happinnovation 20*20

SAMSUNG MEDICAL CENTER

Alcohol, Environment and HCC

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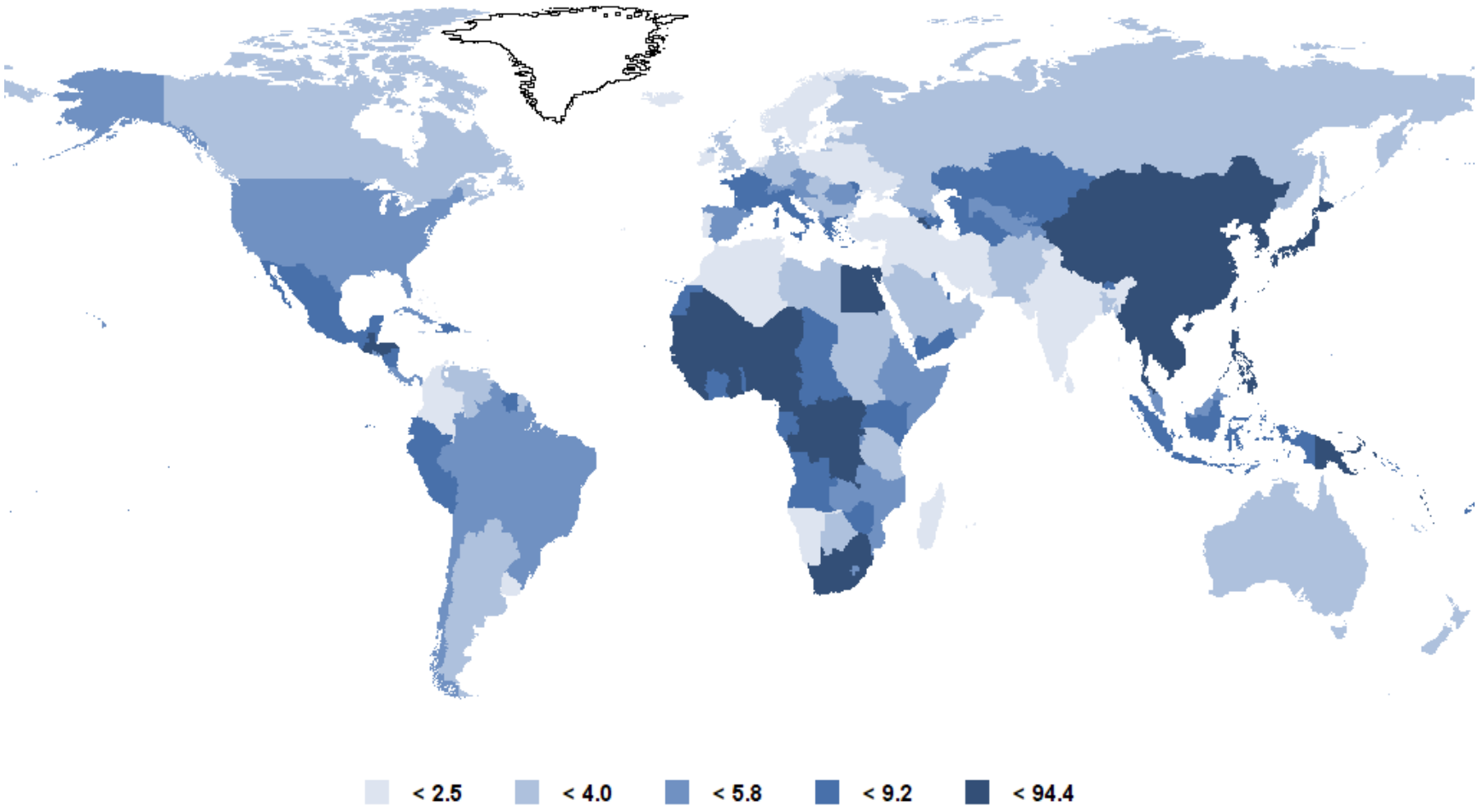
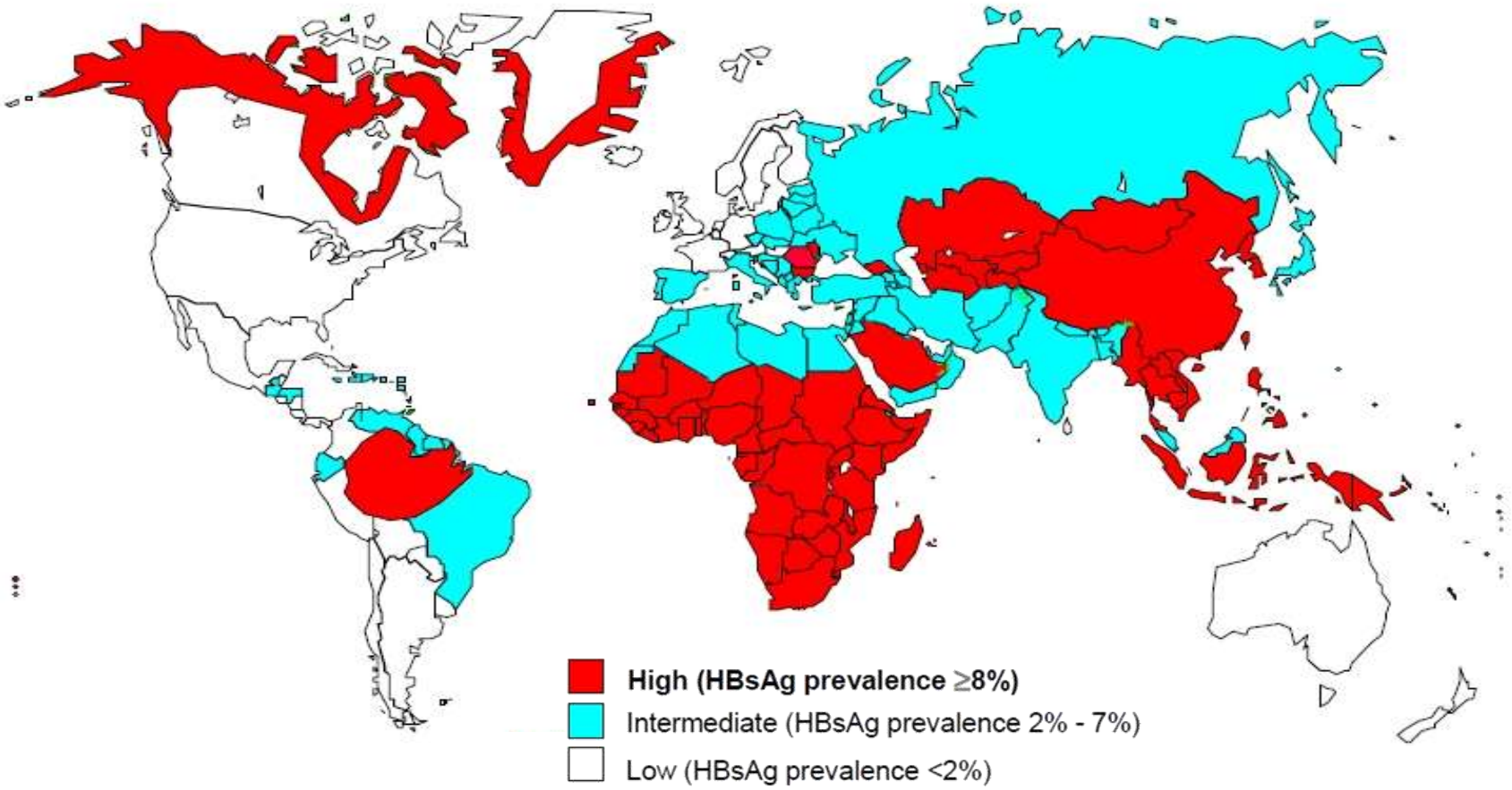
Varied incidence of HCC

