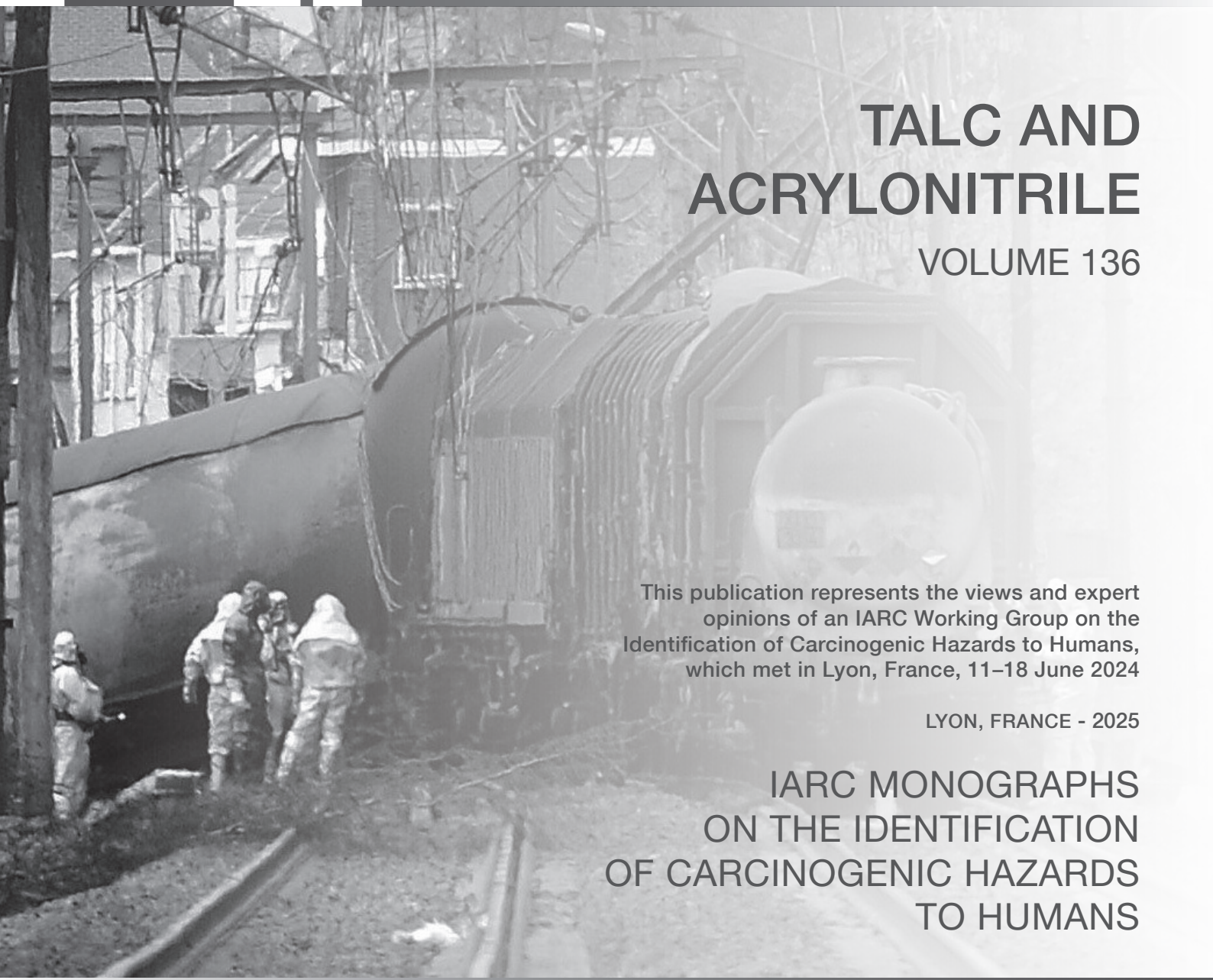
IARC MONOGRAPHS



TALC AND ACRYLONITRILE

VOLUME 136

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IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

World Health Organization

Table S1.13 Exposure assessment review and critique for mechanistic studies in humans exposed to acrylonitrile

