National Toxicology Program
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Appendix G: Shiftwork and Lung Cancer

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List of Tables

Appendix G: Lung Cancer Studies Tables

Appendix G encompasses tables related to human studies on shift work exposure and risk of lung cancer. Tables G-1a to G-1f provide ratings and the rationales for the domains of study quality and study sensitivity. Table G-2 gives detailed results for each evaluated epidemiological study.

Table G-1a. Evaluation of selection bias in lung cancer studies

Reference	Selection Bias rating
Jørgensen *et al.* 2017	+ ? The cohort was clearly defined by exposed/non-exposed for a specific time period and location. Follow-up did not differ by exposure status. Left truncation is an issue in this older survivor cohort. Authors indicated most nurses have to participate in rotating shift work early in their careers, and this is a >44 yr old cohort, so selection of exposure status may not be appropriate. Mortality analysis is likely to miss about 1/3 of cases having longer survival and later death, likely resulting in non-differential (not related to exposure status) misclassification, loss of power, and an underestimation of the risk estimate.
Schernhammer *et al.* 2013	++ ? Cohort is defined by exposure status for a specific time period and location, and follow-up does not appear to differ among exposed and unexposed. Healthy worker survivor effect (HSWE) and left truncation were possible, but stratification by duration of employment helps to mitigate those potential impacts. HWE is also possible given the healthier nurse population.
Schwartzbaum *et al.* 2007	++ ? Only an external analysis was conducted. No evidence of HWE, as the overall SIR for all cancers was approaching unity. HWSE is still possible and may bias results toward the null.
Taylor and Pocock 1972	++ ? Cohort is clearly defined by exposure status for a specified time period and location. Follow-up did not differ between exposed and unexposed. Healthy worker effect (HWE0 was not accounted for in analyses, although mortality rates of cohort were comparable to greater population. Since only workers from large companies with health pre-screening requirements were chosen, selection bias may be present and may non-differentially bias results toward the null.
Yong *et al.* 2014	++ ? The cohort is clearly defined and includes the relevant exposed and unexposed populations for a specific time period and location. Evidence of HWE, as cancer incidence was higher among shift workers and lower among day workers, compared to the general population. There was also no consideration of HWSE in this occupational cohort. In Hammer *et al.* (2015), a validation analysis of the same cohort reported no change in day to shift work for 893 (97%) of the employees, and there was little movement between shifts in this company suggesting HWSE is minimized.
Kwon *et al.* 2015	++ ↔ Cases and sub-cohort (case-cohort study) were chosen from the same cohort by similar methods and criteria, and cohort was clearly defined by exposure status. No evidence that follow-up differed by exposure status. HWE is

Reference	Selection Bias rating
	possible in this study, considering exposed population would need to be healthier in order to work nights.
Parent *et al.* 2012	+++ ↔ Cases and controls selected from the same population using similar criteria; no evidence that selection of subjects was related to both exposure and disease. Distribution of occupations of controls was comparable to distribution in the Canadian censuses, and percentage of those who were shift workers (14.5%) was similar to the general male population.

