

ACETALDEHYDE

Specific class 1 carcinogen associating with the use of alcoholic beverages

Research Unit on Acetaldehyde and Cancer

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Declaration of interest: Board member of Biohit Ltd.

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**Mikko Salaspuro, M.D., Ph.D.
Professor
University of Helsinki,
Faculty of Medicine,
Helsinki, Finland
mikko.salaspuro@helsinki.fi**

Presentation in nutshell

1. Acetaldehyde as a carcinogen
2. ALDH2-deficiency – undisputable evidence for the local carcinogenic action of acetaldehyde in man
3. Major role of oral microbes in local acetaldehyde exposure
4. Contribution of acetaldehyde present in alcoholic beverages to acetaldehyde exposure via saliva
5. Other sources of acetaldehyde exposure
 - Tobacco smoking
 - Food stuffs
6. Minimization of acetaldehyde exposure
 - Drinking habits
 - L-cysteine medical devices and concepts

A key factor in cancer prevention is the identification of a specific carcinogen

ACETALDEHYDE as a carcinogen

- **Causes cancers in experimental animals**
 - Inhalation studies in rats and hamsters
 - Acetaldehyde drinking in rats
- **Acetaldehyde**
 - 25 μ M - 100 μ M \blacktriangleright exponential increase in mutagenic 1,N²-propanodeoxyguanosine adducts
 - 100 μ M - 500 μ M \blacktriangleright exponential increase in mutagenic DNA changes

Similar acetaldehyde levels are found in saliva during alcohol drinking and smoking

Acetaldehyde as a carcinogen

IARC 2007: Substantial mechanistic evidence derived from studies including individuals with ALDH2 gene mutations indicate that acetaldehyde contributes to causing malignant esophageal tumors in man

IARC 2009: Acetaldehyde associated with alcoholic beverages is carcinogenic to humans (**Group 1**)

- Alcohol drinking results in exposure to acetaldehyde, derived from the beverage itself and formed endogenously
- ALDH2-deficiency results in higher relative risks of upper digestive tract cancers

ALDH2-deficiency provides undisputable evidence for acetaldehyde being a local carcinogen in saliva

Alcohol oxidation

ADH

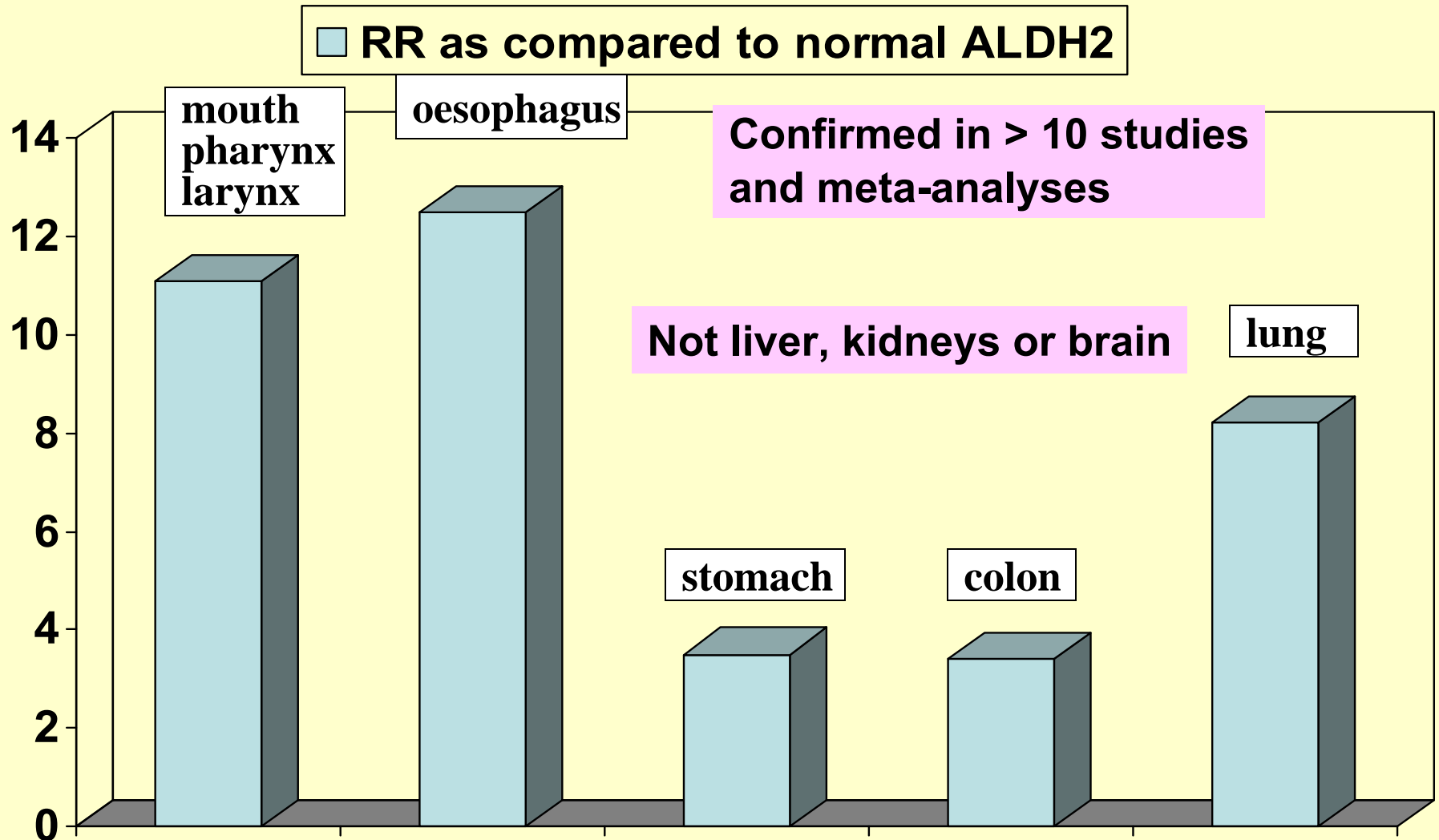
ALDH2

Ethanol \rightleftharpoons Acetaldehyde \rightleftharpoons Acetate

- In 30-65% of Asians
- Homozygotes don't drink at all
- Heterozygotes may become heavy drinkers or alcoholics
- ➔ Results in 4 - 380 -fold risk for upper digestive tract cancer