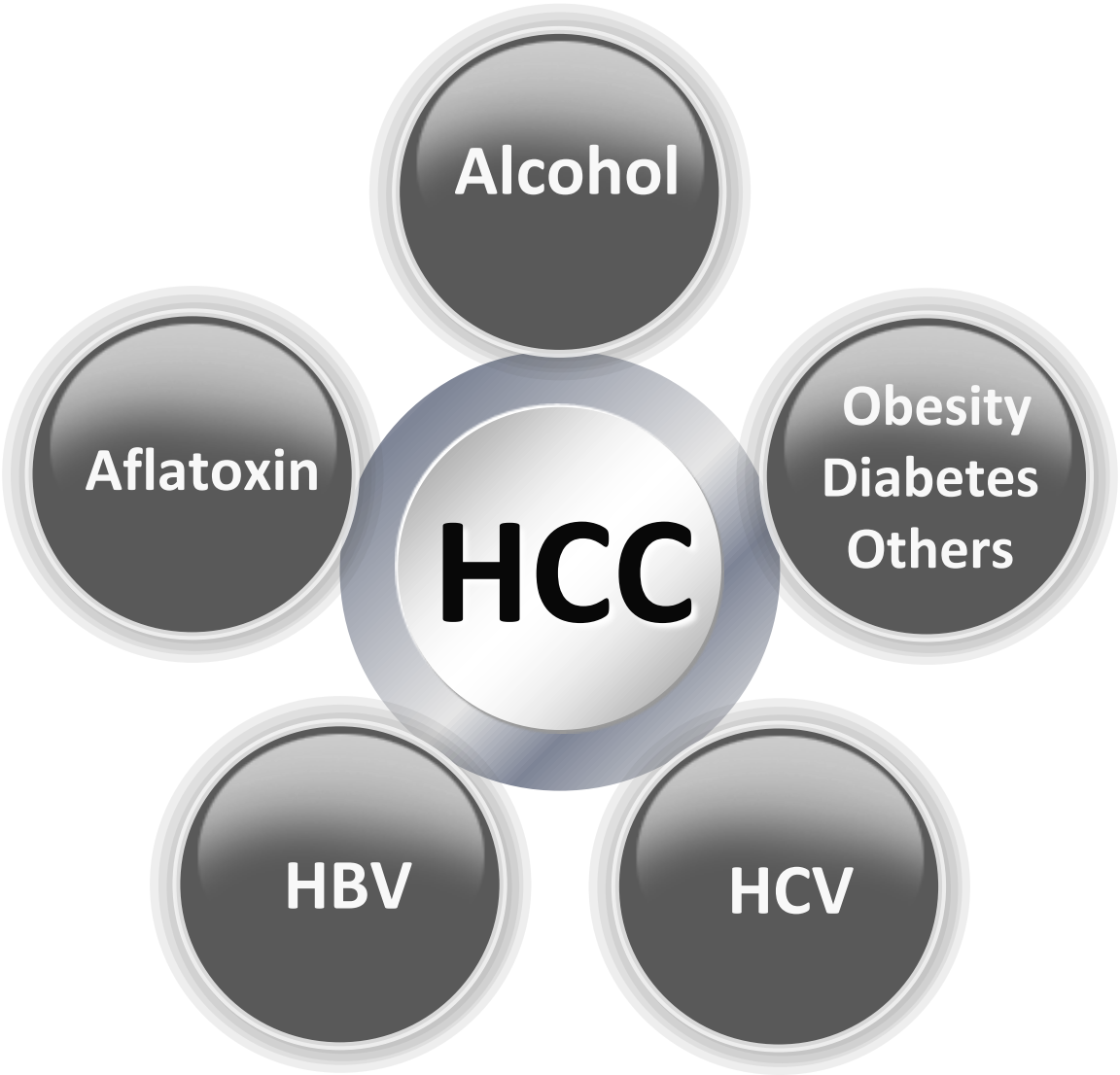


Seroprevalence of HBV

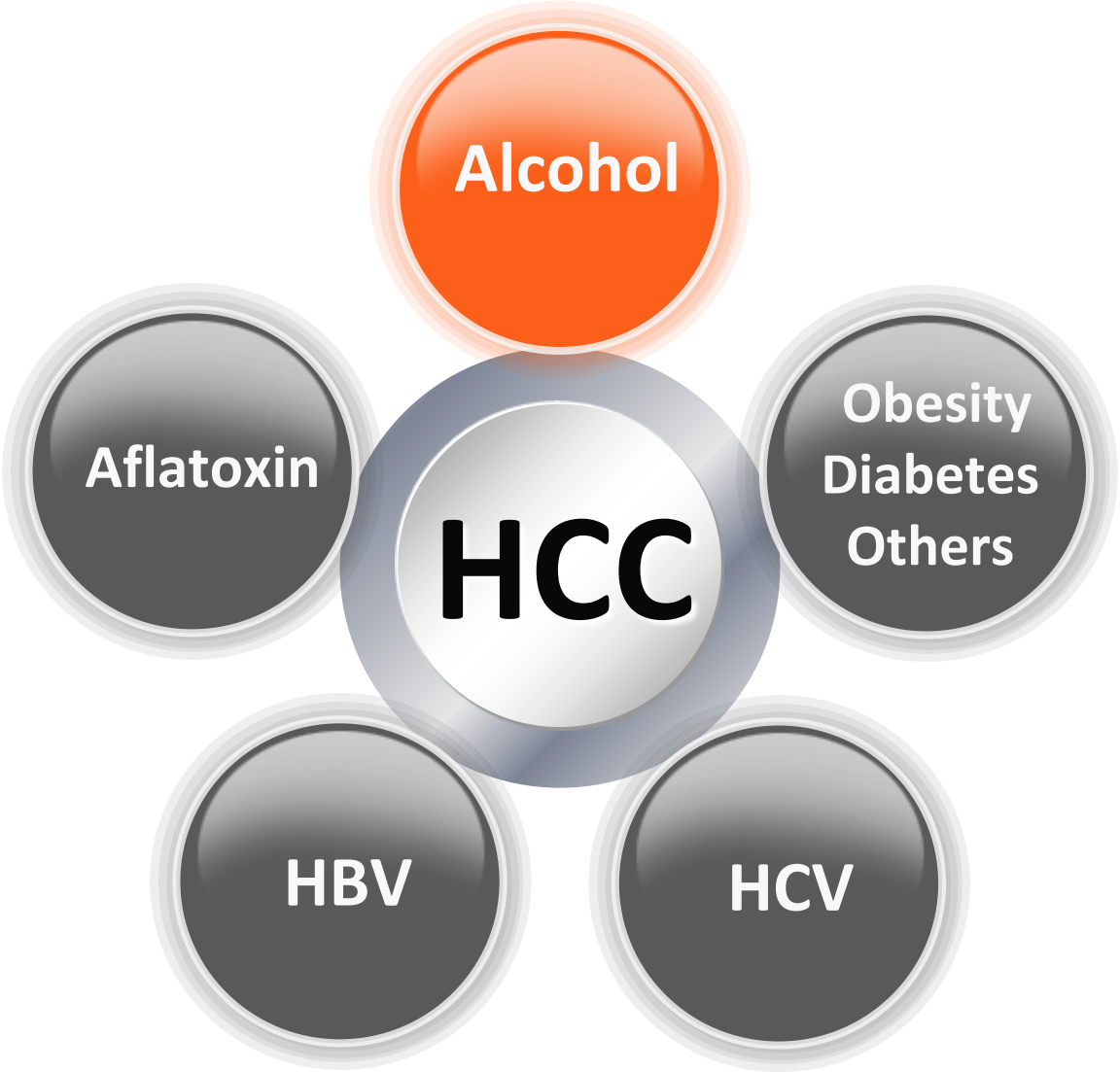


http://www.who.int/vaccines-documents/DocsPDF01/www613.pdf

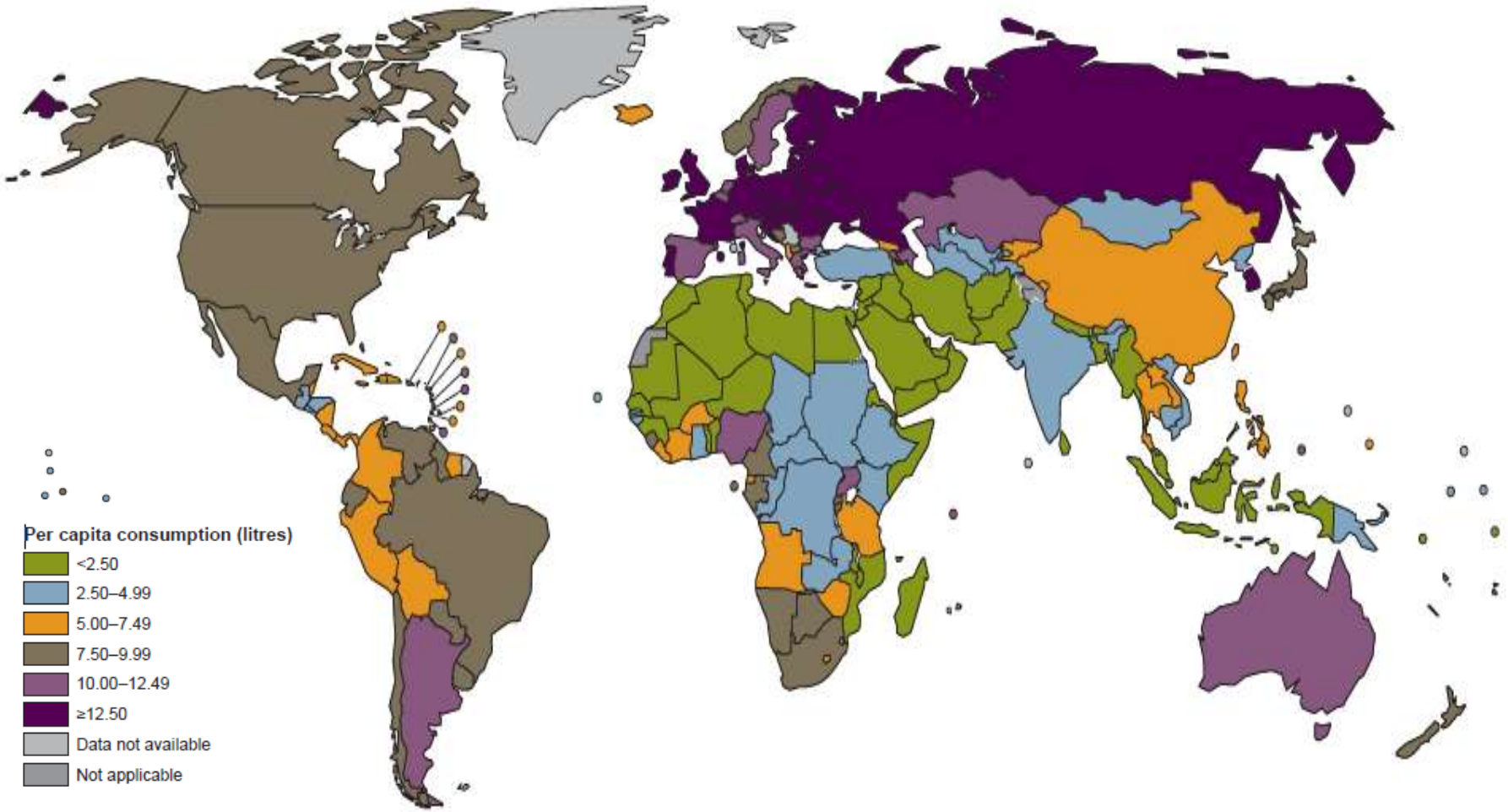
Etiologies of HCC



Etiologies of HCC



Alcohol per capita consumption



WHO Global status report, 2011

One Standard Drink

12 fl oz of regular beer = **8–9 fl oz of malt liquor** (shown in a 12 oz glass) = **5 fl oz of table wine** = **1.5 fl oz shot of 80-proof spirits** ("hard liquor"—whiskey, gin, rum, vodka, tequila, etc.)

about 5% alcohol

about 7% alcohol

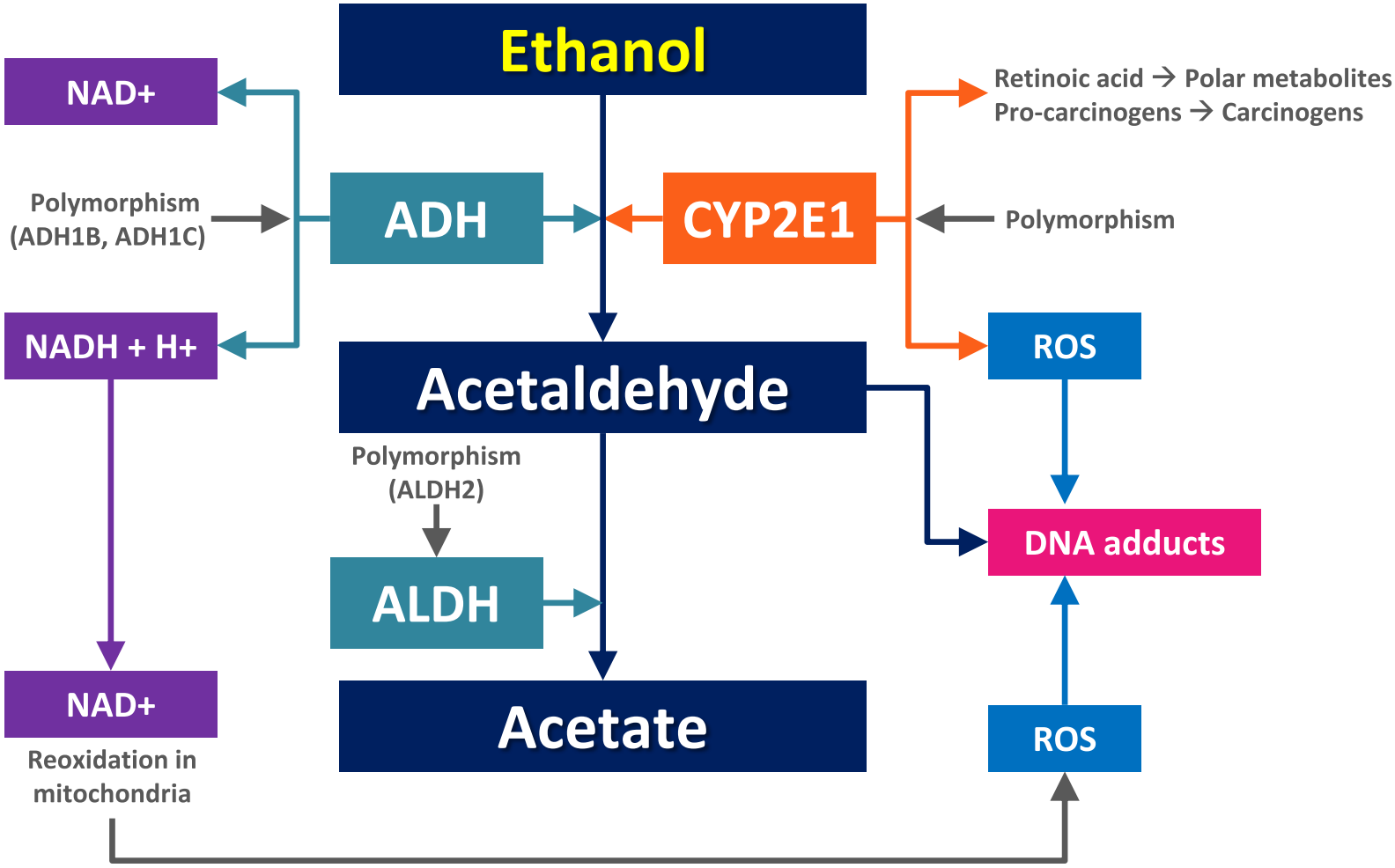
about 12% alcohol

about 40% alcohol

The percent of "pure" alcohol, expressed here as alcohol by volume (alc/vol), varies by beverage.