Table G-1b. Evaluation of exposure assessment methods in lung cancer studies

Reference	Exposure Assessment rating
Jørgensen *et al.* 2017	0 ? Current information on work status at baseline only. No information on past employment status casting doubt on those classified as unexposed. No data on duration of shift schedule and shift work intensity lead to a less sensitive exposure categorization. Furthermore, authors mention the high likelihood of exposure misclassification for nurses whose training involves shift work early in their career.
Schernhammer *et al.* 2013	++ ? Study adequately captures shift schedule and years of shift schedule, but not shift intensity. Exposure may have been misclassified, resulting in bias toward the null due to the nature of the questions asked, (i.e. permanent night work may not have been considered to be rotating.
Schwartzbaum *et al.* 2007	0 ? Night shift work was determined according to percentage of those in each job category reporting shift work in a survey independent of the study cohort. Given the lack of individual-level data on exposure, participants categorized as unexposed are more likely to have been misclassified.
Taylor and Pocock 1972	++ ? Exposure assessment allows for discrimination between exposed and unexposed populations. Shift schedule (day, shift, ex-shift), duration (10+ years vs. <10 years), and shift intensity (day, 3-week rotating, rapid rotating, alternate night/day, double days, etc.) were all captured, but not all quantified in final models. Any exposure misclassification is likely non-differential and will bias toward the null.
Yong *et al.* 2014	+ ? Detailed information on shift work schedule and intensity were used. Years of shift work was also captured, but not prior to 1995. Exposure status prior to 1995 was estimated to be misclassified for both unexposed (1.2%–3.1%) and exposed (9.8%–13.4%) participants based on a sensitivity analysis of 300 participants. Validation study revealed the likelihood of misclassification impacting results was low; however, potential differential misclassification for exposed subjects will bias results toward the null.
Kwon *et al.* 2015	++ ↔ Exposure to shift work was characterized by cumulative years and nights worked, but not by shift schedule or shift intensity. Exposure was not based at an individual-level and relied on a job exposure matrix (JEM), although strict regulations standardized schedules.
Parent *et al.* 2012	++ ↔ Exposure methods reliably discriminate between ever and never exposed. However, no information was gathered on frequency (exposure-level) or types of shifts (fixed or rotating), direction or rate of shift rotation. Timing of shift work was collected but crudely divided as recent (within past 20 years), or distant past (20+ years ago) exposure.

Table G-1c. Evaluation of outcome assessment in lung cancer studies

Reference	Outcome Assessment rating
Jørgensen *et al.* 2017	++ ? Reported causes of death were not histologically-confirmed, rather only based on physician report from death records.
Schernhammer *et al.* 2013	+++ ↔ Outcome methods distinguish between diseased and non-diseased subjects; medically confirmed. Furthermore, lung cancer subtypes were examined
Schwartzbaum *et al.* 2007	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses are conducted independent of exposure status.
Taylor and Pocock 1972	+++ ↔ Outcome methods distinguish between diseased and non-diseased based on the use of death certificates. Unknown who did follow-up ICD-coding or who determined cancer status.
Yong *et al.* 2014	++ ? Outcome methods distinguish between diseased and non-diseased subjects, and follow-up was conducted independent of exposure classification; however, given the development of the registry, some cases may have been missed, although it is likely that this is non-differential misclassification, leading to a bias towards the null.
Kwon *et al.* 2015	++ ? Outcome methods distinguish between diseased and non-diseased subjects. Follow-up and diagnosis were independent of exposure. Disease diagnoses were not histologically confirmed, nor were any lung cancer subtypes examined, so there is potential for outcome misclassification.
Parent *et al.* 2012	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnosis conducted independent of exposure status.

Table G-1d. Evaluation of study sensitivity in lung cancer studies

Reference	Sensitivity rating
Jørgensen *et al.* 2017	+ ? Small number of night and rotating shift lung cancer cases. Poor sensitivity of exposure status due to lack of level, duration, or range of exposure. Adequate follow-up duration.
Schernhammer *et al.* 2013	++ ? The study has a large number of exposed lung cancer cases. Study has a substantial duration of exposure; however, it does not capture level or range of shift work.
Schwartzbaum *et al.* 2007	+ ↔ In men, adequate number of exposed cases of lung/trachea cancer; in women, very small number of cancer cases. Poor categorization of level, duration, and range of exposure to shift work due to the nature of non-specific registries.
Taylor and Pocock 1972	+ ? The study has a substantial number of exposed subjects and a small number of cases with an adequate follow-up duration. For lung cancer, only day, shift, and ex-shift workers were compared for their observed vs. expected mortality, which provides little information on the magnitude of exposure and no information of duration and range of shift work exposure.
Yong *et al.* 2014	+ ? The study had a small-to-moderate number of lung cancer cases. No information on level, duration, or range, and exposure variation is essentially flat across the exposed. Latency follow-up is adequate.
Kwon *et al.* 2015	++ ↔ Study had a large number of exposed cases, a substantial stratification by cumulative years/nights, and accounted for follow-up using 10- and 20-year lag stratification. The study, however, did not measure shift intensity or shift schedules.
Parent *et al.* 2012	++ ? The study has a large number of exposed lung cancer cases, but no information on intensity/frequency or pattern of exposure (e.g., type of shifts); or screening information.