ALDH2-deficiency

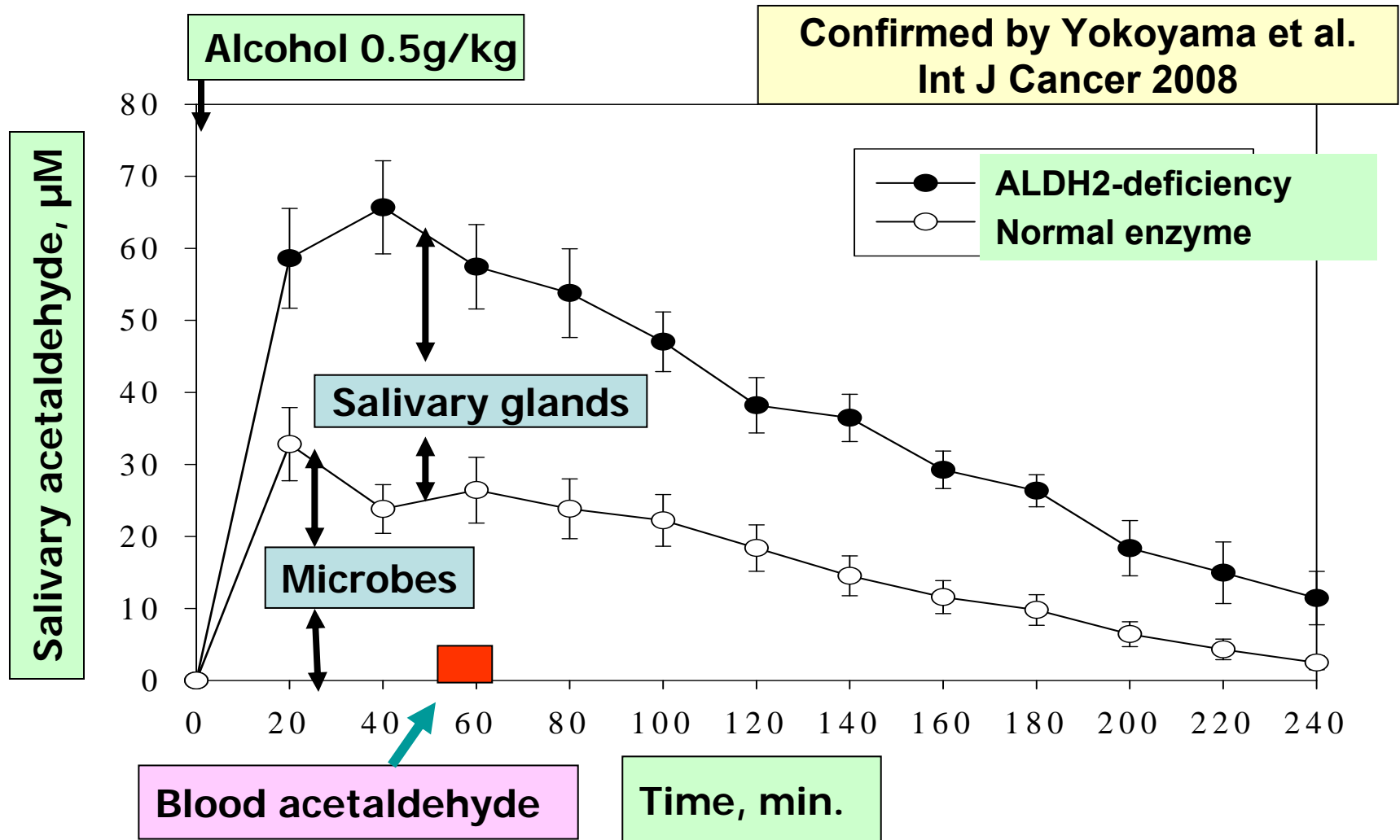
Effect of ALDH2-deficiency on cancer risk of heavy drinkers (Yokoyama et al. Carcinogenesis 1998)



The geographic distribution of *ALDH2*504Lys* allele carrier frequency. (Ann Hum Genet, Li et al. 2009)



ALDH2-deficiency results in enhanced acetaldehyde exposure via saliva (Väkeväinen et al. Alc Clin Exp Res 2000)