Reference **(No. of exposed/controls)**	**What methods were used for the exposure assessment? (incl. data source, environmental and biological measurements etc.)**	**What was the exposure context?** **Specify period over which exposure data gathered, and how historical exposures were accounted for (if relevant)**	**Was exposure assessment qualitative, semiquantitative or quantitative? Describe any exposure groups.**	**Concerns noted on sampling and collection protocols for acrylonitrile measurements**	**What routes of exposure were assessed?** **For general cohort assessments: "all routes (indirectly)"**	**What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure etc.)?** **What was the timing of exposure relative to the outcome?**	**Was there potential for co-exposures to other occupational carcinogens? (Smoking and air pollution carcinogens not identified unless measured.)** **If yes, were these accounted for in analyses?**	**Was there potential for differential exposure misclassification?** **Was there potential for nondifferential exposure misclassification?** **(Likely/unlikely)**	**Summary of methods used to assess exposure**	**Critique of the quality of the exposure assessment** **Potential for misclassification** **Other exposures** **Weaknesses, limitations** **(no explicit value statement)**
All studies: All mechanistic studies were cross-sectional in design. None analysed outcome by exposure level or duration or evaluated homogeneity of exposure within the groups. None adjusted for confounding to occupational carcinogens although several investigated outcome levels by smoking status.										
Studies of occupationally exposed subjects: All occupational studies had or were likely to have had exposure levels higher than in the general population studies.										
Cave et al. (2011) (82/0) highest exposure group *n* = 50	Employer work histories	ABS elastomer/polymer workers in two companies exposed from what appeared to be since the mid-1970s. The mean duration of employment was 21.57 ± 9.17 years (USA)	Semiquantitative levels of acrylonitrile (continuous, but not described in terms measurement units)	NI	Inhalation and dermal. Highest rank = highest inhalation rank or presence of dermal exposure	Cumulative. Exposure occurred at least 3 months before biological sampling	Also evaluated 1,3-butadiene and styrene exposure levels. No indication if carcinogenic pigments or dyes were present but possible. No adjustments made	Nondifferential misclassification. Differential misclassification due to assigning dermal exposure to high exposure category	Cumulative exposure was estimated ranking all jobs on a scale of 0–6 based on exposure level. Means presented by outcome	Limitations: use of air measurements not described; unclear if historical changes considered; NI on exposure levels or latency; exposure group may be heterogeneously exposed; no adjustments made for co-exposures; no control group. Strengths: Employer work histories form the basis of job information; cumulative exposure was estimated; dermal exposure considered; substantial exposure duration; 2 major occupational carcinogens evaluated. Nondifferential exposure likely lower than in other mechanistic studies. This study has the strongest exposure assessment methods of the mechanistic studies.
Ivănescu et al. (1990) (297/145)	NA	Men working with acrylonitrile at an undefined operation for 6 months to 10 years sampled once in three consecutive years. Also 65 participants evaluated longitudinally over 2 years (Romania)	None	NI	Primarily inhalation and some subjects may have had dermal exposure. Neither was assessed	No exposure metric evaluated. Exposure duration: 6 months to 10 years (mean, 3.8–4 years across sample collection dates)	NI. No adjustments made	Nondifferential misclassification	Groups based on blood sampling date. Exposure duration presented as descriptive information.	Limitations: NI on plant operations, exposure levels, latency, dermal exposures or presence of other occupational carcinogens; mean exposure duration < 5 yr; no exposure group (grouped by date of sample collection, which may be heterogeneously exposed); no exposure metric analysed; no adjustments made for co-exposures. Strengths: information on exposure duration but unclear if sufficient time; *n* = 65 in longitudinal study covered 2 years; 5 sets of controls.