Table G-1e. Evaluation of the potential for confounding bias in lung cancer studies

Reference	Confounding rating
Jørgensen *et al.* 2017	Lung: +++ ↔ Study measured all relevant potential confounders.
Schernhammer *et al.* 2013	Lung: +++ ↔ The study measured all relevant potential confounders and used appropriate analyses to address them. Various iterations of models controlling for different subsets of potential confounders were presented.
Schwartzbaum *et al.* 2007	Lung: + ↔ The study did not measure relevant lung cancer confounders such as smoking.
Taylor and Pocock 1972	Lung: + ↔ The study did not measure potential confounders including smoking. Lung cancer rates were similar to the external population across all work types, and therefore, not indicative of unmeasured confounding in the population.
Yong *et al.* 2014	Lung: ++ ↔ The study did not measure potential confounders relevant to the chemical industry.
Kwon *et al.* 2015	Lung: +++ ↔ The study adequately measured potential confounders and controlled for them in their analysis, including accounting for latency using lag models.
Parent *et al.* 2012	Lung: +++ ↔ The study adequately measured potential confounders and controlled for them in their analysis.

Table G-1f. Evaluation of analysis and selective reporting in lung cancer studies

Reference	Analysis rating	Selective Reporting rating
Jørgensen *et al.* 2017	++ ? Inclusion of multiple covariates not related to the exposure and outcome of interest may have attenuated results and widened confidence intervals.	+++ ↔ There isn't any evidence that data or analysis was limited to a subset of data.
Schernhammer *et al.* 2013	+++ ↔ Study used relevant data, appropriate assumptions, and appropriate analytical methods.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the collected data.
Schwartzbaum *et al.* 2007	++ ↔ Study used relevant data, had appropriate assumptions and used adequate methods for an external analysis (SIR).	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data collected.
Taylor and Pocock 1972	+ ↔ Study used relevant data and appropriate assumptions, but an standardized mortality ratio (SMR) would have been more appropriate to determine the magnitude of lung cancer mortality in the sample vs. the population.	+++ ↔ No evidence that reporting was limited to a subset of data, but reporting of analytical results were limited.
Yong *et al.* 2014	+++ ↔ The study used relevant available data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the collected data.
Kwon *et al.* 2015	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis, although unclear why a case-cohort was chosen over a nested case-control study.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of data collected.
Parent *et al.* 2012	+++ ↔ Study used relevant data, appropriate assumptions, and valid methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of data collected.

Table G-2. Evidence from epidemiological cohort and case-control studies on lung cancer and exposure to night shift work