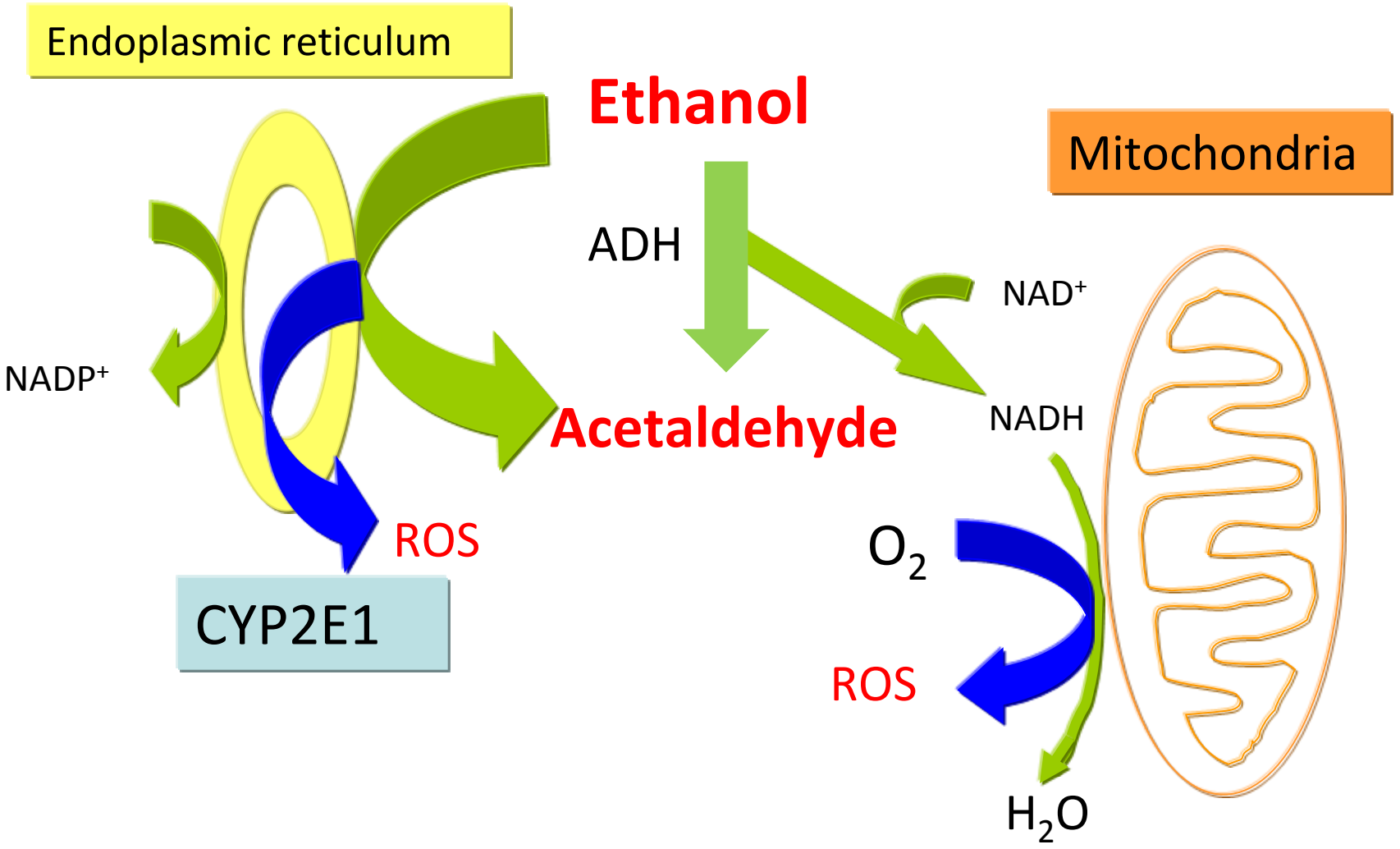
Image from www.niaaa.nih.gov

Alcohol metabolism

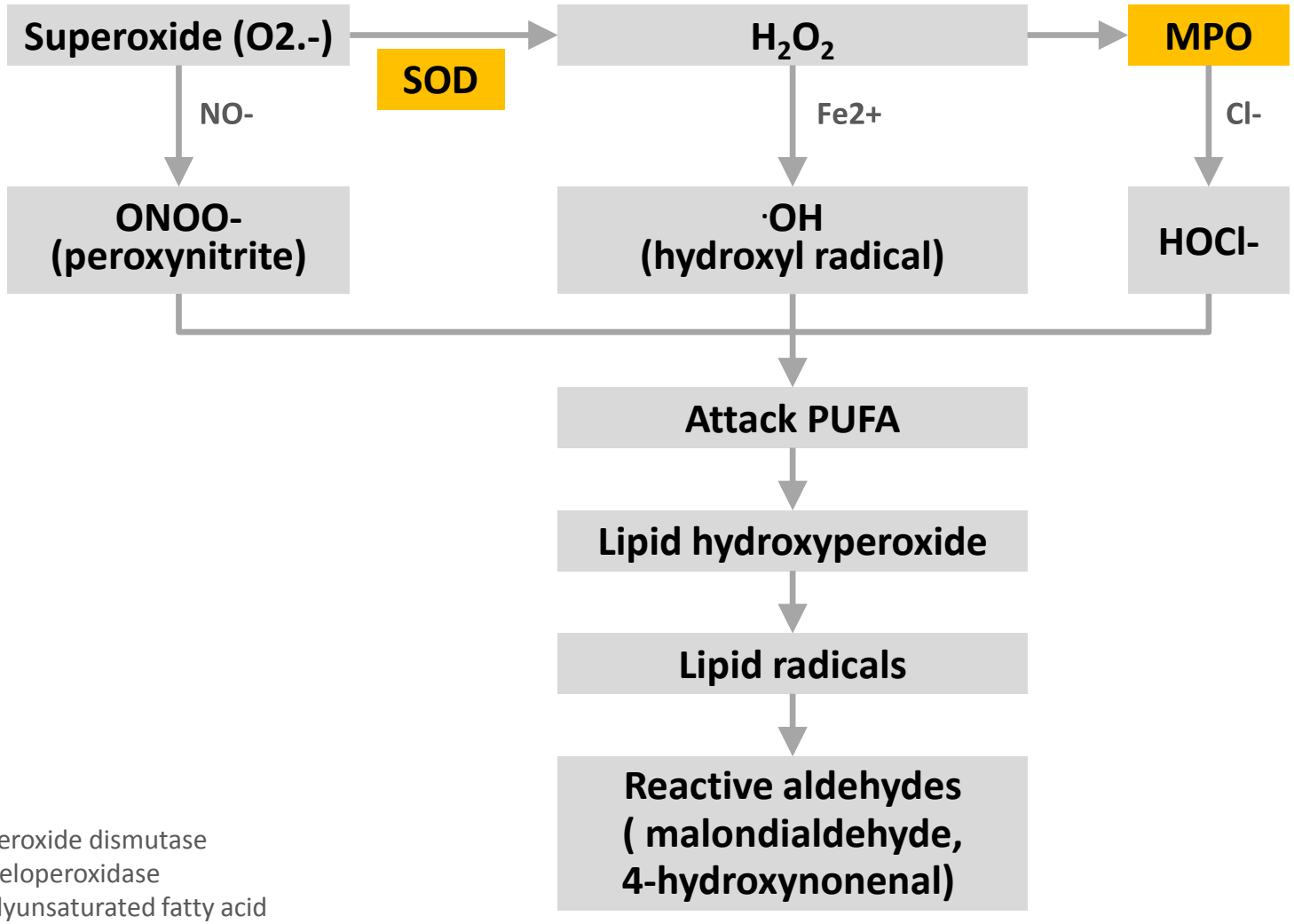


Seitz and Stickel. Nature. 2007

Mechanism of Ethanol-induced ROS production in hepatocytes



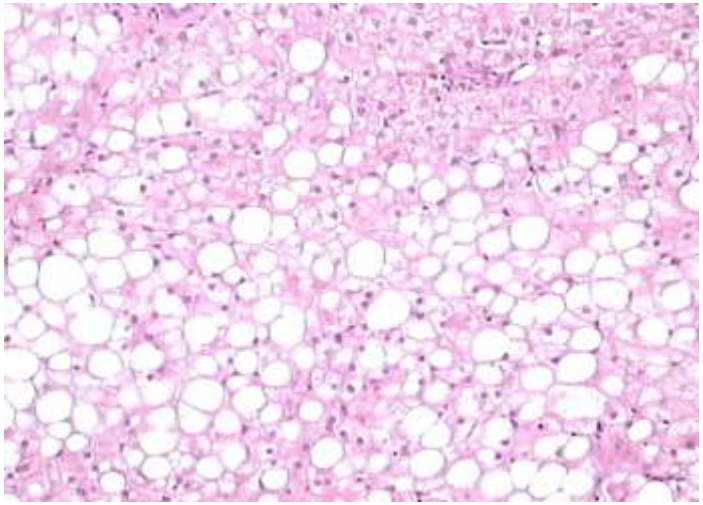
Effects of oxidative stress

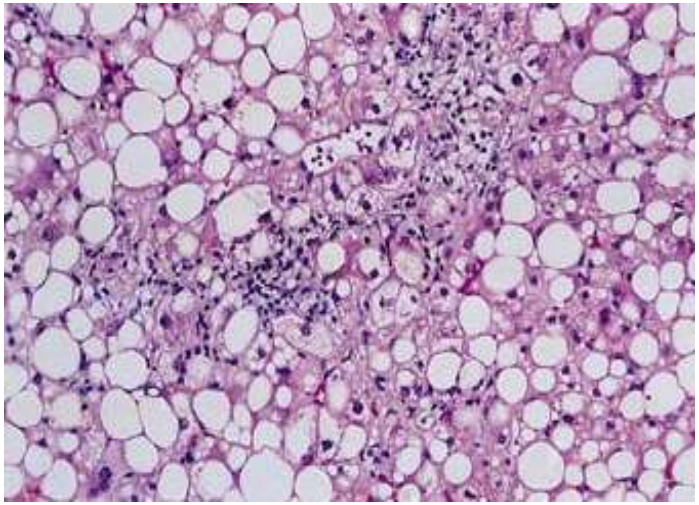


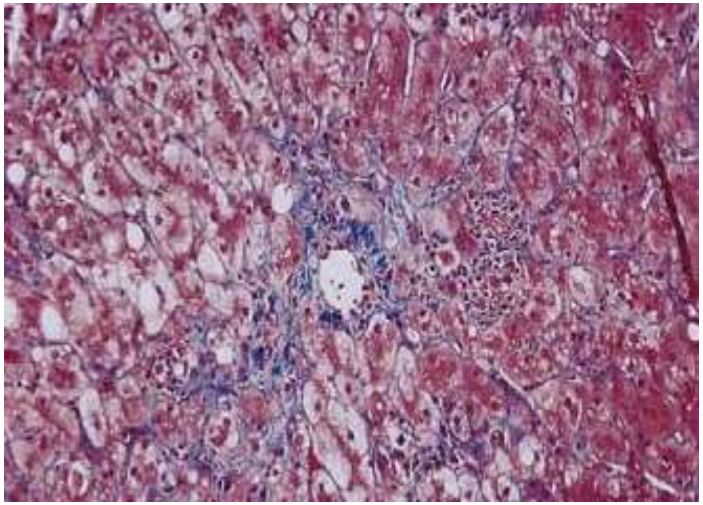
SOD: superoxide dismutase
MPO: myeloperoxidase
PUFA: Polyunsaturated fatty acid