ACETALDEHYDE ► Group 1 carcinogen

What we should know regarding acetaldehyde exposure through alcoholic beverages

1. Relative contributions of:

1. Acetaldehyde present as a congener

2. Endogenous acetaldehyde

1. Role of microbes

2. Role of gene mutations

3. Role of environmental factors

1. Food stuffs containing < 2.8% of alcohol

2. Changes in oral flora

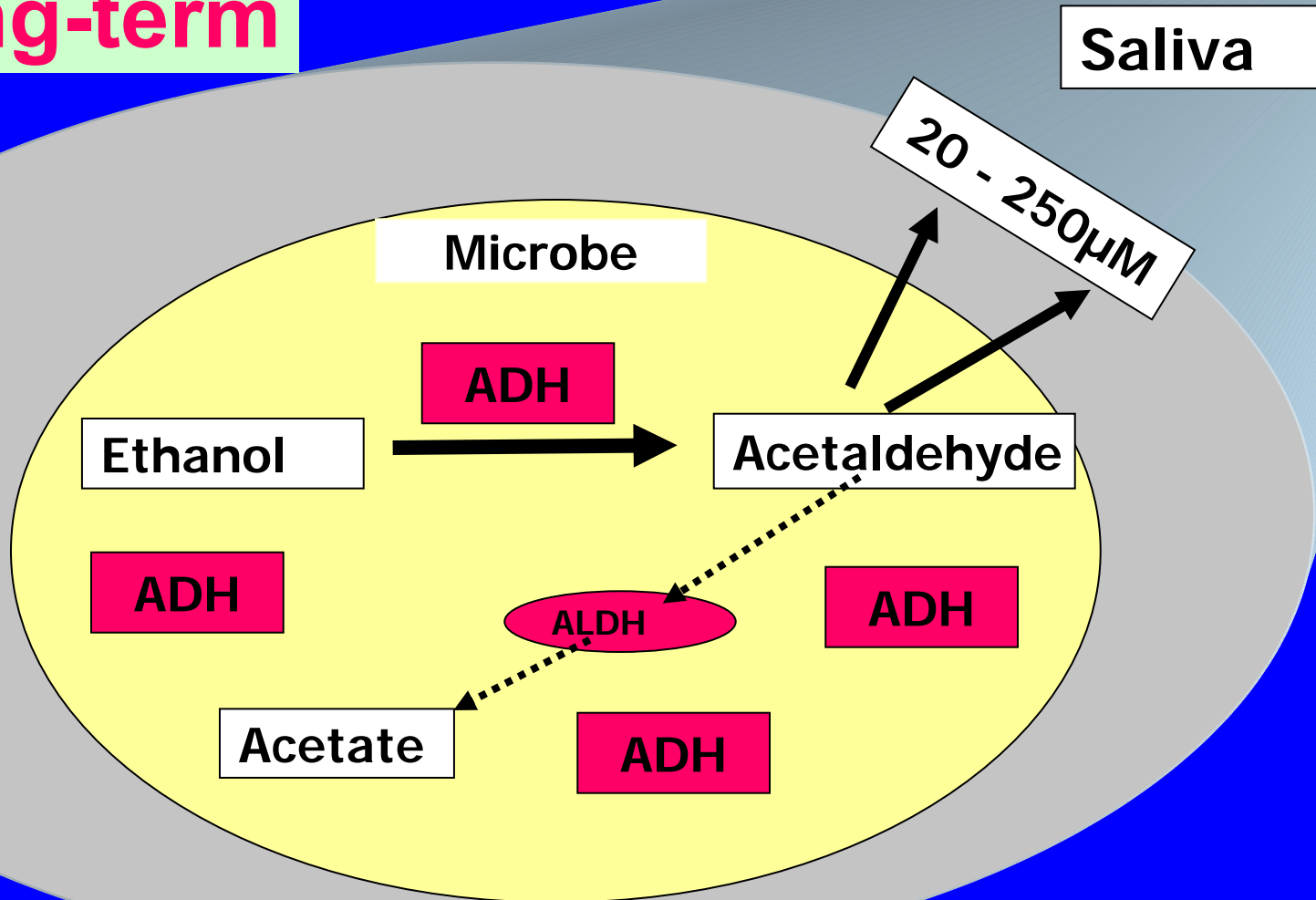
2. Other sources of acetaldehyde exposure

1. Tobacco smoke

2. Food stuffs containing acetaldehyde

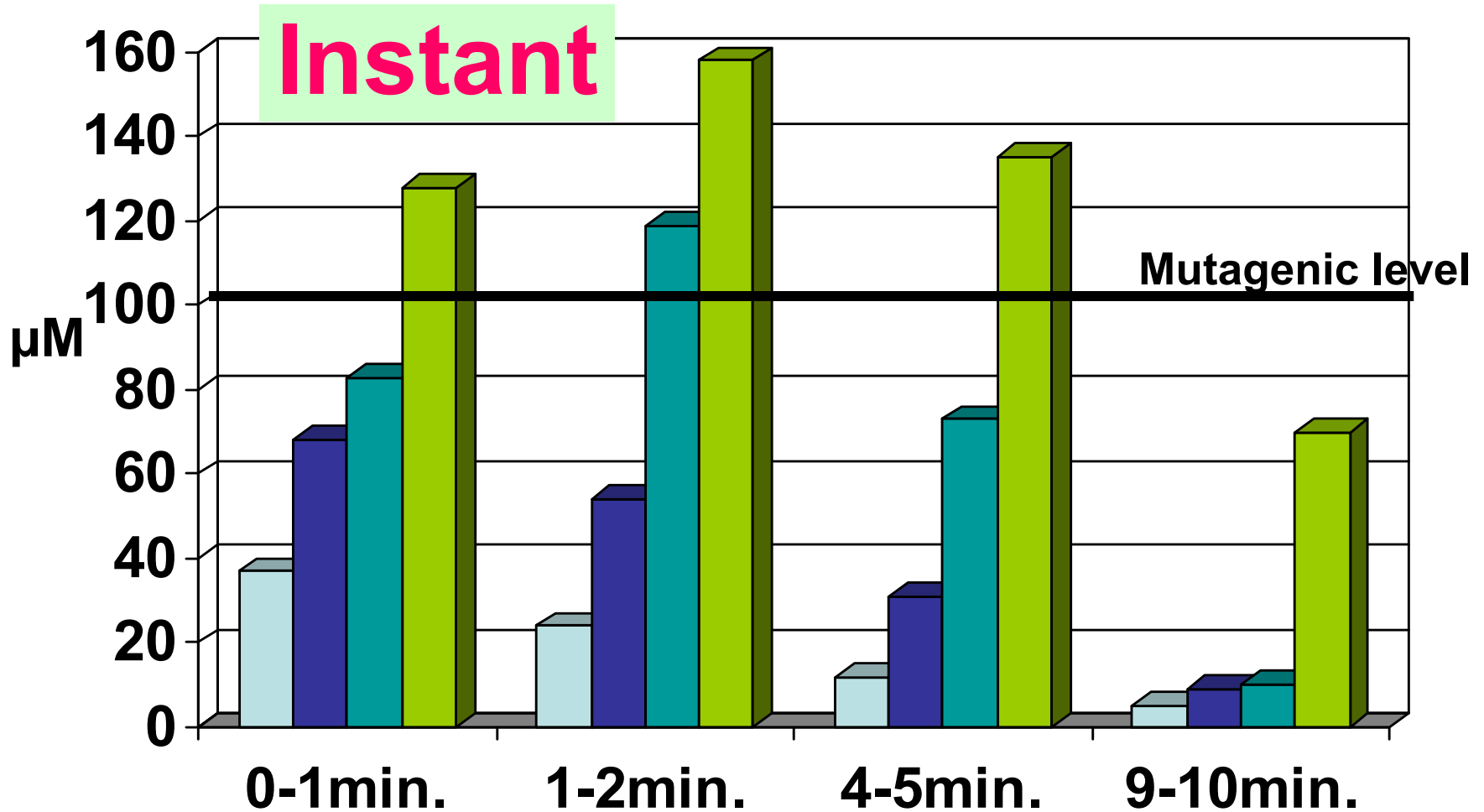
Microbially mediated acetaldehyde formation in saliva

