Research on the Synergistic Effects of Tobacco and Alcohol on Head and Neck Cancer

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I have no conflicts of interest to disclose

Epidemiology of the Interaction of Tobacco and Alcohol Use and Risk of Head and Neck Cancer

- Pooled analysis by the International Head and Neck Cancer Epidemiology Consortium
- Data from 9,146 cases and 8,574 controls
- Odds ratio for smoking and alcohol use and risk of head and neck cancer overall was 5.73.
- Greater than multiplicative interaction between cigarette smoking and alcohol confirmed
- Effects of smoking alone were greater than those of alcohol alone.
- Similar data for subsites: oral cavity, pharynx, larynx; and by sex

M. Hashibe, P. Brennan, P. Boffetta et al. *Cancer Epidemiol. Biomarkers Prev*. 18: 541 (2009)
Similar data for oral cancer in F.W. Mello et al, *Clin. Oral Invest.* 23: 2849-2859 (2019)

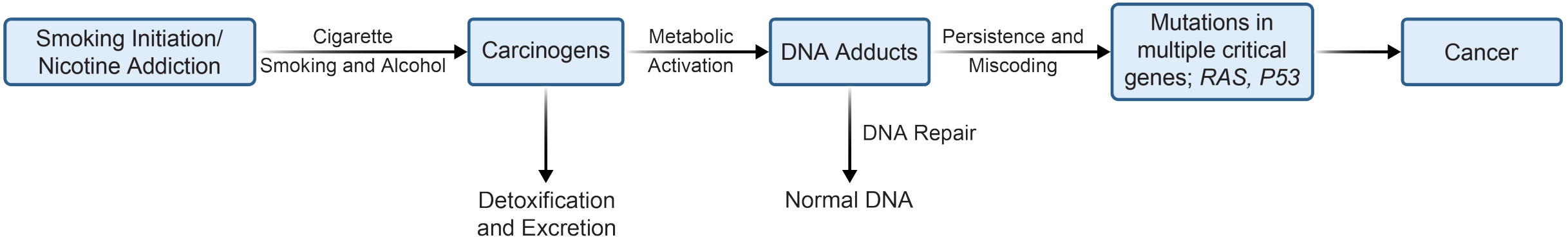
Rationale

The results confirm that there is a greater than multiplicative effect of cigarette smoking and alcohol on the risk of head and neck cancer (oral mucosa, larynx, and pharynx) but the mechanism remains unclear.

Our hypothesis is that oral cell DNA adducts, which are central in the carcinogenic process, will reflect these epidemiologic findings.

Oral cell DNA adducts might be used as warning signs for head and neck cancer susceptibility.

Accepted Overall Mechanism of Tobacco and Alcohol Carcinogenesis: Centrality of DNA Adducts



S.S. Hecht, *J. Natl. Cancer Inst.* 91: 1194-1210 (1999), *Nature Rev. Cancer* 22: 143-155 (2022), U.S. Surgeon General Report, The Health Consequences of Smoking – 50 Years of Progress: 148-151 (2014)