Chronic alcohol consumption leads to liver injury

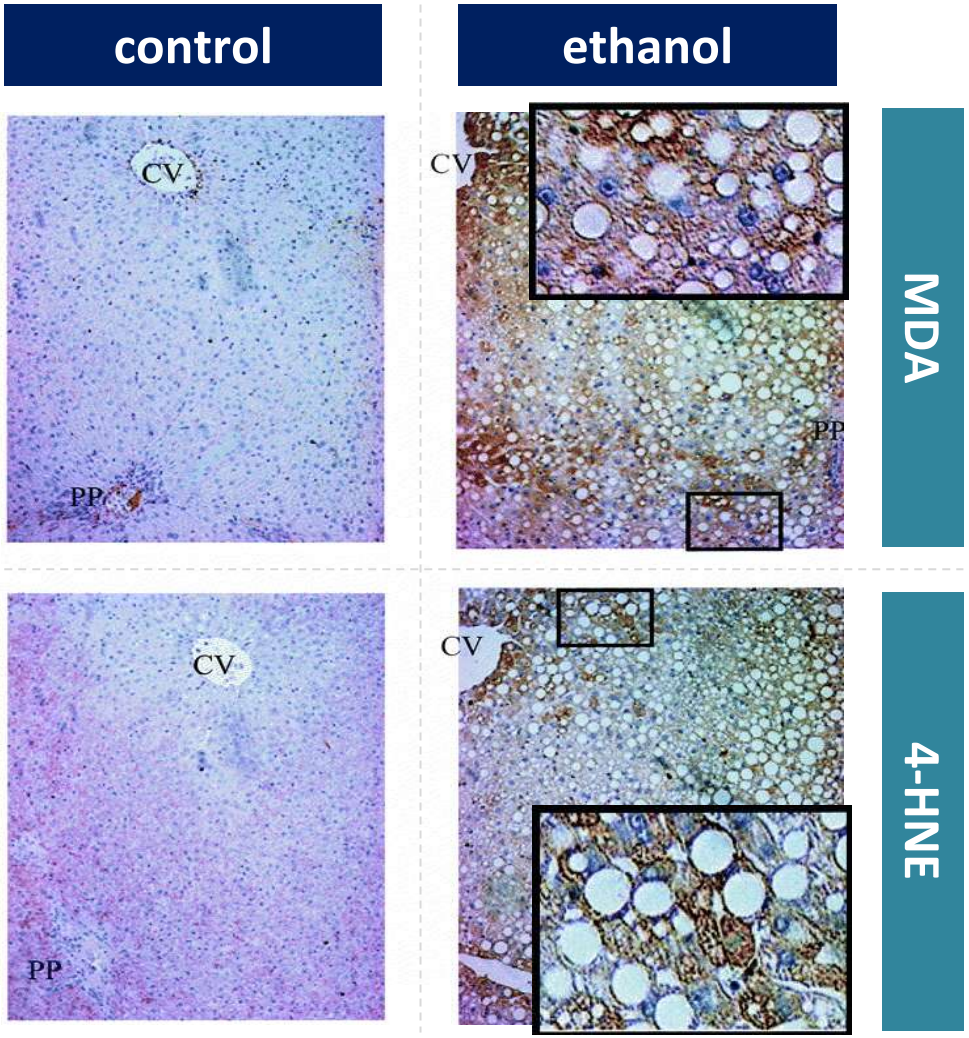
Steatosis	-- fatty liver
Hepatitis	-- inflammation
Fibrosis	-- excess collagen deposition
Cirrhosis	-- tissue scarring





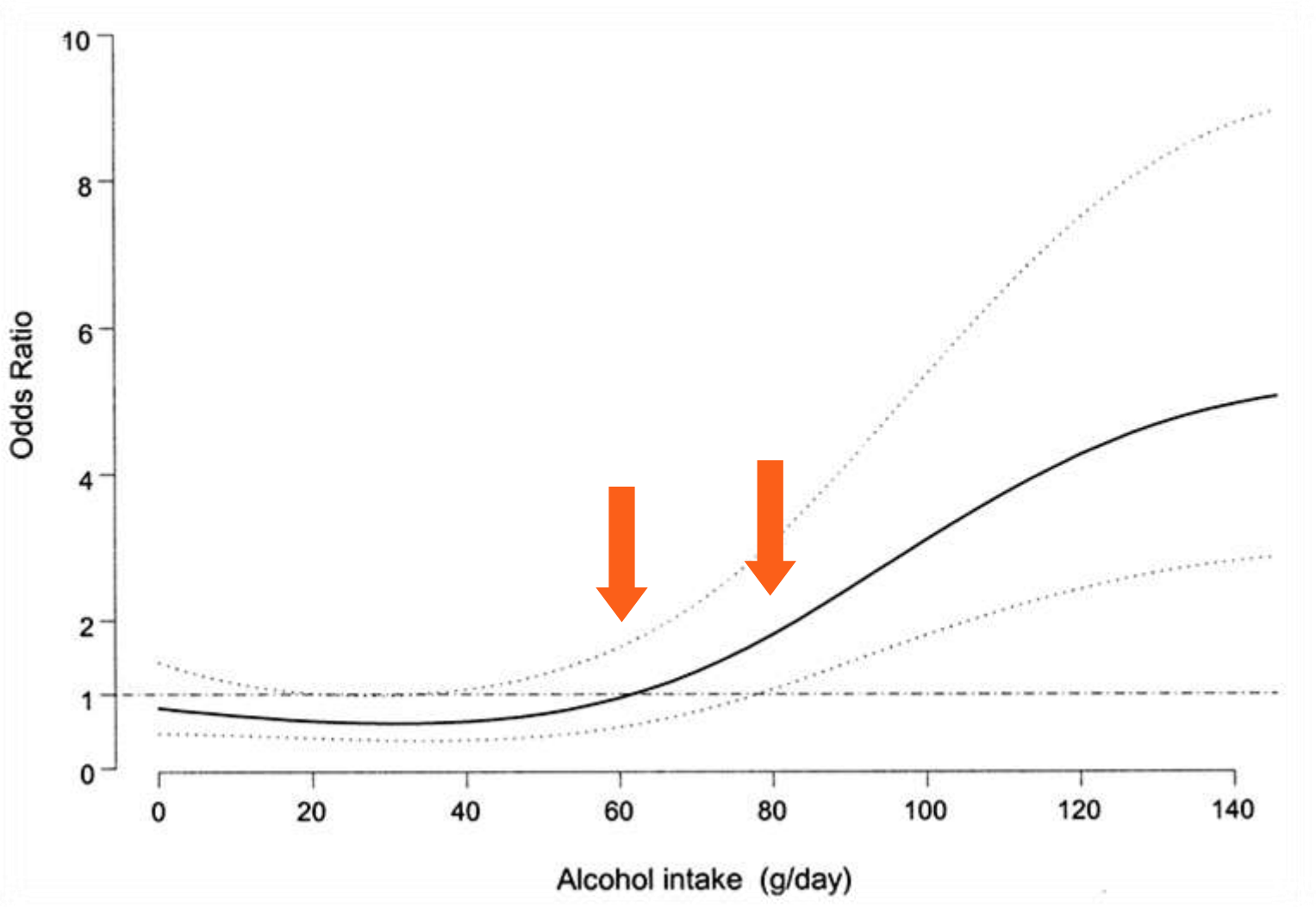


Immunostaining of reactive aldehydes



Sampey BP, Alcoholism; Clinical and experimental Research 2003

Dose of alcohol and HCC



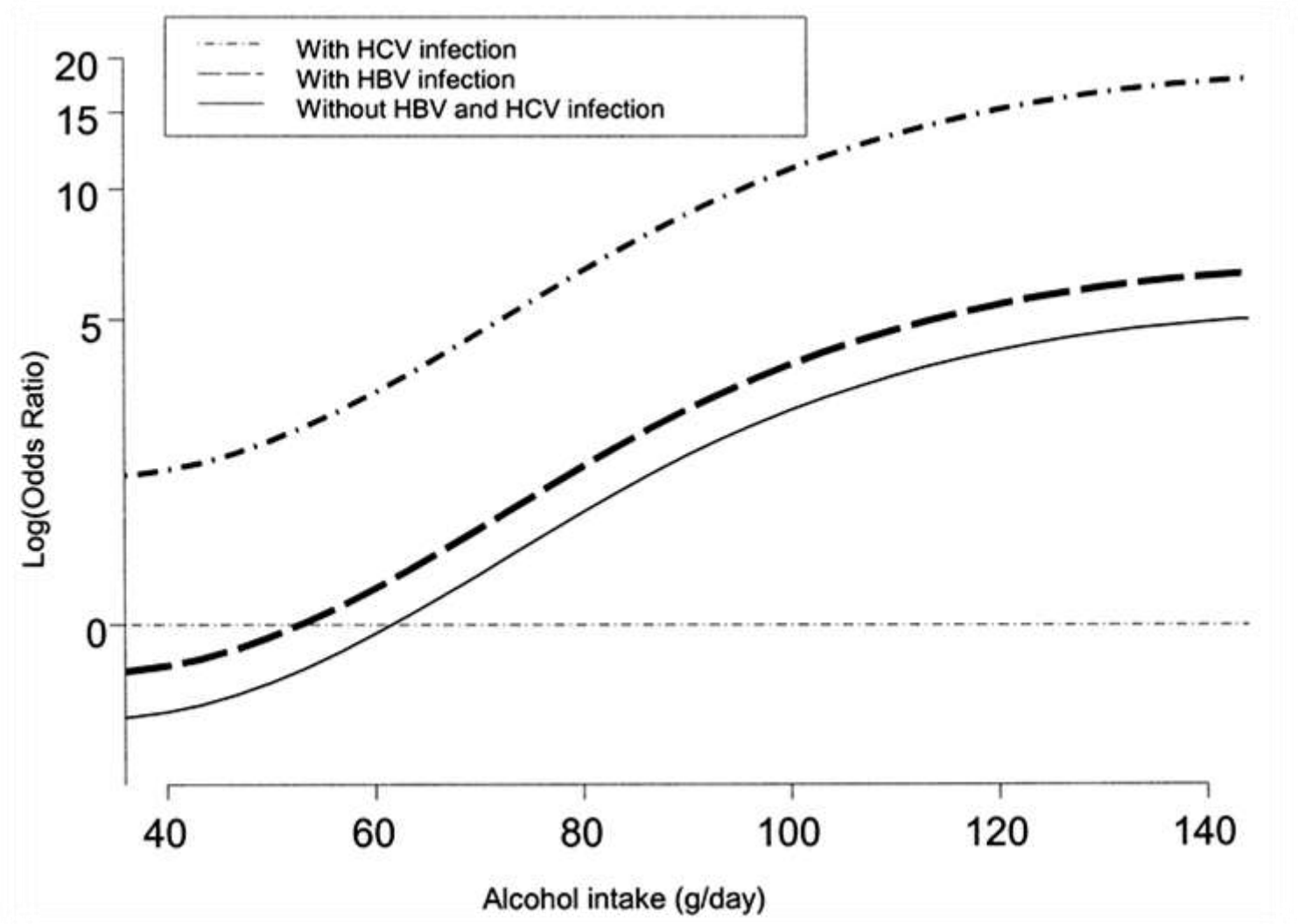
Donato et al. Am J Epidemiol 2002

> 80g/day of alcohol increased HCC

Author/country	Alcohol		Hepatitis C	
	Cases/control (number)	Odds ratio (95% CI)	Cases/control (number)	Odds ratio (95% CI)
Tagger et al,[17] Italy				
Daily alcohol (*g/d*)				
<40	31/219	1.0 (reference)	47/18	26.1 (12.6–54)
40–80	27/157	1.5 (0.7–2.9)	32/7	62.6 (23.3–168)
>80	102/203	7.3 (4.0–13.1)	42/5	126 (42.8–373)
Hassan et al,[5] United States				
Daily alcohol				
No	40/136	1.0 (reference)		19.1 (4.1–89.1)
Yes	75/94	2.4 (1.3–4.4)		53.9 (7.0–415.7)
<80 g/day	33/63	1.7 (0.9–3.7)		
>80 g/day	42/31	4.5 (1.4–14.8)		
Yu et al,[3] Taiwan				
Alcohol use				
No	53/81	1.0 (reference)	8/2	6.1 (1.2–30.1)
Yes	60/44	2.1 (1.2–3.7)	6/0	Unable to calculate

Morgan et al. Gastroenterology 2004

Alcohol and Viral Hepatitis



Donato et al. Am J Epidemiol 2002

Synergism with viral infection and alcohol in HCC development

Interaction Variables		β Coefficient (±SE)	P	OR (95% CI)	S (95% CI)*
Virus	Alcohol				
Negative	Negative			1	
Positive	Negative	2.9 (0.79)	.0001	19.1 (4.1-89.1)	
Negative	Positive	0.87 (0.32)	.006	2.4 (1.3-4.4)	
Positive	Positive	3.9 (1.04)	.0001	53.9 (7.0-415.7)	2.7 (1.1-5.2)
Diabetes	Alcohol				
Negative	Negative			1	
Positive	Negative	0.87 (0.33)	.008	2.4 (1.3-4.5)	
Negative	Positive	0.95 (0.34)	.004	2.6 (1.4-4.9)	
Positive	Positive	2.3 (0.69)	.001	9.9 (2.5-39.3)	2.9 (1.3-4.6)

*S = Synergy Index described by Rothman[9] = $(OR_{11} - 1)/(OR_{01} + OR_{10} - 2)$, where OR_{11} = odds ratio of the joint effect of 2 risk factors; OR_{01} and OR_{10} = OR of each risk factor in the absence of the other.