1. Instant
2. Long-term



Acetaldehyde in saliva after sipping 5ml of each beverage and keeping it in the mouth for 5 seconds

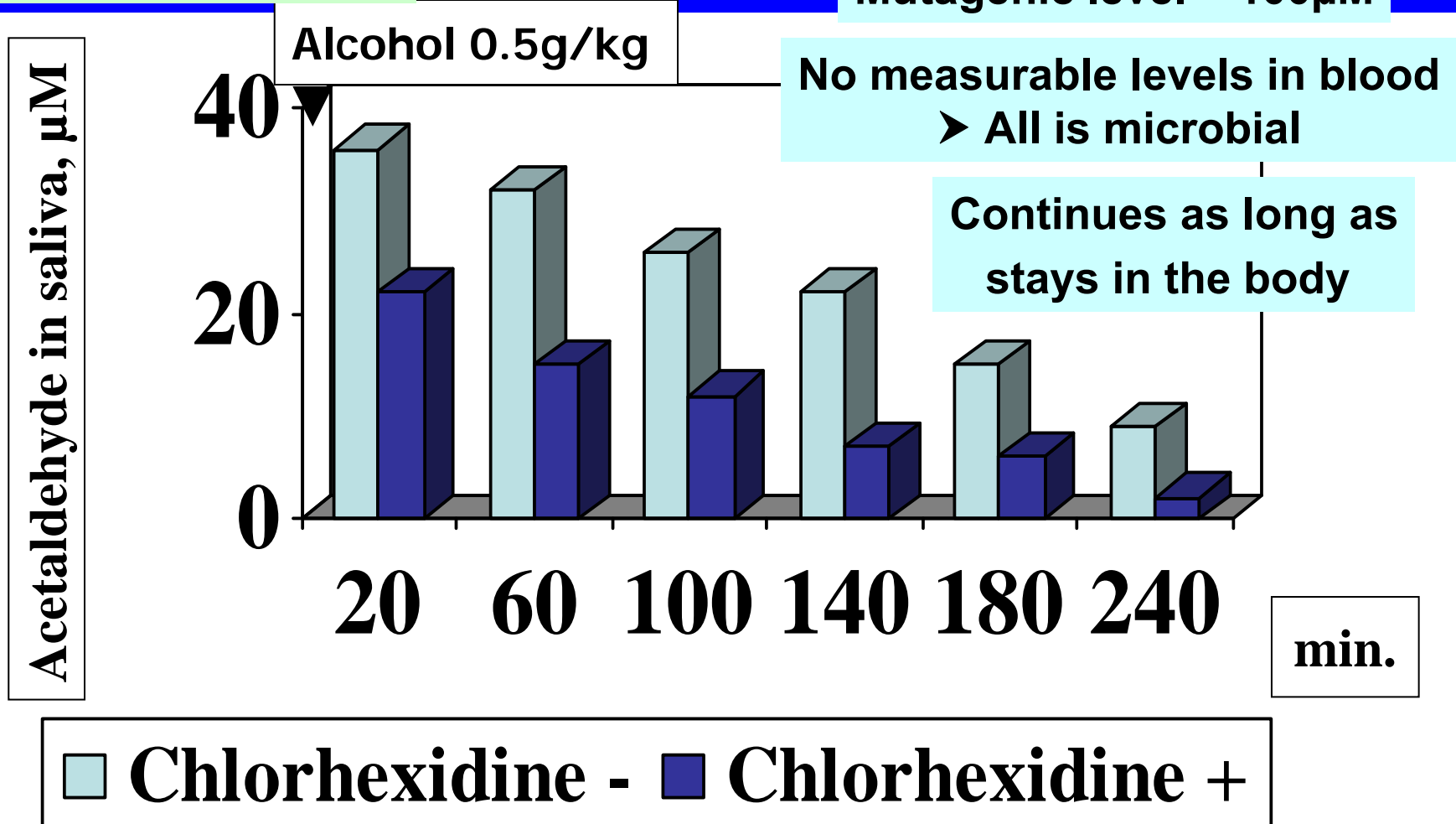
Beer 2,5% Beer 5% Wine 12,5% Ethanol 40%