Acetaldehyde, DNA Adducts, and Oral Cancer Due to Alcohol Consumption

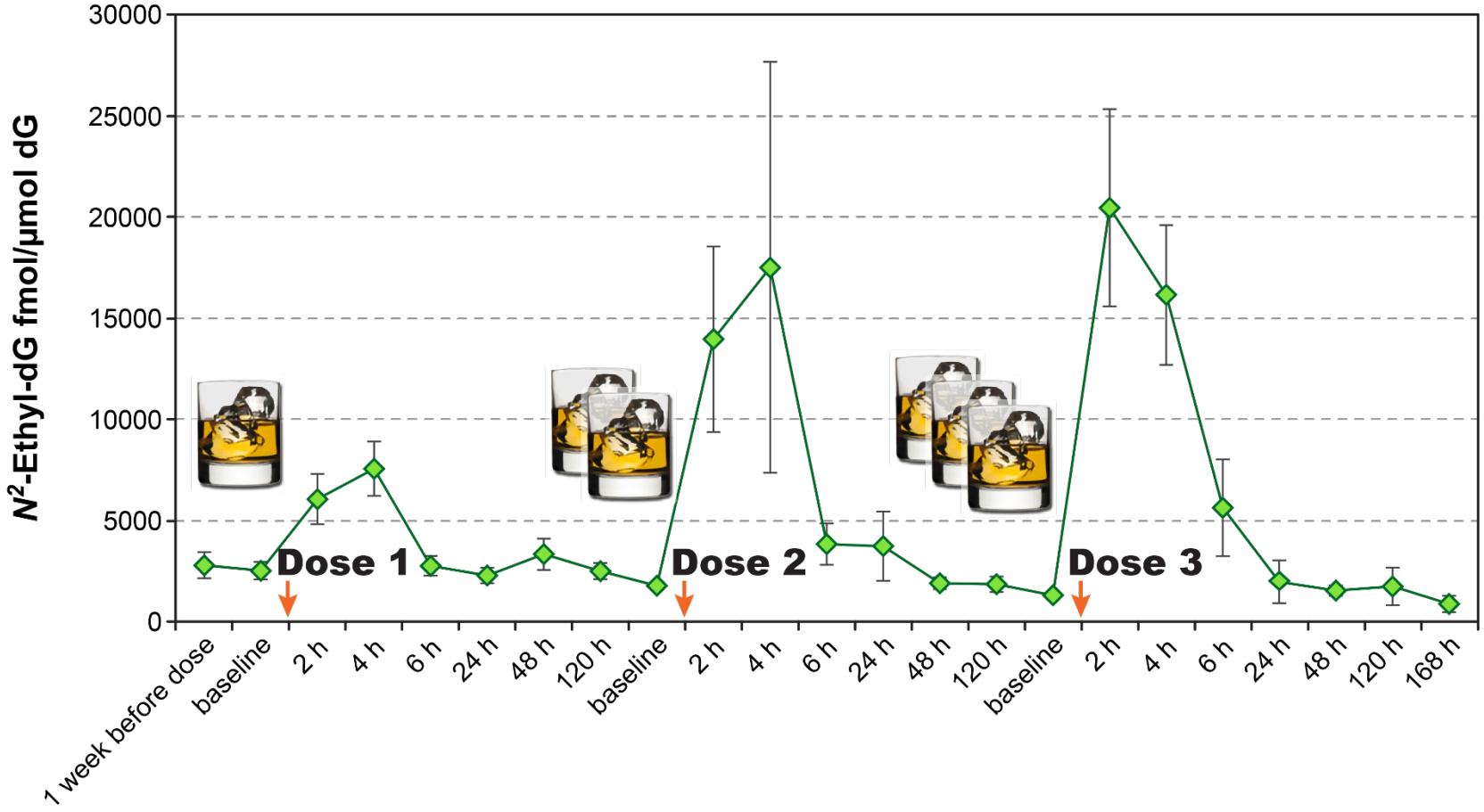
Acetaldehyde is the primary metabolite of ethanol.

IARC Evaluation: Acetaldehyde associated with the consumption of alcoholic beverages is carcinogenic to humans.

- In the body, ethanol is converted to acetaldehyde by ADH and CYP2E1, and acetaldehyde is converted to acetate by ALDH.
- High levels of acetaldehyde are found in saliva after alcohol consumption.
- Carriers of the inactive ALDH2 allele have higher levels of salivary acetaldehyde, higher oral cell DNA adducts, and risk for oral cancer.

International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 100E, Personal Habits and Indoor Combustions, pp 470-472 (2012).

Formation of the Major Oral Cell DNA Adduct of Acetaldehyde in 10 Subjects Who Consumed Alcoholic Drinks to Reach Blood Alcohol Levels of 0.03, 0.05, and 0.07%



S. Balbo et al, *Cancer Epidemiol. Biomarkers Prev.* 21: 601-608 (2012)

Ongoing Investigation of Effects of Cigarette Smoking and Alcohol Consumption on Oral Cell DNA Adduct Formation
5R01 CA-263084-04

Hypothesis: Alcohol consumption enhances oral cell DNA adduct formation by tobacco smoke carcinogens - in addition to acetaldehyde-DNA adducts.