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Tavares et al. (1996) (16/11) Highest exposure group = 7	NI	Polymerization or maintenance mechanic workers exposed in a polymerization plant where acrylonitrile exposure occurred. Mechanics were repairing and cleaning the polymer reactor [Location is assumed to be Portugal]	Qualitative (two job groups)	NI	Inhalation and probably dermal for some subjects. Neither was assessed	No exposure metric evaluated. No information on timing	NI. Other possible occupational carcinogenic exposures such as pigments and dyes possible. No adjustments made	Nondifferential misclassification	2 job groups. CEV levels were outcome.	Nondifferential misclassification likely. Minimal exposure assessment quality Limitations: CEV is an adduct with levels reflecting 4 months exposure, but generally not longer term; exposure group may be heterogeneously exposed; NI on duration of exposure, exposure levels, latency, dermal exposures or presence of other occupational carcinogens; no exposure metric; qualitative analysis by job group; no adjustments made for co-exposures. Strengths: CEV reflects internal exposures from all routes of exposures; office workers in same company are controls and likely unexposed.
Major et al. (1998) (26/32) Highest exposed group *n* = 13	Area acrylonitrile air measurements, interviews	Fibre producers and maintainers workers with possibly 3–10 years of acrylonitrile exposures at a viscose rayon plant (Hungary)	Qualitative (two job groups)	Sampling and analytical methods appear to be appropriate. Area measurements: 0–17.6 mg/m^3 at the start of the study and then, seven months later, 0.3–5.1 mg/m^3. Air measurements not used in the analysis	Likely inhalation with possible dermal exposure for some subjects. Neither was assessed	No exposure metric evaluated. Exposure occurred 3–10 years before biological sampling. Samples were collected pre- and post-shift	Dimethylformamide was a co-exposure. No other chemicals were identified. Separate analyses were performed for dimethylformamide, but no adjustment was made. Other possible occupational carcinogenic exposures such as pigments and dyes possible	Nondifferential misclassification	2 job groups	Nondifferential misclassification. Minimal exposure assessment quality. Limitations: exposure duration was 3–10 yr; NI on source of information, latency, dermal exposures, or presence of occupational carcinogens (other than dimethylformamide); exposure group may be heterogeneously exposed; measurements results were provided but were area samples and relevance to exposure unclear and not used in the analysis; no exposure metric; qualitative analysis by job group; no adjustments made for co-exposures. Strengths: Acrylonitrile levels were provided and are the highest reported for any mechanistic study identified here; pre- and post-shift samples were collected; dimethylformamide identified as

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										co-exposure; controls had no known exposure. Nondifferential misclassification likely. Moderate exposure assessment quality.
Rössner et al. (2002) (49/24)	Area acrylonitrile air measurements	Acrylonitrile-exposed "petrochemical" workers but no further information (Czechia)	Qualitative	NI on air sampling. Indicated analytical method. Area measurements: 0.05–0.3 mg/m^3. Air measurements not used in the analysis	Likely inhalation with possible dermal exposure for some subjects. Neither was assessed	No exposure metric evaluated. Exposure occurred 3 months before blood collection	NI on other possible occupational carcinogenic exposures. No adjustments made	Nondifferential misclassification	Work in an acrylonitrile-exposed petrochemical plant.	Limitations: single exposure group may be heterogeneously exposed; measurements results were area samples and not used in the analysis; NI on plant operations, duration, latency, dermal exposures or presence of other occupational carcinogens; no exposure metric; qualitative analysis by employment in plant; no adjustments made to co-exposures. Strengths: measurements results provided; controls not likely exposed. Nondifferential misclassification likely. Minimal exposure assessment quality.
Xu et al. (2003) (30/30)	Area acrylonitrile air measurements	Male acrylonitrile-exposed workers at an unknown chemical plant having worked no more than 2.8 years at the site [assumed to be in China]	Qualitative	NI on the sampling and analytical method. Area measurements: 0.8 ± 0.25 mg/m^3. Air measurements not used in the analysis	Inhalation and possibly dermal for some subjects. Neither was assessed	No exposure metric evaluated. Exposure occurred ≤ 2.8 years before biological sampling	NI on other possible occupational carcinogenic exposures. No adjustments made	Nondifferential misclassification	Employment in factory.	Limitations: single exposure group and may be heterogeneously exposed; NI on plant operations, latency, dermal exposures or presence of other co-exposures; maximum exposure was 2.8 yr may be insufficient time; measurements results were area samples and not used in the analysis; no exposure metric. qualitative analysis by employment in factory; no adjustments made for co-exposures. Strengths: Exposure levels identified; controls not likely exposed. Nondifferential misclassification likely. Minimal exposure assessment quality.