Hassan et al. Hepatology 2002

Alcohol and smoking

Daily alcohol intake (grams)	Pack-years of smoking	No. of patients with viral hepatitis	No. of HCC deaths	HR	(95% CI)	*p* Value
All patients with viral hepatitis (n = 1990)						
<46.2	<10	996	617	1[1]	(Reference)	
≥46.2	<10	65	46	1.28	(0.94–1.73)	0.1172
<46.2	≥10	676	484	1.28	(1.12–1.46)	0.0003
≥46.2	≥10	239	192	1.72	(1.45–2.05)	<0.0001
Synergy index (95% CI)		1.30 (0.58–2.89)				
Viral hepatitis patients with early-stage tumor[2] (n = 717)						
<46.2	<10	416	197	1[3]	(Reference)	
≥46.2	<10	22	15	1.94	(1.13–3.33)	0.0171
<46.2	≥10	213	119	1.31	(1.01–1.69)	0.0430
≥46.2	≥10	63	49	2.20	(1.57–3.08)	<0.0001
Synergy index (95% CI)		0.96 (0.36–2.56)				
Viral hepatitis patients with advanced tumor (n = 1259)						
<46.2	<10	575	417	1[3]	(Reference)	
≥46.2	<10	43	31	1.07	(0.74–1.55)	0.7184
<46.2	≥10	455	360	1.27	(1.09–1.49)	0.0025
≥46.2	≥10	176	143	1.53	(1.25–1.87)	<0.0001
Synergy index (95% CI)		1.53 (0.41–5.75)				

Shih WL et al. Int J Cancer 2012

10 year abstinence from alcohol leads to decreased HCC-related mortality

Alcohol consumption status	Median daily intake (gram)	No. of participants	No. of HCC deaths	HR	(95% CI)	*p* Value
1031.0–2744.6	64.8	156	120	1.31	(1.07–1.60)	0.0084
>2744.6	160.4	148	118	1.36	(1.11–1.67)	0.0026
p value for trend				0.0006		
Continuing drinker	43.4	414	315	1[2]	(Reference)	
Ex-drinker						
Years since quitting						
<5	51.0	84	57	0.83	(0.63–1.10)	0.1977
5–9	41.7	69	50	0.92	(0.68–1.25)	0.5962
≥10	40.5	83	61	0.74	(0.56–0.98)	0.0343
Never drinker	0	1338	866	0.79	(0.69–0.91)	0.0013

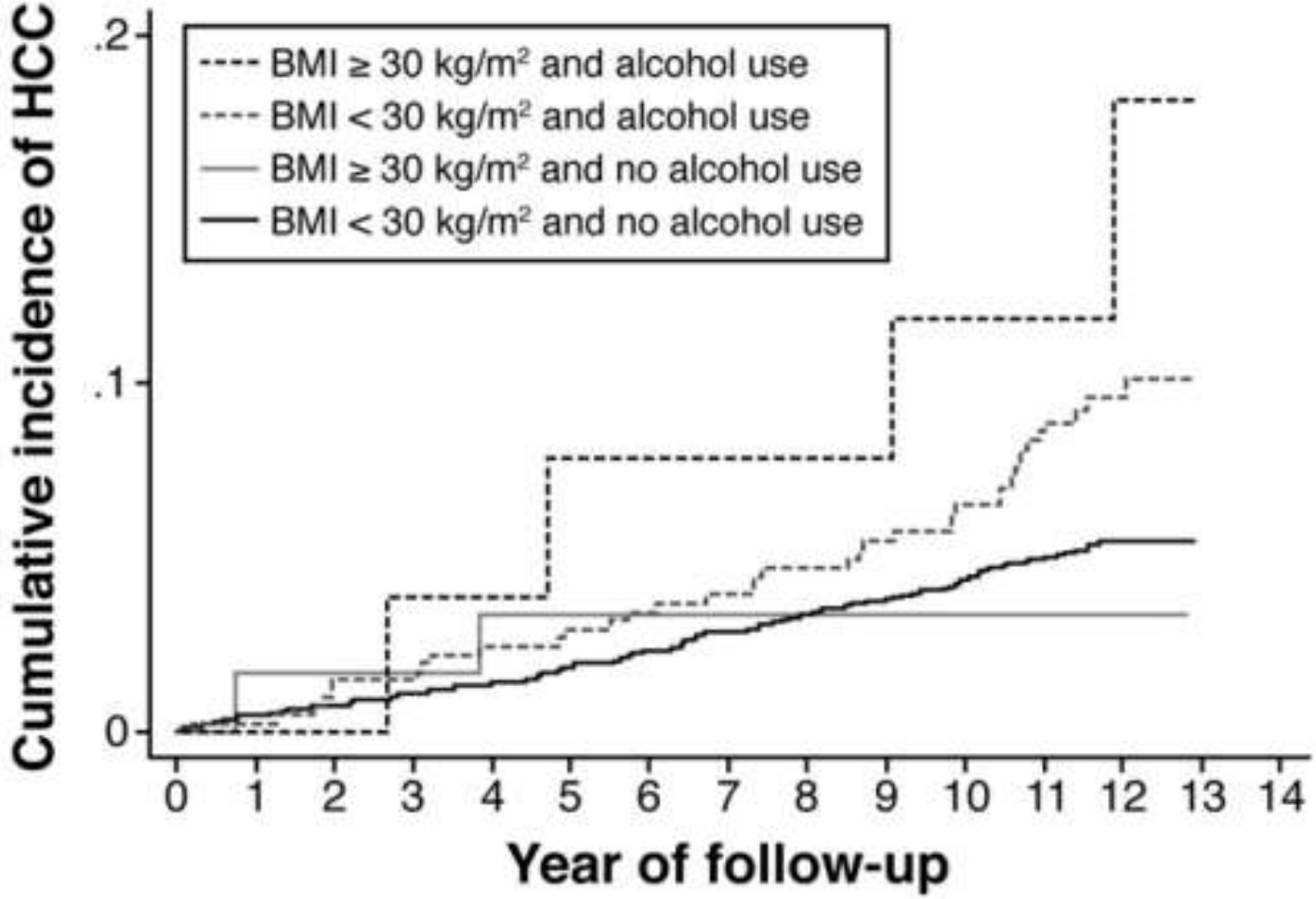
Shih WL et al. Int J Cancer 2012

Alcohol and Diabetes

Factor 1	Factor 2	Cases (n = 295)	Controls (n = 435)	OR (95% CI)[a]	Interaction effect: Additive S (95% CI)[b]	Interaction effect: Multiplicative OR (95% CI)[a]
Diabetes	Alcohol drinking					
No	≤ 4 drinks per day	157	352	1.0		
No	≥ 4 drinks per day	76	45	3.4 (2.2–5.4)		
Yes	≤ 4 drinks per day	43	36	2.5 (1.5–4.0)		
Yes	> 4 drinks per day	19	2	17.3 (3.9–77.6)	4.2 (2.6–5.8)	2.0 (0.4–10.1)
Diabetes	Cigarette smoking[c]					
No	Non/long-term ex-smokers	127	272	1.0		
No	Current/recent ex-smokers	106	125	1.5 (1.0–2.2)		
Yes	Non/long-term ex-smokers	33	28	2.5 (1.4–4.4)		
Yes	Current/recent ex-smokers	29	10	4.9 (2.2–10.9)	2.0 (0.9–3.1)	1.3 (0.5–3.5)
Alcohol drinking	Cigarette smoking[c]					
≤ 4 drinks per day	Non/long-term ex-smokers	125	276	1.0		
≤ 4 drinks per day	Current/recent ex-smokers	35	24	3.3 (1.8–6.1)		
> 4 drinks per day	Non/long-term ex-smokers	75	112	1.5 (1.0–2.2)		
> 4 drinks per day	Current/recent ex-smokers	60	23	5.9 (3.3–10.4)	1.7 (0.9–2.6)	1.2 (0.5–2.6)

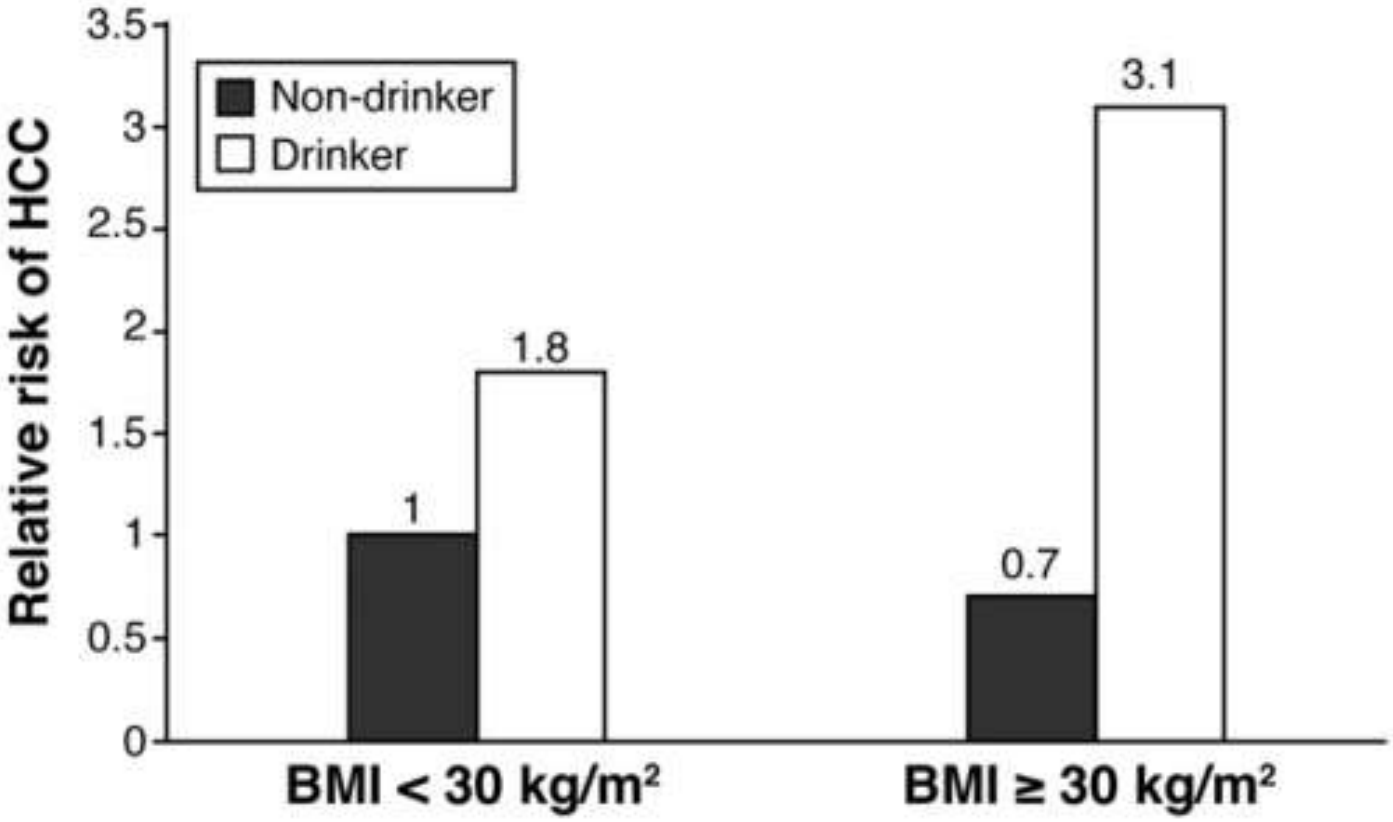
Yuan JM et al. Cancer. 2004.

