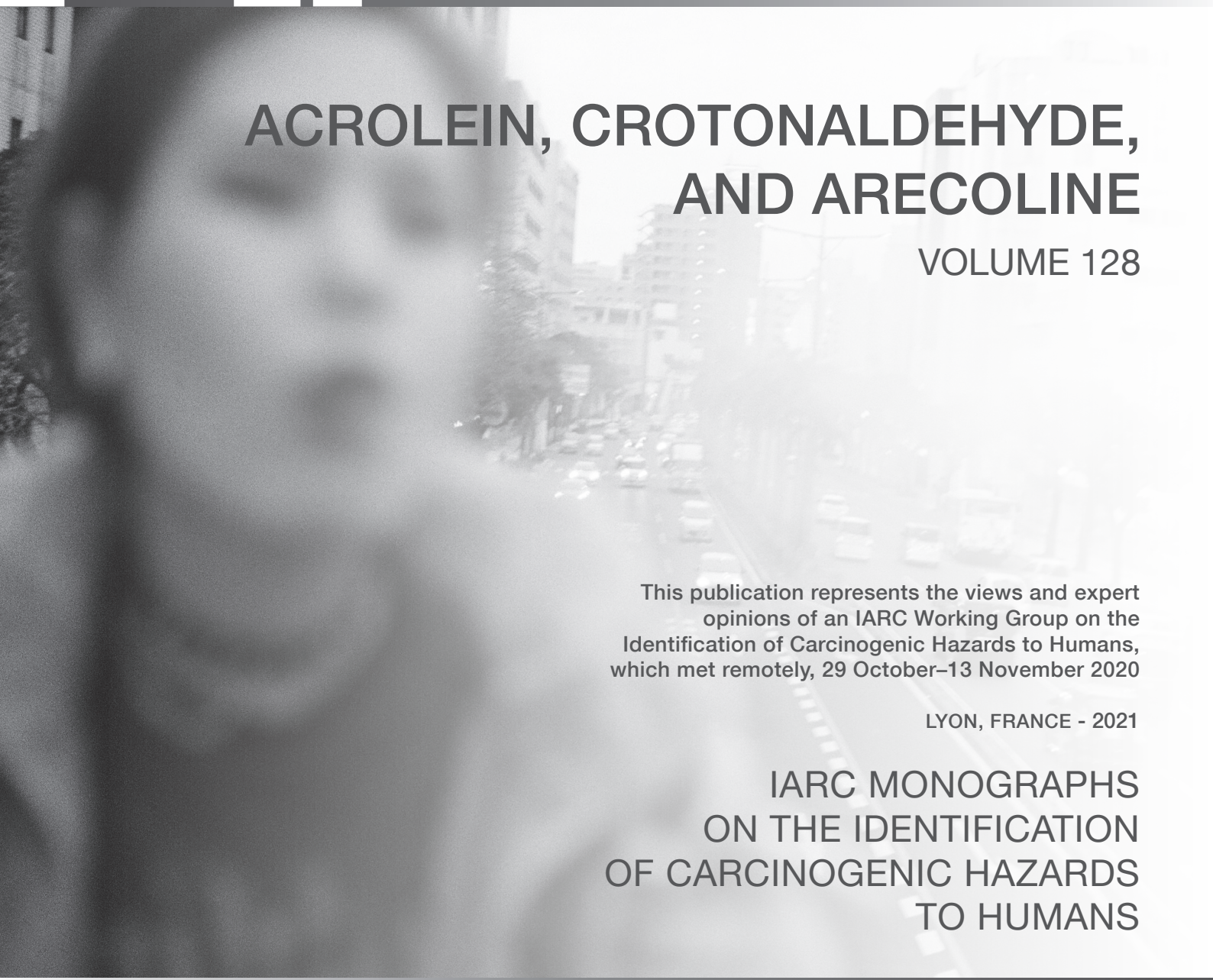
IARC MONOGRAPHS



ACROLEIN, CROTONALDEHYDE, AND ARECOLINE

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International Agency for Research on Cancer

World Health Organization

Table S1.4 Exposure assessment review and critique for epidemiological studies of cancer in humans exposed to acrolein