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Sram et al. (2004) (45/56)	Acrylonitrile area air measurements	Male polymerization making India rubber (Czechia)	Qualitative	NI on the sampling and analytical method. Area measurements: 0.05–0.3 mg/m^3. Air measurements not used in the analysis	Inhalation and probably dermal for some subjects. Neither was assessed	No exposure metric evaluated. Exposure occurred 3 months before biological sampling	NI. Other possible occupational carcinogenic exposures, such as pigments and dyes. No adjustments made	Nondifferential misclassification	Job group	Limitations: single exposure group may be heterogeneously exposed; NI on plant operations, duration, latency, dermal exposures or presence of other co-exposures; measurements results were area samples and not used in the analysis; no exposure metric; qualitative analysis of job group; no adjustments made for co-exposures. Strengths: 2 sets of controls who were unlikely to have been exposed. Nondifferential misclassification likely. Minimal exposure assessment quality.
Sram et al. (2007) (NI/NI)	NI	Male polymerization workers making India rubber (Czechia)	Qualitative	NA	Inhalation and probably dermal for some subjects. Neither was assessed	NI	NI. Other possible occupational carcinogenic exposures, such as pigments or dyes. No adjustments made	Nondifferential misclassification	Job group	Limitations: single exposure group may be heterogeneously exposed; NI on duration, latency; dermal exposures or presence of other occupational carcinogens; no exposure metric; qualitative analysis of job group; no adjustment for co-exposures. Strengths: controls unlikely to have been exposed. Nondifferential misclassification likely. Minimal exposure assessment quality.
Beskid et al. (2006) (61/49)	Acrylonitrile area air measurements	Male polymerization workers making Indian rubber (Czechia)	Qualitative	NI on the sampling and analytical method. Area measurements: 0.05–0.3 mg/m^3 in 2000 and 0.05–0.7 mg/m^3 in 2003. Air measurements not used in the analysis	Inhalation and probably dermal for some subjects. Neither was assessed	No exposure metric evaluated. Exposure occurred 3 months before biological sampling for 39 subjects; NI on the remaining 22 subjects	NI. Other possible occupational carcinogenic exposures, such as pigments and dyes. No adjustments made	Nondifferential misclassification	Job group	Limitations: small sample size; single exposure group exposure group may be heterogeneously exposed; NI on duration of exposure, latency, dermal exposures, or presence of other occupational carcinogens; measurements results were area samples and not used in the analysis; no exposure metric; qualitative analysis of job group; no adjustment for co-exposures.

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										Strengths: Control group was not exposed to acrylonitrile. Nondifferential misclassification likely. Minimum exposure assessment quality.
Caciari et al. (2014) (218/200)	Acrylonitrile area air measurements	Male workers in a plant producing polyacrylonitrile fibres employed for 5–8 years (average, 6.5 years) (Italy)	Qualitative	NI on the sampling and analytical method. Area measurements. Air measurements not used in the analysis	Inhalation and probably dermal for some subjects. Neither was assessed	No exposure metric evaluated. Exposure occurred before sample collection	Levels of other carcinogens used (methacrylate, sulfuric acid) below the recommended time-weighted average and short-term exposure limit, but not adjusted for	Nondifferential misclassification	Work in an acrylonitrile fibres operation	Limitations: single exposure group may be heterogeneously exposed; NI on latency, dermal exposures; duration of employment may be insufficient; measurements results were area samples and not used in the analysis; low exposures (" below the TLV-TWA"); no exposure metric; qualitative analysis of employment in operation; no adjustment for co-exposures. Strengths: identified co-exposures; controls not exposed. Nondifferential misclassification likely. Minimal exposure assessment quality.
General population studies: All general population studies had or were likely to have had exposure levels considerably below the occupational studies. None were likely to have had occupationally exposed subjects. No estimates of exposure duration or air levels were provided. Inhalation was likely due to smoking and air pollution. Dermal and ingestion are not likely to be routes of exposure.										
Schettgen et al. (2004) (29/0) Highest exposure group *n* = 16 (smokers)	Blood, questionnaires	General population (Germany)	Quantitative for CEV. Qualitative smokers vs non-smokers	No concerns	Inhalation	Means, medians and ranges for CEVlevels. No information to suggest questionnaires were administered before blood collection	Measured adducts of acrylamide and glycidamide. No adjustments made	Nondifferential misclassification	Spot blood sample analysed for CEV levels for smokers versus non-smokers	Limitations: CEV is an adduct with levels reflecting 4 months exposure, but generally not longer term;;small sample size in highest exposure group; NI on duration, latency, exposure levels, or presence of other co-exposures (other than smoking); exposure groups were smokers and non-smokers; qualitative analysis for 2 smoking groups; no adjustments made of other exposures; no controls. Strengths: CEV is a highly specific and sensitive biomarker for acrylonitrile in smoking and reflects internal exposures from all routes; CEV means, medians