Alcohol and Obesity



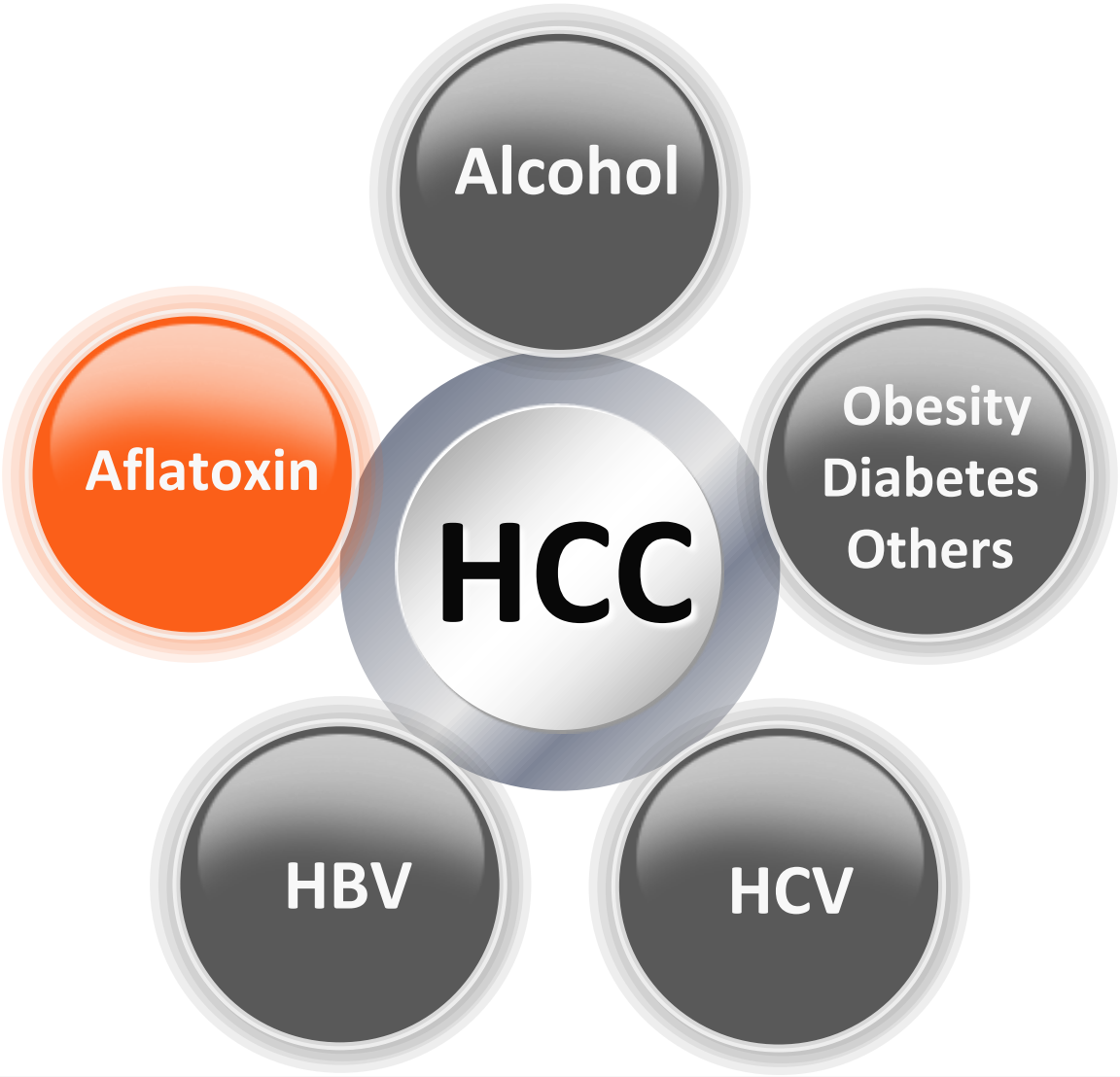
Loomba et al. Clin Gasteroenterol Hepatol. 2010.

Synergism of Obesity in Drinkers



Loomba et al. Clin Gasteroenterol Hepatol. 2010.

Etiologies of HCC



Aflatoxin produced by fungi

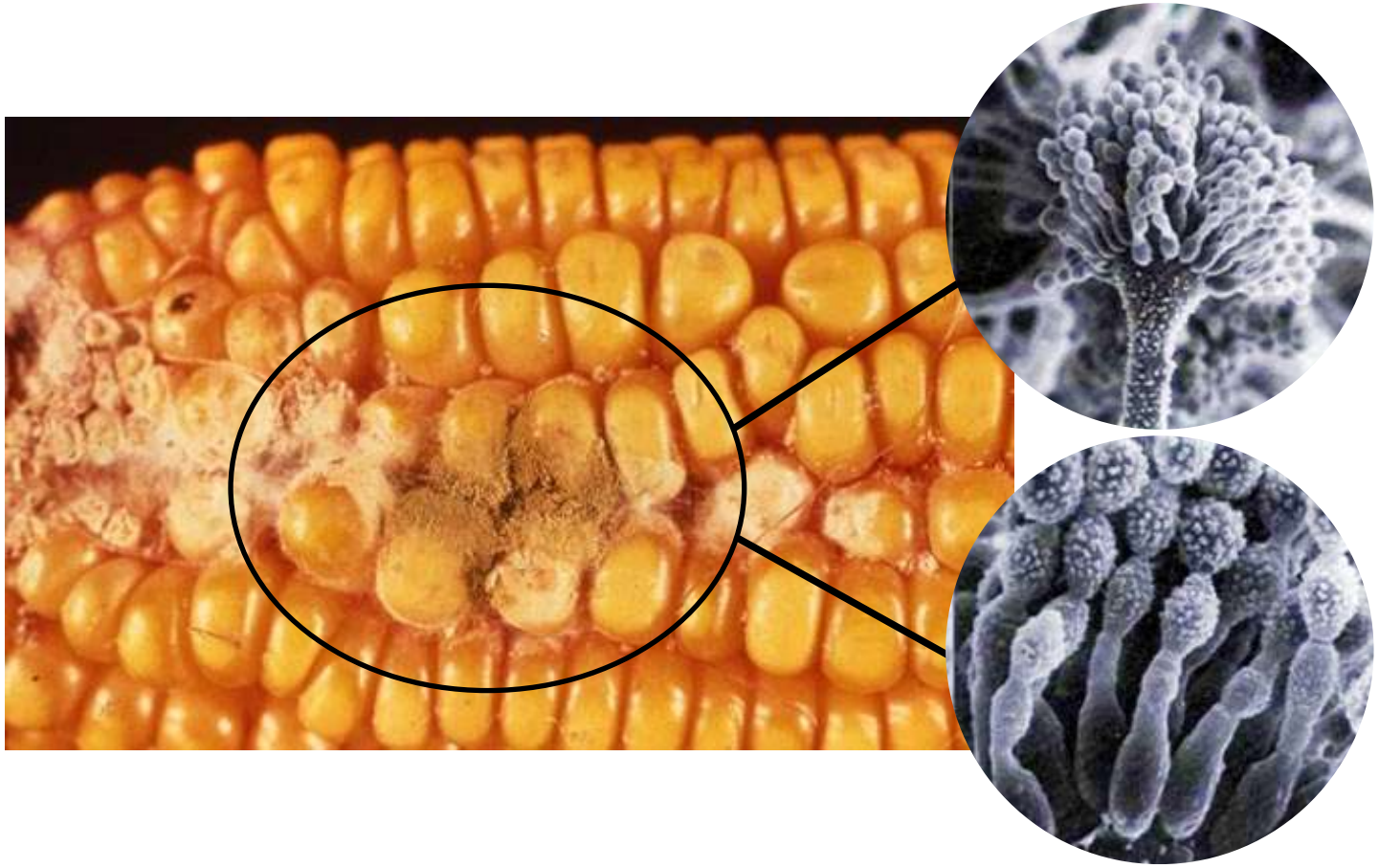
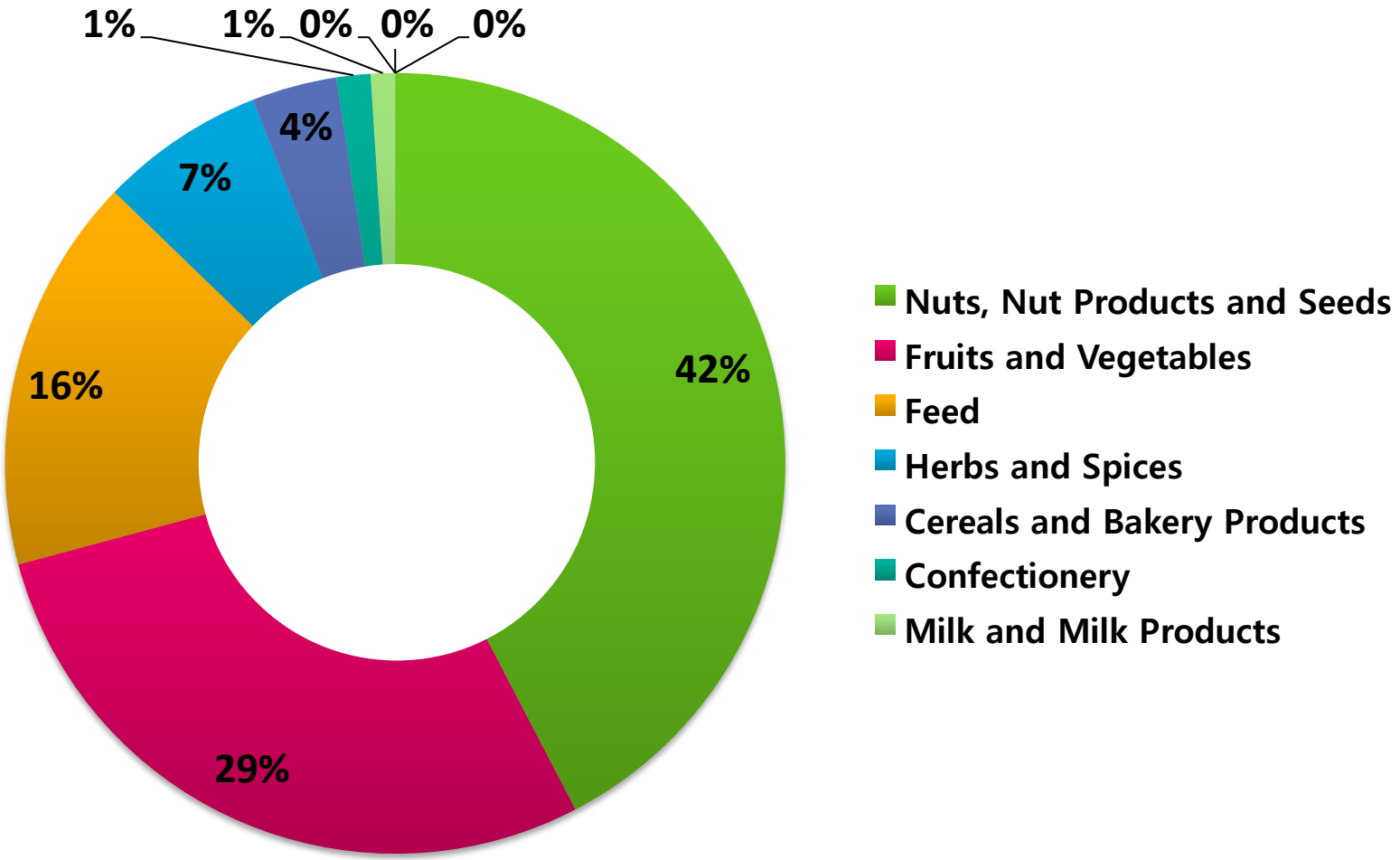