Oral cell DNA adducts will be significantly higher in smokers who are moderate to heavy drinkers than in smokers who are light or non-drinkers, and in non-smokers.

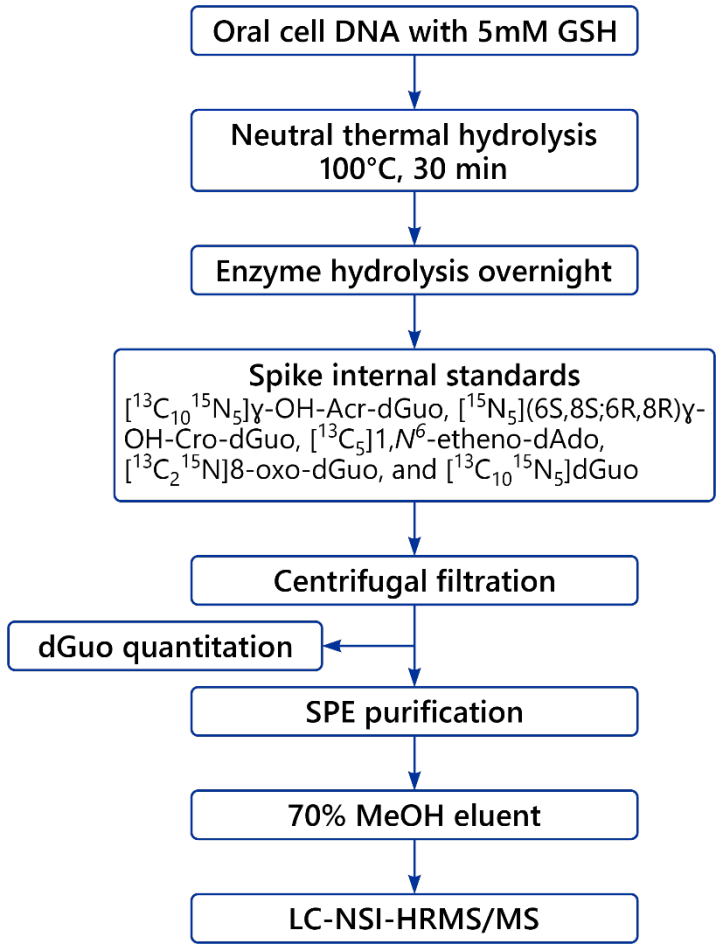
Goal: Oral cell DNA adduct profiles in 100 subjects per group:

- Non-smokers/light or non-drinkers: 60 completers
- Smokers/light or non-drinkers: 90 completers
- Smokers/moderate to heavy drinkers: 39 completers

Longitudinal arm in smokers, 6 months : 45 completers out of 50 proposed

DNA adducts analyzed by liquid chromatography-nanoelectrospray ionization-tandem high resolution mass spectrometry (LC-NSI-HRMS/MS)

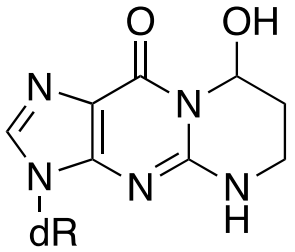
Scheme for LC-NSI-HRMS/MS Analysis of DNA Adducts in Human Oral Cells (0.2 – 10 μg DNA)



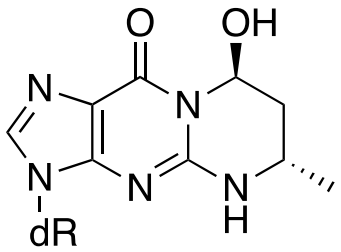
G. Cheng et al, *Chem. Res. Toxicol*. 36: 305-312 (2023)