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Jørgensen *et al.* 2017 Cohort Denmark **Enrollment or follow-up:** 1993-2013	**Population:** Danish Nurse Cohort 18 015 **Exposure assessment method:** questionnaire	**HR Ever exposure by night and rotating shift work**		Age, smoking status, pack years, physical activity, BMI, alcohol consumption, diet (veggies, fruit, meat), pre-existing disease (hypertension, diabetes, MI), self-reported health, stressful work environment, marital status, parity, use of HRT, OC use	**Exposure information:** Day, evening, night, rotating shifts **Strengths:** Nationwide prospective cohort of female nurses with detailed information on work schedules at baseline, and potential confounders. **Limitations:** Small numbers of lung cancer deaths, no information on duration or intensity, type of rotations, or past information on shiftwork. No cancer validation. **Additional results:** - **Confidence in evidence:** No confidence, not included in the assessment
		Day (Reference)	-		
		Night	1.09 (0.65–1.82); 19		
		Rotating	0.96 (0.65–1.42); 33		
Schernhammer *et al.* 2013 Cohort 11 U.S. states **Enrollment or follow-up:** Enrolled 1976; followed 1988–2008	**Population:** Nurses' Health Study - US 78,612 women **Exposure assessment method:** questionnaire	**RR All women: duration of rotating shift work**		Age, Smoking status, age started smoking, # cigarettes smoked / day, time since quitting among past smokers, fruit intake, vegetable intake, bmi, yrs living with someone who smoked, exposure to smoking at work, exposure to someone smoking at home, parental smoking while living with them	**Exposure information:** Ever and duration of rotating shift work **Strengths:** Large prospective study of nurses with well documented follow-up procedures and outcome definitions including lung cancer subtypes, and adequate control for potential confounders. **Limitations:** Exposure assessment may have biased results towards the null as permanent night workers may have been classified as unexposed. No analyses on healthy worker survival in this occupational cohort. **Additional results:** Age/time-period adjusted model and model excluding diet variables saw similar results.
		0 (Reference)	-		
		1–5 yr	1.03 (0.91–1.16); 572		
		6–14 yr	0.96 (0.81–1.14); 177		
		15+ yr	1.28 (1.07–1.53); 164		
		Trend-test *p*-value: 0.03			

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		RR Former smokers: duration of rotating shift work		Age, age started smoking, time since quitting among past smokers, fruit intake, vegetable intake, bmi, yrs living with someone who smoked, exposure to smoking at work, exposure to someone smoking at home, parental smoking while living with them, menopausal status, HRT use, OC use	age-adjusted model only had similar results similar results in age- and time-adjusted model only Results from base model similar to full model Base models are similar to full model Base models show a stronger relationship with increased duration (15+ years) and a positive dose-response trend, but no accounting for smoking. For the 6-14 year and 15+ year categories, base models (not adjusting for smoking), reveal stronger point estimates and a stronger dose-response relationship. **Confidence in evidence:** Evidence
		0 (Reference)	-		
		1–5 yr	0.99 (0.83–1.16); 292		
		6–14 yr	0.86 (0.66–1.1); 78		
		15+ yr	1.06 (0.81–1.38); 68		
		Trend-test *p*-value: 0.92			
		RR Current smokers, duration of rotating shift work		Age, age started smoking, time since quitting among past smokers, fruit intake, vegetable intake, bmi, yrs living with someone who smoked, exposure to smoking at work, exposure to someone smoking at home, parental smoking while living with them, menopausal status, HRT use, OC use, # cigarettes smoked / day	
		0 (Reference)	-		
		1–5 yr	1.01 (0.82–1.24); 203		
		6–14 yr	1.16 (0.89–1.52); 84		
		15+ yr	1.61 (1.21–2.13); 80		
		Trend-test *p*-value: 0.0006			