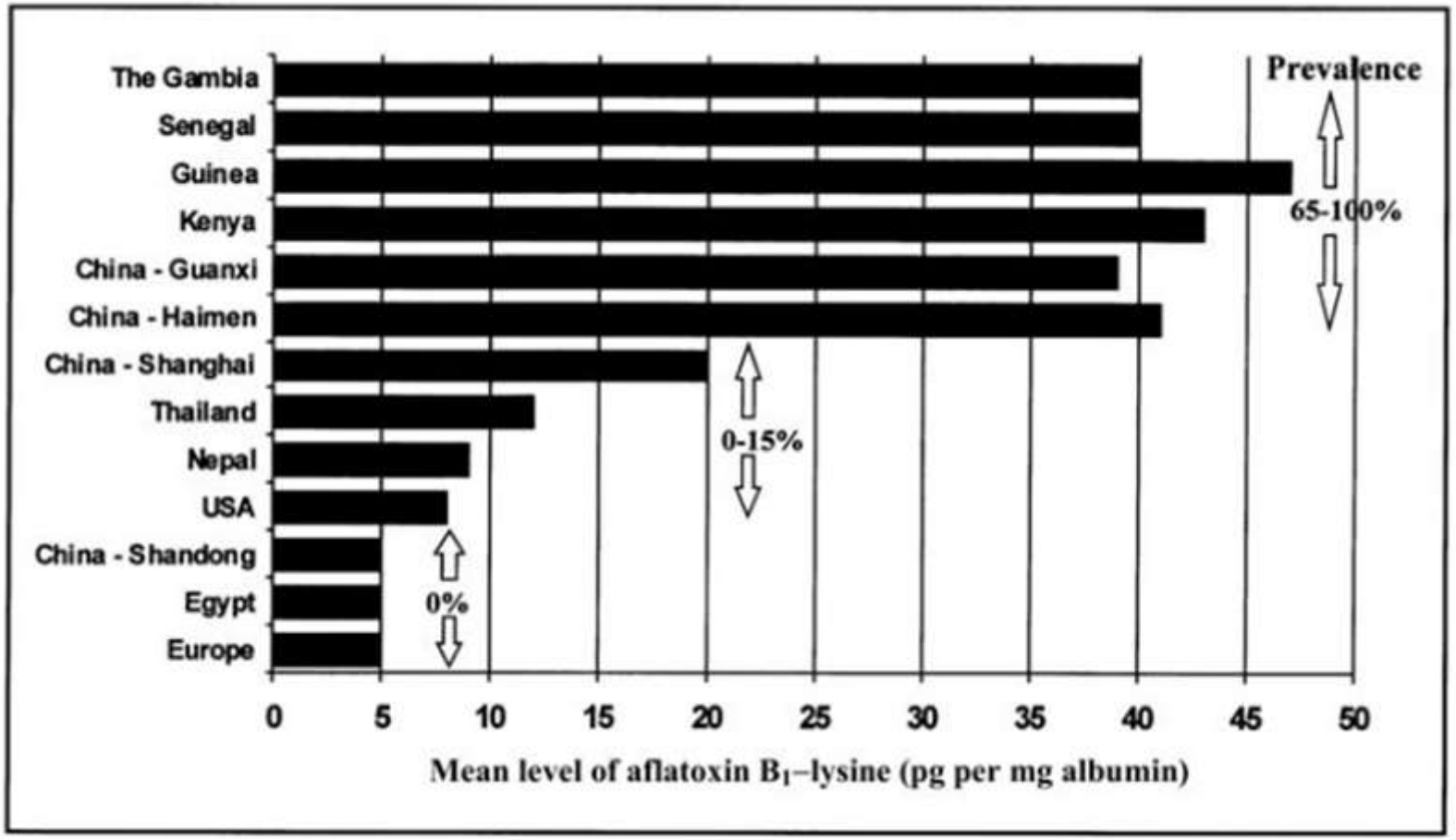
Image from aspergillusflavus.org, biologi.lipi.go.id

Aflatoxin in food



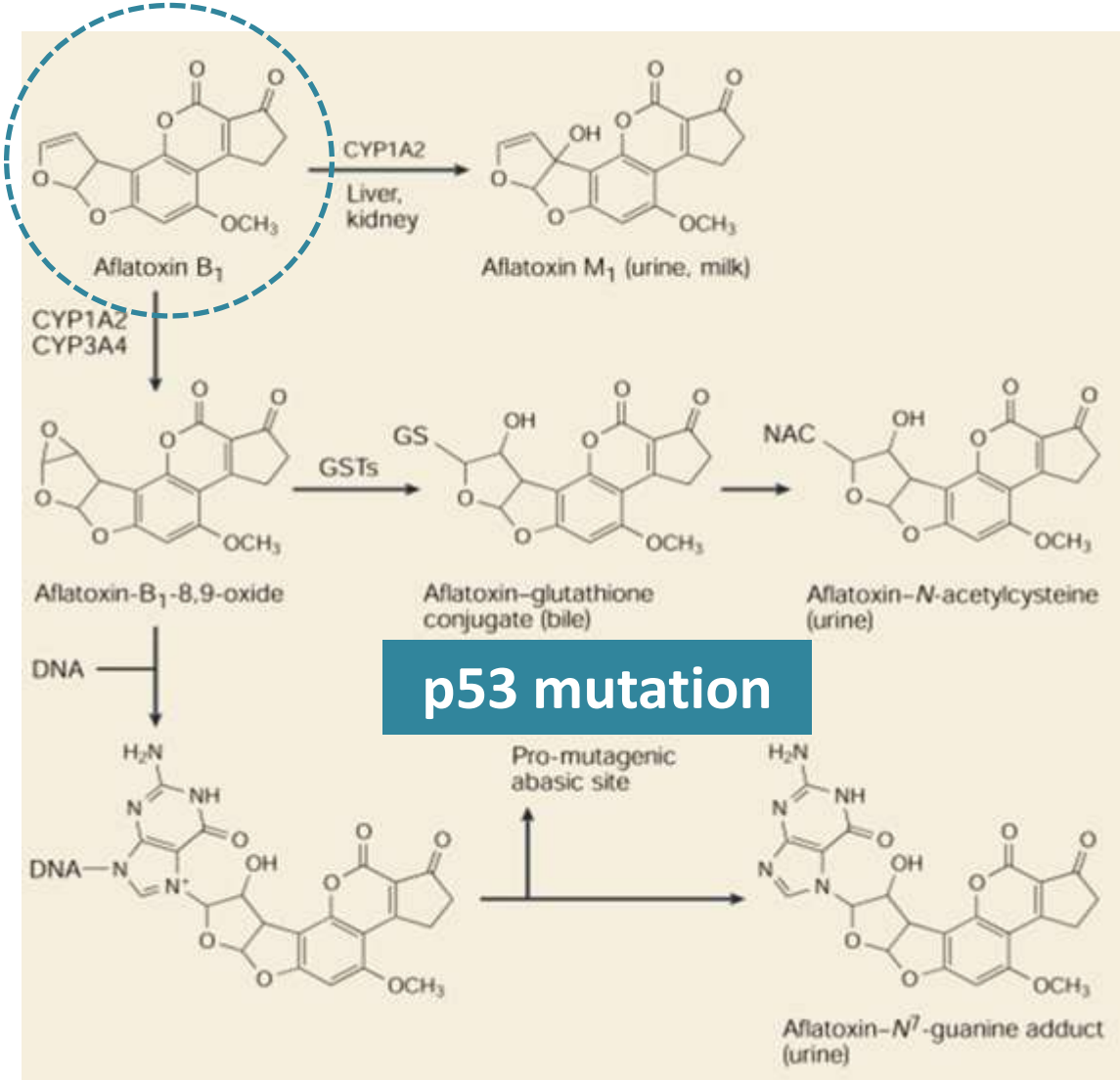
The Rapid Alert System for Food and Feed 2012.

Prevalence of aflatoxin exposure



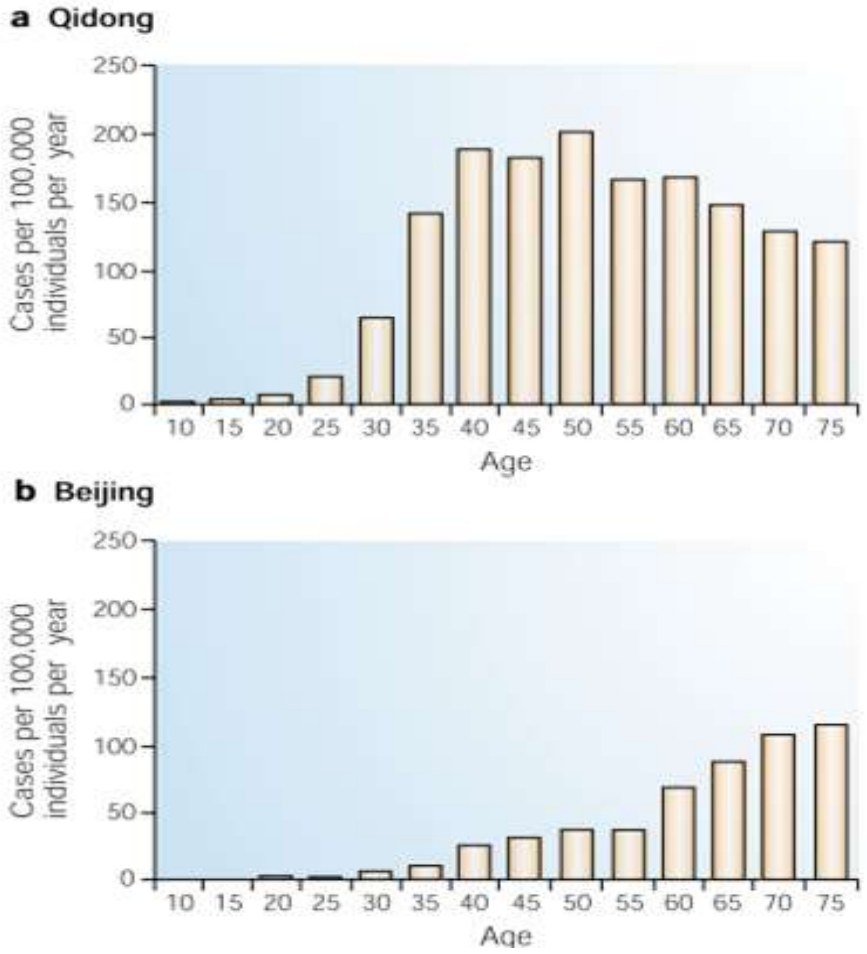
Montesano R et al. J Natl Cancer Inst. 1997.