Acetaldehyde in saliva after alcohol drinking

Long-term

Range 18 - 143 μM
Mutagenic level = 100 μM



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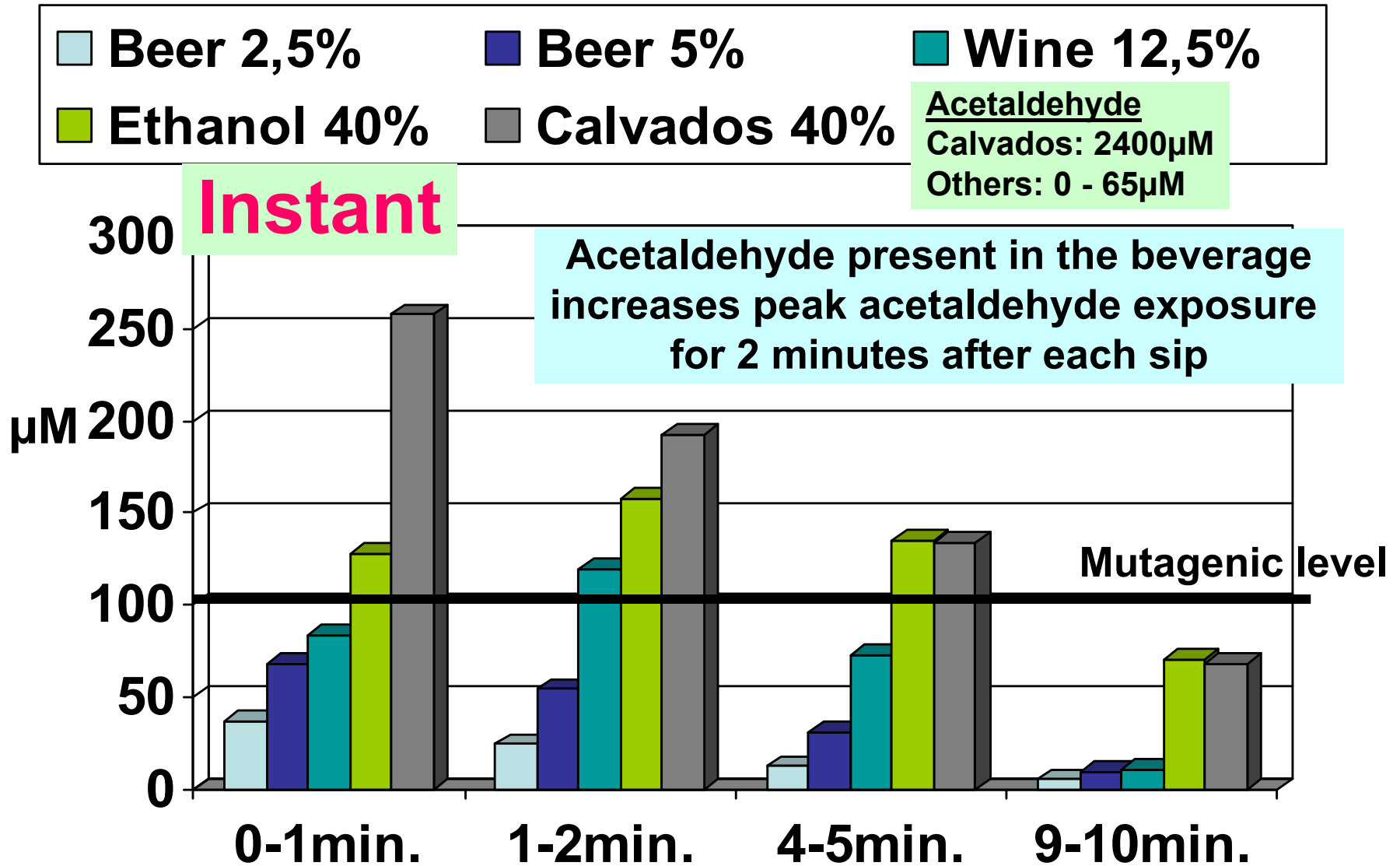
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2. Food stuffs containing acetaldehyde

Acetaldehyde present in alcoholic beverages

	Mean, μM	Range, μM
Wines (n = 213)	773 \pm 760	0 - 4780
Beers (n = 364)	205 \pm 150	0 - 1435
Port wines (n = 27)	1909 \pm 3306	505 - 18139
Sherry (n = 53)	3537 \pm 2482	1132 - 11876
Ciders (n = 11)	1123 \pm 932	343 - 3007
Fruit spirits (315)	1953 \pm 2704	0 - 26280
Cognac (n = 82)	1704 \pm 1096	0 - 4776
Calvados (n=27)	870 \pm 334	437 - 1524
– Home made		ad 4000
Chinese spirits (n = 30)	7419 \pm 3955	755 – 16343
Vodka (n = 72)	61 \pm 70	0 - 287

Acetaldehyde in saliva after sipping 5ml of each beverage and keeping it in the mouth for 5 seconds



Acetaldehyde in saliva after alcohol drinking

INSTANT EFFECTS - Conclusions

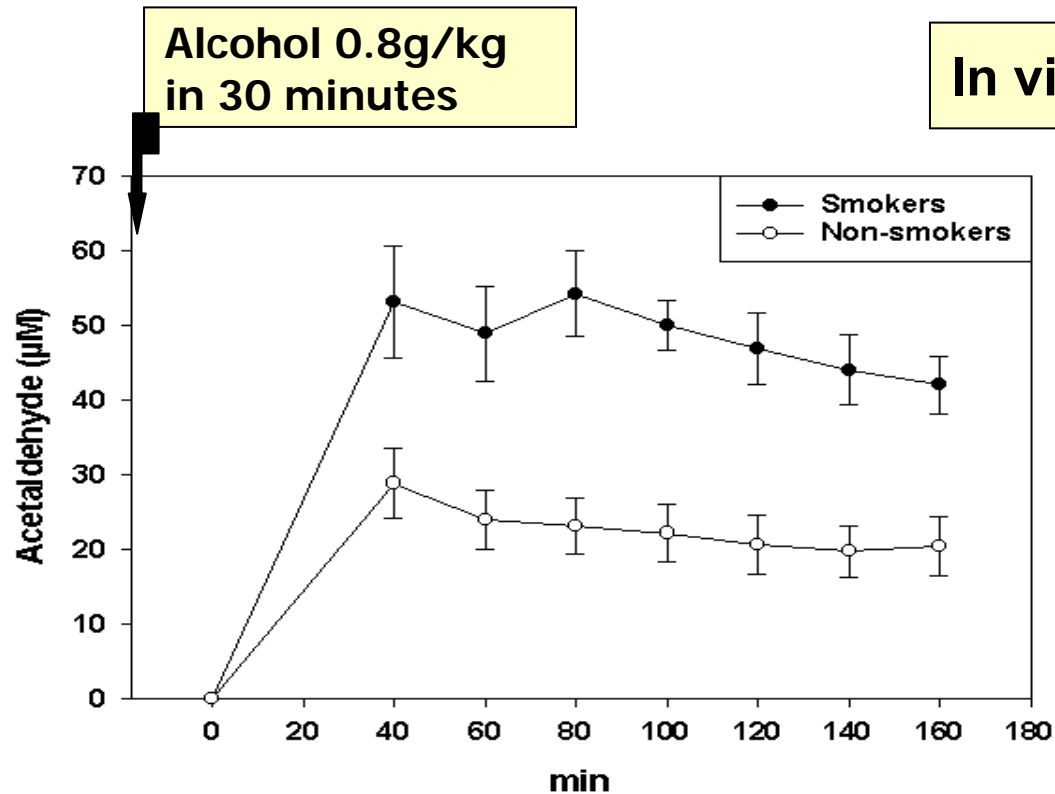
- After each sip of alcoholic beverage ethanol becomes rapidly distributed to the water phase of oral mucosa
- This results in instant microbial formation of acetaldehyde in saliva
- Higher ethanol concentrations and poor oral hygiene result in higher and often mutagenic salivary acetaldehyde levels