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										and ranges provided; measured adducts of 2 other co-exposures. Nondifferential misclassification. Limited informativeness.
Schettgen et al. (2010) (104/0) Highest exposure group *n* = 12 (smokers)	Blood, interviews	General non-smoking population (Germany)	Quantitative for CEV. Qualitative smokers vs non-smokers	No concerns	Inhalation	Average CEV levels. No information to suggest questionnaires were administered before blood collection	Measured adducts of propylene oxide, acrylamide and glycidamide. Subjects selected without known work exposure to acrylonitrile or three other co-exposures. No adjustments made	Nondifferential misclassification	Spot blood sample analysed for CEV levels by passive smoking (yes/no)	Limitations: CEV is an adduct with levels reflecting 4 months exposure, but generally not longer term; small sample size in highest exposure category; NI on duration, latency, exposure levels, or presence of other co-exposures; exposure groups based on 2 passive smoking groups: qualitative analysis based on passive smoking (yes/no): no adjustments made for co-exposures; no controls. Strengths: CEV is a highly specific and sensitive biomarker for acrylonitrile in smoking that reflects internal exposures from all routes; means, medians and ranges provided; measured possible exposure to adducts of 3 other co-exposures. Nondifferential misclassification. Limited informativeness.
De Smedt et al. (2014) (358/116) Highest exposed group (lived < 250 m from derailment) *n* = 40	Blood, questionnaires	Living near a train derailment and that released acrylonitrile and caught fire (Belgium)	Qualitative: four general population groups living near train derailment comprising: (1) a group evacuated hours after the event (< 250 m perimeter of accident) (*n* = 40); (2) a group evacuated days after event: (2a) those went to emergency health services (*n* = 99); and (2b) 10% of those who did not (*n* = 219); (3) a control group outside the evacuation area but who had visited the health services (*n* = 116)	No concerns	Inhalation	Mean, median CEV levels. Exposure occurred 2–3 weeks before biological sampling	NI. Fire could have resulted in a variety of exposures, including some possibly carcinogenic. Acrylonitrile decomposition products: hydrogen cyanide and nitrogen oxides. Subjects asked about occupational acrylonitrile exposure	Nondifferential misclassification. Differential exposure may have occurred due to sewage emissions, Self-selection into the study may have resulted in differential misclassification	Groups characterized by distance from derailment and use of emergency services with CEV levels as outcome	Limitations: subjects were volunteers; small sample size in highest exposed group; bloods may have been collected before substantial metabolism occurred for highest exposed group; NI on the presence of other exposures from fire; second (indirect) source was acrylonitrile-containing sewage system for some subjects; qualitative analytic groups; no adjustments made on co-exposures. Strengths: CEV is a highly specific and sensitive biomarker for acrylonitrile that reflects internal exposures from all routes; moderate sample size; blood

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										collected within 3 weeks of exposure. Nondifferential and possibly differential misclassification. More informativeness than most of the studies reviewed here.
Weinstein et al. (2017) (23/0)	Urine	Women exposed to household wood smoke (Guatemala)	Quantitative for urinary CEMA.	No concerns	Inhalation	Mean and median CEMA levels. No indication of timing	Air levels of PAHs, $PM_{2.5}$ collected and analysed. 8 other urinary metabolites of VOCs analysed	Nondifferential misclassification	3 urinary samples measured for CEMA in a single exposure group	Limitations: CEMA is a metabolite with levels reflecting exposure in hours, but generally not longer term; small sample size; single exposure group; NI on duration, or latency; no adjustment made for co-exposures; no controls; correlation with particulate = 0.59. Strengths: CEMA is a highly specific and sensitive metabolite for acrylonitrile in smoking and reflects all exposure routes over a work shift; measured several other co-exposures. Nondifferential misclassification likely. Moderate exposure assessment quality.
Lin et al. (2018) (*n* = 853/0)	Urine, interviews	General population (Taiwan, China)	Quantitative for urinary CEMA. Two analyses: (1) four categories of CEMA levels; and (2) continuous values used in regression. Qualitative for entire studied population	No concerns	Likely inhalation	Average CEMA levels. Same samples used for exposure and outcome	NI	Nondifferential misclassification	Spot sample: urinary CEMA levels for a single exposure group	Limitations: CEMA is metabolite, with levels reflecting exposure in hours, but generally not longer term; NI on duration, latency, or presence of other co-exposures; single exposure group of entire group; qualitative analysis; no adjustment for co-exposures; no controls. Strengths: CEMA is a highly specific and sensitive biomarker for acrylonitrile and reflects all exposure routes over a work shift; analysis used continuous variables in regression analyses. Nondifferential misclassification likely. Moderate exposure assessment quality.