DNA Adducts Quantified in Human Oral Cells

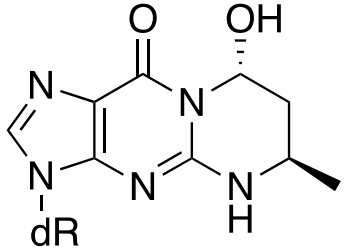
Adducts observed to date:



γ-OH-Acr-dG

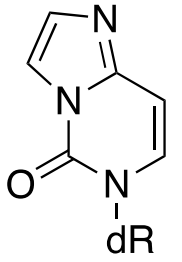


γ-OH-Cro-dG-1

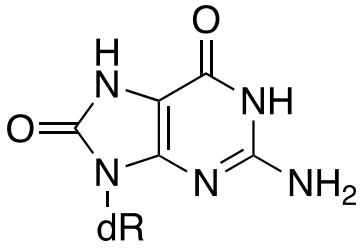


γ-OH-Cro-dG-2

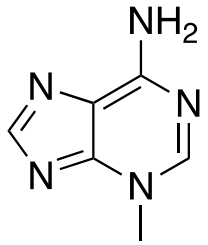
Etheno-dAdo



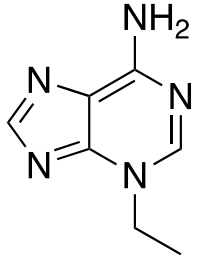
Etheno-dCyt



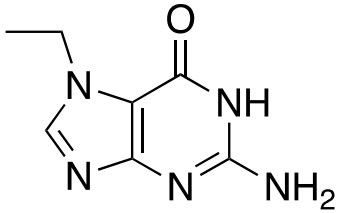
8-oxo-dG



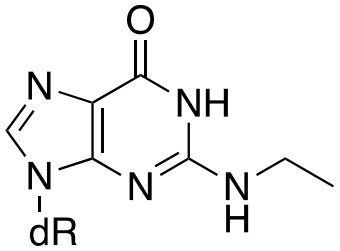
3-Me-Ade



3-Et-Ade



7-Et-Gua



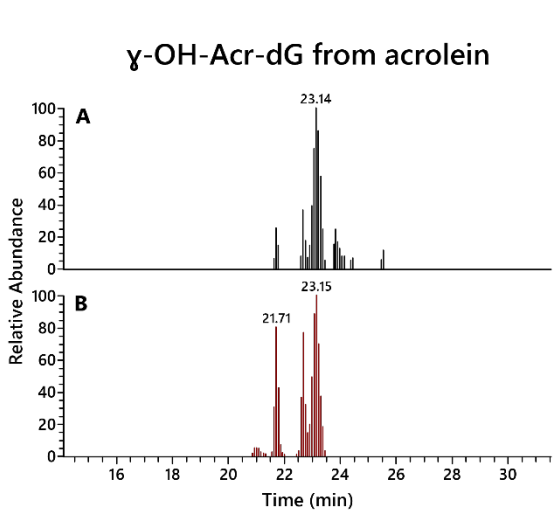
***N*^{2}-Et-dG**

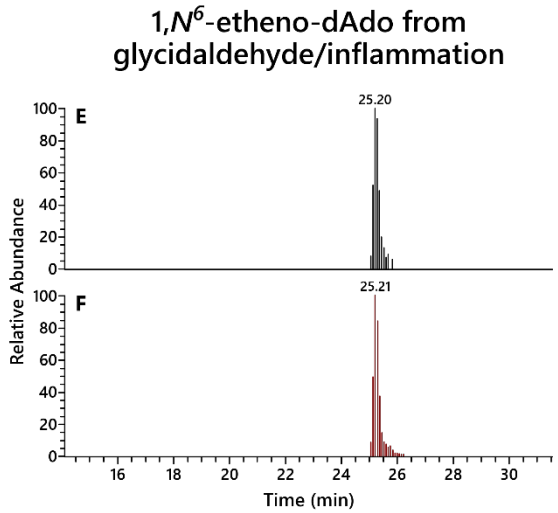
Adducts to be analyzed:

7-Me-G, *O*^{6}-Me-G, 7-POB-G, 7-PHB-G, *O*^{2}-POB-T, *O*^{2}-PHB-T, Py-Py-dI, Me-DNA-phosphate

Representative LC-NSI-HRMS/MS Analyses of Oral Cell DNA Adducts

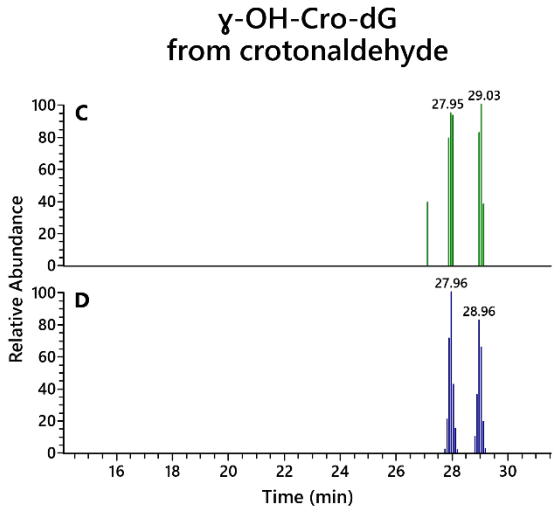
m/z 324 → 208.0829 and
339 → 218.0849

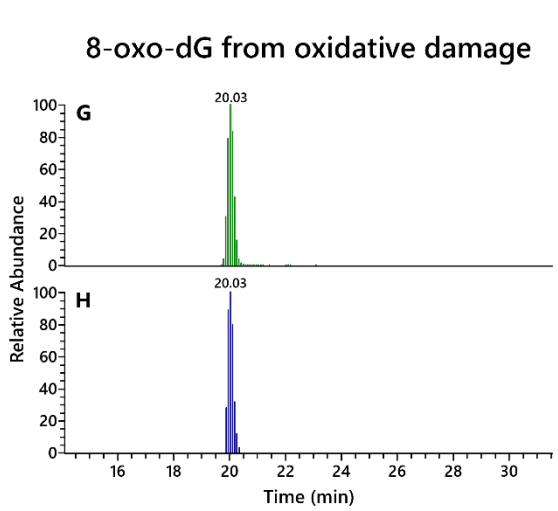




m/z 276 → 160.0618 and
281 → 160.0618

m/z 338 → 222.0986 and
343 → 227.0832

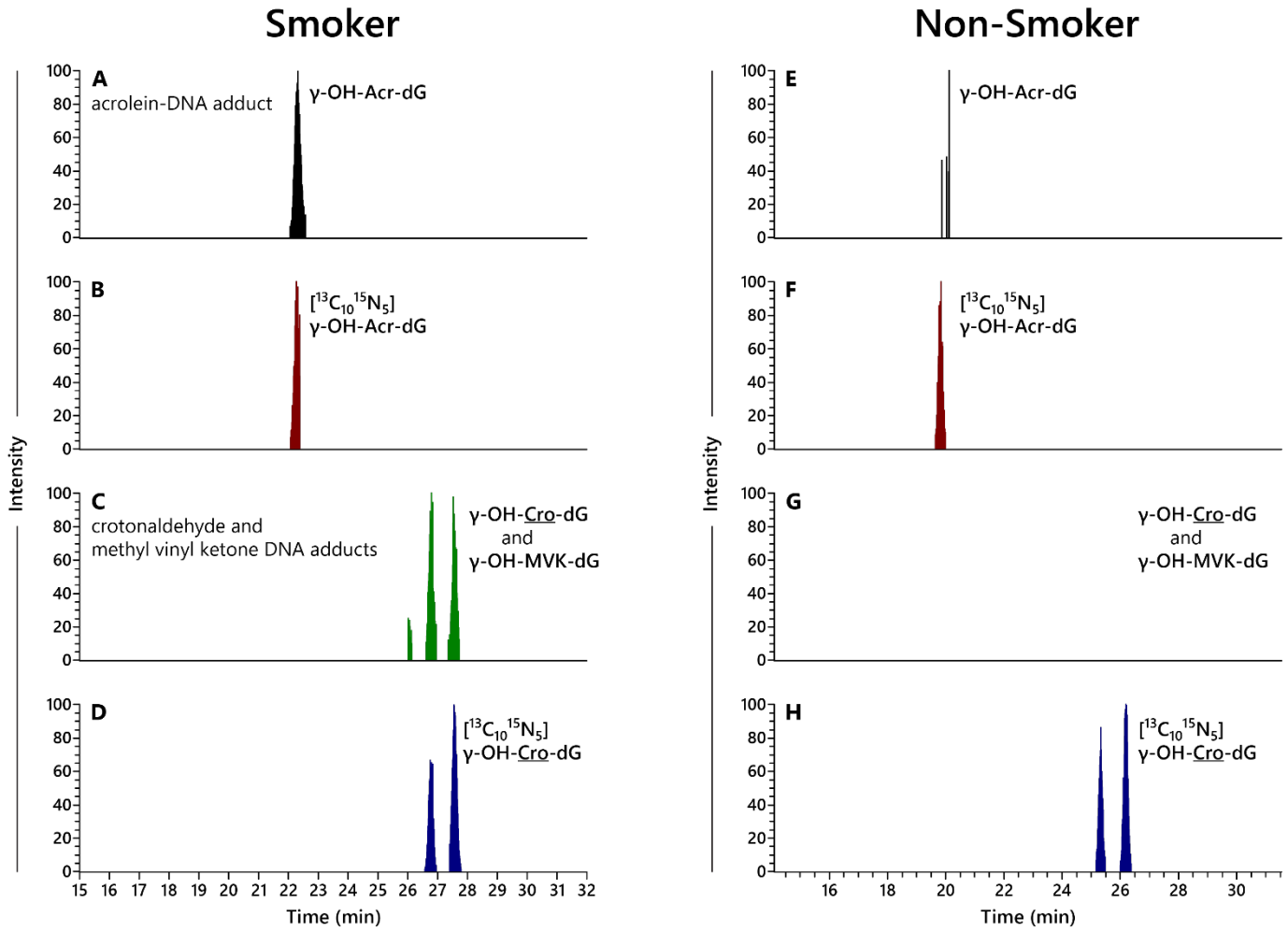




m/z 284 → 168.0511 and
287 → 171.0485

G. Cheng et al, *Chem. Res. Toxicol*. 36: 305-312 (2023)

Representative LC-NSI-HRMS/MS Analyses of Oral Cell DNA Adducts: Effects of Smoking



Additional Mechanistic Considerations: Interaction of Alcohol and Tobacco Carcinogens

- Alcohol may increase the permeability of the oral mucosa to tobacco carcinogens.
- Induction of CYP2E1 by alcohol may lead to increased metabolic activation of certain tobacco carcinogens.
- Activity of carcinogen detoxification enzymes may be decreased by alcohol.
- Competitive inhibition of hepatic CYP enzymes by alcohol may lead to increased carcinogen levels in extrahepatic tissues.
- Tobacco smoke may affect microbiome catalyzed formation of acetaldehyde from ethanol.

IARC Monographs Volume 100E, Personal Habits and Indoor Combustions, pp 163-1656 (2012).
A. Stornetta et al. *Cancers* doi:10.3390/cancers10010020 (2018)

Summary

- There is a greater than multiplicative interaction between cigarette smoking and alcohol consumption for head and neck cancer.
- DNA adducts are central in this process because they cause miscoding in critical cancer genes such as *KRAS* and *TP53*.
- Acetaldehyde, the primary metabolite of alcohol, causes DNA adducts in oral cells of people who drink alcohol.
- An ongoing study is analyzing DNA adducts in oral cells of cigarette smokers, alcohol drinkers, and smokers/drinkers.
- Oral cell DNA adducts might be useful in early detection of the carcinogenic process in people who smoke and drink alcohol.

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