Acetaldehyde in saliva after alcohol drinking

LONG-TERM EFFECTS - Conclusions

- Ethanol is distributed to the saliva from the blood
- Microbial acetaldehyde production in saliva continues as long as ethanol stays in blood and saliva
- In individuals with deficient ALDH2- or high active ADH-enzyme salivary acetaldehyde levels are 2 - 3 time higher than in those with normal enzyme
- Salivary acetaldehyde level is modified by individual characteristics of oral flora
 - Chlorhexidine mouth rinsing ↓
 - Chronic smoking, heavy drinking ↑

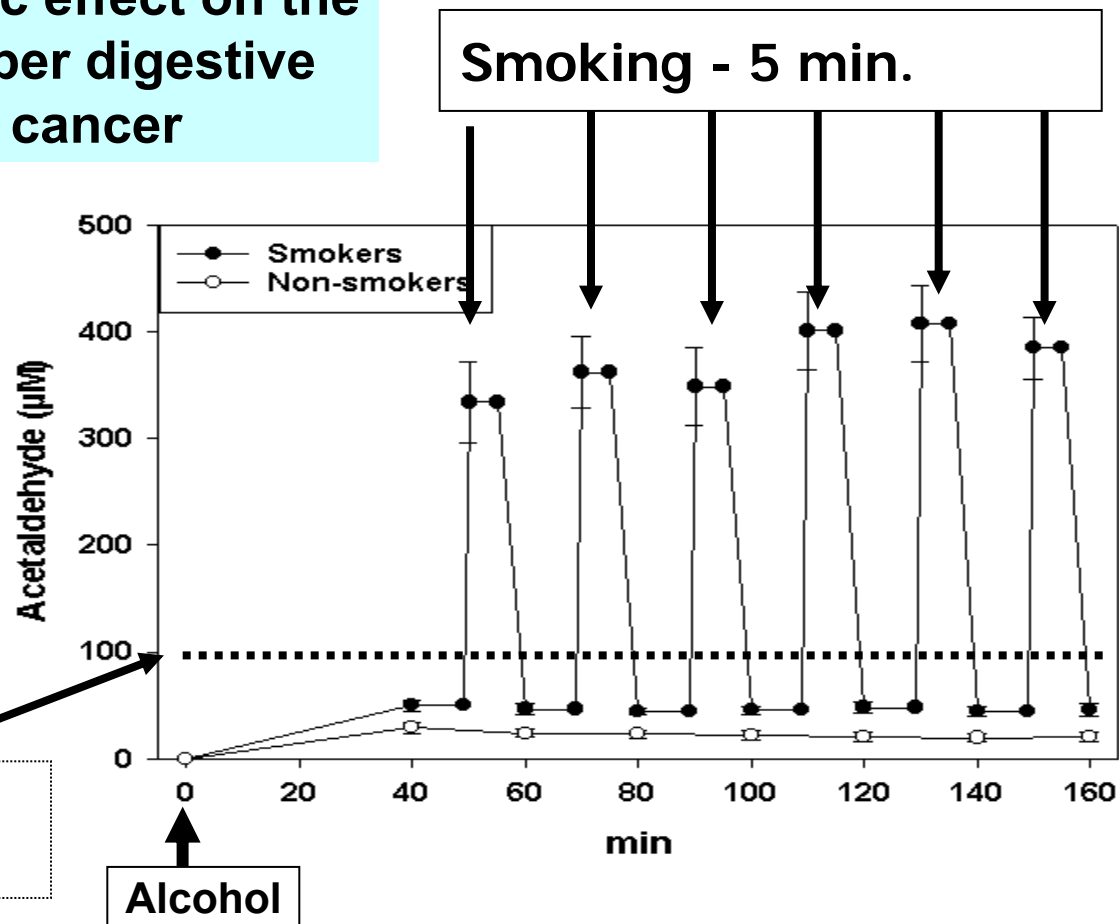
Chronic smoking modifies oral flora to produce more acetaldehyde from ethanol



(Salaspuro V et al. Int J Cancer 2004)

Acetaldehyde of tobacco smoke is readily dissolved into saliva during smoking

Alcohol and smoking has a synergistic effect on the risk of upper digestive tract cancer



Area under the curve
▼
7-fold increase

mutagenic level

ACETALDEHYDE

– the most common human carcinogen

Beverage/food stuff	Acetaldehyde μM	Alcohol %
Alcoholic beverages	0 - 21.500	> 2.8
Milk products		
• before pasteurization	200 - 1000	0.5 - 2.5
• after pasteurization		
– <i>Lactococcus lactis</i>	0	0
• yogurts/kefir		
- <i>Streptococcus thermophilus</i>		
- <i>Lactobacillus Bulgariensis</i>		
	Mutagenic: >100μM	
	200 - 800	0 - 2.5
Home-made beer	500 - 3000	0 - 2.7
Pickled vegetables	20 - 200	0.2 - 1.0
Soya sauces	200 - 1000	0.2 - 2.5

CONCLUSIONS I

WHO/IARC, October 2009

Acetaldehyde present in alcoholic beverages and formed from ethanol endogenously is carcinogenic (Group 1) to humans

This is in sharp contrast with GRAS (Generally Regarded As Safe) status of acetaldehyde as reconfirmed by JEFCA (Joint FAO/WHO Expert Committee on Food Additives) in 1998

CONCLUSIONS II

ALARA principle
(“as low as reasonably achievable”)
according to *Codex Alimentarius*
standards for dealing with contaminants
and toxins and the corresponding EU
legislation should be applied to
acetaldehyde levels present in alcoholic
beverages