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		RR Never smokers, duration of rotating shift work		Age, fruit intake, vegetable intake, bmi, yrs living with someone who smoked, exposure to smoking at work, exposure to someone smoking at home, parental smoking while living with them	
		0 (Reference)	-		
		1–5 yr	1.19 (0.82–1.73); 63		
		6–14 yr	0.75 (0.39–1.45); 11		
		15+ yr	1 (0.51–1.94); 11		
		Trend-test *p*-value: 0.65			
		Adenocarcinoma: RR Duration of rotating shift work		Age, fruit intake, vegetable intake, bmi, yrs living with someone who smoked, exposure to smoking at work, exposure to someone smoking at home, parental smoking while living with them, age started smoking, time since quitting among past smokers, # cigarettes smoked / day in current smokers, menopausal status, HRT use, OC use	
		Never (Reference)	-		
		1–5 yr	1.03 (0.87–1.24); 263		
		6–14 yr	0.92 (0.71–1.2); 74		
		15+ yr	0.91 (0.67–1.24); 50		
		Trend-test *p*-value: 0.4			
		Squamous-cell carcinoma: RR Duration of rotating night shift work		Same as above	
		Never (Reference)	-		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		1–5 yr	0.96 (0.69–1.33); 75		
		6–14 yr	1.01 (0.64–1.6); 25		
		15+ yr	1.45 (0.92–2.3); 26		
		Trend-test *p*-value: 0.13			
		Small cell/oat cell: RR Duration of rotating night shift work		Same as above	
		Never (Reference)	-		
		1–5 yr	1.11 (0.79–1.57); 73		
		6–14 yr	1.4 (0.91–2.15); 34		
		15+ yr	1.56 (0.99–2.47); 29		
		Trend-test *p*-value: 0.03			
		RR Current smokers with 15+ years shift work		Same as above	
		Adenocarcinoma	1.22 (0.74–2.01); NR		
		Small-cell carcinoma	1.57 (0.85–2.89); NR		
		Squamous-cell carcinoma	1.48 (0.68–3.23); NR		
		RR Past smokers with 15+ years shift work		Same as above	
		Adenocarcinoma	0.78 (0.5–1.22); 340		
		Small-cell carcinoma	1.78 (0.82–3.86); 72		
		Squamous-cell carcinoma	1.4 (0.75–2.62); 114		
Schwartzbaum *et al.* 2007 Cohort **Enrollment or**	**Population:** Swedish working women registered in 1960 and 1970 census data. 1,148,661 female workers and 2	**Female: SIR Working in industries with 40% workers on night or rotating shift: Time period**		Age, socioeconomic status, occupational position, county of residence	**Exposure information:** Workplace had rotating schedule or work between 1 and 4 AM **Strengths:** Nationwide cohort of men and women in diverse
		1970	1.13 (0.62–1.89); 14		
		1960 and 1970	1.28 (0.47–2.79); 6		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
follow-up: 1977-1981 (enrollment); 1971-1989 (follow-up)	102 126 male workers **Exposure assessment method:** JEM	**Males: SIR Working in industries with 40% workers on night or rotating shift: Time period**		Same as above	industries followed for 19 years. **Limitations:** In men, adequate number of exposed cases of lung/trachea cancer; in women, very small number of cancer cases. Aggregate exposure data, lack of data on potential confounders or co-exposures such as smoking status. **Additional results:** - **Confidence in evidence:** No confidence, not included in the assessment.
		1970	0.95 (0.88–1.02); 706		
		1960 and 1970	0.9 (0.82–0.99); 397		
Taylor and Pocock 1972 Cohort England and Wales **Enrollment or follow-up:** Employed on 1/1/1956, followed 1956–1968	**Population:** None 8,603 manual workers **Exposure assessment method:** company records	**SIR Type of work**			**Exposure information:** Shift work for 10 years **Strengths:** Company records from 10 diverse companies across the country provided reliable information about shiftwork. **Limitations:** Cancer was not confirmed; exposure metrics were insufficiently detailed for lung cancer; and follow-up was relatively short. Furthermore, no information of potential confounders, including smoking. **Additional results:** - **Confidence in evidence:** Inadequate
		Day	1.09 (0.8–1.33); 95		
		Shift	1.11 (0.9–1.36); 94		
		Ex-shift	1.15 (0.6–1.97); 13		
Yong *et al.* 2014 Cohort Germany **Enrollment or**	**Population:** Male chemical production workers in Rhineland-Palatinate Germany	**SIR External analysis: day vs. rotating shift work**		Age, calendar year	**Exposure information:** Ever worked forward rotating shift work pattern: either 3 x12 hours (day, off, night) or 4 x12 hours (day, off, off, night)