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?
Bittersohl (1975) Cancer (various sites)	Cohort study (n = 220)	Employment records	Being currently employed in aldehyde factory	No	No There were traces of acrolein in the generated product, but no evidence was provided of acrolein in air	Not specified, but presumed to be inhalation	There was no exposure gradient	Employment records. 150 people were said to be employed > 20 years; but there was no discussion if their exposure (or outcome) was different than the 70 who were < 20 years	No, except as noted for "Duration of exposure"	No, they were reported concomitantly	Exposure preceded outcome	Yes, co-exposure occurred by a mixture of aldehydes including acetaldehyde and crotonaldehyde
Ott et al. (1989) Lymphohaematopoietic cancer	Nested case−control	Potential exposure was assumed based on records describing assignment of employees to production units and history of use of chemical substance at production units	Use of chemical in production unit	No	No, exposure was assumed based on analyses of company records. Ever exposed means that the employee worked for 1 day or more with the chemical	None defined	Intensity of exposure was not assessed Exposure was dichotomous	Duration of exposure was not used for acrolein, due to limited number of cases	No	No	Exposure preceded outcome	Yes, 21 "suspect" chemicals were identified based on evidence of carcinogenicity or mutagenicity. Individual workers exposed to one chemical agent were also likely exposed to other agents. However, no specific information of co-exposures with acrolein
Yuan et al. (2012) Lung cancer	Nested case-control study of lung cancer in smokers	Measurement of urinary metabolites for acrolein (HPMA)	Not clear definition of external exposure. All cases and controls were smokers at the time of recruitment	No	Exposure of interest was urinary HPMA, Presumably the main source of external exposure was smoking	Not specified	Information on smoking intensity and duration was collected. Intensity of internal exposure was assessed using a one-off urine sample	Information on duration of smoking was available	No cumulative information on acrolein exposure was available Cumulative smoking data were available, but smoking was not the main exposure of interest	Yes, although the analyses were done after identification of cases and controls, the urine samples were collected at baseline of the cohort	Exposure preceded outcome	Yes, tobacco smoke toxicants; exposure to PAH was assessed too
Yuan et al. (2014) Lung cancer	Nested case−control studies of never smokers with lung cancer, within prospective cohort study	Measurement of urinary metabolites for acrolein (HPMA)	External exposure was not defined	No	Exposure of interest was urinary HPMA, but it was not clear what the source of external exposure was	Not specified It was also not clear what the source of exposure was	Intensity of internal exposure was assessed using a one-off urine sample (cross sectional analysis)	No external exposure was considered, hence no duration of exposure	No	Yes, although the analyses were done after identification of cases and controls, the urine samples were collected at baseline of the cohort	Exposure preceded outcome	Not relevant as industry was not assessed. Study was of never smokers, but other exposures are possible. Metabolites of PAH were also monitored
Tsou et al. (2019) Oral cancer	Case-control study of oral squamous cell carcinoma	Interview on smoking and BQ chewing history. Measurement of acrolein−DNA adducts in buccal cells. Urinary 3-HPMA measurements	External exposure was defined as having a smoking and/or betel-quid chewing history. Not entirely clear if this also included former smokers/BQ chewers	No	No, exposure appeared to be defined by acrolein−DNA adduct in buccal cells; however, results for urinary 3-HPMA were also presented	Inhalation and ingestion	No information on intensity of smoking and BQ chewing. Smoking years and chewing days was used. No difference in acrolein−DNA	Duration of smoking in years and history of BQ chewing was available (latter expressed as chewing days)	As noted for "Duration of exposure"	No	Information on smoking and BQ chewing history was collected. However, acrolein−DNA adducts and urinary HPMA	Yes, tobacco smoke toxicants

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							adducts between healthy smokers and BQ chewers. HPMA was increased in healthy smokers+BQ chewers, compared to BQ or smokers only				were measured in samples from cases and controls. Results suggest that urinary HPMA in healthy subjects is correlated with smoking history	
Hong et al. (2020) Urothelial cancer	Case−control study of urothelial cancer patients with chronic kidney disease in Taiwan, China (62 cases versus 43 controls)	DNA adducts, protein conjugates, urinary analyses of acrolein metabolites	No differentiation between endogenous and exogenous provided, except that cigarette smoking was assessed	Differences in DNA adducts, protein conjugates and metabolites were assumed due to accumulation of endogenous acrolein	No, endogenous exposure was determined based on DNA adducts, protein conjugates, or urinary HPMA	Focus was on endogenous acrolein. Information on smoking and air pollution was collected, but these potential sources of acrolein exposure were considered only as confounders in the analyses	No external exposure assessed. Intensity of exposure was assessed using plasma levels of acrolein−protein conjugates and urinary HPMA	Not assessed	No	No	Unclear. Endogenous accumulation due to kidney disease. It is not clear if the endogenous exposure is a cause or a result of the urothelial carcinomas. Adduct levels were only higher in the tumour but not the normal urothelium of the same person	Yes, ~20% of UC cases were ever smokers

BQ, betel quid; HPMA, *N*-acetyl-*S*-(3-hydroxypropyl)-L-cysteine (-hydroxypropylmercapturic acid); PAH, polycyclic aromatic hydrocarbon; UC, urothelial cancer.

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