HOW TO MINIMIZE
ACETALDEHYDE EXPOSURE

Minimization of acetaldehyde exposure

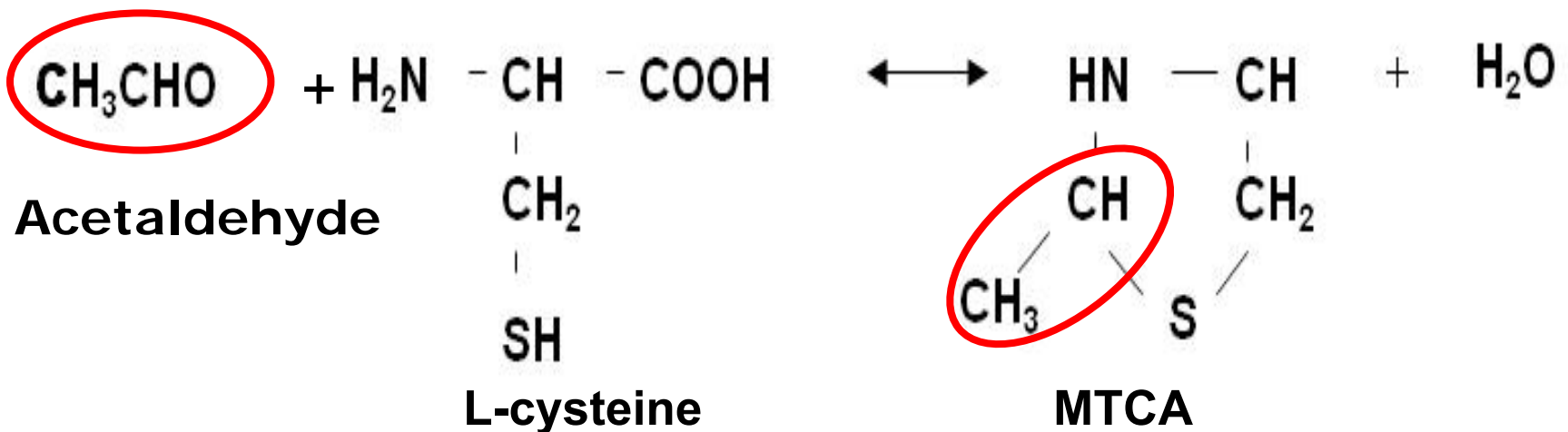
- Moderation of alcohol consumption and quitting from smoking
 - These are major sources of acetaldehyde exposure
- Avoid drinking to intoxication
 - High salivary ethanol level ➤ high salivary acetaldehyde
- Prefer light alcoholic beverages
 - Local microbial acetaldehyde production in the mouth is higher after sipping of strong alcoholic beverages
- Take care of good oral hygiene
 - Microbial acetaldehyde production in the oral cavity is markedly decreased

Minimization of acetaldehyde exposure

- Avoid alcoholic beverages containing high acetaldehyde levels
 - Sherries, port wines, strong fruit beverages
 - Acetaldehyde levels of alcoholic beverages should be informed to the consumers
- Have a sip of water between sips of alcoholic beverages
- Find out whether you belong to risk groups
 - ALDH2-deficient or high active ADH genotype
 - Achlorhydric stomach

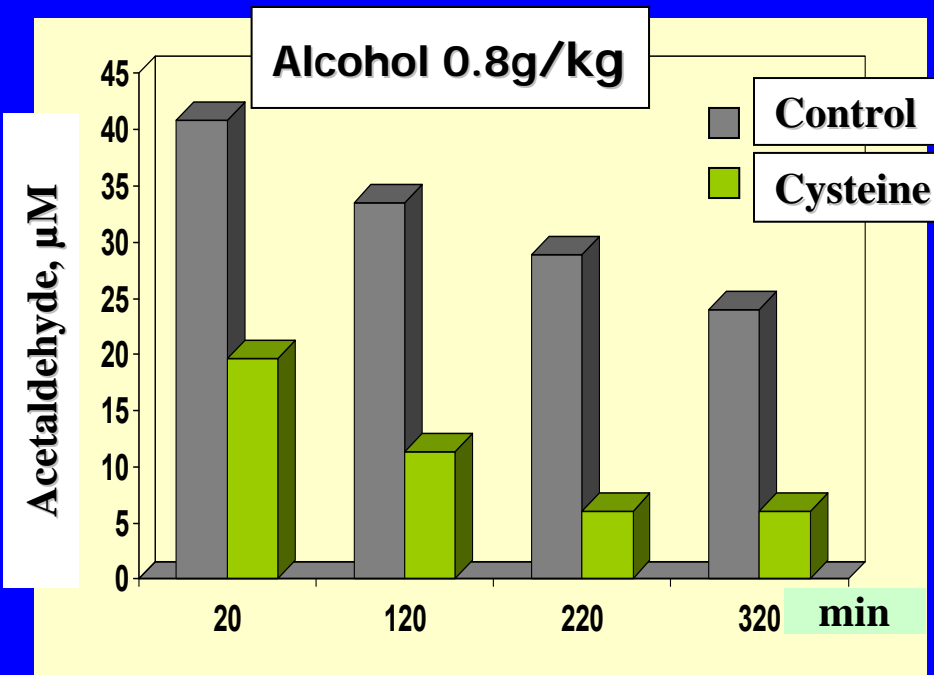
L-CYSTEINE

- Semi-essential sulphur amino acid
- Mean daily intake is 1 - 2 g
- Binds covalently and non-enzymatically with acetaldehyde
 - inactive methylthiazolidinecarboxylic acid (MTCA)



