

# ACROLEIN, CROTONALDEHYDE, AND ARECOLINE

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OF CARCINOGENIC HAZARDS  
TO HUMANS

**Table S1.7 Exposure assessment review and critique for mechanistic studies in humans exposed to crotonaldehyde**

Reference and outcome	What was the study design?	What methods were used for the exposure assessment?	What was the definition of external exposure?	Was endogenous exposure defined?	Was the exposure defined well?	What route of exposure was assessed?	How was the intensity of exposure assessed?	How was the duration of exposure assessed?	Was cumulative exposure assessed?	Was exposure assessed before outcome being ascertained?	What was the timing of exposure relative to the outcome?	Was there known exposure to any other carcinogens?
Nath & Chung. (1994) DNA adducts in human livers	Demonstration study; spot samples of human livers DNA (3 persons)	<sup>32</sup> P-Postlabelling for DNA adducts of crotonaldehyde and acrolein	None	None	No exposure was defined	Unknown	Adduct levels, but no quantitation provided	None	Adducts should accumulate until cell division in liver	No outcome assessed	NA	Unknown
Nath et al. (1996) DNA adducts in lymphocytes and breast tissue	Demonstration study. Cross-sectional study. Blood lymphocyte DNA obtained from 2 males and 2 females, one of each sex was a smoker. DNA also obtained from breast tissue of 3 women	<sup>32</sup> P-Postlabelling for DNA adducts of crotonaldehyde and acrolein	No comparisons made by exposure	No	No	No	Adduct levels but only the range of all samples provided	None	None	No outcome assessed	NA	Unknown
Nath et al. (1998) DNA adducts in oral tissues	Cross-sectional. DNA from gingival tissues from 11 non-smokers and 12 smokers analysed for acrolein and crotonaldehyde adducts	<sup>32</sup> P-Postlabelling for DNA adducts of crotonaldehyde and acrolein	Smokers of non-smokers	Levels in non-smokers	Self-reports, no chemical confirmation of smoking status	Inhalation assumed	Adduct levels and self-reports. No analysis of this data was provided	None	Adducts should accumulate based on the cell lifespan and repair	Adduct levels were outcome	NA	Tobacco smoke
Zhang et al. (2006) DNA adducts in human livers and lungs	Demonstration study. Cross-sectional analysis	LC-MS analysis of crotonaldehyde-derived DNA adducts from 23 human livers and 45 human lungs	None	No	No	None	Adduct levels	None	Adducts should accumulate based on the cell lifespan and repair	No outcome measured	NA	Unknown

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Alamil et al. (2020) DNA adducts in lymphocytes a smoker and a non-smoker	Demonstration study; 2 cross-sectional samples analysed. One smoker and one non-smoker: early method validation. Measured acrolein- and crotonaldehyde-derived DNA adducts	Smoking status from banked samples. No confirmation provided	Smoking status	Non-smoker levels were reported for one person	No. Textual reference to 30 cigarettes/day for the smoker	Inhalation assumed for the smoker	Self-reports/?	DNA adducts measured in lymphocytic DNA. Cells have various life spans. Smoker was a “current” smoker seeking to stop	No. See previous columns	The measurement was the outcome	The measurement was the outcome	Yes, tobacco smoker
Garcia et al. (2013) Alkylated DNA bases in human urine	Cross-sectional survey (demonstration/early stage validation study) one urine sample collected	Measured propanylated dG nucleosides excreted in urine in a densely populated city and a more rural area	None measured. Air pollution?	No except that levels of alkylated bases were lower in the more rural population	No	Inhalation was suggested but route was not controlled	Higher levels of alkylated bases in urine	Considering that the bases are probably excreted daily and no sample time given, the samples integrated exposure over a short time period (day/days?)	No	No outcome measures were made in either population	NA	Acetaldehyde can form the same adducted base as crotonaldehyde. Results imputed to be related to high levels of vehicle exhaust
Zhang et al. (2016) Urinary levels of propanated nucleosides	Demonstration study in 13 volunteers	HPLC-MS/MS	Non-smokers and “not hard drinkers”	Non-smokers and “not hard drinkers”	No dietary or other information provided	Assumed to be endogenous. Not measured	Adducted nucleoside excreted into the urine	Not assessed	No	No	Concurrent	Diet? Alcohol?

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Grigoryan et al. (2019) Serum protein adducts	Case-control study with a cross-sectional analysis of exposure. Samples taken at recruitment Case status defined before sampling	Measurement of agents bound to a specific amino acid of serum albumin	Data on smoking status and alcohol consumption were taken along with other physiological and demographic parameters	There was no difference in diet or other consumption variables between cases and controls. Cases had significantly higher BMI	NA	NA	Adduct levels	NA	NA	Appears diagnosis came first	Cases were identified and samples collected	Unknown
Chen & Lin (2009) DNA adducts	Cross-sectional study of placental DNA from 1 person and lymphocytic DNA from 9 people. Demonstration study	Measurement of acrolein- and crotonaldehyde-derived DNA-adduct levels by HPLC-MS	None	Exposure status of participant not known	No	NA	NA	NA	No	No outcome measured	NA	Acrolein
Chen & Lin (2011) DNA adducts	Cross-sectional study of salivary DNA-adduct levels in 27 volunteers. Demonstration study	Salivary DNA adducts of acrolein and crotonaldehyde (among others)	None	No		None	Adduct levels by individuals	NA	No	No outcome assessed	NA	Yes, 8 adducts were measured
Yang et al. (1999) DNA adducts	Analytic study in breast tissue from patients with breast cancer ( <i>n</i> = 18)	Measurement of Cro-dG1 & 2	No external exposure defined	Cro-dG1 & 2 assumed to result from endogenous generation	No definition of external exposure. Exposure was based on Cro-dG1 & 2 only	Not specified	Intensity of internal exposure was assessed using a one-off sample	No external exposure was considered, hence no duration of exposure	No	No	Not available	NR

BMI, body mass index; HPLC, high-performance liquid chromatography; LC-MS, liquid chromatography-mass spectrometry; HPLC-MS/MS, high-performance liquid chromatography-tandem mass spectrometry; NA, not applicable; NR, not reported.

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