (14.9-18.5)	26.2 (23.1-29.4)	7.9 (6.3-9.6)
% past 12 month abstainers	12.1	12.5	11.8
	(10.8-13.4)	(10.4-14.5)	(10.2-13.4)
% lifetime abstainers	51.8	40.4	62.4
	(49.3-54.3)	(36.9-43.8)	(59.2-65.5)

Government Interventions: What programs/activities exist to reduce harmful exposures to alcohol in Uganda?

- The Liquor Act 1960. This regulates the manufacture and sale of intoxicating liquor and restricts consumption of liquor by children.
- The Enguli (Manufacture and Licencing Act) 1966. This prohibits consumption and export of enguli (any unrefined spirit).
- NCDs department in the Ministry of health for national coordination of NCDs activities, including alcohol.
- Public awareness on harms associated with alcohol drinking.

Government Interventions: What programs/activities exist to reduce harmful exposures to alcohol in Uganda?

- Uganda National Alcohol Control Policy 2019.
- This aims to reduce harmful consumption of alcohol in Uganda. through:
- regulation of production,
- packaging,

- distribution,
- marketing, sale and
- consumption of all alcoholic beverages.

Government Interventions: What programs/activities exist to reduce harmful exposures to alcohol in Uganda?

Others interventions

- Partnership with the WHO SAFER Initiative, launched in 2018.
- Local ordinances on alcohol regulation in 14,6% of districts (Uganda alcohol report, 2022)
- Treatment services for alcohol use disorders (AUD) alcohol related health problems and substance user in Butabika NRH and in some private hospitals.

Challenges

- Lack of an Act of Parliament on alcohol control
- Weak enforcement of the existing regulations
- Varying interests; trade, revenue, health, social function and leisure.
- Emerging evidence on high level of carcinogenic contaminants in alcoholic beverages in Uganda.
- Limited number of higher-level evidence studies in Uganda, esp. risk assessment, due to lack of or limited local research funding opportunities (Jatho et al. 2021).

Recommendations

- Enact a law (Act of Parliament) on alcohol control: regulation of production, packaging, distribution, marketing, sale and consumption of all alcoholic beverage.
- Strengthen enforcement of the existing regulations
- Multi-sectoral consideration and a healthy balance of interest ; trade, revenue, health, use for social function and leisure.
- Fund risk assessment: Monitor the content of alcoholic beverages in Uganda, relative to the permissible level (upper limit).

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Thank you