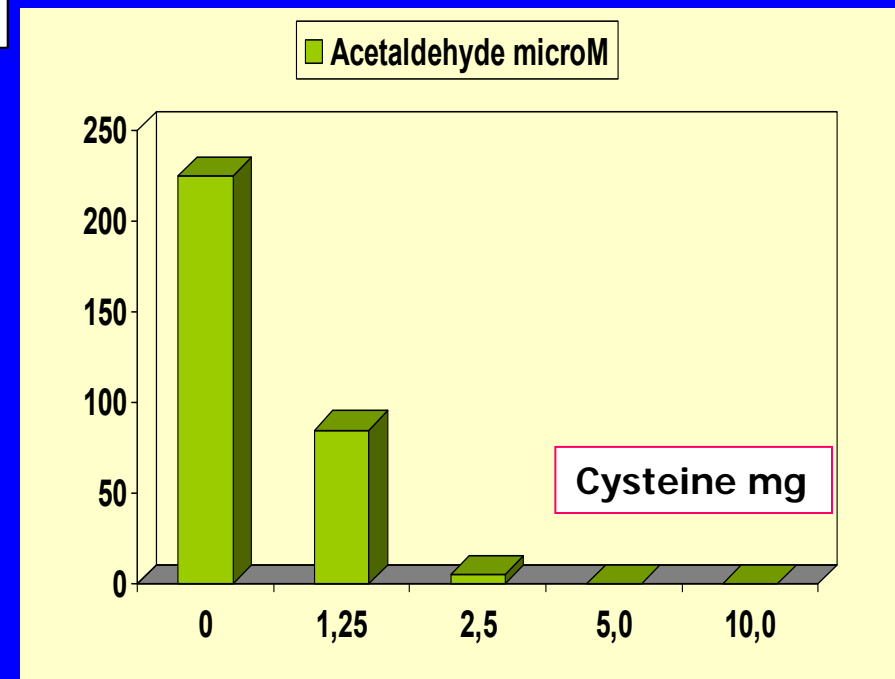
Cysteine binds acetaldehyde in saliva

After a dose of alcohol



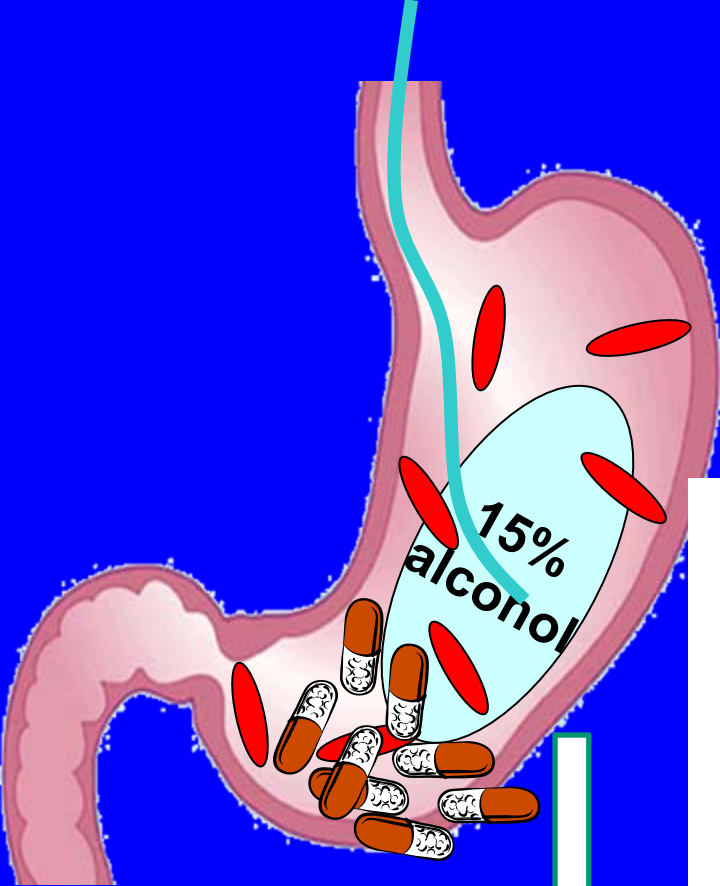
Salaspuro V et al., Int J Cancer 2002


During smoking

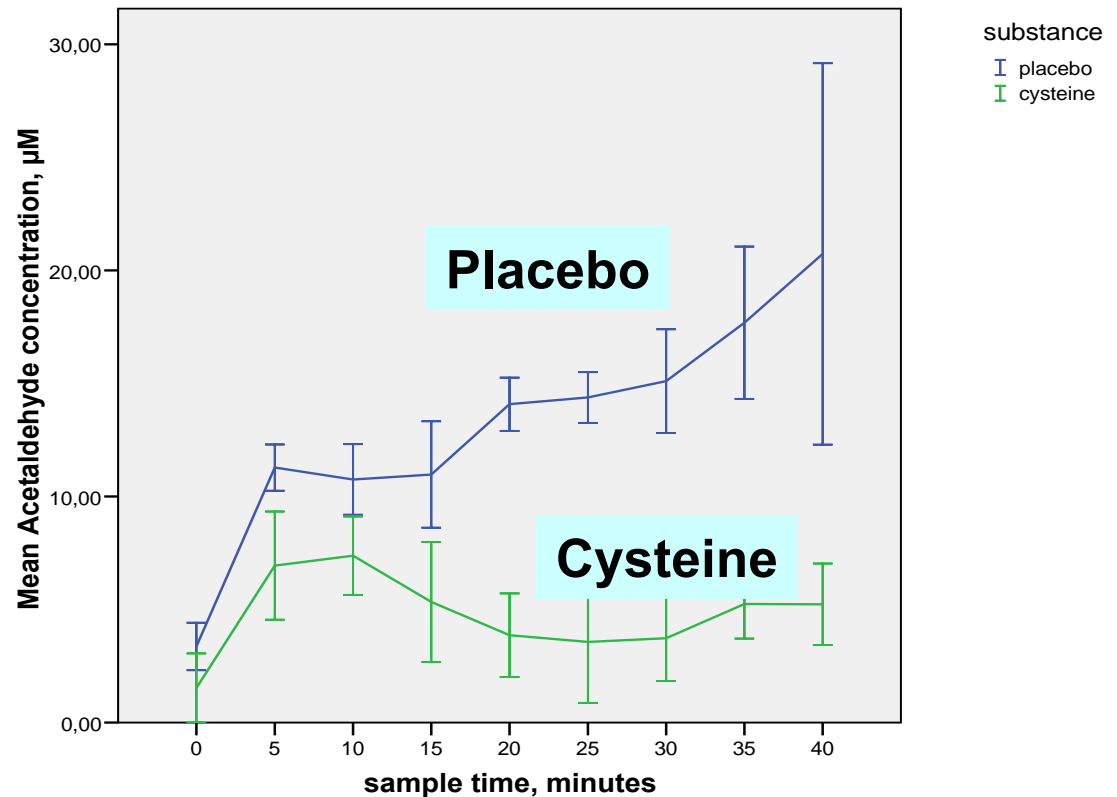


Salaspuro V et al., Cancer Epidemiol Biomarkers Prev 2006

L-cysteine binds 60-70% of acetaldehyde in gastric juice after a dose of alcohol



- Achlorhydric stomach**
- microbes 
 - L-cysteine capsules
 - 15 % alcohol



BIOFOOD CONCEPT

Use of L-cysteine to bind acetaldehyde in food and alcoholic beverages

**Patents and pending patents
owned by Biohit Oyj.**

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Thank you for your attention