Aflatoxin detoxification



Kensler et al. Nature. 2003

High incidence of HCC in Qidong



Kensler et al. Nature. 2003

Analyses of TP53 mutation in HCC

Region/country	No. of HCC analysed	No. with codon 249^{ser} mutation	Reference
Africa			
Mozambique	15	8	Ozturk (1991)
South Africa — Transkei	12	1	Ozturk (1991)
Southern Africa	10	3	Bressac *et al.* (1991)
Senegal	15	10	Coursaget *et al.* (1993)
America			
USA			
Alaska	7	0	Buetow *et al.* (1992)
Alaskans	12	0	De Benedetti *et al.* (1995)
	12	0	Kazachkov *et al.* (1996)
	17	0	Wong *et al.* (2000)
Mexico	16	3	Soini *et al.* (1996)

Stern et al. Cancer Epidemiol. Biomarkers Prev. 2001.

Analyses of TP53 mutation in HCC

Asia			
China			
Qidong	36	21	Scorsone *et al.* (1992)
	25	13	Fujimoto *et al.* (1994)
	20	9	Li *et al.* (1993)
Xian	45	1	Buetow *et al.* (1992)
Beijing	9	0	Fujimoto *et al.* (1994)
Tongan	21	7	Yang *et al.* (1997)
Jiang-su south	16	9	Shimizu *et al.* (1999)
Jiang-su north	15	1	Shimizu *et al.* (1999)
Shanghai	12	1	Buetow *et al.* (1992)
	18	1	Li *et al.* (1993)
	20	4	Wong *et al.* (2000)
Guanxi	50	18	Stern *et al.* (2001)
Hong Kong	26	1	Ng *et al.* (1994a,b)
	30	4	Wong *et al.* (2000)
India	21	2	Katiyar *et al.* (2000)
Indonesia	4	1	Oda *et al.* (1992)
Japan	128	1	Oda *et al.* (1992)
	10	0	Buetow *et al.* (1992)
	43	0	Murakami *et al.* (1991)
	60	0	Hayashi *et al.* (1993)

Stern et al. Cancer Epidemiol. Biomarkers Prev. 2001.

Analyses of TP53 mutation in HCC

Region/country	No. of HCC analysed	No. with codon 249^{ser} mutation	Reference
Korea (Republic of)	6	0	Oda *et al.* (1992)
	35	0	Park *et al.* (2000)
Singapore (Chinese)	44	0	Shi *et al.* (1995)
Taiwan, China	2	0	Oda *et al.* (1992)
	12	0	Hosono *et al.* (1993)
Europe			
France	100	2	Laurent-Puig *et al.* (2001)
Germany	13	0	Kress *et al.* (1992)
	20	0	Kubicka *et al.* (1995)
Italy	20	0	Bourdon *et al.* (1995)
Spain	70	0	Boix-Ferrero *et al.* (1999)
United Kingdom	19	0	Challen *et al.* (1992)
	170	0	Vautier *et al.* (1999)

Stern et al. Cancer Epidemiol. Biomarkers Prev. 2001.

HCC cases attributable to aflatoxin exposure

WHO region/country	Population (millions)[a]	Annual HCC cases	
		HBsAg-negative	HBsAg-positive
Africa			
Democratic Republic of Congo	68	1–173	1–551
Ethiopia	85	11–288	21–643
The Gambia	1.7	1–17	3–117
Kenya	38	11–450	44–2,270
Mozambique	21	73–361	111–1,200
Nigeria	149	1,800–2,940	8,200–13,400
South Africa	48	0–79	0–255
Tanzania	41	1–195	1–554
Zimbabwe	13	19–50	68–249
Total region	755	2,150–9,300	9,230–50,600
North America			
Canada	33	1	1
United States	300	8	1–5
Total region	333	9	2–5
Latin America			
Argentina	40	0–16	0–5
Brazil	190	4–930	3–969
Mexico	109	152–924	14–83
Total region	562	589–2,980	84–2,060
Eastern Mediterranean			
Egypt	81	51–452	37–1400
Iran	66	33–56	4–9
Pakistan	172	116–832	119–851
Sudan	41	58–717	140–5,950
Total region	569	446–3,720	341–13,200
Southeast Asia			
India	1,150	438–11,200	331–16,200
Indonesia	237	203–2,820	160–4,340
Thailand	63	307–439	461–1,100
Total region	~1,734	1,740–17,300	1,460–27,600
Western Pacific region			
Australia	21	0–1	0–1
China	1,300	1,990–4,430	5,300–14,400
Korea	50	5–29	6–45
Malaysia	28	40–372	63–588
Philippines	90	333–462	594–2,330
Total region	~1,740	2,710–6,510	6,310–21,200
Europe			
Eastern Europe	290	94–114	61–244
Southern Europe	144	0–56	0–121
Western Europe	183	5–24	1–7
Total region	617	99–184	62–372
Total (world)	6,280	7,700–40,000	17,500–115,000
Total annual HCC cases attributable to aflatoxin worldwide		25,200–155,000	

[a]Data from Central Intelligence Agency 2009.

Liu and Wu. Environmental Health Perspectives 2010

The combined effects of HBV and aflatoxin

Population [Reference]	Cohort	Cases	Controls	Biomarker	OR
Shanghai, PRC [17]	18,224 Males	50	267	Urinary AF biomarker[d]	3.4 (1.1–10.0) AF alone 7.3 (2.2–24) HBsAg alone 59.4 (16.6–212) AF and HBsAg
Taiwan [18]	12,040 Males 13,758 Females	56	220	Urinary AF metabolites[e]	1.7 (0.3–10.8) AF alone 22.8 (3.6–143.4) HBsAg alone 111.9 (13.8–905) AF and HBsAg
Taiwan [18]	As above	29 HBsAg +ve	21 HBsAg +ve	Urinary AF metabolites[f]	5.5 (1.3–23.4)
Taiwan [23]	4691 Males 1796 Females	33 (20)[g]	123 (86)[g]	AF-albumin	5.5 (1.2–24.5) AF alone 129 (25–659) AF and HBsAg
Taiwan [21]	4841 Male HBsAg carriers 2501 Male non-carriers	43 HBsAg +ve	86 HBsAg +ve	Urinary AFM1	6.0 (1.2–29.0)[a]
Taiwan [20]	12,024 Males 13,594 Females	79 HBsAg +ve	149 HBsAg +ve	AF-albumin	2.0 (1.1–3.7)[b]
Qidong Co., PRC [22]	145 Male HBsAg carriers	22 HBsAg +ve	123 HBsAg +ve	Urinary AFM1[c]	3.3 (1.2–8.7)

Wild and Montesano. Cancer Letters. 2009

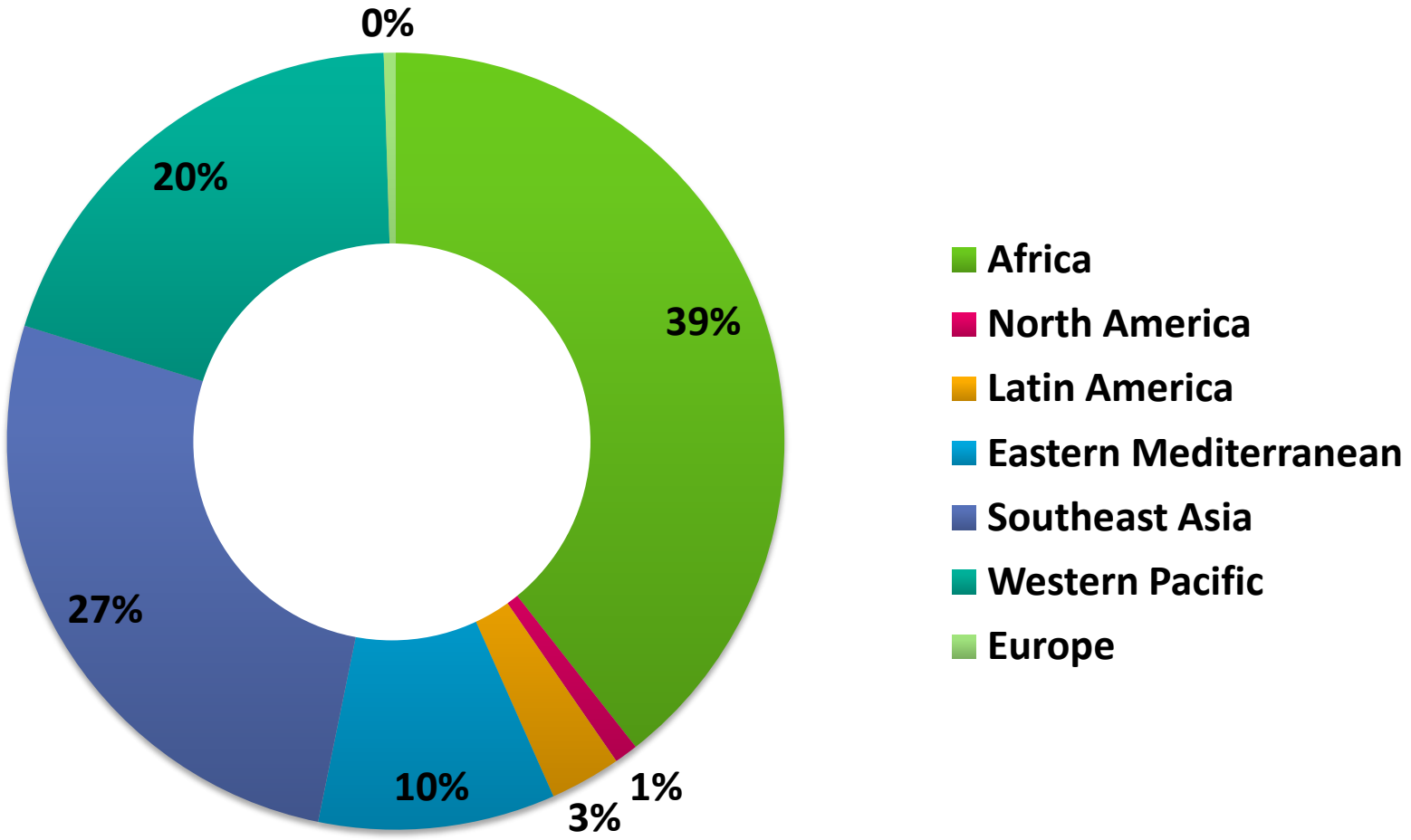
The effects of aflatoxin in advance liver disease associated with HCV

Comparison of clinical features and aflatoxin levels between anti-HCV-positive patients with and without advanced liver disease

Variables	Advanced liver disease (n = 76)	No or mild liver parenchyma change (n = 115)	P value
Age (years)	68.6 ± 6.4	67.7 ± 8.0	0.41
Sex (male:female)	29:47	51:64	0.39
HBsAg	13	11	0.12
ALT (U/L) [median (range)]	52.5 (8–192)	48.5 (5–292)	0.12
Platelet (10^9/L)	9.6 ± 3.0	11.6 ± 2.4	< 0.001
Albumin (g/dL)	4.0 ± 0.4	4.3 ± 0.3	< 0.001
AFP (ng/mL) [median (range)]	10.1 (1.1–10020)	4 (1.1–353)	< 0.001
Aflatoxin (AFB-alb/alb) [median (range)]	11.4 (0–51.4)	6.3 (0–61.4)	0.007

Chen CH et al. Am J Trop Med Hyg. 2007

HCC cases attributable to aflatoxin in the world



Liu and Wu. Environmental Health Perspectives. 2010

Preventive measures for aflatoxin

- Meticulate handling of foods
- HBV vaccination

Summary and Conclusions

- **Alcohol is a carcinogen**
- **Long term intake of >80g/day of alcohol increases the risk of HCC**
- **A synergistic effect of alcohol, viral hepatitis, smoking, diabetes, and obesity is present**
- **Aflatoxin is a carcinogen with combined effects when present with viral hepatitis.**