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Kuang et al. (2022) (one study: 7 adults and 6 children; second study: 259 children/0)	First study: urine. Second study: urine and questionnaires	Non-smoking volunteers exposed to smoker in simulated room for 2 days. Second study: spot sample from children in the general population with passive smoking exposure	Quantitative for urinary CEMA and HEMA. Qualitative (by age) for first study. Semiquantitative (amount, frequency of passive smoking) for second study	No concerns	Inhalation	Cumulative CEMA (within 2 days post exposure) for non-smokers. Pre- and post-exposure urine samples were collected. Same samples used for exposure and outcome	25 other VOCs analysed. No adjustments made	Nondifferential misclassification	Spot sample: urinary CEMA levels by: first study, age; second study: passive smoking (yes/no)	Limitations: CEMA is metabolite, with levels reflecting exposure in hours, but generally not longer term; small sample size; questionnaire source of second study exposure information; NI on exposure duration, latency, co-exposures present; qualitative (adult, children: first study: semiquantitative (amount and frequency of passive smoking: second study), analysis; no adjustments made for co-exposures; no controls. Strengths: CEMA is a highly specific and sensitive biomarker for acrylonitrile in smoking that reflects all exposure routes over a work shift; measured several other co-exposures; collected pre and post exposure samples. Nondifferential misclassification likely. Moderate exposure assessment quality.
Wahlang et al. (2022) (663/0)	Urine, interviews	General population (USA)	Quantitative for urinary CEMA. Qualitative for entire population	The LOD might not be sufficiently low, CEMA was not detected in 40% of the samples	Likely inhalation	Continuous values used in regression analysis. Exposure and outcome variables likely collected simultaneously	15 other VOCs metabolites analysed. No adjustments made	Nondifferential misclassification	Spot sample: urinary CEMA levels relationship to liver biomarkers	Limitations: CEMA is metabolite, with levels reflecting exposure in hours, but generally not longer term; single exposure group; NI on duration, latency, co-exposures; qualitative analysis of entire population; no adjustments made for co-exposures; no controls. Strengths: CEMA is a highly specific and sensitive biomarker for acrylonitrile that reflect all short-term exposure routes; analysis used continuous variables in regression analyses; measured several other co-exposures. Nondifferential misclassification likely. Moderate exposure assessment quality.

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Wahlang et al. (2023) (663/0)	Urine, interviews	General population (USA)	Quantitative for urinary CEMA. Qualitative for entire population	The LOD might not be sufficiently low, CEMA was not detected in 40% of the samples	Probably inhalation	Continuous values used in regression analysis. Exposure and outcome variables likely collected simultaneously	15 other VOCs analysed. No adjustments made	Nondifferential misclassification	Spot sample: urinary CEMA levels relationship to liver biomarkers	Limitations: CEMA is metabolite with levels reflecting exposure in hours, but generally not longer term; single exposure group; NI on duration, latency, co-exposures identified; qualitative analysis of entire population; no adjustments made for co-exposures; no controls. Strengths: CEMA is a highly specific and sensitive biomarker for acrylonitrile that reflects all exposure routes over a work shift; moderate size; analysis used continuous variables in regression analyses; measured several other co-exposures. Nondifferential misclassification likely. Moderate exposure assessment quality.
Riggs et al. (2022) (*n* = 603/0)	Urine, questionnaires	General population (USA)	Quantitative for urinary CEMA. Qualitative for entire population	The LOD might not be sufficiently low, CEMA was not detected in 61% of the non-smokers	Inhalation	Continuous values used in regression analysis. Exposure and outcome variables likely collected simultaneously	$PM_{2.5}$, ozone measured. $PM_{2.5}$, ozone, and 11 other VOCs analysed but no adjustments made	Nondifferential misclassification	Spot sample: urinary CEMA levels relationship to cardiovascular disease biomarkers	Limitations: CEMA is metabolite, with levels reflecting exposure in hours, but generally not longer term; NI on duration, latency; single exposure group; qualitative analysis of entire population; no adjustments made for co-exposures; no controls. Strengths: Strengths: CEMA is a highly specific and sensitive biomarker for acrylonitrile that reflects all exposure routes over a work shift; moderate size; analysis used continuous variables in regression analyses; measured several other co-exposures. Nondifferential misclassification likely. Moderate exposure assessment quality.

ABS, acrylonitrile–butadiene–styrene; CEMA (CNEMA, CYMA), *S*-(2-cyanoethyl) mercapturic acid; CEV, *N*-(2-cyanoethyl)valine; HEMA, 2-hydroxyethylmercapturic acid; LOD, limit of detection; NA, not applicable; NI, no information; $PM_{2.5}$, particulate matter with diameter < 2.5 μm; TLV-TWA, threshold limit value-time-weighted average; USA, United States of America; VOC, volatile organic chemical; vs, versus.

Note: CEMA identified by Whalang as acrolein.

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