		Day	0.48 (0.34–0.66); 39		
		Rotating	0.7 (0.51–0.94); 46		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
follow-up: 2000–2009	27,828 men **Exposure assessment method:** company records	Ratio of rotating shift vs.day	1.46 (0.93–2.3); NR		**Strengths:** Large retrospective cohort with adequate number of cases. **Limitations:** Exposure data did not encompass all employment history; no variation in exposure metrics beyond ever exposure; duration crudely estimated and not used in analysis; only 80% estimated completeness of cancer case reporting; potential confounders not controlled; HWE is evident. **Additional results:** - **Confidence in evidence:** Null evidence
		HR (RR) Internal analysis: day vs. rotating shift work		Age, job level, smoking, employment duration	
		Day	1; NR		
		Rotating	0.93 (0.54–1.63); NR		
Kwon *et al.* 2015 Nested Case-Control Shanghai, China **Enrollment or follow-up:** 1989–1991	**Population:** Female textile workers cohort form Shanghai, China Cases: 1,451; Controls: 3,020 **Exposure assessment method:** JEM	**HR (RR) All women, no lag: Duration of rotating night shift work**		Age, smoking status, parity, endotoxin	**Exposure information:** Ever/never worked rotating night shifts; # of nights worked and years duration **Strengths:** Large, well defined occupational cohort with low rates of smoking, with sufficient number of lung cancer cases; work histories complete for all women; detailed shift work information for each
		Zero (Reference)	-		
		>0 - 17.1 yr	0.76 (0.62–0.93); 259		
		>17.1 yrs –≤ 24.9 yr	0.89 (0.72–1.09); 261		
		>24.9 yrs–≤ 30.6 yr	0.94 (0.76–1.17); 259		
		> 30.6 yr	0.82 (0.66–1.02); 261		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Trend-test *p*-value: 0.294			job including several metrics; data on potential confounders available. **Limitations:** Night shift work was embedded within rotating shift work patterns, with no assigned jobs being exclusively night shift. No detail about rotation schedules or intensity of shift work. Exposure status was collected as an aggregate at the factory level. ICD-9 codes are prone to non-differential misclassification if confirmatory data is not available. **Additional results:** Results from unadjusted model are similar **Confidence in evidence:** Null
Parent *et al.* 2012 Case-Control Montreal, Canada **Enrollment or follow-up:** 1979–1985	**Population:** Montreal population based occupational case-control study of cancer in men 35-70 years of age. Cases: 761; Controls: 512 **Exposure assessment method:** questionnaire	**OR Ever and duration of night shift work**		Age, ancestry, education, family income, respondent status, smoking, beta carotene, occupational exposure to asbestos and silica	**Exposure information:** Ever, cumulative duration, and timing of night work (worked from 1:00 AM–2:00 AM for 6+ months) **Strengths:** Possible to compare risks across cancer sites; complete population-based case-ascertainment system; histologic confirmation of primary cancers; detailed lifetime occupational histories; information on potential covariates; nighttime definition likely to encompass a period pertinent to the hypothetical mechanism of carcinogenesis. **Limitations:** No screening, grade or severity information about prostate cancer; approximately 18% of cases contributed information through proxies. **Additional results:**
		Never (Reference)	-		
		Ever (6+ months)	1.76 (1.25–2.47); 216		
		<5 yr	1.93 (1.22–3.03); 110		
		5–10 yr	1.51 (0.8–2.85); 52		
		10+ yr	1.67 (0.9–3.09); 54		
		Worked nights in past 20 years	1.76 (1.07–2.89); 91		
		Worked nights more than 20 years ago	1.88 (1.13–3.14); 79		
		OR Ever night work: Lung cancer subtypes		Same as above	
		Squamous-cell carcinoma	1.91 (1.27–2.87); NR		
		Small-cell carcinoma	1.62 (1.25–2.47); NR		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Adenocarcinoma	1.46 (0.86–2.5); NR		- **Confidence in evidence:** Evidence

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